Neuroaffectors:
The Neurons Driving Operations in the Physiology of Man
Chapter 16

James T. Fulton–October, 2018

Abstract: The "neuroaffectors" consist of the stage 7 neurons stimulating the glandular modality, the muscular modality and the skeletal modality of the physiological system of animals. Both inorganic molecules and biologicals are employed effectively to provide adequate neuroaffector flexibility within the physiological system. The neuroaffectors are founded on the Electrolytic Theory of the Neuron and employ the same coordinate chemistry principles as all neurons. Specifically, the stage 8 neuroaffectors employ the same dual antiparallel coordinate bond, DACB, found through out the chemical sensory neurons of the animal physiology. In the course of developing the theoretical framework of the neuroaffectors, a hybrid situation was uncovered defining a stage 8 hybrid gland/neuron configuration. The hybrid output hormones, as in the conventional stage 7 neuroaffectors, secrete peptides of variable complexity. Simultaneously, these hybrids accept chemical stimulants at their input structure(s) like a stage 1 chemical sensory neuron. Internally, the stage 8 neuron incorporated the electrolytic processes and mechanisms (including an Activa (electrolytic liquid-crystalline semiconductor amplifying device) common to all neurons. The stage 8 neural hybrids form the principle functional structures within the hypophysis (pituitary gland). The hypothalamus, pituitary, thyroid axis, H-P-T axis, is described in detail as an exemplar of the other axes of the glandular system controlled by the neuroaffectors. The exemplar includes more detailed flow diagrams, including details of the feedback signal employed, than previously published.

Key Words: Neuroaffector, Nitric Oxide, Acetylcholine, hypothalamus, hypophysis, endocrine, exocrine, paracrine, tropic hormones, TSH

Brief Table of Contents 5 January 2019

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Excerpts from

The NEURONS and NEURAL SYSTEM:
a 21st CENTURY PARADIGM

This material is excerpted from the full β-version of the text. The final printed version will be more concise due to further editing and economical constraints.

A Table of Contents and an index are located at the end of this paper.

A few citations have yet to be defined and are indicated by "xxx."

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Neural Concepts

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5 January 2019

16 Neuro-affectors:
The Neurons Driving Operations in the Physiology of Man[1]

In neurobiology, a central aim is to determine the components and circuitry that are responsible for a given brain function. Wilson et al. (2002)

16.1 Introduction

This chapter will expand on the role of neuro-affectors first defined in **Chapter 1**. It will focus particularly on distinct definitions for many of the biological agents affecting the muscular and glandular systems of the body. This will draw attention specifically to the current concepts of the NANC, the non-adrenergic and non-cholinergic neuro-affectors. One of the most important members of NANC is the unusual inorganic chemical nitric oxide. Nitric oxide is commonly described as a short lived free radical. During the 21st Century, the importance of nitric oxide has become more important in biochemistry. Because of its importance, it has led to the description of a new type of neuro-affector labeled nitrergic or nitroergic (for nitroxide-ergic).

When discussing the interface of the neural system and the glandular and muscular systems, another important situation occurs. The stage 7 neurons (block diagram shown below and in **Section 1.1.5**) terminate in a unique axon pedicle that releases various chemicals in order to stimulate muscle tissue or additional elements of the glandular system. These stage 7 neurons are consistent with detailed definitions of glandular cells. As a result these stage 7 neurons can be defines as ending with a chemical synapse–a morphologically and electrolytically defined connection between a stage 7 neuron and either one or more sarcomere (muscle) cells or one or more glandular cells involving *the transfer of chemical agents*.

The stage 7 chemical synapse (with a cleft) is the original type of synapse studied by researchers, such as Cajol, at the beginning of the 1900's and giving impetus to the concept defining all synapses as chemically based during the 20th Century. All other synapses of stages 1 through 6 involved electrical (tight junction) synapses.

The tight junction synapses of stage 1 through stage 6 have been shown to be electrically reversible. This capability is easily demonstrated using multiple probe techniques [2] This capability places a serious impediment in the interpretation of the generic synapse as a chemically dependent functional structure. It is easy to cause the reversal of the diode characteristic exhibited by the tight junction synapse by simply interchanging the three potentials at its terminals. The diode characteristic can be reversed within microseconds. Under the chemical theory of the neuron, this reversal requires the interchange of positions between the vesicles of the axon and the receptor sites of the neurites as well as their attaining functional normality within microseconds. The time requirement is needed to correctly exhibit the diode reversal property. It is proposed this interchange is impossible via the chemical theory of the neuron and the chemical theory of the interneuron synapse is invalid.

The agents transferred between stage 7 neurons and muscle tissue is most generally acetylcholine (at striated muscle) or nitric oxide (at smooth muscle) (**Section 5.1.2.4**).

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[1]Released: 5 January 2019

[2]Eliasof, S. et. al. (1998) Localization and function of five glutamate transporters cloned from the salamander retina. *Vision Res*. vol. 38, pp 1443-1454

- - - - 2nd draft of opening material – October 14, 2018

Because of the need to understand the potential roles of stage 7 neurons relative to the muscular and glandular modalities, it has been necessary to investigate these modalities more than initially expected. As a result, the Chapter is more properly labeled, Neuroaffectors, and the hormonal and muscular modalities. The outline of the chapter reflects this labeling.

Section 16.1 focuses on a broad range of background information needed to properly interpret later sections.
Section 16.2 focuses on the architecture of the stage 6 & 7 neurons.
Section 16.3 focuses briefly on the anatomy of the neuro-glandular interface, citing **Chapter 23**.
Section 16.4 is Reserved
Section 16.5 focuses on the neuro-muscular interface and the *paracrine* submodality.
Section 16.6 addresses the interplay between the neural-glandular-muscular modalities in animal physiology.

The investigation into the glandular and particularly the muscular modalities will be brief and leave many aspects of these modalities un-investigated as they diverge from the main theme of this work. The muscular modality will not be explored because of the limited data on how muscle tissue functions at the detailed level (what is the actual chemical or electronic mechanism involved in contraction?). The neuro-glandular interface is explored in **Chapter 23**.

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The analogy between the processing of L-glutamate into GABA electrostenolytically at the surface of the neural lemma is addressed in **Section 3.2**. The processing of L-arginine into L-citrulline will be developed in detail (**Section 16.5.2.4**).

The interaction between the neural system and the release of various hormones has not been studied in great detail as part of this work. Early secretion based experiments have been based primarily on the concentration of various chemicals near the axons of neurosecretory neurons. Glutamate and GABA have been identified routinely at these locations and therefore claimed to be examples of neuro affectors, when in fact they are neuro-facilitators and neuro-inhibitors respectively through their participation in the adjacent electrostenolytic process powering the neurons.

Acetylcholine (Ach) was one of the earliest potential neuro-affectors based on its ease of chemical identification. While its choline component, a nitrogenous alcohol, is a source of nitrogen and may contribute to the production of nitric oxide, NO, its precise functional role remains a subject of discussion.

> The study of type 4 lemma in the early 20th Century (by Cajal, Golgi & others) gave rise to the belief that all interfaces between tissue of the body involved the transfer of chemical agents. However, it is now clear that ***within the neural system, signal transfer between neurons is entirely by electrons*** and involves type 1, type 2 and type 3 lemma (**Section 5.1.2.4**). Only stimulation of stage 1 sensory neurons and the exudate of stage 7 axon pedicles involve species other than electrons.

The description of the neural system in an electrolytic context provides an abundance of new concepts to be explored. In this context, the major glands can be considered stage 7 neural interfaces with the exocrine and endocrine systems. In addition, the neuron containing endothelial tissue interfacing with the smooth muscle of the cardiac and arterial system becomes a complex of considerable interest.

The interface between the neural system and the glandular system appears to involve a variety of stereo-chemical processes. Many of the molecules involved as precursors to the hormones exhibit considerable stereo-specificity.

The neural/glandular interface appears to be a new and very active area of study. This work will show the intimate connection between stage 7 of the neural system and the initial elements

of the hormonal system. Schmidt & Walter describe NO as "partly a neurotransmitter and partly a hormone[3]." This work will consider NO as a "localized hormone" affecting only tissue within a limited distance due to the short lifetime of this free radical.

Describing the operation of stage 7 neuro-affectors involves very complex reactions described in a previous time as stereochemical. However, this term is now reserved for the description of individual molecules. The stereo-specific interactions between molecules are now considered only a feature of more complex processes that frequently involve catalytic (an inorganic term) or enzymatic (an organic term) reactions. These catalytic processes are known to involve not only stereo-specific interactions but also significant changes in the energy states associated with the components. The complexity of these reactions and resultant molecules appears to be separating into two distinct fields, the development of supramolecules in both the materials engineering and the enzymatic contexts and the design and development of bioorganic molecules in the biological and pharmacological domains. Supramolecules are restricted to multiple molecule complexes that do not employ covalent bonds.

The term bioorganics has become necessary to delineate between the broad field of physical organic chemistry outside of the biological context and the equally or broader field of physical organic chemistry within the biological sphere.

The receptor concept was introduced by pharmacologists in the 19th Century to explain the selective toxicity of plant alkaloids and certain synthetic chemotherapeutic agents[4]. The receptor-substrate context has expanded immensely from the earlier lock-and-key concept of Fischer promulgated in the early 20th Century.

Section 16.7 is included here to discuss the important enteric neural system and its role in the overall enteric system. The enteric system, the complete digestive system, operates largely autonomously and employs several mechanisms that are unique to it and serve to isolate it from the other physiological systems of the organism.

This Chapter will also include some material on the striate and smooth muscle systems, major targets of the neuro-affector neurons and neuro-affector discharges. This discussion will highlight how specific neuro-affectors only affect certain types of muscle tissue and thereby provide a degree of isolation between the neuro-affector chemicals, as well as the operation of the individual muscle types. It will also highlight why the smooth muscles do not require the presence of end-plates as used in striate muscle.

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16.1.1 Organization of the stage 6 & 7 neuro-affector neurons

The study of the neuro-affectors associated with muscle is complicated by a number of factors.

• Much of the work has been performed in the clinical setting where avoiding invasive techniques has been stressed.
• Much of the work has focused on reflex activity that is easily observed in the clinical setting.
• Unlike the external sensory modalities, the somatosensory modality involves a much more entwined arrangement of sensory receptors with multiple types of highly modified end organs.
• It is very difficult to stimulate only one internal sensory receptor neuron without employing invasive techniques.
• It is difficult to excite only a single muscle via the efferent neural pathway. Redundant stage 7 neurons and stage 7 neuron axon pedicles are typical in the excitation of muscle tissue.
• Stage 6 commands to the muscular system typically address multiple muscles simultaneously.
• As observed in the second figure below, some shortcuts have been employed when studying reflex activity. It is common to omit the location of the soma of neurons and employ an unusual

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[3]Schmidt, H. & Walter, U. (1994) NO at work *Cell* vol 78, pp 919-925

[4]Robison, G. Butcher, R. & Sutherland, E. (1971) Cyclic AMP. NY: Academic Press page 22

symbol related to the synapse.

The study of the neuro-affectors associated with the glandular modality is complicated primarily by the diversity of the interface and limited data on the operation of the neural/glandular synapses.

The above conditions make it difficult to isolate the individual neural elements and determine their precise individual roles.

Burn provides a summary of our growth in understanding of the autonomous nervous system[5]. Pierrot-Deseilligny & Burke (P-D & B) have provided a text describing the neuro-effector circuits of the human neural system from a largely clinical perspective[6]. Their text does draw many analogies from the hind limbs of cats. Their text frequently attempts to highlight discredited techniques and analyses of an earlier time period (example, pg 117). At the same time, they do not develop the details related to the operation of the neurons.

> As an interesting observation, because they do not detail the operation of the individual neurons in any functional manner, P-D & B allocate nearly two full pages of their index (with over 100 subtitles) citing subjective discussion of pre-synaptic inhibition in their text.

16.1.1.1 Role of neuro-affectors in overall system

Neuro-affectors are one of the terminal types of neurons in the neural system. The neuro-affectors are found at multiple locations within the system. The locations addressed in this work are primarily at the muscular modality and the glandular modality interfaces. They act to control the muscles and to control the operation of other glandular tissue types primarily through hormonal action. **Figure 16.1.1-1** places the stage 7 neuro-affector neurons in context within the overall system.

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[5]Burn, J. (1975) The Autonomic Nervous System, 5th Ed. Oxford: Blackwell Scientific

[6]Pierrot-Deseilligny, E. & Burke, D. (2005) The Circuitry of the Human Spinal Cord. Cambridge: Cambridge Univ. Press

6 Neurons & the Nervous System

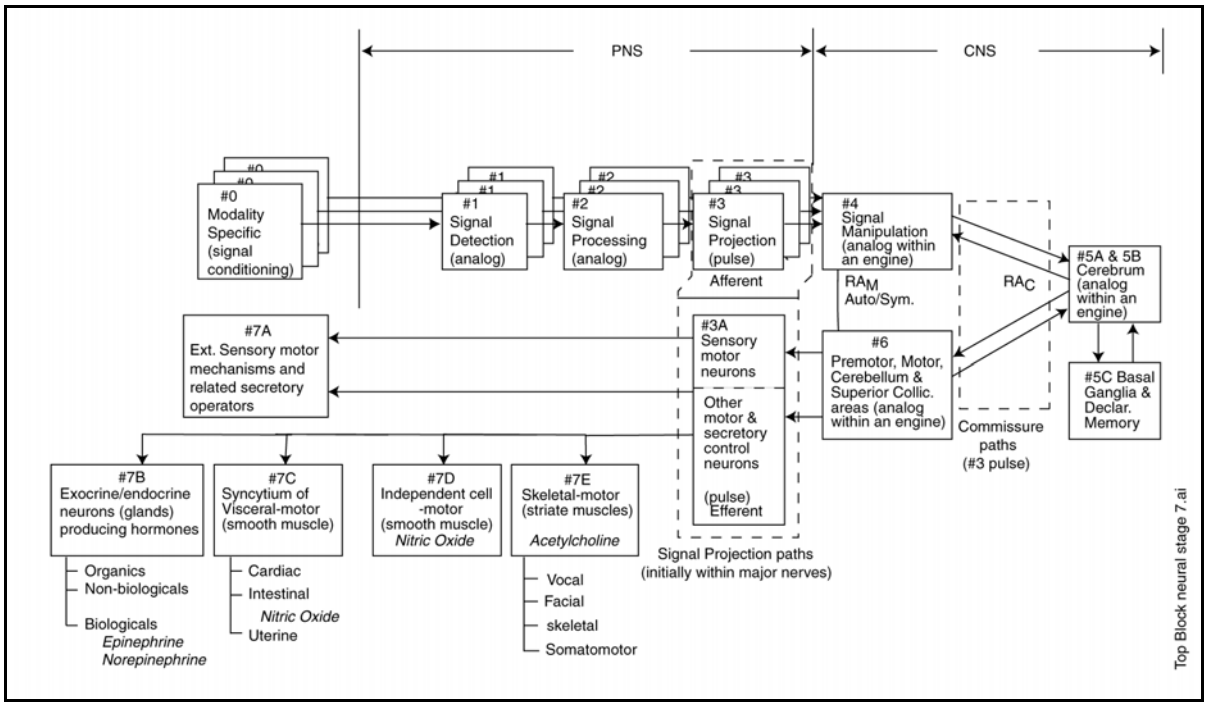

Figure 16.1.1-1 The stage 7 neuro-affector neurons within the overall neural system shown in context. They are fundamentally stage 3 signal projection neurons where the last axon segment has been modified to act as a neuro-glandular interface. They are the major controllers of the muscles and the primary participants in the glandular system. They are believed to produce, and release under neural control, a wide range of organics, non-biologicals and biologicals.

The neuro-affectors are major terminal elements in the neural system and major points of origination in the endocrine and exocrine systems (as well as their subdivisions). The recognized types of terminal elements are shown in the lower left quadrant.

Block 7A is focused on the neural interface with the oculomotor and glandular functions associated with the eyes and with similar activity associated with the external ear of hearing. This activity occurs within the cranium, but there is some controversy over whether it occurs within the CNS. In this work, the stage 7 neural activity occurs outside of the CNS (and the blood-brain-barrier. This activity is reviewed in **Section 8.3** and **Section 8.4.**

Block 7B is focused on the neural/glandular interface excluding the neural interface with the visceral elements.

Block 7C focuses on the neural/visceral elements activity. This activity employes both glandular and muscle interfaces.

Block s 7D and 7E focus on the neural/muscular interface with the smooth and striate (skeletal) muscles respectively. 7E may also include the muscles associated with the hair follicles.

While only electrons are necessary to support neurotransmission along a neural chain, there is need for a considerable number of molecules associated with the stage 7 neuro-affectors, affecting both muscles and other tissue. The mammalian biological system has found it necessary to utilize both striated muscle and smooth muscle, along with the neuro-affectors necessary to control them. The stage 7 neuro-affectors serving the skeletal-motor system are generally believed to release acetylcholine as the primary neuro-affector agent into the end-plates of striate muscle tissue. It is affective in causing the contraction of striated muscle. However, it is ineffective with respect to smooth muscle that is normally in a state of contraction.

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Analyses related to the stage 7B neuroaffectors grew rapidly to expose an entire Crine modality not properly addressed in the literature. As a result a new **Chapter 23** was created to explore the stage 7B neuroaffectors, and the glandular-affectors and hormonal aspects of the Crine modality. Only the analyses associated with stage 7D and 7E neuroaffectors associated with the Crine modality will remain in this chapter as they relate to the neuroaffector/muscular interface.

Spector provided a remarkably similar flow diagram in 1970 to the above block diagram in . **Figure 16.1.1-2** . The stages on the left correspond to those in the previous figure.

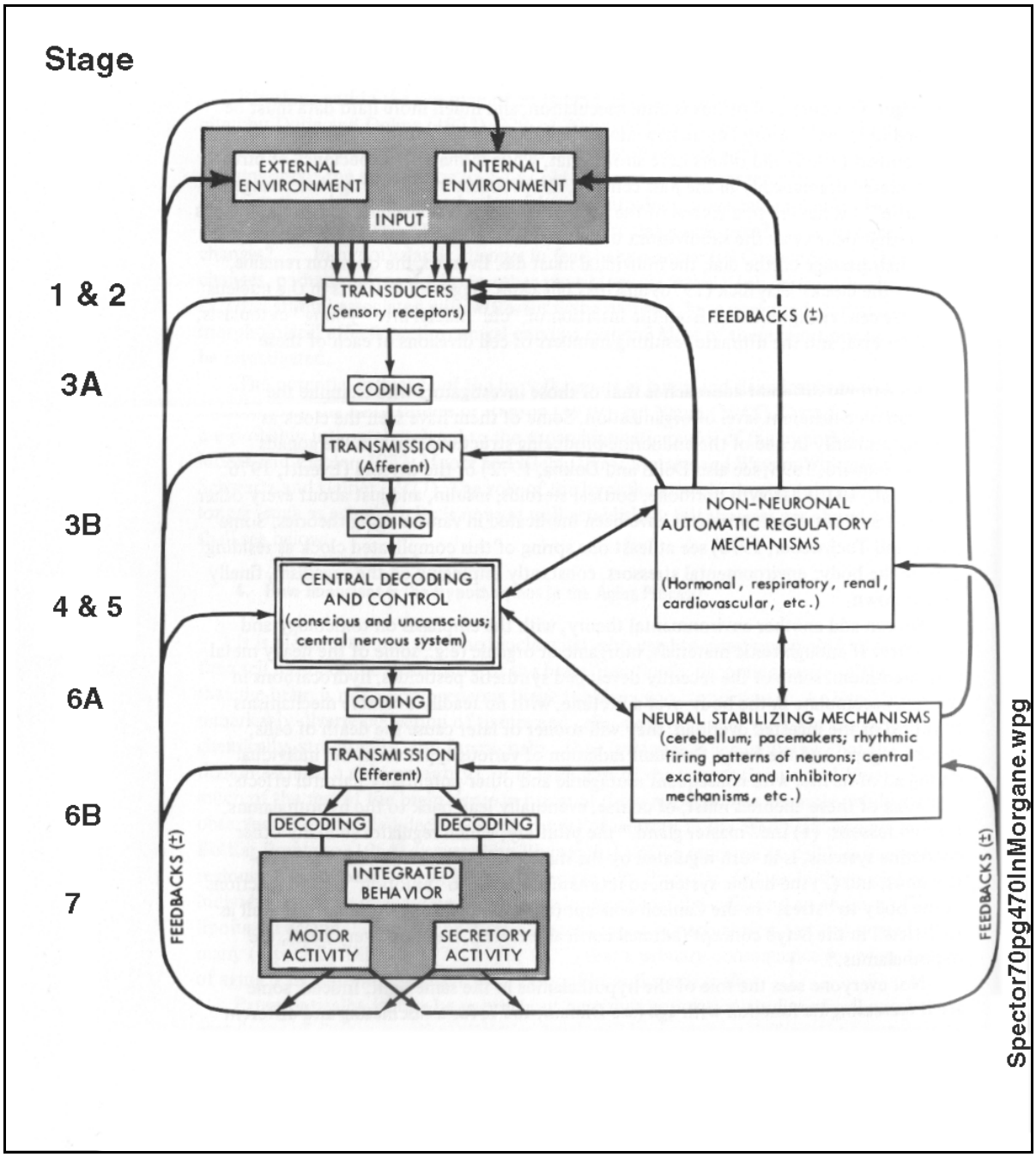

Figure 16.1.1-2 Neural system flow diagram of Spector. The stage numbers have been added to show similarlity to the previous figure. With the exception of the double arrowheads on the two connections on the right, the figure is fully supported by this work. See text. Annotated from Spector, 1970.

The caption in volume 2 of the Handbook is informative. "Omitted are storage and retrieval stations, filters and variable bandpass selectors, . . .both electrical and chemical, and many other known and unknown elements. If the 'Central Decoding and Control' box is limited principally to the unconscious, and if we were to add a box along the input line for thalamus and another for visual input, the central box could easily represent the hypothalamus." This work would suggest the addition of an *additional* visual input is not necessary; such an input is

included in the transducers of stage 1. If both the thalamus and hypothalamus are included in the "Central Decoding and Control" box, the figure would represent the "non-conscious executive" of this work (**Section 15.8**). The two boxes on the right are only suggestive; note the abbreviation, etc., in the listing in each box. The feedback(s) shown in the figure are also largely suggestive with respect to stages 1 and 2. In general, feedback is more effective in stage 4 and 5 that are largely organized as "star" networks. Star networks offer extensive feedback and feedforward capabilities. This work has surfaced very little information suggestive of feedback to the projection neurons of stage 3A & 3B and of 6A & 6B. It is likely the box labeled coding just above the Central Decoding and Control box, should be labeled *decoding*, corresponding to stage 3B.

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The neuro-affector, nitrogen oxide, is the affector of choice for causing the relaxation of smooth muscle. Smooth muscle does not employ end-plates but relies upon the release of neuro-affector agents in the immediate vicinity of the cells (paracrine agents). Smooth muscle is found in two distinct cell configurations; smooth muscle consisting of multiple independently excited cells, and smooth muscle consisting of electrically interconnected muscle cells initially excited by paracrine agents (See the *cardiocytes* of the visceral system, **Section 20.3**). The neuro-affectors serving the intestinal system are generally believed to release nitric oxide as the primary neuro-affector agent. Because of the highly integrated character of the neurons and muscles of the intestinal wall, it is difficult to specify whether the intestine incorporates multi-unit or syncytium type of smooth muscle structures (or both).

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The molecules released by stage 7B neurons at the glandular interface.

The molecules released by stage 7B neurons interfacing with the glandular modality appear to be poorly documented and not widely discussed within the neuroscience community at this time. Chapter 2 of volume 2 of Morgane & Panksepp contains some work in this area. There has been very little academic literature on this subject since 1980. As late as 2005, Harbuz & Lightman[7] (writing in Melmed & Conn) provide only a conceptual cartoon addressing the neural/glandular interface. They suggest both the brainstem and hippocampus provide stimulation to the paraventricular nucleus, PVN, of the hypothalamus. In the same text, Bichet identified two molecules understood to be produced by stage 7 neurons with pedicels located in the posterior hypophysis[8].

> "OT and AVP are synthesized in separate populations of magnocellular neurons (cell body diameter of 20-40 microns of the supraoptic and paraventricular nuclei" of the hypothalamus. OT is oxytocin and AVP is arginine vasopressin. The two peptides differ by only two amino acids. **Section 23.3.3.3** will address these molecules in greater detail.

Knigge et al. in Chapter 2 of volume 2 of Morgane & Panksepp identified closer to a dozen neurohormones originating in the hypothalamus in 1980. They noted at that time, "During the last 10 years it has become obvious that hormones other than oxytocin and vasopressin are synthesized and release by neurons of the central nervous system."

> They note on page 63, "The visualization of LHRH neurons by Barry and Dubois (1973a) not only offered a first indication of their topographical location in the brain but also provided the first definitive evidence that this neurohormone was indeed localized in and probably synthesized by neurons."
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> Their discussion indicates the difficulty of isolating LHRH from the cell bodies of neurons. This work asserts the neurohormones are concentrated in the pedicles of the neuron and

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[7]Harbuz, M. & Lightman, S. (2005) The Neuroendocrine-Immune Interface *In* Melmed, S. & Conn, P. *eds* Endocrinology, 2nd Edition Totowa, NJ: Humana Press Chapter 8

[8]Bichet, D. (2005) Posterior pituitary hormones *In* Melmed, S. & Conn, P. *eds* Endocrinology, 2nd Edition Totowa, NJ: Humana Press Chapter 14

only formed prior to release (**Section 16.5.3**).

16.1.1.1.1 The role of oxycotin

It is not completely clear whether oxytocin released from the stage 7 magnocellular neurons are produced in order to stimulate glandular tissue in the posterior hypophysis or whether oxytocin is released directly into the bloodstream. The reported receptor for oxytocin is found within several organs of the animal body related to reproduction. Gimpl & Fahrenholz have written a major article on the oxytocin system but actually focuses on the oxytocin receptor[9]. While four pages address the genetics of oxytocin, no discussion is presented concerning its origin or mechanism of creation. The remaining 51 pages relate to the oxytocin receptors. Kiss & Mikkelsen wrote a more specific paper on oxytocin, the molecule[10]. They noted, "Oxytocin (OXY) is a very abundant neuropeptide exerting a wide spectrum of central and peripheral effects as neurohormone, neurotransmitter, **or** neuromodulator. In the central nervous system (CNS), the OXY gene is predominantly expressed in magnocellular neurons in the hypothalamic paraventricular (PVN) and supraoptic (SON) nuclei. The magnocellular OXY neurons release their products into the general circulation in the neurohypophysis while the mediocellular OXY neurons secrete elsewhere in the CNS. OXY is also produced in peripheral tissues, e.g., uterus, placenta, amnion, corpus luteum, testis, and heart." Note the highlighted or in the first line, suggesting a problem in defining this molecule functionally. Note also they assert oxytocin is placed directly into the vascular system directly. These features complicate defining whether oxytocin is a stage 7 neurosecretion. As Kiss & Mikkelsen note,

> "Extrahypothalamic OXY synthesizing neurons have been found in the triangular nucleus of the septum, the medial posterior region of the bed nucleus of the stria terminalis and the medial preoptic area in rodents and primates (Sofroniew and Weindl 1978) and oxytocin-expressing neurons have been identified in the anterior commissural, periventricular, paraventricular, supraoptic, and perifornical nuclei as well as the bed nucleus of the stria terminalis and inter-supraoptical-paraventricular (internuclear) islands (Chung et al. 1991). However, to what extent the effect of these neurons might be similar to that one originating in the caudal-dorsal PVN *is not understood*." Emphasis added.

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16.1.1.1.2 The role of oxycotin receptors

In brief (from Wikipedia), "The oxytocin receptor, also known as OXTR, is a protein which functions as receptor for the hormone and neurotransmitter oxytocin. In humans, the oxytocin receptor is encoded by the OXTR gene which has been localized to human chromosome 3p25. The receptor is represented as a trans-membrane protein of the GPCR family..

16.1.1.1.3 The role of stage 7Cneuroaffectors in the vicera

The stage 7C neuroaffectors are associated with the elements of the visceral nerve. The principle elements to be addressed in this chapter are the heart, uterine system and enteric (digestive) systems of the organism. It appears that cardiac and uterine muscle may rely upon other paracrine agents than nitric oxide to isolate their performance from that of other muscle systems. They both appear to employ syncytium modes of operation, typically initiated by stage 7 neuro-affectors. The controlling stage 7 neuro-affectors may be associated primarily with local reflex arcs (rather than depending on the CNS for instructions). In fact, both the cardiac and uterine muscles are controlled by a distinct mini-brain. These mini-brains cause the cardiac and uterine muscles to operate largely independent of the CNS and a variety of other stimulants.

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[9]Gimpl. G. & Fahrenholz, F. (2001) The Oxytocin Receptor System: Structure, Function, and Regulation Physiol Reviews vol 81(2), pp 629-683

[10]Kiss, A. & Mikkelsen, J. (2005) Oxytocin – Anatomy and Functional Assignments: A Minireview *Endo Regulations* vol 39, pp 97-105

In their secretion roles, stage 7 neurons, acting as neuro-affectors may be considered pseudo-enzymes with an expanded capability. They have the ability to act as a substrate for complex stereo-chemical transformations, and release these materials through their surfaces of arginine vasopressin type 3 lemma. They can hold the products of these transformations, hormones or pseudo-hormones, until their timely release under neurological control.

16.1.1.2 Waveforms of stages 3 & 6 neurons associated with muscles

The clinical literature of the peripheral nervous system of the neuro-muscular modality has generated its own nomenclature over the years. This appears to be due largely to the extra-cellular recording techniques employed and the very large area stimulus typically employed (relative to the receptive field of the individual sensory neuron). Both of these factors appear to contribute to what P-D & B describe as "pool problems" in the laboratory (page 16). It is occasionally influenced by the desire to employ noninvasive test techniques with their inherent lack of precision (page 30).

Several specific waveforms have been conceptually defined based on clinical observations. Many of these waves are discussed primarily in the context of reflex actions rather than as stand-alone features.

F waves– "Biologically, the F wave is an artefact: F waves would occur under natural conditions only if a motor axon had an extopic focus that gave rise to an antidromic impulse" (P-D & B, page 21). Typically a low amplitude analog waveform measured close to a muscle.

P-D & B note (page 21), "it is believed that the F response is evoked by antidromic reactivation ('backfiring') of motoneurons." This is an extremely unlikely explanation. The F label arose from early analyses related to the human foot.

H waves–

"H reflexes (or Hoffman reflexes) are produced by percutaneous electrical stimulation of Ia afferents in the parent nerve. The technique is now well codified (Pierrot page 6)."

P-D & B discuss the features of the H waves and how their description has varied significantly during the last few decades (page 1). "The H reflex is produced by electrical stimulation of Ia afferents, which have a lower electrical threshold than α motor axons, particular for stimuli of relatively long duration" (Page 3).

"The H reflex may also be evoked by magnetic stimulation of the parent nerve (or nerve rooot) and appears with the same latency as with electrical stimulation. One advantage of magnetic stimulation is the ease which an J reflex can be elicited from deep nerves, such as the sciatic nerve in the thigh or the sacral nerve roots, which are difficult to access with percutaneous electrical stimulation unless needle electrodes are inserted."

M waves–

The propagation velocity associated with these monopulse waves is generally the average velocity over an unspecified distance (and incorporating an uncounted number of NoR). Values between 70 and 100 meters/sec are typically reported under these circumstances (P-D & B page 64).

16.1.1.3 Terminology associated with the architecture of stage 7

Adrenergic– Dale (1914) defined neurons, of the sympathetic division, that released noradrenaline (norepinephrine) as adrenergic.

Alpha blocking agent– Ergotamine, phentoalamine and other drugs affecting the nervous system like ergotamine.

Alpha blocking receptor–A receptor sensitive to epinephrine but which can be effectively blocked by ergotamine (and a variety of similar compounds).

Aponeurosis– Any of the broad flat sheets of dense fibrous collagenous connective tissue that cover, invest, and form the terminations and attachments of various muscles.

Autonomous nervous system– (a.k.a. involuntary nervous system) Those nerves forming the (ortho)sympathetic and parasympathetic divisions, along with two lesser systems known as the enteric subdivision and cardiac subdivision, of stage 7.

Beta blocking agent– Propanolol, and similar substances that are antagonistic to the action of epinephrine on the heart (cardiac smooth muscle).

Cholinergic– Dale (1914) defined neurons, of the parasympathetic division, that released acetylcholine as cholinergic. The term evolved to be indicative of any molecule that had a negative impact on cell activity. With the recognition of differential input terminals in many cell types, particularly neurons, the term is now archaic.

Cardiac subdivision– That part of the autonomous nervous system relating to the cardiovascular system.

Enteric subdivision– That part of the autonomous nervous system relating to the digestive system.

16.1.2 The characteristics of striate and smooth muscle

"Muscle is generally divided into 3 types; skeletal (or striated), cardiac, and smooth, although smooth muscle is not a homogeneous single category. Striated muscle comprises the great mass of the somatic musculature. It has well developed cross-striations, does not normally contract in the absence of nervous stimulation, lacks anatomic and functional connections between individual muscle fibers, and is generally under voluntary control.' "Smooth muscle lacks cross-striations. The type found in most hollow viscera is functionally syncytial in character and has inherent semi-rhythmic contractile activity. The type of muscle found in the eye and in some other locations is not spontaneously active and resembles striate muscle[11]." The cardiac muscle will be addressed in **Section 20.3**.

[11]Ganong, W. (1975) Review of Medical Physiology, 7th Ed. Los Altos, Ca: Lange Medical Publications pg 32

The smooth muscle can be divided into several subtypes based historically on its functional role but also possibly by its method of excitation. Smooth muscle is most often found in a tonal state in the absence of outside stimulation. It tends to relax upon application of external excitation. **Figure 16.1.2-2** provides a simple caricature of these muscle types.

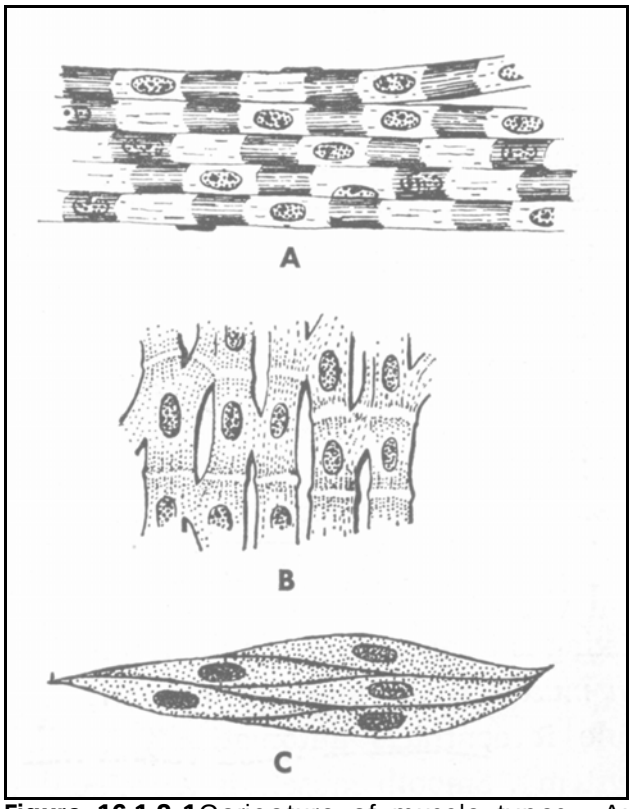

Figure 16.1.2-1 Caricature of muscle types. A; multi-fiber skeletal or striate muscle. B; multi-cellular cardiac smooth muscle. C; multi-cellular intestinal smooth muscle. From Stacy & Santolucito, 1966.

Smooth muscle occurs in highly optimized form in the heart (cardiac muscle), intestines and uterus (uterine muscle). These muscle types are frequently associated with automaticity, the ability to contract and relax rhythmically in the absence of external excitation. As an alternative, these types of muscle when addressing a given function may be associated with individual minibrains controlling only the muscles addressing a single function.

Striate muscle is considered to contract very rapidly compared to the performance of smooth muscle. It exhibits three operating modes, twitch, incomplete tetanus and complete tetanus. A twitch can be elicited by a single action potential from the neuro-affector. After a short but measurable latent period, the twitch response resembles a band limited impulse response. Multiple action potentials separated by 0.5 seconds or more will elicit multiple twitches. With pulses of shorter spacing, the incomplete tetanus response is measured. The total response is integrated over time until it reaches a nominally stable response (but the response is serrated with time). With pulses of still shorter spacing, the response becomes smooth due to the band limited character of the muscle response. See [Figure 16.1.2-4] below from Eyzaquirre & Fidone.

The ocular muscles, because of their dual character must be addressed in greater detail than in the above paragraph (**Section 16.5.1.1**).

16.1.2.1 The electrolytic characteristics of muscle cells EMPTY

16.1.2.2 The transfer function of the neuro-muscle system

There are a multitude of cartoons describing the junction between stage 7 neuroaffectors and striated muscle. **Figure 16.1.2-2** shows a comprehensive cartoon available from the Wikipedia library.

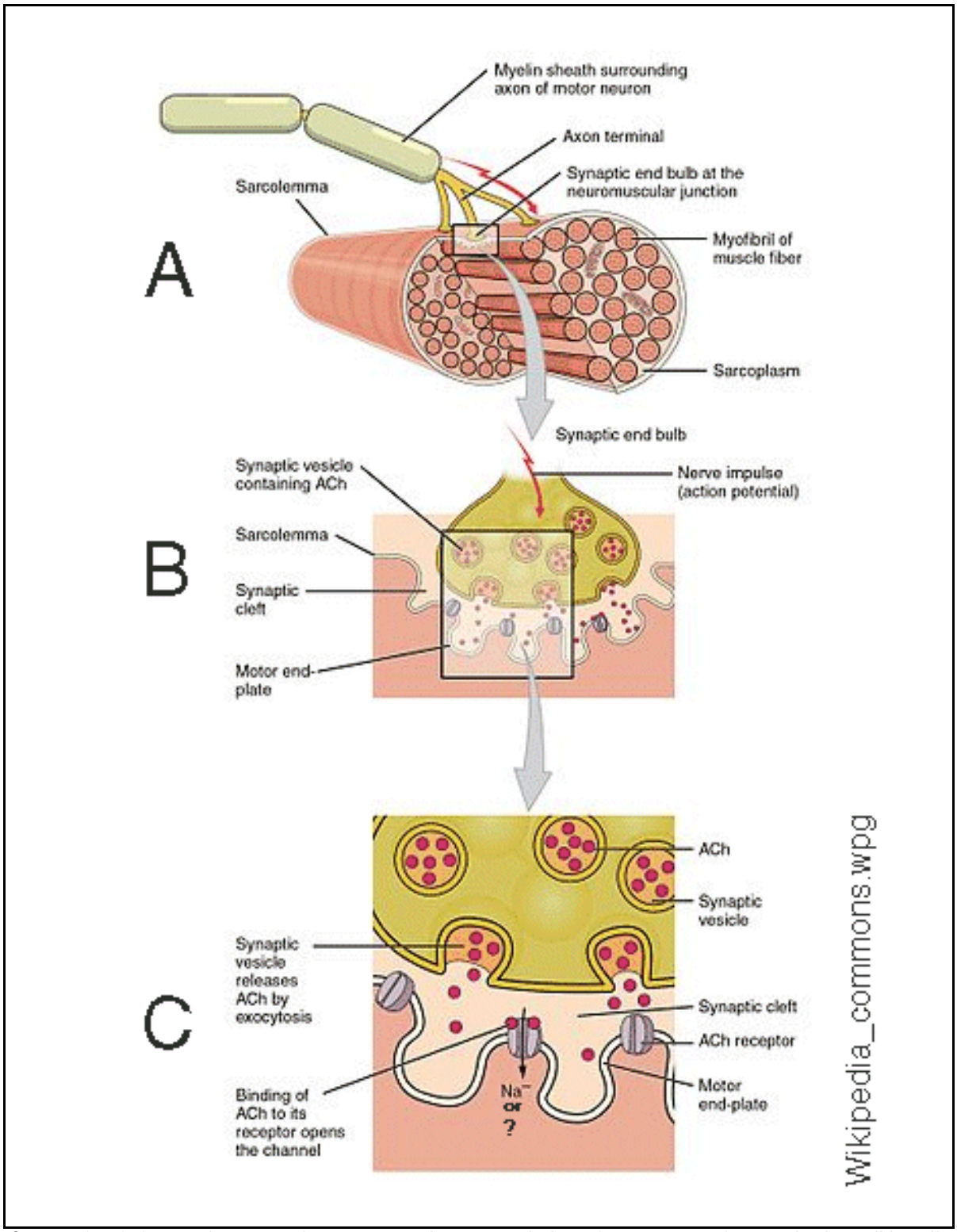

Figure 16.1.2-2 A caricature of a neuron-striate muscle interface. One of many in the Wikipedia Commons file. The figure does not differentiate between striated and smooth muscle but presupposes striated muscle based on the assumption that ACh is the secreted material and its display of myofibrils within the myocyte.

Frame **A** describes the stage 7 neuron as being myelinated until reaching the terminal axon segment which is physically short and consists of multiple pedicles. The pedicles are directly associated with indentations in the sarcolemma of the myocyte known as the motor end plate. It describes the junction between the neuroaffector and the myocyte as a "chemical synapse."

Frame **B** shows the signal arriving at the pedicle as an action potential suggesting that the pedicle acts as an integrator of action potentials prior to the secretion of acetylcholine into the chemical synaptic cleft. It also shows acetylcholine as present and fully formed within storage vesicles.

Frame **C** shows the release of acetylcholine in greater detail, but not how it activates the ACh receptors (**See Section 16.3.2.2**). It assumes the ACh causes pores within the receptors to open and sodium ions to enter the myocyte space. Whether this conventional view is correct or not has yet to be demonstrated. The diameter of hydrated sodium ions is generally larger than the pores postulated under the conventional view. **Section 8.5.4.4** shows the hydrated complex of the sodium ion and water is significantly larger in diameter (9 Angstrom) than the putative internal diameter of the pores in the axolemma typically proposed in the literature (about 2 Angstrom). The axial alignment of the pedicle secretion points and the receptors may represent "artist's license." It is not clear why the receptors should not be aligned with the secretion points.

Figure 16.1.2-3 shows a more realistic representation of a neuron-striate muscle interface provided in Ganong[12].

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[12]Ganong, W. (1975) Review of Medical Physiology, 7th Ed. Los Altos, Ca: Lange Medical Publications pg 56

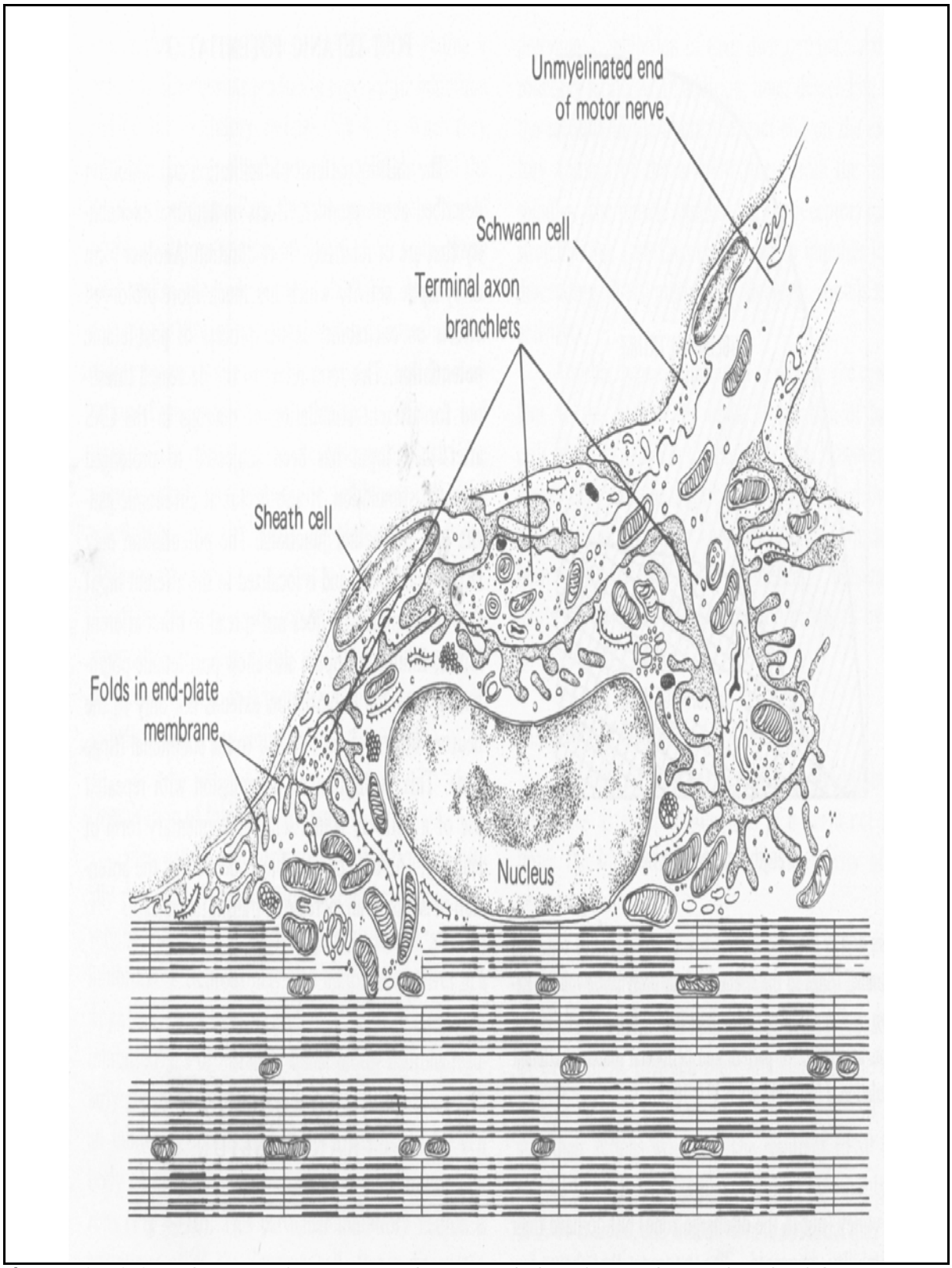

Figure 16.1.2-3 Caricature of a neuron-striate muscle interface. The nucleus is of the myocyte. Sheath cell refers to nucleus of the sarcolemma. See text. From Ganong, 1975

Figure 16.1.2-4 illustrates the low-pass filter characteristic of the neuron pulse frequency to muscle-force transduction[13]. The performance is precisely that of a first-order low-pass filter. Its attack time constant is about 0.2 seconds. Its decay time constant is about one second.

16.1.2.7 The mechanism of external excitation of muscle

Striate muscle has an end-plate associated with each muscle cell that acts as the interface with the neural system. The end-plate is a morphologically complex structure designed to provide intimate contact between several pedicles of the neuro-affector axon and the cell. The contact between the pedicles and the lemma of the muscle cell is intimate. Some authors claim the sarcolemma is penetrated by the end-plate or neural tissue.

Historically, it has been asserted that the pedicles of neuro-affectors of striate muscle release acetylcholine within the end-plate structure and that acetylcholine has a very short life in this environment because of the presence of an enzyme, cholinestrase. However, it is well known that striate muscle will contract under electrical stimulation in the absence of acetylcholine and a functioning end-plate. It is possible to explain the operation of the neuro-affector/muscle interface without involving the use of acetylcholine.

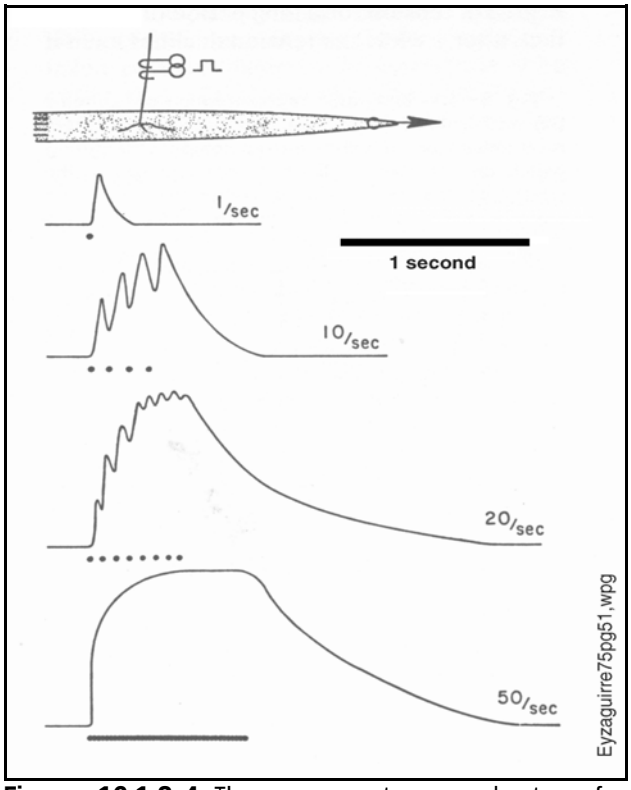

Figure 16.1.2-4 The neuron to muscle transfer characteristic. The initial twitch in response to a single action potential. At 10 pulses/sec, individual twitches begin to merge and an unfused tetanus begins to appear. At 50 pulses/sec, a completely fused tetanus is observed. From Eyzaquirre & Fidone, 1975.

The contraction of striate muscle is typically proportional to the number of action potentials arriving per second at the end-plate. Weak contractions are typically associated with rates of 5 to 10 pulses per second. Strong contractions are typically associated with rates of 50 pulses per second. Striate muscle requires oxygen and lactic acid derived from glycogen for contraction.

While not encountered *in-vivo*, it is possible to introduce a subminimal stimulus by probe that has inadequate pulse amplitude to stimulate a muscle cell. It is also possible to introduce pulses of supramaximal stimulus, consisting of pulses of excessive amplitude. In the region between these extremes, the sumaximal region, the muscle responds linearly with pulse height.

Smooth muscle cells do not exhibit end-plates. The stage 7 neuro-affectors are believed to release nitric oxide (and potentially other agents) in the vicinity of the smooth muscle cells. The nitric oxide operates as a paracrine (pseudo)hormone diffusing into multiple cells from one neuron. Nitric oxide is chemically a free radical. It has a short mean lifetime in the extra-neural matrix. Its lifetime compared to the duration of smooth muscle relaxation will be developed below.

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[13]Ezyaguirre, C. & Fidone, S. (1975) Physiology of the Nervous System, 2nd Ed. Chicago, Il: Year Book Medical Publishers pg 51

16.1.2.8 The effect of nicotine and curare on striate muscle

Striate muscle is subject to external pharmaceuticals that operate via the end-plates. Non-neural excitation by nicotine or relaxation by curare are examples of these agents.

Nicotine and curare when administered simultaneously are antagonistic, suggesting they share a common receptor site on the muscle cell or within the end-plate.

16.1.3 The naming of complex organics and biologicals

The complexity of many of the chemicals involved in the neuro-glandular system defy simple explanation. Similarly, the naming of these entities is equally difficult. Elias has discussed the inconsistencies in chemical naming even at this late date[14]. He provides a number of tables listing the different names for the same chemical over a period of time, generally comparing the IUPAC name with the CAS name of the same time period. These tables make it clear that over a 10-20 year interval, the names of most complex chemicals are changed. The problem is complicated by the different conventions (such as seniorities and choices of source-based or structure-based names) adopted in the inorganic and organic communities. Many of the names depend on the philosophical approach of the naming authority. In the case of the Rhodonines, a family of photoreceptors used in biological vision, the members only vary by the location of an oxygen ligand along the backbone of the underlying molecule. However, the Registry Services division of *Chemical Abstracts* divided the four chemicals into two interdigitated groups and assigned fundamentally different names to the two groups[15]. This work will generally adopt the name used by a cited author rather than attempt to standardize the names of a chemical throughout this work. The Elias work is a marvelous source for describing complex organic and bioorganic chemicals

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As developed throughout much of this work, the neural system does not relate well to the conventional group names used in valence-based chemistry. Similarly, the neural system relies heavily on the theory of coordinate chemistry to explain the operation of nearly all chemical sensory neuron operations and all secretions of stage 7 neuroaffectors affecting the glandular system. The theory of coordinate chemistry relies upon the physical distance between atoms within a molecule regardless of which chemical groups of valence chemistry they are associated with.

With the determination that only electrons and "holes" (the absence of an electron in a liquid-crystalline lattice structure) constitute neuron-to-neuron neurotransmitters, most of the neurotransmitters of the literature and conventional wisdom must be re-catogorized as neuromodulators or neurofacilitators

Section 6.4.1 describes many of the conventional named molecules of organic chemistry in terms of their functional roles under the above coordinate chemistry interpretations and "The Electrolytic Theory of the Neuron." This chapter will extend the tables and hierarchal chemical trees of conventional chemistry to include the major categories of hormones within the glandular system.

16.1.3.1 The definition of a hormone

The definition of a hormone has evolved in multiple directions from its initial brief definition of "a chemical inducing intense biological activity." The early hormones were identified by the resulting intense activity. However, upon further investigation, many hormones were found to induce significant, but not necessarily intense, biological activity. Think of the significant activity associated with the slow or low intensity changes due to the growth hormones. It is also important to recognize a hormone may have a role in suppressing biological activity, either

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[14]Elias, H-G. (2005) Macromolecules, Vol 1. Wiley-VCH Verlag (first of four planned volumes)

[15]Fulton, J. (2005) Processes in Biological Vision. Victoria, BC, CA: Trafford Chapter 5.

directly or through a feedback mechanism. Think of the complex role of the thyroid family of hormones.

It is important to distinguish whether a hormone is defined based on function or on its structural characteristics. The pedagogy of the biology community has drifted toward a structural definition such as "a hormone is a peptide." Some go further and suggest "a hormone is a peptide or steroid." While it appears many hormones are peptides, and many contain nitrogen, the steroids generally do not.

Henry & Norman as editors of the Encyclopedia of Hormones, struggled with this problem in 2003[16],

"Of course, the classical definition of a hormone is that it is a chemical messenger in the body: it is secreted by an endocrine gland and is delivered through the circulatory system to target cells that possess receptors specific for the hormone."

"The Editors have adopted a broader definition of hormone. Hormones can now be considered to include not only chemical messengers in the classical sense, but also local *paracrine* and *autocrine* signals."

Henry & Norman did not include exocrine hormones (pheromones) in their definition. Including the exocrine hormones leads to an even broader functional definition.

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This work will adopt the view that hormones are naturally occurring chemicals that are,
1 secreted by a stage 7 (terminal efferent) neuron, and that induces significant change in the biological activity in one or more biological cells, or
2 secreted by a gland in its response to a hormone from a higher level gland(nominally the hypothalamus or hypophysis) that

- **A**. induces significant change in the biological activity in one or more biological cells.
- **B**. induces significant change in the contents of the digestive tract.
- **C**. induces significant change in the activity of another animal (generally of the same species).

Indices **1**. & **2**. separate the hormones secreted by the *neural* system from those secreted from independent glands of the *hormonal* system. Indices **A B** & **C** separate those hormones functioning within the endocrine & paracrine environments, **A,** from the exocrine environment, **B**. to include the gastric juices (other than inorganic chemicals) in the exocrine environment, and **C**. to include the pheromones of the exocrine environment.

The presence of an autocrine environment is not included in this framework without more evidence that a gland secretes a hormone for purposes of affecting itself. From a system perspective, this does not appear plausible or useful. Most glands constitute very complex structures similar to engines of the neural system. It is not clear that the constituents of these engines require external feedback paths to communicate with other constituents.

Many morphologically defined glands clearly consist of multiple individual hormone secreting elements. In such a situation, an "autocrine" signal originating in one element and terminating in another is not autocrine in the functional context. Page 44 of Henry & Norman supports the idea of separate glandular elements within the morphologically defined adrenal gland by identifying (presumably stage 7)neural paths within the overall gland.

16.1.3.1.1 The definition of the Crine (hormonal) modality

This functional definition of a hormone is more complex, and specific, than that in the Encyclopedia of Hormones (2003), page Li [in roman characters] described above. It is also more useful. It also leads to a broader definition of a ***Crine modality***, consisting of three distinct

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[16]Henry, H. & Norman, A. (2003) Encyclopedia of Hormones. *3 volumes*. NY: Academic Press

• *paracrine,*
• *endocrine &*
• *exocrine* submodalities.

The existence of a truly functional autocrine submodality remains to be demonstrated.

Adopting such a functional definition, the simplest hormone of interest in neuroscience appears to be nitrogen oxide (NO). The next more complicated hormone is probably the amine, acetylcholine. These chemicals, common to the paracrine submodality, are not peptides or steroids and have led to the recent definition of nonadrenergic/noncholinergic, NANC, hormones. This negative label is less than satisfactory. A better label would recognize they are nonpeptide and nonsteroid based, NPNS, hormones. NPNS is harder to use in conversation but more appropriate. Acetylcholine does not meet the definition of a peptide (contains two or more amino acid residues).

As a result of this categorical breakdown, the hormones of the animal system consist of,

1. The NPNS hormones, nitric oxide and acetylcholine, employed in the paracrine submodality.

2. The next category are a group of derivative of tyrosine containing only the one amino acid and not recognizable structurally as a peptide (contains two or more amino acid residues).

3. Then, a large family of peptides represents the numerical majority of hormones. Most of these appear to be proteins containing amino acids in specific stereochemical configurations.

4. Finally, there are a great many steroid-based hormones that contain no peptide residues.

The tyrosine-based and peptide-based hormones dominate the endocrine submodality. The steroid-based hormones appear to dominate the exocrine submodality.

It appears that the ability of NO to pass through the lemma of a cell may put it into a class by itself. It does not require a receptor on the external lemma of a cell. On the other hand, NO does not necessarily require a receptor on the nucleus of a cell.. The receptor may be in the interstitial space surrounding the nucleus. As a result, hormonal receptors can be more appropriately be described as,
• *external receptors,*
• *cytostolic receptors* and
• *nuclear receptors*.

16.1.3.1.2 The broader definition of the Crine (hormonal) pathways

Functionally, hormones may be secreted into one of three environments.

1. They may be secreted with the intent they act only within a local (paracrine) environment.
2. They may be secreted into the cardiovascular or lymphatic systems in order to provide action throughout the (endocrine) environment of the organism.
3. They may also be secreted into the external (exocrine) environment with the intent of causing biological activity within a larger sphere, such as digestion in the oral cavity and the gastrointestinal tract.

In the case of some spiders and other lower species, digestion may occur within the bodies of its prey, rather than within the predators body cavities.

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16.1.3.1.3 The differentiation between neuroaffectors & hormones

The differentiation between the pseudo-neurotransmitters (neuro-affectors) and hormones is a difficult, if not artificial one. Elias chooses to differentiate between them by using the labels, activating agents and messengers respectively (page 67). This differentiation relies upon a question of definition debated in the middle of the 20th Century. Starling & Bayliss described

hormones as "chemical agents which are released from one group of cells and travel via the bloodstream to affect one or more different groups of cells." Huxley proposed an alternate definition placing less emphasis on the mode of transport in 1935. He said "Hormones are regarded primarily as information-transferring molecules, the essential function of which is to transfer information from one set of cells to another, for the good of the cell population as a whole." Robinson et al. reviewed these definitions in 1971 and suggested shortcomings related to each[17]. They built on the transfer of information aspect of Huxley's definition. They expanded the definition to include one type of hormone that acted as a messenger between cells and a second type of hormone that controlled the operation of a cell, a *messenger* and a *maintenance engineer* in their context. They noted that the delineation between these concepts was not crisp but continued to provide a delineation between vitamins and hormones, where vitamins are focused on energy metabolism and not the transfer of information.

There is confusion in the literature concerning the use of the term messenger. In 1971, Robinson et al. stretched the concept of a hormone as a messenger to differentiate between messengers of different order. They defined a hormone as a *first messenger* if it transferred information between a first set of cells and a second set. They defined a *second messenger* as the substance cGMP that is widely found throughout the biosphere and appears to control a variety of processes (by either enhancement or suppression). The participation of cGMP in actual signaling at the molecular level remains unclear. They went on to make three points. First, there may be additional materials that played a role similar to that of cGMP, although they could not document any. Second, they asserted that the method of adenyl cyclase stimulation was unknown. They also suggested that cGMP played a role in the release of a variety of other major hormones, and these hormones could be considered *third messengers*. This idea, and the idea of hormones as messengers in general, has not become baseline and only appears occasionally in more modern works.

In 1996, Dugas has provided an *alternative, and conflicting, interpretation* of the messenger concept[18]. Dugas describes cellular communications along three pathways. The interneural neurotransmitter pathway is associated with the first messenger. The second or chemical messengers consist of hormonal secretions and the third pathway is associated with *de novo* protein synthesis.

Steed & Atwood developed their concept of neurotransmitters and hormones in less than two pages. In general, their concept is that neurotransmitters include a wide range of molecules such as dopamine and acetylcholine while hormones include the conventional list of hormones, the testosterones, growth hormones etc.

The above definitions of hormones and neurotransmitters are fundamentally chemical in character and too narrow to associate with the entire glandular (–crine) system. They also need expansion in the context of the Electrolytic Theory of the Neuron.

A brief listing of hormones, their target tissue and function, aimed at the intermediate school level, is provided in https://schoolworkhelper.net/major-hormones-origin-target-function/ See also **Section 16.8** for a similar cataloging activity.

16.1.3.1.4 The familial structure of hormones

Based on the definition of a hormone earlier in **Section 16.1.3.1**, it is possible to categorize hormones by their chemical identity;

Hormone– A naturally occurring chemical that is secreted by a stage 7 (terminal efferent) neuron or a gland, and that induces significant change in the biological activity in one or more biological cells. Except for the steroids, all known hormones contain nitrogen. Several classes can be defined.

1. Simple "inorganics"– nitrogen oxide (NO)

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[17]Robinson, G. Butcher, R. & Sutherland, E. (1971) Cyclic AMP. NY: Academic Press Chapter 2.

[18]Dugas, H. (1996) Bioorganic chemistry: A chemical Approach to Enzyme Action, 3rd Ed. NY: Springer page 122

2. Simple amines– acetylcholine
3. A series of hormones based on derivatives of tyrosine & tryptophan
4. Simple peptides (consisting of a few amino acid residues)
5. Protein-based hormones (peptides of more than 10 amino residues)
6. Steroid-based hormones
7. Catecholamine hormones–epinephrine & norepinephrine

While epinephrine and norepinephrine are catacholines (7) originating in the adrenal medulla, they are probably derived from tyrosine (3). Thyroxine is also a tyrosine derivative. See Lehninger (1972, page 558)for a list of other hormones and prohormones.

Figure 16.1.3-1 tabulates the major hormones based on this work. The material is drawn from multiple sources and may contain some inconsistencies. Various investigators have assigned multiple anatomical origins to some of these hormones. The prefix to the letter R in the figure indicates the number of peptide residues forming the hormone. Where a "less than" symbol appears, it indicates there are multiple forms of the hormone with some exhibiting fewer residues.

The authors within Melmed & Conn have provided a majority of the peptide residue numbers in this figure[19]. Considerable care is required in labeling the hormones in this figure. The steroid hormones are generally hydrophilic and require the support of transport proteins known as serum-binding proteins. This is accomplished by means of a high affinity ligand-binding domain, LBD, within the serum-binding protein. There are five identified serum-binding proteins; each is associated with a uniquely different class of steroids. The serum-binding proteins are not part of the functional hormone. Henley, chapter 4 in Melmed & conn, identify many of the important steroid hormones.

The paracrine category is limited to those hormones directed to a specific muscular or glandular cell, and that cell alone. The perecrine category is somewhat broader and is a subset of the endocrine category. The perecrine hormones are transported to the hypophysis primarily within the portal existing between the hypothalamus and the hypophysis rather than the bloodstream. These individual hormones may interact with numerous cells of a given functional type within small regions of the hypophysis.

Henley (2005) in Melmed & Conn argues that many of the hormones other authors in Melmed & Conn list as peptide-based (4 or 5), are actually steroid-based (6)–at least ACTH, FSH, LH & LtH. This is becoming recognized by most of the relevant community.

The circulating hormones released by the pituitary stimulate the production of a large variety of hormones from glandular material throughout the organism.

[19]Melmed, S. & Conn, P. *eds* (2005) Endocrinology, 2nd Edition Totowa, NJ: Humana Press

Paracrine

Acetylcholine

Nitric oxide •NO (--N=O)

Pericrine Hormones (from Hypothalamus)

Stimulating (to hypophysis **via the portal**);
Thyrotropin-releasing hormone (TRH, 3R),
Corticotropin-releasing hormone (CRH, 41R),
Growth hormone-releasing hormone (GHRH),
Gonadotropin-releasing hormone (GnRH),

Inhibiting (throughout CNS);
Somatostatin,
Dopamine

Endocrine Circulating Hormones
(from Hypophysis/Pituitary)
Thyrotropin (TSH, 764R)
Corticotropin (ACTH, <24R)
Growth hormone (GH, 191R)
[Luteinizing hormone (LH, 204R)
Follicle stimulating hormone (FSH, 210R)
Prolactin (PRL, 598R)]
Endorphin (MSH, <31R)
Oxytocin (OC)
Vasopresin (AVP)

(from Adrenal gland)
Epinephrine

Hormone family.ai

Exocrine
Pheromones
Gastric juices (from Pancreas)

Figure 16.1.3-1 The familial structure of hormones. The prefix to the letter R in the figure indicates the number of peptide residues forming the hormone. Where a "less than" symbol appears, it indicates there are multiple forms of the hormone with some exhibiting fewer residues. The bracketed hormones are believed to be derived from GnRH. Some hormones are known for their inhibiting capability in the presence of stimulating hormones. Nitric Acid does not fit in this category. See text.

Weigant & Weid in chapter 2 of Hrdina & Singhal, although dated–1981, provides a discussion of the effect of the different forms (residue lengths) of ACTH. Lal & Rastogi, writing in chapter 8, provides additional information.

Henley asserts that the gonadotropin-releasing hormone (GnRH) may actually be released by a stage 7 neuron. "GnRH is synthesized by small populations of neurons in the POA, AH and mediobasal hypothalamus and is released into the hypophysis portal system. GnRH stimulates synthesis and release of LH and FSH, which, in turn, regulate steroidogenesis and gametogenesis.".

16.1.3.2 The -ergic suffix: an unresolved definition and role

The -ergic suffix came into use in the 1960's, prior to the molecular description of adrenalin. The term cholinergic appeared as an abbreviation of acetylcholinergic. At the same time the term adrenergic appeared to identify an agent that opposed the actions of acetylcholine. It appears this opposition was based primarily on behavioral studies. It is difficult to find clear definitions that differentiate between these terms in modern literature. The term nitronergic came into use only after 1990, with the realization that nitric oxide played a role in the neural system not relatable to either the "cholinergic" or "adrenergic" agents.

The challenge of definition became intractable when the molecular structure of adrenalin was determined and it was generally accepted that acetylcholine, dopamine, adrenalin (now called epinephrine) and the derivatives of epinephrine could all be derivable from choline. Today, epinephrine, norepinephrine and dopamine are generally described as catecholamines. They are known to be derived through the aminization of catechol in the biological environment, and not derived from choline as acetylcholine is. Lambert & Kinsley address the derivation of the catecholines superficially[20]. Their sequence of chemical steps in the production of epinephrine is not necessarily exclusive as seen in the multiple "cycles" found in texts on metabolic processes.

This work suggests acetylcholine plays a different functional role than do the catecholamines. The principle role of acetylcholine is as a neuro-affector released from the axons of stage 7 neurons with the goal of stimulating primarily striate muscle cells. The catecholamines are clearly pseudo-hormones acting as stimulative neuro-modulators to neurons found in all stages of the neural system. The acetylcholines, catecholamines and nitric oxide are not antagonistic. Dimensionally, they are orthogonal to each other. Acetylcholine is a neuro-affector of *striate* muscle released at the pedicle of a stage 7 neuron. Nitric oxide is a neuro-affector of *smooth* muscle released at the pedicle of a stage 7 neuron. Catecholamines are neuro-modulators generally influencing the dendroplasm of a wide variety of neurons. They are typically coupled homocyclic rings absent any conjugated bonds and containing no nitrogen.

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Ganong has attempted to differentiate between the neuro-affectors of the autonomic nervous system based entirely on morphological considerations, cell bodies within the spinal cord or outside the spinal cord (page 147 & 151). Stacy & Santolucito have defined neuro-affectors based on their roles in the sympathetic and parasympathetic systems (pg 189). The location of neural cell bodies is primarily one of convenience in the Electrolytic Theory of the Neuron. However, the literature contains many (frequently contradictory) references to the terms dopaminergic, adrenergic, cholinergic, acetylcholine-ergic (ACh-ergic), etc. but few definitions of these terms beyond the conceptual. The problem involves two distinct levels. The same neuro-affector may have different effects when interacting with different receptor-substrate sites and/or different tissue. Simultaneously, the same neuro-affectors are produced by both the sympathetic and parasympathetic branches of the neural system.

The definition of -ergic in Webster's Medical Dictionary is limited in precision. "Exhibiting or stimulating activity especially of (such) a neurotransmitter substance <adrenergic>

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[20]Lambert, K. & Kinsley, C. (2011) Clinical Neuroscience, 2nd Ed. NY: Oxford Univ Press page 135

<dopaminergic>." This leads to the problem of whether an -ergic compound is a stimulant to neurotransmission or a participant in neurotransmission at a synapse. The definition is clear that -ergic refers to a stimulation, and not an inhibition of activity.

The use of the -ergic suffix gained wide usage following the work of the pharmacologists Dahlstrom & Fuxe in the 1960's[21,22]. Their work was carried out using a freeze-dry apparatus cooling a beaker and light microscopy at less than 250X. They observed general fluorescence of the complete neuron following a specific exposure to formaldehyde. Their papers do not include any cytological description of a neuron. No effort was made to record any change in electrical potentials within the neural cells. A 1966 document involved non neuronal cells that exhibited the same fluourescence[23]. They carried out a "highly original series of neuroanatomical studies with a novel histochemical method that had just been developed for mapping monoamines[24]." The protocol involved exposing tissue to formaldehyde and then observing the fluorescence of specific chemicals, like the catecholamines and serotonin. "The work was so unusual it took many years to convince the more skeptical neuroanatomists of their reality."

They defined the first of three regions of the brainstem, the locus ceruleus, as employing noradrenaline, the same chemical used by the sympathetic division of the autonomic system. They defined a second region, the Raphe nuclei of the midbrain and hindbrain, as employing serotonin in a similar role. The third region was centered on the ventral midbrain and used dopamine as a neural agent. As a result, orthodromic neurons to these sources were described as being noradrenergic, serotonergic and dopaminergic. Subsequent investigations have led to the identification of cholinergic, GABAergic neurons. and histaminergic neurons among others.

The writing style of Dahlstrom & Fuxe is unusual. They frequently make very strong statements that can be interpreted to apply well outside of the realm they studied and then draw conclusions based on the word "may"(ex., page 51). In the 1966 paper by Hillarp, Fuxe & Dahlstrom, the tone was more conservative[25]. In all these papers, significant terminology translation is required to correspond to current usage. Dahlstrom & Fuxe provide many micrographs in the 1964 paper showing a variety of neurons of the brainstem that appear to be fluorescing over the entire extent of the lemma of the neuron. The fluorescing could be from the surface of the lemma or from the bulk cytoplasm. In general, the nucleus of the cell is not seen to fluoresce except when diffusion has been allowed to occur for a long interval. Yet, they draw the conclusion the their monoamines are released as neurotransmitters at the synapses. This conclusion requires the surface of the neuron to be completely covered with synapses. This condition is not found in many types of neurons exhibiting highly developed dendritic arborization. They note the accumulation of the monoamines on the surface of the neurons appears "granular" (1966, page 302) However, at 250X, any granularization cannot be associated specifically with any synapse (with active area diameter measured in nanometers or less).

Dahlstrom & Fuxe found their monoamines in the brain stem but not in the more general areas

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[21]Dahlström, A. & Fuxe, K. (1964) Evidence for the existence of monoamine-containing neurons in the central nervous system. I. demonstration of monoamines in the cell bodies of brain stem neurons *Acta Physiologica Scand* Suppl 232, pp 1-55

[22]Dahlström, A. & Fuxe, K. (1965) Evidence for the existence of monoamine neurons in the central nervous system. II. Experimentally induced changes in the intraneuronal amine levels of bulbospinal neuron systems *Acta Physiologica Scand (Eur J Physiol)* Suppl 247 pp 1-36

[23]Dahlström, A. & Fuxe, K. (1966) Monoamines and the pituitary gland *Acta Endocrinologica* vol 51, pp 301-314

[24]Swanson, L. (2003) Brain Architecture. London: Oxford Univ Press pg 149

[25]Hillarp, N. Fuxe, K. & Dahlström, A. (1966)Demonstration and mapping of central neurons containing dopamine, noradrenaline and 5-hydroxytryptamine and their reaction to psychopharmaca *Pharmacol Rev* vol 18, pp 727

of the brain (1964, page 13). Therefore, these particular materials can not be considered general neurotransmitters of the neural system.

While these monoamines have historically been described as neurotransmitters, they play no role in neural signaling, and no confirmed role in synaptic activity. They act more as neurofacilitators and neuroinhibitors by chemically affecting the (non-synaptic) receptor sites on large groups of orthodromic neurons. Thus, they are included here in the class of neuroaffectors. Whether these chemicals should be characterized as hormones is a question of definition. Some of them. like the catecholamines, cannot cross the blood-brain barrier and must be synthesized within the CNS if they are to be used there. When secreted into the blood stream, they are reported to have a half-life measured in minutes, and epinephrine is associated with the short term "fight or flight" phenomenon[26]. It is noted, that the above sources are physically near the hypothalamus, a portion of the neural system that is an obvious hormone generator, and not far from the pituitary (hypophysis). The pituitary is a neuroaffector releasing monoamines[27].

Since the time of Dahlstrom & Fuxe, catecholamine and indoleamine have been recognized as family names rather than discreet compounds. The indoleamines include serotonin. Catecholamines have the distinct structure of a hexane ring with two hydroxyl groups, an intermediate ethyl chain of two carbons, and a terminal amine group. The name comes from the catechol group and the fact the family are derived from the amino acid tyrosine. The family includes dopamine, epinephrine and norepinephrine with L-Dopa as a precursor that can cross the blood-brain barrier. Page 44 of Henry & Norman describe these compounds and how they are derived within the chromaffin cells of the adrenal gland.

Most of the -ergic materials are described in the literature as modulators of neuron performance. When present within the CNS, they are said to modulate the behavioral state of the subject. These are clearly the words used to describe hormones, and not neurotransmitters involved in signaling.

Within the neural system, recognition of the multiple terminal character of a neuron (three for signaling, more for homeostasis) changes the framework for defining neural actions. It is not the character of the stimulant alone applied to the terminals of the neuron but to which (synaptic or non-synaptic) terminal the stimulant is applied. Thus, the same neuron can be both ACh-ergic and anti-ACh-ergic depending on how ACh is applied to the neuron as well as how the neuron is "wired" into the signaling circuit..

The actions of a given neuro-affector on a specific target frequently depend on the chirality of the neuro-affector and the geometry of the binding sites of the target[28]. These are additional characteristics of hormones and not neurotransmitters used in signaling.

Until a consistent set of detailed definitions for these –ergic terms applying to the entire neural system is documented, these terms cannot be used authoritatively.

For the duration of this work, a neuron that responds with an increased output potential in response to a given input , generally an increased depolarization, when exposed to a material will be considered -ergic with respect to that material.

16.1.3.2.1 The "adrenergic" receptor sites as a source of confusion

Illustrating the orthogonality of the catecholines versus the observable reactions are the alpha

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[26]http://en.wikipedia.org/wiki/Catecholamine

[27]Dahlström, A. & Fuxe, K. (1966) Monoamines and the pituitary gland *Eur J Endocrinol* vol 51(2), pp 301-314

[28] Silverman, R. (1992) The Organic Chemistry of Drug Design and Drug Action. NY: Academic Press pp 78-81

and beta adreno-receptor sites. Quoting an old but typical reference[29],

> "The effector cells innervated by the autonomic nervous system have two types of chemically defined adrenoreceptive sites–namely alpha (α) and beta (β) receptors. The alpha receptors have an affinity for both epinephrine and norepinephrine, while the beta receptors have a selectively stronger affinity for epinephrine. *The alpha receptors are generally excitatory but some may be inhibitory.*" and "*The beta receptors are generally inhibitory but some may be excitatory*." [Italics added for emphasis]

The ambiguity over the effect caused by these neuro-modulators is due to their affect on neurons in general and not just stage 7 neuro-affectors. The output of a stage 2, 4 or 6 neural network (which include differencing circuits) may be excitatory or inhibitory after stimulation by a catecholamine. This variability is ultimately projected to the stage 7 neuron-affectors.

16.1.3.3 The potential roles of epinephrine & norepinephrine as hormones

Epinephrine and norepinephrine are released by both the adrenal medulla and nervous system respectively. When released by stage 7 neurons, they are neuroaffectors. Epinephrine and norepinephrine are very similar hormones. When secreted by the adrenal medulla that increases heart rate, blood pressure, cardiac output and blood glucose levels. While epinephrine has slightly more of an effect on the heart, norepinephrine has more of an effect on the blood vessels. Both play a role in the body's natural fight-or-flight reflex when the body is under extreme stress.

It is believed the production of both norepinephrine and epinephrine within the biological system begins with tyrosine, an amino acid found in a variety of foods and a precursor found in the adrenal glands. Tyrosine is converted into a chemical called DOPA and then dopamine, an important chemical in the brain. In the production of norepinephrine and epinephrine, dopamine is converted into norepinephrine which can then be converted into epinephrine.

Nerve cells predominantly produce norepinephrine, although some in the brain produce epinephrine.

The form and binding of epinephrine and norepinephrine are discussed further in **Section 16.1.5.2**.

16.1.3.4 The enzyme and its properties

In the broadest sense, an enzyme is a protein capable of catalytic activity. More precisely, an enzyme is a peptide-based biological copolymer catalyst. As a catalyst, it is unchanged as a result of the reaction it is supporting. Elias (vol 2, pg 538) noted, "Enzymes permit no side reactions and produce no byproducts. While they can cause reaction rates that are higher than comparable non-enzymatic reactions by factors of 10^8 to 10^{20}, they are generally limited to dilute aqueous solutions at moderate temperature and pH."

"The binding of the substrate to the active center increase enormously the *effective* substrate concentration which in turn increase the reaction rate. A typical value of an equilibrium constant for the binding of a substrate to an active centers is 10^4 L/mol which contrast with 10^{-8} L/mol for the complexation of the same group in solution. The effective substrate concentration and thus the reaction rate are increased by a factor 10^{12}!"

Enzyme– A special class of proteins=copolymers of α-amino acids and imino acids that act as soluble polymer catalysts. See antibodies. Enzymes are characterized further:

1. Largest and most highly specialized group of proteins.
2. May work alone or require a cofactor (a metal ion or a complex organic called a coenzyme).
3. Generally described as organic catalysts in a biological system.

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[29]Noback, C. (1967) The Human Nervous System. NY: McGraw-Hill pg 116

4. Generally described as receptors in receptor-substrate complexes.
5. Like other catalysts, they are unchanged as a result of the receptor-substrate reaction with an additional component.

While fundamentally of biological origin, enzymes are now produced widely on an industrial scale.

This work will not accept or use the concept of an enzyme as a receptor in a receptor-substrate complex. Even the term substrate is used so variously as to be virtually useless in the absence of a specific definition.

Enzymes are typically very large molecules. Catalysis usually takes place at an active center or active site consisting of all of the amino acid residues implicated in catalytic process. These amino acids can be grouped into those supporting binding of the substrate, controlling the specificity of the substrate and directly participating in the catalytic process. A single molecule may have multiple independent active centers. In the more highly optimized enzymes, capable of binding to the substrate at multiple points, the active centers tend to form pockets and are frequently labeled active clefts or active cavities.

Because of the complexity of enzymes, it is common to focus on only ***a limited region of the total molecule*** and indicate the rest of the model as being outside a "curly arrow" arena or behind a sawtooth barrier.

16.1.3.4.1 Classes of enzymes

The International Enzyme Commission number (EC number) is a numerical classification scheme for enzymes, based on the chemical reactions they catalyze. The classification system resembles an early Patent Office tree. As a system of enzyme nomenclature, every EC number is associated with a recommended name for the respective enzyme.

Strictly speaking, EC numbers do not specify enzymes, but enzyme-catalyzed reactions. If different enzymes (for instance from different organisms) catalyze the same reaction, then they receive the same EC number. Every enzyme code consists of the letters "EC" followed by four numbers separated by periods. Those numbers represent a progressively finer classification of the enzyme into a class, subclass, sub-subclass and sub-sub-subclass. A broad discussion of this system is available on Wikipedia.

Elias (vol 2, pg 538) has enumerated the six classes of enzymes.

Class 1: oxidoreductases transfer electrons (trivial names, dehydrogenase, oxidase–also synthase);
Class 2: transferases transfer chemical groups (trivial, transaminase, kinase);
Class 3: hydrolases transfer functional groups to water (trivial, lipase, amylase, peptidase);
Class 4: lyases add groups to or transfer from double bonds;
Class 5: isomerases catalyze isomerizations (trivial, isomerase, mutase);
Class 6. ligases form C–C, C–O, C–S, and C–N bonds by cleaving pyrophosphate bonds of adenosine triphosphate (ATP), (trivial, synthetase).

http://www.chem.qmul.ac.uk/iubmb/enzyme/ provides the master list of enzyme classification. No nitric oxide reactions could be found in the EC4 classification, lyases. This listing appears to require considerably documentation beyond a conceptual definition of an enzyme.

http://www.genome.ad.jp/dbget-bin/get_htext?ECtable provides a massive database describing many aspects of enzymatic reactions, listing reaction numbers, reactant numbers, genetic associations, etc.

http://www.expasy.ch/ provides a broader database of proteins, including enzymes.

The EC naming convention generates a series of classes of major interest to this work.

EC 1 Oxidoreductases

EC 1.1 Acting on the CH-OH group of donors
EC 1.4 Acting on the CH-NH2 group of donors

EC 1.4.1 With NAD+ or NADP+ as acceptor
EC 1.4.1.1 alanine dehydrogenase
EC 1.4.1.2 glutamate dehydrogenase
EC 1.4.1.3 glutamate dehydrogenase [NAD(P)+]
EC 1.4.1.4 glutamate dehydrogenase (NADP+)

EC 1.4.3 With oxygen as acceptor
EC 1.4.3.11 L-glutamate oxidase

EC 1.13 Acting on single donors with incorporation of molecular oxygen (oxygenases)
EC 1.13.11 With incorporation of two atoms of oxygen
EC 1.13.12 With incorporation of one atom of oxygen (internal monooxygenases or internal mixed function oxidases)

EC 1.14 Acting on paired donors, with incorporation or reduction of molecular oxygen
EC 1.14.12 With NADH or NADPH as one donor, and incorporation of two atoms of oxygen into one donor
EC 1.14.13 With NADH or NADPH as one donor, and incorporation of one atom of oxygen

EC 1.14.13.39 nitric-oxide synthase, NOS

The names associated with NOS have varied dramatically over the years The currently accepted name is nitric-oxide synthase.

Other names for NOS include; nitric oxide synthetase; endothelium-derived relaxation factor-forming enzyme; endothelium-derived relaxing factor synthase; NO synthase; NADPH-diaphorase

NOS is placed in Class 1: Oxidoreductases; Acting on paired donors, with O2 as oxidant and incorporation or reduction of oxygen. The oxygen incorporated need not be derived from O2; With NADH or NADPH as one donor, and incorporation of one atom of oxygen into the other donor

Systematic name: L-arginine, NADPH: oxygen oxidoreductase (nitric-oxide-forming)

16.1.3.4.2 Enzymatic action from an energy perspective

Page noted, "The two dramatic effects of enzymatic catalysis are molecular recognition and rate acceleration." The words rate acceleration are a poor choice. Rate increase would be a more appropriate term. He suggests that enzymatic activity can lower the activation energy of a reaction by up to 78 kJ/mol and the reaction can proceed at a rate 3×10^{12} faster.

The number of factors influencing enzyme activity is very large, and the importance of these individual factors is inadequately documented at this time. Page has enumerated twenty different potential factors, along with a citation for each[30].

The importance of, and principle action of, enzymes can be described in terms of energy diagrams. Such diagrams can be assembled based only on energy, or they can be expanded to include electron density considerations (and even electron transfer considerations). Hackney[31] has provided a detailed discussion of the energy levels associated with enzymatic

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[30]Page, M. (1987) Theories of enzyme catalysis *In* Page, M. & Williams, A. *eds* Enzyme Mechanisms. London: Royal Society of Chemistry

[31]Hackney, D. (1990) Binding energy and catalysis *In* Sigman, D. & Boyer, P. *eds* The Enzymes. NY: Academic Press Chapter 1

reactions by enumerating several specific species;

- E, the enzyme,
- S, the substrate,
- E·S, the enzyme substrate complex,
- E·TS, the transition state of the uncatalyzed chemical reaction,
- P, the product of the catalysis,
- E·P, the enzyme-product complex,

and describing their energy as in **Figure 16.1.3-2**. Quoting Hackney, "In order to produce catalysis, it is necessary that the binding of S and P be destabilized with respect to the binding of TS. The overall strategy for the enzyme must therefore consist of binding the TS as strongly as possible, while keeping binding to S and P weak. In an extreme limit, this would reduce to the dashed line with no discreet E·S or E·P. In conclusion, he notes the most efficient enzyme would be obtained if all of the intermediate species lie as close to the dashed line as possible.

16.1.3.4.3 An enzyme model

Dugas has clearly described the enzyme model[32]. "*Enzyme models* are generally synthetic organic molecules that contain one or more features present in natural enzymatic systems. They are typically smaller and structurally simpler than enzymes. With the tools of synthetic chemistry, it becomes possible to construct a 'miniature enzyme' which lacks a macromolecular peptide backbone but contains reactive chemical groups correctly oriented in the geometry dictated by an enzyme active site. It is often referred to as the biomimetic chemical approach to biological systems."

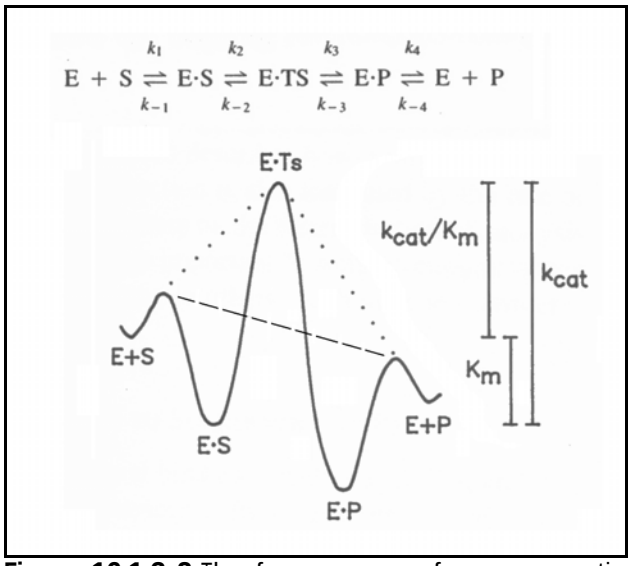

Figure 16.1.3-2 The free energy of an enzymatic reaction. ADD. Adapted from Hackney, 1990.

16.1.4 Broader Glossary

To understand the potential chemical sources leading to neuro-affectors, it is useful to quantify the terms introduced in the above discussions and to introduce certain additional definitions (generally as defined in Lehninger).

Amino acids– Precursors to many organic chemical families (proteins, hormones, vitamins, pigments, etc (pg 557).

Adrenergic– 1. Used to describe neurons believed to release epinephrine (adrenaline) or norepinephrine as a neuro-modulator or *(archaic)* neurotransmitter.
2. The result of neural stimulation similar to that obtained upon application of GABA to the same situation (archaic). **See Sections 8.7.4 & 15.1.2.3.5**.

Antibodies– Side chains emanating from cells that contain specific groups capable of combining with a particular group of a toxin. See Enzymes. Antibodies bind molecules in their ground states whereas enzymes bind their substrates in higher energy states.

Bioorganic chemistry– The discipline concerned with application of the tools of chemistry to the understanding of biochemical processes.

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[32]Dugas, H. (1996) Bioorganic chemistry: A chemical Approach to Enzyme Action, 3rd Ed. NY: Springer page 252

Catalyst– Materials that accelerate chemical reactions by lowering the activation energy. They do not influence the reaction equilibrium and emerge unchanged from the reaction.

Catecholamine– A family name for a catechol group coupled to an amine.

Choline– A nitrogenous alcohol.

Cholinergic– 1. Neurons believed to release acetylcholine as a neuro-affector or (*archaic*) neurotransmitter.
2. The result of neural stimulation opposite to that obtained upon application of GABA to the same situation (*archaic*). **See Sections 8.7.4 & 15.1.2.3.5**.

Cofactor– (*vernacular*, coenzyme) A material required to support an enzymatic reaction. Frequently a reactant providing energy to the overall reaction.

cortisol–

Decarboxylation– The release of CO2 from a more complex molecule. The process releases an electron. In the *in vivo* glutamate —> GABA reaction, this electron is used to power the neural system.

Denitroxification– The release of neutral NO from a more complex molecule. The process requires acquisition of an electron from another source. Denitroxification may occur by neural or enzymatic action.

Endocrine– A gland in communications with the circulatory system.

Energy rich– Compounds that are easily hydrolyzed (frequently in multiple steps), rather than compounds with high thermal dissociation energies.

Enzyme– A special class of proteins=copolymers of α-amino acids and imino acids that act as soluble polymer catalysts. See antibodies. Enzymes are characterized further:

1. Largest and most highly specialized group of proteins.
2. May work alone or require a cofactor (a metal ion or a complex organic called a coenzyme).
3. Generally described as organic catalysts in a biological system.
4. Generally described as receptors in receptor-substrate complexes.
5. Like other catalysts, they are unchanged as a result of the receptor-substrate reaction with an additional component.

Enzyme inhibitor– Any compound that slows or blocks enzyme catalysis.

Reversible inhibitors– bind to enzymes with non-covalent interactions such as hydrogen bonds, hydrophobic interactions and ionic bonds. Reversible inhibitors generally do not undergo chemical reactions when bound to the enzyme and can be easily removed by dilution or dialysis.

Irreversible inhibitors– usually covalently modify an enzyme, and the inhibition cannot therefore be reversed.

Suicidal enzyme inhibitor– An unusual type of irreversible inhibition where the enzyme converts the inhibitor into a reactive form in its active site.

Exocrine– A gland in communication with the external environment.

Gene expression– The biological synthesis of the 22 proteins encoded by DNA. About 240 other proteins, such as citrulline, are synthesized (primarily by post-translational reactions) based on other criteria.

Hormone– A naturally occurring chemical that is secreted by a stage 7 (terminal efferent) neuron, or a gland of the glandular modality, and that induces significant change in the biological activity in one or more biological cells. Except for the steroids, all known hormones contain nitrogen. Several classes can be defined.

1. Simple “inorganics”– nitrogen oxide (NO)

2. Amines– acetylcholine
3. Catecholamine hormones–epinephrine, norepinephrine & dopamine
4. Simple peptides– Cortisol; TSH, thyroid-stimulating hormone, etc
5. Steroids (in some contexts)

Luteinizing hormone– Anterior pituitary tropic hormone controlling the reproductive functions of testes and ovaries. **Follicle-stimulating hormone** works similarly. (pg 367 of Henry & Norman).

Mononucleotide– contains a nitrogenous base, a 5-carbon sugar and a phosphoric acid.

Neuro-affector– A stage 7 neuron that secretes hormonal material affecting either muscular or glandular tissue in an organism.

Neuroendocrinology– The study of the relatinship between the nervous system and the endocrine system (Martin & Reichlin, 1987).

Neuro-mediator–A chemical that mediates; especially : a mediating agent (as an enzyme or hormone) in a chemical or biological process. The action may generate an enhanced neural operation or suppress normal neural operation. The mechanism of application may involve a dedicated receptor or involve occupying a receptor designed to accommodate a different activity. Dopamine may operate by occupying a portion of the glutamate receptors of a specific neuron.

Neuro-secretion– The release of a hormone into the bloodstream by a nerve terminal (Martin & Reichlin, 1987). The hormone may also be secreted into the exterior environment, an exocrine hormone, or locally at a neuromuscular or neuro-glandular interface, a paracrine hormone.

Nitronergic– Used to describe neurons believed to release nitric oxide as a neuro-affector.

Paracrine– 1. A portion of the glandular system acting locally. Further categorized as to whether:
• **merocrine** type where the material is passed through the cell wall,
• **apocrine** type where the material breaks through the wall or separates along with part of the wall or
• **holocrine** type where the cell is destroyed in the process of freeing the specialized substance.
2. That portion of the glandular system within the BBB of the CNS (as used by Hobson, 2001).

Peptide– A chain of condensed amino acids with R groups as side chains (pg 56).

Pharmacokinetics– Mechanisms involving absorption, distribution, metabolism and excretion in a biological context.

Polymer catalysts– Polymers with catalytically active groups. They differ from polymer reagents that change their composition on reaction.

Prodrug– A pharmacologically inactive compound that is converted to an active drug by a metabolic biotransformation.

Carrier-linked prodrug– A compound that contains an active drug linked to a carrier group that can be removed enzymatically.

Bioprecursor– A compound that is metabolized by molecular modification into a new compound which is the active principle or which can be metabolized further to the active drug.

Protein– Typically contains one or more peptide chains.
1. (simple) yield only amino acids on hydrolysis.
2. (conjugated) include a non-amino acid prosthetic group.

Receptor– A chemical structure designed to selectively accept and combine with (usually employing non-covalent bonding) another chemical (the substrate) and prepare it for a further chemical reaction The properties of recognition capacity (related to a specific ligand) and an

amplification component (the ability of the ligand-receptor complex to initiate a biological response) are associated with receptors.

Steroid– Any of numerous naturally occurring or synthetic fat-soluble organic compounds having as a basis 17 carbon atoms arranged in four rings and including the sterols and bile acids, some adrenal and sex hormones, certain natural drugs such as digitalis compounds, and the precursors of certain vitamins.

Substrate– In biochemistry, an essential carrier of certain biological, chemical and/or physical properties. A starting material (educt) in a biological reaction that is converted by a specific enzyme. All educts must be brought into the cell, all products taken out of it.

Supramolecules– Physical molecules that result from the ordered self-association of chemical molecules via several adjacent non-covalent bonds such as hydrogen bonds.

Surfactant– An amphiphilic material.

16.1.5 The potential sites of chemical reaction

When discussing the interaction of the neural and glandular systems, it is necessary to consider a variety of chemical reactions occurring at highly selective sites. **Figure 16.1.5-1**, from Silverman identifies some of these sites associated with a single chemical[33].

The chemical bonds vary greatly in the energy required to form or break them. This energy

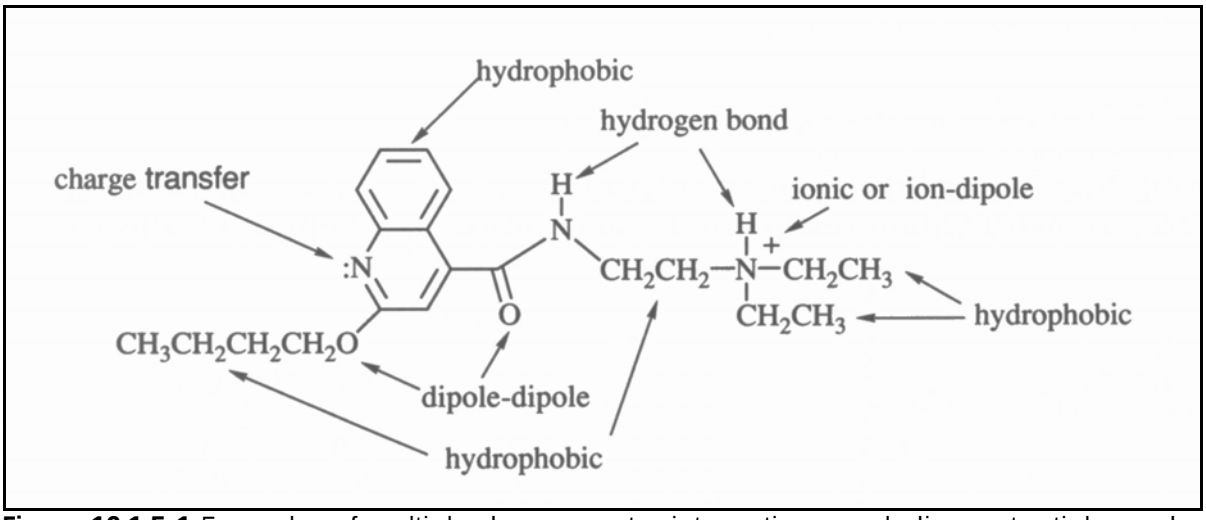

Figure 16.1.5-1 Examples of multiple drug-receptor interactions, excluding potential van der Waals interaction sites. From Silverman, 1992.

ranges from a nominal[34];
- –40 to –110 kcal/mol for covalent bonds
- –5 to – 10 kcal/mol for ionic bonds
- –1 to –7 kcal/mol for ion-dipole and dipole-dipole bonds
- –1 to –7 (most often –3 to –5) kcal/mol for hydrogen bonds.

Silverman describes a special type of molecular dipole-dipole interaction class (page 60), a charge-transfer interaction. When a molecule that is a good electron donor comes into contact with a molecule that is a good electron acceptor, the donor may transfer some of its charge to

[33]Silverman, R. (1992) The Organic Chemistry of Drug Design and Drug Action. NY: Academic Press

[34]Elias, H-G. (2005) Macromolecules. NY: Wiley

the acceptor. These reactions also exhibit a range from –1 to –7 kcal/mol.

Acceptor groups contain electron-deficient π–orbitals, for example, alkenes, alkynes, and aromatic moieties *having electron-withdrawing substituents*, or weakly acidic protons. Cysteine is an effective electron-acceptor.

Donors contain π–electrons, for example alkenes, alkynes and aromatic moieties *with electron-donating substituents*, that have a pair of nonbonding electrons, such as oxygen, nitrogen and sulfur moieties. The aromatic ring of tyrosine and the carboxylate group of aspartate are effective electron-donors.

Histidine, tryptophan and asparagine can act as both electron donors and acceptors.

Even lower energy levels are associated with van der Waal forces between molecules. Silverman suggests levels of –0.5 kcal/mol per bond (page 61).

Steed, Turner & Wallace give a considerably different, and expanded, set of values for these interactions in kj/mol (page 17). They describe at least six different hydrogen bonds.

The hydrogen bond is unique to hydrogen because it is the only atom that can carry a positive charge at physiological pH while remaining covalently bonded in a molecule, and hydrogen is small enough to allow close approach of a second electronegative atom.

16.1.5.1 Neurons employ multiple receptor sites

While seldom highlighted in the literature, neurons typically employ multiple receptor sites. Besides the receptor sites for electrostenolytic processes, they employ specific sites for accepting paracrine and endocrine control agents and (in the case of sensory neurons) specific sensory inputs. Some of these receptor sites may be utilized differently, based on their anatomical location. It appears probable that the same or similar receptor site may be able to sense the presence of organic acids when found on the surface of sensory neuron components exposed to the external environment (olfaction) while also used to accept glutamic acid as part of the electrostenolytic process when exposed to the internal environment of the neural system. This subject will be explored further in the next section.

16.1.5.2 The description of receptor-substrate sites

> The material in this subparagraph is presented for orientation only. It is based on the chemical theory of the neuron, developed and used throughout the 20th Century. It does not represent the coordinate bonding phenomenon so critically important within the biological system. **Section 16.1.3.3** and the last paragraph of this section will address the 21ST Century concept known as the Electrolytic Theory of the Neuron. This is the concept used throughout this work.

For many years, the study of the steric interaction between molecules was based on the concept of a lock and a key first developed by Fischer at the beginning of the 20th Century. Powell expanded the concept in the 1940 to describe a host-guest relationship. This concept has been expanded further to the current receptor-substrate concept. This concept is broader in that it involves not only the conformal geometry of the two materials but also the energy state of the combination (compared to their individual energy states), and the potential for electron transfer to and from a third material..The description of the overall receptor-substrate has recently taken on the label supramolecules. The literature of supramolecules has expanded rapidly[35,36]. The Steed & Atwood volume also includes an updated discussion of the liquid-

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[35]Steed, J. & Atwood, J. (2000) Supramolecular Chemistry. NY: Wiley

[36]Elias, H-G. (2005) Macromolecules, Vol 1: Chemical Structures and Syntheses. & Vol 2: Macromolecules. NY: Wiley-VCH

crystalline state of matter in Chapter 10, while the Elias volume presents a comprehensive survey of the terminology of organic chemistry and its application to supramolecules. Steed, Turner & Wallace have provided a large set of precise definitions particular to the supramolecule field[37]. The complexity of supramolecules is unlimited. Hopfinger has discussed the structural aspects of supramolecules and included a large table of chemical bond lengths[38].

Elias provides very clear and precise definitions of the various types of molecules, even differentiating between chemical molecules and physical molecules. He also reviews the appropriate terminology for describing them when in different states of matter. He clearly differentiates between supramolecules, superpolymers and hyperpolymers. On page 35, he notes the different use of the term "substituted" in organic and inorganic chemistry.

Like the term substituted, the term substrate has an entirely different meaning in inorganic and organic chemistry. The substrate of inorganic chemistry becomes the receptor in organic chemistry and the term (first) reactant of inorganic chemistry becomes the substrate of organic chemistry.

On page 511, Elias describes biopolymers as naturally occurring macromolecules (which can also be described as superpolymers). On page 515, he describes a narrow definition of substrate that limits biological reactions involving substrates to the interior of cells. He also describes the range of molecular transport mechanisms available for transporting a molecule through a cell membrane.

Most receptors are very complex and large enzymes (polypeptide macromolecules). Describing specific enzymes in detail is typically beyond the state of the art, and of limited interest. Dugas provides a broad description of an enzyme (page 171). Dugas describes the site of enzymatic action as an *active center* or catalytic cavity. A single enzyme may have several active centers and it is not clear that the reaction site associated with the substrate is related directly to any specific area of the enzyme. Because of the molecular complexity of the typical enzyme, it is common to only discuss a limited region of the molecule and/or develop a partial *enzyme model* of the enzyme (page 252) applicable to one reaction. Therefore, these receptors are usually described diagrammatically as shown in **Figure 16.1.5-2** *based on the chemical theory of the neuron.* Frames **A** and **B** employ metallic atoms in their molecules. Such molecules are not normally found in physiological systems.

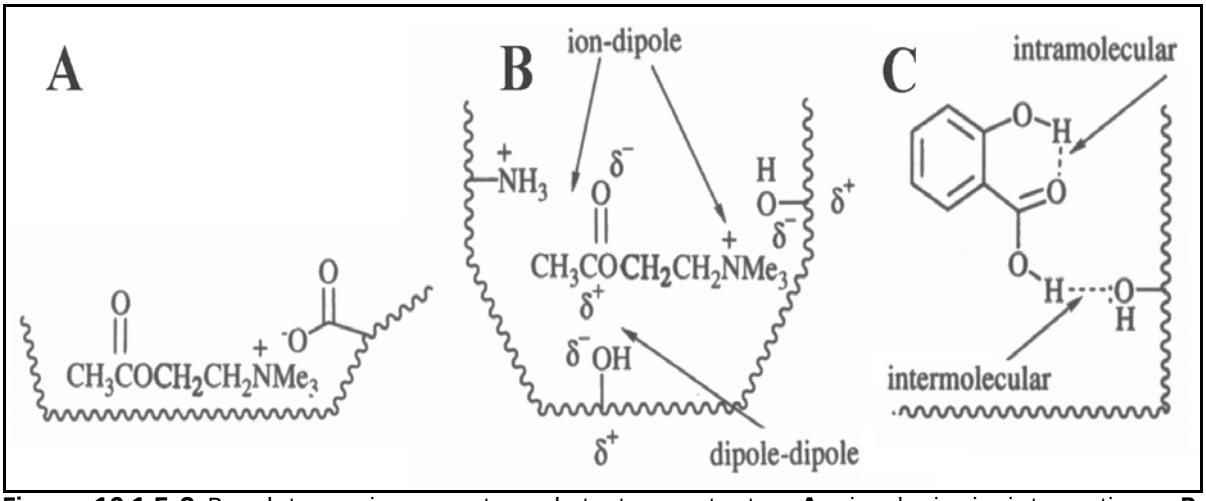

Figure 16.1.5-2 Bond types in receptor-substrate contexts. **A**; simple ionic interaction. **B**; examples of ion-dipole and dipole-dipole interactions. **C**; examples of hydrogen bonds. Adapted from Silverman, 1992.

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[37]Steed, J. Turner, D. & Wallace, K. (2007) Core Concepts in Supramolecular Chemistry and Nanochemistry. NY: John Wiley & Sons

[38]Hopfinger, A. (1973) Conformational properties of macromolecules. NY: Academic Press

Additional material on the conformal chemistry of enzymatic action are found in Starzak (1984 QH 601, both S68 and S796c), in Rusk, in Edwards and in Valquest (in my files).

Silverman has provided a valuable caricature, also based on the archaic chemical theory of the neuron, of binding of substrates to receptors in **Figure 16.1.5-3**. He employed epinephrine and norepinephrine in his caricatures. "If you consider two enantiomers, such as (*R*)-(–)- and (*S*)-(+)-epinephrine, interacting with a receptor that has only two binding sites (frame A),it becomes apparent that the receptor cannot distinguish between them. However, if there are at least three binding sites (frame B), the receptor easily can differentiate them. The (*R*)-(–)-isomer has three points of interaction and is held in the conformation shown to maximize molecular complementarity. The (*S*)-(+)-isomer can have only two sites of interaction (the hydroxyl group cannot interact with the hydroxyl binding site, and may even have an adverse steric interaction); consequently it has a lower binding energy."

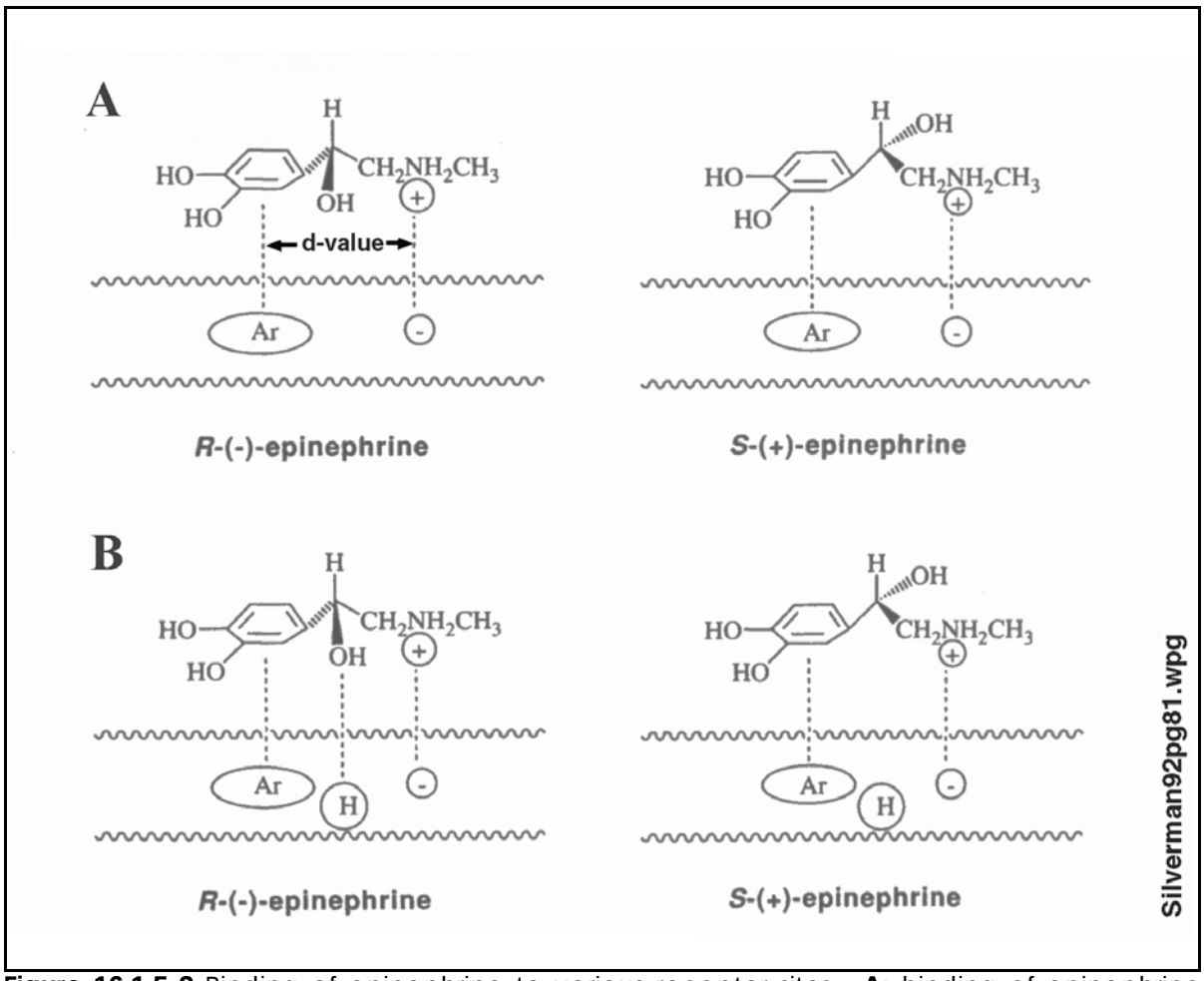

Figure 16.1.5-3 Binding of epinephrine to various receptor sites. **A**; binding of epinephrine enantiomers to two-site receptors. **B**; binding of epinephrine enantiomers to three-point receptors. Under the Electrolytic Theory of the Neuron, the bonds shown in **A**, and the outer pairs in **B**, represent DACBs. See text. From Silverman, 1992,

Silverman's association between two aromatic rings has not stood the test of time. In fact, the symbol AR in each substrate must be represented by a atom capable of sharing a positive charge with the aromatic ring of the hormones in a coordinate bond. Under the Electrolytic Theory of the Neuron, the potential for epinephrine and norepinephrine are not restricted to the

aromatic ring and one other charged ligand within the substrate. Virtually any molecule containing a nitrogen atom and any hydroxyl group can form a DACB with a receptor exhibiting matching d-value (See left frame of **A**). Similarly, any aromatic ring, or C=C (double bond) and any hydroxyl group can form a DACB (See **Section 8.4**). The aromatic ring and double bond can both provide an electrical charge to be shared in a coordinate bond.

The three-point binding of *R*-(--)-epinephrine shown at lower left is known to increase the functionality of epinephrine significantly in medicine based on the work of Shallenberger & Acree.

The ability of a molecule to exhibit multiple d-values (based on the conditions discussed in the paragraphs above) shows in the case of epinephrine and norepinephrine how effective they can be. Each can form DACB's with a variety of receptors within the biological system.

16.1.6 Common inter-modality functional blocks

After completing the analyses in support of Chapter 16 and Chapter 23, a common functional block appeared that could be used for neuroaffectors, glandular-affectors and muscular tissue. The generic functional blocks associated with each of these interfaces is shown in **Figure 16.1.6-1**.

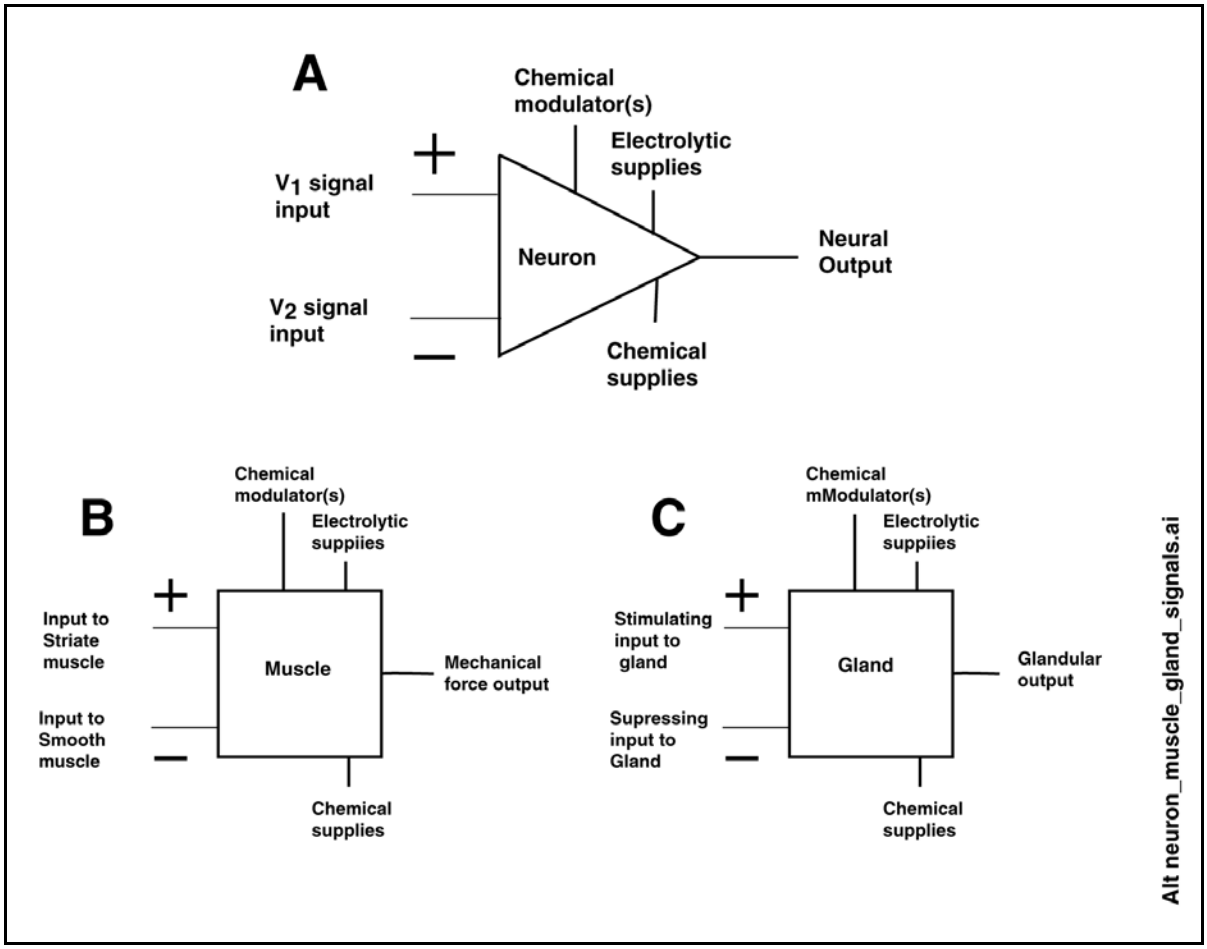

Figure 16.1.6-1 Common inter-modality functional blocks ADD.

Frame **A** shows the neuron functional block used throughout this work (except for the more complex stage 1 sensory receptor neurons). It includes a differential electrical input structure

that makes the labels of adrenergic and cholinergic obsolete with respect to orthodromic signaling. It also accounts for the sensitivity of neurons to chemical modulators. It also provides for the generation of the negative voltage of the internal chambers of the neuron via the electrolytic energy supplies. The output of the neuron is typically a voltage except in the case of the neuroaffectors where it is typically acetylcholine or nitric oxide.

Frame **A** illustrates a neuron as displayed previously but with a defined modulator input. The receptor at this location is primarily to accommodate glandular inputs, such as epinephrine or norepinephrine. The concept is that there can be separate receptors for one or more glandular inputs to a neuron besides the required electrolytic receptor, receptors of neural (electrical) signals and means to accept chemical supplies if required (to support stage 7 neurons). These defined receptor locations are distinct from those required for the cell to maintain homeostasis.

Frame **B** shows a typical muscle functional block. It exhibits the same generic input structure as the neuron and the same inputs for chemical modulators and electrolytic supplies. In addition, it exhibits a chemical supplies terminal where additional sources of energy can be introduced. It appears that striate muscle is only susceptible to stimulation by acetylcholine at the input accompanied by a positive polarity sign. Conversely, the tension inherent in smooth muscle is repressed by stimulation by nitric oxide at the input terminal accompanied by a negative polarity sign.

Frame **C** shows a typical gland functional block. It exhibits the same generic input structure as the neuron and the same inputs for chemical modulators and electrolytic supplies. In addition, it exhibits a chemical supplies terminal where additional sources of energy can be introduced. Based on the modeling of the hypophysis (pituitary) gland by Labrie et al[39],, at least the glands within the hypophysis also exhibit a differential input structure.

The modulator and energy supply terminals in **A**, and probably in **B** and **C**, do not employ protein receptors of the GPCR family. See **Section 3.2.4**. The receptors at these locations are typically amino-phospholipids. The receptor for the electrolytic supplies is known to be phosphatidylserine molecules in a liquid crystalline array forming the outer bilayer of a region of type 2 lemma of the cell involved.

This is the proposed common functional block, whether shown as triangular or rectangular, used in these major modalities in the architecture of the physiology of animals (including humans).

16.1.6.1 Attempts to standardize chemical terminology at the process level–SBNG

Novere et al. note in 2009, "As a group of biochemists, modelers and computer scientists working in systems biology, we believe establishing standard graphical notations is an important step toward more efficient and accurate transmission of biological knowledge among our different communities." They review the wildly varying terminology found in the bioscience literature to describe the nominally same series of reactions in their Figure 1, reproduced here as **Figure 16.1.6-2**. They note the confusion resulting from these inconsistencies. After describing their proposed Systems Biology Graphical Notation, SBGN, they describe some of its merits in their figure 2. However their caption to the figure suggests their proposed solution is incomplete. They note that three separate views are required to represent any complex chemical reaction. They also note, "Each view focuses on only a portion of the semantics of the overall system, trading off diagram comprehensibility against completeness of biological knowledge."

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[39]Labrie,F. Drouin, J. De Lean, A. et al. (1976) *In* Levey, G. *ed.* Hormone-receptor interaction: molecular aspects. *Volume 9 of Modern Pharmacology-Toxicology* NY: Marcel Dekker

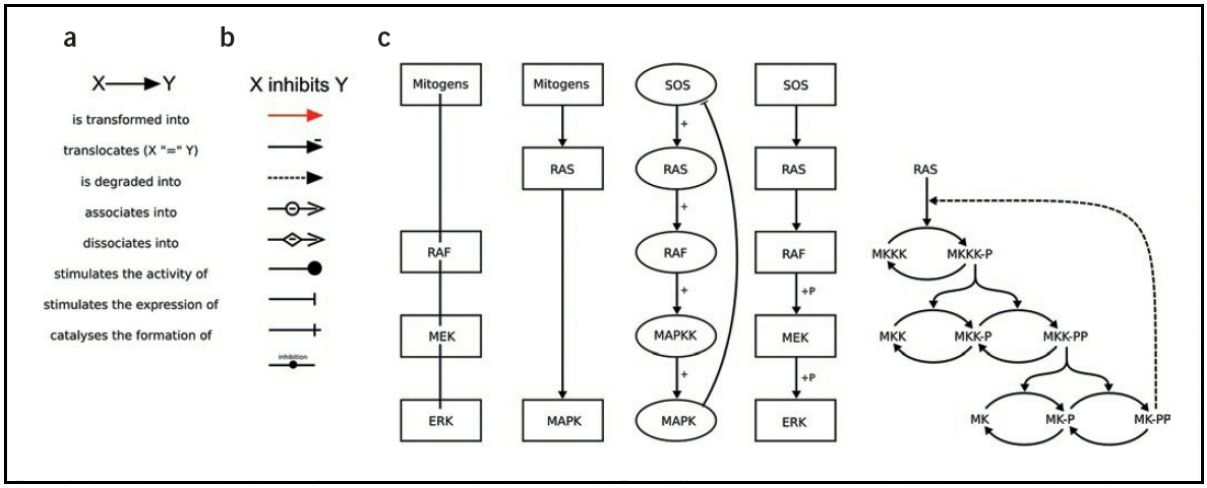

Figure 16.1.6-2 "Inconsistencies and ambiguity of current nonstandardized notations." (A) Eight different meanings associated with the same symbol in a chart describing the role of cyclin in cell regulations (http://www.abcam.com/ps/pdf/nuclearssignal/cell_cycle.pdf. (b) Nine different symbols found in the literature to represent the same meaning. (c) Five different representations of the MAP kinase cascade found in the scientific literature, depicting progressive levels of biological and biochemical knowledge. Citations for each in the original caption. From Novere et al, 2009

This style of notation used in SBGN has not achieved wide acceptance by 2018.

A challenge for the Novere team is to expand their notation to incorporate The Electrolytic Theory of the Neuron and provide a cogent integration of the electrolytic and conventional chemical notations.

Section 16.5.1.2.1 reviews their overly complex conception of the *process diagram* representing the interface between a stage 7 neuroaffector neuron and a striate muscle cell Novere et al. presented. They provided no citation for this figure. They did not specify that their figure only applies only to a striate muscle cell and not to a smooth muscle cell or cardiocyte.

Novere notes, "When a motor neuron generates an action potential, it travels rapidly along the nerve until it reaches the neuromuscular junction, where it initiates an electrochemical process that causes acetylcholine to be released into the space between the presynaptic terminal and the muscle fiber."

The question is what happens then?

Based on the exocrine receptors, it is likely that ACh is likely to form a DACB with the receptor labeled AchR. This bond does not involve a chemical reaction that creates one or more residues.

16.1.7 The mechanisms of enzymatic action

There are three factors determining the reaction rate of an enzyme-assisted reaction:

• substrate binding,
• the turnover number, the number of substrate molecules converted to product per unit of time per molecule of enzyme active site, of the order of 10^3/min (note the term minute instead of second), and
• product release.

Silverman describes six of the most common mechanisms enzymes use to catalyze product:

• approximation, a rate enhancement by proximity, the enzyme serves as a template to bind

the substrate to that it is close to the reaction center,
- covalent catalysis, occurs in several subforms–
  the enzyme may use a nucleophilic amino acid side chain in the active site to form covalent bonds to the substrate intermediate to generate product. The most common active site nucleophiles include the carboxyl group of aspartate or glutamate (Silverman, pg 105).
- general acid-base catalysis,
- electrostatic catalysis,
- desolvation, and
- strain or distortion.

16.1.8 The description and development of medicinal drugs

Silverman has presented a scenario of the drug development process[40]. He notes that drugs are not discovered but tailored from a very small group of lead compounds. "Lead compounds are prototype compounds that exhibit desired biological or pharmacological activity, but may have many other undesirable characteristics, . . ." These lead compounds have frequently been known, and used in folk medicine for centuries. Only two drugs are recognized as being developed without relying upon a lead, penicillin and Librium. Both of these discoveries were serendipitous according to Silverman. Once these two drugs were discovered, they became lead compounds for extensive families of more tailored drugs. The drug Valium was developed by Roche even before Librium reached the market. Valium is estimated to be almost ten times more effective than Librium.

The methods of drug optimization from a lead compound remains primitive. Random screening remains a primary technique. "As a result, less than 1 in 10,000 compounds synthesized in drug companies makes it to the drug market, and, in so doing, it takes about 10 years of research at a cost of $200-250 million (Silverman, page 47)."

16.2 Stage 6, signal implementation & stage 7 signal affectation

Stages 6 & 7 were defined at the very top level in **Section 16.1.1**. Stage 6 is responsible for the conversion of stage 5 instructions into efferent command signals within the CNS and The extended "minibrains" associated with the heart, digestive tract and uterine system via tight (electronic) synapses.

Stage 7 is generally limited to the terminal stage 3 signal projection neurons that are modified to stimulate muscle or glandular tissue directly via a gap (chemical) synapses. Stage 3 signal projection neurons have been defined and explored in detail within **Chapter 9**.

Figure 16.2.1-1 reproduces a schematic prepared by Noback et al. of 2005. As noted in **Section 16.1.3.2**, the use of the terms adrenergic and cholinergic are obsolete under the Electrolytic Theory of the Neuron **and** the differential input structure of typical neurons. This figure appears to build on Noback's understandings described in his 1967 book (page114). The terms cholinergic and adrenergic remain poorly defined and based on the largely conceptual chemical theory of the neuron. Recall that during the 20th Century, cholinergic was shorthand for an activity that responds positively to the release of acetylcholine by a (stage 7*)* ***neuron***. It did not indicate a positive response to choline, a typically passive chemical intermediary when present in the animal system. *Acetylcholine, not choline, is delivered via a local neuroaffector (chemical) synapse*. On the other hand, adrenergic was shorthand for an activity that responds positively to the release of a member of the adrenaline hormone family by a ***gland*** of the hormonal system. The adrenaline harmones are delivered via the *global bloodstream*.

The label adrenergic along the neural paths in the Noback figure should be disregarded. To the extent the targets of the adrenergic path shown involve smooth muscle, they are actually sensitive to the release of nitric oxide by specialized stage 7 neurons (**Section 16.5.3**). The response of the other targets are generally due to neuroaffectors that do not pass down the spinal cord.

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[40]Silverman, R. (1992) Op Cit Chapter 2

Many of the peripheral glands cited in the figure are not served directly by the neural system but rely upon the hormones of the endocrine system, distributed via the vascular system. (**Section 16.3**).

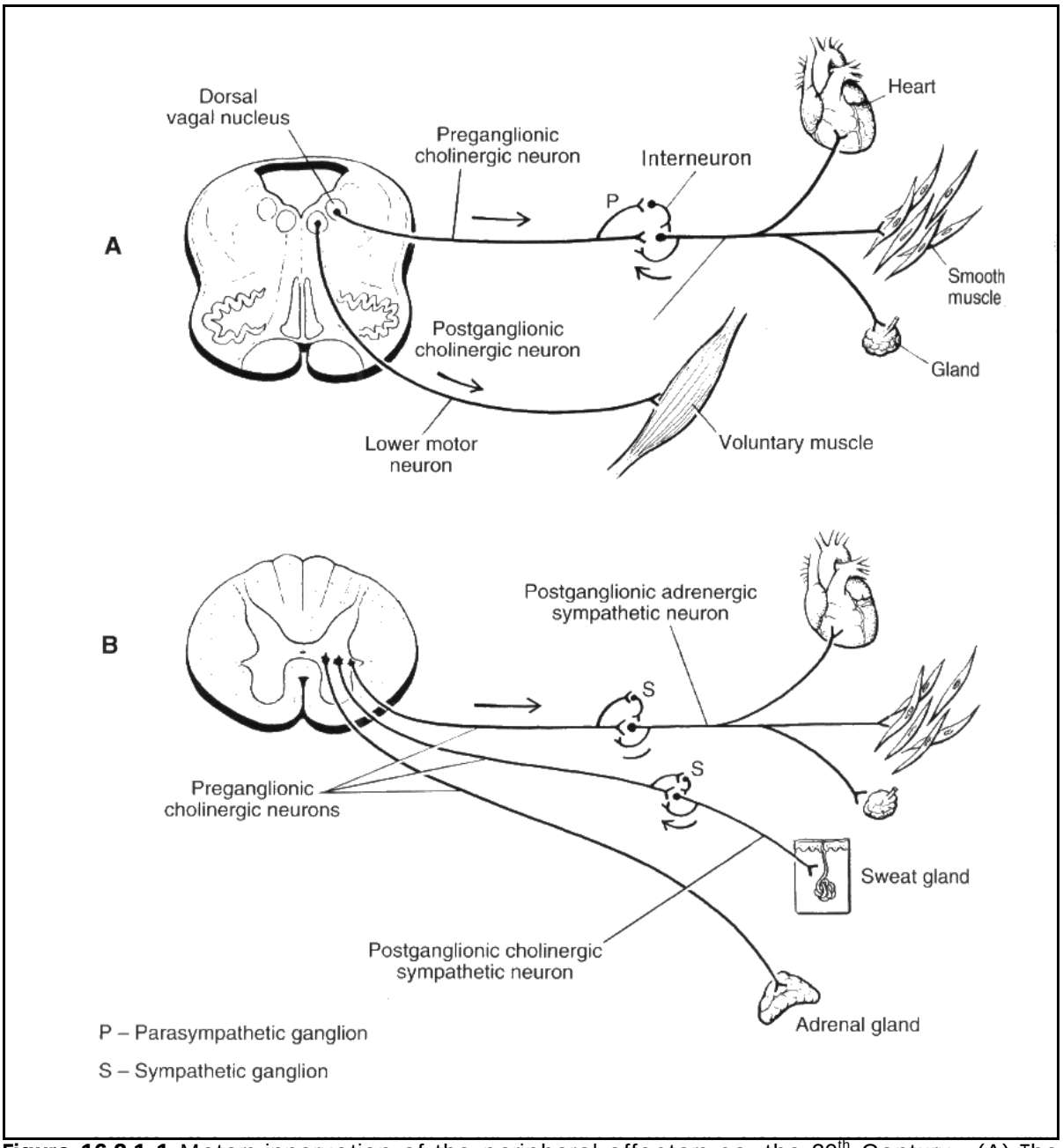

Figure 16.2.1-1 Motors innervation of the peripheral affectors ca. the 20th Century. (A) The parasympathetic outflow from the medulla innervates cardiac muscle, smooth muscle, and glands. The lower motor neuron innervates striated muscle. (B) Sympathetic outflow from the spinal cord innervates cardiac muscle, smooth muscle, and glands. Sympathetic ganglia have interneurons called small intensely fluorescent (SIF) cells, which contain catecholamine, fluorescent dopamine, and norepinephrine. From Noback et al., 2005.

Shipp has presented a comprehensive *review* of stage 6 neural operation from a philosophical

perspective[41]. While comprehensive from that perspective, it does not present specific physiological or electrophysiological data. His figure 8 is generally compatible with, and a simplified version of, the physiological configuration shown in **Section 12.5**. However, the labeling is unconventional from a physiologist's perspective and employs an unusual degree of imprecision (See **Section 11.8.1**). Shipp does note (page 800), "many accounts of motor cortex connectivity do not lend themselves to hierarchical analysis." However, his placement of the MD (premotor cortex) within the designation thalamus in figure 8 is quite unconventional, even when modified by the ambiguous adjective "(central)." This work provides a more complex description of the neural system that cannot be restricted to a hierarchal form. Much of Shipp's terminology appears to have been derived from McFarland & Haber[42].

> It is well recognized there are significant differences in terminology between those laboratory investigators employing the lower primates and those attempting to generalize all of the data available from both the lower primates and the higher primates (much of the latter data based on the effect of lesions, medically defined strokes and autopsy data). In recent times, the availability of non-invasive imaging techniques have greatly advances our knowledge of the functional physiology of the higher primates (particularly humans).

The McFarland & Haber paper was based on extensive laboratory investigations using "twenty adult macaque monkeys (*Macaca nemestrina*). The exploration employed both anterograde and bidirectional tracers in an extensive set of tracing experiments. They treated the thalamic reticular nuclei (TRN) of the monkey as a major inline element of the motor system rather than as a control center overseeing operation of most of the central neural system (CNS). This approach is counter to that used in this work and the description in Baars & Gage of the TRN as a control center. Baars & Gage note (page 250),

> "Keep in mind also that the thalamus is the major *input* hub for the cortex, and also the major cortex-to-cortex traffic hub. . .However, the basal ganglia operate as a major *output* hub, for motor control and executive functions." The subject of two-way communications is also addressed on page 252 relative to vision with "In fact, about 90% of the LGN-V1 fibers are 'running the wrong way'. **Above the LGN, everything is a two-way highway. This is a dominant feature of the brain, and it is a great challenge to understand how two-way connections work**." The emphasis was added because of the critical importance of this statement. **It is in agreement with the hypothesis of this work.**

McFarland & Haber make an effort to determine the relative presence of reciprocal and non-reciprocal neural paths in their experiments. However, it is difficult for an investigator to state definitively that any neural circuit is non-reciprocal without an exhaustive investigation of all signal projection neurons arriving at a given neural engine. As of 2018, this directional delineation has become much easier with the advent of "vector MRI" (**Section 11.7.2.5**), also labeled dfMRI.

Their premise that the TRN is an inline element of the motor modality is diluted by their results in figures 2 through 11. These figures all show extensive communications between the points of their tracer injections into the thalamus (or more broadly multiple engines of the diencephalon) and broad areas of the cerebral cortex of this lower primate species (verging on the paleo-mammalian form or intermediate to the paleo-mammalian and neo-mammalian forms of MacLean (**Section 4.2.3**).

The latter parts of their discussion section are worthy of further study. Their figure 13 is relatively conventional in outlining the signal paths between different layers of cortical substrate but includes the totally undefined terms GP/SN A and GP/SN B. It also treats the thalamus as distinct from the striatum; the latter typically considered an element of the basal ganglia distinctly

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[41]Shipp, S. (2005) The importance of being agranular: a comparative account of visual and motor cortex *Phil Trans R Soc B* vol 360, pp 797-814 doi: 10.1098

[42]McFarland, N. & Haber, S. (2002) Thalamic relay nuclei of the basal ganglia form both reciprocal and nonreciprocal cortical connections, linking multiple frontal cortical areas *J Neurosci* vol 22(18), pp 8117–8132

separate from the thalamus. their section labeled "Functional implications" includes many statements that take on a different implication when supported by a broader, non hierarchal schematic of the CNS. Their last sentence is an important one in the context of the hypothesis of this work, "Thus, information may travel in a relatively parallel manner from cortex to striatum; however, the thalamus is in a position to directly modify those one-way circuits."

The *labeling* of their figure 14 is open to considerable discussion.. The two upper right boxes are clearly portions of stage 5 cognition and the two lower right boxes are clearly portions of stage 6 in this work. Their "Rostral 'Cognitive' Motor" box can be described as receiving *instructions* from the stage 5 cognitive engines but having no cognitive capability of its own. Similarly, their "Caudal 'Executive' Motor" box can be described as generating commands for projection to the motor modality causing physical execution of the instructions but no actual role in the largely declarative executive functions performed within stage 5 ***or*** the primarily non-declarative executive functions performed within the thalamus.

16.2.1 The architecture of stage 6, command signal implementation

Stage 6 can be presented in more detail building on the work of Swanson. **Figure 16.2.1-2** expands on his approach employing pattern generators. The prefrontal engines of stage 5 primarily issue very high level volition instructions. These instructions are elaborated in the premotor areas of stage 6. However, the resulting instructions are still not recognizable by the electrophysiologist. These instructions still control large groups of muscles and may require expansion by the pallidum and/or the cerebellum in order to create afferent groups of commands varying in both intensity and time of occurrence. It is the afferent commands, prepared in large numbers by the stage 6 motor neurons, that exhibit the typical action potential stream appearance that can, in many cases, be correlated with the strength and timing of individual muscle contractions. It is these large numbers of distinctly different neural signals occurring simultaneously that can be thought of as neural patterns created by pattern generators earlier in the system.

The individual neural signals emanating from stage 6 can also exhibit a distinct pattern that varies in time. Because of these two ways to generate patterns, the term pattern generator must be used with additional identifying adjectives.

Notice in this concept that premotor areas are defined that service not only the somatomotor neural system but also the endocrine and autonomous neural systems. Note also the presence of stage 7 neurons beyond the stage 6/stage 7 interface at the surface of the spinal cord.

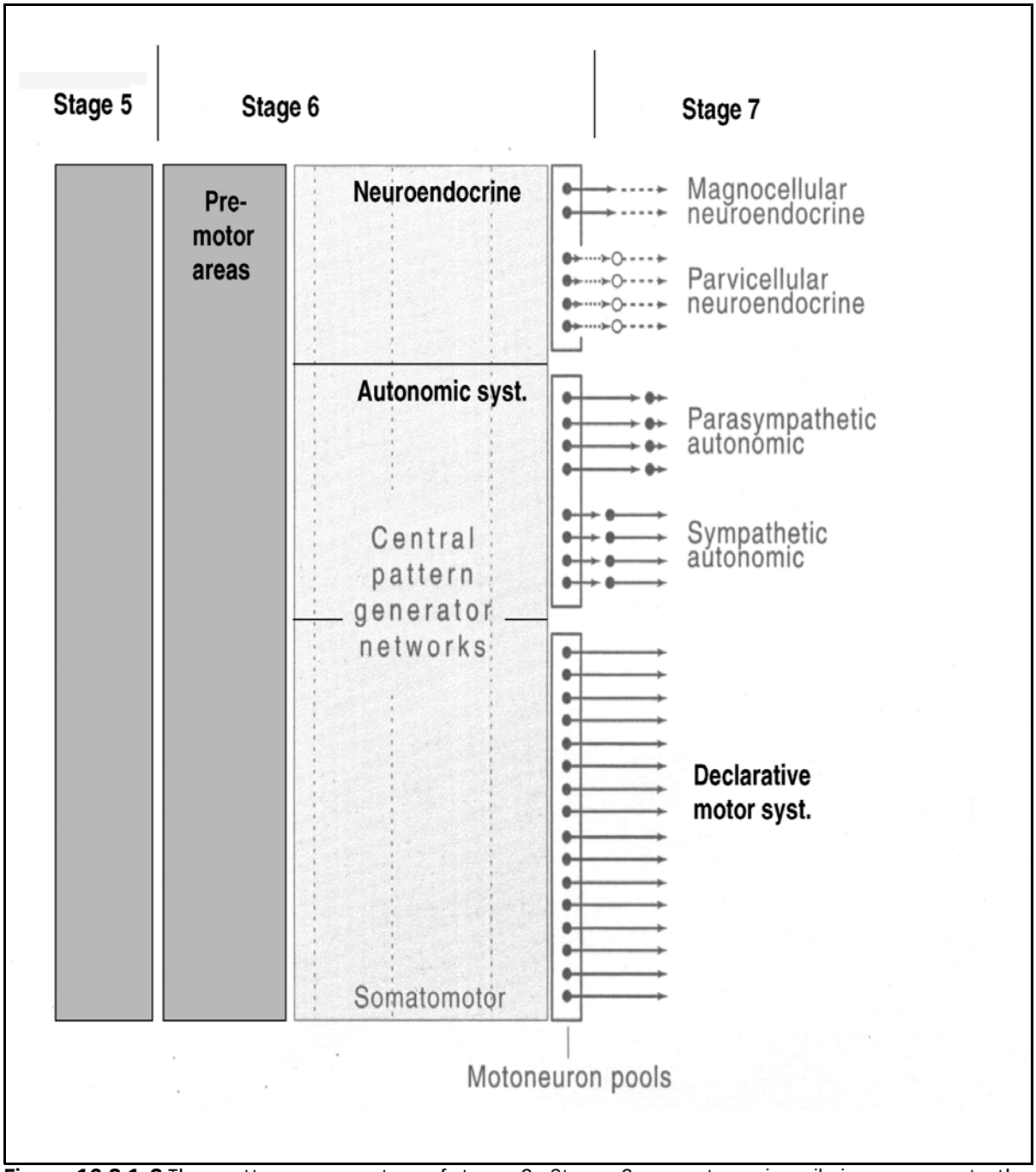

Figure 16.2.1-2 The pattern generators of stage 6. Stage 6 operates primarily in response to the instructions received from stage 5, cognition. The premotor areas interpret these instructions and route them to the "motor" areas that expand them into commands targeted on both the skeletal-motor and visceral subsystems. Expanded from Swanson, 2003.

16.2.2 The architecture of stage 7, command signal affectation

The neurons of stage 7 are modified stage 3 signal projection neurons where there pedicles are modified to release a variety of chemical components in order to affect non-neural tissue. There

are a variety of these chemical neurotransmitters in order to focus their action on specific types of tissue.

16.2.2.1 Application of Dale's Principle

The question arose in the 1930's as to whether a single neuron could release more than one neuroaffector (enzyme, modulator, or other chemical). Only two neuroaffectors were known at the time, acetylcholine and noradrenaline (believed at the time to be adrenaline; and now known as epinephrine). Furthermore, Dale did not address the possibility of separate axon terminations operating differently.

The term "Dale's Principle" was first used by Sir John Eccles in 1954, in a passage reading, "In conformity with Dale's principle (1934, 1952) that the same chemical transmitter is released from all the synaptic terminals of a neurone..."[1][2] Some modern writers have understood the principle to state that neurons release one and only one transmitter at all of their synapses. Others, including Eccles himself in later publications, have taken it to mean that neurons release the same set of transmitters at all of their synapses.

In a 1976 publication, Eccles reinterpreted the principle in a subtly different way:

"I proposed that Dale's Principle be defined as stating that at all the axonal branches of a neurone, there was liberation of the same transmitter substance or substances."[9]

As noted on a Wikipedia page in 2010 without attribution but with citations[43], "The addition of 'or substances' is critical. With this change, the principle allows for the possibility of neurons releasing more than one transmitter, and only asserts that the same set are released at all synapses. In this form, it continues to be an important rule of thumb, with only a few known exceptions.

With the wide range of chemical neuroaffectors known today, the subject is still of considerable interest. Little attention has been given to this principle in recent times.

16.2.2.2 The architecture and structures of stage 7 neuro-affectors

The literature lacks a framework for describing the afferents of the neuroaffectors of the neural system. In this case, the term afferents is used to describe the agents;

1. stereochemically released from the axolemma surface of neuro-affectors,
2. secreted by vesicles in the axolemma of neuro-affectors, or
3. charges released electrolytically at the axolemma pedicle of neuro-affectors.

Figure 16.2.2-1 provides a framework for describing these neuro-facilitators within the neural system. The neuro-affector secretions are logically divided into those affecting nerve tissue and those affecting muscle (and possibly other) tissue. The secretions affecting the nerves can be divided into those effecting nerves directly (*neuromodulators*), produced and consumed locally (*paracrine*), those effecting nerves remotely via the transport capability of the *endocrine* circulation, and those affecting other species at a distance (*exocrine*). See Section 3.5.4 in "Hearing: a 21st Century Paradigm" for additional discussion of the classification of Neural materials.

[43] http://en.wikipedia.org/wiki/Dale's_principle

NERVE NEURO-AFFECTORS

Direct contact (Local)

Primary Neuro-facilitators	**Glutamate, *alt*. Aspartate**
Primary Neuro-inhibitor	**GABA, *alt.* Alanine**
Class 1 Neuro-inhibitors	**L-Dopa, Glycine, Dopamine**
Class 2 Neuro-inhibitors	**Histamine, Serotonin**

Via endocrine system (remote) or of paracrine origin

Neuro-modulators	**Epinephrine**
	Norepinephrine

MUSCLE NEURO-AFFECTORS

Striate Muscle	**Acetylcholine or**
	? Electrical charge
Smooth Muscle	
Visceral	**Nitric Oxide**
Cardiac	
Uterine	**Estrogen--Progesterone**
Multi-unit	

Figure 16.2.2-1 A framework for neuro-affectors. This figure extends a similar figure 3.5.3-3 in the author's book on hearing. This work classifies acetylcholine as a neuro-affector, rather than a Class 2 neuro-modulator as in that work. The major classes of muscle appear to rely on different neuro-affectors in order to maintain their operational independence from the rest of the neural agents present in the overall system.

This discussion separates natural, endogenous, neuro-affector agents from exogenous pharmaceutical agents. It also discriminates between the natural *in-vivo* mechanisms employing the endogenous agents and the generally *in-vitro* and frequently topical application of agents at non-*in-vivo* concentrations.

16.2.2.2.1 Neuro-affectors influencing neuron operation within the neural system

The primary neuro-facilitators and neuro-inhibitors are ubiquitous in the vicinity of all neurons. Their availability at nominal concentrations is crucial to the operation of the neural system. However, their presence at excessive concentrations can cause distortion in the operation of the affected neurons. The primary neuro-facilitator is glutamate (glutamic acid); it is converted into GABA and free CO_2 electrostenolytically at specific type 2 lemma on the surface of all neurons. The conversion of aspartate (aspartic acid) to alanine and CO_2 forms an alternate

primary source of electrical power for the neurons.

Class 1 neuro-inhibitors are defined as those natural neuro-affectors that can bind to the electrostenolytically specific type 2 lemma sites of neurons and thereby interfere with the normal electrostenolytic operation of those sites and thereby suppress the normal performance of the affected neuron(s). Among others, these agents include L-Dopa, dopamine and glycine.

The stereochemistry and reaction chemistry of the primary neuro-facilitators and the class 1 neuro-inhibitors are discussed in detail in **Section 3.3** of the chapter on power supplies. .

Class 2 neuro-inhibitors are defined as those natural neuro-affectors that can interfere with the normal operation of the neuron(s) without occupying the electrostenolytic sites used to power the neurons. When combined with class 2 neuro-facilitators, they form the class 2 neuro-modulator group. The neuro-modulators typically occupy other receptor sites on the specialized type 2 (electrically conductive unidirectionally, i.e., diodes) lemma of the neuron. These agents include acetylcholine, histamine, serotonin and both epinephrine and norepinephrine. The specific mechanisms by which these agents affect neural operation remain under study (**Section 16.1.5.1**). However, they are not neurotransmitters, conveying information between neurons within a synaptic connection, within the context of the electrolytic theory of the neuron.

The literature still lacks detailed mechanisms and chemical equations (as opposed to caricatures) describing the roles of the neuro-modulators and secondary neuro-inhibitors. **Figure 16.2.2-2** illustrates the diverse forms of these agents. **Section 3.3.2** of the power supply chapter discusses the potential role of agents incorporating the glucol group, such as epinephrine, norepinephrine, dopamine and L-Dopa. **Section 16.1.6** addresses the site of application of neuro-modulators as differentiated from neurotransmitters (electrons) and neuroaffectors.

16.2.2.2.2 Neuro-affectors influencing muscle operation

There are a variety of neuro-affectors used to control muscle operations. While the neuro-affectors of striate muscle have been most intensely studied, a variety of specialized neuro-affectors appear to affect specific types of smooth muscle.

Stage 7 neuro-affectors interface with striate muscle through specialized structures known as end-plates. The end-plates are complex structures that include a number of terminal axon branchlets interfacing with the lemma of the muscle cell and protected by Schwann cells and other sheath cells. This arrangement is suggestive of normal current flow from the neuro-affector neuron into the muscle cell but does not totally discount the release of other agents from the stage 7 neuron. The interface is highly specific. Any agent transferred from the neuron to the muscle cell is prevented from reaching other muscle cells.

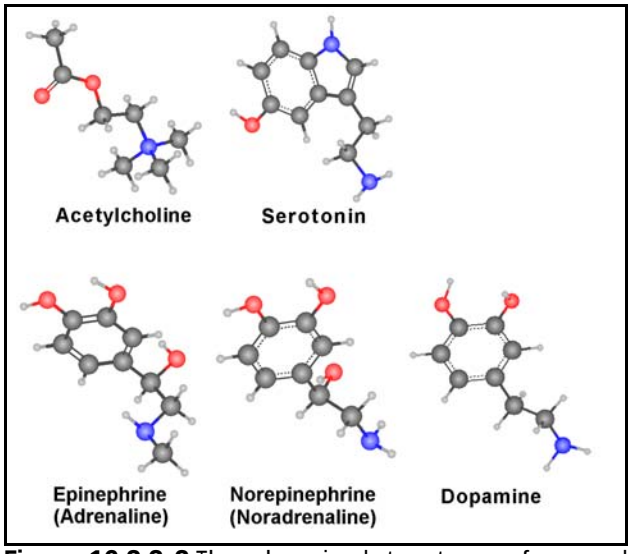

Figure 16.2.2-2 The chemical structures of several neuro-modulators and inhibitors. Molecules in the lower row are all catecholamines and all act as neuro-modulators. Acetylcholine is not an amine. It acts as a neuro-affector agent released by stage 7 neurons. Serotonin is included here as an important agent affecting the neural system, especially in the intestine, but its specific role remains uncertain.

The literature has long discussed the participation of acetylcholine (and sometimes epinephrine and/ or norepinephrine) in the operation of the end-plates of striate muscle. Prior to 1990, similar discussions were held relative to generic smooth muscle.

The common wisdom is that sympathetic stage 7 neuro-affectors release norepinephrine (noradrenaline) and the sympathetic system is frequently described as the adrenergic system. Conversely, the parasympathetic stage 7 neuro-affectors release acetylcholine and the parasympathetic system is frequently described as the cholinergic system. The means by which these agents are employed in muscle activation have not been fully settled.

Following the older common wisdom, the stage 7 neuro-affectors of the enteric system release nitrogen oxide and the enteric system would be described as the nitronergic system.

Stage 7 neuro-affectors interface with smooth muscle through less specific mechanisms. The mechanisms and agents appear to be tailored to support relatively independent muscular structures without interfering with other major muscular structures. The smooth muscle interface does not employ end-plates. It appears to employ the diffusion of agents released by the neuro-affectors in the general vicinity of, and affecting, multiple muscle cells. The primary agents release are not well understood. However, some of the agents are documented. Nitric oxide appears to be the principle neuro-affector agent controlling the intestinal muscles. The primary agent affecting cardiac muscle remains unclear (**Section 20.3**). Estrogen and progesterone are clearly associated with the contractions of the smooth uterine muscles. A fourth class of smooth muscle has been described as multi-unit smooth muscle. However, its detailed definition and mode of operation remains uncertain.

The literature agrees that smooth muscle does not atrophy if it is deprived of its innervation whereas, voluntary (typically striate) muscle normally atrophies in the absence of its innervation.

16.2.2.2.3 Neuro-affectors influencing glandular operation

The neuro-glandular interface has not been studied extensively. This is partly due to the concentration of this interface within the hypothalamus, a difficult to reach element of the animal brain. It may also be due to the variety of technologies required by the successful investigator in this area and the shortcomings of the neuron database based on chemistry. Further details are presented in **Chapter 23** as directed in **Section 16.3**.

16.3 The neuro-glandular interface

The complexity of the neuro–glandular system and its interface with the neural system rivals the complexity of the neural modality itself. This complexity is suggested by **Figure 16.3.1-1**.

This figure justifies providing a new name for the overall modality, the Crine modality.

It shows a potential expanded flow diagram related to the stage 7B, 7D & 7E neuroaffector neurons of **Section 16.1.1.1**. Stage 7B is focused on the hypothalamus-hypophysis and the target tissue. Stage 7A deals with the visual modality and the exocrine sub–modality was not included in the Crine system at the time of creating [**Figure 16.1.1-1**]. The figure can be described as introductory for two reasons,

1. It is difficult to achieve completeness in a figure of this complexity and
2. The relationships illustrated will be more clearly described in **Section 23.3** and **Section 23.4**.

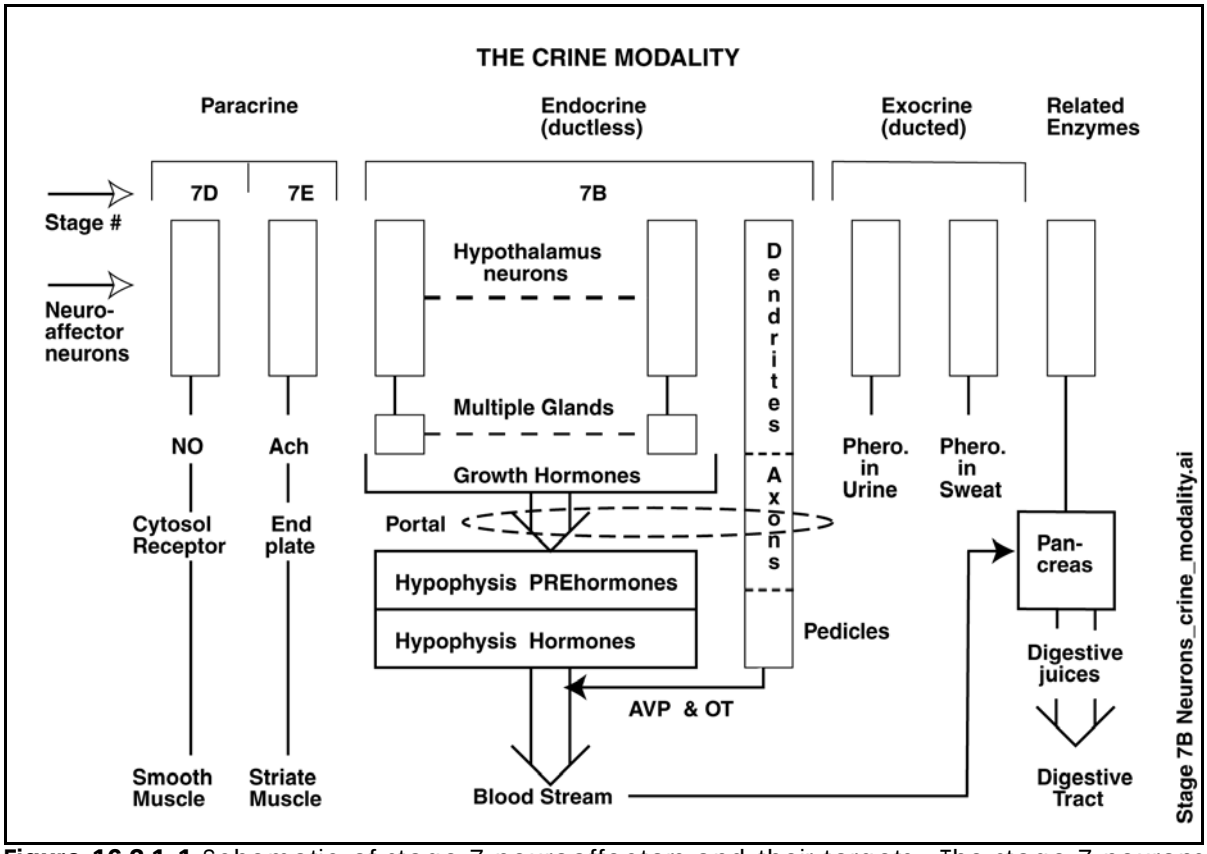

Figure 16.3.1-1 Schematic of stage 7 neuroaffectors and their targets. The stage 7 neurons operate differently when supporting the paracrine, endocrine and exocrine submodalities. Within the paracrine regime, they actually secrete the hormone stimulating the target tissue. When supporting the endocrine submodality, they provide secretions used to create the growth hormones of the hypothalamus, that in turn stimulate the creation of a large number of hormones within the hypothalamus that are distributed to a variety of tissue types via the blood stream. The operation of the exocrine submodality involves more situations. See text.

The neuro–glandular interface related to the endocrine sub–modality has been only superficially studied (primarily by histology) because of its residence almost entirely with the hypothalamus.

This section provides a synopsis of the material in **Section 23.2** and **Section 23.3.**

16.3. Anatomy and physiology of the endocrine system–an overview

The neuro-glandular interface with the endocrine sub–modality has not been studied extensively. This is partly due to the concentration of this interface within the hypothalamus, a difficult to reach element of the animal brain. It may also be due to the variety of technologies required by the successful investigator in this are.

The endocrine sub–modality shares some of the complexity of the neural modality. As a general rule, the glandular modality operates at a slower pace than the neural modality. In many cases, the speed of operation is 100 to 1000 times slower than in the neural modality. Many of the servo loops employed within the glandular modality operate with time constants measured in seconds to days. These time constants are best documented with respect to the activity of the thyroid gland and the TRH and TSH hormones related to it. TRH and TSH are shown in the next figure and addressed more fully in **Section 23.4.3**.

The endocrine sub–modality can be described as operating in stages, not unlike the neural

system. **Figure 16.3.1-2** provides a block diagram expanding and extending stage 7B of the neural block diagram of **Section 16.1.1.** Only the major hormone of endocrinology are shown. Because of the extent and complexity of the glandular modality, **Chapter 23** has been dedicated to the analysis of that modality and its glandular-affectors, hormones. See **section 23.3.1.3** for detailed discussion and complete nomenclature associated with this figure. **Section 23.4** will also expand the endocrine sub–modality into a framework familiar to most readers.

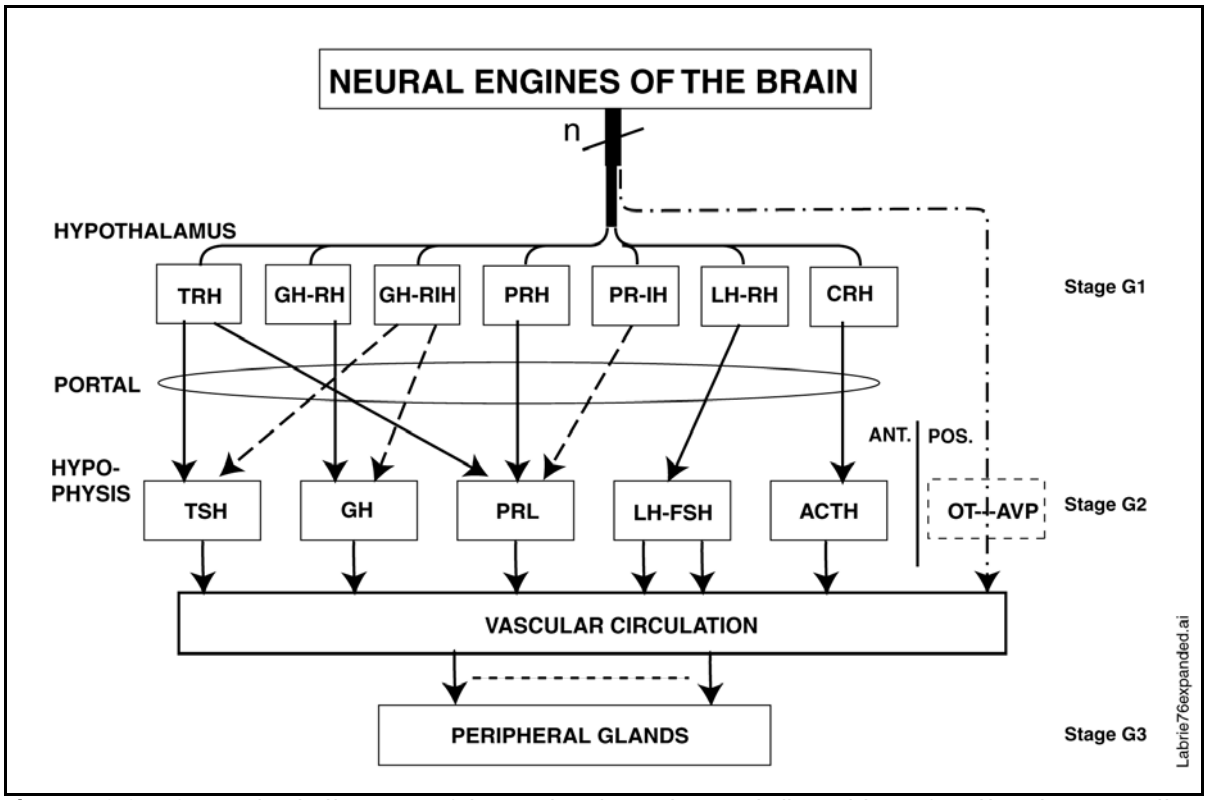

Figure 16.3.1-2 Top Block diagram of the endocrine sub--modality, without feedback, expanding and extending the similar Top Block of the Neural modality. An unknown number, n, of stage 7B neuroaffectors stimulate the hypothalamus. The hormones passing through the portal are considered hormones that stimulate creation of other hormones within the hypophysis but that do not circulate in the blood stream. See text. Compare to Labrie et al., 1976.

In many cases within both the hypothalamus and the hypophysis, large protohormones are present that are cleaved into multiple smaller hormones represented by the abbreviated names above.

The recent text of Melmed & Conn, 2005, does not include any comprehensive graphic similar to that above. Their chapter 1 by Conn, "Introduction to Endocrinology," is only 2.5 pages long and includes no figures.

16.4 (Reserved)

16.5 The neuro-muscular interface EDIT

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While the underlying fundamentals of the architecture of the neuro-muscular interface can not be described authoritatively, it can be described based on its performance. The multiple types

of interaction between the neural and muscular moieties provides great flexibility. This flexibility is further enhanced by the glandular/muscular interface, which is ultimately controlled by the neural system. The neural/muscular system is designed to provide very precise physical responses while the neural/glandular system is designed to control the responses of the organism on a global basis.

The physical responses may involve hundreds of individual muscles in a highly choreographed action controlled by neural commands from the cerebellum of stage 6 in response to instructions from the neurons of stage 5 cognition. The responses are generally in support of conscious cognition (and related closely to declarative memory).

The global responses may involve thousands to millions of muscles (think of hairs standing up on the back of ones neck, and on the morphological extremities) virtually simultaneously. These actions are choreographed by the hypothalamus largely under the control of the non-conscious engines of stage 5 cognition. Only a small number of these activities are reportable via declarative memory.

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Figure 16.5.1-1 from Purves et al[44]. shows a high level caricature of the neural-muscle interface, both afferent and efferent for context, originally by Matthews[45] 40 years earlier. The extensive Matthews paper appears worthy of study. A prior extensive paper by Crowe & Matthews defines much additional information concerning the stage 7 interface with muscles[46].

> In discussing the neuro-effector neurons, a problem in terminology arises. Where efferent signal projection neurons are nominally labeled stage 6, they are in fact identical to all other stage 3 neurons, whether afferent, efferent or present within the stage 5 cognitive areas of the prefrontal cortex. These stage 6 and stage 3 neurons typically include stage 3A encoding neurons that generate action potentials and stage 3B neurons that accept strings of action potentials and demodulate the signals in order to recover the analog waveform. Much of the literature of the neuro-muscular system does not trace a specific signal path back to the originating point of a stage 6 efferent neuron and only focus on the last two millimeters or less of the neuron axon (after and ignoring the presence of any NoR). This makes it difficult to ascertain whether the complete neuron is elongated and truly a stage 6 efferent neuron or whether it is a more focussed stand-alone stage 7 neuron providing the stage 3B demodulating facility following the synaptic interface with a stage 6 neuron.

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[44]Purves, D. Augustine, G. Fitzpatrick, D. et al. eds. (2004) Neuroscience. 3rd Ed. Sunderland, Ma: Sinauer Assoc. page 198

[45]Matthews, P. (1964) Muscle spindles and their motor control *Physiol Rev* vol 44(2), pp 219-288

[46]Crowe, A. & Matthews, P. (1964) The effects of stimulation of static and dynamic fusimotor fibres on the response to stretching of the primary endings of muscle spindles *J Physiol* vol 174, pp 109-131

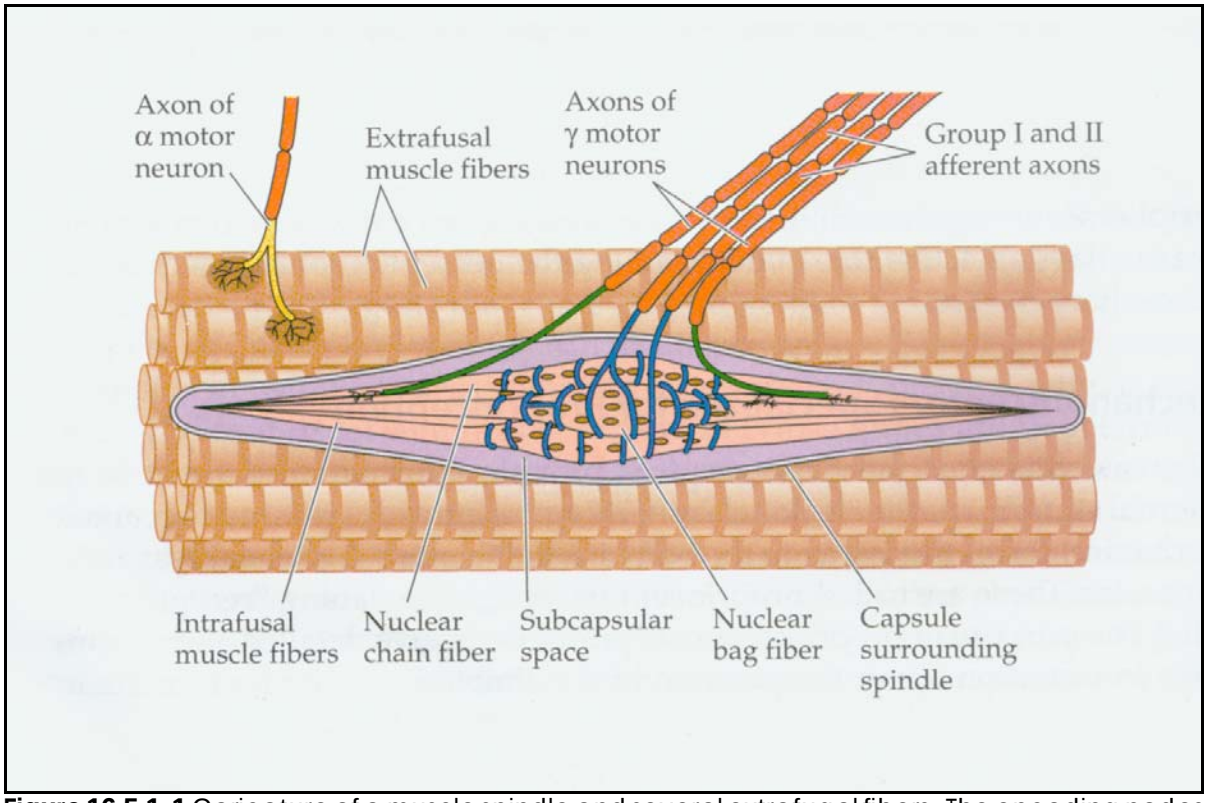

Figure 16.5.1-1 Caricature of a muscle spindle and several extrafugal fibers. The encoding nodes at the denrite/axon interface are clearly shown for the afferent neurons. The aggregation of signals by the arborization of the dendritic structure is also shown. The arrangement of the stage 7 effector neurons is also clearly indicated. After Matthews, 1964 by Purves et al., 2004.

Two distinctly different efferent neuron types are shown in the figure, type α neurons and type γ neurons. Functionally, they are both decoding the action potentials at a capacitively loaded Node of Ranvier at the terminus of the myelinated axon segment and producing an analog signal that is distributed to individual muscle fibers (a stage 3B function).

The representation of the afferent neurons is similar. Both "group I" and "group II" afferent neuron types are also shown in the figure. These are generally labeled spindle type sensory neurons when shown individually in figures. The myelination of these neurons after the first NoR suggest the NoR is the stage 3a encoding element of a complete stage 3 neuron with integrated stage 1 sensing capability. The collection of signals by dendritic structures that aggregate at the stage 3A encoding Node of Ranvier. The summary analog signal is then encoded as an action potential stream and propagated. Notice the figure includes no representations of soma. Ottoson has provided a similar figure (page 134) from 1983 showing slightly more detail relative to the individual muscle fibers.

Figure 16.5.1-2 Shows a schematic of the above caricature using slightly different nomenclature.

Ia afferent neurons– "those originating from muscle spindle primary endings, which are on the central region of both bag and chain fibers (P-D & B page 65)."

Ib afferent neurons– "originate from Golgi tendon organs, which are located exclusively at muscle–tendon or muscle–aponeurosis junctions and not within tendons (P-D & B page 245)." Careful reading of the conventional definition in **Section 16.1.1.2** suggests neurons do not interface with the aponeurosis material but only with the muscle element. The Golgi tendon organs are particularly sensitive to muscle contractions and not to muscle stretching to which they exhibit a high threshold and rapid adaptation.

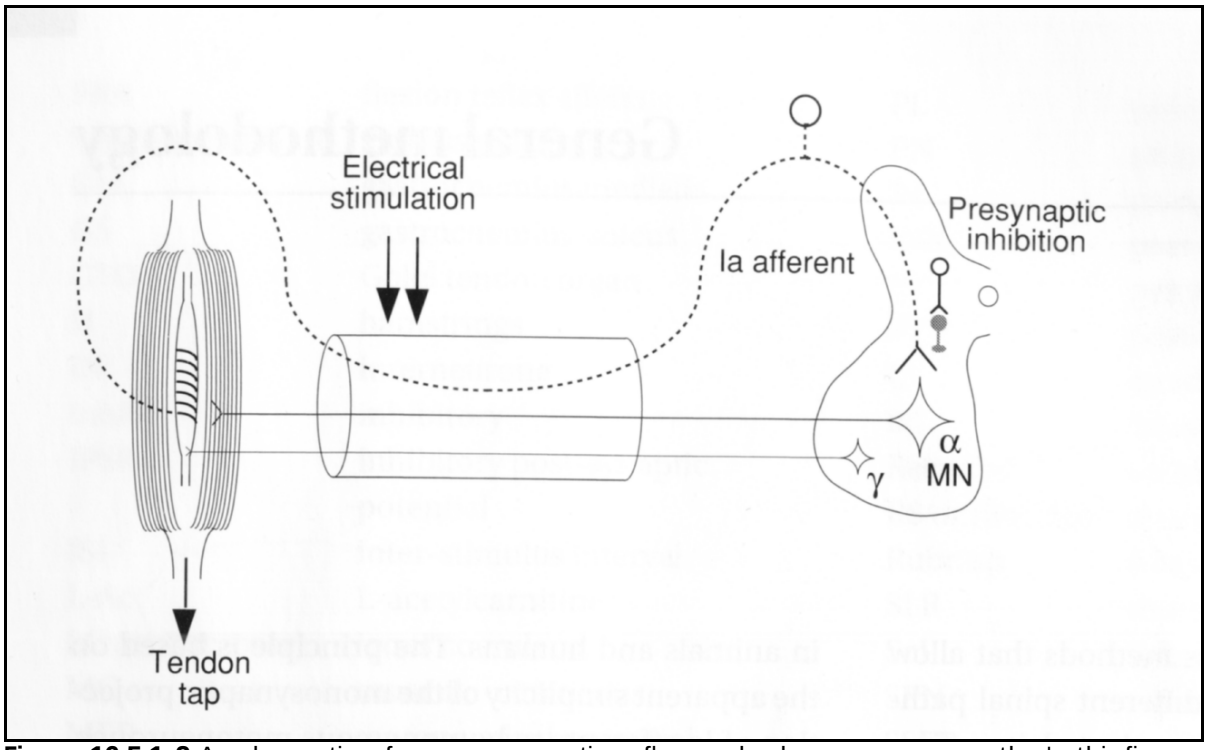

Figure 16.5.1-2 A schematic of a monosynaptic reflex and a homonymous path. In this figure, MN defines the location of motoneurons without defining their point of origin. The assumption is that they originate at a given position along the spinal cord and not in the CNS. "The H reflex is produced by electrical stimulation of 1a afferents, and bypasses muscle spindles." The electrical stimulation occurs somewhere along a nerve (not an individual neuron) and may be limited to non-invasive electrical stimulation. See text. From Pierrot-Deseilligny & Burke, 2005.

P-D & B note specifically that they have omitted the soma of the neurons in the above figure. They have also employed a puckered diamond to caricaturize the synapse in order to simplify their discussions. These may be useful pedagogical techniques. However, they obscure what is really functionally important within the architecture of the neural system. While the positioning of the soma is not functionally important, their location does provide additional information relating to the flow of signal information through the system. Similar, the use of the puckered diamond obscures whether the same afferent neuron continues up the spinal cord to the CNS without involving any synapse (as opposed to multiple Nodes of Ranvier). A similar difficulty arises in determining whether the same afferent neuron originates in the CNS and terminates at the muscle in question or whether there are other synapses and neurons involved in this single path.

In general, the afferent and efferent neurons associated with the spinal cord involve single neurons extending from the sensory receptor to the CNS and from the CNS to the muscle tissue. Reflex arcs at a specific level of the spinal cord generally involve interneurons between the afferent and efferent signal paths. These interneurons are frequently of the stage 3 type and interconnect with the stage 3 afferent and stage 3/6/7 efferent neurons without decoding the action potential signals. The use of an interneuron necessarily introduces two synapses into the reflex path, rather than just one.

The label monosynaptic reflex is meant to suggest only one synapse between the stage 1 afferent sensory neuron and the affected muscle.

There is no assurance the electrical stimulation associated with the H reflex is restricted to a single afferent neural path within the overall nerve being stimulated. This complicates the analysis

considerably.

P-D & B note that the stage 3 action potentials associated with both the Ia & Ib neurons of stage 1 exhibit similar and overlapping propagation velocities (page 245). This relationship is to be expected. They did not provide a number for this parameter.

P-D & B have also defined type Ib interneurons. This terminology is not firmly established and is probably subject to further clarification. They note, "Views about the functional role of Ib pathways have evolved more over the years than for any other spinal circuit (page 244)." They also note on page 245, "these interneurones are co-excited by both type Ia and Ib afferent neurons." Most of the schematics involving Ia and Ib neurons involve caricatures rather than definitive diagrams.

16.5.1 Historical background related to the neural/muscular interface

Pierrot-Deseilligny & Burke (P-D & B) provided an extensive study of the circuitry supporting, and the spinal muscle itself in a 2005 treatise[47]. The treatise is from a physiologist's perspective and relies primarily on non-invasive laboratory techniques. The treatise focuses on the lower human (mammalian) limb. The authors' backgrounds are based on the chemical theory of the neuron. They do not delve into the cytology or histology of individual neurons. "Methods have now been developed to enable indirect but nevertheless valid measurements of spinal interneuronal activity in human subjects, . . This, together with the abnormalities of motor control resulting from lesions in the central nervous system (CNS) and the underlying pathophysiology of movement disorders, is the subject of this book."

Their operational perspective is that the spinal cord is much more than just a pathway. "It is a thesis of this book that the final movement is only that part of the supraspinally derived programme that the spinal cord circuitry deems appropriate. While the capacity of the spinal cord to generate or sustain even simple movements, particularly in human subjects, is limited, the influence that it plays in shaping the final motor output should not be underestimated." This work takes a different view; that it is the CNS (and particularly the stage 6 activity of the cerebellum) that is primary in commanding large groups of muscles to coordinate their activity. The physical spinal cord is indeed a pathway. Only limited neural activity within and near the spinal cord (primarily related to reflex actions (**Section 4.2.3.1**). They focus on the well studied H reflex in their treatise (page xv-xvi).

Recognizing the extent of the material, they note, "For those who want to get to the gist of the matter reasonably quickly each chapter terminates with a resume of its salient points. The resumes can be used on their own without reference to the detailed text.". . . "The final two chapters summarise and synthesise the changes in transmission in spinal pathways during movement and how these changes contribute to motor control." (Page xviii)

The material does not appear to address smooth or cardiac muscle. Page 4 addresses their basic methodology. Their methodology only addresses skeletal muscle under both commanded and reflex activity. While they include considerable experimental data, most of their descriptions of the experiment protocol employ caricatures.

The treatise does not appear to address the chemical synapse at the neuromuscular interface. It does not appear to differentiate between the chemical and electrolytic (or tight) synapses.

Lemon presented a review of the P-D & B treatise[48]. While superficial with regard to the technical

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[47]Pierrot-Deseilligny, E. & Burke, D. (2005) The Circuitry of the Human Spinal Cord: Its Role in Motor Control and Movement Disorders. Cambridge, GB: Cambridge Univ. Press 665 pages; 12 chapters

[48]Lemon, R. (2006) One small step for man *Brain* vol 129, pp 551–554

aspects of the treatise, it did provide some historical perspective leading to the work.

Lemon et al. provided a separate work focused on the physiology of the upper arm muscles[49].

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The major non-hormonal neuro-affectors of the literature include dopamine, epinephrine, norepinephrine, acetylcholine and more recently the simple molecule, nitric oxide. The synthesis of these materials varies significantly, as does their molecular structure. This difference in structure suggests these neuro-affectors affect their targets via different mechanisms.

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Need to introduce sympathetic versus parasympathetic in autonomic subsystems ???

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It is suggested the reader review Chapter 10 talking about the neural system from an anatomy perspective. Swanson published a book on neural architecture in 2003 that was meant for the coffee table[50]. It summarizes his review of the 20th Century common wisdom based on the chemical theory of the neuron and is largely obsolete.

Swanson briefly describes the autonomic nervous system as the "second motor system," and describes its two fundamental identifying features. Each neural path of this system is identified by two neurons in series, one in the brainstem–spinal cord and the other in a peripheral autonomic ganglion. which are referred to as the pre-ganglionic and postganglionic motoneurons of the autonomic system, respectively. Second, he identifies two distinct divisions of the autonomic system, referred to as sympathetic and parasympathetic. Broadly speaking, he notes, "the sympathetic system has short pre-ganglionic (stage 3) and long postganglionic axons (stage 7), uses noradrenaline as a major postganglionic neurotransmitter (stage 7), and tends to act as a whole during stressful situations. In contrast, the parasympathetic system tends to have long pre-ganglionic and short postganglionic axons, use acetylcholine as a major postganglionic (stage 7) neurotransmitter, and acts in a localized way that tends to antagonize the sympathetic system." The stage designations were added.

Most autonomic system innervation is directed toward three cell types: smooth muscle cells, cardiac muscle cells and gland cells.

Swanson summarizes the chemicals released by the stage 7 neurons succinctly.

> "at the neuromuscular junction, nicotinic acetylcholine receptor on the postganglionic membranes mediate the fast synaptic response. It turns out that most if not all neurotransmitter receptors come in flavors or varieties, and this is true for neuromuscular and autonomic ganglion nicotinic receptors, although in both locations they are blocked by curare and, incidentally, stimulated by nicotine (hence the name). The fact that postganglionic parasympathetic neurons release acetylcholine onto visceral targets, whereas postganglionic sympathetic neurons release norepinephrine, has had vastly important implications for pharmacology."

The lack of precision and specificity in the above paragraph illustrates the problems encountere by the chemical theory of the neuron during the 20th Century. There are no poorly defined "flavors or varieties" of neuroreceptors required in the Electrolytic Theory of the Neuron.

Swanson also note another feature of the autonomic system. "Very often, neurotransmitter is not released from a highly specialized synapse like the neuromuscular junction, where the very narrow synaptic cleft assures a one-to-one transfer of information from the presynaptic axon

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[49]Lemon, R. Kirkwood, P. Maier, M. Nakajima, K. & Nathan, P. (2004) Direct and indirect pathways for corticospinal control of upper limb motoneurones in the primate. *Prog Brain Res* vol 143, pp 263–79

[50]Swanson, L. (2003) Brain Architecture. London: Oxford Univ Press pg 149

terminal to a specific region of the post synaptic cell. Instead autonomic neurotransmitters are often released in the vicinity of groups of cells with appropriate receptors, and the transmitters diffuse to interact with appropriate receptors."

Swanson describes the third motor system as the neuroendocrine system centered on the hypothalamus.

Swanson's description of the neural system is consistent with the description of the final common pathway (FCP) defined by Sherrington, illustrated in a figure in Herrick reproduced by Swanson (page 109). In this context, the preganglionic neurons can be considered stage 3 neurons and the postganglionic neurons as stage 7 neurons. Swanson does not address the subject of the Nodes of Ranvier occurring in these neurons nor the character of the signal propagation across these nodes.

Figure 16.5.1-3 summarizes the efferent neural system as envisioned by Swanson. It lacks a discussion of the muscarine acetylcholine receptors, the role of striated muscle in the visceral system and the role of nitric oxide as a stage 7 neuroaffector.

FEATURES OF EFFERENT NEURAL ELEMENTS

Efferent System		Subdivision	Targets	Neuroaffectors
Informal	Formal			
1st motor	Somatomotor		Skeletel Muscles	Acetylcholine (nicotinic)
2nd motor	Autonomic	Sympathetic	Visceral	Norepinephrine
		Parasympathetic	Visceral	Epinephrine
3rd motor	Neuroendocrine		Vascular System	Nitric Oxide

Figure 16.5.1-3 Archaic features of the efferent neural system from Swanson ADD. to complete per text. From Swanson, 2003.

Swanson also summarized the neurotransmitters and neuromodulators of paleocortex of the CNS (pages 149-154) in terms of the work of Dahlstrom and Fuxe. They identified three neurological "systems." System 1 involved noradrenaline which Swanson described as found in the sympathetic division of the autonomic neural system. He says this participation was described in his chapter 6. However that chapter says norepenephrine was the major sympathetic division neurotransmitter. Noradrenaline may have been used as a synonym for norepinephrine. System 2 employed serotonin. System 3 employed dopamine. Non-specific mention was made also of the presence of histamine and GABA.

Figure 16.5.1-4 summarizes a 21st Century interpretation of the efferent materials at the neural/muscular interface, neural/glandular interface, and the neural/cardiocyte interface based on the Electrolytic Theory of the Neuron.

FEATURES OF EFFERENT NEURAL ELEMENTS

Under Development

Efferent System		Subdivision		Targets	Neuroaffectors
Informal	Formal				
1st motor	Somatomotor			**Striated** Muscles	Acetylcholine
				Smooth Muscles	Nitric Oxide
2nd motor	Autonomic	Sympathetic	**(stimulating)**	Visceral	Norepinephrine
		Parasympathetic	**(suppressing)**	Visceral	Epinephrine
3rd motor	Neuroendocrine			Vascular System	Nitric Oxide
Spec. motor	**Cardioid Syst.**			**Cardiocytes**	

Fulton Efferent elements.wpg

Figure 16.5.1-4 21st Century features of the efferent neural/muscular interface. This figure had differentiated between striated and smooth skeletal muscle. This figure has added a special motor category focused on the cardioid system and its specialized cardiocytes (special cells combining analog neural and analog muscular capabilities). This figure has expanded on the functional roles on the elements of the autonomic system. See text. Expanded from Swanson, 2003.

16.5.1.1 Types of muscle interfacing with the neural system BRIEF

There are a variety of muscle tissue used in the animal physiology to achieve various objectives.

1. Striated muscle, also known as skeletal muscle, is the predominant muscle type in the animal physiology (**Section 16.5.1.2.1**). The contraction of this muscle type is the primary means of locomotion, and in more specialized motions, in animals.

2. Smooth muscle is fundamentally different from striated muscle. ***Smooth muscle is frequently used in applications requiring continuous (long term) contraction*** (**Section 16.5.1.2.2**). To alleviate this contraction, a different mechanism is needed than that provided conventionally by the neuro-affectors. This is the role in the NO releasing neuro-affectors.

3. After this brief reference to the subject of cardiocytes and the muscular cells of the intestinal tract will not be discussed in detail in this chapter. They are discussed elsewhere in this work (**Section 20.3** and **Section 20.2** respectively). These muscle-like tissue are actually hybrids of neural and muscular (and/or glandular) tissue.

4. A type of muscle is found embedded in the walls of the vascular system. Its specific form has not been addressed in this work.

5. Another type of hybrid muscle is used in the dual muscle arrangement used in the ocular muscles of vision. The individual ocular muscles consist of two individually controlled striated muscle elements. The first is the conventional “slow” striated muscle used to point converge the

eyes. The second is a "fast" striated muscle used to generate the very rapid but low amplitude tremor of the eyes (up to 50-90 Hertz but amplitudes of only 10 microns or less). See **Section 8.2.**

16.5.1.2 Efferents of the neural system affecting muscular tissue

16.5.1.2.1 Acetylcholine as a stimulant of striated muscle

Acetylcholine plays a prominent role in the conceptual chemical theory of the neuron. There is a wide variety of papers in the pharmacological and histological literature but little in the molecular chemistry arena. Much of the discussion of acetylcholine relies upon its interaction with specific receptors of either the nicotinic or muscarinic type. It is difficult to find agreed upon descriptions of the subsequent reactions in or on the membrane of the target cell.

It is difficult to determine the precise role of acetylcholine from the literature. As late as 1998, Caulfield and Birdsall said[51],

> "Actions of acetylcholine in the periphery are the result of activation of either the ionotropic nicotinic receptor or the metabotropic muscarinic receptor. In the mammalian central nervous system (CNS), both nicotinic and muscarinic receptor subtypes are present on neurons, although there is as yet very limited evidence for a physiological role for nicotinic receptors in synaptic function in the mammalian brain (Role and Berg, 1996)."

Although the title of their article suggests otherwise, it contained little material related to acetylcholine.

It has been difficult to determine whether acetylcholine is a neurotransmitter or a neuromodulator in the conventional chemical context. Sarter and Bruno made this point in 1997[52],

> "Previous efforts aimed at attributing discrete behavioral functions to cortical cholinergic afferents have not resulted in a generally accepted hypothesis about the behavioral functions mediated by this system. Moreover, attempts to develop such a unifying hypothesis have been presumed to be unproductive considering the widespread innervation of the cortex by basal forebrain cholinergic neurons. In contrast to previous descriptions of the role of cortical acetylcholine (ACh) in specific behavioral phenomena (e.g., mediation of the behavioral effects of reward loss) or mnemonic entities (e.g., working or reference memory), cortical ACh is hypothesized to modulate the general efficacy of the cortical processing of sensory or associational information. Specifically, cortical cholinergic inputs mediate the subjects' abilities to detect and select stimuli and associations for extended processing and to allocate the appropriate processing resources to these functions."

Swanson has offered a brief discussion of acetylcholine including a series of definitions (pages 99-102). He notes there may be subtle differences between many of his terms which he describes as "essentially interchangeable." He notes the role of acetylcholine is most understood with respect to synapses known as neuromuscular junctions and found in the somatomotor axons on striated muscle cells. He describes these synapses as having a cleft "with a fairly rigid gap of 20-30 nanometers between the pre- and post synaptic membranes." He asserts the receptors on the most synaptic muscle membrane are blocked by a variety of natural and man-made poisons. The somatomotor system controls the muscles of the subject. His framework is too narrow for the purposes of this work.

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[51]Caulfield, M. & Birdsall, N. (1998) International Union of Pharmacology. XVII. Classification of Muscarinic Acetylcholine Receptors *Pharmacol Rev* vol 50(2), pp 279-290

[52]Sarter, M. & Bruno, J. (1997) Cognitive functions of cortical acetylcholine: toward a unifying hypothesis *Brain Res Rev* vol 23(1-2), pp 28-46

Acetylcholine can be considered a paracrine hormone. As such, it is capable of exciting only one associated muscle cell or it can excite a group of muscle cells over a short distance depending on the topography of the secretory junction. **Figure 16.5.1-5** shows the accepted role of acetylcholine in neuromuscular junctions (among the biochemistry community) where the cleft is confining. In the context of this work, the junction shown involves a stage 7 neuroaffector operating as a paracrine hormone source (**Section 16.1.4**). Only the secretory portion of the neuron is described. It was presented as an example of the use of the SBGN markup language. The control mechanism whereby the electrical portion of the neuron causes the release of acetylcholine is not shown. The symbols used are those of the Systems Biology Graphical Notation, SBGN, markup language discussed in **Section 1.1.6** and detailed in Novere et al[53].

Care must be taken with this figure. No citation was given for the origin of, or additional justification for this figure, Novere et al. did not differentiate between a striate and smooth muscle. Normally the striate muscle relaxes spontaneously following the cessation of stimulation by ACh. Conversely, smooth muscle contracts spontaneously following cessation of its relaxation caused by exposure to nitric oxide (**Section 16.5.1.2.2**). The SNARE box is introduced in the cleft in order to account for a variety of unknowns related to this complex figure. It is not clear why ACh from within the cleft needs to be reconstituted within the synaptic button as shown**.** **Section 16.5.2.2** describes the conventional view that acetylcholine is readily created *in vivo* from the combining of choline and acetyl coenzyme A.

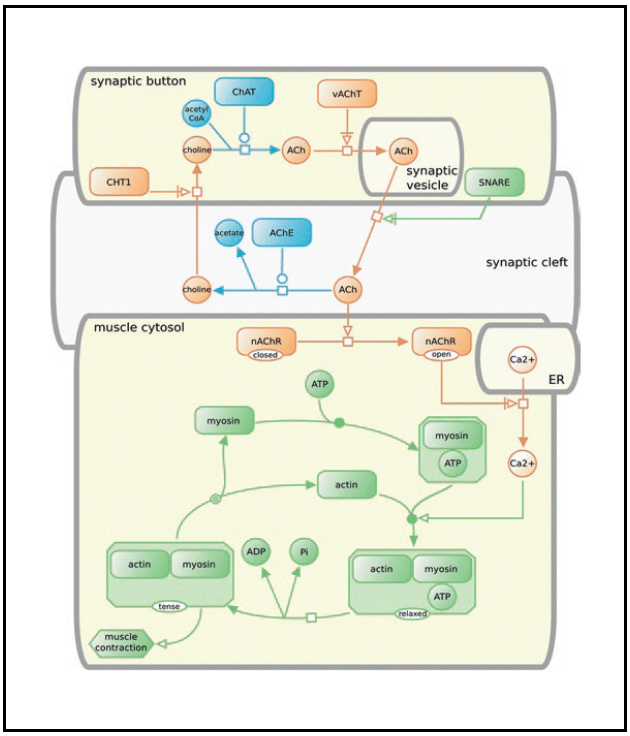

Figure 16.5.1-5 Role of acetylcholine in striated muscle contractions. Caution is advised. The figure is overly complex for the purpose at hand. See text. Figure 3a from Novere et al., 2009. No ultimate source of the figure was provided by Novere et al.

It appears the label synaptic button is equivalent to the major portion of the secretory portion of the neuron. The source of the chemicals within the button are not specified and the character of the "macromolecule" labeled SNARE is not identified. Pfeffer has provided a review of the SNARE hypothesis in a 20 page paper[54]. The paper was not the source of the figure. Her work was based primarily on yeasts but may be applicable to neuromuscular junctions. She sought to avoid the fanciful labels used by some neuro-scientists but introduces her own. This hypothesis depends on a very complex concept not easily understood by the outside investigator. SNARE is an abbreviation for "soluble NSF attachment protein receptor (SNARE). The paper was followed up by Ganley, Espinosa & Pfeffer twelve years later. The SNARE concept has not been widely adopted. As noted in **Section 1.1.6**, the SBGN of 2009 cannot handle voltage or current controlled chemical processes.

16.5.1.2.2 Nitric oxide, NO, the stimulant of smooth muscle

The use of nitric oxide as a stimulant released by stage 7 neuroaffector neurons provides a much

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[53]Novere, N. Hucka, M. Mi, H. et al. (2009) The Systems Biology Graphical Notation *Nature Biotech* vol 27, pp 735-741

[54]Pfeffer, S. (1996) Transport vesicle docking: Snares and Associates *Ann Rev Cell Devel Biol* vol 12, pp 441-461

greater flexibility to the neuro-motor system than would otherwise be available. It allows the close physical presence of striated and smooth muscle without their being excited by a common stimulant, acetylcholine.

The molecular structure of NO can take on several forms based on its environment. The most probable structure for nitric oxide when acting as a hormone is typically that of a free radical, ·NO (note the dot in front of the N). Structurally, ·NO can be described as $(N=O)^+$ but many other forms can be found in the literature. While important in chemical synthesis involving valence chemistry, the sign of the exponent is of no consequence in the regime of coordinate chemistry.

The nominal d-value of the structure, N=O, is generally shown as 1.18 Angstrom but other investigators show the lower bond as firm but the upper bond as resonant. In that case, the d-value is typically shown as 1.21 Angstrom between the centers of the two atoms.

It is possible the free-radical, ·NO will react with some other species before becoming the active stimulant of smooth muscle. Whether ·NO is the active ligand in stimulating smooth muscle needs more verification before describing the actual stimulant-receptor interface. Further effort should be made to quantify the structure of ·NO when present in the biological environment.

Page 60-62 of Henry & Norman, with a figure attributed to Zigmond et al. (1999), discusses ·N=O operation within a synapse in a very argumentive cartoon. It shows the ·N=O being formed within the post-synaptic "element." The presynaptic element is not identified as a neuron. The figure would be much closer to functional reality if; the postsynaptic element was re-labeled a stage 7 neuron, the presynaptic element was renamed a smooth muscle cell and the neuron and glial cells shown were removed, or labeled the non-functional limits of the synaptic cleft. They do contribute, "The half-life of ·N=O is less than 30s; it decays spontaneously to nitrite." They do not explain why the ·N=O is not converted to NO_2 since the result of the decay depends on the surrounding environment.

Schulz & Triggle speculated extensively on the role of nitric oxide in smooth and cardiac muscle function in 1994[55]. They lacked an adequate model of what they were trying to analyze. This prevented their developing a rational theory. **Section 20.3** addresses the role of ·N=O with respect to the cardiocytes.

16.5.1.2.3 Epinephrine and Norepinephrine as stimulants of muscles generally EMPTY

Epinephrine and norepinephrine are hormones of the glandular system and are not associated with *neural* signaling. As noted in **Section 16.4.2**, epinephrine can affect muscles generally if the muscle tissue provides an appropriate epinephrine receptor site ***or*** if the associated stage 7 neuroaffector neuron incorporates such a receptor site.

16.5.2 Chemistry of the neural/ muscular interface–stage7 neurons

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This work makes a clear delineation between the pedicles of stage 7 neurons that secrete complex chemicals (and labeled neuro-muscular junctions or neuro-glandular interfaces) from the pedicles of stage 1-6 neurons that only communicate with other neurites of orthodromic neurons. These two groups exhibit significantly different characteristics. In this work, all connections between axons and neurites are functionally identical. These junctions include the neural junctions within the outer lemma of a neuron, between two axon segments semi-enclosed with in the lemma (and called Nodes of Ranvier), and junctions that are clearly separating axon segments from neurite segments (and called synapses).

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[55]Schulz, R. & Triggle, C. (1994) Role of NO in vascular smooth muscle and cardiac muscle function *TiPS* vol 15, pp 255-259

As noted by Zucker[56], "From 1952 to about 1985, exocytosis in neurons was studied mainly at neuromuscular junctions and selected giant synapses by electrophysiology and electron microscopy. Early advances were followed by a period of relative stagnation as these techniques appeared to reach their full potential." Expanding briefly, the foundation of the discussion of synapses was developed based primarily on atypical stage 7 neuromuscular junctions and the investigation of non-mammalian, non-phasic giant axons of the squid. The stage 7 investigations, and the description of electrical currents using ionic symbolisms (Na^+ for a entering cell current, K^+ for an exiting current, etc.) were the major element that caused a long period where the discussion of neuron operation was dominated by the chemical theory of the neuron. It is important to note, the scientific record of the neuron is based entirely on microamperometric measurements. Great efforts have been made to demonstrate passage of chemical constituents through the neuron lemma under operational conditions without reportable positive results.

> The Na^+ current associated with the chemical theory of the neuron is actually due to an electron charge leaving the axoplasm of the neuron under The Electrolytic Theory of the Neuron. Similarly, the K^+ current of the chemical theory is actually an electron charge entering the axoplasm via the electrostenolytic power supply (**Section 1.2.5** and **Section 3.1.1 in PBH**[57]).

As shown earlier in this work, the neuron does not rely upon the passage of ions, like Na^+ and K^+ or Cl^- through its membranes for neural operations. It does depend on the ionic transport of these materials when bound to other atoms and molecules for homeostasis. The actual operation of the neuroactive part of a neuron, excluding homeostatic operations, is shown in **Figure 16.5.2-1** for Stage 2 through stage 6 neurons as developed in **Section 1.2.2.**

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[56]Zucker, R. (1996) Exocytosis: a molecular and physiological perspective *Neuron* vol 17, pp 1049-1055

[57]Fulton, J (2008) Hearing: A 21st Century Paradigm. Bloomington, In: Trafford *on line* as "Processes in Biological Hearing," https://neuronresearch.net/hearing

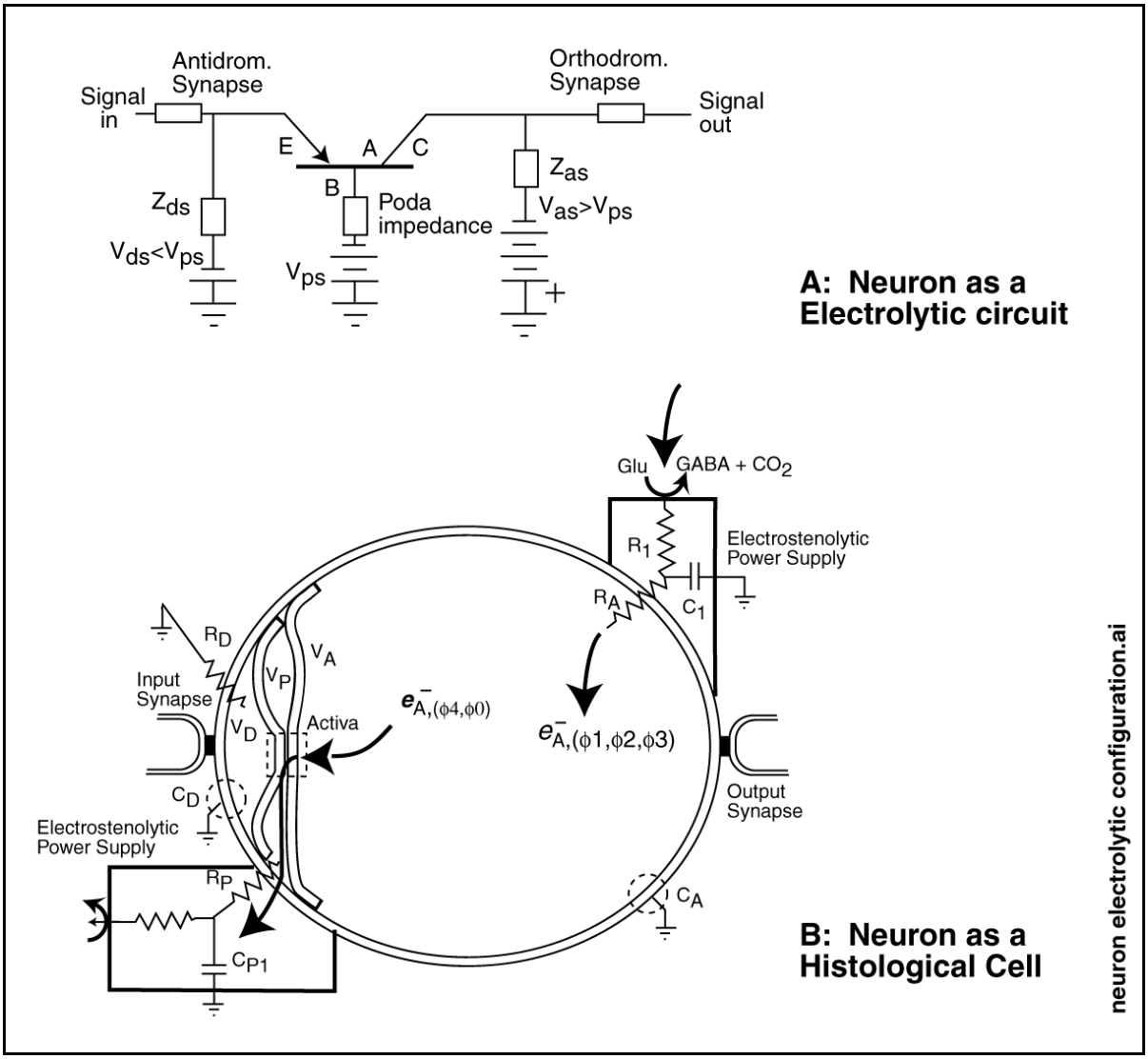

Figure 16.5.2-1 Schematic and histological view of a stage 2 through 6 neuron. A; the fundamental schematic of any stage 2 through stage 6 neuron. B; the histological configuration of any stage 2 through stage 6 neuron. Electrons are supplied to the axon chamber by the electrostenolytic power supply at upper right. Electrons leave the axon chamber via the Activa and the poditic circuit at lower left. The net electron charge on the axolemma capacitance, C_A, determines the potential of the axoplasm. C_A is part of the impedance Z_{as} in frame A.

Stage 7 neurons are more complex in that the output synapse is drastically changed in character and function. The electrical synapse (frequently referred to as a tight junction) is replaced by a chemical synapse. Thus, the pedicle not only reflects the potential of the axoplasm but releases chemicals, created within the pedicle and stored in vesicles, by exocytosis. These additional processes will be developed in the following sections.

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The literature contains a wide variety of discussions of neurotransmitters, neuromodulators and neuromediators in the absence of a framework in which to define these terms precisely. **Section 3.5.4** provided a framework for defining the neurotransmitter and neuro modulators involved in nominal neuron operation. However, that left a large number of pharmacological materials

undefined. This section is designed to provide a framework for these materials. It will adopt the distinction made by Karczmar et al[58]., "It must be further clarified that the term "modulator," as used in this book, refers solely to endogenous or bioactive substances, but not to pharmacological agents or toxins." Pharmaceuticals are primarily used to replace or inhibit the endogenous materials.

The challenge is simplified if the blood-brain barrier is used as a dividing line between those chemicals found in or injected into the CNS space and those chemicals found outside of the CNS space.

As shown beginning with Section 16.5, the generic stage 7 neuroaffector is capable of producing and secreting a range of chemical materials, including proteins. **Chapter 23** will explore additional possibilities. It is only a question of genetic programming that determines whether it develops a secretory capability and what it secretes when excited.

Many other types of non-neuron cells are also capable of producing and secreting complex chemicals. As an example, the retinal pigment epithelium produces and secretes the chromophores of vision without apparent direction from the neural system.

Based on this capability, it is proposed that only the stage 1 sensory and stage 7 affector neurons secrete these specialized materials. Stage 2 through 6 neurons are non-secretory and depend on electrons and holes for neurotransmission.

As examples, the visual sensory neurons produce and secrete protein materials forming their disks, while the auditory sensory neurons produce but do not secrete protein materials to form their cilia.

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Ganong has described a number of materials found within the spinal chord as neuromediators (page52). He did not list these materials. By extracting the materials discussed in his text, the following listing can be prepared. ***His listing did not include nitric oxide, NO.*** It is added here for discussion purposes.

Material	Archaic Source Descriptors	Descriptive functions
Norepinephrine	Adrenergic neurons	
Dopamine	Dopanergic neurons	
Serotonin	Serotonergic neurons	
acetylcholine	Cholinergic neurons	
(nitric oxide)		

He has also defined direct and indirect inhibition but in a very complex time sensitive manner (page 53).

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[58]Karczmar, A. Koketsu, K. & Nishi, S. (1986) Autonomic and Enteric Ganglia. NY: Plenum Press pg 65

16.5.2.1 The molecular structure of acetylcholine ADD

Figure 16.5.2-2 shows the chemical structure of acetylcholine. While it is nitrogenous, and therefore an amine, strictly speaking it is not an amino acid, or the derivative of an amino acid. The molecule is susceptible to dissociation at the oxygen bond closest to the nitrogen.

16.5.2.2 The biological formation of acetylcholine ADD

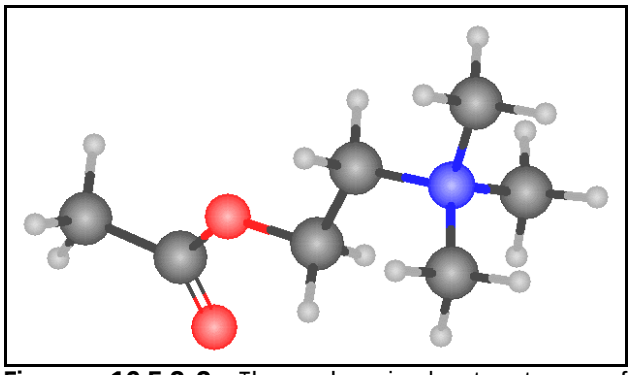

Figure 16.5.2-2 The chemical structure of acetylcholine.

Acetylcholine is synthesized biologically from choline and acetyl coenzyme A, through a complex rearrangement. **Figure 16.5.2-3** shows the resultant structure. Acetylcholine is formed with the pedicles of stage 7 neurons (neuroaffectors).

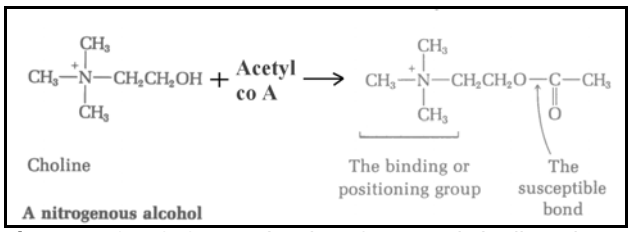

Figure 16.5.2-3 Synthesis of acetylcholine in a typical stage 7 neuroaffector. The reaction is mediated by the enzyme, Choline acetylase. It is stored in clear synaptic vesicles.

16.5.2.3 The molecular structure of nitric oxide

Nitric oxide is a simple free radical shown generally as –N=O, or ·NO. It has an average mass of 30.006 Da. ChemSpider catalogues it under the ID of 127983. Both of the atoms in this free radical have incomplete inner electron shells. This provides ·NO a great range of activity within the chemical field. Its participation could be via valence chemistry or coordinate chemistry. Its short lifetime as a free radical may be an important factor in its stimulation of smooth muscle. Most investigators have suggested that NO, in some form, is able to pass through the smooth muscle lemma with ease.

Under the valence chemistry regime, Nitric oxide is described as a free radical, i.e., it has an unpaired electron, which is sometimes denoted by a dot in its chemical formula, i.e., ·NO. Nitric oxide is also a heteronuclear diatomic molecule.

Nitric oxide has only been recognized as a neuro-affector since the 1980's. This recognition of the role of nitric oxide has been expanding rapidly since 1990. It appears to be the primary neuro-affector of smooth muscle within the cardiac, vascular and other systems. The full extent of this role is still unclear.

The mechanism of nitric oxide generation has been explored extensively *in-vitro* and through stereochemical modeling. This section will review the fundamental chemistry and **Section 16.5.2.4** will review the information available concerning the enzymatic production of neuronal nitric oxide (NO) by neuronal nitric oxide synthase (nNOS). However, there has been no known discussion of how the generation and release of Nitric oxide is controlled by the neural system *in-vivo*. Proposals in this area are presented in **Section 16.5.2.5**.

Nitric oxide is now known as the endothelium-derived relaxing factor (EDRF), a hormone. Stryer notes verbosely[59], "The endothelium (inner lining) of blood vessels uses nitric oxide to signal the surrounding smooth muscle to relax, thus resulting in vasodilation and increasing blood flow. Nitric oxide is highly reactive (having a lifetime of a few seconds), yet diffuses freely across membranes. These attributes make nitric oxide ideal for a transient paracrine (between adjacent cells) and autocrine (within a single cell) signaling molecule." The autocrine designation and function are not supported in this work. See **Section 16.5.3.3**. Marin & Rodriguez-Martinez indicate EDRF was only identified in 1980 and it was in 1987 that Palmer et al. demonstrated that EDRF was in fact NO.

16.5.2.4 The biological formation of nitric oxide

Stuehr presented a major paper on the enzymes of the L-Arginine involved in the production of the free radical nitric oxide, ·NO, in 2004[60]. Stuehr was working in the nutrition area but was aware of the growing interest in the free radical, ·NO, in a broader area of both physiology and medicine. **Figure 16.5.2-4** reproduces figure 1 of Stuehr. The figure is very similar to figure 10 of Spindel (2005). Stuehr notes,

"A family of enzymes called the NO synthases (NOSs, EC1.14.13.39) catalyze the oxidation of Arg to NO and L-citrulline, with NADPH and O2 serving as cosubstrates (6). The NOSs first hydroxylate a terminal guanidino nitrogen of Arg to generate N-hydroxy-L-arginine (NOHA) as an enzyme-bound intermediate. NOHA is then oxidized further by the enzyme to generate NO plus L-citrulline (Fig. 1). Three related NOSs are expressed in mammals, along with several splice variants . NOS-like enzymes are also coded for in the genomes of most life forms, including bacteria. The mammalian NOSs have a similar structure and composition. They are all homodimeric, heme-containing flavoproteins. The NOS flavins transfer NADPH-derived electrons to the heme (Shown in Figure 2).

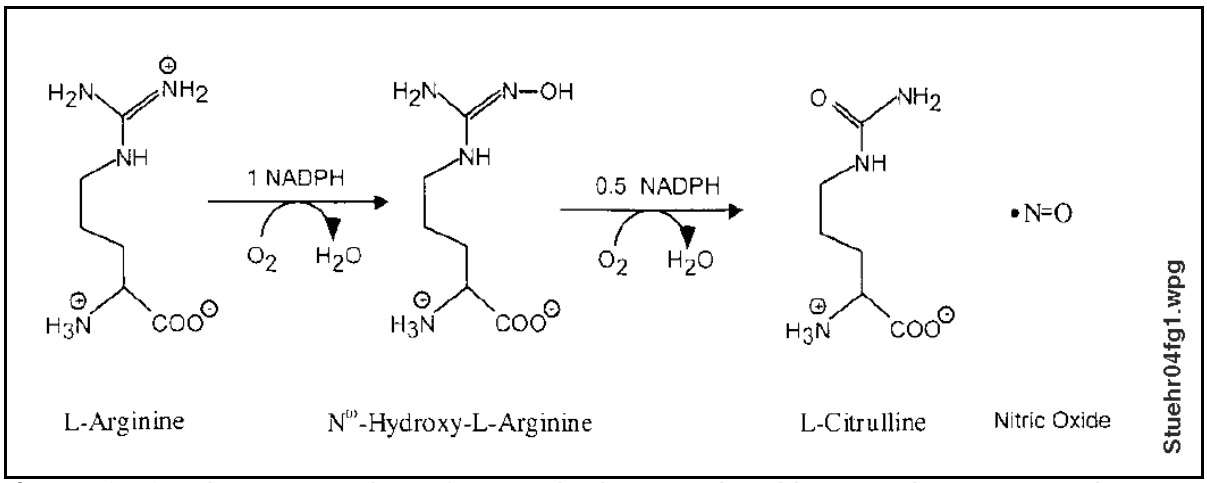

Figure 16.5.2-4 The two reactions of NO synthesis as catalyzed by NOS. The NADPH and oxygen requirements of each reaction are shown. From Stuehr, 2004.

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[59] Stryer, L. (1995). Biochemistry, 4th Edition. W.H. Freeman and Company. p. 732. ISBN 0-7167-2009-4.

[60] Stuehr, D. (2004) Enzymes of the L-Arginine to Nitric Oxide Pathway *J Nutrition* pp 2748S-2751S

Stuehr focuses his attention on the role Heme plays in the overall creation of ·NO. His discussion is outside the scope of interest here. A full discussion of the creation of the free-radical is found in **Section 16.6.1.1.**

Ortiz et al. have provided citations, including Stuehr (2004), and further discussion and data on the nitric oxide synthase, NOS[61].

Knight & Landweber published a paper addressing the genetic code involved in arginine to citruline conversion[62]. It also reviewed the basics of RNA coding as of that time. Note citrulline is a non-protein amino-acid.

16.5.2.4.1 The stereo-specificity of L-arginine

The pores of type 3(arg) lemma are stereo-specific for L-arginine. Once L-arginine has entered the cytosol, it attaches to an unidentified nuclear feature. However, no reaction creating L-citrulline and NO will occur unless an electron is transferred to the L-arginine complex from the axoplasm of the neuron through the lemma. Following the reaction, L-citrulline is no longer a satisfactory stereochemical partner at the reaction site and it will drift off into the surrounding cytosol. Marin & Rodriguez-Martinez (**Section 16.5.3.3**) indicate citrulline is recycled to a derivative of L-arginine in a closed loop operation.

Ghosh & Salerno have provided a substantial paper including a discussion of the binding sites of the L-arginine molecule[63]. The molecule is known to bind with a wide variety of materials. The list of Ghosh & Salerno is not exhaustive. Most of their potential binding sites do not appear to be relevant to the chemistry of the stage 7 neuroaffector neuron.

Mansuy & Boucher have offered additional information on the stereo-specific binding of L-arginine in their proposed configuration[64] reproduced from the work of Crane et al[65]. While providing additional detail about the potential binding of L-arginine, the material does not establish that their configuration has any relationship to the release of NO by the neural system *in-vivo*. They do focus on the cleavage of the CN(OH) bond of NOHA and the formation of citrulline and NO. Their summary is important. After reviewing the applicability of their work to NOS II, they note the following. "Thus a good NO-producing quanidine substrate for the two latter isozymes (NOS I and NOS III) remains to be found." While their search was broad, it did not include the asymmetrical lipids of biological lemmas.

As in the case of the stereo-specificity of glutamate, it is the carboxyl terminus of L-arginine that is of primary interest with regard to its binding to the type 5 lemma of the neuron. The remainder of the molecular backbone may contribute secondary features in this binding.

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[61]Ortiz de Montellano, P. Nishida, C. Rodriguez-Crespo, I. & Gerber, N. (1998) Nitric oxide synthase structure and electron transfer *Drug Metab Disposition* vol 26(12), pp 1185-1189

[62]Knight, R. & Landweber, L. (1998) Rhyme or reason: RNA-arginine interactions and the genetic code Chem Biol vol 5, pp R215-R220 http://biomednet.com/elecref/10745521005R0215
0

[63]Ghosh, D. & Salerno, J. (2003) Nitric oxide synthases: domain structure and alignment in enzyme function and control *Front Biosci* vol 8, pp d193-209 [PubMed: 12456347]

[64]Mansuy, D. & Boucher, J-L. (2004) Alternative nitric oxide-producing substrates for NO synthases *Free Rad Biol Med* vol 37(8), pp 1105-1121

[65]Crane, B. Arvai, A. Ghosh, D. et al. (1998) Structure of nitric oxide synthase oxygenase dimer with pterin and substrate *Science* vol 279, pp 2121-2126

It is interesting to note that glutamic acid, L-arginine and hemoglobin all have exposed carboxyl groups that can participate stereo-chemically with the external structures of type 2 neurolemma.

The geometry of the arginine molecule is shown in **Figure 16.5.2-5** along with its reaction product, citrulline. In a different context, Lehninger indicates citrulline is the precursor of arginine (page 73). The carboxyl group in these molecules is arranged very similarly to that in glutamic acid and potentially one of the carboxyl groups of hemoglobin. The reaction converting arginine to citrulline clearly requires two atoms of oxygen. However, the reaction forming citrulline and the release of NO is apparently quite complex. It probably involves a second stereo-specific interaction with hemoglobin, the most readily available source of oxygen within the body. Alternately one of the closely related cytochromes may replace the hemoglobin. Mansuy & Boucher focus on cytochrome P450 (pg 1107).

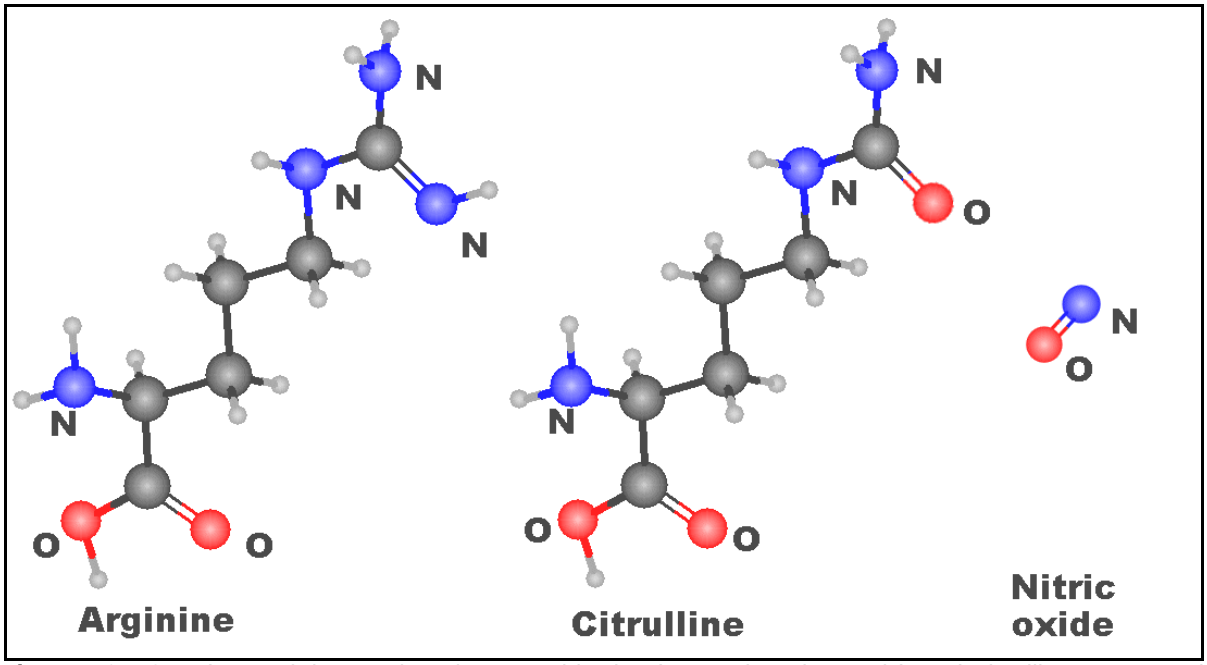

Figure 16.5.2-5 The arginine molecule, a positively charged amino acid and citrulline, a neutral molecule. The positive form of arginine has two hydrogens associated with the upper right nitrogen. The carboxyl group, and adjacent structures, form an excellent structure for stereo-specific union with the nuclear body within the cytosol of the neuroaffector neurons.

The chemistry of the reaction of L-arginine and an oxygen bearing reactant to release NO is the subject of considerable discussion. Even the question of whether the cytochromes can capture and release oxygen in support of such a reaction appears to be clouded by antagonistic articles in the literature. The 1970 edition of Lehninger makes a clear distinction between hemoglobin as an oxygen carrier and the cytochromes as electron carriers (page 377). On the other hand, he describes the oxygenated hemoglobin as oxyhemoglobin rather than dioxyhemoglobin as used by more recent authors. The journal, Free Radical Biology & Medicine, has prepared a series of reviews concerning NO donors[66] (although their web presence is not quite as advertised). Mansuy Boucher & Clement have provided a variety of potential reactions in one

[66]King, S. B. Serial Review: Mechanisms and Novel Directions in the Biological Applications of Nitric Oxide Donors http://www.sfrbm.org/journal.cfm The forum was inactive in early 2008

of these articles[67]. Mansuy & Boucher have provided a recent review[68]. They conclude their Discussion and their Abstract (both restricted to enzymatic reactions) with the following references to NOS I and NOS III: "Thus, a good NO-producing quanidine substrate for the two latter isozymes remains to be found." The summary includes a variety of potential structures and reactions.

The proposed summary electrolytic reaction chemistry is shown in **Figure 16.5.2-6**. It is the same as detailed in the literature. The arginine takes up a stereo-specific position on the molecularly asymmetrical type 2(Arg) lemma of the neuro-affector and is held there by hydrogen bonds associated with the two oxygen ions of the carboxyl ligand. The electrical field associated with the arginine is established by its electrical connection with the axoplasm of the neuro-affector. An excited pair of oxygen atoms are made available to the arginine by a nearby source tentatively identified as a cytochrome. Whether this source is also stereo-specifically associated with the lemma or with arginine itself is not clear. The excited oxygen is believed to begin a cleavage of the N^{ω} atom by joining to the arginine as shown. The resulting structure is known as NOHLA, Nitrogen-hydroxy-L-arginine. This structure remains stereochemically associated with the lemma and resolves into L-citrulline by the freeing of a nitric oxide molecule as shown on the right. The L-citrulline is no longer attracted to the type 2(Arg) specific lemma and drifts away from the reaction site. The site is now available for occupancy by another arginine molecule.

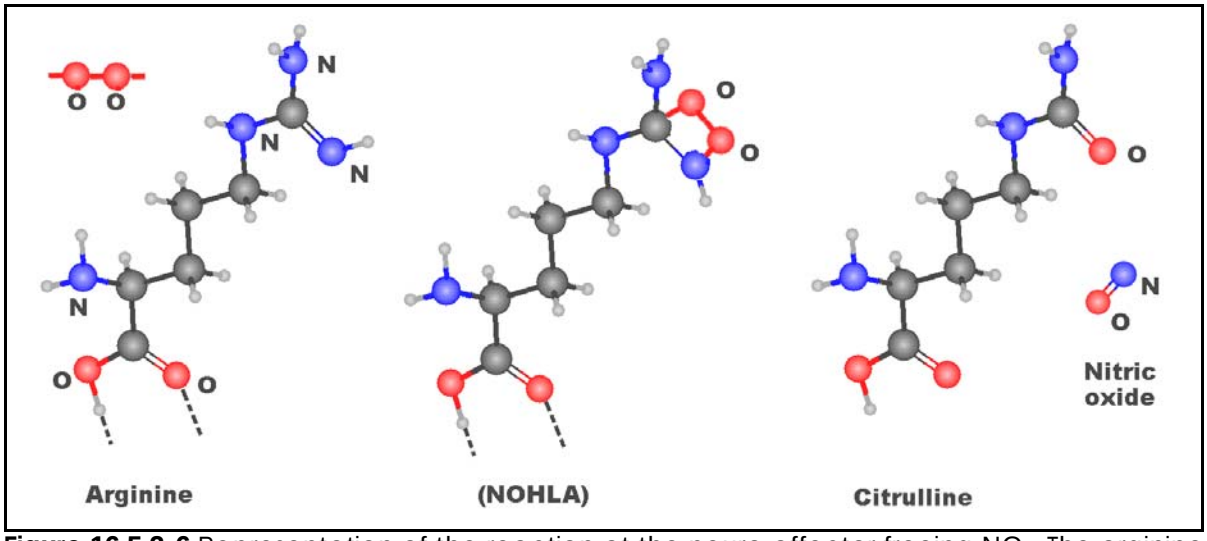

Figure 16.5.2-6 Representation of the reaction at the neuro-affector freeing NO. The arginine is shown held stereochemically to the type 2(Arg) lemma by hydrogen bonds. The excited oxygen attacks the molecule and causes a number of rearrangements (one of which is shown in the center of the figure, each of which is described by the label NOHLA. The final rearrangement results in the formation of citrulline and nitric oxide, both of which are free to leave the surface of the lemma.

The number of type 3(arg) sites (pores) associated with each neuro-affector neuron is not known but is is likely to be a large number able to pass a significant number of nitric oxide molecules per minute. Similarly, the precise operation of the neuron supporting this process is not known. It could be operating as a phasic neuron with the axon exhibiting individual action potentials or the neuron could be operating as decoding stellite neuron, in which case, the axoplasm would proceed to exhibit a potential considerably less negative than its resting potential for the

[67]Mansuy, D. Boucher, J-L. & Clement, B. (1995) On the mechanism of nitric oxide formation upon oxidative cleavage of C=N(OH) bonds by NO-synthases and cytochromes P450 *Biochimie* vol 77, pp 661-667

[68]Mansuy, D. & Boucher, J-L (2004) Alternative nitric oxide-producing substrates for NO synthases *Free Rad Biol Med* vol 37(8), pp 1105-1121

duration of its excitation by previous stage 3 neurons.

16.5.2.4.2 Enzymatic reaction of L-arginine releasing NO

The process of NO release from Arginine *in-vivo* remains controversial for at least two reasons. First, the chemistry proposed in the literature contains many unusual, and possibly illogical mechanisms. Second, the chemistry proposed exhibits no direct relationship with the neural system that controls it, at least in the unique applications where the time course of the process can be studied in detail. For purposes of this chapter, any proposed chemical reactions claimed to be associated with the neuro-affector role must be controllable by that neuro-affector neuron.

The literature contains a variety of approaches to the NO liberating task when performed enzymatically. Many of the discussions note the unusual mechanisms suggested. The proposed mechanisms involved have frequently been based on computational modeling and various constituents known to be available in the vicinity of the affected muscle or neural tissue. Some of the earliest work was presented by Stuehr et al[69]. Marletta provide a minireview of his work in 1993[70]. The assumptions and points of speculation were clearly indicated. Mansuy, Boucher & Clement explored many of the potential chemistries in 1995[71]. Crane et al. provided additional exploratory work[72]. Montelano et al. have provided a useful discussion of NOS structures[73]. Moncada & Higgs have provided a recent report from a medical perspective[74]. Mansuy & Boucher[75] and Steuhr[76]. have provided the most recent material related to enzymology.

The complexity of the chemical materials involved often cause the authors to employ shorthand notations in describing their work. See **Section 16.6.1.1**. None of the purely chemical reactions resulting from in-vitro experiments show any rational relationship to the in-vivo electrolytic reaction proposed here or the actual physiology of smooth muscle relaxation.

Boudka describes one potential reaction of L-arginine releasing NO involving its interaction with an iron coordinated proto-porphyrin XI, which he describes using the notation PP_{IX}-Fe where the Fe proceeds from an oxidation state of Fe^{III} to Fe^{II} and back. Other work has indicated a broader range of excited states for the iron. Some of these are unknown to experimental chemistry. **Figure 16.5.2-7** shows the proposed reactions from Boudka based on the earlier work of Mansuy & Boucher. An intermediary known as NOHLA (Nitrogen-hydroxy-L-arginine) or NOHA is involved. Stuehr recently provided a similar figure with additional stereochemical information about the interaction of arginine with an enzyme.

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[69]Stuehr, D. Kwon, N. Nathan, C. et al. (1991) N^{ω}-hydroxy-L-arginine is an intermediate in the biosynthesis of nitric oxide from L-arginine *J Biol Chem* vol 266(10), pp 6259-6263

[70]Marletta, M. (1993) Nitric oxide synthase structure and mechanism *J Biol Chem* vol 268(17), pp 12231-12234

[71]Mansuy, D. Boucher, J. & Clement, B. (1995) On the mechanism of nitric oxide formation upon oxidative cleavage of C=N(OH) bonds by NO-synthases and cytochromes P450 *Biochimie* vol 77, pp 661-667

[72]Crane, B. Arvai, A. Ghosh, D. et al. (1998) Structure of nitric oxide synthase oxygenase dimer with pterin and substrate *Science* vol 279, pp 2121-2126

[73]Montellano, P. Nishida, C. Rodriguez-Crespo, I. & Gerber, N. (1998) Nitric Oxide Synthase Structure and Electron Transfer *Drug Metab. Dispos*. Vol 26(12), pp 1185-1189.

[74]Moncada, S. & Higgs, A. (2002) The L-arginine-nitric oxide pathway *N Eng J Med* vol 329, pp 2002-2012

[75]Mansuy D, Boucher J. (2004) Free Radical Biol Med vol 37, pp 1105. [PubMed: 15451052]

[76]Stuehr, D. (2004) Enzymes of the L-Arginine to Nitric Oxide Pathway *J. Nutr* vol 134, pp 2748S–2751S

62. Miller RT, Martasek P, Omura T, Masters BSS. Biochem Biophys Res Commun 1999;265:184. [PubMed: 10548511]
63. Wink DA, Feelisch N, Fukuto J, Chistodoulou D, Jourd'heuil D, Grisham MB, Vodovotz Y, Cook JA, Krishna M, DeGraff WG, Kim S, Gamson J, Mitchell JB. Arch Biochem Biophys 1998;351:66. [PubMed: 9501920]

While many of the equations found in the literature show O_2 in reaction with NOHA/NOHLA, it should be noted that O_2 combines with NO in aqueous solution and thereby removes the NO from the desired end product. It is only reasonable to speak of two ions of oxygen reacting with arginine when they are combined with the iron atom of hemoglobin.

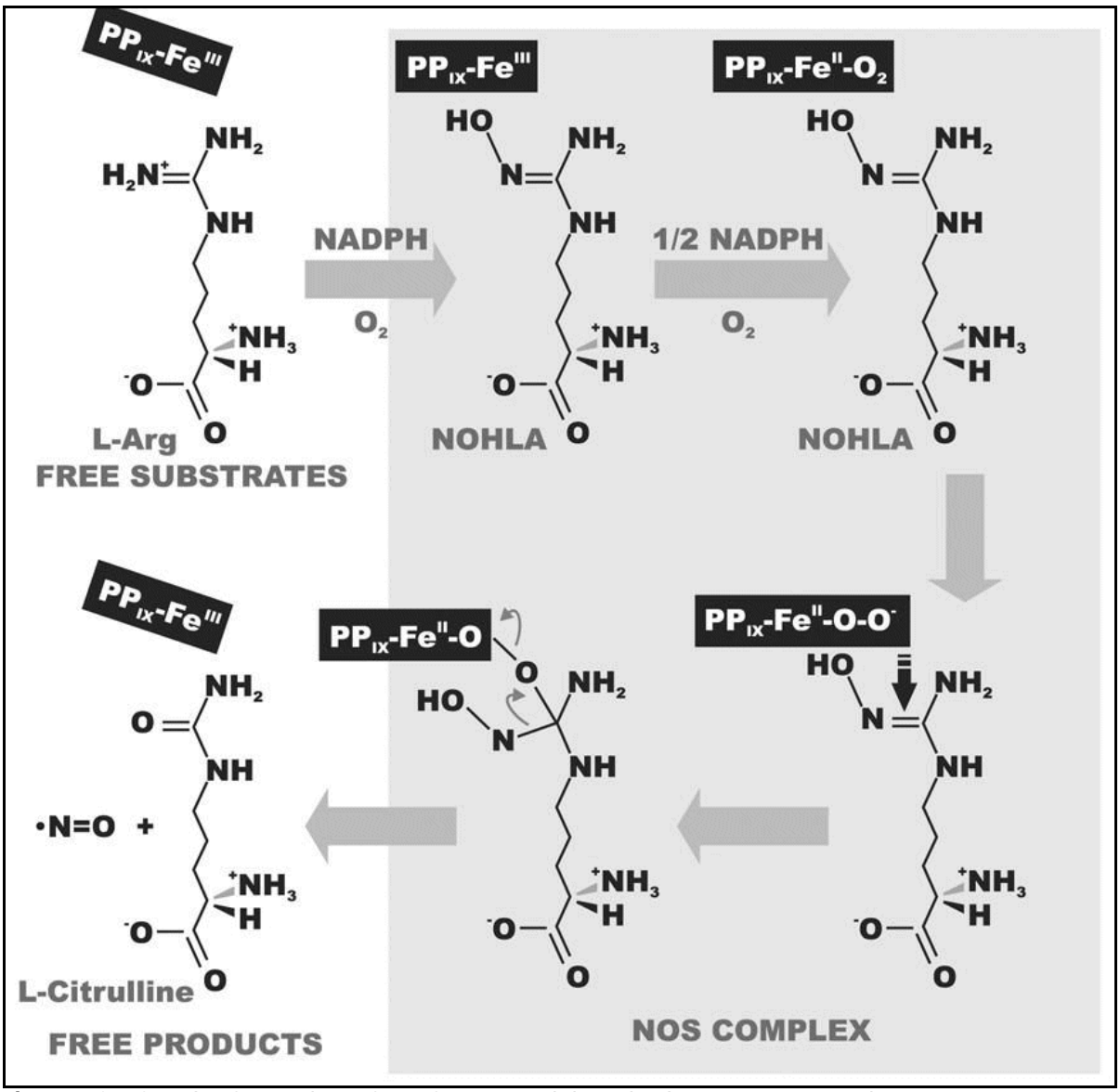

Figure 16.5.2-7 The formation of NO from L-arginine via the NOHLA complex. See text.

16.5.2.5 The nominal mechanism of NO release by neurons

A potential enzymatic release of NO has been formalized. However, the adopted equations are compatible with an alternate approach wherein the necessary energy and electrical charge are obtained directly from the neural system without employing any conventional enzyme.

The nominal release of NO from arginine has been described using many forms of a single equation. In its simplest form, equation (A) of **Figure 16.5.2-8** is used. This brief equation frequently shows the NO to be in an excited state because other peripheral events are not described. Nitric oxide is highly reactive (having a lifetime of a few seconds).

(B) shows the equation defined by the International Enzyme Commission under EC 1.14.13.39, Nitric-oxide synthase. This reaction has been given the number RN= R00557. Notice the racemic form of the citrulline is not specified. This form does not show the activated state of the oxygen usually associated with this reaction. Nor does it indicate the believed source of that oxygen.

H_4B = (6R)-5,6,7,8-tetrahydrobiopterin (Lehninger, page 443). H_4B is a cytochrome similar to hemoglobin. In its oxidized form, H_4BO_2, it contains two ions of oxygen. As in hemoglobin, these ions are easily released. If held in the appropriate position, these oxygen ions are ideally located to react with arginine to form citrulline and release NO.

(C) shows an alternate form of the equation stressing the energy difference introduced by the NADPH –> $NADP^+$ transformation.

NADP, nicotinamide adenine dinucleotide 2'-phosphate;
NADPH, the reduced form of **NADP**;
NADP+, the oxidized form of **NADP**
NADPH oxidase, nicotinamide adenine dinucleotide phosphate oxidase, a membrane-bound enzyme complex that faces the extracellular space.

The terminology associated with these molecules has changed significantly over the last 50 years. Some texts describe NADPH as a co-enzyme. However, the fact it is changed during the reaction eliminates it from a strictly enzymatic role. The designation cofactor more properly represents its role in furnishing a chemical group as part of the reaction. No energy balance table has been located, showing that the energy difference provided by this reaction is needed in the release of NO. The required energy difference can be shown more generically as in (D).

These molecules have been studied intensely in their role in photosynthesis. Their role in paracrine neuroaffectors is less appreciated.

(E) introduces an alternate notation where the energy is supplied as a voltage difference. For the above NADPH –> $NADP^+$ transformation, this activation potential is 0.34 volts.

Equations (B) through (E) show the oxygen in the unexcited molecular form. However, it is not believed that this form of oxygen can participate in the rearrangement of L-arginine necessary to release NO. (F) and (G) show the reaction stressing its electrochemical nature and hemoglobin as a source of oxygen.

(F) shows the complete reaction as it might occur on the surface of the axolemma of a neuron with the change in charge shown using the expression n H^+. This form would be found most often in discussions related to enzymes. No other enzyme is actually required as the plasmalemma acts as the receptor for the reaction. Both L-arginine and hemoglobin are changed during the reaction.

(G) shows the complete reaction with the expression +n H^+ replaced by the equivalent –n e^-. The (G) formulation would be more commonly found in electrochemistry discussions. The reaction still requires the appropriate positioning of the cytochrome relative to the L-arginine to achieve a reaction. No other enzyme is required.

The order of terms in (G) groups the reactants first and the energy changes second in describing the reaction. Both of the energy changes can be associated with the neuron supporting the reaction.

Marin & Rodriguez-Martinez (page 113, discussed below) have provided the ultimate in conceptually diagraming the release of NO at the detailed level.

16.5.3 Operations of the stage 7 pedicle at a muscular interface

16.5.3.1 Introductory data from Pierrot-Deseilligny & Burke

Much of the earlier work associated with the neuro-muscular elements involve clinical investigations. These generally have involved interneuron probing rather than intraneural (penetration of the cell wall). As a result, the measurements generally have amplitudes in the 50-200 μV range (*not the millivolt range*) and it is difficult to avoid cross talk from adjacent unidentified neurons. **Figure 16.5.3-1** from Pierrot-Deseilligny & Burke illustrate these challenges.

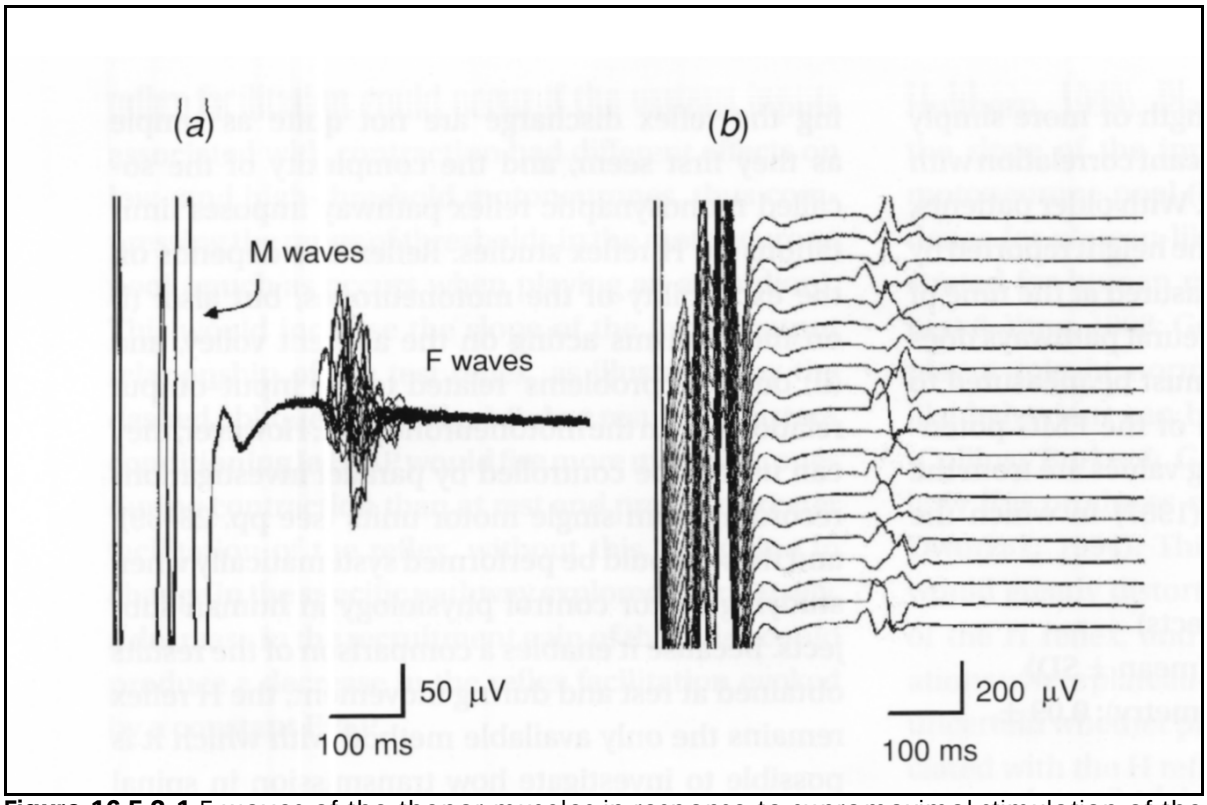

Figure 16.5.3-1 F waves of the thenar muscles in response to supramaximal stimulation of the median nerve at the wrist at 1 Hz. Note the uniform character of the M waves shown versus the nonuniform character of the F waves presumed to correlate with the M waves. The chaotic form of the f waves suggest considerable interference in the recordings from many adjacent neurons operating in a choreographed but not simultaneous manner. See text. From Pierrot-Deseilligny & Burke, 2005.

Note the chaotic character of the F waves presumed to correlate with the M waves. They are clearly not individual stage 3 monopulse waveforms generated within stage 3 neurons or Nodes of Ranvier (NoR). The very low amplitude suggests they are signals recorded extra cellularly and their shape suggests they are summations of multiple monopulse waveforms. While part of an

overall choreographed movement (including the neural path associated with the M wave), the neurons of the F-wave are not synchronized.

Pierrot-Deseilligny & Burke make the interesting comment (page 22), "Biologically, the F wave is an artefact: F waves would occur under natural conditions only if a motor axon had an extopic focus that gave rise to an antidromic impulse." It is difficult to interpret this sentence beyond the fact that F waves are artefacts. The neural system does not normally support antidromic pulses beyond the first Node of Ranvier encountered within a stage 3 axon, and electrical (tight junction) synapses being active diodes do not support antidromic signal transmission.

16.5.3.2 Examples of Stage 7 neurons interface with motor muscle

Castellucci & Kandel[77] have provided very good and extensive data on the electrical (neural) and muscular activity found in the gill of an invertebrate system, the marine gastropod mollusc *Aplysia californica*. This animal has a countable number of neurons in a well studied configuration. "In the abdominal ganglion that controls its gill, there are about 2000 neurons. Its neurons are exceptionally large. The largest cells are gigantic and can reach up to 1 mm in diameter." The stage 3 neurons of the animal clearly generate action potentials with a total duration of about 10 millisec. duration. Although the temperature of the animals during testing was not presented in this paper, it can be assumed that it was room temperature or less based on the width of the action potentials.

Figure 16.5.3-2 shows the muscle response to various rates of action potential generation. The clear character of the response as an integral of the individual stimuli over time is quite evident. The supporting data for this figure is extensive but cannot be included here. Frame (a)1 shows some delay in the response. Frame (a)2, using the same scales, is more appropriate. Frame (a)2 shows the full dynamic range of the muscle in response to a series of equally spaced action potentials. Frame (b) shows a degree of "relaxation" as a function of time in the muscle traces following each action potential. The frame also shows the subthreshold build up in the axon potential prior to the monopulse action potential generated for stimuli above threshold. The scales on the right in frame (b) are somewhat unusual. The voltages are in the same order as the waveforms. The upper scale is the voltage of the gill muscle displacement measuring device.

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[77]Castellucci, V. & Kandel, E. (1976) An invertebrate system for the cullular study of habituation and sensitization *in* Tighe, T. & Leaton, R. *eds*. Habituation. NY: Lawrence Erlbaum Assoc.

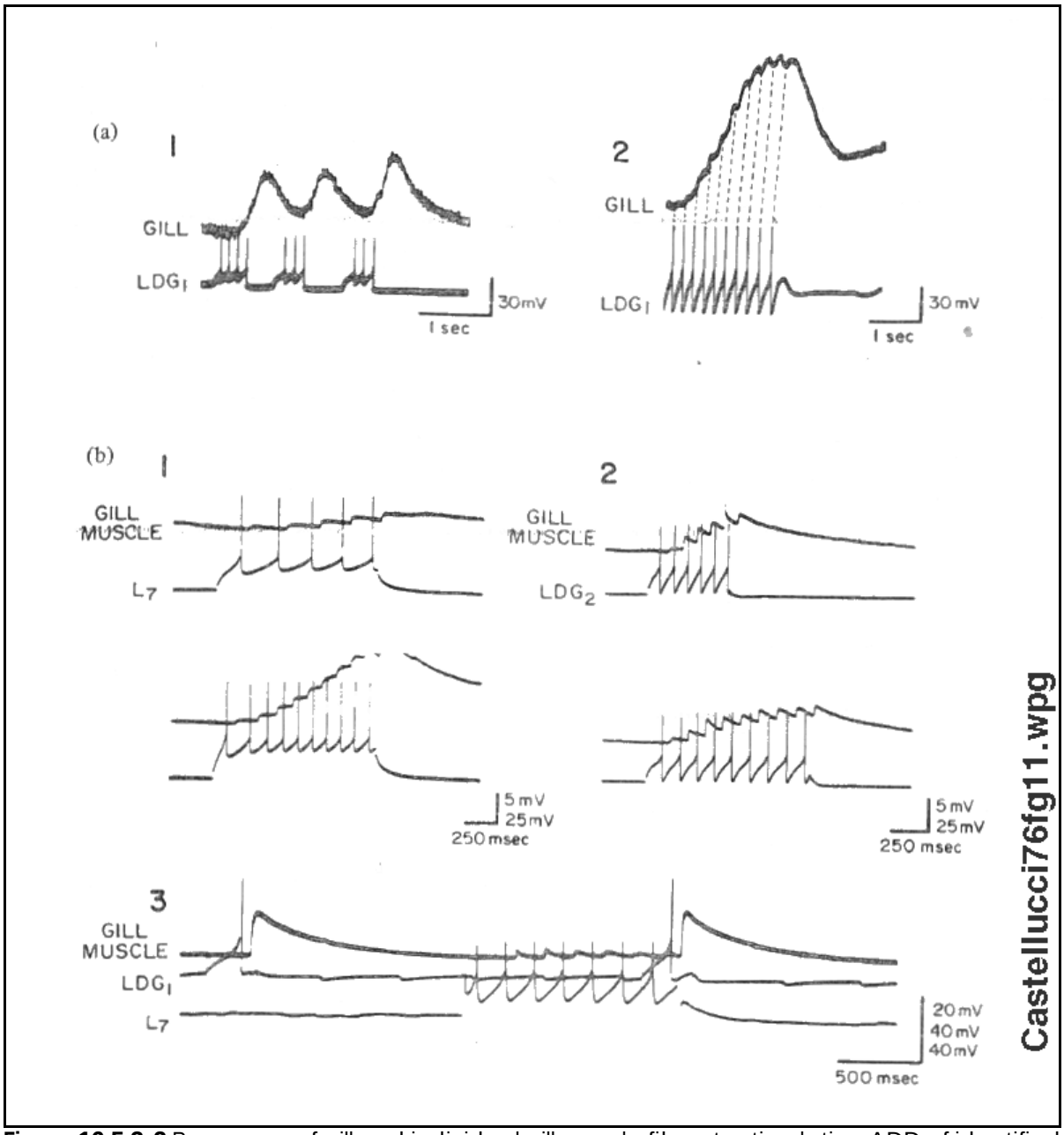

Figure 16.5.3-2 Responses of gill and individual gill muscle fibers to stimulation ADD of identified motor cells. The discussion accompanying this figure is extensive. See text. From Castellucci & Kandel, 1976

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Nitric oxide is the simplest of the hormones. It is secreted by the pedicle of stage 7 neuroaffectors under local conditions to stimulate myocytes of smooth muscle tissue. It exhibits a d-value of 1.176 Angstrom 117 pico-meters when in its basic structural form without hydration. Some texts give its d-value as 1.15 Angstrom.

16.5.3.3 Stage 7 neuron interface with smooth muscle–Nitric oxide

A generalized process can be associated with secretion by the neuro-affector cells. This generalized process can be diagramed for nitrogen oxide in conceptual form in **Figure 16.5.3-3**. The figure is divided into three equivalent frames to aid in understanding the potential realization of the concept. The following textual discussion applies equally to each frame of the figure.

A similar figure appears in **Section 16.5.3.4** addressing the striate muscle interface.

The left portion of the figure shows a stage 6 command projection (pulse) neuron. It is effectively converted into a stage 7 neuroaffector neuron by the addition of a pedicle specifically modified to secrete the hormone, nitric oxide into the cleft of a chemical synapse leading to the tissue of a smooth muscle cell(s). The vertical dash-dot line divides the totally electrolytic regime on the left from the hormonal regime of the pedicle on the right. The vertical dash-double dot line divides the pedicle from the target smooth muscle cell.

While the pedicle is supported by the homeostatic portion of the neuron on the left, it can be considered a functionally separate entity with its own chemical supply interface and possibly its own electrostenolytic supply interface. The pedicle contains mechanisms for producing hormones and releasing them into the paracrine space normally associated with the smooth muscles.

Only the positive going input terminal, V_1, is used in stage 6 and 7 neurons with the input signal, V_1, applied as shown. The upper frame shows the conventional auxiliary terminals of the neuron with the extension of the chemical supplies to the pedicle to augment the supply of arginine from the matrix surrounding the neuron.

The pedicle is shown as containing a supply of both NOS & NADPH, (see **Section 16.5.2.4** & **Section 16.5.2.5**), that is isolated from the arginine reservoir (generally described as a vesicle), by a voltage controlled valve. When the valve is opened by monopulses from the axon (or axon segment), the NOS & NADPH mixes with the L-arginine to produce ·N=O spontaneously. A residue of L-citrulline is produced according to the simplified equation from **Section 16.5.2.5**,

L–arginine + O_2 + energy –> L–citrulline + ·N=O

The free-radicle nitric oxide is able to pass through the vesicle and pedicle lemma into the synaptic (chemical) cleft and on through the lemma of the smooth muscle cell. The nitric oxide relaxes the myofibrils of the smooth muscle rapidly. The relaxation is believed to last for a period with a duration that is the combination of the decay time constant of the nitric oxide and the myofibrils of the muscle cell. This time constant is thought to be on the order fractions of a second to a few seconds in most cases.

> **Formation of Free Radicals**– Normally, when a chemical reaction takes place, bonds break and reform with some redistribution of atoms and rearrangement of bonds to form new, stable compounds. Normally, bonds don't split in such a way as to leave a molecule with an odd, unpaired electron. However, weak bonds can split this way, and when they do, free radicals are formed. Free radicals are highly unstable and quickly react with other compound. . ." *Appendix B, Biochemical Structures and Pathways*.

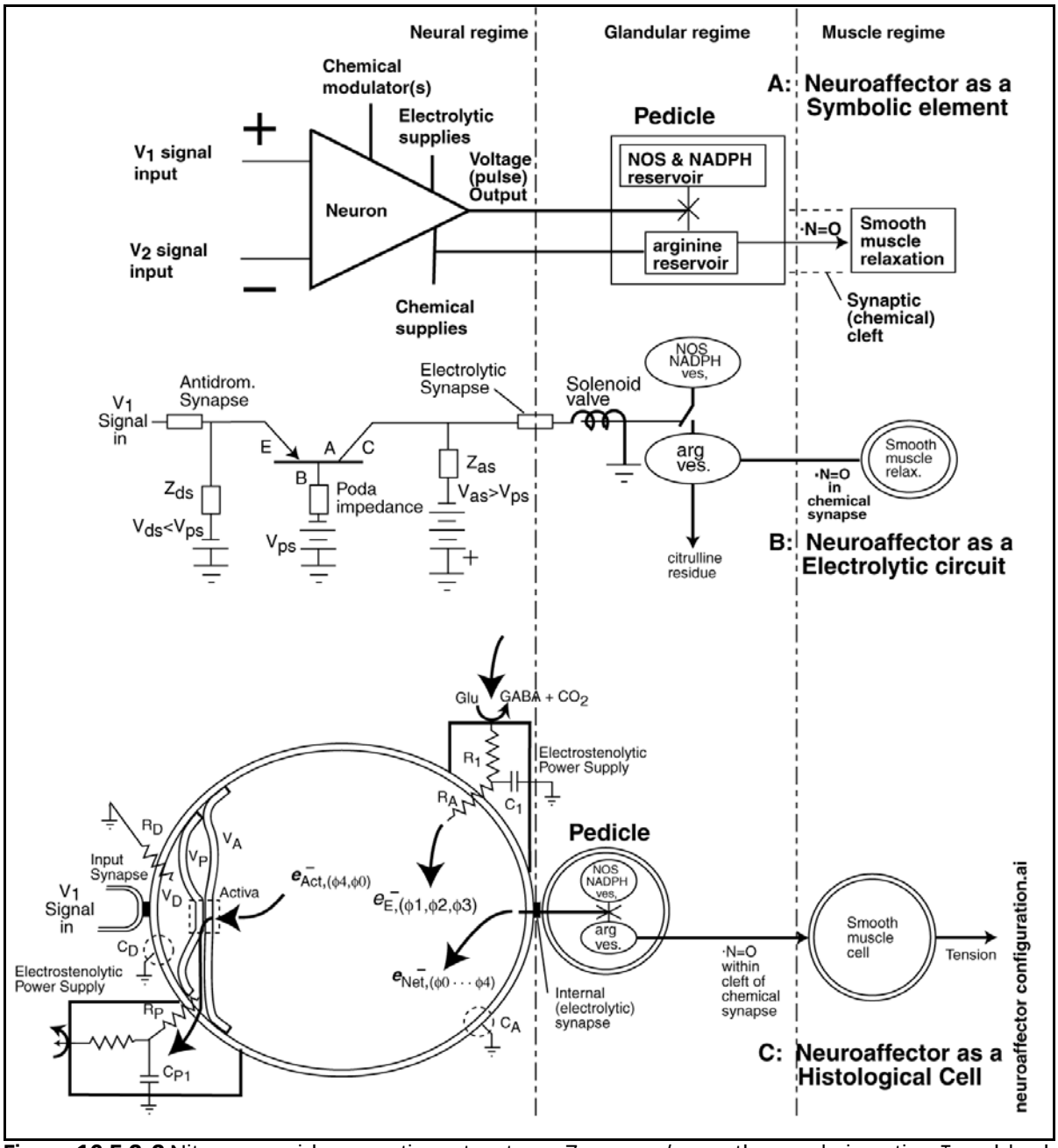

Figure 16.5.3-3 Nitrogen oxide secretion at a stage 7 neuron/smooth muscle junction Top; block diagram. Center; schematic diagram. Bottom; cytological diagram. See text.

The role of the "paracrine hormone" nitric oxide in stimulating smooth muscle without involving an "end-plate" has only recently been explored. This mechanism was unknown prior to the 1990's when the role of nitrogen oxide entered the physiological repertoire. In the following paragraphs, Ignarro et al. suggests that the muscle cell lemma is highly porous to NO and that the receptor is "nuclear, i.e., is located within the cytosol rather than on the surface of the muscle cell!! It is proposed that the arginine vesicle and the pedicle lemma is also porous to ·N=O.

The capability of nitric oxide to pass through vesicle walls and cell lemma *is not shared*

with acetylcholine within the striated muscle interface of **Section 16.5.3.4**. A more complex mechanism is required and that mechanism is associated with the end plate structure of the striate muscle interface.

The middle frame shows the neuron in its conventional electrolytic notation. An electrolytic (tight) synapse is shown leading to the glandular portion of the figure. It is cytologically represented by the pedicle of the neuron. A new symbol has been introduced, a solenoid controlled valve with the line through the solenoid shown as connecting to a valve controlling the release of NOS & NADPH into the arginine reservoir. Upon the mixing of these molecular species, the free radical ·N=O is released to make its way to the smooth muscle via the paracrine duct, a.k.a., the synaptic cleft.

The solenoid and valve combination is used to suggest it is the change in electrical potential within the pedicle that causes the mixing of the chemical constituents. This has yet to be demonstrated but provides a concept worth experimental attention.

When the ·N=O reaches the exterior lemma of the smooth muscle, it passes freely through the lemma and interacts with the myocytes of the muscle directly causing the relaxation of the normally contracted myofibrils (and subsequent relaxation of the entire smooth muscle). No element or mechanism is required to support this action.

The bottom frame attempts to show the neuroaffector/smooth muscle interface in a more cytological manner.

The portion of the neuroaffector in the neural regime is shown with an outer bilayer lemma. This lemma is formed primarily of type 1 (totally insulating) lemma. The primary exception is areas of type 2 lemma supporting the two external synapses and the two external points of electrostenolytic activity providing electrical power to the internal Activa. There will also be one or more areas of type 3 lemma supporting the transport of large molecules in support of homeostasis (not shown).

The pedicle of the stage 7 neuroaffector can be considered a totally separate element of the neuron connected to the neuron portion by a conventional electrolytic (tight) synapse. In that case, it may have access to the necessary chemical supplies by its own segments of type 3 lemma and potentially its own electrolytic power via a region of type 2 lemma dedicated to the electrostenolytic process like that shown for the neuron portions of the neuroaffector at upper right.

The electron currents, e_X^- where X is a placeholder, shown flowing in and out of the axoplasm in the lower left frame of the figure are best shown in a serape representation. These currents vary significantly in time according to the phases shown in parentheses following the subscript name in the figure. **Section 9.2.4** develops the serape representation frequently used in conventional non-linear electronic circuits as it applies to the neural circuit. **Figure 16.5.3-4** provides such a serape of the neuroaffector /smooth muscle interface.

The lower frame, labeled **B** is the serape applicable to virtually any stage 2 through stage 6 neuron. In this case, the neuron is excited by a long rectangular pulse. The neuron is biased and its capacitances are appropriate to generate a single monopulse (action potential). The stimulation ends prior to the refractory interval that controls when a second pulse can be generated. Phase 0 constitutes the initial rising portion of the action potential after the integrated energy of the stimulation has exceeded the voltage threshold, V_{thresh}, for generating an action potential. Phase 3 represents the decay of the action potential. When the amplitude of the decaying waveform reaches its initial pre-stimulus level (in this case –61 mV), the neuron enters its refractory interval.

The upper frame, labeled **A** has been added to illustrate the response of each myocyte of a muscle cell. The upper horizontal scale has a zero that is aligned with the zero of the horizontal scale of frame **B**. In other respects, the response shown is in caricature. because the data is not available to be more precise. The response shows a delay from the start of phase 0 due to the time required to release the ·N=O from the pedicle and the time for the ·N=O to enter the muscle cell and stimulate the myocyte. Upon stimulation the smooth muscle myocyte relaxes from its quiescent (contracted) condition according to an equation that is unknown. The relaxation will exhibit a relaxation time constant. Upon termination of stimulation by ·N=O, the

myocyte will begin to return to its contracted state with the tension characteristic also exhibiting a time constant that is currently not documented.

Note: *There is no reason for any of the time constants associated with these functional phases to be equal within the muscle or within the neuroaffector.*

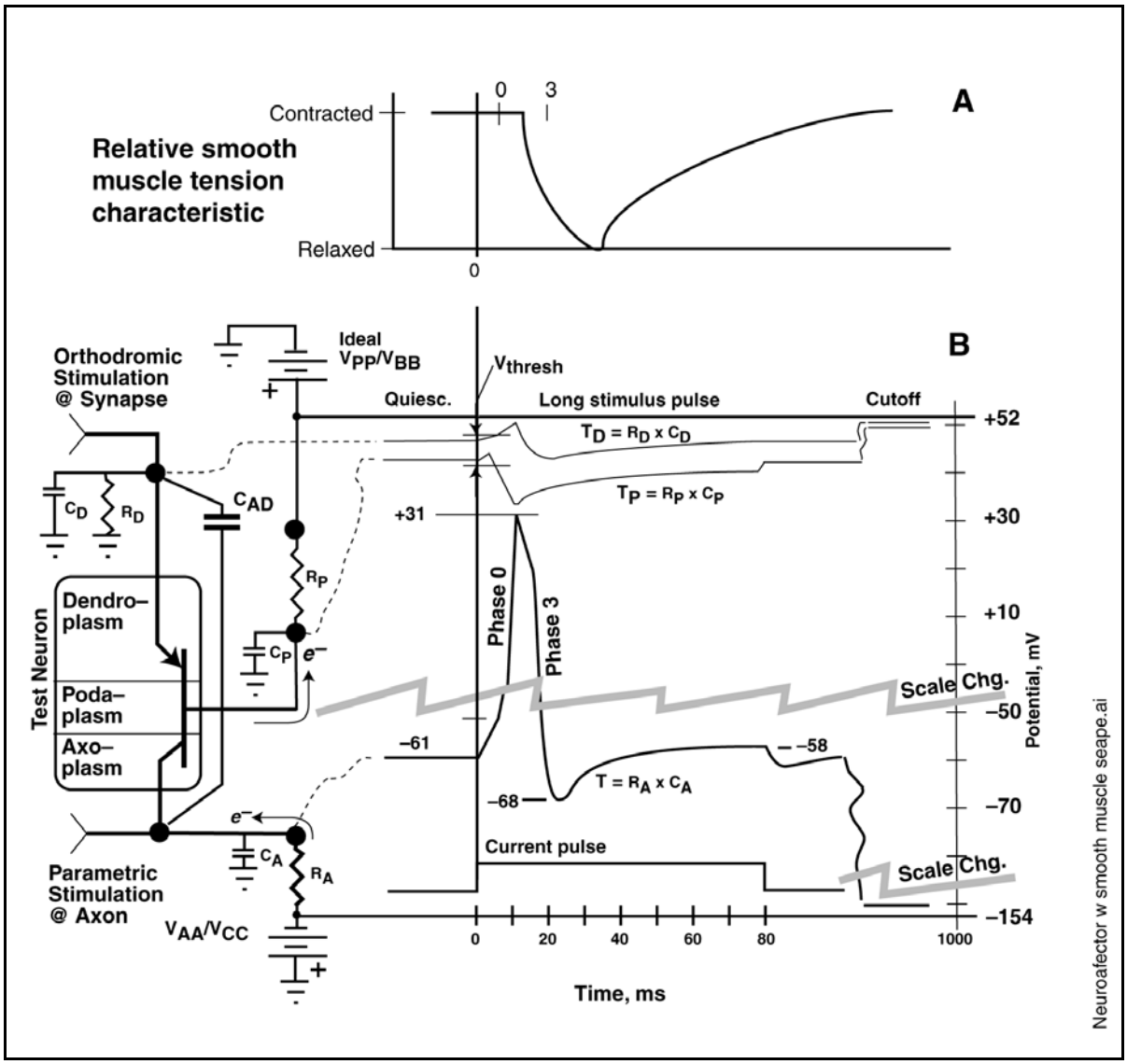

Figure 16.5.3-4 Serape of neuroaffector/smooth muscle interface ADD. Expanded from the prototype in **Section 9.2.4**. Look to that section for most of the nomenclature. See text.

16.5.3.3.1 Literature on formation and release of ·N=O

In 1987, Ignarro et al. published a paper asserting that the endothelium-derived relaxing factor, EDRF, was the same as nitric oxide based on their similar effects related to the smooth muscle

of vascular endothelium[78]. The authors were primarily pharmacists. They performed extensive testing on both arterial and vein strips before making their assertion.

Also in 1987, Palmer et al. demonstrated that nitric oxide was the active material underlying the endothelium-derived relaxing factor, EDRF[79] The noted,

> "The biological activity of EDRF and of NO was measured by bioassay. The relaxation of the bioassay tissues induced by EDRF was indistinguishable from that induced by NO. Both substances were equally unstable. Bradykinin caused concentration-dependent release of NO from the cells in amounts sufficient to account for the biological activity of EDRF. The relaxations induced by EDRF and NO were inhibited by haemoglobin and enhanced by superoxide dismutase to a similar degree. Thus NO released from endothelial cells is indistinguishable from EDRF in terms of biological activity, stability, and susceptibility to an inhibitor and to a potentiator. We suggest that EDRF and NO are identical."

Ignarro et al. noted, "The chemical procedures described here and the report of Palmer et al. for detecting NO are not entirely specific for NO *per se* and are incapable of distinguishing NO from a labile nitroso compound. The possibility exists, therefore, that EDRF is a labile nitroso substance that spontaneously releases NO. EDRF cannot be NO_2^- because NO_2^- is a relatively stable species that causes vascular smooth muscle relaxation only at very high concentrations. In much the same manner that other pharmacologically active substances have been subsequently discovered to occur endogenously, NO, which was first described as one of the most potent vascular smooth muscle relaxants in 1979, now appears to exist naturally in mammalian cells as EDRF.

The endogenous NO receptor, unlike most other receptors, is located intracellularly and is the heme group bound to soluble guanylate cyclase. NO is highly lipophilic and readily permeates vascular smooth muscle cells to activate soluble guanylate cyclase, elevate tissue cyclic GMP levels, and relax the muscle. Moreover, the requirement of guanylate cyclase-bound heme for enzyme activation by NO is well documented (with citations)."

> In the endogenous situation, the NO is released from a stage 7 neuron adjacent to one or more muscle cells. Whether the receptor is actually a heme group bound to soluble guanylate cyclase relies on the citations and may need confirmation by a second laboratory.

"Authentic NO produced identical actions to those of EDRF, and the actions of both were antagonized by common inhibitors. Finally, both EDRF and NO were inactivated by superoxide anion and stabilized by superoxide dismutase.")

Ignarro et al. noted the lability of NO, with a half amplitude time constant of 3-5 Sec, when associated with artery or vein tissue. They noted, NOcould be stored several hours in the absence of oxygen.

Garg & Hassid provided more confirming evidence in 1989[80].

The article by Rybalkin et al. appears relevant to an understanding of the operation of smooth muscle in particular, including the key roles played by nitric oxide and the PDE family

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[78]Ignarro, L. Buga, G. Wood, K. et al. (1987) Endothelium-derived relaxing factor produced and released from artery and vein is nitric oxide Vol 84(24), pp. 9265-9269

[79]Palmer, R. Ferrige, A. & Moncada, S. (1987) Nitric oxide release accounts for the biological activity of endothelium-derived relaxing factor *Nature* vol 327, pages 524–526

[80]Garg, U. & Hassid, A. (1989) Nitric oxide-generating vasodilators and 8-bromo-cyclic guanosine monophosphate inhibit Mitogenesis and proliferation of cultured rat vascular smooth muscle cells *J Clin Invest* vol 83, pp 1774-1777

(phosphodiesterases) in the control of the key substance, cGMP[81]. It also addresses the role of nonadrenergic/noncholinergic (NANC) neurons, i.e., nitric oxide releasing neurons. Unfortunately, his text provides little support for his figure 2, and it only presents a caricature of the processes initiated by nitric oxide. The paper does not highlight any type of syncytium present in smooth muscle. In an accompanying paper, Friebe & Koesling[82] discuss the role of NO as a signaling molecule–a neuro-affector in the parlance of this paper. For many years, NO was known only as the "endothelium-derived relaxing factor" (EDRF). From a signaling perspective, the source of this NO was the neurons within the endothelium.

The release of NO has been postulated as arising primarily from L-arginine. The mechanism for this release has been assumed to involve an enzymatic reaction, and much work has been done *in-vitro* to demonstrate potential chemical paths providing this result. However, the potential for a pseudo-enzymatic mechanism associated directly with the neural system has not been explored. This work suggests such a pseudo-enzymatic mechanism is quite likely.

Interest in the study of nitric oxide blossomed after it was identified as the previously defined endothelium-derived relaxing factor (EDRF) proposed by Furchgott & Zawadski in 1980[83].

Joyner & Dietz have provided a broad overview of the role of NO in the skeletal and vascular systems[84].

16.5.3.3.2 Recent concept of the neuroaffector/smooth muscle interface

Marin & Rodriguez-Martinez also provided a comprehensive review of NO from a medical perspective[85]. Their figure 1, illustrating their conception of the synapse between an endothelial cell and smooth muscle is reproduced here as **Figure 16.5.3-5**. The extensive labeling used will not be defined here but will be found in the original caption. The figure complements and supports the previous figure in this work but does not address how the enzymes are isoloated from L-arginine prior to activation of the process on NO generation. They only suggest that "acetylcholine, bradykinin (BK), ADP, etc." are involved in the activation via an undefined receptor (R).

They begin their Introduction with the assertion, "The new concept considering vascular endothelium an endocrine gland has replaced the old one considering endothelium an inert component of the vessel." They offer no citation, but the assertion is accepted here. The paper provides many citations in support of their review. They address the means of chemical supplies of arginine entering the pedicle and reference Bogle et al., 1996 and Kerwin et al., 1995. Bogle et al. explore what they call system y^+, a proposed system for transporting L-arg, L-orh, L-lys, L-NMMA & L-NIO across the cell membrane. In their caricature of figure 6, they also suggest that L-citrulline is re-circulated back into the L-arg pool after the release of NO. This would suggest the arrow between O2 and Citrulline in the figure from Marin & Rodriguez-Martinez should be reversed to indicate an internal loop. The original definition of the y^+ system was by White in

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[81]Rybalkin, S. Yan, C. Bornfeldt, K. & Beavo, J. (2003) Cyclic GMP Phosphodiesterases and Regulation of Smooth Muscle Function *Circ Res* vol 93, pp 280-291

[82]Friebe, A. & Koesling, D. (2003) Regulation of Nitric Oxide-Sensitive Guanylyl Cyclase *Circ Res* vol 93, pp 96-105

[83]Furchgott, R. & Zawadzki, J. (1980) The obligatory role of endothelial cells in the relaxation of arterial smooth muscle by acetylcholine *Nature* vol 288, pp 373-376

[84]Joyner, M. J. & Dietz, N. M. (1997) Nitric oxide and vasodilation in human limbs *J App Physiol* vol 83, pp 1785-1796

[85]Marin, J. & Rodriguez-Martinez, A. (1997) Role of vascular nitric oxide in physiological and pathological conditions *Pharmacol Ther* vol 75(2), pp 111-134

1985[86]. The defined y^+ system was associated with all types of cells. At that time he noted, "We have not yet isolated the membrane proteins responsible for these processes, and thus, our understanding of amino acid transport is based entirely on kinetic experiments." "The transport of neutral amino acids rarely occurs by a single transport system, but in many cases, the mediated transport of arginine, lysine and ornithine is restricted to a single system. For many cell types, this transport system has similar characteristics and is called system y+. This review will focus on the features and properties of system y^+ in mammalian cells. Its major conclusion was "Cationic amino acid transport in all cell types tested shows an Na+-independent component that is called system y+. This transport system is distinct from systems A, ASC and L, and the various anionic systems." These alternate systems are addressed on page 356. These were all largely conceptual.

Bogle et al. do not explore how NO exits the cell into the paracrine space.

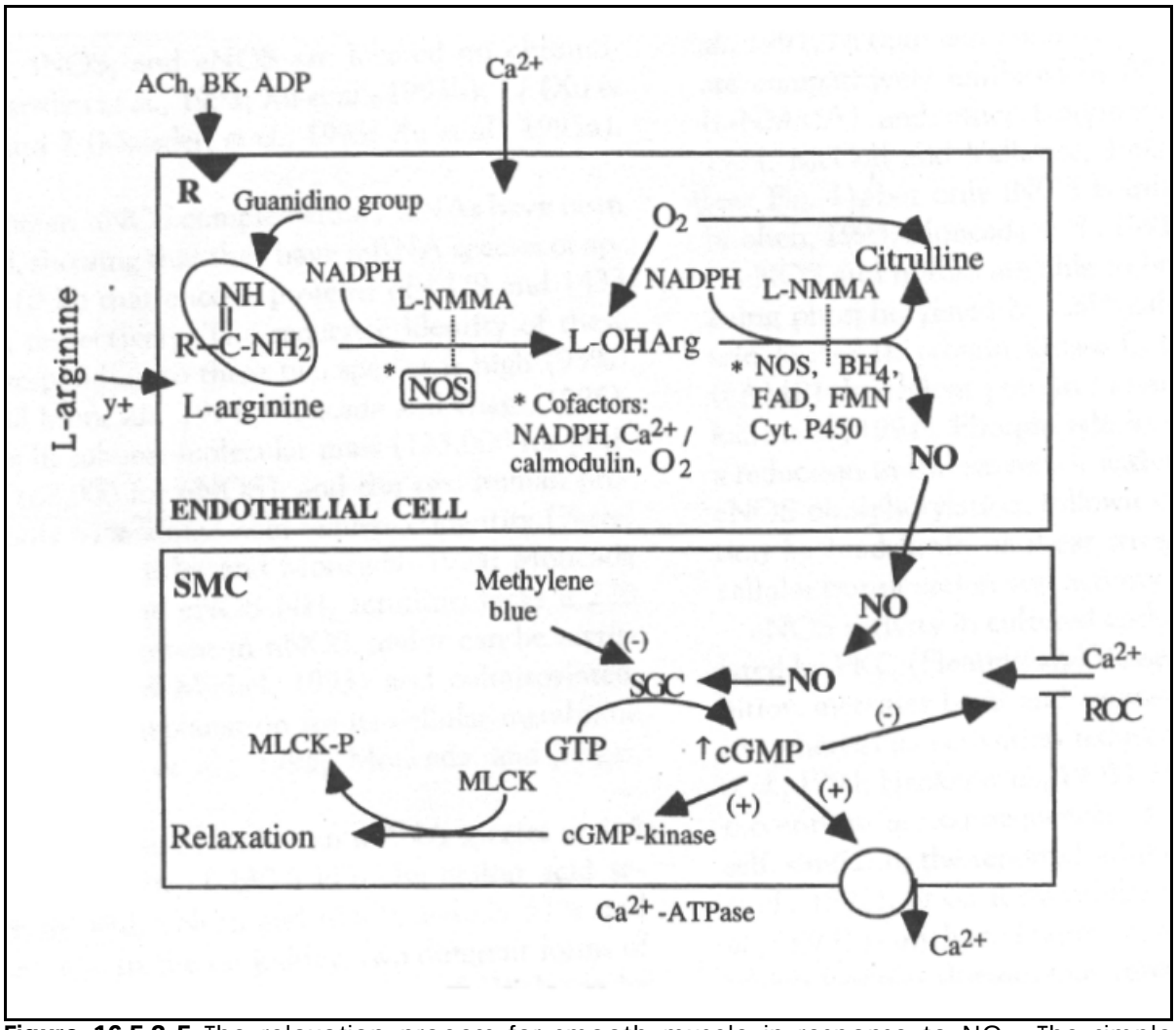

Figure 16.5.3-5 The relaxation process for smooth muscle in response to NO. The simple movement of NO between the pedicle of a neuroaffector and smooth muscle is shown. The labeling is that of the original paper. The entry of L-arginine via the y+ mechanism is noted. See text. From Marin & Rodriguez-Martinez, 1997

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[86]White, M. (1985) The transport of cationic amino acids across the plasma membrane of mammalian cells *Biochimica et Biophysica Acta* vol 822, pp 355-374

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Boudka has provided a wide ranging study of the role of nitric oxide in biological systems[87]. He explores the formation of nitric oxide in three different contexts; enzymatic NO synthesis by NOS, enzymatic reduction of nitrogen oxides, and non-enzymatic production of NO. The paper includes 442 references. Several of these will be cited below.

While commonly spoken of as a gas, the free radical NO dissolves in water (a few ml/100ml of H_2O at biological temperatures) and other fluids of the body. The material of interest in biology is actually aqueous NO. Its lifetime as a free radical is reported to be in seconds.

The majority of the investigations of NO release have used the pharmacological perspective. These studies have been primarily *in-vitro*. This section will expand the discussion to present an alternative NO release mechanism from a neurological perspective that involves a more global model of the biological system.

The release of NO through the action of a nitric oxide synthase (NOS) has been most widely studied. Alderton et al. have estimated 16000 papers have been published describing potential NOS configurations since their identification in 1989[88]. Most of these studies have been *in-vitro* or computationally based. If the prototypical situation is described, it frequently involves endothelial tissue. The protocols used in the *in-vitro* studies frequently diverge considerably from the *in-vivo* neural-based situation of interest here.

Alderton et al. have noted (page 603), "NO is now known to be synthesized in a large number of different tissues playing a wide variety of physiological roles." Its major role is in relation to the relaxation of smooth muscle. This action is counter to the more conventional excitatory role of neuro-affectors. Alderton et al. conclude their paper with a long list of outstanding questions related to the role of NO synthases. The release of NO directly by the neurons has been less widely studied. Steed & Atwood note, "The terminals of the axons of the parasympathetic nerves (part of the autonomic nervous system the body's unconscious response mechanism) release NO (page 84).

Three separate conceptual NOSs have been defined. Alderton et al. have summarized them as; nNOS (also known as Type I, NOS-I and NOS-1) being the isoform found (and predominating) in neuronal tissue, iNOS (also known as Type II, NOS-II, and NOS-2) being the isoform which is inducible in a wide range of cells and tissues and eNOS (also known as Type III, NOS-III, and NOS-3) being the isoform first found in vascular endothelial cells. These conceptual designations will obviously change with additional understanding. The close relationship between eNOS and nNOS should be clear based on the close relationship between stage 7 neurons and endothelial tissue.

Keilhoff et al. have recently discussed the role of nNOS as the dominant nitric oxide supplier to dorsal root ganglia[89]. However, they do not discuss the creation of NO from its ultimate source. Their activity is focused on comparisons between wild and knock-out (KO) mice.

When describing the operation of the NOS's, several intermediaries have been identified. The labels of these intermediaries has changed with the rapid expansion of the field, while initially described as NHA (N^{ω}–hydroxy-L-arginine), it has more recently been described as NOHA or NOHLA.

iNOS, and for the moment eNOS, are not of major interest in this discussion. It is not clear how

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[87]Boudko, D. (2007) Bioanalytical profile of the L-arginine/nitric oxide pathway and its evaluation by capillary electrophoresis *J Chromatogr B Analyt Technol Biomed Life Sci*. vol 851(1-2), pp 186–210.

[88]Alderton, W. Cooper, C. & Knowles, R. (2001) Nitric oxide synthases: structure, function and inhibition *Biochem J* vol 357, pp 593-615

[89]Keilfoff, G. Fansa, H. & Wolf, G. (2002) Neuronal nitric oxide synthase is the dominant mitric oxide supplier for the survival of dorsal root ganglia after peripheral nerve axotomy *J Chem Neuroanat* vol 24, pp 181-187

much of the work of the Ghosh group[90] applies to type I, or nNOS conventionally associated with the neurons. Most of it appears focused on iNOS.

16.5.3.3.3 Proposed concept of the neuroaffector/smooth muscle interface

When discussing the enzymatic action of NOS in producing NO, it is important to avoid the exclusive expression "the" in favor of the inclusive expression "an." There is no proof that the enzyme NOS is necessary to release NO in the vicinity of smooth muscle. Alderton et al. continued in 2001, "Perhaps most surprisingly for those not familiar with the field is that it remains a matter of much debate as to whether NOS directly synthesizes NO or not." This work will introduce an alternate electrolytic method of NO release that does not involve any conventional enzymatic action. Specifically, it is proposed that ·N=O is a free radical that is produced spontaneously by arginine in the presence of oxygen in accordance with **Figure 16.5.2-6**.

16.5.3.3.4 Continuing controversy over ·N=O production *in vivo*

The chemistry associated with the reduction of L-arginine by NOS *in-vitro* remains highly controversial because of the variety of products that might be produced depending on the conditions of the experiment. Alderton et al. conclude that "it is still an open question as to whether NO or NO^- is the immediate product of NOS; it seems likely that under different conditions *in-vitro* it is possible to get either product." Other authors focus on the designation •NO. Alderton et al. have also described the chemistry of NOS as novel. Mansuy et al[91]. have provided three different chemical reactions that might be involved in the release of NO. The conversion of arginine is spontaneous in the Alderton et al. caricature. This is not necessarily the situation encountered *in-vivo*.

The process of denitroxification requires acquisition of an electron in order to result in neutral species. Stage 7 neurons provide an electron in consonance with the change in axoplasm potential controlling the release of neutral NO.

Figure 16.5.3-3 shows the release of ·N=O under neurological control. Bredt and Snyder have provided a review of the state of knowledge relating to nitric oxide in 1992. They note its presence in mammals was only recognized in 1988. In 1992, its preponderant locations within the physiological system did not correspond to the locations of neurons in general, only with the location of neuro-affector neurons and the adjacent smooth muscle tissue. They also note its ambivalent role when considered a neurotransmitter. Example; the free radical nitric oxide is not stored in vesicles. They suggest it is released by a "highly controlled," putative enzyme, nitric oxide synthase (NOS). In fact, it is released electrolytically upon formation from NOHLA. The transfer of charge through the type III lemma into the electrostenolytic region stereo-specific to arginine is controlled by the potential between the dendroplasm and the podaplasm. This potential controls the potential of the axoplasm. NO is only released from its progenitor when the potential of the axoplasm becomes more positive than a specific threshold value. The proposed chemistry associated with the neuro-affector mechanism is more straightforward as shown in the lower portion of the figure. There is no need for any participation by NADPH or for any nitric oxide releasing synthase (NOS). The required energy is ultimately obtained from the glutamate/GABA conversion. However, the precise steps in the conversion of arginine to citrulline and the release of NO or NO^- are not known. The electron previously provided *in-vitro* by the conversion of NADPH to $NADP^+$ is now provided by the reservoir of electrical charges within the axoplasm. When the axoplasm is brought to a more positive level than its quiescent value, an electron can be provided to the electrostenolytic conversion of arginine just as it is by NADPH in the Petrie dish. A voltage change as large or larger than that noted by Bredt and Snyder is available.

The release of ·N=O under neurological control in **Figure 16.5.3-3** can be compared to the

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[90]Ghosh, D. & Salerno, J. (2003) Nitric oxide synthases: domain structure and alignment in enzyme function and control Front Biosci vol 8, pp d193-209

[91]Mansuy, D. Boucher, J. & Clement, B. (1995) On the mechanism of nitric oxide formation upon oxidative cleavage of C=N(OH) bonds by NO-synthases and cytochromes P450 *Biochimie* vol 77, pp 661-667

largely conceptual equivalent in figure 4 of Moncado & Higgs[92]. While the electrostenolytic release of NO at the surface of the neuron can be considered catalytic in nature, it is clearly not enzymatic and does not require the presence of any protein-based enzyme.

Bredt and Snyder have identified NO as a neural efferent[93] affecting smooth muscle, particularly in the penis of male mammals. They suggest PDE-5 inhibitors act separately from ·N=O in prolonging erections.

16.5.3.3.4 Vasodilation and ·NO

Garg & Hassid[94] developed the process of vasodilation and focused on several vasodilators other than NO. They all contained, and may be able to release NO. They noted,

> "The purpose of this study was to determine if vasodilator drugs that generate nitric oxide, inhibit vascular smooth muscle mitogenesis and proliferation in culture. Three chemically dissimilar vasodilators, sodium nitroprusside, S-nitroso-N-acetylpenicillamine and isosorbide dinitrate, dose-dependently inhibited serum-induced thymidine incorporation by rat aortic smooth muscle cells. Moreover, 8-bromo-cGMP mimicked the antimitogenic effect of the nitric oxide-generating drugs."
>
> "We now report that three such structurally dissimilar drugs, as well as 8-bromo-cGMP, effectively inhibit DNA synthesis and proliferation of rat aortic smooth muscle cells in culture."

One of their conclusions was, "These results suggest that endogenous nitric oxide may function as a modulator of vascular smooth muscle cell mitogenesis and proliferation, by a cGMP-mediated mechanism."

A second conclusion was, "We now report that three such structurally dissimilar drugs, as well as 8-bromo-cGMP, effectively inhibit DNA synthesis and proliferation of rat aortic smooth muscle cells in culture."

It appears their may be different timelines applicable to the vasodilation function, the DNA synthesis and the proliferation of new cells.

16.5.3.4 Stage 7 neuron/striate muscle interface–acetylcholine

Section 2.7.2 develops the neural/striate muscle interface in some detail.

Figure 16.5.3-6 provides a variant of [**Figure 16.5.3-3**] in support of the neuroaffector/striate muscle interface.

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[92]Moncado & Higgs (1986) Archidonate metabolism in blood cells and the vessel walls *Clinics in Haematology* vol 15, pp 273-278

[93]Bredt, D. S. & Snyder, S. H. (1992) Nitric oxide, a novel neuronal messenger *Neuron* vol 8, pp 3-11

[94]Garg, U. & Hassid, A. (1989) Nitric oxide-generating vasodilators and 8-bromo-cyclic guanosine monophosphate inhibit mitogenesis and proliferation of cultured rat vascular smooth muscle cells *J Clin Invest* vol 83(5), pp 1774-1777 https://doi.org/10.1172/JCI114081

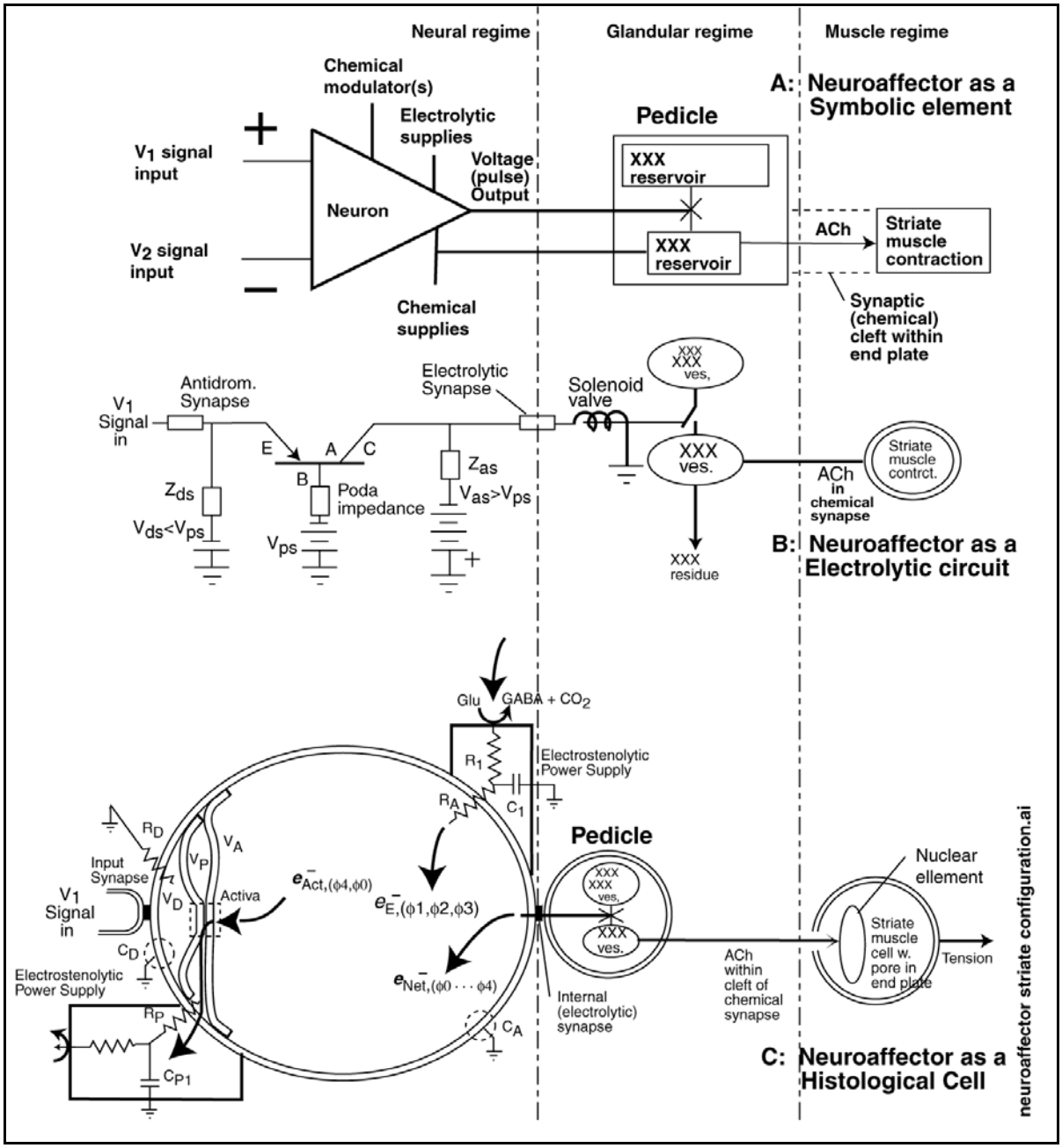

Figure 16.5.3-6 The neuroaffector/striate muscle interface MODIFY and ADD. Much of the terminology follows that used in the equivalent figure for the smooth muscle interface.

The electron currents, e_X^- where X is a placeholder, shown flowing in and out of the axoplasm in the lower left frame of the figure are best shown in a serape representation. These currents vary significantly in time according to the phases shown in parentheses following the subscript name in the figure. **Figure 16.5.3-7** provides a serape type representation of the neuroaffector /striate muscle interface.

The lower frame, labeled **B** is the serape applicable to virtually any stage 2 through stage 6 neuron. In this case, the neuron is excited by a long rectangular pulse. The neuron is biased and its capacitances are appropriate to generate a single monopulse (action potential). The stimulation ends prior to the refractory interval that controls when a second pulse can be

generated. Phase 0 constitutes the initial rising portion of the action potential after the integrated energy of the stimulation has exceeded the voltage threshold, V_{thresh}, for generating an action potential. Phase 3 represents the decay of the action potential. When the amplitude of the decaying waveform reaches its initial pre-stimulus level (in this case –61 mV), the neuron enters its refractory interval.

The upper frame, labeled **A** has been added to illustrate the response of each myocyte of a muscle cell. The upper horizontal scale has a zero that is aligned with the zero of the horizontal scale of frame **B**. The small numbers above the horizontal axis indicate the starting time of phase 0 and the ending time of phase 3. In other respects, the response shown is in caricature. because the data is not available to be more precise. The response shows a delay from the start of phase 0 due to the time required to release the acetylcholine, ACh, from the pedicle and the time for the ACh to travel through the paracrine duct and to stimulate the muscle cell via the endplate, and for the "2nd messenger" released by the myo-receptor of the end plate to stimulate the internal myocyte. Upon stimulation the striate muscle myocyte deviates from its quiescent (relaxed) condition and contracts according to an equation that is unknown in the context of this work. The contraction will exhibit a contraction time constant. Upon termination of stimulation by ACh, the myocyte will begin to return to its relaxed state with the tension characteristic also exhibiting a time constant that is currently not documented.

> **Note:** *There is no reason for any of the time constants associated with these functional phases to be equal within the muscle or within the neuroaffector.*

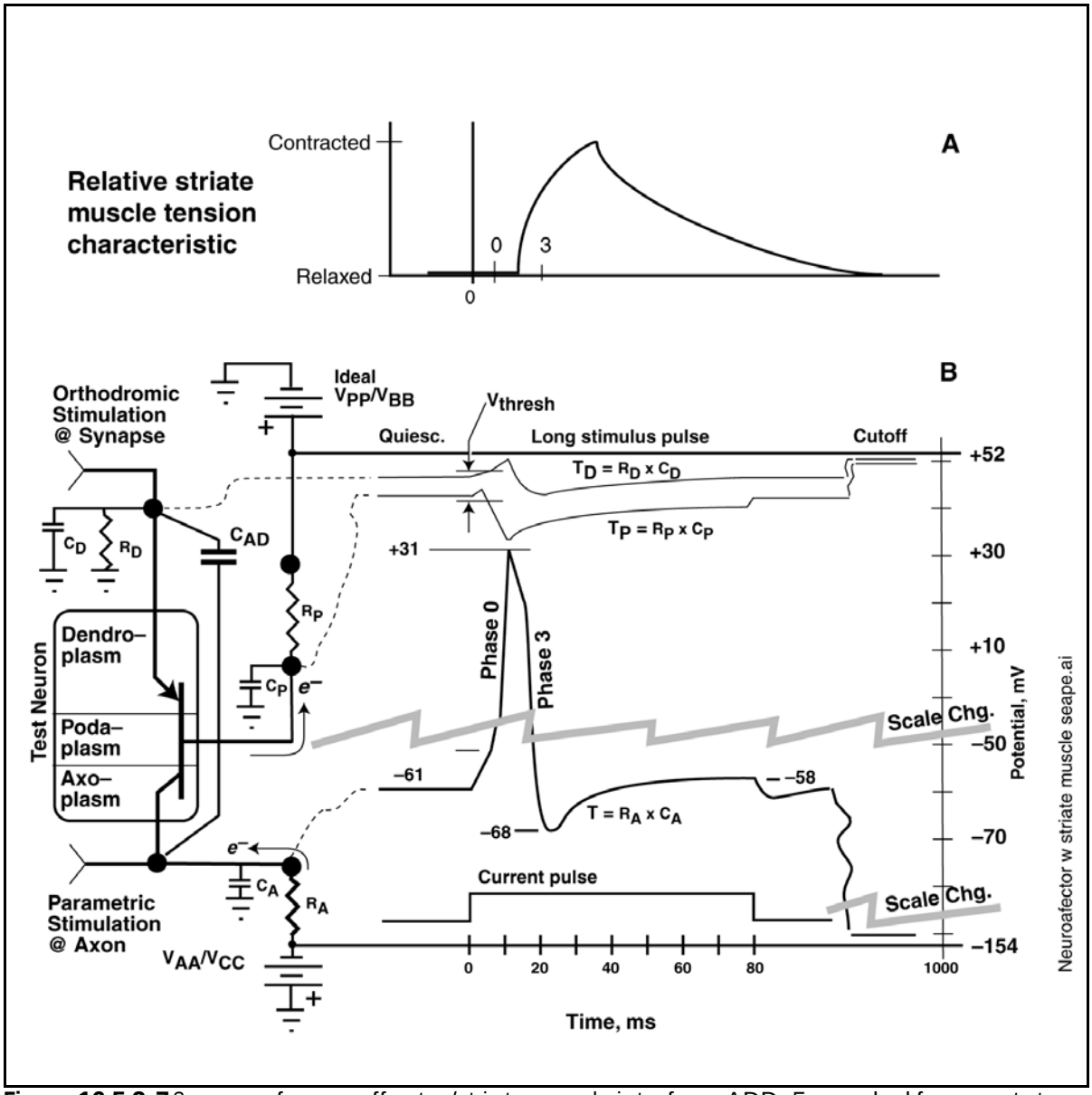

Figure 16.5.3-7 Serape of neuroaffector/striate muscle interface ADD. Expanded from prototype in **Section 9.2.4**. Look to that section for most of the nomenclature. See text.

16.5.3.4.1 Literature on formation and release of Acetylcholine

Novere et al. provide a complex representation of the formation, release and reconstitution of acetylcholine in their figure 3a (shown in **Section 16.5.1.2.1** of this work) using their proposed SBGN language (**Section 16.1.6.1**). However, after the initial formation of acetylcholine from choline and acetyl co A enzyme, the remainder of the figure (lacking any source citation or discussion) is totally conceptual. They have not demonstrated that ACh requires reconstitution after its functioning within the cleft of the stage 7 neuroaffector neuron/muscle cell interface. If the interface of the paracrine system resembles that typical exocrine system interface, the ACh is not destroyed in a chemical reaction based on valence chemistry.

16.5.3.4.2 The concept of a lemma pore for acetylcholine

Acetylcholine is a large molecule relative to the spacing of molecules in the liquid crystalline bilayers of the external lemma of any cell. It is unlikely that it can pass through a pore in that lemma without a significant mechanism to aid that transport. The mechanism is probably similar to the mechanism of of phagocytosis.

Acetylcholine (ACh) is an organic chemical that functions in the brain and body of many types of animals, including humans. Its primary role is as a neuroaffector—a hormone released by stage 7 neurons to stimulate *striated* muscle tissue. Parts in the body that use or are affected by acetylcholine are referred to as cholinergic. Substances that interfere with acetylcholine activity are called anticholinergics.

O-Acetylcholine, Molecular Formula C7H16NO2, Average mass146.207 Da, Monoisotopic mass 146.117554 Da, ChemSpider ID182.

O-acetylcholine has d-values of 3.729 and 4.849 Angstrom as determined from Discovery Suite 4.1 based on the Jsmol file of Chemspider.

16.6 Interplay of the neural-glandular-muscular modalities in animal physiology

This section is duplicated in **Section 23.9**.

The interplay of the neural-glandular-muscular modalities offers an immense capability, and flexibility, to the physiology of any animal. The neural modality and the glandular modalities effectively operate in quadrature. The result is that the capabilities of each modality are multiplied together in order to describe the overall potential capability.

Figure 16.6.1-1 illustrates in block form the options for combining the neural, muscular and glandular modalities. Frame **A** illustrates a neuron as displayed previously but with a defined modulator receptor site. The receptor at this location is primarily to accommodate glandular inputs, such as epinephrine or norepinephrine. The concept (applicable to all three frames of the figure) is that there can be separate receptors for one or more glandular inputs to a neuron besides the required electrolytic receptor, neurite receptors of neural (electrical) signals and chemical inputs if required (to support stage 7 neurons). These defined receptor locations are distinct from those required for the cell to maintain homeostasis.

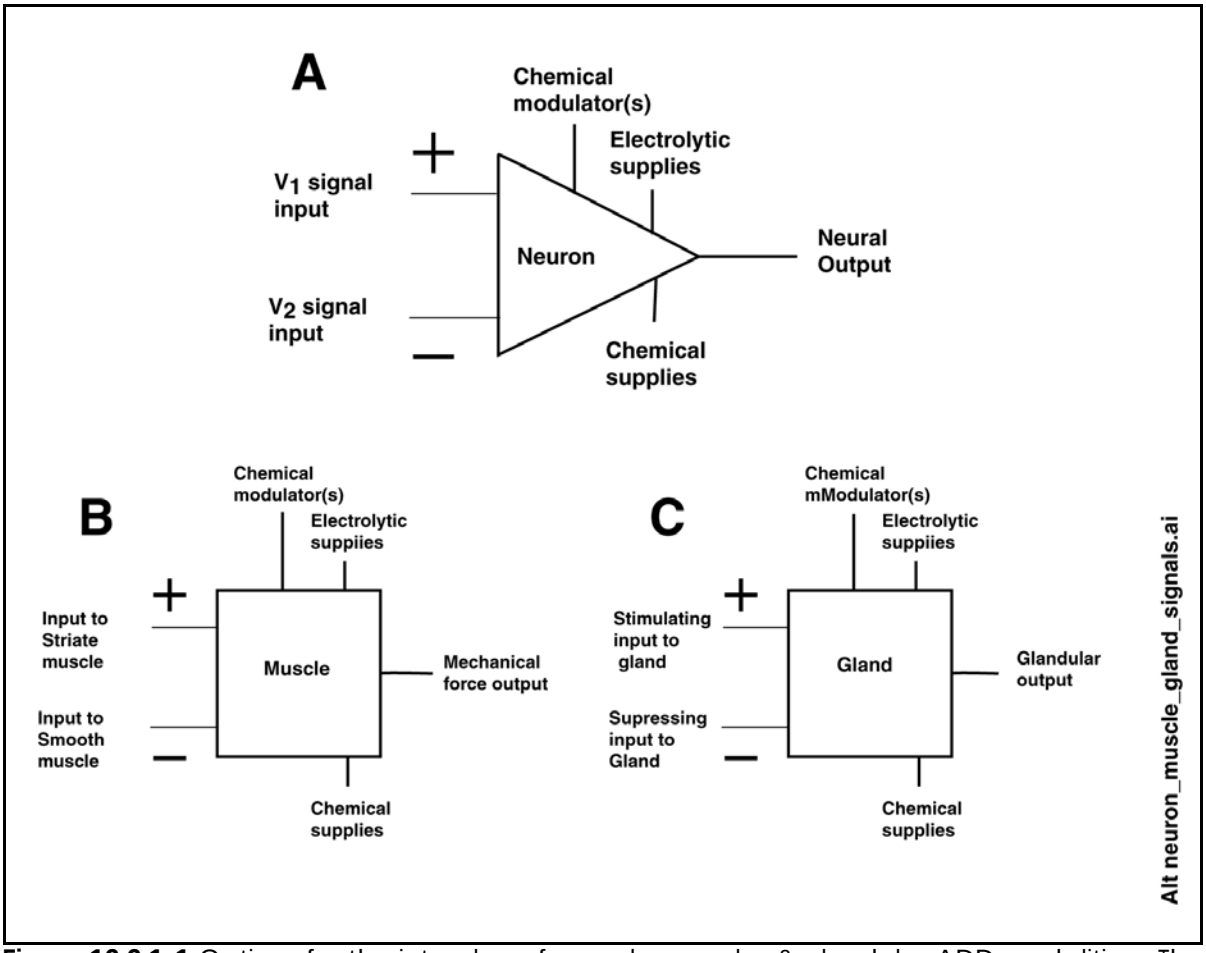

Figure 16.6.1-1 Options for the interplay of neural, muscular & glandular ADD modalities. The input signals for the neurons of stage 1 through stage 7, frame **A**, typically enter the cells via type 2 lemma as part of a tight (electrical) synapse (typically without the need for any receptor). The receptors for the modulators and the electrolytic supplies also utilize type 2 lemma but with a distinctive receptor molecule present. The chemical supplies may enter the cell via type 3 lemma. See text.

With the flexibility offered by the multiple neural signal inputs accompanied by possible modulator inputs, stage 7 neurons can exhibit great flexibility. The flexibility is much lower for stage 3 and stage 6 neurons who generally operate in the pulse mod of signaling. Most stage 1 neurons contain their own mechanism for controlling their input signals and providing automatic gain control (**Section 2.5.3** & **Section 8.1.2.5**). They do not need the flexibility of modulators and their input signals are controlled by the environment.

Frame **B** illustrates a muscle cell in block form. The same supporting receptors are shown with the output in the form of a mechanical force. The input is shown as two alternatives. The upper, positive, input causes a striated muscle to contract when stimulated by acetylcholine, ACh. The lower, negative input causes a smooth muscle to relax when stimulated by ·NO. Again, the chemical supplies are those provided in addition to those required for homeostasis.

Frame **C** illustrates a gland in block form. If representing a gland of the hypothalamus or hypophysis, the same supporting receptors are shown with the output in the form of a another hormone. The input is shown as two alternatives. The upper, positive, input causes an increase in hormonal output. The lower, negative, input causes a reduction in hormonal output

(regardless of what hormone stimulates this negative input terminal. The same supporting receptors are shown with the output in the form of a hormone. The input can be any hormone that can stimulate the receptor associated with the appropriate receptor. Again, the chemical supplies are those provided in addition to those required for homeostasis.

If frame **C** represents a peripheral gland. The potential input terminals, the electrostenolytic, and chemical supply terminals operate the same. However, the output can be considered to be hormones, or be given a different functional name, like gastric juices, perspiration, etc.

In the cases represented by frames **A**, **B** & **C**, the modulator receptors are sensitive to and selective for hormonal stimulants. Their selectivity may allow multiple hormones at each location (such as both thyroxine and either epinephrine or norepinephrine.) The potential enzyme protecting the receptor might even accommodate a master key system allowing different hormones to stimulate multiple cells in selected groups. The neurons, muscles and glands can each take advantage of the flexibility offered by the modulator channel.

The modulator and energy supply terminals in **A**, and probably in **B** & **C**, do not employ protein receptors of the GPCR family. See **Section 3.2.4**. The receptors at these locations are typically amino-phospholipids. The receptor for the electrolytic supplies is known to be phosphatidylserine molecules in a liquid crystalline array forming the outer bilayer of a region of type 2 lemma of the cell involved.

16.6.1 A hair follicle as an exemplar

Figure 16.6.1-2 illustrates a typical hair follicle of animals (including humans). The figure is available on Wikipedia. The figure is very complex because it is trying to account for virtually every aspect of the follicle and its immediate surrounding. This includes a variety of somatosensory neurons besides the one directly connected to the hair. It also includes many features associated with the vascular system. The figure shows separate sweat and sebaceous glands.

Sebaceous glands are microscopic exocrine glands in the skin that secrete an oily or waxy matter, called sebum, to lubricate and waterproof the skin and hair of mammals.

Dihydrotestosterone acts as the primary androgen, or pheromone, in the sebum of human hair follicles.

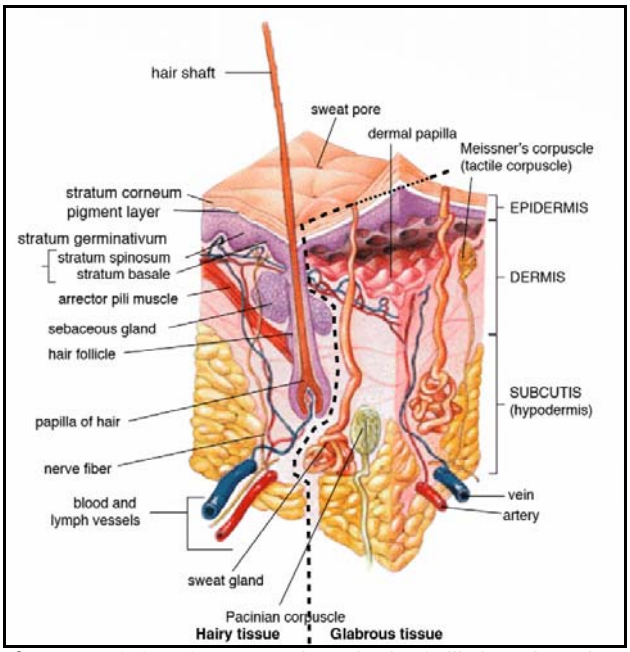

Figure 16.6.1-2 Complex hair follicle showing muscular, glandular and neural elements. See text.

Figure 16.6.1-3 provides a block diagram illustrating this same follicle in simplified form. Note the convergence of the neural

modality and the glandular (Crine) modality. A more schematic representation requires more specific knowledge of the physical interplay between the striate muscle and the sensory receptor of the neural system.

The hair is also known as a vilia. For prominent whisker hairs, the vilia are known as vibrissa. The ability of the subject to control the movement of its hairs varies significantly with species.

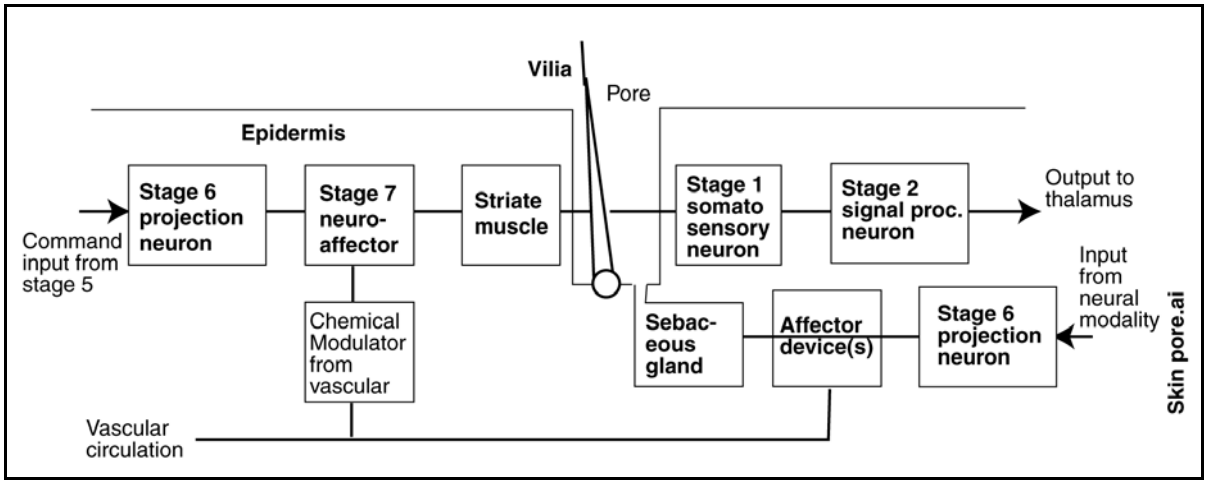

Figure 16.6.1-3 Block diagram of a hair and sweat gland in a pore ADD.

The hair is controlled as to its pointing by striate muscle (on the left). However this muscle is controlled by the stage 7 neuron shown which can receive two independent inputs; a fast input via stage 6 of the neural modality and a slower input via the endocrine system. Simultaneously, the position of the hair is sensed by the stage 1 somatosensory neuron (on the right). The somatosensory neuron may be more integrated with the striate muscle than suggested here. Simultaneously, and independently, the sebaceous gland is capable of releasing pheromones in the sebum (the total excretion of this gland).

The sebaceous gland is exocrine in its primary role. However, it may receive stimulation from the endocrine system. It is not clear from the earlier figure whether the sebaceous gland relies upon the vascular circulation for glandular stimulation or upon the neural system. This gland may be supported by multiple affectors.

It is noted that both the motions of the hair and the content of the sebum are individually susceptible to stimulation by both the neural and glandular modalities. The weighting of which sources in this figure are relied upon for stimulation is highly dependent on the species involved.

16.6.2 [Reserved]

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