Functional Anatomy of Synaptic Transmission

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Axonal Conduction and Synaptic Transmission: Electrical Signs and Ionic Fluxes

To the pharmacologist, in particular, the distinction between axonal *conduction* and synaptic or neuroeffector *transmission* is highly important because the actions of essentially all major drugs used in current clinical practice for their effects on the peripheral nervous system, as well as the actions of many centrally-acting drugs, can be explained in terms of their modifications of various stages of the latter process. The one obvious exception to this generalization is represented by the local anesthetics, which as they are generally employed produce blockade of axonal conduction. However, as these drugs are usually administered, either by local infiltration peripherally or by intrathecal or epidural injection along the spinal cord, they reach only axonal structures or dorsal root ganglion cells in significant concentrations. When local anesthetic agents are injected intravenously into experimental animals, they too block synaptic transmission at various sites, at doses far below those having any measurable effect on axonal conduction.

The electrical signs and their underlying ionic fluxes in axonal conduction and synaptic transmission can be summarized as follows.[1, 2, 3] If a microelectrode is inserted into a giant axon, such as that of the squid, or within a neuronal cell body, and the potential difference between the internal and a closely adjacent external electrode is recorded, it will be found that the internal electrode is approximately 70 millivolts (mV) negative to the external one. This internal *resting potential* (RP) of approximately −70 mV is essentially a diffusion potential, dependent chiefly upon two factors:

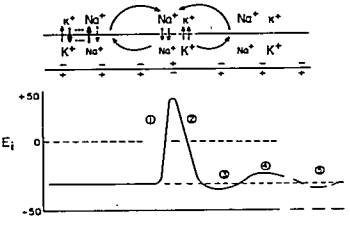

FIG. 1. *Steps in axonal conduction of the nerve action potential (NAP).*

Upper diagram. The *resting potential* (left) is based chiefly on the relatively high internal concentration of, and permeability of membrane to, K^+, with its resultant tendency for passive diffusion outward (*light arrow*); the relative impermeability to Na^+, indicated by *dashed arrow;* active transport mechanism for extrusion of Na^+ and uptake of K^+, indicated by *heavy arrows.* In the active region of the *spike* (*center*), reversed polarization is associated with sudden increase in permeability to Na^+ (upsweep), succeeded by increase in permeability to K^+ (downsweep); adjacent regions are activated by eddy currents (*curved arrows*).

Lower diagram indicates concomitant changes in internal potential with upsweep (1) and downsweep (2) of spike, followed by overshoot (3), negative afterpotential (4), and positive afterpotential (5).

(After Hodgkin, A. L., and Huxley, A. F., *J. Physiol.* 117: 500–544, 1952; others.)

the considerably higher internal concentration of potassium ion ($K^+_{in} > K^+_{ex}$), and the relatively high selective permeability of the resting axonal or neuronal membrane to potassium. Although the other ions present in the intra- and extracellular fluid also influence the RP, their total contribution is relatively minor. Now, if an electrical or other stimulus of sufficient intensity is applied to the resting axon, it will initiate a self-propagated spike or nerve action potential (NAP) which will travel the full length of the neuron in either direction (fig. 1). The upsweep of the spike, at the

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peak of which the internal potential is reversed from negative to positive, is due to a sudden, selective increase in the permeability of the axonal membrane to sodium ion, so that it flows down its concentration gradient ($Na^+_{ex} > Na^+_{in}$) from the outside to the inside; this is abruptly succeeded by a selective increase in permeability to potassium ion, the outflow of which produces the downsweep of the spike. The surrounding eddy current associated with the initial influx of Na^+ triggers off the same sequence of permeability changes in the next portion of the axon, and this brings about the self-propagation of the NAP. In myelinated axons, these processes can occur only at the relatively unmyelinated nodes of Ranvier; hence, jumping or saltatory conduction takes place, a major factor in the relatively high speed of conduction in such axons. The mechanisms of both the triggering and the successive selective permeability changes involved in the NAP are at present unknown; it has been proposed that the release of acetylcholine (ACh) by the eddy current is a critical step,[4] but most of the evidence weighs against this hypothesis.[5] The initial spike of the NAP, described above, is succeeded by less intense, more prolonged positive and negative afterpotentials, which reflect in part the metabolically-activated transport process for extruding Na^+ and accumulating K^+, and hence for maintaining the concentration gradients of these two cations across the neuronal membrane. From the foregoing description it is apparent that anoxal conduction is essentially an electrical or electrochemical process.

When the NAP arrives at the axonal terminal, it brings about the release of a neurohumoral transmitter, the agent responsible for the chemical propagation of the impulse across the synapse or neuroeffector junction (fig. 2). Electron microscopic studies and homogenate fractionation of nervous tissue have provided convincing evidence that the transmitters are stored in the synaptic vesicles, spherical structures approximately 500 Angstrom units (AU) in diameter, which are packed relatively densely at essentially all mammalian presynaptic terminals.[6, 7] The mobilization of calcium ion from the extracellular fluid or axonal membrane to the intracellular fluid of the axonal terminal is undoubtedly an essential step in the discharge of the transmitter from the synaptic vesicles to the exterior. Other possible presynaptic events involved in transmitter release are discussed below.

Following its release, the transmitter diffuses across the synaptic cleft, which ranges in width from 100 to 500 AU at various sites, and combines with specific receptors at the postjunctional membrane. Although none of the receptors has yet been characterized chemically, those which react with positively-charged transmitters (such as acetylcholine and norepinephrine) undoubtedly consist of negatively-charged groups (such as carboxyl, phosphate, or sulfhydryl) incorporated within the postjunctional membrane in highly specific orientation with respect to the other constituents of the membrane, in particular the "pores" for the passage of ions.[8] A transmitter can cause either excitation or inhibition at a given synapse. In the former case, its combination with the receptor results in a nonspecific increase in permeability to essentially all ions; the most important in this respect are Na^+ and K^+, which flow down their concentration gradients (Na^+ from outside to inside, K^+ from inside to outside), resulting in partial depolarization of the neuronal membrane which is recorded as the excitatory postsynaptic potential (EPSP). Unlike the NAP, the EPSP remains localized, but if it is of sufficient intensity the EPSP serves as a stimulus to initiate electrogenically a propagated NAP. The combination of an inhibitory transmitter with its receptors causes a selective increase in permeability to the smaller ions only, and here chiefly K^+ and Cl^- are involved; the combination of the outflow of the former and the inflow of the latter results in a stabilization or hyperpolarization of the membrane, recorded as the inhibitory postsynaptic potential (IPSP). Whether a NAP will be fired within a given period is dependent upon the algebraic sum of all the EPSP's and IPSP's that impinge upon the neuron's dendrites and soma at that time. Years ago, Sherrington expressed much the same idea in his characterization of the anterior horn cell as the "final common pathway," which could either fire or remain silent in accordance with the total balance of excitatory

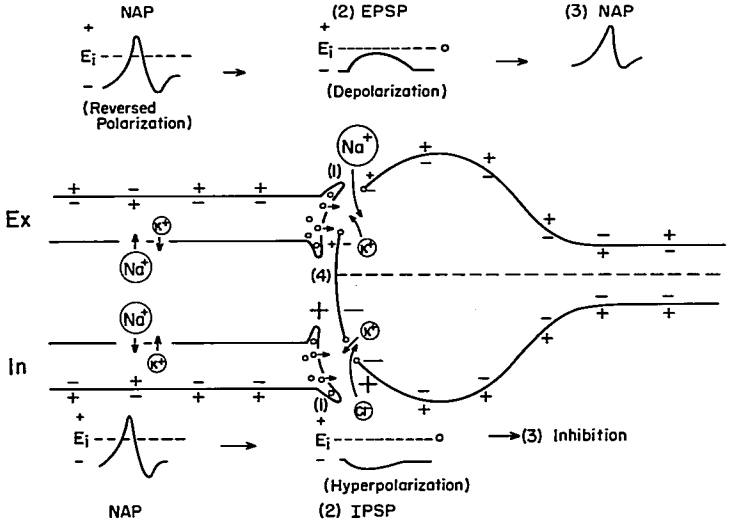

FIG. 2. *Steps involved in excitatory (Ex) and inhibitory (In) neurohumoral transmission.*
1. The nerve action potential (NAP), consisting in a self-propagated reversal of negativity (the internal potential, E_i, goes from a negative value, through zero potential, indicated by the broken line, to a positive value) of the axonal membrane, arrives at the presynaptic terminal and causes release of the excitatory or inhibitory transmitter.
2. Combination of the excitatory transmitter with postsynaptic receptors produces a localized depolarization, the excitatory postsynaptic potential (EPSP), through an increase in permeability to all ions (Na^+ and K^+ chiefly involved). The inhibitory transmitter causes a selective increase in permeability to the smaller ions (K^+ and Cl^- chiefly involved), resulting in a localized hyperpolarization, the inhibitory postsynaptic potential (IPSP).
3. The EPSP initiates a conducted NAP in the postsynaptic neuron; this can, however, be prevented by the hyperpolarization induced by a concurrent IPSP.
The transmitter is dissipated by enzymatic destruction or by diffusion.
(After Eccles (2); others. Reproduced from The Pharmacological Basis of Therapeutics (Goodman, L. S. and Gilman, A., Ed.) 3rd Edition, 1965, p. 409; The Macmillan Company, New York.)

and inhibitory impulses acting upon it from spinal and supraspinal pathways. The extreme complexity of this process is indicated by recent estimates from electron microscopic studies that as many as 50,000 boutons may terminate on the soma and processes of a single anterior horn cell.

Neurohumoral Transmitters

Acetylcholine (ACh) and norepinephrine (NE) are the most firmly established neurohumoral transmitters at present; the fibers in which they function in this capacity were termed by Dale cholinergic and adrenergic, respectively. The cholinergic pathways include (1) postganglionic parasympathetic fibers, (2) preganglionic sympathetic and parasympathetic fibers, (3) somatic motor fibers to skeletal muscle, and (4) certain fibers of the central nervous system (CNS). In addition to the adrenergic postganglionic sympathetic fibers, the evidence from both pharmacologic and histofluorescence studies that there are adrenergic pathways in the CNS now seems convinc-

ing.[9,10] Furthermore, at certain sites such as the basal ganglia, dopamine, which is ordinarily the immediate precursor of NE, appears to function as a transmitter.[11] The only fibers of the peripheral nervous system for which the transmitter has not yet been identified are the primary afferent fibers, which arise from the dorsal root ganglia and synapse within the CNS. Moreover, positive identification of the remaining excitatory and inhibitory transmitters of the CNS is still lacking. Possible candidates include 5-hydroxytryptamine (5-HT, serotonin), gamma-aminobutyric acid (GABA), substance P (a polypeptide), and a variety of mono- and dicarboxylic amino acids.

Morphology of Synapses

The synaptic or neuroeffector junction that has been most extensively studied by both light and electron microscopy is the motor endplate (MEP) of skeletal muscle (fig. 3).[12,13,14] As the motor nerve fiber approaches the muscle fiber, the former loses its myelin sheath, then terminates as a series of coils which, viewed from above has a pretzel-like appearance. The motor nerve terminal lies in a depression, known as the synaptic gutter, on the surface of the muscle fiber. There appears to be no organized cellular structure within the synaptic cleft, the space between the lower surface of the axoplasmic membrane and the modified sarcoplasmic membrane, or the subneural apparatus. The latter is folded into a complex series of invaginations which greatly increase its surface area; it is at the surface of this membrane that the receptor sites are presumably located. The distance across the synaptic cleft here is approximately 500 AU; its edges at the surface of the muscle fiber appear to be covered over by teloglial cells, derivatives of the Schwann sheath cells, as is the upper surface of the axonal terminal. Within the axonal terminal are dense concentrations of both synaptic vesicles and mitochondria; the former represent packets or quanta of ACh (estimated at approximately 1,000 molecules

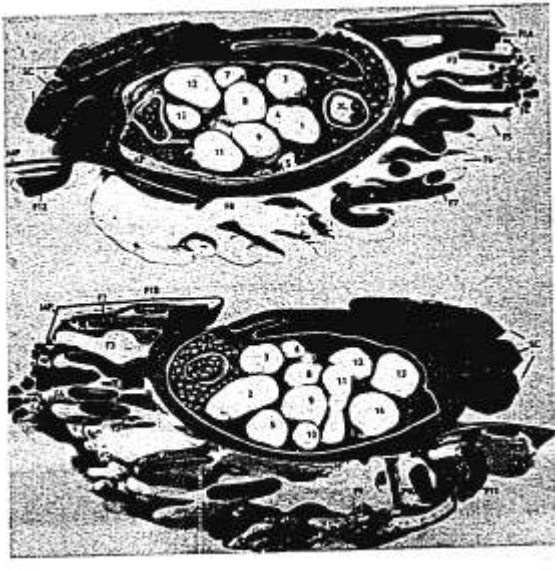

FIG. 3. *Motor endplate of skeletal muscle.* Three-dimensional reconstruction of part of a motor endplate, based on electron micrographs of serial sections. Magnification approximately ×38,000. Labeled items include Schwann cell components (*SC*), a process of which protrudes into an invagination (*I*) of the terminal axon plasma membrane (*AP*); muscle fiber plasma membrane (*MP*) and its folds (*F*, numbered); synaptic vesicles (*S*) in selected regions; mitochondria (nos. 1 to 15); double membrane components (X_1 and X_2).
From Andersson-Cedergren, 1959.[13]

per vesicle), and the latter contain oxidative enzymes that probably provide energy for the preliminary steps in its synthesis.

There are several morphologic types of synapses within the mammalian CNS, including axosomatic, axodendritic, and axo-axonic, but all have more or less the same basic structure (fig. 4).[15, 16, 17] For a complete account of the several types and the possible physiologic significance of their variations, the reader is referred to De Robertis' monograph.[15] The synaptic clefts elsewhere are narrower than that of the neuromuscular junction, the distance between the pre- and postsynaptic membranes ranging from 120 to 300 AU. Both membranes show significant thickening and increased electron density at their region of apposition. They are bridged by a series of thin, parallel intersynaptic filaments which apparently serve to anchor their spatial relationship. At many synapses, a subsynaptic web of fine filaments or canaliculi extends from the postsynaptic membrane into the underlying cytoplasm for variable distances; its function is not known. In the same region of axosomatic synapses, at several sites, dense accumulations of Nissl substance (the ribonucleic acid of the endoplasmic reticulum) have been noted; this observation has raised the interesting speculation of the possible involvement of Nissl substance in protein synthesis associated with the consolidation of memory trace and learning.

In the superior cervical ganglion of the cat, the mammalian autonomic ganglion that has been studied in greatest detail,[18] most of the synapses are axodendritic and occur *en passage;* that is, instead of ending at fixed points, the preganglionic terminals run side-by-side with the dendrites and make repeated synaptic contacts with them. At such points of contact, the Schwann sheath cells are absent and the axons are swollen and packed with synaptic vesicles. A similar relationship occurs between both the cholinergic and adrenergic postganglionic fibers and their innervated smooth muscle fibers.[19] Such an arrangement permits the almost simultaneous action of the transmitter along a considerable portion of the length of the postjunctional membrane.

In several lower vertebrates, there have been described fused synapses at various sites,

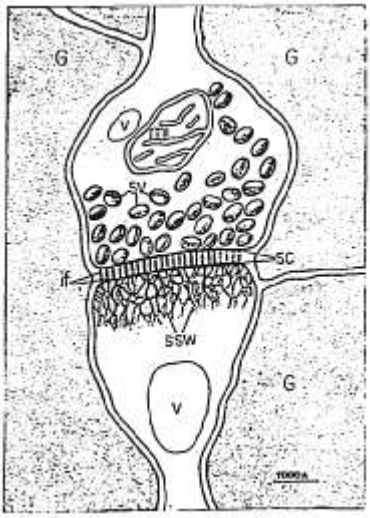

FIG. 4. *Diagram of a synapse of the brain cortex of the rat.*

At the top, the presynaptic component shows one mitochondrion (mi), a vacuole (v) and numerous synaptic vesicles, some of which are adjacent to the presynaptic membrane. The synaptic cleft (sc) is crossed by parallel intersynaptic filaments of about 50 AU and separated by 100-AU intervals. These filaments are fixed to both the pre- and subsynaptic membranes, which are slightly thickened and denser than the other surface membranes. Within the postsynaptic component there is a web of filaments (or canaliculi) of about 80 AU, which is implanted on the subsynaptic membrane on one side and extends for varying distances into the postsynaptic cytoplasm. This is the so-called subsynaptic web (ssw) of De Robertis *et al.* G-glial process that surrounds the synapse.

From De Robertis, 1964.[15]

at which no space intervenes between the pre- and postjunctional membranes and the presynaptic terminal is devoid of synaptic vesicles. Correlated with this type of structure is physiologic evidence of electrical coupling of impulse transmission without the participation of a neurohumoral transmitter.[20, 21] However, no such synapses have been noted in the mammalian nervous system to date.

FIG. 5. *Electron microscopic histochemical localization of acetylcholinesterase at the motor endplate of mouse intercostal muscle.*

A high-magnification (×63,000) view of the junctional complex, showing the axonal terminal (A) containing mitochondria (M) and numerous synaptic vesicles (v), the junctional cleft (jc), and junctional folds of the sarcolemma (sm). The electron-dense granules, 40 to 50 AU in diameter, represent gold sulfide, the reaction product in the gold-thiolacetic acid method for acetylcholinesterase and nonspecific cholinesterase. The axolemma (al) exhibits marked enzymatic activity both on the surface facing the primary junctional cleft (jc_1) and at the surface facing the teloglial Schwann cell sheath (S) (the axonal terminal is somewhat separated from the Schwann cell in this micrograph). Where the plane of section is perpendicular to the sacrolemma (arrows), the particles form a dense line about 120–140 AU in thickness. A few particles are also present in the primary (jc_1) and secondary (jc_2) junctional clefts possibly indicating some diffusion of the reaction product.

From Davis, R. and Koelle, G. B., *J. Cell Biol.* 34: 157–171, 1967.

Distribution of Enzymes Related to Neurohumoral Transmitters

There are important differences between cholinergic and adrenergic fibers with respect to the distributions and functions of the enzymes involved in both synthesis and distribution of their respective transmitters, ACh and NE.

Choline acetylase (choline acetyltransferase, ChAc) catalyzes the final step in the synthesis of ACh, *i.e.*, the transfer of an acetyl group from acetyl coenzyme A to choline. While the enzyme itself is probably synthesized in the neuronal perikaryon and transported along the axon to its terminals, the synthesis of ACh appears to take place almost exclusively at the latter sites. Although some disagreement exists, the ChAc at most synapses appears to be bound to the membranes of the synaptic vesicles.[6, 7] An active transport system in the axonal membrane concentrates choline from a low level in the extracellular fluid to a higher cytoplasmic level.[22]

A series of enzymes of varying degrees of specificity is involved in the synthesis of norepinephrine from phenylalanine, through tyrosine, dihydroxyphenylalanine (DOPA), and dopamine, as discussed in subsequent chapters of the present symposium. These enzymes also are probably transported from their sites of synthesis in the perikaryon to the axonal terminal. However, histofluorescence studies have shown that significant concentrations of NE occur throughout the perikaryon and axon as well. At the terminals of the latter, the NE is distributed chiefly between two mobile pools, within the cytoplasm and the granules or vesicles, respectively, and an intragranular reserve pool where it is complexed as an adenosine triphosphate (ATP) salt.[23]

At all sites of cholinergic transmission a high concentration of acetylcholinesterase (AChE) which promotes the rapid hydrolytic inactiva-

TABLE 1. Actions of Drugs on Synaptic and Neuroeffector Transmission

Mechanism of Action	System	Drugs	Effect
1. Interference with synthesis of transmitter	Cholinergic	Hemicholinium	Depletion of ACh
	Adrenergic	α-Methyl-*p*-tyrosine	Depletion of NE
2. Metabolic transformation by same pathway as precursor of transmitter	Adrenergic	α-Methyldopa (Aldomet)	Displacement of NE by false transmitter (α-Me-NE)
3. Blockade of transport system of axonal membrane	Adrenergic	Imipramine, Amitriptyline	Accumulation of NE at extracellular sites
4. Blockade of transport system of storage granule membrane	Adrenergic	Reserpine	Destruction of NE by mitochondrial MAO, and depletion from adrenergic terminals
5. Displacement of transmitter from axonal terminal	Cholinergic	Carbachol	Cholinomimetic
	Adrenergic (rapid, brief)	Ephedrine, tyramine	Sympathomimetic
	Adrenergic (slow, prolonged)	Guanethidine	Depletion of NE from adrenergic terminal
6. Prevention of release of transmitter	Cholinergic	Botulinus toxin	Anticholinergic
	Adrenergic	Bretylium	Antiadrenergic
7. Mimicry of transmitter at postsynaptic receptor	Cholinergic		
	Muscarinic	Methacholine	Cholinomimetic
	Nicotinic	Nicotine	Cholinomimetic
	Adrenergic		
	Alpha	Phenylephrine	Sympathomimetic
	Beta	Isoproterenol	Sympathomimetic
8. Blockade of endogenous transmitter at postsynaptic receptor	Cholinergic		
	Muscarinic	Atropine	Cholinergic blockade
	Nicotinic	*d*-Tubocurarine, Hexamethonium	Cholinergic blockade
	Adrenergic		
	Alpha	Phenoxybenzamine	α-adrenergic blockade
	Beta	Propranolol	β-adrenergic blockade
9. Inhibition of enzymatic breakdown of transmitter	Cholinergic	Anticholinesterase agents (physostigmine, diisopropyl phosphorofluoridate (DFP))	Cholinomimetic
	Adrenergic	MAO inhibitors (Pargyline, Nialamide)	Accumulation of NE at certain sites; potentiation of tyramine.

tion of ACh, is present. Hence, anticholinesterase (anti-ChE) agents, by preserving released endogenous ACh, can produce effects that resemble the continued activation of all cholinergic fibers. At the MEP of skeletal muscle, most of the AChE is located at the postsynaptic membrane (fig. 5); however, in sympathetic ganglia of the cat the AChE is almost exclusively presynaptic, whereas its relative distribution between the pre- and postsynaptic membranes varies at other cholinergic junctions.[12, 24] In addition, variable amounts of AChE are present in a great variety of noncholinergic neurons. The possible physiologic significance of these distributions is discussed in the final sections of the present chapter.

The two enzymes chiefly responsible for the breakdown of NE are monoamine oxidase (MAO) and catechol-O-methyltransferase (COMT). The former is present in the mitochondria of adrenergic terminals and elsewhere, while the cytological localization of the latter is uncertain. However, neither MAO nor COMT appears to play a significant role in terminating the effects of adrenergic nerve impulses, comparable to that of AChE in cholinergic transmission. Apparently this is accomplished at adrenergic terminals by a combination of diffusion of released NE and its active uptake back across the axonal membrane and subsequently across the membranes of the storage granules. At least two active transport systems are involved in this process; interference with either has been shown to constitute an important mechanism of drug action, as noted below.[23, 25, 26]

Pharmacology of Synaptic Transmission

As stated in the introduction, the actions of most drugs used clinically for their effects on the peripheral nervous system, as well as those of several centrally-acting drugs, are due to their modifications of various stages of synaptic transmission. On the basis of the foregoing presentation, several specific examples can be given (table 1). No attempt will be made here to discuss the effects of the listed drugs on specific organ systems or their clinical applications, since this material is covered in detail in the references cited and in other chapters of this symposium. However, a few words of explanation in regard to the table are in order.

Most of the drugs listed in table 1 are in clinical use or have been in the past. A few, such as hemicholinium (item 1), are used only as experimental laboratory tools or are primarily of toxicological interest (*e.g.*, botulinus toxin, item 6). An extremely interesting compound that falls within both categories but is not listed in the table is the puffer fish poison, tetrodotoxin. This is one of the very few substances that block axonal conduction selectively; it does so by preventing the selective permeability to sodium ion that is responsible for the rising phase of the NAP.[27]

False adrenergic transmitters, such as α-methyl-NE (item 2), act similarly to NE but are much less potent. Hence, their formation and replacement of the normal transmitter at its storage sites results in a decrease in adrenergic tone.

The accumulation of NE at certain sites in the CNS following the administration of imipramine or related drugs (item 3) is believed to be responsible for their antidepressant action.

In the cholinergic system, muscarinic receptors are located on autonomic effector cells, and nicotinic receptors at the MEP of skeletal muscle; both types of receptor are present on the neurons of autonomic ganglia and of the CNS (items 7 and 8). This accounts for the relative selectivity of various cholinomimetic and cholinergic blocking agents at the aforementioned sites. The distinction between alpha- and beta-adrenergic receptor sites, and the consequent effects of their selective activation and blockade, are discussed in subsequent chapters.

Tyramine (items 5 and 9) ordinarily has relatively weak sympathomimetic actions, brought about chiefly by its releasing endogenous NE, but it is a much more effective substrate for MAO than is NE. The combination of these two factors accounts for the severe toxic reactions that follow the ingestion of foods rich in tyramine (*e.g.*, Roquefort cheese, pickled herring) by patients receiving MAO-inhibitors.

Notably absent from the table are the gen-

eral anesthetics, hypnotics, sedatives, and several other classes of important centrally-acting drugs. Although these agents have been widely used clinically and investigated intensively for many years, their specific mechanisms of action are still largely speculative. It is likely that they affect aspects of neuronal metabolism, permeability, transport, or ultrastructure that are not yet sufficiently understood to permit the determination of their modification by drugs.

Recent Proposals of a Presynaptic Function of Acetylcholine

The aforementioned findings of the predominant or exclusive localization of AChE at the presynaptic membranes of certain cholinergic synapses[24, 28] and its presence in various noncholinergic neurons[29] have focused attention on the possible presence of cholinergic receptors also at such sites. Certain electron microscopic findings[30] and a considerable amount of pharmacological evidence[31-37] point in the same direction. Accordingly, it has been proposed that, at many sites of cholinergic transmission, the ACh released initially by the NAP may act at the same axonal terminals to prolong their depolarization and hence amplify the amount of ACh discharged to activate the receptors at the postsynaptic membrane.[28, 30] Similarly, ACh has been proposed to activate the release of the actual transmitter at the axonal terminals of a variety of noncholinergic neurons, including the neurosecretory cells of the neurohypophysis,[40] adrenergic neurons,[34] primary afferent fibers,[36] and inhibitory neurons of the CNS.[37, 41, 42] The proposed mechanisms of presynaptic functions of ACh in both cholinergic and noncholinergic transmission are summarized in figure 6. If this hypothesis proves correct, more attention undoubtedly will be directed in the future toward the development of drugs to modify cholinergic synaptic activation and blockade at the presynaptic membrane. The focusing of attention on events at the presynaptic terminals of adrenergic neuroeffector junctions in recent years has resulted in a wealth of new therapeutic agents,[43] as is amply illustrated in table 1 and in the chapters that follow.

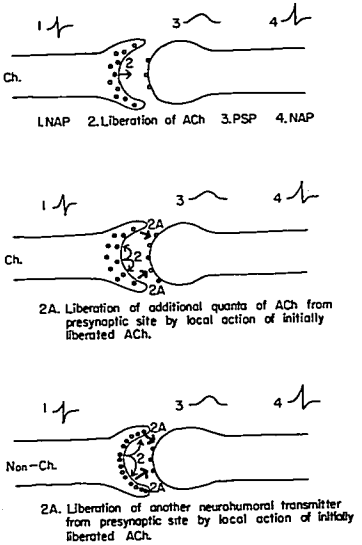

FIG. 6. *Proposed presynaptic function of acetylcholine in cholinergic and noncholinergic transmission.*

A. Standard concept (details shown in fig. 2).

B. Proposed presynaptic function in cholinergic fibers. Acetylcholine considered to act first at terminal from which liberated to activate release of (2A) additional quanta of ACh, which produce the PSP.

C. Proposed presynaptic function in noncholinergic fibers. (1) NAP liberates (2) ACh from presynaptic terminals, which acts at same terminals to effect release of (2A) another synaptic transmitter; latter produces (3) PSP, which initiates (4) NAP.

From Koelle, 1962.[39]

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The American Board of Anesthesiology, Inc.

Announcement of Policy Change

Continuing advances in sciences related to anesthesiology have resulted in significant increases in the total fund of knowledge in recent years, and the extension of training facilities and reorientation of curricula to three years of training offer new opportunities for advanced training and continuing education. Because of these changing conditions the Board has adopted the following change in policy which it hopes will encourage greater use of these opportunities.

Any individual whose application has been declared void by reason of failure to take or pass either the written or oral examination may submit a new application if it be accompanied by written certification from the director of an approved three-year residency program that the applicant has received counsel relative to a course or program of study.

Such application shall be subject to the fees, rules and privileges that apply at that time and if the applicant is adjudged to meet existing requirements he will be admitted to the examination system. This privilege shall apply retroactively without limitation but in all instances the candidate must pass both the written and oral examinations under the new application.