GANGLIONIC TRANSMISSION[1]

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Synaptic Potentials

Stimulation of sympathetic ganglia in the presence of curare-like drugs gives rise to a slowly occurring surface potential consisting in sequence of an initial negative potential (N wave), a positive potential (P wave) and a late negative potential (LN wave). The triphasic waveform has been identified in ganglia of the turtle (1), rabbit (2–4), frog (5–10), rat (11), and cat (12). In each species, pharmacological analysis of the several potentials has indicated that although transmission of the three potentials was mediated by cholinergic processes, functionally distinctive cholinoceptive sites were present in the ganglia. Whereas the N wave was depressed by the further addition of curare-like drugs, the P and LN waves were depressed by drugs related to atropine. In addition, some evidence has been presented to indicate that the P wave resulted from a two-step process involving cholinergic and adrenergic transmission (3, 7). It is clear from the foregoing that ganglionic transmission must be regarded now in terms of an intricate interaction among diverse systems. The questions remaining, however, are centered primarily around the problem of determining the precise relationship that exists between synaptic events and the several surface waveforms.

The synaptic potential is regarded as the primary indicator of the postjunctional action of the transmitter substance. When the synaptic potential is characterized by a depolarization (decrease in membrane potential) that leads to the generation of action potentials or facilitates the transmission process, the potential is designated as an excitatory postsynaptic potential (EPSP). By contrast, when the synaptic potential is characterized by a hyperpolarization (increase in membrane potential) that results in the suppression of synaptic activity, the potential is designated as an inhibitory postsynaptic potential (IPSP). Other characteristics of the synaptic potential include a time-course that is prolonged when compared with the action potential, and a change in amplitude that varies inversely with the distance between the site of generation and the site of recording. It is against this background that the relationship between the N, P and LN waves and synaptic events should be considered.

There is little reason to question the proposal that the N wave recorded

[1] The survey of literature pertaining to this review was concluded in May 1968.

from the surface of sympathetic ganglia is mediated by the same processes that underlie the EPSP recorded from single ganglion cells by means of microelectrodes (12–14). Both potentials are nonregenerative events, have relatively long time-courses, give rise to action potentials upon attaining critical amplitudes, and are modified in the same way by inorganic ions and drugs. Because of these parallel characteristics, it is reasonable to conclude that the N wave reflects the primary postsynaptic event leading to the transmission of impulses in sympathetic ganglia. By contrast, evidence for the proposal that the atropine-sensitive P wave reflects the presence of a slowly occurring IPSP and that the atropine-sensitive LN wave reflects a slowly occurring EPSP, has been more difficult to establish.

Libet (12) found in mammalian sympathetic ganglia that the P and LN wave had a postjunctional origin (probably ganglion cell soma) that was under the control of the preganglionic nerve terminals. Like the N wave, the P and LN waves decreased in amplitude when the recording electrode was moved away from the ganglion surface to the postganglionic nerve and could not be detected when the electrode was placed on the preganglionic nerve. These observations were viewed by Libet to indicate a postjunctional origin for both potentials. Evidence for prejunctional control of the waveform included the findings that (*a*) antidromic stimulation of the postganglionic nerve failed to evoke the triphasic waveform; (*b*) tetanic orthodromic stimulation enhanced the amplitude of all components of the waveform; and (*c*) decreasing transmitter output by decreasing the ratio of Ca/Mg in the bathing fluid depressed all components of the waveform. In general, the observations support the earlier findings (3) that all three waveforms contained a cholinergic step in their activation.

By means of intracellular recording from the cells of amphibian ganglia it has been possible (*a*) to demonstrate the presence of heterogeneous cholinoceptive sites; (*b*) to determine their intraganglionic distribution; and (*c*) to obtain some data on the question of slowly occurring IPSP's and EPSP's in sympathetic ganglia and their relationship to the P and LN waves (5–10). It is important to note that two major cell types exist in the amphibian ganglia (6, 15). Those cells receiving preganglionic inputs from B fibers (rapid conduction) are termed B neurons and those cells receiving inputs from preganglionic C fibers (slow conduction) are termed C neurons. It is also worth noting that there is an anatomical separation of the B and C preganglionic inputs to the ganglion cells of the caudal ganglia of the sympathetic chain that makes it possible to activate independently either the B or C neurons of the ganglia of the frog.

In the main, the slowly occurring IPSP was found only in the C neurons (6, 7). When evoked by a single shock, the slow IPSP persisted for approximately 750 msec and attained amplitudes of about 2 mV. These values were increased to 2 to 4 sec and 5 to 15 mV when the C neurons were stimulated at a rate of 10 to 20 shocks/sec for 1 sec. The synaptic delay for the IPSP was of the order of 100 msec. An IPSP was observed in C neurons

when tetanic volleys of 40 to 80 per sec were applied to B neurons. The pharmacological characteristics of the slow IPSP were generally similar to those of the P wave of mammalian ganglia. The slow IPSP was unaffected by curarelike drugs but sensitive to blockade by low concentrations of atropine. In contrast to the P wave of mammalian ganglia, however, the slow IPSP of frog ganglia was resistant to blockade by dibenamine. The best evidence for a slowly occurring EPSP with characteristics similar to the LN wave was obtained in frog sympathetic ganglionic B neurons (6, 7). An atropine-sensitive slow EPSP with amplitudes of 2 to 5 mV and duration of 20 to 30 sec was was found in about one-third of the cells after brief periods of preganglionic B fiber stimulation.

Thus, in the frog sympathetic ganglion the distribution of synaptic potentials was as follows: the initial EPSP and slowly occurring IPSP were more readily detected in C neurons, and the initial EPSP and the slowly occurring atropine-sensitive IPSP more readily found in B neurons. In the superior cervical ganglia of the rabbit, intracellular recording revealed the presence of all three types of postsynaptic potentials in the same ganglion cell (16).

Up to this point it has been possible to demonstrate that the surface potentials and intracellularly recorded slow potentials have most of the electrophysiological characteristics necessary to warrant the conclusion that they are or reflect synaptic potentials. It now remains to be determined if these potentials fulfill the criteria established for synaptic potentials by determining whether they (*a*) modify transmission through the curare-sensitive system, or (*b*) provide an alternative pathway for transmission to occur by way of atropine-sensitive sites.

While it is true that atropine has actions on a variety of ganglionic activities, there is no evidence to show that it modifies transmission of single impulses when used in the doses required to abolish the several waveforms and PSP's. It is important to bear this in mind since the proposal that the slow waves reflect inhibitory or excitatory modulating influences in the ganglia requires that their abolition lead to significant changes in transmission. The best indications for a modulating influence of these atropine-sensitive systems have been obtained only when rapid repetitive preganglionic stimulation was used. As a consequence, these experiments may be difficult to interpret because of the complexities introduced by the combination of repeated tetanic preganglionic stimulation, the administration of classical ganglionic blocking drugs, and the need for atropine-like drugs for purposes of pharmacological analysis. In many instances it is not possible to determine if the altered response was due to the application of atropine or the prior conditioning of the ganglia with tetanic stimulation. These limitations notwithstanding, studies have been reported which show some excitatory and inhibitory relationships between the surface waveform and synaptic transmission.

Using the isolated superior cervical ganglion of the rat, Dunant & Do-

livo (11) reported that low concentrations of atropine enhanced homosynaptic facilitation. Homosynaptic facilitation was studied by the use of appropriately spaced pairs of preganglionic stimuli. In the presence of atropine, the increase in the amplitude of the second spike of the pair was greater than that observed in untreated ganglia. They reported also that there was a temporal correlation between the decay of the P potential and the enhancement of spike amplitude that occurs spontaneously during the course of 6 to 10 hr. In general, these findings are similar to those of Libet (17) and both authors interpret their findings to indicate a causal relationship between the P potential and homosynaptic facilitation. One possible source of disagreement comes from the findings by Takeshige & Volle (18) that small doses of atropine had no effect in the cat sympathetic ganglion on the increase in spike amplitude that occurred when the frequency of preganglionic stimulation was increased over the range of 0.1 to 3.0 cps.

Dunant & Dolivo (11) also found that small doses of atropine depressed the posttetanic potentiation (10 cps) of test volleys and partially abolished the afterdischarge produced by tetanic stimulation of ganglia treated with physostigmine. Both effects of atropine were attributed to the abolition of the LN wave. Once again, the findings are similar to the earlier reports of Libet (17) relating facilitation of transmission to the LN wave, and the findings of Takeshige & Volle (18, 19) showing atropine-sensitive posttetanic depolarization and the atropine-sensitive transmission of action potentials during repetitive stimulation of ganglia treated with physostigmine and *d*-tubocurarine.

With a somewhat similar approach, Nishi & Koketsu (9) have shown that tetanic stimulation (50/sec for 20 sec) of bullfrog ganglia treated with nicotine caused an afterdischarge of the ganglion cells that persisted for as long as 5 min. When subjected to pharmacological analysis, the afterdischarge was found to be made up of a component that was sensitive to blockade by atropine (early afterdischarge) and a component that was unaffected by atropine (late afterdischarge). Coincidental with the two afterdischarges was the occurrence of bimodal surface depolarization which was termed the LN wave and the late late negative wave (LLN wave). Intracellular recording revealed a slow EPSP (LN wave) and a late slow EPSP (LLN wave) in ganglia stimulated at a rate of 10 to 50 cps in the presence or absence of nicotine. When evoked in the presence of nicotine, the slow EPSP and late slow EPSP triggered in the afterdischarges. Atropine prevented the early afterdischarges, the LN wave, and the slow EPSP but had no effect on the late afterdischarges, the LLN waves or the late slow EPSP. The latter findings were regarded as evidence for noncholinergic transmission.

It is noteworthy also that brief tetanic stimulation during the afterdischarge of ganglia treated with nicotine caused a marked inhibition of the firing (8, 10). The inhibition of the afterdischarge was associated with a P wave (recorded extracellularly) and both the inhibition and the P wave

were prevented by atropine. Accordingly, it was suggested that the inhibition and P wave were related events and that the P wave was due to slow IPSP. Once again, these are complicated experimental designs that involve the use of several drugs and tetanic stimulation, and caution should be exercised in the interpretation of the findings.

Drug-Evoked Potentials

The similarities between the activity produced by preganglionic stimulation and that produced by the application of acetylcholine have provided an important part of the evidence establishing acetylcholine as the mediator of transmission in the ganglia. The ganglionic depolarization evoked by acetylcholine and the EPSP (N wave) have similar physiological and pharmacological properties. Both are slowly occurring waves of depolarization that are localized to the ganglion cell body and are depressed by curare-like drugs (e.g., 13, 14).

Koketsu, Nishi & Soeda (20) have found that the iontophoretic application of acetylcholine to frog ganglion cells evoked a bimodal wave of depolarization. The fast component of the waveform required 15 to 500 msec to attain peak amplitude; the peak time for the slower component was 5 to 10 sec. In general, the amplitude of the slower component was one-fourth that of the fast component. When the fast component exceeded the threshold (−40 to −45 mV), single or repetitive action potentials were generated. The slow component never attained the amplitude required to induce firing. Whereas the fast component was blocked by curare-like drugs, the slow component was blocked by atropine. Thus, there was some pharmacological correspondence between acetylcholine-induced potentials and trans-synaptic slow potentials.

The contention that applied acetylcholine imitates the transmission process in frog ganglia has been questioned by Riker (21). In 69 cells from 17 frogs' ganglia, Riker found that acetylcholine (5.5 m*M*) added to the stream of saline solution flowing through the ganglia caused depolarization of each cell (2 to 26 mV) but firing of only eight cells. Since the rise time to peak depolarization was 500 msec for most of the cells, the failure of acetylcholine to cause firing was not attributed to a slow onset of action. Moreover, the action potentials generated in the eight cells in response to acetylcholine had characteristics similar to antidromically-activated action potentials. On the basis of these observations, the conclusion was reached that acetylcholine failed to satisfy the requirements of mimicry.

However, a number of points must be raised before this conclusion can be accepted. First, it is important to know the threshold membrane voltage for firing in each of the cells that failed to respond to the acetylcholine. Regardless of the site of depolarization produced by acetylcholine, it must be established that the depolarization either reached or failed to reach the threshold for firing. The possibility that 5.5 m*M* acetylcholine caused a depolarization that failed to reach the threshold for firing is suggested by the

fact that when the concentration was increased to 16.5 m*M*, firing occurred in five out of 12 cells in four ganglia. Second, if the concept of mimicry is to be challenged, it must be proven that the material acting on the junction was acetylcholine. It has been shown in the isolated superior cervical ganglion of the rabbit that acetylcholine applied to the sucrose gap chamber reaches the ganglion primarily as choline (4). Third, there is no compelling reason why the spikes activated by acetylcholine under these conditions should have the configuration of spikes activated by preganglionic nerve stimulation. Since the depolarization produced by 5.5 m*M* acetylcholine persisted for 30 sec to 2 min, there is no basis for expecting the action potentials to be any different from those produced by persistent depolarization of ganglionic cell soma evoked by other means (direct depolarizing current). Accordingly, the appearance of a spike with a contour similar to spikes activated by antidromic stimulation does not indicate a priori that the spike was activated at some site distal to the synaptic surface or originated at the postganglionic nerve. (This issue should not be confused with the fact that acetylcholine-induced blockade of the orthodromic spike may unmask the synaptic potential (22). As described below, the mechanism of blockade by depolarizing cholinomimetic drugs may involve several processes.)

Finally, the question of mimicry notwithstanding, an explanation must be provided for the failure of depolarization by acetylcholine to cause spike generation more consistently. Regardless of the ultimate identity of the transmitter process, depolarization to adequate values of ganglion cells should lead to the activation of action potentials, since in frog sympathetic ganglia, the threshold for spike activation was the same for direct stimulation of the ganglionic cells and the synaptic potentials (44). While there is general agreement that applied acetylcholine may act at many sites in the ganglia, the possibility that firing was not observed because of blockade at the axon hillock or postganglionic axon cannot explain the data, since there was no depression of antidromically evoked spikes by the doses of acetylcholine used. In summary, it is not reasonable to expect applied drugs to reproduce faithfully the transmission process unless they are applied to the synaptic surface in exactly the same way as the transmitter is applied by the nerve ending. Nowhere is the difference between transmitter action and applied acetylcholine more apparent than in the rate of rise to peak amplitude. Whereas the time to peak amplitude for applied acetylcholine was approximately 500 msec (21), the time to peak amplitude for the synaptic potential was 5 msec.

It has been suggested that the slow IPSP of sympathetic ganglia is mediated by catecholamines released from chromaffin cells to act upon the ganglion cell soma (3, 5, 11, 12). In keeping with this suggestion is the finding that epinephrine and norepinephrine caused hyperpolarization (5 mV or more) of both the C and B neurones of frog ganglia (7). Note should be made, therefore, that while the catecholamines hyperpolarized both cell types, the slow IPSP occurred primarily in the C neurones. In addition, dibenamine depressed the slow IPSP only weakly in frog ganglia (6). Fur-

thermore, frog ganglia, unlike mammalian ganglia, do not demonstrate adrenergic nerves terminating on the ganglion cell bodies or axons (23). Thus, the potential role for catecholamines in ganglionic transmission has not been resolved by the more recent experiments.

The alternative possibility that acetylcholine itself, may function as the transmitter for the P wave (IPSP) is based on the finding that cholinomimetic substances have been shown to evoke surface potentials in the superior cervical ganglion of the cat, and consisting of hyperpolarization followed by depolarization (24, 25, 26). Muscarine, methacholine, and oxotremorine caused ganglionic hyperpolarization and blockade that was prevented by atropine (26). The drugs also caused ganglionic depolarization and firing that were sensitive to blockade by atropine (26, 27). These findings are in contrast to those obtained with methacholine in frog ganglia (28), where the cholinomimetic substance was shown to cause depolarization sensitive to blockade by either hexamethonium or atropine and a blockade of transmission during and after the period of depolarization. In connection with the latter finding, there is some evidence in the cat that the blockade of transmission produced by methacholine may be unrelated to the hyperpolarization of the cells coinciding with the blockade (25).

Most of the drugs related to muscarine have been shown to cause in mammalian ganglia a low amplitude depolarization and firing that were sensitive to blockade by atropine-like drugs. These include muscarine (26, 27, 29), carbachol (27), oxotremorine (26), pilocarpine (19), and synthetic compounds known as McN-A-343 (30), and AHR-602 (26).

Atropine-Sensitive Transmission

Hilton & Steinberg (31) have concluded that the hypertensive response to an elevation of intracranial pressure is mediated in part by way of atropine-sensitive sites in autonomic ganglia. Whereas treatment of animals with large doses of chlorisondamine caused a partial reduction in the pressor response to increased intracranial pressure, the combination of chlorisondamine and atropine-like drugs caused an almost complete reduction of the response.

More direct evidence of atropine-sensitive transmission has been obtained in mammalian sympathetic ganglia treated with repetitive preganglionic stimulation and a variety of drugs (32, 33). Trendelenburg (32) made the observation that nicotine unmasked atropine-sensitive transmission in the superior cervical ganglion and enhanced the response to nonnicotinic stimulating agents. The demonstration of muscarinic transmission in the stellate ganglia of the dog was based on a study of the effects of hexamethonium-like drugs on the response of the heart to preganglionic stimulation over a wide range of frequencies (33). Under these conditions, the hexamethonium-like drugs displaced the frequency-response relationship toward higher frequencies of stimulation. By contrast, the combination of atropine and hexamethonium blocked the effects of preganglionic stimulation. In a study of the effects of anticholinesterase inhibitors on the two

forms of transmission in the stellate ganglion, it was found that transmission through nicotinic sites was not altered by doses of physostigmine that caused marked potentiation of transmission through muscarinic receptors (34). Although the full significance of the findings remains to be established, they accord with the earlier demonstration of the unmasking of muscarinic sites in sympathetic ganglia by anticholinesterase agents and other depolarizing procedures (18).

Ganglionic Blockade by Nicotinic Drugs

The application of carbachol, tetramethylammonium, or acetylcholine to isolated sympathetic ganglion cells of the frog, activated either by preganglionic shocks or antidromic postganglionic stimulation, caused a complex pattern of events to occur (22). When applied in adequate doses, each of the drugs caused a decrease in the resting membrane potential, a decrease in membrane resistance and, initially, a blockade of the action potential activated either by orthodromic or antidromic stimulation. Although the antidromic spike, membrane resistance, and membrane depolarization had the same time-course of recovery, blockade of the orthodromic spike persisted beyond this period. Thus, the point was made that the response of frog ganglion cells to nicotinic drugs was composed of two components, one coinciding with depolarization and the other, after depolarization has subsided. Because the drugs also caused a decrease in the amplitude of the miniature synaptic potentials, it was concluded that the drugs depressed the postjunctional chemosensitive receptors.

In a similar series of experiments, Riker (35) presented data on the blockade of transmission produced by acetylcholine. The conclusion that acetylcholine caused blockade by an effect on the unmyelinated presynaptic nerve terminal and not by depolarization of the ganglion cell was based on the observations that (*a*) acetylcholine depressed the orthodromic spike in doses that had no effect on the antidromic spike; (*b*) the relief of acetylcholine-induced depolarization by hyperpolarizing currents failed to restore transmission; (*c*) there was no obvious relationship among dose of acetylcholine, blockade of transmission, and extent of depolarization; and (*d*) extrinsic depolarizing currents failed to block the orthodromic spike. There is little doubt that these findings represent an impressive array of data to show the separation of ganglionic depolarization and blockade of transmission.

Several factors should be kept in mind when considering these experiments. First, the data do not preclude depolarization blockade by acetylcholine. The classic demonstration that large doses of acetylcholine and other nicotinic drugs prevent ganglionic responses to specific and nonspecific (e.g., potassium) stimulants is explained best in terms of ganglionic cellular depolarization. Ginsborg & Guerrero (22) showed that acetylcholine depressed the antidromic spike by depolarization of the cell soma. Second, there is no evidence to show that the block was due to acetylcholine and not to choline (*vide supra*). Finally, it is not possible in sympathetic ganglia to

identify with certainty a presynaptic locus of inhibition with this technique. As indicated above, the decrease by acetylcholine in the amplitude of miniature synaptic potentials indicates a depression of postjunctional sensitivity of the chemoreceptive sites.

Electrophysiological evidence to date has been interpreted by some (21, 22, 35) to deny the existence of an excitatory presynaptic site of action for acetylcholine, carbachol, and related drugs. By contrast, there is rather direct evidence to show that carbachol caused the release of acetylcholine into the fluid perfusing the superior cervical ganglion of the cat (36, 37). The ability of carbachol to cause the release of acetylcholine can be explained only in terms of a presynaptic site of action. Thus, the electrophysiological evidence for excluding a presynaptic site in frog ganglia of excitatory action of carbachol and acetylcholine must be reconciled with the data obtained in the cat. In this connection, Koketsu & Nishi (38) have reported that acetylcholine depolarized the preganglionic nerve of the bullfrog and rat sympathetic ganglia. The depolarization was depressed by nicotine or *d*-tubocurarine, was unaffected by atropine, and was enhanced by anticholinesterase agents. In keeping with this finding are the additional observations that a slow negative potential was evoked in the preganglionic nerve terminal by repetitive stimulation and the neurally evoked potential and was enhanced by anticholinesterase agents. Whether the depolarization leads to excitation and transmitter release or blockade of the nerve endings remains to be determined.

Gebber (39) has provided additional evidence to show that nicotine, like acetylcholine, may cause ganglionic blockade by mechanisms unrelated to depolarization of the cells. Interpretation of the data is complicated by the facts that a large population of cells was monitored simultaneously, and by the diverse actions of nicotine. For example, part of the evidence for a dissociation of depolarization and blockade was the fact that tetanic preganglionic stimulation antagonized the block. However, tetanic stimulation will antagonize nicotine-induced block when applied some time after the block has been established but not early in the time-course of the block (unpublished experiments by the author). Thus, it is possible to have the situation occur where surface depolarization was present because some cells were depolarized but transmission was blocked because many cells were desensitized. Under these conditions, tetanic stimulation would be expected to antagonize the block of transmission for those cells previously depolarized but now desensitized. Clearly, if a test for depolarization blockade is to be made, it must be performed at the appropriate time, since prolonged depolarization may lead to any number of undefined changes in the ganglion cells (desensitization, sodium inactivation, etc.).

With tetramethylammonium as the prototypical drug, Gebber & Volle (39) described a dual blockade of transmission in the superior cervical ganglion of the cat that was characterized by a sequential pattern of depolarization, interphase recovery, and hyperpolarization. Because the blockade occurring during the period of hyperpolarization was antagonized by the prior

administration of ouabain, Gebber & Volle suggested that the hyperpolarization was due to a metabolic exchange of sodium and potassium ions and was the basis of the late-occurring blockade. Later studies showed that dimethylphenylpiperazinium caused a blockade of transmission with features essentially the same as those of tetramethylammonium (40, 41). However, when the concept of a metabolically generated hyperpolarization and blockade was tested by studying the effects of dimethylphenylpiperazinium on transmission in ganglia perfused with a medium containing lithium ions as a partial substitution for sodium ions, it was found that the hyperpolarization was abolished but the blockade of transmission was increased (42). Accordingly, there was clear evidence to indicate that the ability of tetramethylammonium and dimethylphenylpiperazinium to cause hyperpolarization was unrelated to their ability to block transmission. However, it is possible that the drug-induced hyperpolarization did depress the ganglionic responses to injected drugs, since the firing evoked by 5-hydroxytryptamine and potassium ions was depressed by dimethylphenylpiperazinium during the period of hyperpolarization (42, 43).

A mixed action of nicotine on sympathetic ganglia has been observed when repeated injections of relatively large amounts of the drug were made (45). As expected, all stimulating agents were ineffective when applied to the ganglion immediately after the administration of nicotine. However, during the persistent blockade produced by the repeated doses of nicotine, the responsiveness to muscarinic and a number of nonnicotinic stimulating agents either recovered to control values or was enhanced. In the case of angiotensin, the facilitation of the response during nicotine-induced blockade of transmission was prevented by hexamethonium. For this reason, the possibility was raised that there was a slight, persistent depolarization during the late phase of blockade by nicotine. Electro-physiological data to support this view have been obtained (39). Alternatively, it is possible that the late effect of nicotine reflected a curare-like action of nicotine. Ganglionic stimulation by muscarinic drugs has been shown to be enhanced by *d*-tubocurarine and mecamylamine (46–49). As was found with nicotine, hexamethonium prevented the excitatory effects of *d*-tubocurarine.

Conclusions

Although the precise role played by the several systems present in sympathetic ganglia remains to be determined, it is now quite clear that they do exist and must be taken into consideration in future studies of the transmission process. While techniques used in most studies have been adequate to demonstrate the activation of the three cholinergic synaptic events, it must be kept in mind that the procedures for activation of the atropine-sensitive sites have been relatively complicated. Obviously, the question of a physiological role for the several sites is clouded by the technique used.

From the viewpoint of the pharmacology of transmission, it is clear that attention must be given not only to pharmacologically distinctive cholino-

ceptive sites, but also to the possibility that applied drugs may have actions at a number of anatomical sites. Accordingly, depolarization induced by a drug may cause firing at one site and blockade at another. As always, care must be exercised when attempts are made to understand naturally occurring mechanisms on a refined level on the basis of applied drugs.

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