THE AUTONOMIC PHARMACOLOGY OF THE BLADDER

N. TAIRA
Department of Pharmacology, Tohoku University School of Medicine, Sendai, Japan

INTRODUCTION

The mammalian urinary bladder (called simply the bladder in the present review) receives both parasympathetic and sympathetic innervations. However, the response of the bladder to parasympathetic nerve stimulation is particularly resistant to blockade by atropine, unlike that of the heart and the iris. Because of this atropine-resistance most pharmacological works on the bladder have been devoted to elucidation of the nature of parasympathetic postganglionic fibers. The bladder consists of two functionally different units, the detrusor and the trigone, and the two units respond differently to sympathetic nerve stimulation and to exogenous catecholamines. Moreover, the responses show considerable species differences. Thus, the mode of action of the released transmitter and of exogenous catecholamines have also been the main subject of the autonomic pharmacology of the bladder. By use of pharmacological tools that have been developed in the past two decades some of these problems have been solved, but some still remain unsolved. The present review is, thus, inevitably concerned with these problems. Information obtained by modern morphological techniques about termination of parasympathetic and sympathetic postganglionic fibers in the bladder appears helpful for pharmacological understanding of the nature of these fibers and their site and mode of action. Therefore, the present review starts with a brief account of this.

TERMINATION OF PARASYMPATHETIC AND SYMPATHETIC POSTGANGLIONIC FIBERS IN THE BLADDER

Histochemical studies with the light microscope carried out so far on the cat, dog, rabbit, and rat bladders (1–4) have indicated that there is a rich and uniform distribution of acetylcholinesterase (AChE)-positive fibers in all layers of not only the detrusor muscle but also the trigone or corresponding area. El-Badawi & Schenk (1) have described how such fibers, unquestionably parasympathetic postganglionic, form a neuroterminal plexus that surrounds individual smooth muscle cells in the bladder wall. Electron microscopic studies of the cat (5), guinea-pig (6), mouse (7), and rat (6, 8) bladders have also revealed that nerve fibers are related to smooth muscle cells in such great intimacy that every smooth muscle cell has single axon

terminals at the narrow intercellular space. Although these single nonmyelinated axons are ensheathed by Schwann cells, the terminal axons are partially free of their Schwann cell sheath and come to lie within 400–600 Å of the smooth muscle cell membranes (5, 8). Sometimes, especially in the mouse bladder, these partially unsheathed axons form depressions or grooves on the surface of the smooth muscle cells. In these instances the space between the axonal and smooth muscle cell membranes is about 200 Å. The partially unsheathed axons contain synaptic vesicles, mostly agranular and 200–400 Å in diameter, and mitochondria (8). In the bladder such nerve-muscle contact is considered to construct parasympathetic neuromuscular synapses in the functional sense. Such neuromuscular synapses, however, are not specific for the bladder. Essentially the same type of neuromuscular synapses has been found in the sphincter pupillae of the rabbit iris, which is likewise profusely innervated by parasympathetic postganglionic fibers (9). In view of this, even with the aid of the electron microscope, the question why the parasympathetically induced contraction is easily blocked by atropine in the sphincter pupillae and not in the bladder cannot be answered.

As elsewhere, fluorescence histochemical techniques have played a definitive role in elucidation of termination of adrenergic sympathetic postganglionic fibers in the bladder (1–4, 10). In contrast to uniformly profuse termination of parasympathetic postganglionic fibers in all muscle layers throughout the bladders of cats, dogs, rabbits, and rats, termination of adrenergic fibers shows a marked regional difference in the same species. In the muscle layers of the trigone, or corresponding area, adrenergic fibers are abundant, while toward the dome they become sparser (1, 2, 4, 10). Finally, at the dome adrenergic fibers are found only between groups of muscle fibers or between muscle bundles except around the blood vessels (1). Hamberger & Norberg (10) have even described how the detrusor muscle is essentially devoid of adrenergic innervation. Even in the trigone area strands of fine varicose fibers with yellow or yellow-green fluorescence, which is characteristic of primary catecholamines, are not associated with individual smooth muscle fibers (1). In contrast to the less intimate relation of adrenergic fibers to the detrusor muscle, in the cat, dog, and rabbit bladders fluorescent adrenergic nerve terminals form basket-like arrangements around nonfluorescent or AChE-positive ganglion cells in intramural ganglia (3, 10). On the basis of this observation, Hamberger & Norberg (10) have suggested that adrenergic fibers may control the detrusor muscle indirectly by modifying parasympathetic ganglionic transmission. El-Badawi & Schenk (3) have proposed both direct and indirect control of the detrusor by adrenergic sympathetic fibers.

Nature of Parasympathetic Neuromuscular Transmission in the Bladder

As described above, the detrusor muscle of the bladder is profusely innervated by AChE-positive fibers. Despite this histochemical feature the

bladder contraction caused by parasympathetic nerve stimulation or by nicotinic ganglionic stimulating agents is highly resistant to blockade by atropine or atropine-like agents (11–30). Normally, however, the bladder contraction caused by muscarinic agents or anticholinesterases is readily abolished by atropine (12–21, 23–26, 28–30). Because of this abnormal behavior of the bladder toward atropine, research on the autonomic pharmacology of the bladder has been very much concerned with the problem of the nature of chemical transmission between parasympathetic postganglionic fibers and the detrusor muscle. Despite the atropine-resistance, until the middle 1950s the concept that parasympathetic postganglionic fibers to the bladder, even if not all, are cholinergic, had been based mainly on potentiation by anticholinesterases of the bladder contraction caused by pelvic (preganglionic) nerve stimulation (17) and on the presence of an acetylcholine (ACh)-like substance in the bladder (31), as well as on the partial effectiveness of atropine itself (11). However, doubt remains as to whether the potentiation by anticholinesterases might have been due to their actions at the ganglionic level, and if the source of the ACh-like substance might have been of preganglionic origin. Thus, after the middle 1950s more rigorous experiments have been performed to test these points by using the bladder in which parasympathetic fibers are considered to be purely postganglionic. In addition, experiments have been done on such bladders by using pharmacological tools that impair specifically cholinergic transmission, i.e., *botulinum* toxin and hemicholinium-3.

Most bladder strips from the rabbit (19) and the rat bladder (24, 25) have been shown to be pharmacologically ganglion-free and consequently innervated by purely postganglionic fibers of the parasympathetic nerves. In most strips from the rabbit bladder, contractions caused by electrical stimulation of the nerve fibers adjoining the blood vessels are unaffected by hexamethonium or tetraethylammonium (TEA) (19). The preparations are unresponsive to a nicotinic ganglionic stimulating agent, 1,1-dimethyl-4-phenylpiperazinium iodide (DMPP) (19). Contractions of the rat bladder both in vitro (24, 32) and in situ (25) elicited by electrical stimulation of the vesical nerves adjoining the ureter are unaffected by hexamethonium-like agents. The in vitro preparations are unresponsive to nicotinic ganglionic stimulating agents (24, 32). Histological examination has also demonstrated that the rat bladder is almost devoid of ganglion cells (33). In such ganglion-free bladder preparations anticholinesterases, i.e., physostigmine (19, 24, 25), neostigmine (19), or diisopropyl fluorophosphate (DFP) (19), potentiate the neurally induced contraction, which is partially reduced by atropine or hyoscine (19, 24, 25). In these preparations there appears to be no reason to ascribe the potentiation by anticholinesterases to their actions at the ganglionic level or actions of the protected ACh of preganglionic origin on the musculature. Anticholinesterases potentiate in situ the bladder contraction produced by nicotinic ganglionic stimulating agents in rats (25) and dogs (30). This could be strong evidence supporting the concept that ACh is the parasympathetic postganglionic transmitter in the bladder, if the

action of these agents is confined to cholinoceptive sites of only postganglionic neurons. However, no exact information is available as to whether the action of the nicotinic ganglionic stimulating agents is purely postganglionic. Recently it has been found that in the dog the bladder contraction produced by a muscarinic ganglionic stimulating agent, 4-(*m*-chlorophenylcarbamoyloxy)-2-butynyltrimethylammonium chloride (McN A-343) is greatly potentiated by physostigmine (30). Since the response to McN A-343 is resistant to blockade by hexamethonium or TEA, its possible preganglionic action can be excluded and thus its action is purely postganglionic (30). Thus, this finding can be evidence for the concept of cholinergic neuromuscular transmission in the bladder.

Carpenter (34) has demonstrated that contractions of bladders isolated from rats intoxicated by *botulinum* type D toxin were reduced to 25% of those of control bladders in response to transmural stimulation. In accordance with the suppressed contraction, the amount of ACh-like substance liberated from *botulinum*-intoxicated bladders was significantly less than that from controls.

Hemicholinium-3, which is said to impair cholinergic transmission by interfering with a choline-transport mechanism to intraneuronal sites of acetylation (35), gradually abolishes the bladder contraction in response to parasympathetic nerve stimulation in rats (24, 25, 32). The block caused by hemicholinium-3 is characteristic in being more apparent at high stimulus frequency (24, 32) and partially antagonized by choline (24, 32).

The content of ACh-like substance (24) and its output (34, 36) have been measured in the rat isolated bladder. During transmural stimulation at 15 Hz the output of ACh-like substance increased about 150 times above the resting level (36). *Botulinum* toxin specifically disrupted the release of ACh-like substance without affecting its content in the bladder (34). Chesher (33) has shown that transmural stimulation of the guinea-pig bladder caused a 200-fold increase in output of ACh-like substance and identified the substance as ACh by paper chromatography. Although the guinea-pig bladder is not ganglion-free histologically, there was no significant difference in the ACh content between the ganglion-rich and ganglion-poor halves of the bladder (33). Therefore, Chesher (33) has considered that the released ACh had been stored predominantly in parasympathetic postganglionic fibers.

Several hypotheses have been proposed to explain the atropine-resistance of the parasympathetically induced contraction of the bladder. One can recall the hypothesis proposed by Dale & Gaddum (37) to explain the atropine-resistant vasodilatation of the submaxillary gland caused by electrical stimulation of the chorda tympani. The hypothesis is that endogenous ACh is released in such close proximity to the receptive mechanism that atropine cannot prevent its access thereto. Ursillo & Clark (19) have explained the atropine-resistance in the bladder in such a way as to indicate that the cholinoceptive sites activated by endogenous ACh may be inaccessi-

ble to atropine. However, as mentioned in the preceding section, no morphological basis has been found to support the hypothesis of Dale & Gaddum (37), which Ambache (18) designated the proximity theory, and that of Ursillo & Clark (19). Huković, Rand & Vanov (24) have offered another explanation: that endogenous ACh is released at postsynaptic muscarinic receptors in sufficiently high concentrations to overcome the atropine block.

As opposed to the concept that parasympathetic postganglionic fibers of the bladder are cholinergic, Henderson & Roepke (14, 15) first suggested that the atropine-resistant portion of the bladder response to parasympathetic nerve stimulation might be mediated through noncholinergic fibers. Recently Ambache & Zar (29) have extended Henderson & Roepke's view and put forward the hypothesis, based on experiments on the guinea-pig detrusor muscle preparations, that most parasympathetic postganglionic fibers of the bladder, if not all, are noncholinergic. However, it appears that their concept is based exclusively on negative results with atropine, which are not essentially different from those of previous workers, and on those with morphine. Morphine has been reported to diminish the ACh output in the guinea-pig gut (38). In contrast to the results of Ambache & Zar (29), Huković, Rand & Vanov (24) have obtained positive results with morphine in the rat isolated bladder. Therefore, it is still premature to abandon the concept that parasympathetic postganglionic fibers of the bladder are cholinergic. Nevertheless, the problem of the atropine-resistance of the parasympathetically induced contraction of the bladder remains unsolved.

The parasympathetically induced contraction of the bladder is resistant to blockade by adrenergic neuron blocking agents (24, 29, 30, 39), alpha-adrenergic blocking agents (29), antagonists of 5-hydroxytryptamine (5-HT) (24, 25, 29), and antihistamines (29). Thus, it is unlikely that norepinephrine (NE), 5-HT, or histamine might be a possible transmitter of parasympathetic postganglionic fibers. In the guinea-pig bladder ATP elicits the contraction resembling that produced by transmural stimulation (29). However, a role of ATP as a possible parasympathetic postganglionic transmitter is also ruled out because the effect of ATP shows marked tachyphylaxis (29). Bradykinin also is excluded as a candidate for the transmitter because of its slow onset and development of action on the guinea-pig bladder (29). Thus, even if the parasympathetic postganglionic transmitter is not ACh as claimed by Ambache & Zar (29), no alternative transmitter has yet been found.

Pharmacological Properties of Parasympathetic Ganglia of the Bladder

In contrast to the conflicting view of the nature of chemical transmission between parasympathetic postganglionic fibers and the detrusor muscle, ganglionic transmission at the parasympathetic ganglia of the bladder is unanimously claimed to be cholinergic. The property of ganglionic cholinoceptive sites subserving physiological transmission elucidated so far are nic-

otinic. Evidence is as follows: Transmission at the parasympathetic ganglia is suceptible to blockade by large amounts of nicotine or by hexamethonium-like agents (14, 17, 23, 27, 30, 40–42). Nicotinic ganglionic stimulating agents, DMPP and nicotine, cause a prompt contraction of the dog bladder in situ (11, 16, 20, 21, 28, 30, 43–45), of the rat bladder in situ (25), of the human isolated detrusor muscle preparations (46), and of the guinea-pig isolated bladder (23). The antagonism of the stimulant action of DMPP or nicotine by hexamethonium-like agents has been demonstrated in the dog bladder in situ (16, 21, 30, 43), in the rat bladder in situ (25) and in the guinea-pig isolated bladder (23).

As opposed to the generally accepted view that in the bladder the nicotinic receptors are located at the parasympathetic ganglia, Gyermek (20) has suggested that the nicotinic receptors are located at the parasympathetic effector sites. This supposition has been offered as an explanation of the atropine-resistant and hexamethonium-sensitive contraction of the dog bladder elicited by pelvic nerve (mostly parasympathetic preganglionic) stimulation or by intra-arterial DMPP or ACh after atropine (20). However, Chesher & James (26) have failed to obtain evidence supporting the supposition of Gyermek (20). Conversely, Chesher & James (26) have concluded that the nicotinic receptors are confined to the ganglion cells, since the effect of nicotine in producing the contraction of the guinea-pig bladder in vitro was completely abolished by denervation by cooling or anoxia. The observation by Taira, Matsumura & Hashimoto (45) that the effect of DMPP on the dog bladder was abolished by tetrodotoxin also supports the conclusion by Chesher & James (26). Tetrodotoxin is shown to abolish only the neurally mediated response of smooth muscle organs elsewhere (47–49).

It has been well established that sympathetic ganglia have excitatory muscarinic receptors in addition to the nicotinic ones (50). In contrast, it has been considered that parasympathetic ganglia may lack the excitatory muscarinic receptors. This has been derived from the negative results with McN A-343, which stimulates the muscarinic receptors at sympathetic ganglia (25, 51, 52). However, Taira, Matsumura & Hashimoto (28, 30) have recently presented evidence showing that the parasympathetic ganglia of the dog bladder possess excitatory muscarinic receptors distinct from the nicotinic ones. Their observations are as follows: McN A-343 given into the caudal vesical arteries caused a phasic contraction of the bladder in situ in most dogs. The phasic contraction was abolished by tetrodotoxin and potentiated by physostigmine. The stimulant action of McN A-343 on the bladder was susceptible to blockade by small doses of atropine and resistant to blockade by hexamethonium or TEA, unlike that of DMPP. Possible involvement of adrenergic neurons in the response to McN A-343 has been ruled out by its resistance to blockade by an adrenergic neuron blocking agent, guanethidine. In dogs, Levy & Ahlquist (21) have observed that intravenous McN A-343 elicited a contraction of the bladder, although these workers have not stated whether the action of McN A-343 is exerted on the

parasympathetic ganglia or on the musculature of the bladder. Conversely, Vanov (25) failed to find any stimulant action of McN A343 on the rat bladder in situ. Thus, the presence of the excitatory muscarinic receptors at the parasympathetic ganglia of the bladder may depend on species. Even in the dog bladder, the role played by the excitatory muscarinic receptors at the parasympathetic ganglia is unknown.

Vesical ganglia of the dog (53) and autonomic ganglia of the rat, which send motor fibers to the bladder (25), appear to possess specific receptors for 5-HT. Although it has not been stated explicitly whether these ganglia are parasympathetic or sympathetic, indirect evidence has shown that the ganglia are presumably parasympathetic (25, 53). In the dog bladder the ganglionic 5-HT receptors are responsible for a phasic component of biphasic contractions caused by 5-HT, and are blocked by cocaine or morphine and not by 2-bromolysergic acid diethylamide (BOL). The subsequent tonic contractions, which are antagonized by BOL but not by cocaine or morphine, are ascribed to activation of 5-HT receptors on the musculature. Both responses are resistant to blockade by atropine and hexamethonium (53). In the rat bladder, contractions due to activation of the ganglionic and muscular 5-HT receptors are not distinguishable in shape. As in the guinea-pig gut (54), the presence of the ganglionic 5-HT receptors is presumed on the basis of the finding that the contractions of the rat bladder in situ caused by 5-HT possess a morphine-sensitive and methysergide-resistant component (25). Methysergide antagonizes the muscular action of 5-HT (24, 29).

Nature of Postganglionic Fibers of the Hypogastric Nerves of the Bladder

In most mammalian species postganglionic fibers of the hypogastric nerves of the bladder are predominantly adrenergic. As can be found in the review by Gruber (55) and papers by Elliott (56) and of Ingersoll, Jones & Hegre (57), responses of the bladder to hypogastric nerve stimulation vary depending not only upon species but individual animals. In cats, dogs, and rabbits the response is relaxation either preceded or not by a brisk contraction (11, 12, 27, 30, 56–58). In cats and dogs both responses are progressively reduced by adrenergic neuron blocking agents, i.e., bretylium or guanethidine (27, 30, 39). In cats the contractile response is diminished by pretreatment with a catecholamine depletor, syrosingopine, in keeping with a decrease in the NE content of the bladder (39). In cats the contractile response is augmented by blocking agents of NE uptake, i.e., cocaine and imipramine (39). The contractile response is reduced by alpha-adrenergic blocking agents (27, 56) and the relaxation by beta-adrenergic blocking agents (27).

Recently Mantegazza & Naimzada (59, 60) have suggested that in the guinea-pig bladder, postganglionic fibers of the hypogastric nerves are not adrenergic but may be cholinergic. Their supposition is based on the following observations: The contraction caused by electrical stimulation of the

hypogastric nerves was abolished by hexamethonium and potentiated by anticholinesterases but not affected by either adrenergic neuron blocking agents or alpha-adrenergic blocking agents (59, 60). Their supposition can be reinforced by the observation that the guinea-pig bladder did not respond to exogenous catecholamines (61).

Site and Mode of Action of the Adrenergic Hypogastric Nerves and of Exogenous Catecholamines

Classically it has been claimed that the trigone area responds to hypogastric nerve stimulation with contraction (11, 56) and the detrusor with relaxation (56), and correspondingly the former contracts and the latter relaxes in response to exogenous epinephrine (12, 62). In the rabbit bladder the contraction of the trigone area caused by epinephrine is converted to relaxation by treatment with ergotoxin (62). Therefore, adrenergic receptors subserving contraction of the trigonal muscle are alpha-adrenergic in modern terminology. This classical finding has been confirmed by Edvardsen & Setekleiv (61) on cat and rabbit bladders by using modern pharmacological tools. In their experiments, muscle strips from the trigone area responded to NE and epinephrine with contractions that were sometimes increased by a beta-adrenergic blocking agent, propranolol, and blocked by alpha-adrenergic blocking agents, i.e., phentolamine or phenoxybenzamine. When alpha-adrenergic blocking agents were given first, relaxation appeared in the preparation and was blocked by subsequent administration of propranolol. These results indicate that the trigone area also possesses beta-adrenergic receptors responsible for relaxation. Since the trigone area is densely innervated by adrenergic fibers (1, 4, 10), the released NE will activate directly both the alpha- and beta-adrenergic receptors of the trigonal musculature. Usual predominance of the contraction of the trigone area in response to hypogastric nerve stimulation is considered to be due to predominance of the alpha-adrenergic receptors.

As opposed to the classical view (56), it has been demonstrated that in the cat and dog bladders in situ all portions of the bladder respond to hypogastric nerve stimulation with a prompt contraction which is immediately followed by relaxation (57, 58). In the cat bladder in situ hypogastric nerve stimulation causes a contraction capable of expelling about half of the bladder content when the bladder outlet is kept open (27, 61). The initial contraction is followed by cessation of rhythmic contractions and by reduction of the bladder tone (relaxation) (27, 61). These can be taken to indicate biphasic responses of the detrusor to hypogastric nerve stimulation. The initial contraction is reduced by phenoxybenzamine and the subsequent relaxation is converted to a contraction by propranolol (27). Thus, the biphasic response of the detrusor to hypogastric nerve stimulation can be well interpreted in terms of the alpha- and beta-adrenergic receptors in the detrusor muscle (27). The validity of this concept is reinforced by evidence obtained by experiments on the isolated detrusor preparations (61). Detrusor muscle

strips from the cat and rabbit bladders respond to NE, epinephrine, and isoproterenol with cessation of spontaneous contractions and with relaxation, both of which are blocked by propranolol. These muscle strips also possess the alpha-adrenergic receptors, since the response to NE or epinephrine is converted by propranolol to the contraction, which is blocked by phenoxybenzamine. It is evident from these results (61) that in the detrusor of the cat and rabbit bladders the beta-adrenergic receptors are predominant although the alpha-adrenergic receptors are also present. Similar findings have been reported on the detrusor muscle preparations of the human bladder (46). Since the contractile response through the alpha-adrenergic receptors has a shorter latency than the relaxation through the beta-adrenergic ones (61), the contraction, if present, precedes the relaxation upon hypogastric nerve stimulation.

Although the explanation of the biphasic response of the detrusor to hypogastric nerve stimulation in terms of the alpha- and beta-adrenergic receptors in the musculature appears plausible, a recent histochemical study (10) has demonstrated that the detrusor is essentially devoid of adrenergic innervation and instead adrenergic fibers terminate around parasympathetic ganglion cells in the intramural ganglia. Since exogenous epinephrine inhibits synaptic transmission at sympathetic ganglia (63), Hamberger & Norberg (10) have taken their morphological findings to indicate that the sympathetic hypogastric nerves may exert their influence on the bladder by modifying parasympathetic ganglionic transmission. Essentially the same pattern of adrenergic innervation has been found in the cat intestine (64, 65). Therefore, Norberg (64) has proposed a hypothesis that in the intestine, adrenergic fibers exert their relaxing effect indirectly through inhibition of parasympathetic myenteric ganglion cells by released NE rather than directly on the smooth muscle cells. Gershon (66) has tested this hypothesis in the gastrointestinal tract of guinea pigs and rabbits. Contrary to the hypothesis, he has concluded that the effect of adrenergic nerve stimulation is due to direct action of the released NE on the smooth muscle cells. At present no pharmacological experiments particularly designed to elucidate this point have been carried out on the bladder. In the cat bladder in situ simultaneous stimulation of the hypogastric nerves reduces the contractile effect of pelvic nerve stimulation (*27*). In this instance possible participation of sympathetic inhibition of parasympathetic ganglionic transmission may not be ruled out. However, relaxation of the cat bladder in situ caused by hypogastric nerve stimulation is not different in the presence or in the absence of the pelvic nerve supply (*27*). In the dog bladder in situ removal of all nervous activity by tetrodotoxin does not change substantially the bladder tone and the rhythmic contractions (45). Thus, it appears unlikely that the sympathetic hypogastric nerves cause relaxation of the detrusor only through inhibition of parasympathetic ganglionic transmission. El-Badawi & Schenk (1) have demonstrated that in the detrusor, adrenergic fibers are found between groups of muscle fibers or between bundles of

muscle. Thus, the released NE will act directly on the detrusor muscle cells after diffusion over a considerable distance, although its ganglionic action in the intramural ganglia is not excluded.

When intact, the hypogastric nerves exert a tonic influence on the bladder (67, 68). Since in the whole bladder the beta-adrenergic receptors are predominant in the detrusor and the alpha-adrenergic ones prevail in the trigone area, during the collecting phase the detrusor relaxes through activation of the beta-adrenergic receptors by the released NE to retain urine, and the trigone area contracts through that of the alpha-adrenergic receptors to close the outlet. In the dog bladder in situ isoproterenol lowers the maximal voiding pressure and increases the bladder capacity (69, 70) and the action of isoproterenol is antagonized by a beta-adrenergic blocking agent, sotalol (70).

Supersensitivity of the Bladder

The spastically paralytic bladder showing autonomous contractions develops in patients with lesions of both pelvic nerves (71, 72). Such a bladder is also created experimentally in dogs by bilateral section of the pelvic nerves or, to a lesser degree, of the ventral sacral roots (72). As a mechanism for this, Lapides et al (71) have suggested the development of supersensitivity of the bladder to ACh. In man, cats, and dogs, section of both pelvic nerves constitutes parasympathetic decentralization of the bladder. At present, however, no information is available on the basis of well controlled animal experiments about whether the chronically parasympathetically decentralized bladder develops supersensitivity. Unlike the bladder of cats and dogs, the rat bladder can be denervated parasympathetically. Carpenter & Rand (36) have reported that 4–8 days after denervation the sensitivity of the rat bladder to ACh or carbamylcholine is not changed significantly from that of the normal.

In contrast to bilateral section of the pelvic nerves or the ventral sacral roots, section of both hypogastric nerves produces no apparent dysfunction of the bladder (72, 73). In man, cats, and dogs this procedure means the sympathetic denervation of the bladder. Since electrical stimulation of the hypogastric nerves causes a prompt contraction of the bladder in cats, Sigg & Sigg (39) have investigated whether the sympathetic denervation makes the bladder supersensitive to uncover a contractile response to exogenous NE that might be masked by predominant relaxation in the normal bladder. However, the sympathetically denervated bladder did not become supersensitive to respond with contraction to exogenous NE, although the comparably treated nictitating membrane became supersensitive. In interpreting the discrepant results on the two sympathetically innervated organs, one should keep in mind that the cat bladder responds to exogenous NE predominantly with relaxation (39), unlike the nictitating membrane. One may recall Elliott's statement (56) that lesions of the nerves of the inhibitor muscle-nerve system result in a more prolonged inhibition by epinephrine but not in greater irritability. In cats the hypogastric nerves are predominantly inhibi-

tory on the bladder (67, 68). In the cat bladder blockers of NE uptake also failed to uncover a contractile response to exogenous NE (39).

Conclusion

Despite a growing body of evidence favorable to the cholinergic nature of parasympathetic postganglionic fibers of the bladder, no satisfactory explanation of the atropine-resistance of the parasympathetically induced contraction of the bladder has been offered. Therefore, some investigators maintain that most of these fibers are noncholinergic. In some species the parasympathetic ganglia of the bladder appear to possess the excitatory muscarinic receptors in addition to the nicotinic ones. In most species postganglionic fibers of the hypogastric nerves of the bladder are adrenergic. The mode of action of these nerves and of exogenous catecholamines is well interpreted in terms of the alpha- and beta-adrenergic receptors in the musculature. The alpha-adrenergic receptors are responsible for contraction and are present predominantly in the trigone, while the beta-adrenergic ones are responsible for relaxation and prevail in the detrusor. However, some discrepancies are found between the pharmacological explanation of the site and mode of action of adrenergic nerves in the bladder and the morphological observations of their distribution. It is still obscure whether the parasympathetically decentralized or sympathetically denervated bladder develops supersensitivity.

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