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A CONTRIBUTION TO THE INNERVATION OF THE URINARY BLADDER OF THE CAT

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The present investigation arose from the general interest in these laboratories in ganglion-blocking drugs. Whilst studying the effect of these drugs on the pelvic nerve–bladder preparation of the cat an anomalous response to atropine was observed, and this led to an investigation of the innervation of the urinary bladder of the cat, by comparing the effects of nerve stimulation and autopharmacological agents before and after blocking with appropriate drugs.

In reviewing the literature, Gruber (1933) concluded that 'the bladder is innervated by the sympathetic and parasympathetic systems, each supplying both motor and inhibitor impulses, and that there is no difference between the effects of these two systems, except the possibility that the parasympathetic nerves carry stronger motor impulses'. Langworthy, Kolb & Lewis (1940) stated that only the parasympathetic nerves, arising chiefly from the ventral root of the second sacral nerve in the cat, may be regarded as motor to the detrusor muscle, whereas the sympathetic (hypogastric) nerves are motor to the muscles of the ureters, Bell's muscles and the crista of the urethra, those sympathetic fibres running to the fundus supplying only the vascular system (Langworthy & Murphy, 1939). Evans (1936) came to the same conclusion, whereas Kuntz & Saccomanno (1944) believe that some sympathetic fibres innervate the detrusor muscle.

It is generally recognized that atropine reduces tone and rhythmic activity in the bladder. Langley & Anderson (1895) and Langley (1911) found that very large doses of atropine partially inhibited bladder contraction due to sacral nerve root stimulation. This was not confirmed by Henderson (1923), although Teitelbaum & Langworthy (1941), using a different method of stimulation, supported the findings of Langley & Anderson (1895). Henderson & Roepke (1934, 1935) found that peripheral stimulation of the pelvic nerves in dogs produced contraction of the bladder which was fairly well maintained for short periods. Small doses of acetylcholine injected intra-arterially had a similar effect. However, after atropine, stimulation of the pelvic nerves still

produced as large a contraction as before, but this was not maintained, whilst doses of acetylcholine which were effective before atropine, were completely inhibited after atropine. Larger doses of acetylcholine were still effective in causing a spike contraction, although as with pelvic nerve stimulation, the contraction was poorly maintained. These authors suggested that two separate mechanisms exist, one for the production of the initial contraction and one for the maintenance of tone. The first mechanism, produced by pelvic nerve stimulation and large doses of acetylcholine after atropine, they referred to as the 'ganglionic contractile' response, suggesting that the large doses of acetylcholine were stimulating the neurones of the parasympathetic ganglia and not the fibres of the detrusor muscle. They believed this response to be mediated by non-cholinergic fibres. The other mechanism, seen only with relatively prolonged pelvic nerve stimulation and small doses of acetylcholine before atropine, they named the 'peripheral tonic' effect.

Langworthy *et al.* (1940) found that stimulation of the sympathetic fibres to the bladder caused a rise of pressure followed by a fall below the original level, if the volume was constant, and if the pressure was constant a decrease followed by an increase in volume occurred. Excitatory and inhibitory effects have been ascribed to adrenaline, according to the conditions of the experiment.

The work reported in this paper has been confined to experiments on the cat, the species on which most previous work has been done, since although Langworthy *et al.* (1940) believe that the physiology of the bladder is similar in all species, Elliott (1907) found considerable species differences.

METHODS

In situ *experiments*

Experiments were performed on female cats anaesthetized with chloralose (80 mg/kg) intravenously; in one experiment pentobarbitone sodium was used. The operative procedures allowed sufficient time for the ether used for induction to be blown off before the experiment began. This was important since Macdonald & M'Crea (1930) have shown that different depths of ether anaesthesia reverse the response to certain drugs.

After exposure of the bladder by a median incision, a urethral cannula was inserted and tied in place. The bladder was emptied and partially refilled with 20–25 ml. warm 0·9 % (w/v) NaCl. The rectum was divided posterior to the inferior mesenteric artery, and evisceration performed as far anteriorly as the duodenum; the ureters were left intact. The urethral cannula was connected with rubber tubing to a saline manometer for recording pressure changes. These were not strictly isometric (5 cm saline pressure was equivalent to a volume change of 2·5 ml.). In a few experiments volume changes were recorded with a piston recorder, using a pressure bottle partly filled with saline and adjusted to a height of 5–20 cm so that the bladder remained partially filled with fluid.

Most of the experiments in which the vesical branches of one pelvic nerve were stimulated were performed after section of both hypogastric nerves. The vesical branches of the right pelvic nerve, found beneath the fat surrounding the neck of the bladder, were cut, care being taken to damage the blood supply as little as possible. In a few experiments these nerves were not sectioned. Those of the left side were similarly dissected, and the cut peripheral ends of two or three strands placed

together over a pair of silver electrodes. The abdominal walls were raised and the chamber so formed covered with a cotton-wool pad, moistened with 0·9% (w/v) NaCl.

In experiments in which stimulation was applied to the second ventral sacral nerve the procedure was modified thus: the vesical branches of the pelvic nerves were left intact and the abdominal incision closed. The animal was then placed in a prone position and the sacral region of the spinal cord exposed. Except for the nerve to be stimulated, all the nerve roots and the cord itself were removed from this region.

For peripheral stimulation of one hypogastric nerve to the decentralized bladder, the sacral region of the spinal cord with its nerve roots was excised before exposure of the bladder; the vesical branches of the pelvic nerves were left intact.

In all these experiments square wave stimuli of 1–2 V, 10 msec duration, 5 per sec, were applied for 5 sec every 1 or 2 min.

In most experiments drugs were injected into the jugular vein. In others close arterial injection was given through a cannula inserted in the inferior mesenteric artery, the iliolumbars, external iliacs and caudal arteries being ligated: both internal iliac arteries were tied distal to the point of origin of the umbilical arteries.

The drugs used were hexamethonium and tetraethylammonium bromides, atropine and eserine sulphates, acetylcholine chloride, adrenaline and L-noradrenaline hydrochlorides, dihydroergotamine methanesulphonate (DHE) and benzo-(diethyl-amino-methyl)-2-dioxan (883 F). Doses in the text refer to these salts. The effect of anoxia on the bladder was studied by clamping the abdominal aorta.

In vitro *experiments*

Organ-bath experiments. Lourie's (1952) preparation, but using cat bladders distended with 20–25 ml. Ringer-Locke solution containing NaCl 9·0 g, KCl 0·42 g, $CaCl_2$ 0·24 g, $NaHCO_3$ 0·15 g, dextrose 1·0 g, glass distilled water 1 l., and placed in a 130 ml. bath, was used to study the effect of drugs directly on the bladder musculature.

Perfusion experiments. To study the effect of drugs directly on the vessels of the bladder, experiments were performed on isolated bladders perfused with oxygenated Ringer-Locke solution at $38 \pm 1°$ C. In these experiments the bladder was partially re-filled with 20–25 ml. warm 0·9% (w/v) NaCl and the urethral cannula clamped. The ureters were tied and cut, as were the iliolumbars, external iliacs and caudal arteries. The internal iliac arteries were tied below the origin of the umbilical arteries. At this stage the animal was heparinized and the perfusion cannula inserted into the abdominal aorta just anterior to the point of origin of the external iliac arteries. The bladder was then removed and the perfusion rate recorded with a Stephenson recorder as for the rabbit ear preparation of Burn & Robinson (1951).

RESULTS

Effect of peripheral stimulation of the vesical branches of one pelvic nerve

Intermittent stimulation was applied because this gave regular contractions for several hours, whereas the bladder adapted fairly rapidly to continuous stimulation. The optimum rate of stimulation was about 5 per sec and when applied for 5 sec this gave submaximal contractions with a latent period of onset of a second or two, the contractions continuing for 2 or 3 sec on cessation of stimulation. Relaxation was then rapid at first, but usually taking 20–40 sec to completion, and sometimes longer. Stimulation was, therefore, applied every 1 or 2 min. With a stimulus duration of 0·1 msec the contractions were very small at a rate of 5 per sec, and irregular at 20 per sec; stimulus durations of 1·0 and 10 msec gave equally good responses and only the latter duration was

used in the main experiments. The bladder generally showed a certain amount of spontaneous activity which was usually of small amplitude and low frequency. Evans (1936) previously found that cutting the pelvic nerves resulted in complete absence of action potentials and almost complete cessation of manometric movements.

Effect of hexamethonium. The invariable response to intravenous injection of hexamethonium was partial or complete inhibition (depending on the dose) of the contractions caused by peripheral stimulation of the vesical branches of one pelvic nerve. The effect was often maximal at 1 min. Recovery was slow, requiring at least 20 or 30 min. A dose of 0·25 mg/kg was often very effective initially, but the sensitivity of the preparation decreased, and later even 1·0 mg/kg produced only a slight effect. In some experiments the tone of the bladder was also reduced. The response to hexamethonium was obtained equally well after atropinization and with the vesical branches of the other pelvic nerve intact.

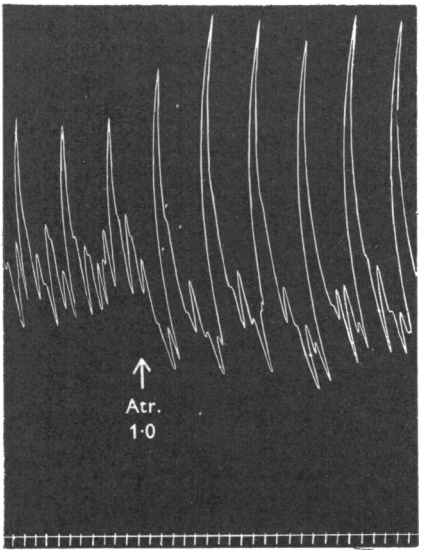

Fig. 1. Cat, ♀, 2·5 kg, pentobarbitone sodium. Tracing showing volume changes in bladder to peripheral stimulation of vesical branches of left pelvic nerve. Vesical branches of right pelvic nerve and both hypogastric nerves intact. Effect of 1·0 mg/kg atropine sulphate. Time: 30 sec.

Effect of atropine and eserine. Atropine had the following effects. The tone of the bladder was lowered (Figs. 1, 2), although when pressure changes were recorded in the decentralized bladder the tone was initially low, and this effect was not very marked. The spontaneous bladder movements were diminished; this was well shown in experiments in which these contractions were initially

particularly large. Evans (1936) observed complete cessation of spontaneous bladder movements for up to 20 min after atropine. The other effect of atropine, which has not previously been described, was an increase in the height of the contractions on stimulation of the vesical branches of the pelvic nerve (Fig. 1). This effect, which was seen at 1 min, was maintained for at least 20 min. The effect was observed when volume changes were recorded under conditions of constant pressure (Fig. 1) and therefore could not be accounted for by the

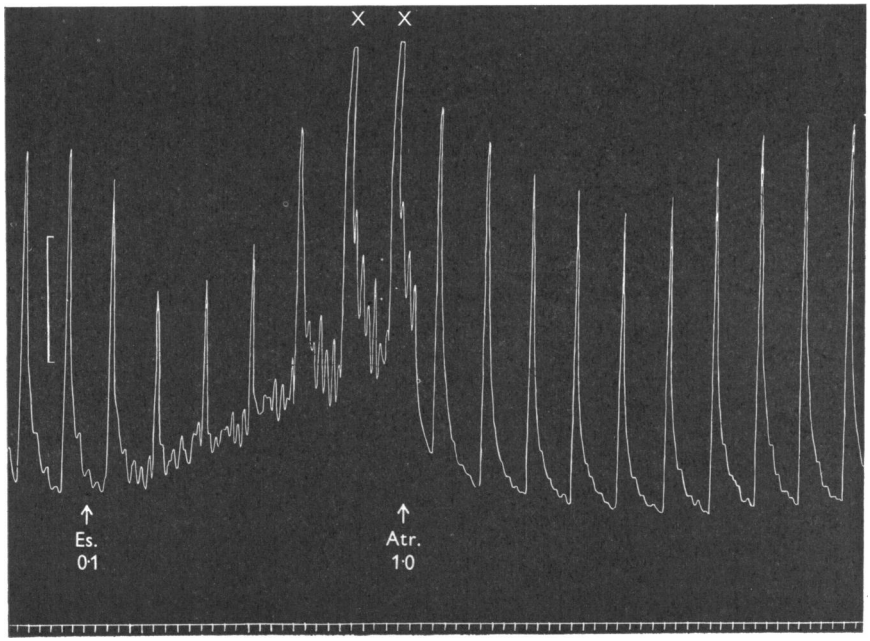

Fig. 2. Cat, ♀, 1·75 kg, chloralose. Tracing showing pressure changes in bladder to peripheral stimulation of vesical branches of left pelvic nerve. Vesical branches of right pelvic nerve and both hypogastric nerves sectioned. Effect of eserine sulphate followed by atropine sulphate. Figures indicate doses in mg/kg. × indicates manometer overflowed. Vertical scale: 5 cm water pressure. Time: 30 sec.

decrease in tone. The increased response to atropine occurred with doses of 0·1 to 10·0 mg/kg; usually the effect with 0·1 mg/kg was maximal; smaller doses were not investigated. The phenomenon was observed when the parasympathetic innervation of one side was intact, and when both hypogastric nerves were also intact (Fig. 1). Only the first injection of atropine was effective; a second injection after the responses had been reduced by hexamethonium produced no further effect. Eserine (0·1 mg/kg) initially reduced the response to nerve stimulation (Fig. 2) and then, as the tone of the bladder began to rise and the spontaneous movements became of larger amplitude, the contractions to

nerve stimulation increased and became larger than before eserine. At this stage, atropine (1·0 mg/kg) reversed the effects on tone and spontaneous movements produced by eserine and the responses to nerve stimulation were reduced but then settled at a level above the height of the contractions before eserine and atropine (Fig. 2).

Effect of stimulating the peripheral part of the ventral root of the second sacral nerve

In these preparations, in which complete decentralization of the bladder was assured, the tone of the bladder was initially minimal. The response to hexamethonium was identical with that obtained when the vesical branches of the pelvic nerve were stimulated—the contractions were inhibited. The effect of

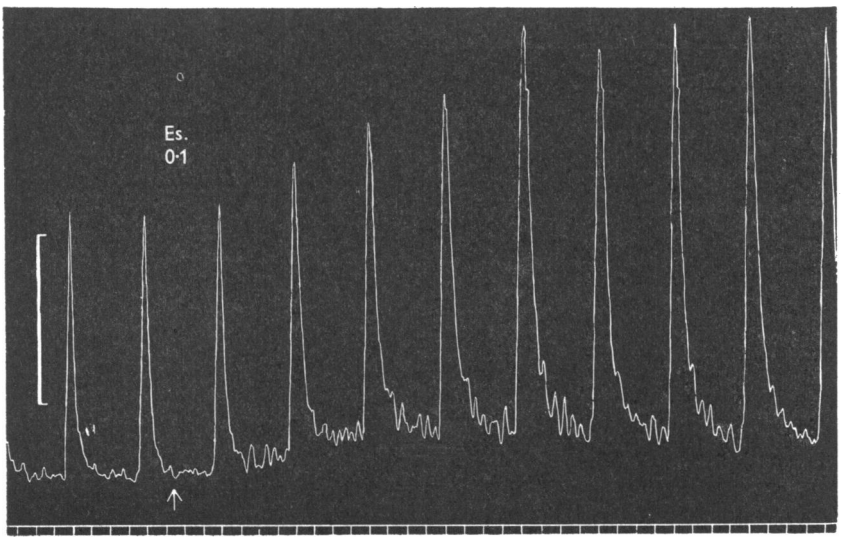

Fig. 3. Cat, ♀, 3·0, chloralose. Tracing showing pressure changes in bladder to peripheral stimulation of ventral root of second left sacral nerve. Sacral region of spinal cord destroyed and both hypogastric nerves sectioned. Effect of 0·1 mg/kg eserine sulphate. Vertical scale: 5 cm water pressure. Time: 30 sec.

atropine, however, was different. Although there was sometimes a slight augmentation, this was transient; sometimes there was a slight reduction (with 1·0 mg/kg) possibly due to the weak local anaesthetic action of this compound. After the response had been potentiated by eserine (Fig. 3), it was invariably reduced by atropine. Eserine caused a slight and gradual increase in tone as well as a gradual increase in the height of contractions; its effect on spontaneous contractions and on tone were less than in the pelvic nerve–bladder preparation. DHE in a dose usually found sufficient (4 mg/kg) to block hypogastric stimulation was without effect on sacral root stimulation.

Effect of peripheral stimulation of hypogastric nerves

Peripheral stimulation of the hypogastric nerve on one side is characterized by contraction of the bladder, followed by relaxation below the resting level. This relaxation may occur whilst stimulation is still in progress (Elliott, 1905, 1907), or be seen during the recovery phase, as in the present experiments (Fig. 7). When the tone of the bladder was very low, as in Fig. 4, this greater relaxation was of course not seen. Atropine (1 mg/kg), eserine (0·1 mg/kg) and hexamethonium (10 mg/kg) were without effect on nerve stimulation, although the response was usually blocked by DHE (Fig. 4). In this experiment only 2 mg/kg were required and the block was complete by 28 min.

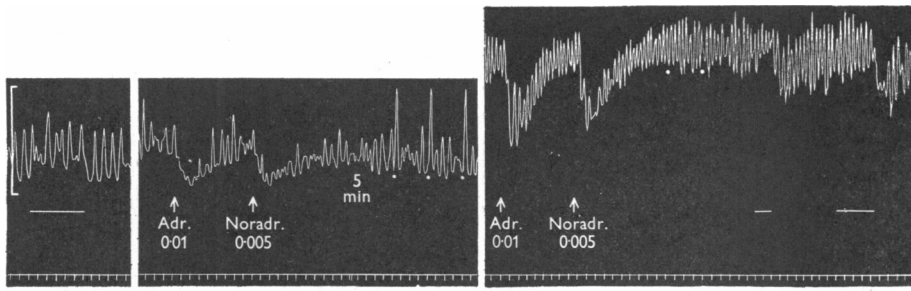

Fig. 4. Cat, ♀, 3·0 kg, chloralose. Tracing showing pressure changes in bladder. Sacral region of spinal cord destroyed and both hypogastric nerves sectioned. (*a*) Effect of clamping the abdominal aorta in otherwise untreated preparation. (*b*) Effect of adrenaline and L-noradrenaline hydrochlorides, and peripheral stimulation of one hypogastric nerve. (*c*) 18 min after 2 mg/kg dihydroergotamine methanesulphonate. Effect of adrenaline and L-noradrenaline hydrochlorides, peripheral stimulation of one hypogastric nerve, and clamping the abdominal aorta. Hypogastric stimulation (·); abdominal aorta clamped (——). Figures indicate doses in mg/kg. Vertical scale: 5 cm water pressure. Time: 30 sec.

Usually 4 mg/kg of DHE were required to produce complete block, in one such experiment block being complete after two doses of 2 mg/kg DHE injected 15 and 11 min beforehand. In other experiments (Fig. 7) even larger doses had little or no effect. Schofield (1952) found that 2 mg/kg DHE completely blocked hypogastric stimulation to the rabbit's uterus after 43 min. 883 F, in a dose found effective (5 mg/kg) in altering the response to adrenaline and L-noradrenaline, did not block the effect of peripheral stimulation of the hypogastric nerve. This drug, unlike DHE, is known to be an effective antagonist of circulating adrenaline whereas its antagonism to sympathetic stimulation is slight.

Effects of adrenaline and L-noradrenaline

Effects on the decentralized bladder in situ. Intravenous injection of adrenaline and L-noradrenaline produced rapid relaxation of the bladder and a slow

recovery. L-Noradrenaline was about twice as potent as adrenaline in producing a similar response (Fig. 4*b*). During or just preceding the relaxation phase following small doses of adrenaline, the bladder sometimes responded by a small contraction. This was often seen merely as an interruption of relaxation and only occurred with small doses. DHE, which caused an increase in tone, did not reduce the inhibition caused by adrenaline or L-noradrenaline (Fig. 4*c*). However, after 883F (5 mg/kg), which often caused a transient increase in tone of the bladder, small doses of adrenaline (5–15 μg/kg), produced a marked contraction (Fig. 5*b*). This response was unaffected by the tonic state of the bladder and was independent of the effect on the carotid blood pressure. The contraction was sometimes followed by a slight relaxation below the original level (Figs. 5*b*, 10*b*). Larger doses of adrenaline (50 μg/kg) still caused relaxation. The contraction to small doses of adrenaline was not maintained unless the dose of 883F was repeated. In one preparation there was no reversal of the relaxation caused by intravenous L-noradrenaline after 883F, although a slight reduction in response was observed. In other preparations, the effect of L-noradrenaline was reversed, but to a smaller extent than adrenaline. In order to study this phenomenon further, experiments were performed on the isolated bladder and perfused bladder *in vitro* (see below). The effects of intra-arterial injections were also studied. By this method, relatively large doses of both adrenaline and L-noradrenaline still produced relaxation and this was followed by an increase in tone. Smaller doses produced only contraction (Fig. 6). This contraction was more pronounced with adrenaline than with L-noradrenaline.

In vitro *experiments*. On the bladder suspended in an isolated organ bath, adrenaline and L-noradrenaline caused relaxation. By careful selection of doses, it was possible to reduce these responses with 883F. This drug, which caused an increase in tone, was placed in the bath 1 min before adrenaline or L-noradrenaline. After a further 1 min, the bath was repeatedly washed out until the tone of the bladder returned to its previous level. In no experiment was the relaxation to adrenaline or L-noradrenaline converted into contraction by 883F, and L-noradrenaline was again twice as potent as adrenaline in causing relaxation. DHE also increased the tone in this preparation. On the isolated perfused bladder, adrenaline and L-noradrenaline caused vasoconstriction, and this was inhibited but not reversed by 883F. There was some evidence that adrenaline was more potent than L-noradrenaline on this preparation.

Effect of clamping the abdominal aorta on the decentralized bladder

A very slight increase in tone of the bladder occurred when a clamp was applied to the abdominal aorta supplying the decentralized bladder *in situ* (Fig. 4*a*). Removal of the clamp caused a slight relaxation below the original

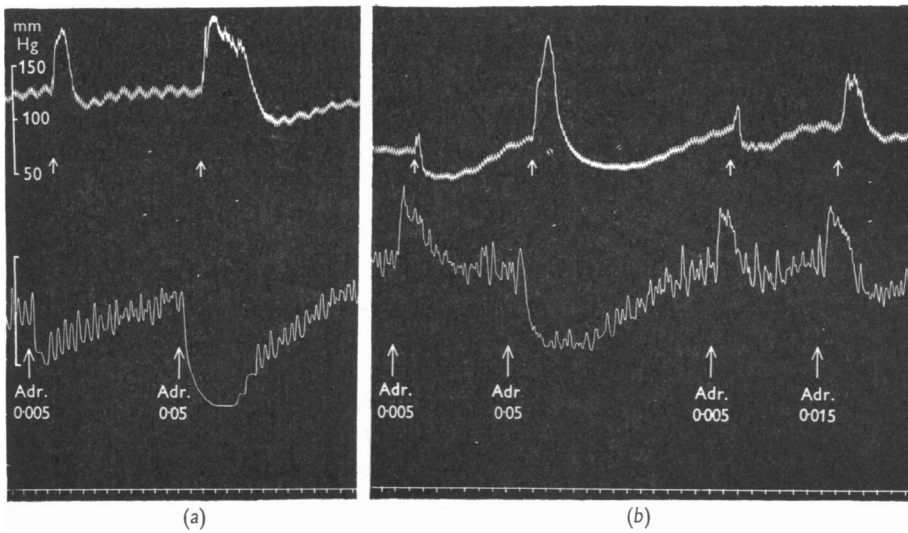

Fig. 5. Cat, ♀, 2·25 kg, chloralose. Tracing showing carotid blood pressure (upper record) and pressure changes in bladder (lower record) to injection of adrenaline hydrochloride. Vesical branches of both pelvic nerves and both hypogastric nerves sectioned. (*a*) Effect of 0·005 and 0·05 mg/kg adrenaline. (*b*) 12 min after 5 mg/kg 883 F, effect of 0·005, 0·015 and 0·05 mg/kg adrenaline. Blood pressure in mm Hg. Vertical scale: 5 cm water pressure. Time: 30 sec.

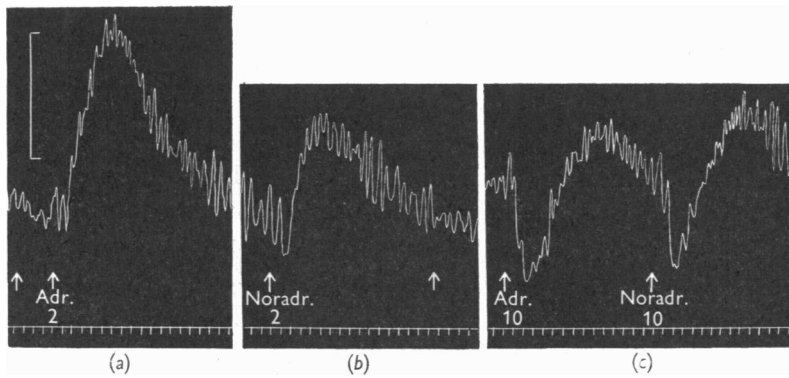

Fig. 6. Cat, ♀, 2·25 kg, chloralose. Tracing showing pressure changes in bladder. Sacral region of spinal cord destroyed and both hypogastric nerves sectioned. Intra-arterial injections. (*a*) Effect of 2 μg adrenaline hydrochloride. (*b*) Effect of 2 μg L-noradrenaline hydrochloride. (*c*) Effects of 10 μg adrenaline and L-noradrenaline hydrochlorides. Blank arrows in (*a*) and (*b*) are control injections of 0·4 ml. 0·9% (w/v) NaCl. Vertical scale: 5 cm water pressure. Time: 30 sec.

level, unless the tone was minimal, as in the experiment shown. After a dose of DHE sufficient to raise the tone of the preparation, but insufficient to block hypogastric stimulation, clamping the aorta caused a rapid contraction, the relaxation following removal of the clamp falling well below the original level (Fig. 7). The response was thus similar to hypogastric stimulation. After a full blocking dose of DHE, the application of the clamp to the abdominal aorta had little or no effect (Fig. 4*c*). Removal of the clamp still produced relaxation.

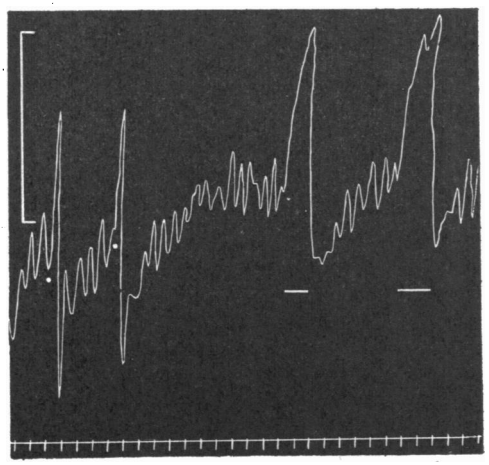

Fig. 7. Cat, ♀, 2·25 kg, chloralose. Tracing showing pressure changes in bladder. Sacral region of spinal cord destroyed and both hypogastric nerves sectioned. Previously injected with 10 mg/kg hexamethonium bromide, 1 mg/kg atropine sulphate and a total of 6 mg/kg dihydroergotamine methanesulphonate which in this preparation did not block the hypogastric nerve. Hypogastric stimulation (·). Abdominal aorta clamped (——). Vertical scale: 5 cm water pressure. Time: 30 sec.

Effect of acetylcholine on the decentralized bladder

Acetylcholine caused contraction of the bladder (Figs. 8*a*, 9 and 10*a*). The effect was potentiated by eserine (Fig. 8*b*) and incompletely inhibited by atropine (Figs. 8*c*, 9 and 10*a*). Thus after atropine the effects of small doses of acetylcholine were abolished, although larger doses of acetylcholine still caused contraction, which were now more rapid in onset and recovery (confirming the observations of Henderson & Roepke, 1934), and were followed by a marked relaxation with a slow recovery (Figs. 9, 10*a*), unless eserine had also previously been injected (Fig. 8*c*). These large doses of acetylcholine after atropine had a pressor action on the carotid blood pressure; and the relaxation phase of the bladder response resembled the normal response to injected adrenaline.

It was, therefore, thought possible that this relaxation might be due to the release of adrenaline from the adrenal medulla (and possibly other chromaffine

tissue). This was confirmed by injection of 883F (Fig. 10*a*), it having been shown that after this drug adrenaline, which normally causes relaxation, then causes contraction; acetylcholine now caused a biphasic contraction, the first

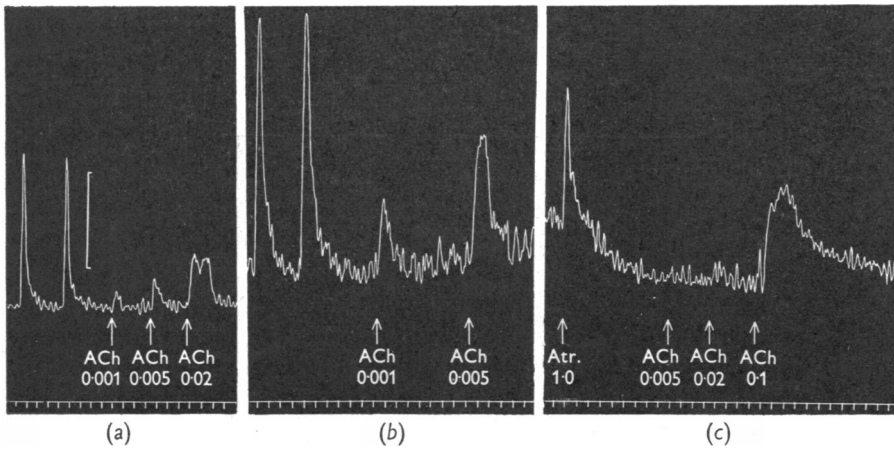

Fig. 8. Cat, ♀, 2·75 kg, chloralose. Tracing showing pressure changes in bladder to peripheral stimulation of ventral root of second left sacral nerve and to acetylcholine chloride. Sacral region of spinal cord destroyed and both hypogastric nerves sectioned. Between (*a*) and (*b*) 0·1 mg/kg eserine sulphate 20 min before (*b*). Between (*b*) and (*c*), 35 min. Figures indicate doses in mg/kg. Vertical scale: 5 cm water pressure. Time: 30 sec.

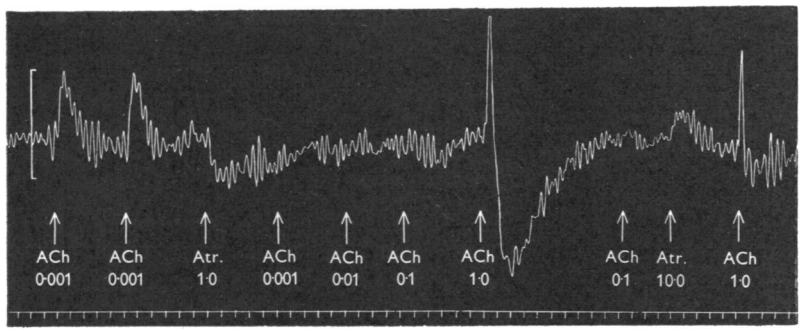

Fig. 9. Cat, ♀, 2·25 kg, chloralose. Tracing showing pressure changes in bladder to injection of acetylcholine chloride before and after atropine sulphate. Sacral region of spinal cord destroyed and both hypogastric nerves sectioned. Figures indicate doses in mg/kg. Vertical scale: 5 cm water pressure. Time: 30 sec.

phase due to the direct action of acetylcholine and the second due to the reversed effect of adrenaline. In addition, it was found that the contractile response to large doses of acetylcholine after atropine was almost completely abolished by a large dose of hexamethonium, thus confirming Henderson &

Roepke's (1934) hypothesis that the response was due to stimulation of the ganglia.

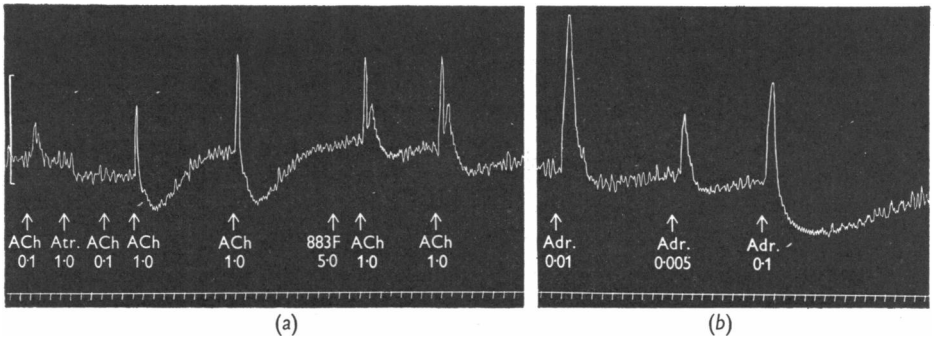

Fig. 10. Cat, ♀, 3·0 kg, chloralose. Tracing showing pressure changes in bladder to acetylcholine chloride. Sacral region of spinal cord destroyed and both hypogastric nerves sectioned. (*a*) Effect of acetylcholine before and after atropine sulphate and 883 F. (*b*) Effect of adrenaline 10 min after (*a*). Figures indicate doses in mg/kg. Vertical scale: 5 cm water pressure. Time: 30 sec.

Effect of atropine on the decentralized bladder

Immediately following injection of atropine, before the tone was reduced, the bladder sometimes responded by a small contraction. This contraction was potentiated by eserine (Fig. 8*c*).

DISCUSSION

Hexamethonium had no effect on peripheral stimulation of the hypogastric nerve; this suggests that the efferent fibres contained in this nerve are post-ganglionic. The fact that atropine and eserine were without effect on peripheral hypogastric stimulation, whereas DHE had a blocking action, indicates that these nerves are adrenergic.

Intravenous injections of L-noradrenaline were more effective than adrenaline in causing relaxation in the decentralized bladder. A similar relationship was seen in the isolated bladder. On the other hand, after compound 883 F, or by intra-arterial injection of small doses, adrenaline was more effective than L-noradrenaline in causing the bladder to contract. Adrenaline was also more effective than L-noradrenaline in causing vasoconstriction in the perfused bladder. The similarity between the effect on the bladder of clamping the abdominal aorta in the presence of a vasoconstrictor (DHE) and the effect produced by stimulating the hypogastric nerve peripherally, might indicate that contraction of the bladder in these circumstances is due to anoxia of the detrusor muscle caused by vasoconstriction of the bladder vessels. However, the anomaly remains that compound 883 F inhibited vasoconstriction caused by adrenaline in the perfused bladder, whereas in the whole animal contraction of the bladder caused by adrenaline was best seen after compound 883 F.

Atropine was found to facilitate contraction of the bladder produced by peripheral stimulation of the vesical branches of the pelvic nerve, although this effect was hardly apparent when the sacral nerve was stimulated peripherally. Furthermore, eserine initially reduced contractions in the pelvic nerve–bladder preparation, whereas in the sacral nerve–bladder preparation, eserine potentiated the contractions. Bülbring (1946) described an increased effect of atropine on contractions of the freshly prepared phrenic nerve–diaphragm preparation, attributing this to a state of acetylcholine excess. A similar explanation might account for the differences between pelvic and sacral nerve–bladder preparations, since it is likely that in the pelvic nerve–bladder preparations nervous decentralization was incomplete, the bladder, therefore, being subjected to a continual release of acetylcholine from unsectioned nerve fibres. The parasympathetic supply to the bladder was unaffected by DHE. Munro (1953), who made similar observations on the isolated guinea-pig intestine, suggested that the increased response after atropine was due to an unmasking of adrenergic fibres resistant to adrenergic blocking drugs.

In agreement with the findings of Henderson & Roepke (1934, 1935), it was found that the effect on the bladder of small doses of acetylcholine was inhibited by atropine, larger doses of acetylcholine producing rapid contractions which were greatly reduced by hexamethonium. This confirms these authors' hypothesis that after atropine large doses of acetylcholine stimulate the postsynaptic neurones, although it fails to explain why the nervous impulses so generated are not blocked at the parasympathetic nerve endings by atropine. An alternative explanation to that given by previous authors that there is a non-cholinergic parasympathetic innervation, is that the receptors of the bladder musculature, whilst responding to acetylcholine (and pilocarpine), are of the type from which atropine is easily displaced by the initial burst of nervous impulses.

Atropine sometimes produced a small contraction preceding the fall in tone, and this was increased by previous injection of eserine. Prof. J. H. Burn has suggested (personal communication) that this might be due to a transient acetylcholine-like action, since the immediate effect of atropine given to human subjects is a slowing of the pulse rate and moistening of the palms before the onset of the reverse effects, the slowing of the pulse previously being attributed to stimulation of the vagal centre.

SUMMARY

1. Pressure (and volume) changes were recorded in decentralized bladders of female cats under chloralose anaesthesia. Experiments on isolated bladders were also performed.

2. The response to peripheral stimulation of one hypogastric nerve was

abolished by dihydroergotamine and unaffected by hexamethonium, atropine and eserine.

3. In preparations where the tone had been increased by dihydroergotamine, clamping and unclamping the abdominal aorta produced a similar effect to hypogastric stimulation.

4. Injected intravenously, adrenaline and L-noradrenaline relaxed the bladder, but after compound 883F, caused contraction. Injected intra-arterially, small doses of adrenaline and L-noradrenaline caused contraction. In the isolated organ, 883F reduced the relaxation and inhibited the vaso-constriction produced by adrenaline and L-noradrenaline.

5. Hexamethonium inhibited the response to peripheral stimulation of the parasympathetic supply. Atropine increased the response to stimulation of the vesical branches of the pelvic nerve; eserine initially reduced this response, but potentiated the effect of stimulating the ventral root of the second sacral nerve.

6. After atropine, a large dose of acetylcholine produced a contraction similar to nerve stimulation, but followed by a phase of relaxation which was reversed by 883F. Atropine sometimes caused a small contraction before lowering tone, and this was increased by eserine. Eserine alone increased tone.

7. The innervation of the bladder is discussed in the light of these findings.

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