ANALYSIS OF THE ADRENERGIC RECEPTORS IN THE URINARY TRACT OF DOG

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As early as 1906 Dale (1) reported that adrenaline causes relaxation of detrusor muscle and contraction of the vesical sphincter. However, the response of ureter to sympathomimetic amines is indefinite; some experiments indicate that the motility and tone of the ureter are lessened (2) while in the rabbit Ahlquist (3) observed a stimulant effect of the amines on the ureter. A similar effect was observed on the isolated ureters of buffalo (4), dog and pig (5–8). Ergotamine has been shown to block the stimulant effect of adrenaline on the vesical sphincter (1) but it does not block the inhibitory effect on the detrusor muscle (1). The ergotamine block indicates that the effect of adrenaline on the vesical sphincter was mediated through the alpha adrenergic receptors and the effect on the detrusor muscle could be through the beta receptors (3). Furthermore, on the basis of relative potencies of different sympathomimetic amines, Ahlquist (3) proposed alpha adrenergic receptors for the stimulant action on the ureter. The use of beta receptor blocking agent, dichloroisopropyl noradrenaline (DCI) has helped in demonstrating the presence of beta receptors in various tissues (9). The existence of beta receptors in the urinary bladder of cat has been recently demonstrated (10). The present work was undertaken to analyse the adrenergic receptors in the ureter, detrusor muscle and vesical sphincter of dog with the help of alpha as well as beta receptor blocking agents.

METHODS

Forty-two mongrel dogs of either sex were used in this study. They were anaesthetized with pentobarbitone sodium administered intravenously (30 mg/kg), bilaterally vagotomized and maintained on positive pressure artificial respiration. The blood pressure was recorded from a common carotid artery by means of a mercury manometer on smoked paper. The femoral vein was cannulated with a polythene tube for administering the drugs.

The activities of the smooth muscles of the ureter, urinary bladder wall (detrusor) and the vesical sphincter were recorded by the following techniques.

1. Method for recording transureteric flow

The effects of catecholamines on transureteral flow was studied by the method used by Ahlquist (3) and Abraham and Pickford (11). The ureter of one side was exposed
by a midline abdominal incision. The pelvis and the distal ends of the ureter were can-
нуты with polythene tubes. The lumen of the ureter was perfused with normal saline
through the upper end and the outflow from the lower end was recorded by an electronic
drop recorder. The height of the saline reservoir was adjusted at the start of the experi-
ment to give a minimum flow of 5–8 drops in one outburst. The height of saline reservoir
was not changed subsequently during the experiment.

2. Method for recording intravesical pressure

The lower ends of both the ureters were ligated and the intravesical pressure was
recorded with a water manometer by passing a polythene tube through the urethra. The
intravesical pressure was initially set at a pressure of 20 cm of water by adjusting the height
of the water reservoir connected to the manometer through a three-way cock. The changes
in the intravesical pressure produced by the catecholamines were recorded on a smoked
paper.

3. Method of recording bladder sphincteric activity

The idea of studying bladder sphincteric activity was taken from Langley (12) who
was able to measure the tonus of rabbit cardiac sphincter by determining its resistance to
water pressure. In this study a minimal flow of saline was obtained through bladder
sphincter by maintaining a constant intravesical pressure.

The urinary bladder was exposed in male dogs and polythene tubes were passed into
the cavity of the bladder through the distal end of each ureter. The intravesical pressure
was controlled by forcing normal saline through these tubes from a 10 litre pressure bottle.
The pressure in the bottle was increased by means of a rubber bulb and measured by means
of a mercury manometer connected in parallel to the bottle.

After filling the bladder with normal saline from the pressure bottle a polythene tube
was passed into the bladder through the external urethral opening. The outflow of
saline through the polythene tube indicated its entry into the bladder cavity. The tube
was then gradually withdrawn till the flow of saline stopped, and this indicated that the
open end of the tube was just distal to the sphincteric level. This was confirmed post
mortem. A constant intravesical pressure of 50 mm of Hg was maintained throughout
the experiment to permit a minimal flow of the saline through the vesical sphincter. The
outflow was recorded by an electronic drop recorder and changes in the flow were indica-
tive of sphincteric activity.

RESULTS

1. Effect of catecholamines on transureteral flow

Effect of catecholamines were observed in doses ranging from 1 μg/kg to 6 μg/kg. The
effect of a single dose of agonist on transureteral flow lasted from 2.0 to 2.5 minutes.

Noradrenaline and adrenaline caused a transient cessation of transureteral flow while
isoprenaline increased it. Dibenzylamine (10 mg/kg) or yohimbine (1 mg/kg) blocked the
constrictor effect of noradrenaline and adrenaline and propranolol (2.5 mg/kg) or DCI
(10 mg/kg) blocked the relaxant effect of isoprenaline. Alpha and beta adrenergic block-
Results of typical experiments are shown in Figs. 1 and 2. The upper tracing shows blood pressure and lower tracing represents transureteral flow. The control effects of noradrenaline (4 μg/kg) are shown in the first panel (Fig. 1). The second panel shows the blockade of noradrenaline effect after yohimbine (1 mg/kg). Similarly in Fig. 2 control effects of isoprenaline (6 μg/kg) are shown in the first panel and the second panel shows the blockade of isoprenaline effect on transureteral flow, after propranolol (2.5 mg/kg).

2. Effects of catecholamines on intravesical pressure

Effect of different doses (1 μg to 6 μg/kg) of catecholamines on the intravesical pressure
was studied. Adrenaline, noradrenaline and isoprenaline decreased the intravesical pressure indicating relaxation of detrusor muscle. This effect lasted from 2 to 3 minutes and was blocked by nethalide (10 mg/kg). Isoprenaline was more potent than adrenaline.

![Graph showing effect of adrenaline, noradrenaline, and isoprenaline on intravesical pressure](image1)

**Fig. 3.** Effect of adrenaline (AD) (3 μg/kg), noradrenaline (NA) (3 μg/kg) and isoprenaline (ISP) (3 μg/kg) on intravesical pressure in dog. Upper tracing shows blood pressure and lower tracing, intravesical pressure. Adrenaline (AD), noradrenaline (NA) and isoprenaline (ISP) produced a fall in intravesical pressure (first three panels) which was almost blocked after a dose of 10 mg/kg nethalide (Neth) (last panel). Note that the same dose of isoprenaline produced a much greater fall in intravesical pressure in comparison to adrenaline and noradrenaline.

![Graph showing effect of adrenaline, noradrenaline, and isoprenaline on vesical sphincter outflow](image2)

**Fig. 4.** Effect of adrenaline (AD) (3 μg/kg), noradrenaline (NA) (3 μg/kg) and isoprenaline (ISP) (3 μg/kg) on the flow through vesical sphincter in dog. Upper tracing shows blood pressure and lower tracing shows, outflow of fluid through vesical sphincter. Note that both adrenaline and noradrenaline decreased the outflow while isoprenaline increased it. Dibenzyline (Dib) (10 mg/kg) blocked the effect of adrenaline and noradrenaline but not of isoprenaline.
and noradrenaline. The results of one such experiment are shown in Fig. 3. The upper tracing shows the blood pressure and the lower tracing shows the intravesical pressure. The control responses of adrenaline (3 μg/kg), noradrenaline (3 μg/kg) and isoprenaline (3 μg/kg) are shown in the first three panels respectively. The last panel shows the blockade of the relaxant effect of the drugs after administration of nethalide (10 mg/kg).

3. Effect of catecholamines on vesical sphincter

Noradrenaline and adrenaline decreased the flow through the vesical sphincter while isoprenaline increased it in doses ranging from 1–4 μg/kg. Dibenzyline (10 mg/kg) blocked the stimulant effect of adrenaline and noradrenaline on the sphincter but not the relaxant effect of isoprenaline. The relaxant effect of isoprenaline was blocked by DCI (10 mg/kg). Fig. 4 shows the results of a typical experiment. Upper tracing shows the blood pressure and lower tracing represents the outflow of fluid through vesical sphincter. The control responses of adrenaline (3 μg/kg), noradrenaline (3 μg/kg) and isoprenaline (3 μg/kg) are shown in the first panel. In the second panel the effects of these drugs after administration of dibenzyline (10 mg/kg) are shown. The effects of adrenaline and noradrenaline are blocked but isoproterenol response is unaffected.

DISCUSSION

Ahlquist (3) proposed that the adrenergic receptors in the ureter are of the alpha type. In the present study evidence has been provided for the presence of beta adrenergic receptors in the ureter, bladder and vesical sphincter of the dog.

Various workers (3–5, 7, 8) have shown that sympathomimetic agents produce contraction of the ureteric musculature. We have also observed that adrenaline and noradrenaline cause transient cessation of transureteral flow which is indicative of contraction of the ureteric musculature. This constrictor effect was blocked by dibenzyline or yohimbine, thus, confirming the presence of alpha receptors in the ureter. Isoprenaline which mainly acts on the beta receptors increases transureteral flow and this effect was blocked by DCI. These experiments confirm the presence of alpha receptors in the ureter and provide evidence for the presence of beta receptors. The former have excitatory and the latter, inhibitory action on the smooth muscle of the ureter.

Isoprenaline, adrenaline and noradrenaline caused relaxation of the detrusor muscle in decreasing order of potency as indicated by their effect on the intravesical pressure. Other workers (1, 13) have also shown that adrenaline and noradrenaline cause relaxation of the detrusor muscle but were unable to block this effect by alpha adrenergic blocking agents. Garret (14) studied the effect of adrenaline and noradrenaline in spinal dogs and failed to observe any effect on intravesical pressure with doses upto 20 μg/kg. However, Boyarsky et al. (10) recently observed an inhibitory effect of very high doses of isoprenaline (1–3 mg/kg) on the urinary bladder. In the present study much smaller doses of adrenaline, noradrenaline and isoprenaline (3 μg/kg) were found to exert a clear cut inhibitory effect on the bladder. Garret (14) could not observe the inhibitory effect of adrenaline and noradrenaline in acutely spinal transected dogs. His failure could be
due to atony of the bladder on account of the acute spinal section. The blockade of the inhibitory effect of catecholamines on the urinary bladder by nethalide confirms the presence of beta inhibitory receptors in the detrusor muscle.

Dale (1) observed the stimulant effect of adrenaline on vesical sphincter, which was blocked by ergotamine. In the present study we have observed that both adrenaline and noradrenaline cause contraction of vesical sphincter and this effect is blocked by dibenzyline. On the other hand isoprenaline causes relaxation of the vesical sphincter. This action of isoprenaline is antagonized by DCI but not by dibenzyline showing that the relaxation of vesical sphincter is subserved by beta type of adrenergic receptors.

SUMMARY

The nature of adrenergic receptors of the urinary tract of dog has been analysed by observing the effect of adrenaline, noradrenaline and isoprenaline on the transureteric flow, intravesical pressure and on the flow through vesical sphincter. The effect of alpha and beta adrenergic blocking agents on the responses of these sympathomimetic amines has also been studied. The study has demonstrated the presence of inhibitory beta receptors in the ureter, detrusor muscle and vesical sphincter in addition to excitatory alpha receptors in the ureter and sphincter.

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