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In vitro Effects of Prostaglandins on the Guinea Pig Detrusor and Bladder Outlet*

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Summary. The effects of prostaglandins on the urinary bladder and urethra were determined using guinea pig detrusor and urethral muscle strips in an in vitro muscle bath. Prostaglandins E_1, E_2, F_{1a} and F_{2a} caused contraction of detrusor strips and relaxation of strips from the bladder outlet. Their mechanism of action appears to be mediated through the sympathetic nervous system in both the detrusor and outlet with some direct relaxation effects in the outlet.

Key words: Prostaglandin, Bladder, Urethra, Guinea pig.

INTRODUCTION

Prostaglandin (PG) was the name given by von Euler to an acidic, lipid-soluble factor extracted from human seminal plasma and sheep vesicular glands which possessed activity in stimulating smooth muscle and lowering blood pressure (28). Chemically, prostaglandins are 20-carbon chain unsaturated fatty acids (5, 33) and are divided into five types (types A to F) based on the function of the cyclopentane ring (3).

Prostaglandins are formed from inactive, endogenous polyunsaturated fatty acids within cells and are released in response to nervous, chemical or mechanical stimuli. They are extremely potent and appear to be an essential intermediary between the stimulus and the cellular response. Their activity is usually of short duration due to rapid metabolic inactivation within the cells of formation or in the nearby fluid. The rapid inactivation of each prostaglandin at its specific site of action serves as a localising mechanism to prevent it from exerting an effect in other parts of the body (10).

Extensive investigation of prostaglandins has revealed that these biologically active lipids exhibit a wide variety of effects on smooth muscle organs, uterus (5, 23), ureter (4, 6, 20, 34), bronchus (4, 5, 27, 32), seminal vesicles (17), vas deferens (17) and intestines (5, 17, 21, 30).

The post-ganglionic neurotransmitter in the bladder is believed to be acetylcholine, but the bladder is somewhat refractory to atropine suggesting that the post-ganglionic neurotransmitter is non-cholinergic (2). This observation plus the known activity of prostaglandins on other organ systems has led us to investigate the activity of prostaglandins on the smooth muscle of the lower urinary tract.

MATERIAL AND METHODS

Adult guinea pigs weighing 600 to 800 g were sacrificed in a carbon dioxide chamber and the bladder and urethra were immediately removed en bloc. Detrusor strips approximately 4 mm wide and 20 mm long and posterior urethral strips 3 mm wide and 10 mm long were obtained.

The strip was placed in a 20 ml tissue bath and immersed in Locke's # 2 solution. The bath was encircled by a water jacket that was maintained at 37°C by a circulating pump. One end of the strip was fixed to the base of the bath and the other end to a Grass force transducer by a 6-0 silk suture. The force transducer was attached to a Harvard Micromanipulator by which the length and tension of the muscle strip could be adjusted. The force transducer was in turn connected to a Sanborn polygraph. The entire system was then calibrated so that positive or negative deflections

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on the polygraph print-out could be directly read as change in force in milligrams.

The length of the muscle strip was slowly and gradually increased until the strip was under 1 g tension. The strip was then maintained at 1 g tension and experiments were begun after the tissue exhibited spontaneous contractile activity.

The various drugs were injected directly into the 20 ml bath and the muscle response recorded. At the completion of each experiment the solution in the bath was removed and the bath and muscle were washed several times with Locke's # 2 solution. The tissue was allowed to re-equilibrate and further experiments were performed when the original baseline was achieved.

Four different prostaglandins were tested; PGE_1, PGE_2, PGF_{1a}, PGF_{2a}. Each of the prostaglandins was tested against specified prostaglandin antagonists (polyphloretin phosphate PPP, dibenzoxazepine hydrazide-SC19220 and 17-oxa-prostanoic acid), against alpha-adrenergic blockade (phentolamine), beta-adrenergic blockade (propranolol), cholinergic blockade (atropine) and ganglionic blockade (hexamethonium). Drug dosages in these experiments are expressed in micrograms per millilitre of bath. From 7 to 15 experiments were conducted for each drug at each dosage level.

RESULTS

Preliminary experiments revealed an inconsistent response of detrusor strips to each of the prostaglandins. An increase in tension (contraction) was noted in approximately two-thirds of the responses (Fig. 1) while a decrease in tension (relaxation) or biphasic response was noted in one-third of the responses (Figs. 2, 3 and 4).

When a strip exhibited relaxation or a biphasic response, it did so for all the prostaglandins at all dosages; when a strip exhibited a contractile response it did so far all the prostaglandins at all doses and never exhibited a relaxation or biphasic response.

The correlation between resting tension and change in detrusor length was determined for several detrusor strips. For each strip as the length was increased the resulting resting tension increased in a Starling curve manner; tension did not correlate with percentage length from strip to strip (Fig. 5), each strip exhibiting its own individual length-tension response.

The response of detrusor strips to a 5 μg/ml dose of the prostaglandins at varying detrusor lengths and tension was measured. The response to prostaglandins correlated with detrusor length in a Starling curve manner for each of the 4 prostaglandins (Fig. 6). The maximum detrusor response to prostaglandins occurred at a length of about 190% of resting length. All relaxation

Positive Detrusor response

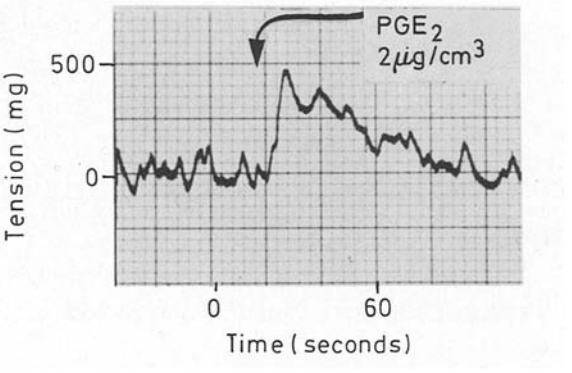

Fig. 1. Typical contraction of detrusor strip in response to prostaglandin E_2

Detrusor–Negative response

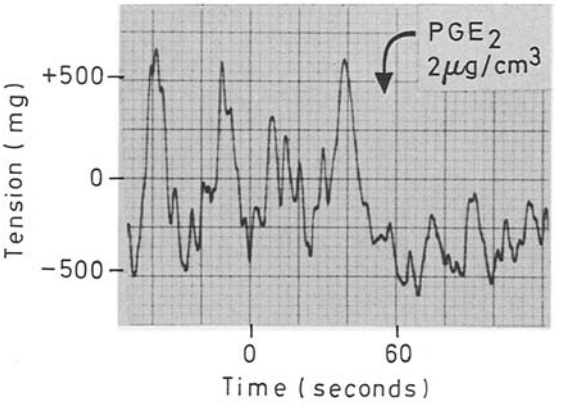

Fig. 2. Relaxation of detrusor strip in response to prostaglandin E_2

Detrusor–Diphasic response

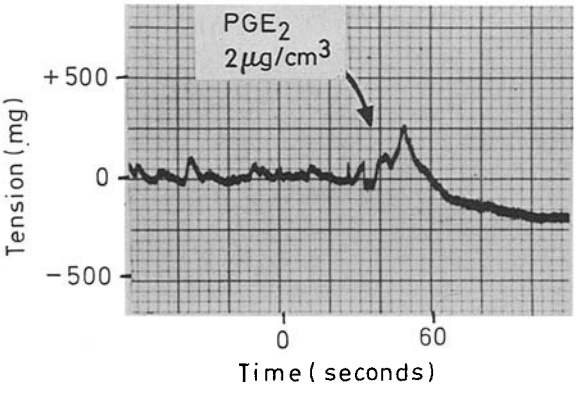

Fig. 3. Biphasic response (contraction followed by relaxation) of detrusor strip elicited by prostaglandin E_2

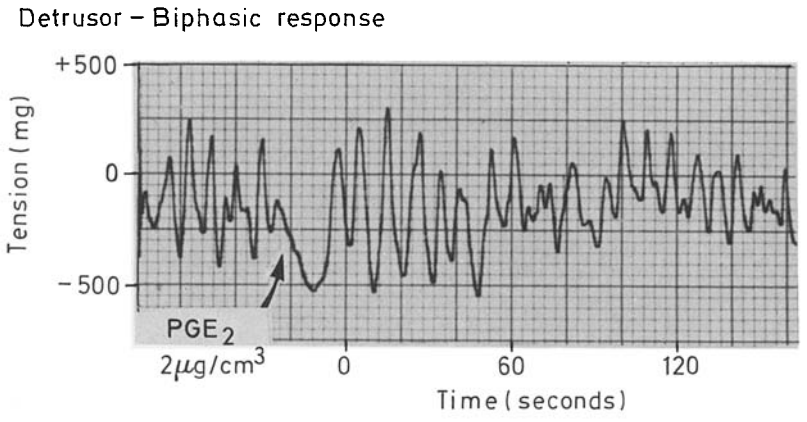

Fig. 4. Biphasic response (relaxation followed by contraction) of detrusor strip elicited by prostaglandin E_2

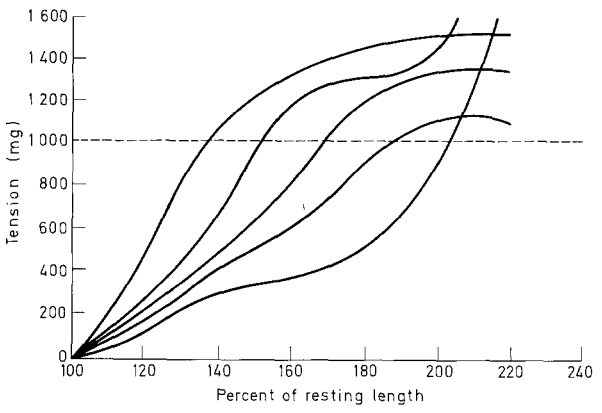

Fig. 5. Changes in baseline tension resulting from progressive lengthening of unstimulated detrusor strips

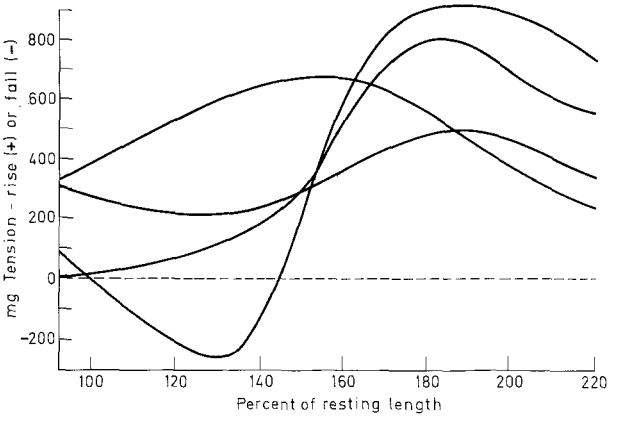

Fig. 6. Response of detrusor strips to 5 μg/ml prostaglandin at varying lengths of the strip

and biphasic responses and some contractile responses occurred at lengths of 140% or less. At lengths of greater than 140% of resting length the response was always a contraction for all 4 prostaglandins at all doses.

All data expressed for the response of the detrusor to prostaglandins is based on a detrusor strip length of 190% of resting length.

1. Detrusor Response to Prostaglandins

At a detrusor strip length of 190% of resting length the response of the detrusor strips to varying concentrations of the 4 prostaglandins was determined. Nine experiments were performed for each dose level of each of the prostaglandins. The results are noted in Figs. 7 and 8. The contractile responses of the detrusor strips were essentially identical for all 4 prostaglandins at concentrations of 0.25-2.0 μg/ml bath. At a concentration of 5.0 μg/ml, PGF_{1a} and PGF_{2a} exhibited greater activty than PGE_1 and PGE_2. The average response lasted about 20 s. No relaxation or biphasic responses were noted at a detrusor strip length of 190% of resting length.

Atropine (1 μg/ml) significantly reduced or abolished the response to low doses (0.5 - 1.0 μg/ml) of prostaglandins. Atropine (1 μg/ml) reduced by 50% the response to medium doses (2 μg/ml) of all 4 prostaglandins but had no effect on the response to high doses of prostaglandins (5 μg/ml).

Alpha-adrenergic blockade (phentolamine-10 μg/ml) markedly depressed or abolished the response to 5 μg/ml of all prostaglandins and the resultant response was below baseline (relaxation) in many cases.

Beta-adrenergic blockade (propranolol - 10 μg/ml) had little effect on the response of detrusor strips to all 4 of the prostaglandins.

The prostaglandin-blocking agents had the following effect on the responses of strips of prostaglandins: SC19220 (2 μg/ml) had no effect on any of the responses to prostaglandin doses of 2 to 5 μg/ml; PPP (0.05 μg/ml) had no effect on the response to 1-5 μg/ml of PGE_1 and PGE_2 but it reduced by 50% the response to 1-5 μg/ml PGF_{1a} and PGF_{2a}; 5 μg/ml of 17 oxa-prostanoic acid had no effect on the response to 1-5 μg/ml

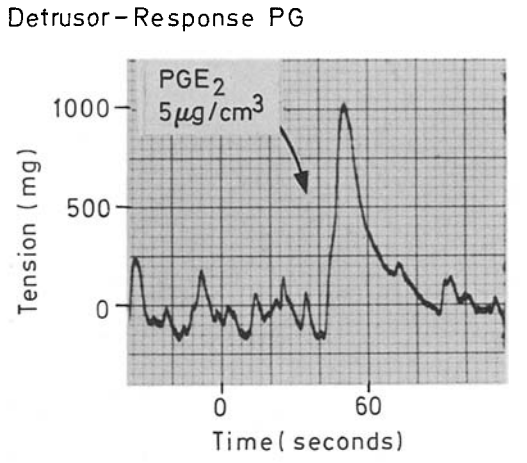

Fig. 7. Typical contractile response to prostaglandins of detrusor strip placed at 190% resting length

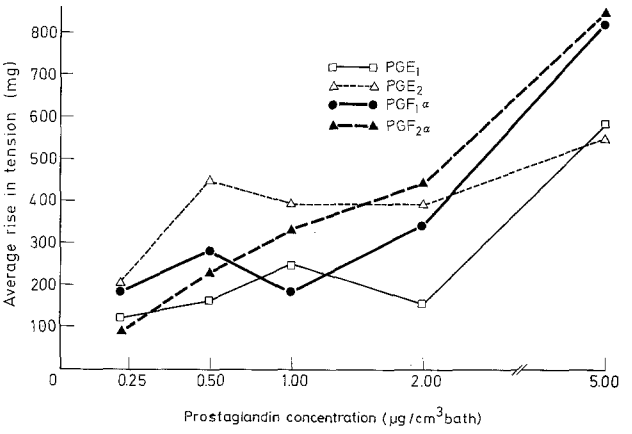

Fig. 8. Detrusor dose-response curves for the four prostaglandins tested

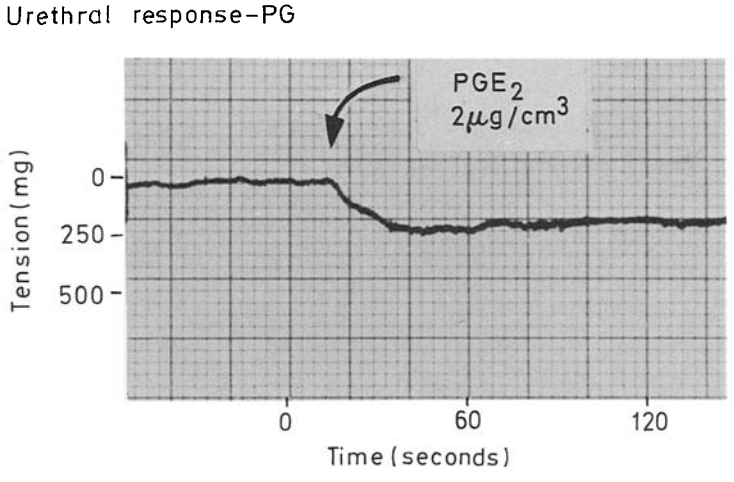

Fig. 9. Typical urethral strip response (relaxation) to prostaglandins

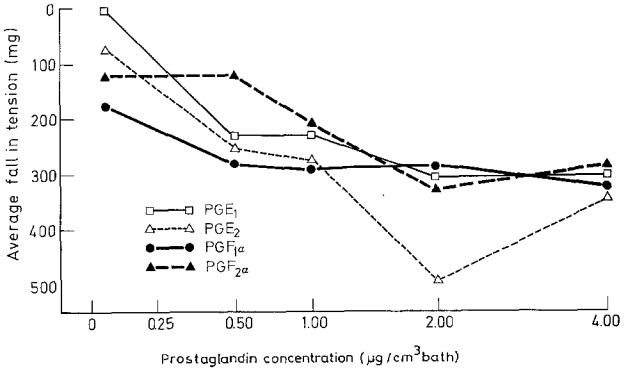

Fig. 10. Urethral dose-response curves to four prostaglandins tested

of prostaglandin E_1. It blocked nearly completely the responses to PGE_2 and PGF_{2a} and reduced by 50% the response to 1-5 μg/ml of PGF_{1a}.

Ganglionic blockade (hexamethonium - 300 μg/ml) did not affect the response of the detrusor to any of the prostaglandins.

The combination of atropine (1 μg/ml) and hexamethonium (50 μg/ml) abolished completely the response to all 4 prostaglandins (1-5 μg/ml).

2. Urethral Response to Prostaglandins

The effect of prostaglandins on the urethra was determined on urethral strips placed on 1 g tension. Fifteen experiments were conducted for each drug at each dosage level.

All 4 prostaglandins, at doses of 0.05-2.0 μg/ml decreased the tension of urethral strips by an average of 200-300 mg tension (Figs. 9 and 10).

The magnitude of the responses was not dose-related except for PGE_2 which caused a dose-related decrease in tension. In comparing the magnitude of the responses to the 4 prostaglandins, there were no significant differences except for PGE_2 which had a greater depression (relaxation) effect at higher doses. The average duration of urethral relaxation induced by the prostaglandins was about 45 min in spite of repeated washings of the strips.

Atropine (1 μg/ml) reduced the response to 1 μg/ml of PGF_{1a}, PGE_2 and PGF_{2a} by 5-19%. It reduced the response to 1 μg/ml of PGF_{1a} by 40 to 100%.

Ganglionic blockade by hexamethonium (300 μg/ml) reduced the response to PGE_1 and PGE_2 by 63-75%. It reduced the response to PGF_{1a} and PBG_{2a} by 15-27%.

The combination of atropine (1 μg/ml) and hexamethonium (300 μg/ml) reduced the response to all 4 prostaglandins by 62-73%.

Beta blockade by propranolol (3 μg/ml) reduced the response to all 4 prostaglandins by 67-79%.

At a dose of 1.5 μg/ml epinephrine elicited a contraction of the urethral musculature (increased tension). PGE_1 and PGE_2 given after the epinephrine decreased the magnitude of the contraction induced by epinephrine. Epinephrine given after the prostaglandin converted the relaxation induced by the prostaglandins into a contraction.

The effects of the prostaglandin blocking agents were as follows: 17-oxa-prostanoic acid (5 μg/ml) completely blocked the response of the urethra to all 4 prostaglandins; SC19220 (2 μg/ml) completely blocked the response of the urethra to PGE_1, PGE_2 and PGF_{2a} and it blocked the response to PGF_{1a} by 80-83%; PPP (0.05 μg/ml) completely blocked the response to PGF_{1a} and PBG_{2a} and it blocked the response to PGE_1 and PGE_2 by 73-78%.

DISCUSSION

Prostaglandins affect smooth muscles of various organs directly or indirectly through the autonomic nervous system (29). The mechanism is probably due to prostaglandins inhibiting the release of or modulating the effects of norepinephrine liberated at certain neuro-effector sites in conjunction with cyclic AMP (10). Thus, prostaglandins are viewed as chemical modulators.

It is thought that prostaglandin Es are formed within the post-junctional region of a variety of organs as a result of the action of the neurotransmitter norepinephrine and diffuse into the synaptic cleft and then act at prejunctional sites by a feedback mechanism on the nerve terminal to curtail or inhibit the further release of transmitter (8, 17). It is also thought that PGEs have a secondary action at post-junctional sites causing a change of norepinephrine effects (8, 11). PGEs usually inhibit adrenergic transmission by depressing responses to norepinephrine at the post-junctional level and sometimes specifically by inhibiting the release of the transmitter from nerve terminals. The PGFs facilitate responses produced by sympathetic nerve stimulation and occasionally increase the responsiveness of the effects to norepinephrine (8, 19).

Prostaglandin production in the lower urinary tract has been confirmed. Ghoneim et al. (15) cannulated the vena cava of dogs and assayed the concentration of prostaglandins in venous samples during various stages of vesical distention. They found a significantly increased release of PGE_2 with vesical distention which was most pronounced during maximal vesical distention and immediately after evacuation of the bladder. They suggested that prostaglandins were released from the urethra in response to autonomic stimuli. Gilmore and Vane (16) isolated a prostaglandin-like substance in response to distention of the dog's bladder and suggested that prostaglandin release may be a response to stretch of the bladder; a local mechanism to resist the distorting force or to accommodate to it.

1. Detrusor

Several investigators have found that prostaglandins E_1, E_2, F_{1a} and F_{2a} induce contractions of detrusor strips from various laboratory animals and humans (1, 2, 9, 18, 24). The magnitude of the contractile response of human detrusor strips to PGF_{2a} was about 65% of the magnitude of their response to acetylcholine (ACh) (1).

In vitro work (9, 18) suggests that prostaglandins affect the tone and spontaneous activity of the detrusor. Indomethacin, an inhibitor of prostaglandin biosynthesis, reduced the tone and spontaneous activity of human detrusor strips. Addition of PGE_2 or PGF_{2a} reversed the effect of indomethacin resulting in a return of tone and spontaneous activity. In vivo guinea pig and rabbit detrusor tone and motility increased in response to PGE_1 (4, 29). PGF_{2a} induced a slight increase in intravesical pressure lasting 10 min in dogs in vivo (29) while Hills (18) noted contractions of the detrusor were elicited by PGF_{2a} in vivo in various animals.

Other investigators (1, 2, 24) have found that the activity induced by prostaglandins in detrusor strips from rabbits and humans is unaffected by methysergide, atropine, eserine, phentolamine, propranolol, phenoxybenzamine, mepyramine, SC19220 or PPP. Taira (29) found that tetradotoxin or physostigmine did not affect the response of the detrusor to PGF_{2a}. He concluded that the response to prostaglandins is not neural excitation nor mediated via the cholinergic sys-

tem and that PGF_{2a} probably elicits a contraction by direct action on the musculature.

In vitro and in vivo prostaglandins have been found to potentiate the action of ACh on guinea pig and rat bladders (4, 22). The response of increased tone and spontaneous activity induced by physostigmine in rabbit detrusor strips is prevented by prior addition of indomethacin or hyoscine. From these data Hills (18) suggests there may be a link between ACh output and prostaglandin production in the bladder preparation.

Shuttleworth and Bultitude (9, 26) attest to the effects of prostaglandins on the lower urinary tract clinically. Twenty-one female patients in chronic urinary retention who were unable to mount a detrusor contraction in spite of the absence of neurological deficit or outlet obstruction were treated by instilling 0.5 mg PGE_2 intravesically. Fourteen of the 21 patients responded with a feeling of urgency at smaller volumes followed by a sustained detrusor contraction resulting in voiding and good bladder emptying. The majority of the patients continued to void with ease for 3 months or more after a single instillation of the prostaglandin. This technique was used with similar success in post-prostatectomy chronic retention in males. They speculate that prostaglandins act either by sensitizing the cholinergic receptors to ACh or by increasing the production and/or release of ACh.

We were able to demonstrate a consistent contractile response of detrusor strips to all 4 prostaglandins at detrusor lengths of greater than 140% of resting length. At detrusor length of less than 140% resting length the response to all 4 prostaglandins at doses was variable which may explain the absent or sluggish response of detrusor strips to prostaglandins reported by some investigators (2, 4, 22).

Atropine competitively blocked the prostaglandin-induced contractile response suggesting that prostaglandins act through the cholinergic system. Interestingly, atropine inhibits the response of the detrusor to ACh in a similar manner (competitive inhibition). However, the response of the detrusor to prostaglandins is blocked by alpha-adrenergic blockade suggesting that prostaglandins act through alpha-adrenergic receptors.

Ganglionic blockade by hexamethonium did not after the response of the detrusor to prostaglandins. However, the combination of hexamethonium and atropine abolished the response of the detrusor strips to all 4 prostaglandins.

Although the prostaglandin blocking agents used in this investigation exert their effect primarily by inhibiting the synthesis of endogenous prostaglandins, they have been shown to inhibit the actions of exogenous prostaglandins in vitro (25). In this investigation the effects of the prostaglanddin blocking agents were variable. However, PPP and 17-oxa-prostanoic acid did alter some of the prostaglandin-induced responses.

We interpret these data as an indication that prostaglandins exert their effect on the detrusor by acting through the sympathetic nervous system. We postulate that prostaglandins stimulate the sympathetic ganglionic neurones resulting in a stimulation of alpha-adrenergic receptors in the detrusor (Fig. 11). It has been shown that sympathetic, parasympathetic and interneurone ganglia are present in the smooth muscle of the lower urinary tract (7, 12-14). Unpublished data by us using ganglionic stimulating and blocking agents confirms the presence of autonomic ganglia in in vitro muscle strips.

Transmission through autonomic ganglia is mediated by both muscarinic and nicotinic receptors. Transmission via nicotinic receptors is generally the primary route of transmission in autonomic ganglia and these receptors are blocked by hexamethonium. A secondary role of ganglionic transmission is via muscarinic receptors and these receptors can be blocked competitively by atropine (31).

Atropine competitively blocks the response of the detrusor to prostaglandins by interrupting transmission through the muscarinic receptors of the autonomic ganglia. An alteration of the response to prostaglandins is not detected if blockade by hexamethonium alone is used because transmission via nicotinic receptors plays a minor role in the ganglionic transmission in response to prostaglandins. However, with high doses of prostaglandins in the presence of atropine, transmission through the nicotinic and muscarinic receptors in these ganglia occurs. This could explain the inability of atropine to block the activity of high doses of prostaglandins. Blockade of nicotinic and muscarinic receptors in the ganglionic neurone interrupts both pathways

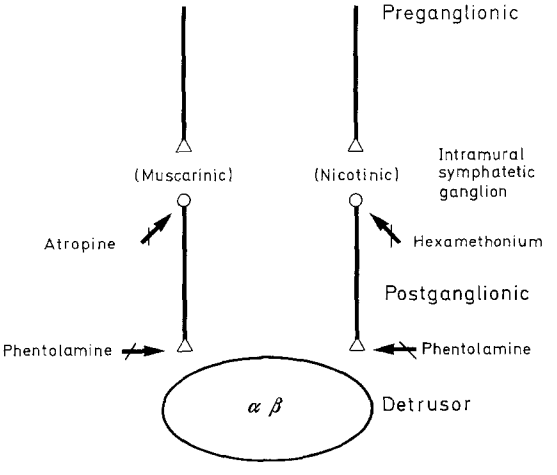

Fig. 11. Proposed mechanism of action of prostaglandins on detrusor

for ganglionic transmission resulting in an absence of a response of the detrusor to prostaglandins. This could explain the inability of atropine to block the activity of high doses of prostaglandins.

Phentolamine blocks the response of the detrusor to prostaglandins by blocking the alpha-adrenergic receptors so they become unresponsive to stimulation by released norepinephrine.

2. Bladder Outlet and Urethra

The response of the bladder outlet and urethra has not been previously studied in vitro. Ghoneim et al. (15) surgically separated the bladder body from the trigone in vivo and measured intravesical and intraurethral pressures simultaneously. Urethral resistance was found to decrease as the bladder was distended. Prior treatment with indomethacin (inhibitor of prostaglandin biosynthesis) blocked this response of the urethra to vesical distention. In a second experiment the body of the bladder was removed leaving the trigone and urethra in situ in dogs. PGE_2 infused intra-arterially induced a dose-dependent reduction in urethral resistance while PGF_{2a} induced a dose dependent increase in urethral resistance. These authors concluded that prostaglandins have a direct effect on the urethra.

We have found that the application of prostaglandins E_1, E_2, F_{1a} and F_{2a} to muscle strips from the bladder outlet and urethra results in consistent long-lasting relaxation.

Our data suggest that the activity of prostaglandins on the bladder outlet is mediated both through the sympathetic division of the autonomic nervous system as well as directly on the smooth muscles of the outlet (Fig. 12). Their primary mechanism of action appears to be via stimulation of beta-adrenergic receptors in the outlet as evidenced by the altered response to prostaglandins after beta-adrenergic blockade with propranolol. As in the detrusor, prostaglandins appear to act at sympathetic ganglia. Atropine or hexamethonium alone partially alter the activity of prostaglandins and in combination reduce the response by 60-70%. The results of the interaction between prostaglandins and epinephrine are compatible with stimulation of alpha and beta adrenergic receptors by epinephrine and prostaglandins; the unoccupied receptor is stimulated when the second drug is added.

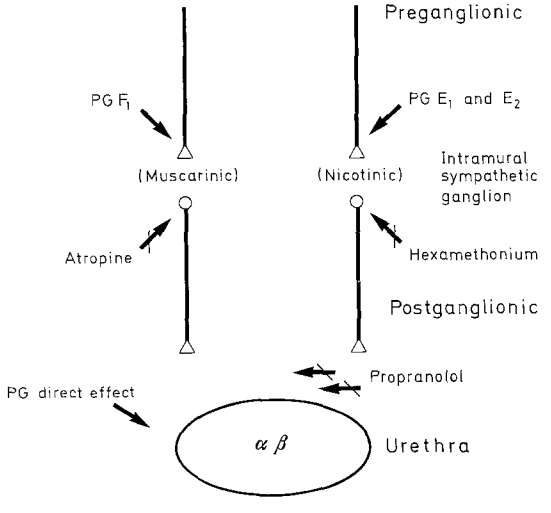

Fig. 12. Proposed mechanism of action of prostaglandins on bladder outlet

Prostaglandins also appear to have a direct effect on the smooth muscle of the bladder outlet. Blockade of both nicotinic and muscarinic receptors in the ganglion by atropine and hexamethonium or blockade of beta-adrenergic receptors by propranolol does not abolish the effects of prostaglandins completely. However, prostaglandin blocking agents almost completely block the response of the outlet to prostaglandins.

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