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The Action of Bromocriptine on Human Detrusor Muscle

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Summary. The pharmacological effects of bromocriptine on human detrusor muscle were investigated by an in vitro isometric method. Both a direct stimulating effect and an anticholinergic effect were demonstrated. These effects, together with an alpha-adrenergic blocking effect reported in a previous paper, are correlated with the published clinical effects of bromocriptine in patients with primary and secondary unstable detrusors.

Key words: Bromocriptine, Unstable detrusor, Autonomic receptors.

In a previous communication (11) we reported a series of in vitro isometric studies of the action of bromocriptine on the smooth muscle of the human prostate and prostatic capsule. This investigation had been prompted by varying reports from clinical trials of bromocriptine for the relief of benign prostatic obstruction. As a result of these studies we concluded that bromocriptine had both a direct stimulant effect, an alpha-adrenergic blocking action and an anticholinergic effect on the human prostatic muscle, and we concluded that any beneficial effect on the obstructive manifestations of benign prostatic hypertrophy could well be due to the direct pharmacological effects rather to a hormonal effect.

In addition to its effect on the obstructive symptoms, some evidence of an effect on the irritative symptoms associated with benign prostatic hypertrophy has been reported. Farrar and Pryor (5) described a significant improvement in frequency, nocturia and urgency in such patients treated with bromocriptine, and they suggested that the bromocriptine was acting to modify unstable detrusor activity. In a subsequent paper, Farrar and Osborne (6) reported symptomatic improvement in fourteen out of twenty-four patients treated with bromocriptine for detrusor instability. On the other hand, Abrams and Dunn (1) found no significant improvement in a group of patients with non-obstructive unstable detrusors treated with bromocriptine. The possibility that any clinical improvement noted might be due to a sensory action rather than a motor effect was investigated by O'Boyle and Parsons (9), but no evidence for such an action was found.

In an attempt to elucidate this matter further, and having regard to our findings in the prostatic muscle, we investigated the direct pharmacological actions of bromocriptine on strips of bladder detrusor muscle removed at operation.

MATERIAL AND METHODS

Strips of smooth muscle approximately 2 mm wide by 2 cm long were removed from the dome of the bladder at operation. The isometric reactions of the muscle strips to the addition of bromocriptine alone and in combination with adrenergic and cholinergic stimulators and blockers were investigated. Full details of the technique used and of the preparation of the bromocriptine solution have been given in our previous publication (11). Fifty-one isometric experiments were performed on the detrusor strips.

RESULTS

1. Bromocriptine Alone

The effect of the addition of bromocriptine alone (65 μg/ml) was examined in twenty-eight in-

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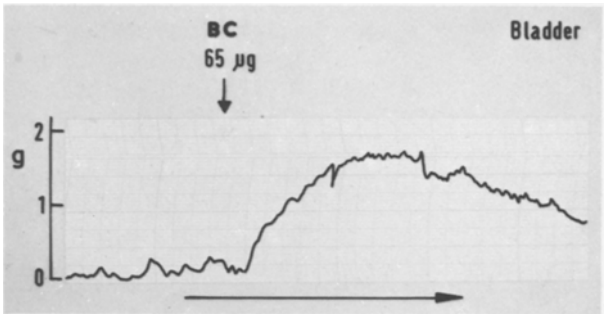

Fig. 1. Increase in tension of detrusor muscle strip produced by addition of bromocriptine (BC)

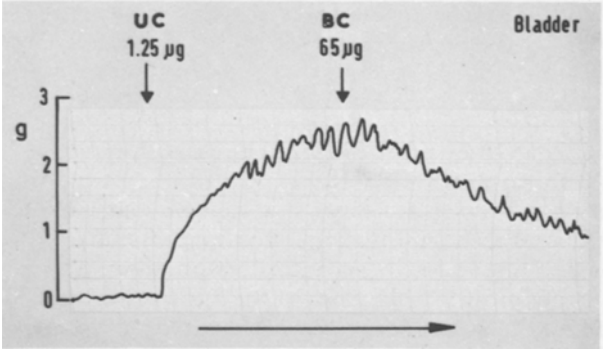

Fig. 2. Cholinergic stimulation of detrusor muscle strip by bethanechol (UC), counteracted by addition of bromocriptine (BC)

stances. In sixteen of these there was a definite increase in tension (Fig. 1) and in another five there was an equivocal increase in tension. In six instances there was no observable effect, and in one case there was a diminution in tension. The addition of atropine (10 µg/ml) did not abolish the increase in tension produced by bromocriptine.

2. Effect of Bromocriptine on Cholinergic Stimulation

Addition of bethanechol (Urecholine), in various concentrations from 1.25 µg/ml to 10 µg/ml, produced the expected increase in tension due to cholinergic stimulation of the detrusor in all twelve instances tested. In nine of these the addition of bromocriptine (65 µg/ml) produced an anticholinergic effect with a diminution in tension (Fig. 2). In two cases this effect was equivocal and in one case there was no effect. In three of the cases, in which an anti-cholinergic effect was obtained, the subsequent addition of atropine (10 µg/ml) produced an additional anti-cholinergic effect. The anti-cholinergic effect of the bromocriptine could be partially overcome by increasing the concentration of the cholinergic stimulant.

3. Effect of Bromocriptine on Adrenergic Stimulation

Adrenergic stimulation of the muscle strips was produced with nor-adrenaline in concentrations of 1 µg/ml and 2 µg/ml in five experiments, and with isoproterenol (Isuprel) in a concentration of 10 µg/ml in six experiments. In the case of nor-adrenaline a beta-response with a drop in tension was obtained in all instances, and was not influenced by the addition of bromocriptine (65 µg/ml) in four of the five cases. In the remaining case the addition of bromocriptine resulted in a slight increase in tension which did not reach the original base-line. When isoproterenol was used there was no significant response in two instances, but in the other four a relaxation corresponding to a beta-response was again obtained. In two of these four cases no effect was observed on the addition of bromocriptine, and in the other two a slight rise in tension, not approaching the original base-line, was seen.

DISCUSSION

The results of the above investigation on the direct pharmacological actions of bromocriptine on the human bladder detrusor muscle correspond well with our earlier findings in the prostate and prostatic capsule. An anticholinergic effect was again demonstrated and was found to be weaker than that of atropine. As mentioned in our previous paper, it is not clear whether this is a true cholinergic blocking effect or whether it is an anticholinergic action due to its well recognised dopamine receptor agonist action. This causes intracellular accumulation of cyclic AMP, hyperpolarisation of post-synaptic membranes and hence a reduced sensitivity to acetyl-choline. The net effect, however, is the same whatever the mechanism may be.

The beta-adrenergic type of response obtained by the addition of both nor-adrenaline and isoproterenol to the muscle preparations accords well with the known preponderence of beta-adrenergic receptors in the dome of the bladder, and hence it was natural that no alpha-blocking effect of bromocriptine could be demonstrated experimentally in this tissue. Gibson et al. (7, 8), in experiments on peripheral blood vessels and on the ano-coccygeus muscle in the rat, have shown that the alpha-adrenergic blocking effect of bromocriptine is relatively powerful. Hence, in the prostate and prostatic capsule with their rich alpha-adrenergic receptor content (3), this blocking action is prominent, and effectively counteracts the direct stimulating effect of bromocriptine (11). In the detrusor on the other hand, the paucity of alpha-receptors makes the alpha-blocking effect virtually non-

existent, and the direct stimulating effect of bromocriptine on the muscle is then unopposed and is clearly manifest, as seen in these experiments. It is noteworthy that the one detrusor specimen in which a reduction in tension was obtained on the addition of bromocriptine was found to have been taken inadvertantly from close to the bladder neck, where the alpha-receptor content is high.

The relationship of these experimental findings to the clinical effects reported in the literature is of interest. It is clear that, in contradistinction to its action on the prostate, the simple net effect of bromocriptine on the human detrusor muscle is to increase the tone. It could only be by virtue of its relatively weak anticholinergic effect, acting on a bladder being subjected to cholinergic stimulation, that a reduction in tone could be anticipated. Although the so-called "idiopathic" or "primary" detrusor instability may well include a variety of aetiological causes, there is really no evidence that it is due to parasympathetic overactivity, and it is well recognised that the relatively much more powerful standard anticholinergic drugs are clinically disappointing in these cases. Hence, the lack of significant benefit from treatment with bromocriptine reported in most of the cases of idiopathic detrusor instability is to be expected. Of particular interest is the improvement reported in the irritative symptoms associated with bladder outlet obstruction. We have reported a number of times (2, 4) on the beneficial effects produced on these symptoms by the administration of alpha-adrenergic blocking agents used in the symptomatic treatment of benign prostatic obstruction. It would seem likely that the similar effect of bromocriptine in these patients is also associated with its relatively powerful alpha-blocking activity. The exact mechanism of this action is not clear as yet, but work reported recently by Rohner et al. (10) may provide a clue to this. They have shown that, following chronic outflow obstruction in the dog, a change occurs in the relative proportions of alpha and beta receptors in the dome of the detrusor, and the net reaction of the detrusor muscle to sympathetic stimulation changes from a decrease to an increase in tension. If a similar change occurs in the human detrusor as a result of chronic prostatic obstruction it could be causally related to detrusor instability, and could hence explain the benefit obtained by alpha-adrenergic blockade, whether this is produced by bromocriptine or by the more usual blocking agents such as phenoxybenzamine.

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