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The Pharmacological Action of Bromocriptine on the Human Prostate

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Summary. In-vitro isometric studies of the effects of bromocriptine on the human prostatic capsule and prostatic adenoma reveal transient direct stimulant actions, alpha-adrenergic blocking effects and anticholinergic effects. The mechanism of the latter effect is discussed. It is suggested that these direct pharmacological actions may at least partly explain the clinical improvement reported in some cases of benign prostatic obstruction and detrusor instability treated with bromocriptine.

Key words: Bromocriptine, Prostate, Adreno receptors, Cholinergic receptors.

Amongst the many substances investigated in recent years for possible therapeutic effects on benign enlargement of the prostate has been bromocriptine (2 bromo- α -ergocryptine mesilate: C. B. 154. Sandoz). The rationale for this use has been based upon its central prolactin inhibiting effect, together with experimental evidence that prolactin enhances androgen binding to the prostatic cells and has an effect upon prostatic size (7). A few clinical trials have so far been reported, with variable but not very impressive results (3, 11).

We have drawn attention in the past to the possibility that substances thought to have a hormonal effect on the prostate, may in fact produce an effect due to a direct pharmacological action on the prostatic smooth muscle tissue (10). In view of the fact that bromocriptine is a synthetic ergot alkaloid of the polypeptide type, a group of drugs known to have a variety of pharmacological effects on smooth muscle, it was decided to investigate the possibility of a direct action of this substance on human prostatic tissue.

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MATERIALS AND METHODS

Material was obtained from the enucleated adenoma and the anterior prostatic capsule at the time of retropubic prostatectomy, as described in a previous publication (1). This was placed immediately in Krebs-Ringer solution at 5°C, and subsequently examined isometrically in a muscle chamber containing the same solution at 37°C, aerated with 97% oxygen and 3% CO_2. The tension in the strip was recorded via a Grass force-displacement transducer (FT. 03C) attached to a Grass Recorder, calibrated to a sensitivity of 20 mm deflection per gram tension. The strips were subjected to a resting tension of from 0.5-1.0 gram, and the recovery of spontaneous activity awaited. Following this, the effects of the addition of bromocriptine and various other pharmacological agents, as detailed below, were investigated. Bromocriptine is not soluble in water, and the solution for investigation was prepared in Hartmann's solution with the aid of Propylene Glycol, Tween 80, and a few drops of tartaric acid, and tested at final concentrations of 10^{-4}, 10^{-5} and 10^{-6} molar. The solvent itself was tested for activity on the strips, and found to be inert. Altogether, 86 experiments (48 on the adenomatous tissue and 38 on the prostatic capsule) were performed.

RESULTS

a) Prostatic Adenoma

1. Bromocriptine Alone. Out of 14 cases, an initial transient rise in tension occurred in 7. This was followed in 4 cases by a reduction in tension and a diminution in the spontaneous contractions (Fig. 1). In 2 additional cases, this inhibitory ef-

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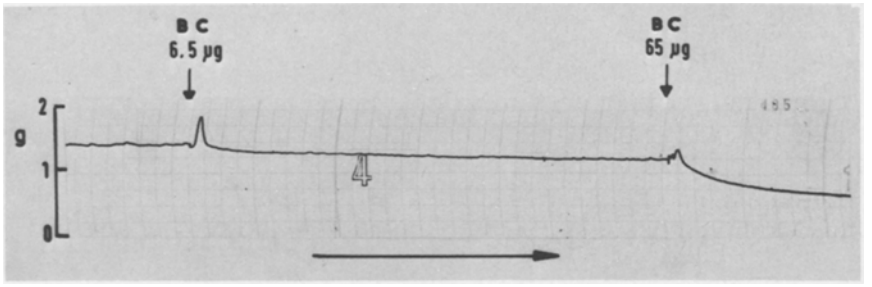

Fig. 1. Effect of Bromocriptine alone, on adenoma. Note initial transient contraction, followed by diminution of tension

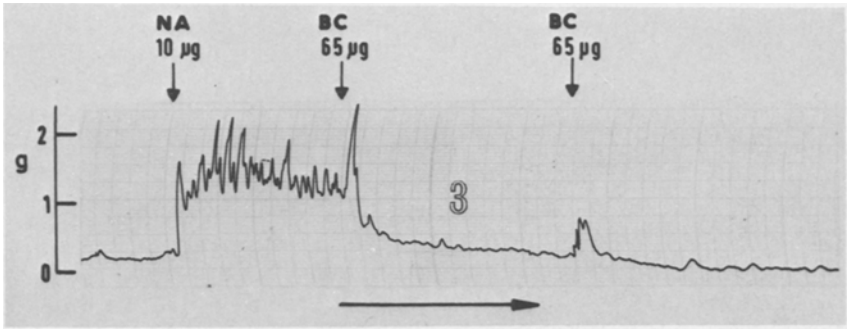

Fig. 2. Alpha-adrenergic stimulant effect of Noradrenaline on adenoma, blocked by subsequent addition of bromocriptine. Note transient contraction on addition of the bromocriptine on each occasion

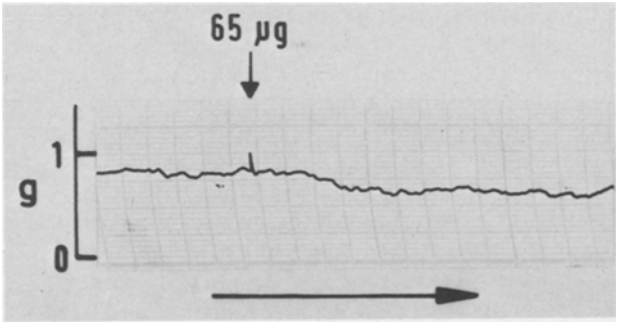

Fig. 3. Effect of Bromocriptine alone, on the prostatic capsule. There is a decrease in tension, following a minimal transient contraction

fect occurred without the initial rise in tension. In the remaining 5 cases no effect was produced.

2. Effect of Bromocriptine on Alpha-Adrenergic Stimulation. Stimulation of the alpha-adrenergic receptors in the adenomatous tissue was produced by Nor-adrenaline (13 cases), Aramine (3 cases) and Neosynephrine (phenylephrine) (10 cases), and the effect of bromocriptine on this response was examined. In 22 cases the alpha-stimulant was added first and the bromocriptine subsequently, in 4 cases the order was reversed. Addition of the alpha-stimulator produced the expected rise in tension in all cases, and subsequent addition of the bromocriptine reduced or abolished this effect. In several of the experiments there was an initial transient increase in tension immediately upon adding the bromocriptine, prior to the inhibitory effect (Fig. 2). In the 4 cases in which the bromocriptine was added first there was a reduction in tension with this, but a rise again on adding the noradrenaline (2 cases) or the neosynephrine (2 cases). Further addition of bromocriptine in one of the latter cases again reduced the tension.

3. Combined Effect of Bromocriptine and Phentolamine on Alpha-Adrenergic Stimulation. This was investigated in 8 cases. In all cases, as was to be expected, the phentolamine blocked the alpha-stimulator, and in 5 of them the bromocriptine appeared to give an additional inhibitory effect.

b) Prostatic Capsule

1. Bromocriptine Alone. In 6 out of 10 cases there was a diminution in tension in the strip (Fig. 3), 4 of them being associated with an initial transient contraction. In the remaining 4 cases, there was no effect.

2. Effect of Bromocriptine on Alpha-Adrenergic Stimulation. Bromocriptine abolished the rise in

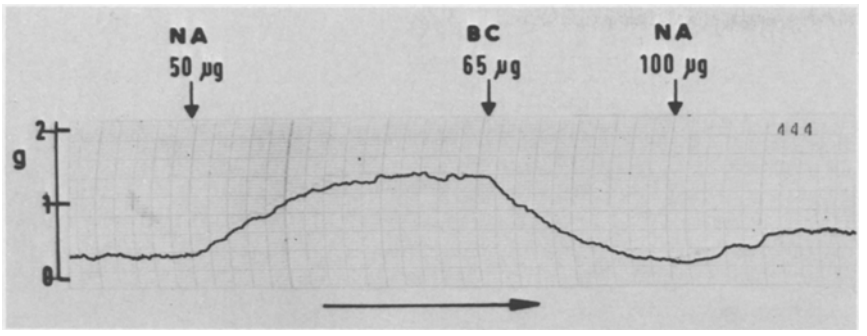

Fig. 4. Alpha-adrenergic stimulant effect of Noradrenaline on capsule, blocked by subsequent addition of bromocriptine. Further addition of high concentration of Noradrenaline partly overcomes blocking effect, with moderate rise in tension

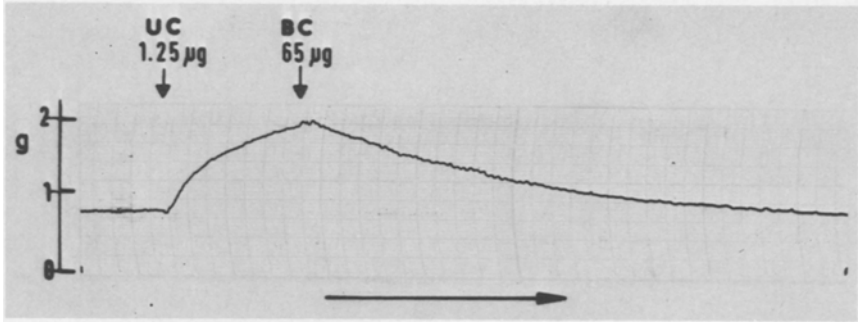

Fig. 5. Contraction of capsule due to cholinergic stimulation with Urecholine, counteracted by subsequent addition of Bromocriptine

tension produced by alpha-adrenergic stimulation with noradrenaline, aramine, or neosynephrine in all 8 cases tested (Fig. 4), and prevented the alpha-adrenergic response when given first in a further 3 cases tested, unless a very high concentration of the stimulant was given. Addition to phentolamine in one case caused a decreased tension.

3. Effect of Bromocriptine on Cholinergic Stimulation. Stimulation of the cholinergic receptors in the capsular tissue by means of urecholine (bethanechol chloride) produced a rise of tone in all 16 cases tested, and subsequent addition of bromocriptine counteracted this rise in all cases (Fig. 5). Subsequent addition of the cholinergic blocker atropine in 2 cases did not have any further action.

DISCUSSION

The findings in the above experiments clearly indicate the existence of a direct pharmacological effect of bromocriptine on the smooth muscle in the capsule and adenomatous portions of the human prostate. Ergot alkaloids of the polypeptide type, to which group of compounds bromocriptine belongs, are generally found to have both a direct stimulating effect on the muscle itself, and an additional alpha-adrenergic blocking effect. In the case of bromocriptine, Lew et al. (8), working on bovine and rat tissues, reported evidence of an alpha-adrenergic blocking effect, Flückiger (5) showed considerable alpha-adrenoreceptor blocking action on canine femoral vein strips, and Parkes, in a review article (9) states that bromocriptine has a weak antagonist effect on alpha-adrenoreceptors. The findings in our present series of experiments show evidence in support of the existence of both actions on the human prostate. The initial transient rise in tension observed on the addition of the bromocriptine, both in the untreated preparations and in those pretreated with noradrenaline, may be interpreted as being due to the direct stimulant effect on the smooth muscle. We have demonstrated the presence of alpha-adrenergic receptors in both the adenoma and in the capsule of the enlarged human prostate (1), and the typical response obtained in both tissues by the addition of the alpha-adrenergic stimulants noradrenaline, aramine, and neosynephrine was abolished in the present series of experiments by the subsequent addition of bromocriptine, or prevented by its prior administration. This blocking action is relatively weak, and in some experiments could be overcome by further addition of the alpha-stimulants, or on the other hand be enhanced by the further addition of the powerful alpha-blocker, phentolamine. The

inhibitory effect noted in a number of cases without any prior alpha-adrenergic stimulation may be interpreted as being dependent upon the initial degree of alpha-activity in the resting tonus of the preparation.

Cholinergic receptors have been shown by us to be present in the prostatic capsule but not in the prostatic adenoma (1), and this fact was illustrated in these experiments by the action of urecholine on the specimens of capsule tested. The effectiveness of the subsequent addition of bromocriptine in abolishing this contraction appears to indicate a blocking action on the cholinergic receptors, in addition to that already demonstrated on the alpha-adrenergic receptors. A similar antagonistic effect to the action of acetylcholine on intestinal smooth muscle has been reported by Flückiger (5). This finding could be due to a direct antagonistic effect of the bromocriptine itself on the cholinergic receptors, or could be mediated via its principal action as a dopamine receptor agonist (12). There is good evidence that the dopamine receptor is a component of adenyl cyclase, stimulation of which causes an intracellular accumulation of cyclic-AMP. This results in hyperpolarisation of post-synaptic membranes, resulting in a reduced sensitivity to acetyl-choline. Thus, in effect, there exists a dynamic equilibrium between cholinergic and dopamine functions, and stimulation of the dopamine receptors could result in an anti-cholinergic effect (6).

Whatever may be the exact mechanism of the pharmacological action of bromocriptine on the prostate, it is evident that the net effect is to oppose any rise in tension produced by alpha-adrenergic or cholinergic stimulation, and in many cases to reduce the resting tone of the smooth muscle in the capsule and the adenoma. In so doing, this will result in a reduction in the urethral closure pressure in the prostatic region, and hence produce a reduction in the outflow obstruction which could account for the beneficial clinical effects reported by Farrar and Pryor (3), and by Serment et al. (11) in a proportion of their patients treated with bromocriptine. This action would be relatively weak as compared with the effect of the classical alpha-adrenergic and cholinergic blockers such as phenoxybenzamine, phentolamine and atropine. In addition, the beneficial effect of a reduction in urethral closure pressure would to some extent be counteracted by the concomitant anticholinergic effect on the detrusor, and would limit its pharmacological effectiveness in benefiting patients with benign prostatic obstruction, especially as compared with the clear benefit seen with alpha-blocking agents alone (2). At the same time, this combination of the two actions might explain the beneficial effects of bromocriptine on the unstable detrusor reported by Farrar and Osborne (4), and this aspect of the subject is at present under further study.

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