Leading Article

Bromocriptine, dopamine and glaucoma

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The pharmacological control of intraocular pressure (IOP) is as complex as any other physiological system. The influence of the parasympathetic side of the autonomic nervous system, acting through muscarinic cholinergic receptors, has long been known, and cholinergic agonists such as pilocarpine are widely used in treatment of glaucoma. The sympathetic nervous system influences IOP in a remarkable way; agonists and antagonists at alpha and beta adrenoceptors all lower IOP, probably by a variety of pharmacological actions which result in reduction of aqueous humour formation on one hand and decrease in outflow resistance on the other (Mishima, 1982; Mittag, 1983). Several drugs acting at adrenoceptors are used in management of glaucoma, including adrenaline, timolol (a beta-receptor antagonist) and guanethidine (which reduces noradrenaline release).

The enzyme carbonic anhydrase is involved in aqueous humour formation, and inhibitors of the enzyme such as acetazolamide, and dichlorphenamide still have a place in treatment.

There is considerable evidence that prostaglandins, particularly PGE₂ and PGF₂₂, can reduce IOP in several species (Bito *et al.*, 1983), and it is probable that precipitation or aggravation of glaucoma by corticosteroids is due to their reduced production. If a stable prostaglandin analogue can be synthesized with topical activity in the eye, it might well prove of value in glaucoma.

The influence of dopamine receptor activity on IOP had not been recognized until recently, although it was known to be a neurotransmitter in the retina. A variety of dopamine receptor agonists, however, including bromocriptine, lergotril and pergolide, have now been shown to produce dose- and time-related ocular hypotension in rabbits and monkeys (Potter & Burke, 1982). Studies in normal volunteers showed that oral bromocriptine, 1.25 mg, produced a significant reduction in IOP at 3 and 4 hours after administration when compared with placebo under double-blind conditions (Mekki *et al.*, 1983), the reduction being comparable

in magnitude with that produced in healthy volunteers by oral or topical beta-adrenoceptor antagonists. A similar reduction in IOP was produced by 0.01% bromocriptine eye drops when compared with placebo in normal volunteers (Mekki *et al.*, 1984). No change in systemic blood pressure, pupil diameter or plasma prolactin level accompanied these changes in IOP. Dopamine receptors are classified pharmacologically into D₁ and D₂ receptors, bromocriptine being an agonist at D₂ receptors. The role of D₂ receptors in the ocular hypotensive action was demonstrated in normal subjects by pretreating them with intravenous metoclopramide which completely abolished the fall in IOP produced by oral bromocriptine without influencing it when given alone (Mekki & Turner, 1985).

Does bromocriptine lower IOP in ocular hypertension and glaucoma? The evidence of this is direct and indirect. Direct evidence has recently been provided by Wayyes *et al.* (1986) who studied 8 patients with chronic open-angle glaucoma, receiving treatment with pilocarpine or timolol eye drops. Bromocriptine in a single oral dose of 2.5 mg produced a significant reduction of more than 25% in IOP when compared with placebo. Indirect evidence was provided anecdotally by Lustig (1983) who reported that some patients with glaucoma who also had Parkinson's disease showed a fall in IOP when treatment was commenced with bromocriptine for their neurological disorder. He then proceeded to give bromocriptine 2.5 mg orally to patients with glaucoma but without Parkinson's disease, and found that it increased the fall in IOP produced by timolol in four of five patients.

If these preliminary observations are confirmed in further prospective long-term trials, low dose topical or oral dopamine receptor agonists such as bromocriptine may be added to the list of drugs used in treatment of glaucoma. The mechanism of action is unclear. Some dopamine agonists are also partial agonists at alpha adrenoceptors, but the absence of change in pupil diameter suggests that alpha adrenoceptors are not primarily involved. Dynamic studies of aqueous flow in rabbits have indicated that the effect of bromocriptine is produced, at least in part, by suppression of aqueous humour formation (Potter *et*

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al., 1984), but D₂ receptors have not yet been demonstrated in the ciliary body. It is possible that they are present on presynaptic adrenergic nerve endings there,

modulating the release of noradrenaline on to beta adrenoceptors involved in aqueous production, but this awaits investigation.

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