

Central dopaminergic and noradrenergic components of bromocryptine-induced locomotor activity in mice

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Bromocryptine (2-bromo- α -ergocryptine; CB 154) has therapeutic activity in Parkinson's disease, attributed to a stimulation of central dopamine (DA) receptors (Corrodi, Fuxe, Hokfelt, Lidbrink & Ungerstedt, 1973; Fuxe, Corrodi, Hokfelt, Lidbrink & Ungerstedt, 1974; Johnson, Loew & Vigouret, 1976). Degeneration of both DA and noradrenaline (NA) neurones may contribute to the symptoms of Parkinsonism. We have therefore examined the roles of both DA and NA in bromocryptine-induced locomotor activity in mice and related these to biochemical changes.

Bromocryptine (10 mg/kg, i.p.) stimulates locomotor activity in normal mice, an effect that is inhibited by pretreatment with pimozide (1 mg/kg, i.p.), FLA 63 (bis 4-methyl-1-homopiperazinylthiocarbonyl disulphide; 25 mg/kg, i.p.) and phenoxybenzamine (20 mg/kg, i.p.) but not by propranolol (20 mg/kg, i.p.). Reserpine (10 mg/kg, i.p. 18-24 h previously) markedly reduced and α -methyl-*p*-tyrosine (AMPT; 200 mg/kg, i.p.) completely abolished, bromocryptine (10 mg/kg, i.p.) induced locomotor activity. This suggests that the locomotion induced by low doses of bromocryptine depends on the functional integrity of synthesis and storage of both DA and NA. The fall of whole brain NA and DA following AMPT (200 mg/kg 1 h prior to death) was reduced 2 h after bromocryptine (5 mg/kg, i.p.) during the period of hyperactivity. In conjunction with the behavioural

results, this suggests feedback inhibition of both DA and NA neurones due to receptor stimulation.

High doses of bromocryptine (20-160 mg/kg, i.p.), while causing hyperactivity after a delay, cause a marked initial suppression of locomotion, which can be reversed by administration of apomorphine (2 mg/kg, i.p.) or clonidine (2 mg/kg, i.p.).

Bromocryptine (40 mg/kg, i.p.) enhanced the AMPT fall in NA 2 h following administration during the period of behavioural suppression, but had no effect on DA levels. This suggests that the higher doses of bromocryptine inhibited NA receptors and, indeed, the *in vitro* mouse limbic forebrain NA (10^{-5} M) sensitive adenylate cyclase system was inhibited by the addition of bromocryptine (IC_{50} 9.4×10^{-9} M). The ability of bromocryptine to interact with DA systems was, however, confirmed by the ability of the drug (10^{-10} to 10^{-6} M) to displace [3 H]-haloperidol for its binding site in rat striatal preparations (IC_{50} 4.3×10^{-8} M).

The findings are interpreted as showing a complex involvement of both cerebral NA and DA in the locomotor activity produced by bromocryptine in rodents. The effects of this drug appear to be dose-dependent and may also involve actions on both pre- and post-synaptic monoamine sites.

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Location of receptors mediating hypothermia after injection of dopamine agonists in rats

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The intracerebroventricular injection of dopamine agonists in rodents causes hypothermia, which is

blocked by pimozide (Kruk, 1972). The location of the receptors involved is uncertain, but from indirect evidence striatal (Glick & Marsanico, 1974) or hypothalamic (Cox, Ary & Lomax, 1975) sites have been postulated.

We have attempted to define the site of action more precisely by injecting dopamine and apomorphine into the lateral ventricle, caudate nucleus, third ventricle and preoptic-anterior hypothalamus. Injections were made in a dose volume of 1 μ l through previously implanted guide cannulae. Both rectal and tail skin

Table 1 Effect of intracerebral injection of apomorphine and dopamine

Drug	Mean change in core temperature ($^{\circ}\text{C} \pm \text{s.e. mean}$)			
	PO/AH	CN	IIIIV	LV
Saline	+0.2 \pm 0.1	+0.1 \pm 0.1	-0.2 \pm 0.1	+0.4 \pm 0.2
Apomorphine	1.25 μg	-0.3 \pm 0.1*	-	-0.3 \pm 0.2
	5.0 μg	-0.8 \pm 0.3**	-0.2 \pm 0.1	-0.3 \pm 0.1
	10.0 μg	-1.0 \pm 0.2**	-0.2 \pm 0.2	-0.6 \pm 0.1*
	20.0 μg	-0.9 \pm 0.2**	-0.6 \pm 0.2*	-0.8 \pm 0.3
Dopamine	5.0 μg	-0.4 \pm 0.1*	-	-
	10.0 μg	-0.7 \pm 0.2**	-	-0.5 \pm 0.1
	20.0 μg	-0.8 \pm 0.2**	-0.2 \pm 0.1	-

Mean of maximum change in core temperature occurring within 40 min of injection into preoptic-anterior hypothalamus (PO/AH), caudate nucleus (CN), third ventricle (IIIIV) and lateral ventricle (LV). n = between 4 and 11 observations, * $P < 0.05$, ** $P < 0.01$.

temperatures were measured. Although a fall in core temperature was always preceded by a rise in skin temperature, the change in core temperature was more consistent and was used in the expression of results (Table 1). Of the sites tested the preoptic-anterior hypothalamus was the most responsive. When equieffective doses of apomorphine were compared, the time for maximum response was significantly shorter after intrahypothalamic injection (5 μg = 7.0 \pm 2.0 min) than after either third ventricular (10 μg = 18.5 \pm 1.4 min) or intracaudate injection (20 μg = 20.0 \pm 5.7 min).

These results suggest that the most likely site of action of dopamine and apomorphine after intracerebral injection is the preoptic-anterior hypothalamus. That dopamine receptors are involved

is indicated by the finding that an i.p. injection of pimozide 0.5 mg/kg antagonized the effect of intrahypothalamic injections of each of the agonists.

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Comparison of the effects of dopamine and noradrenaline on single cortical neurones

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Cortical neurones can respond with both excitation and depression to microelectrophoretically applied noradrenaline (NA) (Johnson, Roberts, Sobieszek & Straughan, 1969). We have recently presented evidence that the excitatory responses are mediated by α -adrenoceptors, whereas the depressant responses

are mediated by β -adrenoceptors (Bevan, Bradshaw & Szabadi, 1976). Cortical neurones are also sensitive to dopamine (DA), both excitatory and depressant responses having been described (Bevan, Bradshaw & Szabadi, 1975; Stone, 1976). However, it has not yet been established whether DA and NA act at pharmacologically distinct receptors on these cells.

Single spontaneously active neurones were studied in the somatosensory cortices of halothane-anaesthetized rats. All the drugs were applied by microelectrophoresis.

The direction of the responses (excitation or depression) evoked by DA and NA were compared on 46 cells. All these cells responded in the same direction to the two catecholamines, 30 being excited and 16 being depressed by both drugs.