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Further evidence for a dopamine receptor stimulating action of an ergot alkaloid

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Several recent reports have suggested that some, at least, of the group of alkaloids present in ergot (*Claviceps purpurea*) may have a potent stimulating action on dopamine receptors in the mammalian central nervous system, and that this effect could contribute to the marked behavioural effects produced by them[1,6,11]. One of these reports concerned the alkaloid agroclavine which was shown to induce stereotyped sniffing and gnawing behaviour in rats at the low dose of 1–2 mg/kg, s.c.[11]. Such induced stereotypy is usually considered indicative of an activation of central dopamine receptors[8,9]. The present series of experiments was therefore designed to examine the effects of agroclavine directly on central neurones in order to try and obtain more direct evidence for such an action. Unit responses to agroclavine have been compared with responses to dopamine, noradrenaline and 5-hydroxytryptamine and attempts have been made to antagonise these responses.

All experiments were performed on male rats weighing 250–300 g and anaesthetised with urethane 1.25 g/kg, i.p. Conventional microiontophoresis techniques were used as described in detail elsewhere[10–12] to apply drugs to spontaneously active randomly encountered cells in the parietal cerebral cortex. One barrel of the 5-barrelled micropipettes was filled with a 200 m*M* solution of agroclavine (base) made in distilled water containing either 1.5 m*M* tartaric acid[2] or 200 m*M* ascorbic acid. The pH of the resulting solution was approximately 4.0. One barrel also contained a solution of tartaric or ascorbic acid at pH 4.0 as a control of H^+ effects. A third barrel contained 200 m*M* sodium chloride at pH 4.0 for current balancing[10] and checking current effects.

The remaining barrels were filled with solutions of either 200 m*M* dopamine hydrochloride, pH 4.0; 200 m*M* (—)noradrenaline bitartrate, pH 4.0; 50 m*M* 5-hydroxytryptamine creatinine sulphate, pH 4.5; or 200 m*M* chlorpromazine hydrochloride, pH 4.0.

Recording of cell activity was achieved through a single micropipette containing 1 *M* potassium acetate attached to the multibarrel assembly[12] via an Ekco instantaneous ratemeter onto a Servoscribe pen recorder.

The results of applying agroclavine and dopamine and either noradrenaline or

TABLE I

A COMPARISON OF NEURONAL RESPONSES TO AGROCLAVINE AND DOPAMINE, NORADRENALINE AND 5-HYDROXYTRYPTAMINE

D = depression; E = excitation; N = no response; — = not tested.

Responses to agroclavine	*Responses to dopamine*				
	D	*E*	*N*	—	
D	20	1	2	0	No. of cells responding in same way = 35/45 = 78%
E	1	5	2	0	
N	4	0	10	0	
—	0	0	0	0	
	Responses to noradrenaline				
	D	*E*	*N*	—	
D	15	0	5	3	No. of cells responding in same way = 18/37 = 48%
E	4	0	2	2	
N	8	0	3	3	
—	0	0	0	0	
	Responses to 5-hydroxytryptamine				
	D	*E*	*N*	—	
D	14	0	4	5	No. of cells responding in same way = 17/35 = 48%
E	5	0	1	2	
N	8	0	3	1	
—	0	0	0	0	

5-hydroxytryptamine to 45 spontaneously active units are shown in Table I. It may be deduced from these results that 78% of the cells tested responded in the same way to agroclavine and dopamine, whereas only 48% responded in the same manner to agroclavine and noradrenaline or 5-hydroxytryptamine. This suggests that agroclavine could be acting on dopamine receptors.

In an attempt to confirm this further we have tried to antagonise responses to the various agonists with chlorpromazine, an antagonist primarily at central dopamine receptors[15]. Fig. 1 illustrates records of the firing rate of a cell which is depressed by dopamine, agroclavine and 5-hydroxytryptamine. The application of chlorpromazine proves able to block responses to the former agents while leaving 5-hydroxytryptamine responses unaffected. Chlorpromazine was ejected with a current of 25 nA in these experiments since ejection with larger currents sometimes caused a reduction of spike height, presumably due to local anaesthetic properties of the drug. This specific blockade of dopamine and agroclavine was seen on 9 of 12 cells tested, using 5-hydroxytryptamine or noradrenaline as control. The latter substances were unaffected by chlorpromazine on these cells.

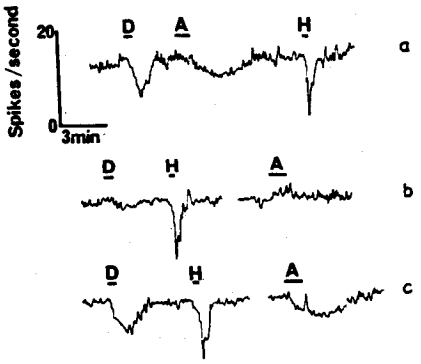

Fig. 1. Records of the firing rate of a cortical neurone, depth 1040 μm, during the iontophoretic application of dopamine 60 nA (D), agroclavine 100 nA (A), and 5-hydroxytryptamine 50 nA (H). a: before; b: immediately after; and c: 4 min after the iontophoresis of chlorpromazine 25 nA for 3 min.

The question arises in studying the cerebral cortex of the validity of discussing a 'dopamine receptor' since there is no large dopamine-containing neuronal system ascending to the cortex recognised at present. Nevertheless, the recent work of Thierry *et al.*[13,14] has clearly indicated the presence of possible dopaminergic nerve terminals in the cortex, and the clear, reproducible dopamine responses described in the present paper, together with their specific antagonism by chlorpromazine, supports this possibility.

It is also a difficulty with microiontophoretic experiments whether a lack of response of a neurone can be classified as a result. Certainly there can be a good deal of variation of drug ejection between pipettes, or between different barrels of a pipette[7]. However, it was found in the present experiments that units responding or not responding to the various drugs were interspersed during any one experiment. That is, there was no occasion on which more than two consecutive units were unaffected by any drug, and this would indicate that there was no long-lasting blockage or defect in a drug barrel. When, as in the present experiments, one is *comparing* units' responses to various agents, then, with the knowledge that there is no permanent damage to any barrels it is surely legitimate to classify non-responses as results on the assumption that any variation of drug ejection during an experiment is equally likely to affect any of the drugs at any one time.

Corrodi *et al.*[1] have obtained evidence favouring a stimulation of dopamine receptors by ergocornine and 2-bromo-α-ergokryptine. Johnson *et al.*[6] have used a number of ergot alkaloids and, using the induction of stereotypy on rats as an indicator of dopamine-receptor activation, concluded that many were able to stimulate these receptors. Lysergic acid diethylamide (LSD-25) has also been reported to induce stereotypy in rats[4], and some of the behavioural effects of LSD and *also of agroclavine* can be antagonised by the administration of chlorpromazine[3,5].

From the present experiments it is felt that the similarity of action of agroclavine and dopamine and the fact that both substances are susceptible to antagonism by

chlorpromazine lends support to these suggestions that agroclavine and possibly other ergot alkaloids may have an agonistic action at central dopamine receptors.

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