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Short communication

ANTAGONISM BY DERIVATIVES OF LYSERGIC ACID OF THE EFFECT OF DOPAMINE ON *HELIX* NEURONES

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The hyperpolarising action of dopamine on specific neurones in the isolated brain of the snail was blocked by low doses of lysergic acid diethylamide or methysergide. Pethidine, in higher doses, also blocked the dopamine response. Chlorpromazine, strychnine, picrotoxin, atropine, amantadine, tubocurarine, bicuculline and ergometrine were ineffective as dopamine antagonists.

Dopamine receptors **Lysergide** **Methysergide** **Pethidine** **Snail neurones**

1. INTRODUCTION

With the accumulation of evidence that dopamine is a transmitter in the mammalian central nervous system it has been suggested that some drugs which affect the mammalian brain do so by an action involving dopamine receptors (Ernst, 1965; Van Rossum, 1966; Cools and Van Rossum, 1970).

In the brain of the snail, *Helix aspersa*, there are identifiable neurones which are hyperpolarised and inhibited by dopamine (Kerkut and Walker, 1961). From a study of the structural requirements for dopamine-like activity in the brain of *Helix* it was concluded that the action of dopamine on these cells is mediated via specific dopamine receptors (Woodruff and Walker, 1969).

In the present communication we report the initial results of a survey in which we have screened compounds which affect the mammalian central nervous system as potential antagonists of the *Helix* dopamine receptor.

2. METHODS

Experiments were performed on dopamine-sensitive neurones in the right parietal ganglion of the isolated brain of *Helix aspersa*. Intracellular recordings of action potentials were obtained using previously-described methods. Dopamine was applied either iontophoretically, using a 1 sec ejecting pulse (200 to 1000 nA) or by bath addition in a dose of 1 to 5 nmoles (Woodruff and Walker, 1969). The standard dose of dopamine was applied at 5 min intervals until 3 or 4 constant responses had been obtained. The substance under investigation as a dopamine antagonist was then added to the bath (10 ml capacity) in a volume of 1 ml and left for 5 min. The standard dose of dopamine was then again applied. If antagonism to dopamine had occurred, the preparation was washed several times with snail Ringer and again tested for its response to dopamine. If no antagonism had occurred 15 min after the application of 0.5 μmole or more of the drug under investigation, the preparation was abandoned.

The following drugs were used; chlorpromazine

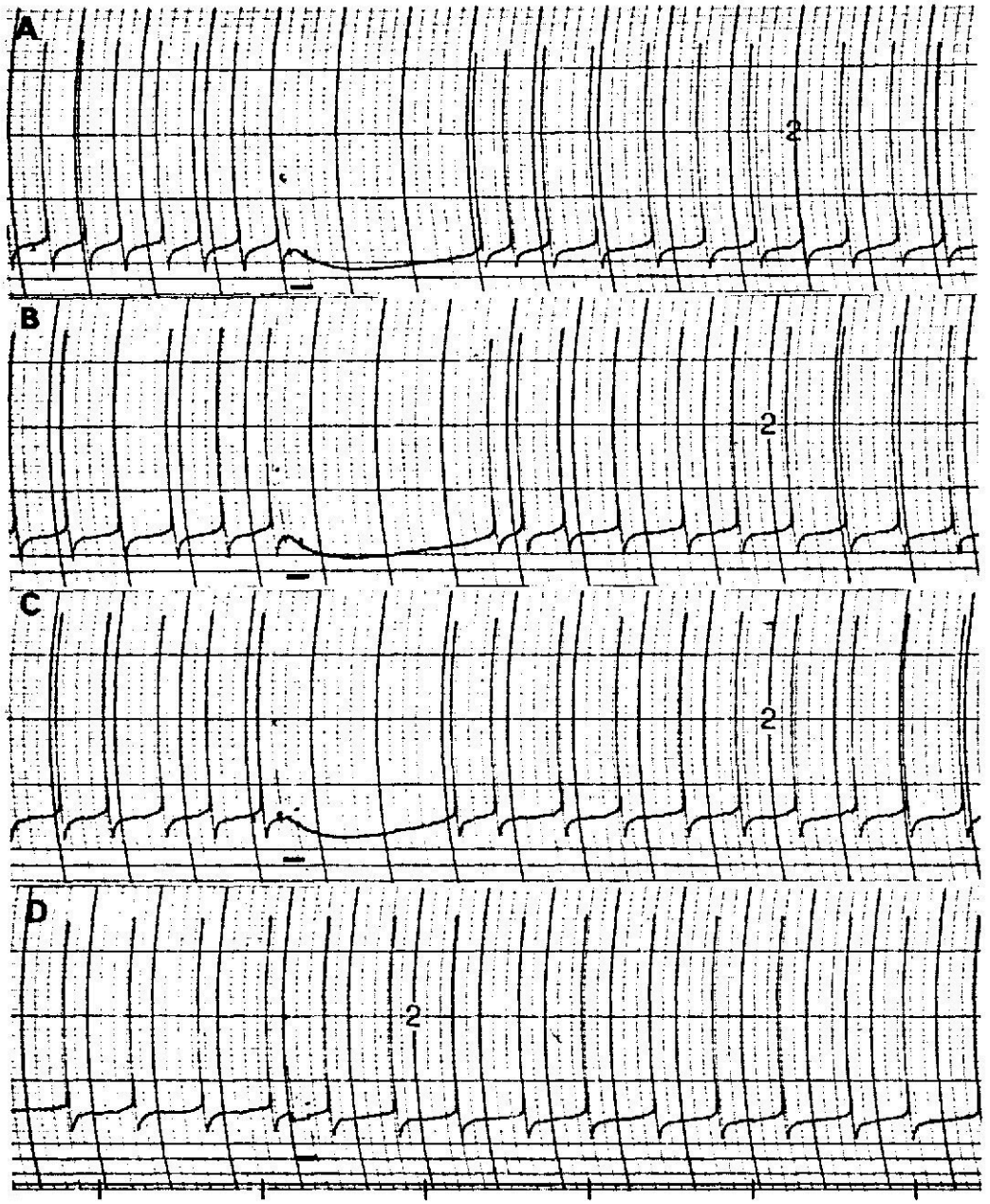

Fig. 1. Action potentials recorded from single neurones in the isolated brain of the snail. A and B are records from 1 cell, C and D are from a second cell. In both neurones the action potentials were 95 mV in amplitude. Dopamine was applied iontophoretically (500 nA) at the horizontal bar. A and C are control responses; the hyperpolarising responses produced by dopamine were 10 mV and 8 mV respectively. In B, in the presence of chlorpromazine (0.7 μmole), the dopamine response was unchanged. In D, after the addition of lysergic acid diethylamide (0.01 μmole), the dopamine response was completely abolished. Time calibration 10 sec.

HCl, strychnine HCl, bicuculline HCl, picrotoxin, D-lysergic acid-diethylamide-D-tartrate, atropine sulphate, (+)-tubocurarine chloride, methysergide maleate, amantadine HCl, pethidine HCl.

Each drug was tested on at least 3 different snail brain preparations.

3. RESULTS AND DISCUSSION

The specific dopamine-induced renal vasodilatation in the dog (Goldberg et al., 1968) is blocked by high doses of chlorpromazine (Brotzu, 1970). Chlorpromazine also blocks the action of dopamine on the crayfish stretch receptor (McGeer et al., 1961). However, chlorpromazine had no detectable dopamine-blocking action on *Helix* neurones. In fig. 1 the hyperpolarisation produced by the iontophoretic application of dopamine was unchanged after the addition of 0.7 μmole chlorpromazine. In further experiments 3.0 μmoles of chlorpromazine had no effect on the dopamine response, although this amount of chlorpromazine caused a sharp decile in the amplitude of the action potentials. It has previously been shown that haloperidol is similarly devoid of dopamine-blocking activity on *Helix* neurones (Woodruff et al., 1970).

The following compounds were also found to have no effect on the responses to dopamine after the addition of the amounts indicated; picrotoxin (0.5 μmole), strychnine (0.5 μmole), amantadine (5.0 μmoles), bicuculline (1.0 μmole), (+)-tubocurarine (0.5 μmole), atropine (1.00 μmole), ergometrinine (0.5 μmole).

Lysergic acid diethylamide was found to be a powerful antagonist of the dopamine response in *Helix*. In fig. 1 the hyperpolarisation produced by dopamine was completely abolished by 0.01 μmole of LSD. The dopamine antagonism produced by LSD (0.002 to 0.02 μmole) was usually not reversible by washing the preparation for 30 min. Methysergide (0.002 to 0.02 μmole) also produced a long lasting block of the dopamine response.

Pethidine (1.0 μmole) antagonised the action of dopamine on *Helix* neurones; the effect of this compound was readily reversed on washing.

Lysergic acid diethylamide is an antagonist of certain actions of 5-hydroxytryptamine (Gaddum, 1953). However, the action of LSD described in the present paper is not necessarily related to its ability to block 5-HT since the neurones used in the present study are depolarised by 5-HT, yet are hyperpolarised by dopamine. Furthermore, although LSD (0.002 to 0.02 μmole) blocks the actions of both 5-HT and dopamine on these neurones, the antagonism to 5-HT is readily reversed by washing, whereas the dopamine block is very long lasting.

LSD and methysergide are chemically related to ergometrine which is also a potent dopamine antagonist in *Helix* (Walker et al., 1968). However, the isomer ergometrinine was shown in the present study to have no dopamine blocking activity.

A study of the actions of other lysergic acid derivatives and other 5-HT antagonists on the dopamine response in *Helix* might provide more information concerning the relationship between the receptors for dopamine and for 5-hydroxytryptamine.

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