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Further evidence for the stimulation of rat brain dopamine receptors by a cyclic analogue of dopamine

The cyclic analogue of dopamine, 2-amino-6,7-dihydroxy-1,2,3,4-tetrahydronaphthalene (ADTN) was suggested as a likely stimulant of dopamine receptors (Woodruff, 1971). The results of recent studies suggest that ADTN is indeed a potent agonist at dopamine receptors in the mammalian brain (Woodruff, Elkhawad & Pinder, 1974; Munday, Poat & Woodruff, 1974) and on specific snail neurons (Pinder, Buxton & Woodruff, 1972).

In the present study, experiments were performed on female Wistar Albino rats (about 150 g), anaesthetized with urethane (1·2 to 1·5 g kg^{-1}). Extracellular recordings of action potentials were obtained from single neurons in the caudate nucleus using standard stereotaxic techniques. The six-barrelled "parallel" electrodes used were similar to those described by Crossman, Walker & Woodruff (1974). The recording barrel was filled with 5M NaCl; other barrels were filled with 1·5M NaCl, DL-homocysteic acid (0·05M, pH 8 to 9), dopamine HCl (0·1M, pH 4 to 5) and ADTN HBr (0·1M, pH 4 to 5). Using the barrel containing 1·5M NaCl the technique of current balancing (Salmoiraghi & Weight, 1967) was used for the iontophoretic ejection of drugs.

All of the neurons were stimulated to fire by the continuous application of homocysteic acid (2 nA). Recordings were made from a total of 15 dopamine sensitive neurons in the caudate nucleus of 3 rats. Dopamine (30 to 60 nA, applied for 15 to 60 s) caused complete inhibition of firing of the cells. Every neuron inhibited by dopamine was also completely inhibited by ADTN (30 to 60 nA applied for 15 to 60 s). ADTN was approximately equipotent with dopamine. Neurons not affected by dopamine were similarly insensitive to ADTN.

Additional behavioural experiments were performed on 6 adult male rats with unilateral lesions of the nigro-striatal pathway produced by the injection of 6-hydroxydopamine HBr (8 μg in 4μl of 0·9% NaCl containing ascorbic acid 0·2 mg ml^{-1})

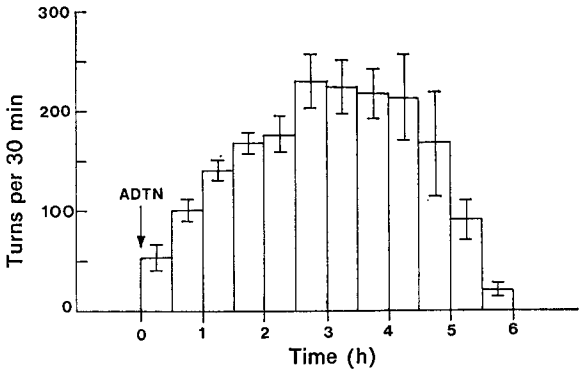

FIG. 1. Turning produced by the intraventricular injection of 150 μg ADTN into rats with unilaterial lesions of the nigro-striatal tract. All turns were towards the innervated side. Values are the means of experiments on six rats. The standard errors of mean are indicated.

into the substantia nigra on one side, using the method of Ungerstedt (1971). Nine days after the induction of the lesion the rats were injected with 150 μg ADTN into the lateral ventricle, using the method of Noble, Wurtman & Axelrod (1967). The injections of ADTN were made unilaterally on the same side as the lesion. Turning behaviour was measured with a microswitch and an electronic counter (Ungerstedt & Arbuthnott, 1970).

Each animal responded to ADTN with strong and long-lasting turning towards the innervated side (Fig. 1). The duration of action of ADTN was about 6 h. The intraventricular injection of 0·9% NaCl caused no turning behaviour. Iversen, Horn and Miller (personal communication) have recently obtained similar results with ADTN in lesioned rats. We have previously shown that unilateral injections of 150 μg ADTN into the ventricles of non-lesioned rats causes strong and long-lasting stimulation of motor activity, but little turning.

These results offer additional evidence from electrophysiological and behavioural studies that ADTN is a potent and long-lasting agonist at dopamine receptors in the rat brain.

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