histochemical results which clearly indicated the existence of DA terminals in the rat cerebral cortex.

In further experiments: 1-^{3}H-dopamine uptake was estimated in homogenates of the chronically isolated suprasylvian gyrus and compared to that of the contralateral side. ^{3}H-dopamine uptake was markedly reduced 27 days after the operation and the residual ^{3}H-amine uptake was not sensitive to benztropine or desipramine. 2-^{3}H-CA synthesis from ^{3}H-tyrosine was no more detectable in slices of the chronically isolated suprasylvian gyrus (27 days). Thus these two techniques lead to similar results: both types of catecholaminergic terminals degenerate in the chronically isolated area and dopaminergic as well as noradrenergic terminals, are exclusively of extracortical origin. This latter fact suggests the absence of dopaminergic interneurons in the cat neocortex.

The authors discuss the possibility that this dramatic decrease in the CA available, secondary to deafferentation, could be in part responsible for the augmented duration of the epileptiform after discharge in the chronically isolated cortex.

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The effect of dopamine receptor stimulants on locomotor activity and cyclic AMP levels in the rat striatum

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Stimulation of central dopamine receptors leads to enhanced locomotor activity (Van Rossum & Hurkmans, 1964) and dopamine stimulates striatal adenyl cyclase preparations (Kebabian, Petzold & Greengard, 1972; Miller, Horn, Iversen & Pinder, 1974). This work examines the interrelationship between the actions of three potential dopamine receptor stimulants upon both locomotion and cyclic AMP levels in the caudate nucleus of rats.

Drugs dissolved in 5μl of 0.9% NaCl were injected into the lateral ventricles of male Wistar rats using the method of Noble, Wurtman & Axelrod (1967). Twenty minutes later individual animals were placed in an Animex type DSE activity meter and large movements recorded on sensitivity 10 for 24 hours. Cyclic AMP was measured in the striatum and cortex by the *in vitro* system of Munday, Poat & Woodruff (1974). The cyclic AMP was extracted and estimated using a bovine muscle protein (Gilman, 1970). Injections of 2-amino-6, 7-dihydroxy-1,2,3,4-tetrahydronapthalene (ADTN) caused a stimulation of motor activity. There was a lag of 1-2 h before the onset of the effect and once initiated the stimulation continued for up to 18 hours.

The activity characteristically consisted of forward walking, rearing and running movements. Activity was increased to 260% of controls after a 50μg injection and a maximum stimulation of 648% occurred at 200 μg (6 rats in each group). The dimethylether of ADTN injected over a similar dose range was without effect. Ergometrine, 50 or 100 μg, also stimulated locomotor activity, although rearing movements were absent. The time course of the effect was also different, the lag period being short (10-20 min) and the duration 5 hours. The locomotor stimulation induced by either ADTN or ergometrine was abolished by pimozide (0.1 mg/kg i.p.) or haloperidol (0.5 mg/kg i.p.) injected 30 min before intraventricular injection.

Dopamine and ADTN (30 μM) caused striatal cyclic AMP levels to rise to 339 ± 97.3% (4) and 269 ± 33.8% (4) of control levels. Basal levels were in the range 13-18 pmoles cAMP/mg protein. Ergometrine (30 μM) caused a smaller but highly significant stimulation (160 ± 14.3% (6)). The dimethylether of ADTN was ineffective even at 100 μM. Dopamine and ADTN were equipotent at 10, 30 and 100 μM which agrees with iontophoretic studies (Woodruff, Elkhawad, Crossman & Walker, 1974). At 30 μM all three compounds were without effect upon cortical cyclic AMP, but at 100 μM dopamine and ergometrine caused an approximate doubling of the levels.

These results support the contention that ergometrine and ADTN stimulate dopamine receptors in the striatum, the dimethylether of ADTN being ineffective. We have presented evidence for the involvement of cyclic AMP in the behavioural response to these drugs.

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Inhibition of dopamine-sensitive adenylate cyclase in rat basal ganglia and other hormone sensitive adenylate cyclase systems by neuroleptic drugs.

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Homogenates of brain areas containing dopaminergic synapses respond to low concentrations of dopamine by increased cyclic AMP production. The action of dopamine is inhibited by neuroleptic drugs, and mimicked by dopamine agonists (Kebabian, Petzold & Greengard, 1972; Miller, Horn, Iversen & Pinder, 1974). Neuroleptics also inhibit other adenylate cyclase systems (Wolff & Jones, 1970). In the present study we have investigated the specificity of inhibition of these various systems and their possible significance to the mode of action of neuroleptics.

Dopamine-sensitive adenylate cyclase in rat striatum was assayed as previously described (Miller *et al.*, 1974). Stimulation produced by dopamine (10^{-4}M) in striatal homogenates was inhibited by (+)-butaclamol with an IC50 of 1.8×10^{-7} M. (−)-butaclamol, however, was ineffective. Butaclamol is a neuroleptic of novel structure and is the first to exhibit optical isomerism. Its interaction with the dopamine receptor appears to differ from any other neuroleptic so far described. It is known that the neuroleptic activity of butaclamol resides solely in the (+) isomer. This again illustrates the close correspondence between neuroleptic activity and dopamine receptor blockade.

The inhibition caused by (+)-butaclamol was competitive with dopamine except at high drug concentrations (10^{-5}M). Inhibition of the effect of dopamine by other neuroleptics at concentrations approximately equal to their IC50 values proved also to be competitive. This included drugs of the phenothiazine, butyrophenone and dibenzodiazepine classes such as thioridazine, haloperidol, clozapine and loxapine. Phenothiazines and butyrophenones also both acted within one minute of their addition to the assay system.

Neuroleptic drugs were also tested on other hormone sensitive adenylate cyclase systems such as the β-adrenoceptor linked system in isolated adipocytes and the glucagon-sensitive system in liver plasma membranes. Inhibition of adenylate cyclase in these systems occurs at higher drug concentrations than in the dopamine-sensitive systems. Thus, for example, the IC50 for chlorpromazine in the β-adrenoceptor system was approximately 2×10^{-4}M against a maximally stimulating concentration of 10^{-4}M noradrenaline, whereas the corresponding IC50 for the dopamine-sensitive cyclase was 1×10^{-6}M. Inhibition of the glucagon-sensitive system occurred at chlorpromazine concentrations (10^{-4}M) which did not inhibit basal enzyme activity in liver plasma membranes although at higher drug concentrations basal activity was