tyramines may have a function of their own in neuronal transmission.

We thank the Psychiatric Services Branch, Province of Saskatchewan and the Medical Research Council of Canada for financial support.

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Pre- and postsynaptic actions of neuroleptic drugs

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In the present studies neuroleptic drugs of various chemical classes were compared as inhibitors of the postsynaptic dopamine-sensitive adenylate cyclase in rat striatum (Miller, Horn & Iversen, 1974), and for their ability to influence a variety of presynaptic mechanisms in dopaminergic nerve terminals of this brain area (Seeman & Lee, 1975). Sixteen chemical analogues of the butyrophenone haloperidol were tested as inhibitors of the dopamine-sensitive adenylate cyclase, using a fixed concentration of 100 μM dopamine. The drugs inhibited the dopamine response with IC_{50} values ranging from 1 μM to greater than 100 μM, and the results showed a good correlation between dopamine antagonist potencies in this system and the known *in vivo* effects of the same drugs as apomorphine antagonists in the dog (data from Drs P. Laduron & P. Janssen). In intact synaptosome preparations from rat striatum apomorphine was a potent inhibitor (IC50 = 0.2 μM) of the conversion of tritiated L-tyrosine to catechols. Other dopamine-mimetic drugs (epinine, dopamine and 2-amino-6, 7-dihydroxy-1,2,3,4, tetrahydronaphthalene, ADTN) had similar inhibitory effects on tyrosine hydroxylation, and were approximately equipotent with apomorphine. Noradrenaline was also effective but less potent than the other compounds, and at high concentrations (10 μM) phenylephrine and isoprenaline also had some inhibitory actions. The effects of dopamine, noradrenaline, epinine and ADTN were significantly reduced in the presence of the dopamine uptake inhibitor benztropine (2 μM), suggesting that they act at least in part by inhibition of intra-synaptosomal tyrosine hydroxylase after uptake into dopaminergic synaptosomes. The actions of apomorphine, however, were unaffected by benztropine, suggesting a direct action on presynaptic 'autoreceptors' at dopaminergic terminals. All of the compounds were at least 50 times less potent as inhibitors of free tyrosine hydroxylase in detergent-containing striatal homogenates. The inhibitory effects of apomorphine on tyrosine hydroxylation in intact synaptosomes were partially reversed by various neuroleptic drugs (see also Christiansen & Squires, 1974), and this appeared to be due to a competitive antagonism between these drugs and apomorphine at presynaptic receptor sites. The neuroleptics themselves, however, also tended to inhibit tyrosine hydroxylation when added alone. Haloperidol, spiroperidol and pimozide were particularly potent in reversing the presynaptic actions of apomorphine on tyrosine hydroxylation, being active at concentrations of less than 10^{-7} M. Neuroleptic drugs had some actions as inhibitors of ^{3}H-dopamine uptake and as dopamine releasers in striatal synaptosomes. They also antagonized the release of ^{3}H-dopamine evoked by protoveratrine. None of these effects, however, occurred at very low drug concentrations and the butyrophenones were no more potent than chlorpromazine. It is concluded that neuroleptics possess actions on both pre- and postsynaptic sites in the striatum, but that the postsynaptic actions are most likely to be crucial in determining the clinical activity of these drugs.

R.J.M. is an M.R.C. Scholar.

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Monoamine oxidase activity in distinct populations of rat brain mitochondria

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Lai, Walsh, Dennis & Clark (1975) separated three distinct populations of mitochondria from rat brain by discontinuous Ficoll gradient. The mitochondria were metabolically active and relatively free of non-mitrochondrial material. Two of the mitochondrial populations (SM and SM2) were derived from synaptosomes and the remainder were 'free' mitochondria (M).

Johnston (1968) described two forms of monoamine-oxidase (MAO) in rat brain—type A and type B—on the basis of inhibition studies. Later work has shown that serotonin (5-HT) and phenylethylamine are preferentially deaminated by type A and type B MAO respectively, whereas tyramine is a substrate for both types of the enzyme. Type A MAO is relatively sensitive to clorgyline and type B to deprenyl.

Three populations of mitochondria were prepared by a modification of the procedure of Lai, Walsh, Dennis & Clark (1975). The three populations exhibited distinctly different MAO activities when assayed with 5-HT and phenylethylamine as substrates in a radiometric technique similar to that described by Robinson, Lovenberg, Keiser & Sjoerdsma (1968).

Table 1 MAO activity in mitochondrial populations

n	*Mitochondria*	*5-HT*	*Phenylethylamine*
8	M	51.6 ± 16,4	15.6 ± 7.5
8	SM	117.5 ± 16.6	31.7 ± 5.8
8	SM2	106.6 ± 3.0	51.8 ± 4.6

Results (mean ± s.d.) expressed as nanomoles product formed/mg protein per 30 min (analysis of a contingency table gave $\chi^2 = 48$ $P > 0.0001$).

Inhibition studies with clorgyline and deprenyl revealed that MAO of the lighter synaptosomal mitochondria (SM) was considerably more sensitive to inhibition by clorgyline than the M or SM2 mitochondria or a crude mitochondrial preparation. SM mitochondrial MAO was inhibited approximately 50% by 10^{-12} M clorgyline. The same population of mitochondria (SM) was the least sensitive to deprenyl although the differences in inhibition of MAO of the three sets of mitochondria were less pronounced with deprenyl than with clorgyline. When percentage inhibition of MAO activity was plotted against concentration of clorgyline or deprenyl double sigmoid curves resulted for all three mitochondrial populations with the plateaus suggesting A:B MAO ratios of about 4:1 for SM and 1.5:1 for M and SM2.

In agreement with previous findings (Youdim & Sourkes, 1965) heat inactivation at 50°C for 1 h resulted in the loss of about 15% of MAO activity of a crude mitochondrial preparation when tyramine was used as substrate. In contrast the purified mitochondria M, SM and SM2 lost approximately 75% of enzyme activity when similarly treated.

Attempts to fractionate further the SM mitochondria will be discussed.

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