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Tyraminergic mechanisms in rat striatum

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Small concentrations of para-tyramine (*p*-TA) and meta-tyramine (*m*-TA) have been observed in the rat brain (Philips, Durden & Boulton, 1974; Philips, Davis, Durden & Boulton, 1975). Reserpine administration is known to impair the storage mechanisms for neural amines (see review by Shore, 1972) and markedly reduces *p*-TA levels in *Octopus* ganglia (Juorio & Philips, 1975). The accumulated evidence prompted us to investigate the effects of reserpine administration on the concentrations of *p*-TA and *m*-TA in the rat caudate nucleus. For comparison, the effect on the dopamine (DA) concentration was also investigated.

Male Wistar rats of 150-200 g body weight were used throughout. The animals were killed by decapitation and the caudate nuclei quickly dissected out and frozen on dry ice. Tissues from 5 animals were pooled, weighed (approximate weight 300 mg), homogenized and fractions were removed for estimation of the amines. *p*-TA and *m*-TA were estimated as their dansyl derivatives by the mass spectrometric integrated ion current technique through the use of deuterated internal standards (Philips, Durden & Boulton, 1974; Philips, Davis, Durden & Boulton, 1975). DA was estimated fluorimetrically (see Juorio & Philips, 1975).

The concentrations of *p*-TA and *m*-TA in the rat caudate nucleus are respectively 1240 and 4810 times smaller than those of DA (Table 1). All three amines are significantly reduced after subcutaneous administration of reserpine (Table 1); the largest dose (10 mg/kg) reduced concentrations of *p*-TA, *m*-TA and DA by more than 80%, while 6 h after a dose of 0.4 mg/kg, the levels of the three amines were reduced by half (Table 1). These results strongly suggest that striatal tyramines are stored by a reserpine-sensitive mechanism. Recent experiments have shown that the turnover of tyramines in neural tissues is very fast (Wu & Boulton, 1974; Juorio & Philips, 1975; Boulton, Juorio, Philips & Wu, 1975) and that *p*-TA is associated with a brain synaptosomal fraction (Boulton & Baker, 1975). The present findings are further evidence that

Table 1 Effect of reserpine on the concentration of *p*-tyramine (*p*-TA), *m*-tyramine (*m*-TA) and dopamine (DA) in the rat caudate nucleus.

Dose	*Time after injection*	*p-TA*	*m-TA*	*DA*
mg/kg	*h*	*ng/g*	*ng/g*	*ng/g*
–	–	10.1 ± 0.9 (13)	2.6 ± 0.2 (11)	12500 ± 737 (13)
0.2	24	11.9 ± 0.9 (3)	2.5 ± 0.2 (3)	10067 ± 263 (3)**
0.4	6	5.0 ± 0.5 (4)***	1.4 ± 0.06 (4)***	6540 ± 417 (4)***
0.4	12	10.6 ± 0.4 (4)	1.8 ± 0.1 (4)**	8444 ± 219 (4)***
0.4	24	8.3 ± 0.6 (6)	2.0 ± 0.1 (6)*	7273 ± 441 (6)***
0.4	96	8.8 ± 0.8 (4)	2.0 ± 0.1 (4)*	8107 ± 231 (4)***
1.0	24	1.5 ± 0.4 (8)***	0.47 ± 0.2 (9)***	1444 ± 90 (9)***
10.0	24	0.6 ± 0.3 (4)***	0.40 ± 0.11 (4)***	490 ± 40 (8)***

Reserpine was administered subcutaneously. Results are given in ng/g fresh tissue (± s.e. mean) and corrected for recoveries. Student's *t*-test. $*P < 0.025$, $**P < 0.01$, $***P < 0.001$.

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

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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.

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