Do anti-psychotic drugs act by dopamine receptor blockade in the nucleus accumbens?

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There is evidence that central dopamine receptor blockade is responsible for the therapeutic actions of neuroleptic drugs. Two major dopaminergic systems of neurones have been described. One (the nigrostriatal system) shows degeneration in Parkinson's disease, and it has been suggested that extra pyramidal side effects of neuroleptic drugs result from actions on striatal dopamine receptors. A second dopaminergic system terminates in the 'limbic forebrain' region (nucleus accumbens, olfactory tubercle, frontal cortex). Since the anti-psychotic potency of neuroleptic drugs can be dissociated from their extra pyramidal effects it has been suggested that antipsychotic drug actions are related to blockade of 'limbic forebrain' receptors (Bunney & Aghajanian, 1974).

We have attempted to test this hypothesis by studying the effects of drugs with differing ratios of extrapyramidal and therapeutic effects on dopamine turnover in the nucleus accumbens and corpus striatum.

Male Sprague-Dawley rats, weighing 200-220 g were injected with one of the following drugs: chlorpromazine HCl; thioridazine HCl; fluphenazine HCl in dose-ratios approximately equivalent to their therapeutic effects (N.I.M.H., Psychopharmacology Service Center, Collaborative Study Group, 1964). Animals were killed by decapitation, the brains rapidly removed and the striatum and nucleus accumbens dissected out. Dihydroxyphenylacetic acid (DOPAC) and homovanillic acid (HVA) concentrations were measured fluorimetrically.

The effects of the three drugs on dopamine turnover as assessed by HVA accumulation show quite marked differences in the two brain areas (Figure 1). Whereas the rank order of potencies of the three drugs on dopamine turnover in the corpus striatum is related to their ability to give rise to extra pyramidal side effects, the same doses produce approximately equal effects on dopamine turnover in the nucleus accumbens. The changes appear to be consistent with the hypothesis that anti-psychotic drugs act by blockade of dopamine receptors in the nucleus accumbens. Further experiments have investigated the possibility that differences in drug-induced changes in striatal HVA are due to differences in anti-muscarinic blocking potencies (Miller & Hiley, 1974).

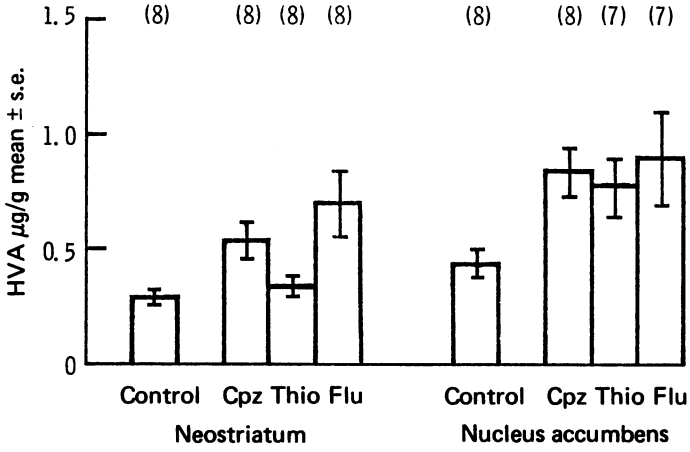

Figure 1 Effects of phenothiazine on HVA concentration in neostriatum and nucleus accumbens. The results show the means ± s.e. mean.
Cpz—Chlorpromazine 5 mg/kg
Thio—Thioridazine 5 mg/kg
Flu—Fluphenazine 0.25 mg/kg

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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. $*P < 0.025$, $**P < 0.01$, $***P < 0.001$.