Dopamine turnover in the corpus striatum and the limbic system after treatment with neuroleptic and anti-acetylcholine drugs

Neuroleptic drugs produce both extrapyramidal and antipsychotic effects in man. These two actions are often considered to be correlated. Anti-acetylcholine drugs can, however, eliminate the extrapyramidal manifestations without markedly influencing the antipsychotic effect (Goldman, 1961; Freyhan, 1961; Brune, Morpurgo & others, 1962). The drug-induced extrapyramidal signs are in all likelihood due to a functional lack of dopamine in the corpus striatum as is the spontaneous and postencephalitic parkinsonism (Hornykiewicz, 1966). The neuroleptic drugs also increase the turnover of dopamine in the corpus striatum, probably due to a compensation for the functional deficiency of it (Andén, Carlsson & Häggendal, 1969). Many dopamine-containing nerve terminals also occur in the limbic system, *i.e.*, in the nucleus accumbens, the olfactory tubercle, the dorsolateral part of the nucleus interstitialis striae terminalis and the central nucleus of the amygdala (Andén, Dahlström & others, 1966). In the present work, the concentration of the main dopamine metabolite, homovanillic acid (HVA), has been determined in the corpus striatum and in the limbic system of rabbits treated with a neuroleptic drug (haloperidol), with an anti-acetylcholine drug (trihexyphenidyl), or with a combination of these two drugs. The distributions of dopamine and HVA in the brain of untreated rabbits have also been studied.

Adult, white rabbits, 1·4–2·3 kg, were killed by an intravenous injection of air. The brains were dissected as fast as possible on ice and the brain parts of two rabbits were pooled. After removal of the corpus striatum, the greater part of the limbic system (amygdala, preoptic area, olfactory tubercle, nucleus accumbens, nucleus interstitialis striae terminalis, septum but not hippocampus or gyrus cinguli) was obtained by incisions just in front of the optic chiasm and through the rhinal fissures. The occipital cortex was then excised, avoiding contamination of striatal or limbic tissue. The dopamine was determined spectrofluorimetrically after extraction with 0·4 N perchloric acid, cation exchange chromatography and oxidation (Carlsson & Waldeck, 1958; Carlsson & Lindqvist, 1962). The HVA was determined spectrofluorimetrically after freezing on dry ice, extraction with 0·1 N HCl, anion exchange chromatography and oxidation (Andén, Roos & Werdinius, 1963; Korf, Roos & Werdinius, 1971). The homogenate of the corpus striatum was divided into two aliquots. To one, 3 μg HVA were added. The recovery through the whole procedure was 91 $\pm$ 2·1% (mean $\pm$ s.e., n = 27). No correction for recovery was made.

The corpus striatum contained about three times as much dopamine as the limbic system (Table 1). The concentrations do not indicate the actual density of the dopamine nerve terminals since many parts of the limbic system lack the amine whereas the whole corpus striatum except the globus pallidus is rich in it.

The concentration and the amount of HVA were also higher in the corpus striatum than in the limbic system (Table 2). The differences were less than for dopamine. No significant quantities of dopamine or HVA were found in the occipital cortex, which was used as a control.

After treatment with haloperidol, the HVA in both the corpus striatum and the limbic system was increased to more than twice the normal concentration (Table 2; *cf.* Andén, Roos & Werdinius, 1964). Pretreatment with trihexyphenidyl gave a partial but statistically highly significant inhibition of this haloperidol-induced rise in the striatal HVA. On the other hand, the elevation of the limbic HVA was apparently

Table 1. *Dopamine concentration (μg/g) and content (μg/animal) in the corpus striatum, the limbic system and the occipital cortex of untreated rabbits.*

Brain region	μg/g*	μg/rabbit*
Corpus striatum	5·16 ± 0·180	2·42 ± 0·065
Limbic system	0·93 ± 0·025	0·76 ± 0·016
Occipital cortex	0·02 ± 0·003	0·03 ± 0·003

* Mean ± s.e. of 8 experiments.

Table 2. *Homovanillic concentration (μg/g) in the corpus striatum, the limbic system and the occipital cortex of rabbits untreated or treated with trihexyphenidyl HCl (40 mg/kg i.p., 4½ h), haloperidol (0·2 mg/kg i.v., 4 h) or trihexyphenidyl plus haloperidol.*

	Treatment					Difference†		
Brain region	A No drug treatment	B Trihexyphenidyl	C Haloperidol	D Trihexyphenidyl + haloperidol	Variance within groups	A–B	A–C	C–D
Corpus striatum	3·15 (8)*	2·95 (3)	7·74 (8)	6·22 (8)	0·30966	$P > 0·05$	$P < 0·001$	$P < 0·001$
Limbic system	1·12 (8)	1·13 (3)	2·40 (8)	2·55 (8)	0·04754	$P > 0·05$	$P < 0·001$	$P > 0·05$
Occipital cortex	0·05 (8)	0·06 (3)	0·07 (8)	0·07 (8)	0·00090	$P > 0·05$	$P > 0·05$	$P > 0·05$

* Mean in μg/g with number of experiments in parenthesis.

† Statistical analysis by one-way analysis of variance followed by *t*-test.

unchanged. Trihexyphenidyl alone did not markedly influence the level of HVA either in the corpus striatum or in the limbic system.

In conclusion, the neuroleptic-induced increase in dopamine turnover can be inhibited in the corpus striatum but not in the limbic system by pretreatment with an anti-acetylcholine drug. This differential effect may indicate that the neuroleptic-induced extrapyramidal and antipsychotic effects are due to a lack of dopamine in the corpus striatum and in the limbic system, respectively.

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Department of Pharmacology,
University of Göteborg, Fack,
S-400 33 Göteborg 33, Sweden.

NILS-ERIK ANDÉN

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