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Effects of Clozapine, Thioridazine, Perlapine and Haloperidol on the Metabolism of the Biogenic Amines in the Brain of the Rat

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Abstract. The effects of clozapine, thioridazine, perlapine and haloperidol on the metabolism of the biogenic amines in the brain of the rat have been investigated.

Haloperidol, perlapine and thioridazine induce catalepsy and enhance the turnover of DA in the striatum, as indicated by the dose-dependent increase in the DA-metabolites, HVA and DOPAC. These effects are due to blockade of dopaminergic transmission, haloperidol being far more potent than perlapine or thioridazine. Clozapine differs from these agents in that it elevates the concentration of striatal DA. The increase of the concentrations of HVA and DOPAC by clozapine is not accompanied by development of catalepsy. Therefore, clozapine seems to influence striatal DA by a mechanism other than DA-receptor blockade.

All four drugs enhance the turnover of NA in the brain stem. This effect is probably secondary to the blockade of NA-receptors. There was no correlation between the effects on NA-metabolism and the EEG-arousal inhibitory activities of these agents or their clinical antipsychotic effects.

Clozapine increase the concentration of 5-HT and 5-HIAA in the brain. This effect was not seen with the other drugs. Perlapine seems to enhance the turnover of 5-HT, whereas haloperidol reduces the 5-HT concentration. Thioridazine appears to have no effect on the metabolism of 5-HT.

Key words: Clozapine – Thioridazine – Perlapine – Haloperidol – Noradrenaline – Dopamine – Serotonin – Rat Brain.

Clozapine is a novel antischizophrenic drug that may be classified among the major tranquillizers with strong sedative activity. In man, this drug was found to lack extrapyramidal side-effects (Angst *et al.*, 1971). The pharmacological profile suggests that clopazine is without effect on the nigro-striatal system, although electrophysiological evidence indicates that clozapine, in common with the cataleptogenic neuroleptics, increases the electrical exitability of neurons in the striatum, as shown by a decreased stimulation threshold and by a prolongation and increase of the amplitude of caudatum spindles (Stille, 1970; Stille *et al.*, 1971; Sayers and Kleinlogel, 1973). Biochemical investigations in the rat revealed that clozapine, in contrast to the cataleptogenic neuroleptics, increases the content of dopamine (DA) in the striatum (Bürki, 1973; Bürki *et al.*, 1973, 1974). An increase in the DA-turnover, as indicated by a raised homovanillic acid (HVA)-concentration in the striatum, was observed only after very high doses of clozapine (Bartholini *et al.*, 1972). Therefore, the biochemical and pharmacological profiles of action of clozapine differ in important aspects from those of the cataleptogenic neuroleptics (Bürki, 1973; Bürki *et al.*, 1974).

In subsequent neurochemical investigations, the results of which are reported here, it was thought of interest to compare clozapine not only with cataleptogenic neuroleptics but also with psychotropic drugs which are thought to act preferentially on the ascending reticular system (Stille *et al.*, 1971). Therefore, we have included thioridazine, an established major tranquillizer, and perlapine, a sleep-promoting drug structurally related to clozapine but lacking antischizophrenic activity in man (Stille *et al.*, 1973). Table 1 summarizes the main pharmacological actions of the agents used in the present study (Stille and Hippius, 1971; Stille *et al.*, 1973). Clozapine, thioridazine and perlapine impair the arousal reaction induced by arecoline or by electrical stimulation of the reticular formation. Perlapine and thioridazine are weakly cataleptogenic, whereas clozapine has no cataleptogenic activity. Neither clozapine nor perlapine or thioridazine provides protection against apomorphine-induced steretypies. Haloperidol, on the other hand, is without effect on the arousal reaction, but is strongly cataleptogenic and protects against apomorphine stereotypies. It was, therefore, included in this study as an example of a typical cataleptogenic neuroleptic.

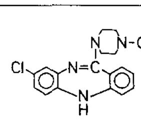
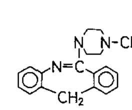
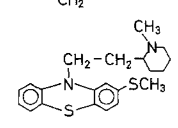
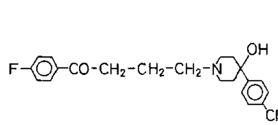
Materials and Methods

Animals. Male RAC rats weighing 120–170 g, obtained from Tierfarm AG, Sisseln, Switzerland, were used. The rats were kept in air-conditioned rooms at 25 °C and 50% air humidity and fed with Nafag pellets (Nafag AG, Gossau, Switzerland) and water ad libitum.

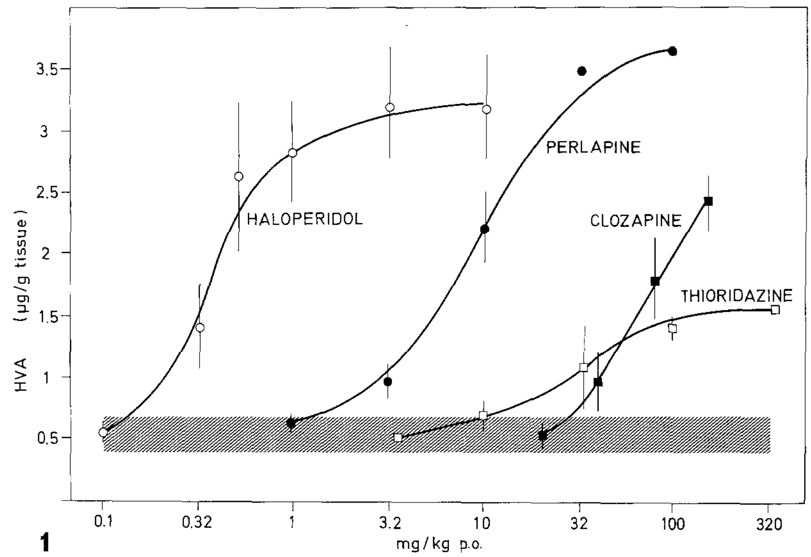
Drugs. Perlapine and clozapine were each dissolved in 1.25 molar equivalents of hydrochloric acid and diluted with water. Haloperidol solution (Cilag Chemie AG, Schaffhausen, Switzerland) was diluted with 0.9% sodium chloride solution. Thioridazine was dissolved in water. Treatment schedules are described in the respective tables.

Biochemical Determinations. After decapitation of the rats, the brains were dissected and the tissues were put on dry ice immediately. For the determination of DA, HVA, 3,4-dihydroxyphenylacetic acid (DOPAC), and noradrenaline (NA), the tissues were homogenized in 0.4 N perchloric acid, using a Polytron PT 20 OD S homogenizer (Kinematica, GmbH, Luzern), and the homogenates were centrifuged at 12 800 g for 10 min at 0–4 °C. The supernate was decanted and the pellet re-homogenized and re-centrifuged under the same conditions. The pooled supernates were used for analysis. From the perchloric acid supernates of the pooled striata of 5 rats, HVA was extracted with ether at pH 2, and re-extracted from the ether phase with tris buffer pH 8.5. Oxidation of HVA was effected with ferricyanide in ammonia solution (Andén, Roos, and Werdinius, 1963). DOPAC was extracted from the perchloric acid supernates of the pooled striata of 2 rats with *n*-butyl acetate, and re-extracted from the *n*-butyl acetate phase with ethylenediamine solution for fluorimetric determination according to Spano and Neff (1971). DA was determined in the pooled striata of 4 rats after adsorption from the neutralized perchloric acid extract on aluminium oxide, elution with diluted perchloric acid, and oxidation with periodate according to Anton and Sayre (1964). NA was determined fluorimetrically in the pooled brain stems of 4 rats after adsorption from the neutralized perchloric acid extract on aluminium oxide (Anton and Sayre, 1962), elution with diluted perchloric acid and oxidation with ferricyanide (Euler and Lishajko, 1961). The turnover rate of NA was assessed after blockade of the dopamine-β-hydroxylase with diethyldithiocarbamate (DDC), as described by Carlsson, Lindqvist, Fuxe, and Hökfelt (1966). DDC (500 mg/kg s.c.) was administered 15 min after the drugs, the rats were killed 2 hrs later and the NA content in the brain stem determined. For the determination of serotonin (5-HT) and 5-hydroxyindoleacetic acid (5-HIAA), the pooled whole brains of 2 rats were homogenized in 0.1 N hydrochloric acid containing 0.5% ascorbic acid, the proteins precipitated by addition of zinc sulfate and sodium hydroxide, and the reaction mixtures were filtered to yield a clear solution which was used for the determinations. 5-HIAA was extracted from this solution at pH 1–2 with butyl acetate and re-extracted from the butyl acetate phase at pH 7 with phosphate buffer 0.1 M. 5-HT was extracted at pH 10 with *n*-butanol and re-extracted from the butanol with diluted hydrochloric acid. 5-HT and 5-HIAA were determined fluorimetrically in the hydrochloric acid and phosphate buffer solutions, respectively, sufficient hydrochloric acid being added in each case to give 3N-solutions (Giacalone and Valzelli, 1969). The

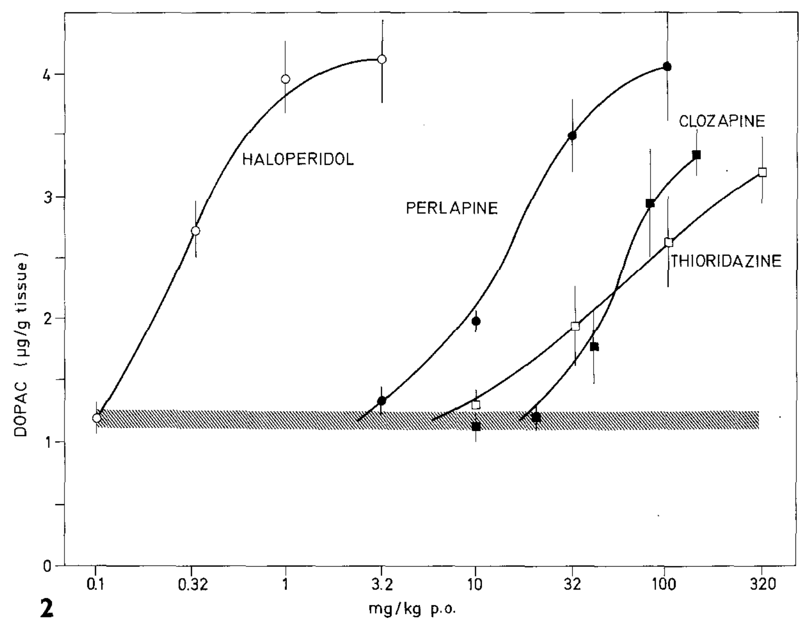
Table 1

Drugs		Catalepsie[a] (rat) ED50 mg/kg p.o.	Apomorphine antagonism[a] (rat) ED50 mg/kg s.c.	Inhibition of arousal-reaction[b] (rabbit): Stimulation of reticular formation ED(threshold 150%) mg/kg i.v.	Arecoline injection ED (blockade) mg/kg i.v.
CLOZAPINE		inactive	inactive	1.5	1.1
PERLAPINE		6.8	inactive	3.2	0.9
THIORIDAZINE		17	inactive	2.4	2.1
HALOPERIDOL		0.3	0.14	inactive	inactive

[a] From Stille and Hippius, 1971
[b] From Stille et al., 1973



1



2

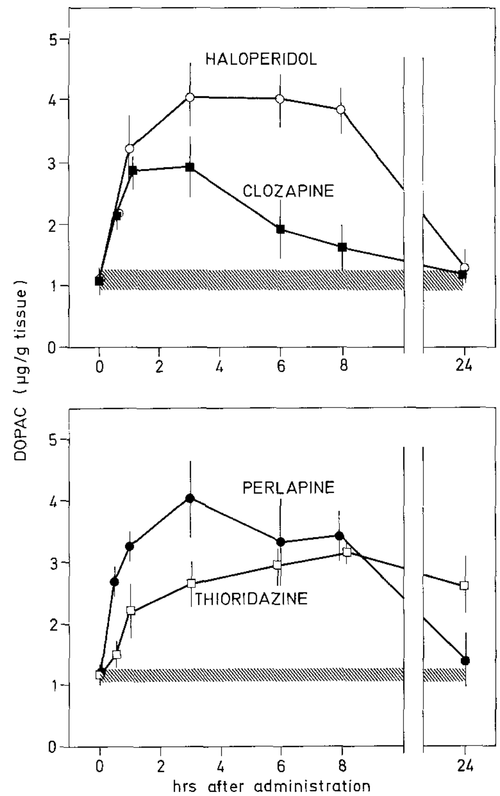


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Fig. 1. Homovanillic acid content of rat striatum after treatment with psychotropic drugs. Drugs were given 3 hrs before sacrifice. Vertical bars indicate S.D. of 4–12 determinations. Stippled area is $\bar{x} \pm$ S.D. of controls (0.51 µg/g ± 0.09, $N = 17$)

Fig. 2. 3,4-Dihydroxyphenylacetic acid content of rat striatum after treatment with psychotic drugs. Drugs were given 3 hrs before sacrifice. Vertical bars indicate S.D. of 4–10 determinations. Stippled area is $\bar{x} \pm$ S.D. of controls (1.08 µg/g ± 0.14, $N = 10$)

Fig. 3. 3,4-Dihydroxyphenylacetic acid content of rat striatum after treatment with psychotropic drugs. Rats were killed 0.5–24 hrs after a single oral dose of 3 mg/kg haloperidol (○), 80 mg/kg clozapine (■), 100 mg/kg perlapine (●), or 100 mg/kg thioridazine (□). Vertical bars indicate S.D. of 4–10 determinations. Stippled area is $\bar{x} \pm$ S.D. of controls (1.08 µg/g ± 0.14, $N = 10$)

turnover of 5-HT and 5-HIAA was assessed after blockade of the tryptophan hydroxylase with 6-fluorotryptophan (6-FTP) (Peters, 1971). 6-FTP (250 mg/kg i.p.) was administered 15 min after the drugs, and the animals were killed 2 hrs later and the 5-HT and 5-HIAA contend determined.

Results

Dopamine Metabolism in the Striatum. The marked increase in the DA-metabolites HVA and DOPAC in the striatum following treatment with the psychotropic drugs clozapine, perlapine, thioridazine and haloperidol suggests that these agents affect the turnover of striatal DA. The increase in the acid metabolites is dose-dependent (Figs. 1 and 2) and persists for several hours (Fig. 3). The potency of these drugs with respect to their effects on the concentrations of the acid metabolites decreases in the order haloperidol > perlapine > clozapine ~ thioridazine. Thioridazine differs from the other compounds in that the curve relating HVA-concentration to dose is unusually flat (Fig. 1).

Clozapine enhances the concentration of striatal DA (Fig. 4). This effect is particularly marked after repeated administration of the drug (Bürki, 1973; Bürki *et al.*, 1973, 1974) and has not been observed with any of the cataleptogenic neuroleptics tested (Asper *et al.*, 1973). On the contrary, neuroleptics such as haloperidol (Fig. 4) decrease the content of striatal DA after a single administration. After repeated administration this effect is much reduced (tolerance). Neither perlapine nor thioridazine appear to affect the concentration of striatal DA irrespective of whether these drugs are given in a single dose or daily for a week.

Noradrenaline Metabolism in the Brain Stem. All four drugs cause a significant acceleration of NA-disappearance (turnover) after synthesis inhibition with DDC (Table 2). The relative potency of the drugs seems to decrease in the following order: Haloperidol > clozapine > thioridazine ~ perlapine. A similar order of potency for the drugs haloperidol, clozapine and thioridazine has been reported by Keller *et al.* (1973) who measured the increase in the NA-metabolite 3-methoxy-4-hydroxyphenylethyleneglycol (MOPEG) in rat brain. High doses of clozapine or haloperidol also cause a decrease in the NA-content, as has also been found by other investigators (Bartholini *et al.*, 1973).

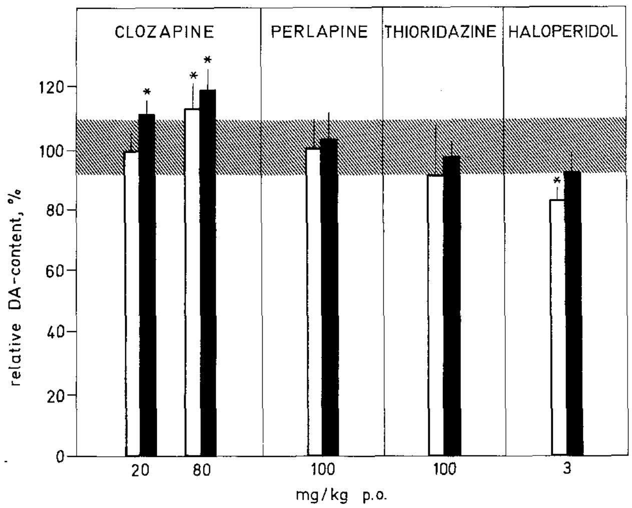

Fig. 4. Relative dopamine content of rat striatum after one (□) or seven daily (■) doses of psychotropic drugs. Rats were killed 2.25 hrs after the last drug administration. The dopamine content of the control groups (8.30–9.05 μg/g) for each drug-treated group was arbitrarely set to 100. Vertical bars indicate S.D. of 5–9 determinations. Stippled area is $\bar{x}$ ± S.D. of controls (100% ± 9). Statistical comparison between drug-treated and control animals with *t*-test: * $P < 0.01$

Serotonin Metabolism in Whole Brain. Clozapine enhances the content of 5-HT and 5-HIAA in the brain of the rat (Table 3), but has no effect on the turnover of 5-HT as measured by the method of synthesis inhibition with 6-FTP. This effect is only seen with 80 mg/kg but not with 20 mg/kg. Perlapine has no effect on the concentration of the two indole com-

Table 2. Noradrenaline content of rat brain stem

Drugs	Dosage mg/kg p.o.	*N*	Noradrenaline content μg/g tissue (mean ± S.D.)	*N*	Noradrenaline content after DDC μg/g tissue (mean ± S.D.)
None		10	0.75 ± 0.04	10	0.29 ± 0.05
Clozapine	20	10	0.70 ± 0.10	10	0.22 ± 0.03**
	100	5	0.60 ± 0.03***	5	0.14 ± 0.01***
None		10	0.81 ± 0.07	10	0.37 ± 0.06
Perlapine	100	5	0.76 ± 0.07	5	0.26 ± 0.03**
None		10	0.78 ± 0.11	10	0.34 ± 0.04
Thioridazine	32	5	0.84 ± 0.07	5	0.35 ± 0.02
	100	5	0.74 ± 0.09	5	0.26 ± 0.03**
None		5	0.81 ± 0.05	5	0.33 ± 0.03
Haloperidol	3	5	0.84 ± 0.08	5	0.29 ± 0.03*
	15	7	0.71 ± 0.05*	7	0.27 ± 0.02**

Rats were killed 2.25 hrs after drug administration. DDC (500 mg/kg s.c.) was given 15 min after the drugs and 2 hrs before the killing of the rats. *N* represents the number of determinations, each of them performed on the pooled homogenates of brain stem of 4 rats. Statistical comparison with *t*-test: * $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$.

Table 3. Serotonin and 5-hydroxyindolacetic acid content of rat whole brain

Drugs	Dosage mg/kg p.o	Serotonin content		Serotonin content after 6-FTP		5-Hydroxyindolacetic acid content	
		N	μg/g tissue (mean ± S.D.)	*N*	μg/g tissue (mean ± S.D.)	*N*	μg/g tissue (mean ± S.D.)
None		10	0.58 ± 0.08	10	0.31 ± 0.06	10	0.51 ± 0.03
Clozapine	20	10	0.55 ± 0.09	5	0.35 ± 0.09	10	0.45 ± 0.05
	80	7	0.74 ± 0.10**	7	0.33 ± 0.05	7	0.77 ± 0.10***
None		10	0.63 ± 0.09	10	0.34 ± 0.06	10	0.51 ± 0.03
Perlapine	100	7	0.55 ± 0.10	6	0.26 ± 0.06*	7	0.53 ± 0.06
None		10	0.67 ± 0.06	10	0.31 ± 0.06	10	0.50 ± 0.02
Thioridazine	100	10	0.66 ± 0.03	6	0.32 ± 0.05	10	0.51 ± 0.06
None		10	0.59 ± 0.02	10	0.26 ± 0.04	10	0.52 ± 0.02
Haloperidol	15	8	0.54 ± 0.05**	8	0.28 ± 0.04	8	0.54 ± 0.08

Rats were killed 2.25 hrs after drug administration. 6-FTP (250 mg/kg i.p.) was given 15 min after the drugs and 2 hrs before killing of the rats. *N* represents the number of determinations, each of them performed on the pooled homogenates of whole brain of two rats. Statistical comparison with *t*-test: * $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$.

pounds but enhances the turnover of 5-HT. Haloperidol lowers the concentration of 5-HT, but is without effect on the turnover of 5-HT and on the concentration of 5-HIAA. Thioridazine has no apparent influence on the metabolism of 5-HT.

Discussion

The profile of neurochemical action of clozapine differs in various respects from that of cataleptogenic neuroleptics (Bürki, 1973; Bürki *et al.*, 1973, 1974) and, as is shown in this paper, also from psychotropic drugs with sedative activity, such as perlapine and thioridazine.

It is well known that the extrapyramidal manifestations of cataleptogenic neuroleptics like haloperidol correlate with alterations in the metabolism of DA in the striatum. DA-turnover is increased, the DA-content being decreased or remaining unchanged. It is widely accepted that catalepsy, apomorphine antagonism and the enhanced turnover of DA are consequences of a single drug action, i.e. blockade of DA-receptors causing feedback activation of presynaptic dopaminergic neurons. Perlapine and thioridazine exhibit weak cataleptogenic activity and enhance the concentrations of HVA and DOPAC. It appears, therefore, that these drugs also cause DA-receptor blockade which, however, is much less pronounced than that of cataleptogenic neuroleptics. Neither perlapine nor thioridazine provide protection against apomorphine-induced stereotypies. Clozapine is neither cataleptogenic nor does it antagonize apomorphine stereotypies and, in contrast to all other neuroleptics tested and to perlapine, increases the striatal DA-concentration.

Chronic application of cataleptogenic neuroleptics to rats induces a hypersensitivity in the striatal DA-receptors to the actions of apomorphine and other stimulants (Schelkunov, 1967; Møller-Nielsen *et al.*, 1974). No sign of DA-receptor hypersensitivity was observed after treatment of rats for several days with 80 mg/kg clozapine p.o. (Sayers *et al.*, 1974). These findings, together with the observed increase in striatal DA, suggest that clozapine does not interfere with dopaminergic transmission in the way the cataleptogenic neuroleptics do, and that the increased concentrations of HVA and DOPAC after high dosage of clozapine are due to some action other than DA-receptor blockade.

Clozapine enhances the turnover of NA (Sedvall and Nybäck, 1972; Bartholini *et al.*, 1973; Bürki, 1973; Bürki *et al.*, 1974), as do cataleptogenic neuroleptics (Carlsson and Lindqvist, 1963; Gey and Pletscher 1968; Andén *et al.*, 1970), thioridazine or perlapine. The increased turnover of NA is probably due to blockade of NA-receptors which, via a feedback mechanism, causes an activation of presynaptic noradrenergic neurons. After repeated administration of clozapine or cataleptogenic neuroleptics, tolerance develops toward NA-turnover stimulation (Bürki, 1973; Bürki *et al.*, 1974). Noradrenergic neurons, originating in the medulla and pons and sending projections throughout the brain, have been postulated to mediate tonic cortical activation (Jones *et al.*, 1973). Nybäck and Sedvall (1970) suggested that the enhancement of the NA-turnover may correlate with the sedative properties of drugs. In actual fact, all neuroleptics tested as well as perlapine cause sedation, although perhaps there are differences in quality. In particular, haloperidol does not impair the electroencephalographic arousal (Stille *et al.*, 1973) and yet is very effective in enhancing the turnover of NA. Therefore, no correlation exists between the actions of these drugs on the noradrenergic system and their effect on the arousal reaction, or indeed their antipsychotic effect in man, as is suggested by the absence of antischizophrenic activity of perlapine.

Clozapine raises the levels of 5-HT and 5-HIAA in the brain. This effect was not seen after perlapine, thioridazine or haloperidol. Perlapine increases the turnover of 5-HT, whereas haloperidol reduces its concentration. With the data available it is at present not possible to correlate these changes with pharmacological parameters. Alterations in the metabolism of central 5-HT have been discussed in relation to sleep (Bobillier *et al.*, 1973), depression (for discussion see Schubert, 1973) and a variety of other phenomena (Gitlow *et al.*, 1972). Further investigations must show whether the effects of clozapine on central 5-HT are relevant to its clinical actions.

To summarize, the biochemical profile of action of clozapine differs considerably from that of cataleptogenic neuroleptics like haloperidol and from drugs which are thought to act preferentially on the ascending reticular system, such as thioridazine and perlapine. Clozapine increases the concentrations of DA and 5-HT in the brain. At present it is not clear by which mechanism clozapine induces these changes in the amine concentrations. Thioridazine and perlapine, which like clozapine impair the reticular arousal reaction, and which exhibit a pharmacological profile of action in many respects similar to that of clozapine (Stille *et al.*, 1971), do not increase the brain levels of DA and 5-HT. This suggests that clozapine affects central dopaminergic and serotonergic systems by a mechanism of action that is different from that of thioridazine and perlapine. In particular, clozapine causes no DA-receptor blockade, whereas thioridazine and perlapine are weak DA-receptor blockers. Strongly cataleptogenic agents like haloperidol, on the other hand, are potent DA-receptor blockers, even at very low doses. The relevance of the biochemical actions of clozapine to its clinical effects still has to be established.

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