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 cataplexy 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 cataplexy. 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.
ridazine provides protection against apomorphine-induced stereotypes. Haloperidol, on the other hand, is without effect on the arousal reaction, but is strongly cataleptogenic and protects against apomorphine stereotypes. 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 12,800g 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 Werdenius, 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 (Anton and Sayre, 1964), elution with diluted perchloric acid, and oxidation with periodate according to 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 diethylthiocarbamate (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 turnover rate was calculated according to Euler and Lishajko (1961).

Table 1

<table>
<thead>
<tr>
<th>Drugs</th>
<th>Catalpse a (rat)</th>
<th>Apomorphine antagonism b (rat)</th>
<th>Inhibition of arousal-reaction c (rabbit)</th>
<th>Stimulation of reticular formation d (amphetamine)</th>
<th>Arecoline injection e (mouse)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CLOZAPINE</td>
<td>inactive</td>
<td>inactive</td>
<td>1.5</td>
<td>2.0</td>
<td>2.5</td>
</tr>
<tr>
<td>PERLAPINE</td>
<td>6.8</td>
<td>inactive</td>
<td>3.2</td>
<td>1.9</td>
<td>0.9</td>
</tr>
<tr>
<td>THIORIDAZINE</td>
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<td>inactive</td>
<td>2.4</td>
<td>2.1</td>
<td></td>
</tr>
<tr>
<td>HALOPERIDOL</td>
<td>0.3</td>
<td>0.14</td>
<td>inactive</td>
<td>0.02</td>
<td>inactive</td>
</tr>
</tbody>
</table>

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