Effect of Chlorpromazine and Some of Its Metabolites on Synthesis and Turnover of Catecholamines Formed from $^{14}$C-Tyrosine in Mouse Brain

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Abstract. Rates of accumulation and disappearance of labelled catecholamines formed from $^{14}$C-tyrosine in mouse brain in vivo were determined. The effects of chlorpromazine (CPZ) and the following metabolites were studied: desmethyl-CPZ, didesmethyl-CPZ, 7-hydroxy-CPZ, CPZ-sulphoxide and CPZ-N-oxide. As we have found previously CPZ accelerated both accumulation and disappearance of $^{14}$C-dopamine indicating that synthesis and turnover of brain dopamine are accelerated. All the metabolites, with the exception of CPZ-sulphoxide, accelerated accumulation and disappearance of $^{14}$C-dopamine to about the same extent as did the parent compound. Neither CPZ nor the metabolites significantly affected the accumulation and disappearance of $^{14}$C-noradrenaline. The accelerated turnover of brain dopamine is probably a consequence of a central receptor blockade, which by a compensatory feed-back mechanism activates the presynaptic neurons. The results indicate that sulphoxidation of CPZ interferes with the action of CPZ on brain dopamine receptors, and that the clinical effects of CPZ may be mediated at least partly by its metabolites.

Key words: Dopamine Synthesis -- Chlorpromazine Metabolites -- Neuroleptics -- Phenothiazines.

In experiments performed during the last few years we have demonstrated that chlorpromazine (CPZ) and other neuroleptic drugs accelerate synthesis and turnover of dopamine (DA) formed from $^{14}$C-tyrosine in the brain of rat and mouse in vivo (Nybäck and Sedvall, 1968, 1970). In regional studies on rat brain, the effect of CPZ was confined almost exclusively to DA metabolism in the striatum (Nybäck and Sedvall, 1969; Nybäck, 1971). Interruption of the nerve impulse activity in the nigro-striatal DA pathway, by an acute stereotaxic lesion, blocked the stimulatory effect of CPZ on synthesis and turnover of striatal DA (Nybäck and Sedvall, 1971; Nybäck, 1971). This indicates that the effect of CPZ on the metabolism of DA is mediated by an indirect mechanism, presumably an increased nerve impulse activity in the nigro-
striatal DA pathway. These results support and extend previous findings with other methods indicating that CPZ blocks central dopamine receptors which induces a compensatory feed-back activation of the presynaptic neurons (Carlsson and Lindqvist, 1963; Andén et al., 1964; Laverty and Sharman, 1965; Da Prada and Pletscher, 1966).

Following administration of CPZ to man, the drug often disappears rapidly from the circulation, while, concomitantly several metabolites appear in plasma (Curry and Marshall, 1968). Since there appears to be poor correlations between clinical effects and plasma concentrations of CPZ, it has been suggested that improvement of psychotic patients is mediated by CPZ metabolites (Curry et al., 1972). A number of metabolites of CPZ have been identified in human urine, such as desmethyl-CPZ, didesmethyl-CPZ, CPZ-sulphoxide, CPZ-N-oxide, 7-hydroxy-CPZ and CPZ-propionic acid (Usdin, 1971). Some metabolites have been shown to possess psychoactive properties (Posner et al., 1962; Manian et al., 1965). Therefore we considered it of interest to investigate whether some CPZ metabolites accelerate synthesis and turnover of brain dopamine as does the parent compound.

**Methods**

The experiments were performed in male NMRI mice, weighing 18—20 g. The following substances were dissolved in saline and injected i.p. at a dose of 10 mg/kg in 0.5 ml: Chlorpromazine chloride (Hibernal, Leo), desmethyl-chlorpromazine (nor1CPZ), didesmethyl-chlorpromazine (nor2CPZ), chlorpromazine-sulphoxide (CPZ-SO), 7-hydroxy-chlorpromazine (7-OH-CPZ) and chlorpromazine-N-oxide (CPZ-NO). The rectal temperature of the animals was regularly controlled during the experiments and kept at about 37°C by an infra-red lamp.

**Accumulation of Labelled Catecholamines**

Twenty-five minutes after administration of saline or drugs 14C-tyrosine (uniformly labelled, 397 mCi/mmol, 7 µCi/animal/0.4 ml saline) was infused into a tail vein at a constant rate for 20 min with the animals kept in small restraining cages. Immediately after the infusion the animals were killed and the contents of endogenous and labelled tyrosine, DA and NA was determined in the brain as described below.

**Disappearance of Labelled Catecholamines**

14C-Tyrosine (7 µCi/animal) was administered i.v. by a pulse injection. Two hours later, when the specific activity of brain catecholamines had started to decline, one group of animals were killed. Saline