Effect of chlorpromazine and some of its metabolites on the accumulation of homovanillic acid in brain of mice

Chlorpromazine and several other neuroleptic drugs increase brain levels of homovanillic acid (HVA) (Andén, Roos & Werdinius, 1964) and accelerate synthesis and turnover of dopamine formed *in vivo* from [^{14}C] tyrosine in brain of rat and mouse (Nybäck & Sedvall 1968). To explain these findings it has been suggested that chlorpromazine blocks central dopamine receptors and activates a feed-back mechanism accelerating synthesis and release of dopamine from presynaptic neurons (Carlsson & Lindqvist, 1963; Nybäck & Sedvall, 1971; Andén, Corrodi & others, 1971).

In man, chlorpromazine is rapidly metabolized (Curry & Marshall, 1968) and a number of metabolites have been identified in the urine, including desmethyl-, didesmethyl- and 7-hydroxy-chlorpromazine and the sulphoxide and *N*-oxide (Usdin, 1971). Some of the metabolites have been shown to be psychoactive (Posner, Hearst & others, 1962; Manian, Efron & Goldberg, 1965). Since there is a poor correlation of plasma concentrations of chlorpromazine and the desired clinical effects, it has been suggested that improvements in patients may be mediated at least partly by its metabolites (Curry, Lader & others, 1972).

Nybäck & Sedvall (1972) have found several metabolites to be effective in increasing the synthesis and turnover of dopamine from [^{14}C]tyrosine in the mouse brain. We have investigated the effect of these metabolites on the levels of homovanillic acid in the mouse brain.

Male NMRI mice (18–20 g) were injected with the substances in Table 1. The drugs were dissolved in saline immediately before use and were injected intraperitoneally at 10 mg/kg. The mice were warmed with an infrared lamp to maintain body temperature at 37°.

The animals were killed 90 min after injection and the brains were removed and homogenized in 40% ethanol and the homogenate centrifuged. The supernatant was evaporated, reconstituted in sodium chloride solution, acidified to pH 2 and extracted with ethyl acetate. The methyl ester-heptafluorobutyryl derivatives were prepared and the samples analysed for HVA on a LKB Model 9000 combined gas chromatograph-mass spectrometer (see Sjöquist, Dailey & others, 1972 for details).

Table 1 shows that all the metabolites with the exception of chlorpromazine sulphoxide increased the levels of HVA in the brain. The results are exactly analogous to those of Nybäck & Sedvall (1972), who using the same metabolites, found that only the sulphoxide failed to accelerate the synthesis and turnover of dopamine from [^{14}C] tyrosine.

Thus, the finding that several of the major metabolites of the drug increase syn-

Table 1. *Effect of chlorpromazine and some of its metabolites on the accumulation of HVA in the mouse brain.*

Treatment	HVA (nmol/g brain)[a]
Saline	1·55 ± 0·15
Chlorpromazine	3·81 ± 0·47[b]
Desmethyl chlorpromazine	3·58 ± 0·43[b]
Didesmethyl chlorpromazine	2·30 ± 0·34[b]
Chlorpromazine sulphoxide	1·68 ± 0·24
7-Hydroxy-chlorpromazine	2·93 ± 0·44[b]
Chlorpromazine-*N*-oxide	2·63 ± 0·28[b]

(*a*) The values represent the mean ± s.d. from 7 animals per group.

(*b*) $P<0·001$.

thesis and turnover of dopamine (Nybäck & Sedvall, 1972) is confirmed and the suggestion that several of the metabolites have antipsychotic properties (Lal & Sourkes, 1971; Nybäck & Sedvall, 1972) is further supported.

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Evidence for α-methyl-*m*-tyramine as a false dopamine-like transmitter

We have shown previously that after administration of α-methyl-*m*-tyrosine (αMMT), its decarboxylation product, α-methyl-*m*-tyramine (MMTA), accumulates specifically in the corpus striatum of rats and rabbits concomitant with a lowering of dopamine content in that brain region, while metaraminol, the β-hydroxylated product of MMTA, accumulates in noradrenaline-containing areas of the brain (e.g., hypothalamus) while at the same time the level of noradrenaline is lowered in these areas (Dorris & Shore, 1971a). A false transmitter role for the noradrenaline analogue, metaraminol, in noradrenergic neurons has been well established (Muscholl, 1966). The specific localization of the dopamine analogue, MMTA, in a dopamine-rich area of the brain and its release by (+)-amphetamine (Dorris & Shore, 1971b), a drug which releases dopamine (Carlsson, Fuxe & others, 1966) suggests that, like metaraminol in noradrenergic neurons, MMTA acts as a false transmitter in dopaminergic neurons (Dorris & Shore, 1971a, 1971b). This report presents further evidence for this hypothesis.

Apomorphine induces a compulsive gnawing activity in rats, apparently by stimulation of striatal dopamine receptors (Ernst, 1967), and the drug retards the decline of brain dopamine content after blockade of tyrosine hydroxylase (Andén, Rubenson & others, 1967). This effect of apomorphine is thought to result from a reflexly decreased impulse flow in dopaminergic neurons after dopamine receptor activation by the drug (Andén & others, 1967). Haloperidol, on the other hand, by blocking