Effect of 3,4-dimethoxyphenethylamine on monoamine-depleted rats

3,4-Dimethoxyphenethylamine (homoveratrylamine, "pink spot", DMPEA), the *O*-methylated product of dopamine, is a controversial substance because it has been claimed by some, but not others, to be present in the urine of patients with schizophrenia and Parkinson's disease (for literature see Narasimhachari, Plaut & Leiner, 1972). Friedhoff, Schweitzer & others (1972a, b) recently reported that dopamine can be converted into DMPEA *in vivo*, thus even if it is absent in urine, small amounts could be present in the brain. This led us to initiate some further studies on the central effects of DMPEA.

Ernst (1965) and Barbeau, Tetreault & others (1966) found that a major pharmacological effect of DMPEA is its ability to produce a catatonia or hypokinetic, rigid cataplexic syndrome in some laboratory animals such as mice, rats and cats, but not dogs. Barbeau & others suggested that this effect is caused by interference with the normal metabolism of dopamine in the central nervous system. Some of our recent studies, however, indicated a *direct* effect of DMPEA on the central nervous system and the preliminary observations presented here support this concept.

Male Sprague-Dawley albino rats, 140–160 g (Hilltop Labs) were used. All experiments were made at a room temperature of 23 ± 1°. All drugs were given intraperitoneally. All animals were pretreated with reserpine, 5 mg kg^{-1}, and 20 h later received α-methyltyrosine methyl ester hydrochloride (αMT), 250 mg kg^{-1} calculated as free base. Preliminary observations indicated that in such monoamine-depleted rats, DMPEA gave more consistent responses after monoamine oxidase inhibition. Accordingly, nialamide, 100 mg kg^{-1}, was given 1 h before DMPEA, 40 mg kg^{-1} (which was the dose used in all experiments). In such animals, within 15 min DMPEA caused a typical cataplexic syndrome consisting of a pronounced rigid akinesia and tremor. Their hind limbs were fully extended in a spread-eagle fashion, usually with the hind limbs fixed in a clasped position. A severe tremor usually developed within 30 min and most rats succumbed within 2 h.

In an attempt to delineate the sites of action of DMPEA, studies were made of the effects on the DMPEA syndrome of certain drugs which are known to have specific sites of action on the central nervous system. These drugs were: atropine sulphate, 3 mg kg^{-1}, methysergide, 1 mg kg^{-1}, apomorphine hydrochloride, 0·5 mg kg^{-1}, and L-dopa methyl ester hydrochloride, 50 mg kg^{-1} free base. LSD, 1 mg kg^{-1}, was included for the purpose of comparison with its non-hallucinogenic analogue, methysergide. The atropine and methysergide were given 40 min after the nialamide and 20 min before DMPEA. The L-dopa and apomorphine were given 15 min after the DMPEA, at which time the rigidity syndrome was fully developed. Controls were run simultaneously, using the monoamine-depleted rats given nialamide, followed by 0·9% NaCl solution at appropriate intervals. Nine rats were used in each experiment.

Since the syndrome in control rats was very pronounced and always quite typical, any drug treatment which would even partially restore motor activity easily could be ascertained visually. The animals were placed in individual cages and observed for 4 h. The ability of the animals to flex its fully extended limbs and to recover or partially recover spontaneous or pain-induced locomotion, was considered as a positive effect of the drug under investigation.

Atropine failed to modify the syndrome: Methysergide replaced the DMPEA rigidity with a swimming-like movement, but with the limbs still held in the spread-eagled position. This behaviour usually lasted about 1 h at which time the rats died. LSD caused an effect similar to that of methysergide, the rats showing a stereotyped

abnormal gait. L-Dopa and apomorphine also failed to modify the DMPEA syndrome although apomorphine tended to slightly decrease the rigidity.

The failure of atropine or methysergide to block the DMPEA effect indicates that DMPEA does not act mainly by stimulating acetylcholine or 5-HT receptors. In our earlier studies, LSD, L-dopa and apomorphine, in the doses employed, were found to dramatically antagonize the akinesia and to cause hyperexcitability and running episodes in rats pretreated with reserpine and αMT (see Menon & Clark, 1972, Menon, Clark & Aures, 1972). In the present study all these drugs were incapable of antagonizing the DMPEA syndrome. In other words, DMPEA clearly blocked the effects of LSD, L-dopa and apomorphine. Although the sites of action of LSD are not fully known, L-dopa and apomorphine are known to act by stimulating the central dopamine receptors and it may be concluded tentatively that the DMPEA rigidity is due to its blockade of this system. Thus it seems possible that an excessive formation of DMPEA could have an effect on the CNS that might be more pronounced when degeneration of the dopaminergic nerves has occurred. Thus the use of DMPEA, under the conditions described, may be useful as a pharmacological tool to determine deficiency of dopamine in the central nervous system.

Supported by a fellowship (Stephen Prepas) from the Parkinson's Disease Foundation, New York; by Astra Pharmaceuticals AB, Sweden; and by the Veterans Administration. We are grateful to Dr. Hans Corrodi, Astra AB, Södertälje, Sweden, for generous supplies of the L-dopa and α-methyltyrosine methyl ester hydrochlorides and to Sandoz Pharmaceuticals, Inc., Hanover, New Jersey, for the methysergide.

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February 21, 1973

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