Investigation into the Possible Influence of Chlorinated Amphetamine Derivatives on 5-Hydroxytryptamine Synthesis in Man

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Abstract. In test animals, 4-chloro-N-methylamphetamine (CMA) and 4-chloroamphetamine (4-CA) cause a decrease in the cerebral 5-HT and 5-HIAA concentrations; they exert no appreciable influence on catecholamine concentrations. In man, these compounds have a therapeutic effect on depression. In terms of antidepressant effect, they resemble not so much the nonchlorinated amphetamine derivatives as the true antidepressants.

This paper considers the question whether the influence of CMA and 4-CA on the 5-HT metabolism is based on inhibition of 5-HT synthesis. No arguments to support this hypothesis were found; findings obtained did support the postulate that these compounds are 5-HT depletors.

In conclusion, a possible explanation of the antidepressant effect of chlorinated amphetamine derivatives is offered.

Key-Words: Serotonin — 4-Chlorinated Amphetamines — Antidepressants — Depression — Central Stimulants.

Introduction

The cerebral content of 5-hydroxytryptamine (5-HT) and its principal metabolite 5-hydroxyindoleacetic acid (5-HIAA) diminishes in various test animals under the influence of 4-chloro-N-methylamphetamine (CMA) (Pletscher et al., 1963) and 4-chloro-amphetamine (4-CA) (Fuller et al., 1964; Frey and Magnussen, 1968; Kaergaard Nielsen et al., 1968) (Fig.1). The concentrations of noradrenaline (NA) and dopamine

\[
\begin{align*}
\text{CH}_3 & \\
\text{C}_1 & \\
\text{CH}_2\text{-CH-NH}_2 & \\
\text{CH}_3 & \\
\text{C}_1 & \\
\text{CH}_2\text{-CH-NH-CH}_3 & \\
\end{align*}
\]

\[\text{p-Chloro-Amphetamine} \quad \text{p-Chloro-Methylamphetamine}\]

Fig.1. Some 4-chlorinated amphetamine derivatives
show no appreciable change. This, however, does not necessarily rule out an influence on the catecholamine metabolism. Strada et al. (1969) recently reported that, in the rat brain, the normetanephrine concentration increases while those of desaminated and desaminated/O-methylated NA metabolites diminish in response to 4-CA. This might indicate an increased extraneuronal NA utilisation. Since the absolute amount of NA remains unchanged, a compensatory increase in NA production must be expected in this case. This has not so far been investigated.

According to Pletscher et al. (1964, 1966), chlorinated amphetamine derivatives interfere with the storage or the uptake of 5-HT in the intraneuronal depots. They regard these compounds as 5-HT releasers. The intraneuronal enzyme monoamine oxidase (MAO) would then govern the breakdown of the released 5-HT. This mechanism explains the decrease in 5-HT concentration but not that in 5-HIAA concentration, which under these circumstances would be expected to increase, if anything. If CMA indeed interferes with either the uptake or the storage of 5-HT, then a second mechanism must be postulated to explain the decrease in 5-HIAA concentration: e.g. MAO inhibition (Pletscher et al., 1966) or degradation of the released 5-HT via a MAO-independent route (Van Woudenberg et al., 1970).

The more obvious explanation of the simultaneous decrease of the 5-HT and 5-HIAA content of the brain: inhibition of 5-HT synthesis, was rejected by Pletscher et al. (1964). They found that CMA inhibits neither tryptophan hydroxylase (in the liver) nor 5-hydroxytryptophan (5-HTP) decarboxylase, nor the uptake of tryptophan in the brain. The same applies to 4-CA (Fuller et al., 1964). On the other hand Sanders-Bush and Sulzer (1969) recently reported indirect evidence compatible with the hypothesis that 4-CA may be a selective inhibitor of cerebral tryptophan hydroxylase.

In man, CMA as well as 4-CA have an antidepressant effect (Van Praag et al., 1969a, 1969b; Kits and Van Praag, 1970; Van Praag and Schut, 1970). In view of hypotheses which relate antidepressant activity to changes in central monoamine metabolism (Coppen et al., 1963; Bunney and Davis, 1965; Schildkraut, 1965; Van Praag, 1962, 1967; Lapin and Oxenburg, 1969; Carlsson et al., 1969), it seemed of importance to establish whether chlorinated amphetamine derivatives interfere with 5-HT synthesis in man.

**Methods**

Fifteen patients recently hospitalized with various types of depression, were given CMA (90 mg daily) or 4-CA (75 mg daily) for four weeks starting in the second week after admission. The drugs were distributed