In vitro Studies on the Possible Effects of 1-Aminoadamantanes on the Serotonergic System in M. Parkinson

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Summary

Synaptosomes, synaptic vesicles, and membranes were isolated from rat brain homogenates by differential and density gradient centrifugation in sucrose. Synaptosomes incorporated serotonin (5-HT) with two different uptake mechanisms, high affinity: $K_{\text{H}} = 47 \text{nM}$ and low affinity: $K_{\text{L}} = 660 \text{nM}$. Both uptake mechanisms are non-competitively inhibited by the potential antiparkinson drugs 1-aminoadamantane (amantadine, $D_1$: $K_{\text{H}} = 57 \text{~µM}$, $K_{\text{L}} = 96 \text{~µM}$) and 1-amino-3,5-dimethyladamantane (memantine, $D_145$: $K_{\text{H}} = 97 \text{~µM}$, $K_{\text{L}} = 150 \text{~µM}$). The incorporated 5-HT is released from synaptosomes on incubation with high concentrations (0.5—5 mM) of the drugs or on electrical stimulation with rectangular pulses of alternating polarity. Subthreshold concentrations of these drugs (5—50 µM) which are too low to liberate 5-HT increase the electrically stimulated release of 5-HT.—The effect of $D_1$, $D_145$, and electrical stimulation on DA release parallels the results observed with 5-HT.

The uptake of 5-HT into isolated synaptic vesicles and the binding to isolated nerve ending membranes is non-competitively inhibited by 1-aminoadamantanes. $D_145$ inhibits the binding of 5-HT to membranes more effectively ($K_i = 0.95 \text{~mM}$) than its uptake into vesicles ($K_i = 1.2 \text{~mM}$) contrasting with $D_1$ which is a weaker inhibitor affecting vesicular uptake ($K_i = 2.5 \text{~mM}$) slightly more than membrane binding ($K_i = 3.1 \text{~mM}$).

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The results obtained suggest that, in addition to other mechanisms like receptor stimulation, 1-aminoadamantanes may act in parkinsonian patients by enriching the transmitter content in the synaptic cleft.

**Introduction**

Since Schwab's observation (Schwab et al., 1969) that 1-aminoadamantane leads to an improvement in rigor, akinesia, and tremor of parkinsonian patients, clinical, pharmacological, and electrophysiological studies have been performed to elucidate the effect of 1-aminoadamantane and its derivatives on dopaminergic mechanisms in extrapyramidal function. According to these studies 1-aminoadamantane (D 1) and its C-alkyl derivative 1-amino-3,5-dimethyladamantane (D 145) can be classified as dopaminergic drugs since they stimulate dopamine receptors. The two drugs differ, however, regarding their effect on noradrenaline receptors. In contrast with the parent compound, D 1, which stimulates both dopamine (DA) and noradrenaline (NA) neurons (Strömberg et al., 1970; Farnebo et al., 1971; Maj et al., 1972) D 145 does not affect NA receptors (Svensson, 1973; Maj et al., 1974).

Clinical pharmacological studies indicate that besides the dopaminergic system 5-HT metabolism is also affected in M. Parkinson but not in other extrapyramidal disorders (Chase, 1974). There is accumulating evidence that in M. Parkinson the observed decrease in brain 5-HT concentration (Bernheimer et al., 1961) and in 5-HIAA level of the lumbar spinal fluid (Chase, 1972) is associated with the severity of akinesia and rigidity (Chase, 1974). Structural degenerations of the serotonergic system, however, have not been observed in the brain system of parkinsonian patients. Though the changes in 5-HT metabolism may reflect secondary functional effects of dopaminergic interaction rather than a primary disorder of serotonergic neurons, dopaminergic drugs like D 1 or D 145 may also affect the serotonergic system. 5-HT neurons may be influenced in two ways by these drugs: (1) through direct effects on 5-HT neurons, (2) through primary stimulation of DA receptors which in turn activate the 5-HT system. Though D 1 and D 145 have slight effects on the 5-HT level in rat brain, the results obtained are inconsistent. This might be explained by different doses which have been applied (Maj, 1973; Maj et al., 1974; Tanaka et al., 1973; Wesemann and Schollmeyer, 1973). Results obtained from neurophysiological and neuropharmacological in vivo studies with 1-aminoadamantanes are inconclusive since they do not discriminate between drug effects