

## Alterations in dopamine uptake in rat corpus striatum induced by combinations of stress and $\Delta^8$ -tetrahydrocannabinol ( $\Delta^8$ -THC)

J.M. LITTLETON & K.I. MACLEAN\* (introduced by G. BROWNEE)

Department of Pharmacology, King's College, London WC2

Cannabinoids produce behavioural changes dependent on the environmental conditions under which they are administered (e.g. Carlini, Hamaoui & Martz, 1972). Biochemical changes, also, may be influenced by environment (Littleton & MacLean, 1974). We now report that environment alters the effect of  $\Delta^8$ -THC on rat striatal dopamine uptake.

Male, Wistar rats, 120-160 g, were kept under 'normal' conditions (housed in groups of four, free access to food and water) for 14 days before every experiment. Rats under 'stressful' conditions were isolated with access to water but not food for 24 h before being killed. Environmental temperature was  $21 \pm 1^\circ\text{C}$ , the lighting cycle 12 h light (7.00-19.00) and 12 h dark. Animals received  $\Delta^8$ -THC (10 mg kg<sup>-1</sup> i.p.) or vehicle (Tween-80, 4% in saline i.p.) 2 h before being killed (11.00-11.30). Uptake of <sup>3</sup>H-dopamine into striatum was estimated using the method of Palfreyman, Palfreyman & Clark (1975).

$\Delta^8$ -THC pretreatment produced a non-significant reduction in striatal dopamine uptake of rats kept under normal environmental conditions. Striatal preparations from rats kept under stressful conditions showed a small increase in striatal dopamine uptake compared with those from normally-housed rats.  $\Delta^8$ -THC pretreatment under stressful conditions produced a significant ( $P < 0.02$ ) increase in striatal dopamine uptake compared with preparations obtained from Tween-treated, stressed animals. Under 'normal' conditions,  $\Delta^8$ -THC produced an uptake of  $96.5\% \pm 12.4\%$ , whilst under 'stressful' conditions  $\Delta^8$ -THC produced an uptake of  $149.1\% \pm 9.0\%$ , these values being expressed as a percentage  $\pm$  s.e. mean ( $n = 8$ ) of the appropriate controls.

Previous work on the *in vitro* effect of  $\Delta^8$ -THC indicates a reduction of dopamine uptake into striatal synaptosomes (Banerjee, Snyder & Mechoulam, 1975). The apparent reversal of this  $\Delta^8$ -THC-induced change by stress, recalls the *in vitro* findings of List, Bartram, Nazar & Harclerode

(1975) that high concentrations of steroids reverse the effect of  $\Delta^9$ -THC on metabolism in mouse brain homogenates.

Our results also explain the previous finding (Littleton & MacLean, 1974) that striatal dopamine depletion after inhibition of dopamine synthesis was reduced by  $\Delta^8$ -THC only in stressed animals. This increase in dopamine uptake could contribute to the maintenance of dopamine stores and hence reduce the rate of their depletion. In *in vivo* experiments on the conversion of <sup>3</sup>H-tyrosine to <sup>3</sup>H-dopamine, we have observed no concomitant alteration in striatal dopamine synthesis.

In conclusion, these experiments provide important evidence for the alteration, by stress, of the biochemical effects of  $\Delta^8$ -THC. When  $\Delta^8$ -THC is administered in a stressful environment it causes an apparent increase in striatal dopamine uptake. This change implicates central dopaminergic function in the abnormal behaviour patterns induced by  $\Delta^8$ -THC when administered to stressed animals. The mechanism by which the biochemical effect of  $\Delta^8$ -THC is altered by environment is currently under investigation.

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## References

- BANERJEE, S.P., SNYDER, S.H. & MECHOULAM, R. (1975). Cannabinoids: influence on neurotransmitter uptake in rat brain synaptosomes. *J. Pharmac. exp. Ther.*, **194**, 74-81.
- CARLINI, E.A., HAMAOU, A. & MARTZ, R.M.W. (1972). Factors influencing the aggressiveness elicited by marihuana in food-deprived rats. *Br. J. Pharmac.*, **44**, 794-804.
- LIST, A.F., BARTRAM, S.F., NAZAR, B.L. & HARCLERODE, J. (1975). Interactions of  $\Delta^9$ -tetrahydrocannabinol, adrenal steroids and ethanol. *J. Pharm. Pharmac.*, **27**, 606-607.
- LITTLETON, J.M. & MACLEAN, K.I. (1974). The effect of  $\Delta^8$ -tetrahydrocannabinol ( $\Delta^8$ -THC) on dopamine metabolism in the rat corpus striatum: the influence of environment. *Br. J. Pharmac.*, **51**, 117P.
- PALFREYMAN, M.G., PALFREYMAN, E.S. & CLARK, M.S.G. (1974). Effects of benapryzine, a new antiparkinson drug, on dopamine uptake into corpus striatum. *Eur. J. Pharmac.*, **28**, 379-383.