Cannabis and amphetamine-induced stereotypy in rats

Amphetamine induces hyperactivity and stereotyped behaviour both in animals and man (Randrup & Munkvad, 1967) which is inhibited by neuroleptic and cataleptogenic drugs (Arnfred & Randrup, 1968). Δ^9-Tetrahydrocannabinol (Δ^9-THC), the major psychoactive component of cannabis tincture has been reported to induce a cataleptic reaction (Pertwee, 1972) and, therefore, the effect of cannabis on amphetamine-induced stereotypy was investigated.

Male Sprague-Dawley rats (200–300 g) were treated on one occasion only with cannabis or its solvent medium followed after 30 min by amphetamine (2·5 mg kg^{-1}, i.p.). The petrol-soluble fraction (b.p. 40–60°) of tincture of cannabis B.P.C., which includes Δ^9-THC (2·4%) and most other cannabinoids, was suspended in 10% propylene glycol/1% Tween 80/saline and then administered intraperitoneally in a range of doses equivalent to 0·5–10·0 ml kg^{-1} of the tincture.

The abnormal behaviour patterns characteristic of amphetamine-induced stereotypy: sniffing, rhythmic head and body movements, gnawing, licking and biting, were scored individually using the scoring system: absent (0), minimal (1), moderate (2) and maximal (3). Maximum intensity occurred after 60–90 min. After amphetamine alone the proportion and intensity of the stereotypy components is dose-related, a low dose (2·5 mg kg) inducing a high level of sniffing with minimal signs of the other behaviour patterns, higher doses however resulting in the reduction of sniffing and its replacement by an increase in the frequency and intensity of the mouth, head and body movements (Naylor & Olley, 1972).

Pretreatment with cannabis extract significantly modified the amphetamine-induced behaviours in a dose-dependent manner above 2·0 ml kg^{-1}, reducing or abolishing the sniffing behaviour and increasing the rhythmic head and body movements ($P = 0{\cdot}01$). Cannabis pretreatment, however, did not potentiate the gnawing, licking and biting behaviour as would have been predicted if the effects were simple overall potentiation of amphetamine.

Earlier work (Naylor & Olley, 1972) had evaluated amphetamine induced stereotypy on a single composite scale. This, however, was found to be inappropriate in this study since at least three independent groups of behaviour patterns emerged. These were firstly sniffing, secondly rhythmic head and body movements and thirdly, gnawing, licking and biting.

Since these components of stereotypy become separable by cannabis this may suggest that these types of behaviour could be mediated through different systems in the brain. This view is supported by the work of Taylor & Snyder (1971) who suggest that noradrenaline is selectively involved in mediating amphetamine-induced locomotor activity, while dopamine is concerned in the compulsive gnawing syndrome. Our findings that cannabis reduces sniffing and potentiates the gross head and body movements may thus suggest a selective effect on the two catecholamine systems.

Alternative hypotheses involve the possibility that cannabis may act on different sites in the brain, since recent evidence is accumulating from the work of Costall & Naylor (1973a, b) that both extrapyramidal and mesolimbic dopaminergic systems are involved in the mediation of stereotyped behaviour. It is also possible that the metabolism of amphetamine could be changed by cannabis leading to its inhibition or to an altered proportion of metabolites and the parent compound, which have differing pharmacological and biochemical effects with respect to release and uptake mechanisms of catecholamines (Taylor & Sulser, 1973).

It is worthy of comment that cannabis, a reputed cataleptogenic drug, which might be expected to antagonize amphetamine-induced stereotypic behaviour potentiated some facets while abolishing others. However, catalepsy, as defined by Munkvad,

Pakkenberg & Randrup (1968) and tested by the method of Costall & Olley (1971), was not induced in these rats but prostration, an atonic depressed appearance with the animal still retaining its desire and capacity to move from an abnormal position, was detected and studied in animals after cannabis pretreatment. It was found that only the doses exceeding 1 ml kg^{-1} tincture of cannabis B.P.C. induced signs of prostration, the highest dose (10 ml kg^{-1}) grossly affecting all the animals.

Thus cannabis has been differentiated from neuroleptic cataleptogenic agents by its complex interaction with amphetamine.

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Accumulation of acetylcholine and aromatic monoamines by interaction with adenosine-5′-triphosphate

Biogenic monoamines, such as, for example, catecholamines and 5-hydroxytryptamine, are thought to accumulate in subcellular storage organelles by two different mechanisms, i.e. by an active transport at the level of the granular membrane and by interaction with nucleotides present in high concentration in the organelles (intragranular mechanism) (Pletscher, Da Prada & others, 1974). Evidence of accumulation by interaction with adenosine-5′-triphosphate (ATP) has been presented in a diffusion system consisting of two chambers separated by an artificial lipid membrane impermeable to ATP. One of the chambers contained ATP, the other did not. In this system, noradrenaline originally present in equal concentration in both chambers accumulated against an apparent concentration gradient in the chamber containing ATP (Berneis, Da Prada & Pletscher, 1974).

In the present work, these experiments have been extended to other amines using a new system for equilibrium dialysis with an artificial non-lipid containing membrane. In this system, in contrast to that used before, the passage of the amines through the membrane was rapid and unhindered, and the diffusion of amines with low lipid solubility (e.g. acetylcholine) could also be determined.

A Dianorm equilibrium dialyser (Diachema AG, Birmensdorf/Zurich, Switzerland) made of Teflon and containing two microchambers separated by a "spectropor 3TM membrane" (M.W. cut-off: 3500) (Spectrum Medical Industries Inc., Los Angeles, USA) (Fig. 1) was used for all experiments. Both chambers were filled with the same