whole brain or in selective brain regions (C. striatum, hypothalamus). The biosynthesis of ^{3}H-dopamine and ^{3}H-noradrenaline from intravenously injected ^{3}H-tyrosine was enhanced in the whole brain by all three cannabinols. Concomitantly an increased concentration of ^{3}H-dihydroxyphenylacetic acid (DOPAC) was found. DMHP was more active than Δ^8 or Δ^9-THC, but no qualitative differences were observed. Biosynthesis was also studied *in vitro* with slices of C. striatum and of hypothalamus obtained from rats pretreated with these cannabinols. Measurements of tritiated water, noradrenaline and dopamine formed from ^{3}H-tyrosine added to the incubation medium showed a particular enhancement of tyrosine hydroxylation in the C. striatum by Δ^9-THC and in the hypothalamus by DMHP. No striking effects on 5-HT and 5-HIAA concentrations were observed.

All three cannabinols elevated plasma corticosterone and at the same time lowered the cholesterol ester content of the adrenals in intact rats but not after hypophysectomy. Δ^9-THC (30 mg/kg) displayed a longer duration of action than the other two analogs. It increased the concentration of plasma free fatty acids for at least two hours.

These results indicate that the cannabinols enhance noradrenaline and dopamine turnover in the rat brain most probably by stimulating tyrosine hydroxylase activity. On the other hand the cannabinols obviously stimulate the pituitary gland to release ACTH as demonstrated by the adrenal and lipolytic activities.

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The effect of hashish on noradrenaline concentration and uptake in the brain

1. Hashish extract was injected i.p. into rabbits. Ninety minutes following the injection the animals were killed and noradrenaline (NA) content of various parts of the brain estimated fluorometrically.

It was found that hashish extract causes changes in the amine content of the brain which vary both in magnitude and sign, depending upon the particular area examined. Thus endogenous NA content of the quadrigeminal area and hypothalamus postero-superior increased significantly while that of cerebellum was inversely affected in the hashish treated animals.

2. An investigation of the NA content of hypothalamus in hashish sublimate treated animals was carried out using histochemical fluorescence

techniques. An increase in the amine concentration of the terminal axonal varicosities of hypothalamus was observed in these animals as compared to controls.

With regard to the possible mechanisms responsible for such an increase, the idea of a facilitation of NA uptake by hypothalamus of hashish treated animals was tested *in vitro*. Thus slices of rabbit brain hypothalamus were incubated with ^{3}H-NA in the presence or absence of various concentrations of synthetic THC. Preliminary experiments indicated that the uptake of NA from the medium remains unaffected by THC. Similarly slices prepared from the hypothalamus of the brain of rabbits injected i.p. with cannabis extract did not show significant differences in NA uptake as compared to slices prepared from control animals. The value of the results obtained in these preliminary experiments is somehow limited due to possible variations encountered in obtaining homogeneous hypothalamic slices of the particular areas which showed increased green fluorescence or increased NA content.

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The effect of tetrahydrocannabinols on central monoamine neurons

The effects of Δ^8 and Δ^9-tetrahydrocannabinol (THC) on amine turnover and amine uptake-storage mechanisms in central dopamine (DA), noradrenaline (NA) and 5-hydroxytryptamine (5-HT) neurons were investigated using a combined histochemical and biochemical approach. Amine turnover was evaluated with the help of tyrosine and tryptophan inhibitors and intraventricular injection of tritiated amines. Amine uptake-storage was evaluated *in vivo* and *in vitro* with isotope and histochemical techniques. It was found that Δ^9-THC in a dose of 25 mg/kg, i.p., caused a stimulation of ^{3}H-NA, ^{3}H-DA and ^{3}H-5-HT uptake into the NA, DA and 5-HT neurons respectively. *In vitro* Δ^9-THC (10^{-4} *M*) did not cause any stimulation of ^{3}H-NA or ^{3}H-5-HT uptake in slices from cerebral cortex. Furthermore, it was found that Δ^8 and Δ^9-THC increased NA turnover in practically all parts of the brain, e.g. the cortex cerebri and the hypothalamus. On the other hand, the DA turnover in the neostriatum and the limbic forebrain but not in the median eminence was decreased. Unlike the psychotomimetic drugs of the indolalkylamine type such as *d*-LSD and psilocybin Δ^8 and Δ^9-THC increased the 5-HT turnover in the nuc. suprachiasmaticus. It is concluded that there are marked effects on central monoaminergic transmitter mechanisms after exposure to Δ^8 and Δ^9-THC.