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COMMUNICATIONS

Interactions of Δ^9-tetrahydrocannabinol, adrenal steroids, and ethanol

A characteristic of cannabis is the lability of responses produced by the active ingredients in the crude drug. Cannabis has been reported to elicit effects ranging from mild sedation to psychotic and paranoid manifestations. Although some response differences may be of pharmacogenetic origin, a variety of factors seems capable of influencing reactions to cannabis. Ambient temperature, for example, alters both toxicity and hypothermic responses in rodents (Haavik & Hardman, 1973; Haavik, 1974) and the presence of testosterone has also been found to account for differences in drug potency between males and females (Cohn, Barratt & Pirch, 1974).

Of particular interest are the interactions between stress and cannabis. Carlini, Masur & others (1972) demonstrated that numerous stressors; viz., hunger, cold, morphine withdrawal, and deprivation of rapid eye movements, can alter the response of rodents to cannabis. In man, a survey of psychotic reactions revealed a greater frequency and intensity of adverse reactions among cannabis users living in stressful situations (Talbott & Teague, 1969).

Interactions between stress and cannabis suggest that some component of the stress response is capable of modifying the actions of cannabis. An hypothesized role of adrenal steroids was tested in adrenalectomized male Swiss albino mice (Carworth Farms) maintained under one of three schedules of corticosterone treatment, simulating conditions of (1) no adrenal steroids, (2) non-stress levels, or (3) high stress levels of adrenal steroids. These conditions were taken from Leshner (1971). The influence of Δ^9-THC on tissue respiration of brain homogenates 2 h after intraperitoneal injection of the drug was measured as described by Nazar, Harclerode & others (1974). Because some investigators have used ethanol to solubilize cannabinoids in

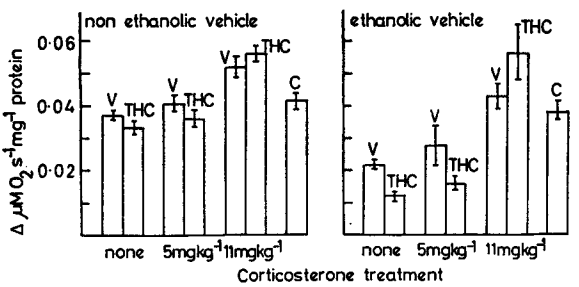

FIG. 1. Respiration in mouse brain homogenates as measured by oxygen consumption (mean with s.d.) after succinate-ADP stimulation. Adrenalectomized mice were maintained on 0·9% saline in their drinking water and received one of three corticosterone treatments: (1) No steroid administered; i.e., steroid vehicle only; (2) Daily corticosterone replacement (5 mg kg^{-1}, s.c.) for 4 days; (3) Daily corticosterone replacement (5 mg kg^{-1}, s.c.) for 4 days plus a "stress-level" dosage (11 mg kg^{-1}, s.c.) 2 h before death. Each ml of steroid vehicle consisted of 9 mg NaCl, 5 mg sodium carboxymethyl cellulose-7, 4 μl polysorbate 80, and 9 μl benzyl alcohol. All Δ^9-THC treated animals received 25 mg kg^{-1} of the drug i.p. 2 h before death. The drug vehicle consisted of physiological saline 1% Tween 80, 10% propylene glycol. The ethanolic vehicle included the addition of 5% (w/v) ethanol. Non-drug treated animals received drug vehicle only. The control groups were intact and received none of the above treatments. Each group contained five mice.

aqueous vehicles, this study was replicated with 5% (w/v) ethanol added to the injection vehicle. This yields a $3 \times 2 \times 2$ factorial design (corticosterone levels $\times$ drug treatment $\times$ composition of drug vehicle).

In all instances, endogenous rates of respiration were stimulated by addition of succinate, and further stimulated by adenosine diphosphate (ADP), indicating that the respiratory chain was functional and phosphate acceptor control remained intact. The mean respiration rates after succinate + ADP stimulation are presented in Fig. 1. Details of the procedure are described in the legend.

Analysis of variance indicated that brain homogenate respiration was significantly influenced by the level of corticosterone administered ($F = 3{\cdot}030$, $P<0{\cdot}0001$) and the presence of ethanol in the vehicle ($F = 191{\cdot}06$, $P<0{\cdot}0001$). Δ^9-THC, on the other hand, did not exert a singular effect on respiration ($F = 3{\cdot}80$, $P<0{\cdot}1$) but was found to interact significantly with the level of corticosterone ($F = 60{\cdot}134$, $P<0{\cdot}0001$) and the presence of ethanol ($F - 51{\cdot}53$, $P<0{\cdot}0001$). With low levels of corticosterone, Δ^9-THC depressed respiration below that of animals receiving vehicle. With stress levels of corticosterone, Δ^9-THC stimulated tissue respiration above that of animals receiving vehicle. This dual effect of Δ^9-THC was even more pronounced when ethanol was added to the carrier vehicle. Finally, an interaction among all three variables was found to be significant ($F = 16{\cdot}97$, $P<0{\cdot}0001$).

Cellular respiration has been used previously by several other investigators to measure cannabis-induced changes in metabolism (Bose, Saifi & Bhagwat, 1963; Mahoney & Harris, 1972; Sprague, Rosenkrantz & others, 1972; Dembert & Harclerode, 1974; Nazar & others, 1974; Shahar & Bino, 1974). Although the role of cellular respiration in the psychotropic action of cannabis has not been delineated, the observations reported here demonstrate that the state of adrenal activity as well as the composition of injection vehicle can significantly influence an animal's metabolic reaction to cannabis.

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