higher in FLA 63-treated animals compared with control animals. These increases in tissue concentrations could result from the markedly decreased renal elimination of barbitone in FLA 63-treated animals, particularly as barbitone is known to be excreted almost entirely in the urine without undergoing significant biotransformation (Williams 1959).

In 1974, Jonsson & Lewander showed in the rat that FLA 63 significantly increased amphetamine-induced increase in motor activity. They also found that pretreatment with FLA 63 was associated with a significant increase of amphetamine concentration in brain and plasma. Recently we found that disulphiram markedly enhanced amphetamine toxicity in the rat (Sharkawi et al 1978).

FLA 63 is considered as a more specific inhibitor of DβH than disulfiram. However, the present experiments indicate that FLA 63 affects barbitone disposition and pharmacological activity in a manner similar to that produced by disulfiram (Sharkawi & Cianflone 1978). Unpublished experiments from this laboratory show that both FLA 63 and disulfiram prolong morphine-induced analgesia in the rat and prolong sleep induced by chloral hydrate and phenobarbitone in mice. Thus, it seems that FLA 63 has a pharmacological profile that is similar to disulfiram. This should not seem surprising since both compounds are closely related chemically.

The present experiments and those of Jonsson & Lewander (1974) indicate that FLA 63 can alter the disposition of some centrally acting drugs. Consequently, their pharmacological activity is altered. Thus, it seems prudent that this effect of FLA 63 on drug disposition and elimination should be taken into consideration when FLA 63 is employed as an inhibitor of DβH to assess the role of dopamine and noradrenaline in the pharmacological actions of certain centrally acting drugs.

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The effects of Δ^9-tetrahydrocannabinol, cannabidiol, and shock on plasma corticosterone concentrations in rats

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Barry & Buckley (1966) have reported that in rats, stress caused a pituitary-adrenal activation, as measured by increased plasma corticosterone concentrations. Furthermore, Kubena et al (1971) demonstrated that in rats Δ^9-tetrahydrocannabinol (Δ^9-THC) in doses of 2–16 mg kg^{-1} also caused pituitary-adrenal activation. This was corroborated by Kokka & Garcia (1974) for 5–20 mg kg^{-1} doses of Δ^9-THC. Graham & Li (1973) found that cannabidiol, another major naturally occurring cannabinoid, had no observed effects on either the cardiovascular or respiratory systems of the rat.

Other studies in this laboratory have examined the action of Δ^9-THC on several endocrine organs including the gonads (List et al 1977) and the thyroid (Nazar et al 1977). Our latest study was designed to examine the effect of Δ^9-THC and CBD on the normal pituitary-adrenal activation response to stress.

Male albino rats (Camm Wistar strain), 175–325 g, were housed separately and maintained at constant room temperature 20 °C on a 12 h light–12 h dark schedule with free access to food and water. The test procedures were performed during the lighted phase. The Δ^9-THC and CBD were obtained from the National Institute of Mental Health and suspended in 1% Tween 80, 10% propylene glycol, and 89% physiological saline (0·9% NaCl) for injection. The control injection contained the same volumes of Tween 80, propylene glycol, and saline as were included in the highset dose of Δ^9-THC or CBD in each experiment. Δ^9-THC and CBD injected animals received 5 mg kg^{-1} doses. All injections were intraperitoneal and in a volume of less than 1 ml. Electric shocks of 60 V (5 shocks, of 3 s duration with 9 s interval) were administered over 1 min 15 min before decapitation and collection of trunk blood. Serum samples were assayed fluorometrically for plasma corticosterone, as described by Perhach & Barry (1970), 1 h after injection of cannabinoid.

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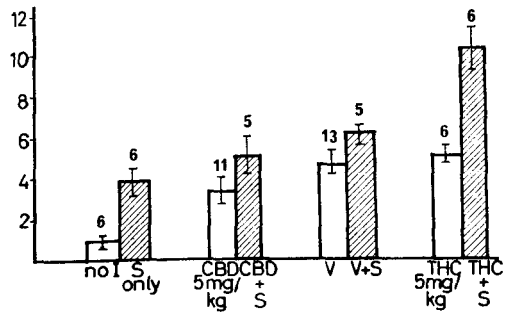

FIG. 1. Plasma corticosterone concentrations (ordinate: $\mu g\ ml^{-1}$) of shocked and non-shocked rats treated with Δ^9-tetrahydrocannabinol or cannabidiol 1 h after injection and 15 min after shock. Open columns are values for unshocked rats, hatched columns are for rats shocked for 1 min at 15 min before death. Values given are mean ± standard error of the mean. Numbers refer to the number of animals in each group. Abcissa: injection/injection + shock. S = shock; I = injection. V = vehicle.

The first part of this study was designed to compare the effects of 5 mg kg^{-1} doses of Δ^9-THC and CBD on plasma corticosterone concentrations. Fig. 1 shows that CBD depressed corticosterone values below vehicle-injected controls ($P < 0.03$) and below Δ^9-THC ($P < 0.01$) treated animals. Results for the controls that received no injections were significantly less than those for rats injected with CBD ($P < 0.03$), vehicle ($P < 0.003$), and Δ^9-THC ($P < 0.001$).

The second part of this study was designed to compare the combined effects of a stressor (electric shock) and either a 5 mg kg^{-1} dose of CBD or Δ^9-THC on plasma corticosterone concentrations. Fig. 1 shows that shocked rats treated with Δ^9-THC had statistically higher corticosterone concentrations than shocked rats that were treated with either nothing ($P < 0.002$), CBD ($P < 0.002$) or vehicle ($P < 0.008$). The magnitude of the increased corticosterone values in the shocked rats treated with Δ^9-THC was approximately twice that found in either the shocked rats treated with CBD or injected with vehicle. Also, shock would appear to override the depressive effect of CBD on corticosterone values.

Plasma concentrations of corticosterone are sensed by the limbic structures, specifically the hippocampus (Sawin 1969). The limbic system may selectively accumulate corticosterone by an active uptake mechanism and has a high concentration of corticosterone binding proteins (McEwan et al 1972). If corticosterone concentrations saturate binding proteins, corticotrophin releasing factor (CRF) secretion is inhibited (Drew & Slagel 1973). When plasma corticosterone values are low, as sensed by the amygdala and forebrain, CRF inhibition is removed (Drew & Slagel 1973).

Stress has been found to cause an increase in both plasma ACTH and plasma corticosterone. Apparently, high plasma concentrations of corticosterone do not shut off CRF release in the presence of intense stimulation of the median eminence by nervous impulses from other parts of the brain (Sawin 1969). Drew & Slagel (1973) have shown that Δ^9-THC at doses of 9 mg kg^{-1} impairs corticosterone uptake by hippocampus and septum, thereby causing an increase in the secretion of CRF.

Both stress and Δ^9-THC have each been shown to raise plasma corticosterone concentrations in rats. We have shown that the combination of stress and 5 mg kg^{-1} Δ^9-THC results in higher corticosterone values than either stress or Δ^9-THC alone. Thus it seems that the effects of Δ^9-THC and stress to increase corticosterone values may be independent of one another. Furthermore, we see that in rats CBD has an effect opposite that of Δ^9-THC or stress in that it results in lower corticosterone values than vehicle-injected controls. It is possible that, unlike Δ^9-THC, CBD does not impair corticosterone uptake by the hippocampus and septum, which in Δ^9-THC-treated animals seems to cause a 'falsely triggered' increase in the secretion of CRF. CBD may in effect enhance corticosterone uptake by the limbic structures which would explain the lower corticosterone concentrations of CBD-injected animals compared with vehicle injected controls.

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