Pharmacology Biochemistry & Behavior, Vol. 23, pp. 13–15, 1985. © Ankho International Inc. Printed in the U.S.A. 0091-3057/85 $3.00 + .00

The Quasi-Morphine Withdrawal Syndrome: Effect of Cannabinol, Cannabidiol and Tetrahydrocannabinol

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Received 21 May 1979

CHESHER, G. B. AND D. M. JACKSON. *The quasi-morphine withdrawal syndrome: Effect of cannabinol, cannabidiol and tetrahydrocannabinol.* PHARMACOL BIOCHEM BEHAV **23**(1) 13–15, 1985.—Δ-9-tetrahydrocannabinol (THC), the main psychoactive principle of cannabis, has been shown to attenuate the exhibition of signs of the quasi-morphine withdrawal syndrome in rats. Cannabinol (CBN) showed the same activity but required a dosage of approximately eight times that of THC to produce an equivalent effect. Cannabidiol was without effect at the dosage levels used. The efficacy of these cannabinoids and the potency differences recorded in this study are in accord with their effects on other behaviours, both in experimental animals and in man. The activity of THC and CBN was not affected by the narcotic antagonist, naloxone.

Δ-9-tetrahydrocannabinol Cannabinol Cannabidiol Quasi-morphine withdrawal syndrome Naloxone

DELTA-9-tetrahydrocannabinol (THC) is capable of antagonizing many of the withdrawal signs elicited by the administration of naloxone to morphine-dependent rats and mice [2, 8, 9]. THC is also a potent antinociceptive agent in experimental animals [3,4 , 5], but its mechanism of action is apparently different from that of the narcotics because its effect is not antagonized by naloxone or nalorphine [5, 12, 16]. We have recently shown that THC is able to antagonize the quasi-morphine withdrawal syndrome (QMWS) in rats [16], a syndrome elicited by the administration of a potent phosphodiesterase inhibitor and naloxone [6]. The QMWS signs resemble those of true narcotic withdrawal, and like the latter, are inhibited in a stereospecific manner by the narcotic agents. The order of potency of the narcotics in attenuating the QMWS is in close agreement with their clinical potency [6].

In the present paper, we describe some studies which investigate the activity of the three principal cannabinoids, THC, cannabinol (CBN) and cannabidiol (CBD) on the QMWS.

METHOD

Male Sprague-Dawley rats (140–240 g) were housed in groups of 4–5 under ambient lighting (0800–2000 hr) at 22±2′ and were allowed food and water ad lib until the time of the experiment. Rats were distributed randomly to the treatment groups.

Rats were observed for signs of the QMWS for two 15 min periods beginning 45 and 60 min after the administration of the phosphodiesterase inhibitor, 3-isobutyl-1-methylxanthine (IBMX) 15 mg/kg SC. Immediately after the first observation period (60 min after IBMX), naloxone (3 mg/kg SC) was administered. The cannabinoids (THC 5 or 10 mg/kg; CBN 5, 20 or 80 mg/kg; CBD 5, 20 or 80 mg/kg or vehicle control) were administered (IP immediately after the IBMX. Control rats for the effect of IBMX were administered an equivalent volume of saline (SC).

Each experimental session was conducted with 4 rats and the results presented here are the cumulated data from 200 rats (i.e., 20 each for the 8 cannabinoid and the two control groups, IBMX and saline). Two experimental sessions were conducted on each experimental day, the first beginning at approximately 1000 hr and the second at about 1400 hr. Allocation of the dosage for each group of 4 rats was randomized to ensure an equitable distribution of all treatments over both the time of day and the time over the experimental period of about eight weeks.

The experimental design was the same as that described previously [16]. In the present studies, IBMX significantly increased the incidence of only 10 of the 17 behavioural signs observed (rearing, grooming, wet-dog shakes, head shakes, chewing, paw licks, ptosis, squeak on touch, diarrhoea, and rapid respiration). However, two of these signs, ptosis and squeak on touch, are characteristic signs also produced by THC and CBN. Therefore in the analysis of data these two signs were excluded and the remaining 8 were regarded as constituting a QMWS and the results of each treatment were calculated from the effect on the incidence of these 8 signs.

All signs were scored as present (1) or absent (0). For each dosage group a total "withdrawal score" for each of the signs was summed and the means determined. The means for each sign were transformed by $y=/x+0.5$ [14] and the sum of the transformed scores for all signs calculated, the means determined and this value is referred to in the text as the "mean withdrawal score." Between group comparisons were made by paired Student's *t* test (2-tailed).

3-Isobutyl-1-methylxanthine (IBMX, Sigma) and naloxone hydrochloride (Endo) were dissolved in saline. THC, CBD and CBN (National Institute on Drug Abuse) were dissolved in propylene glycol and diluted to produce a suspension containing the cannabinoid in 20% propylene glycol and 1% tween 80, in saline (0.9%). These suspensions were prepared freshly each day. An injection volume of 1.0 ml/kg was used for all drugs except IBMX (10 ml/kg).

RESULTS

Results are depicted in Fig. 1. where it can be seen that all doses of THC and CBN produced a significant reduction in the mean withdrawal score. In both cases, naloxone was without effect on the attenuation of these signs by either of the cannabinoids. In contrast, CBD was without effect on the exhibition of the QMWS signs, and naloxone did not produce any change in this behavioural pattern.

DISCUSSION

The major finding in the present study was the demonstration of the activity of CBN, and the inactivity of CBD even at high dose levels, in modifying the signs of the QMWS. As in our earlier study, THC also antagonized the QMWS, and the reduction in the QMWS withdrawal score produced by 10 mg THC/kg was approxiamtely equivalent to that produced by 80 mg CBN/kg. A similar potency difference between THC and CBN has been found for the antinociceptive effects of these cannabinoids. Using the mouse hot-plate method, Chesher *et al.* [5] found a THC:CBN ratio of 1:7. It is also interesting that THC has been shown to be more potent than CBN (and CBD to be inactive) in a wide variety of other pharmacological parameters, e.g., ether-induced anaesthesia [10] and intestinal motility in mice [1]. In man also it has been reported [11] that when administered by slow intravenous infusion, CBN produces a psychic effect that is similar to but less potent than that produced by THC. These authors estimated a potency ratio of THC:CBN of 1:6, and found CBD to be inactive. Similarly, CBD appears to be inactive in experimental animals as an antinociceptive agent [5, 7, 12, 13, 15].

The difference in activity between the three cannabinoids would suggest that certain structural requirements are necessary for the withdrawal-attenuating effects of the cannabinoids. It is tempting to draw a correlation between the effects of THC and CBN in attenuating the signs of the QMWS and the effects of these agents as antinociceptives in mice and their psychoactivity in man. In all of these effects CBN is less active than THC, and CBD is without activity. The potency ratios THC:CBN are similar in these effects.

Another interesting observation was the inability of naloxone to antagonize the effect of THC [16] or CBD (this paper), confirming that opiates such as morphine [16], and the cannabinoids, THC and CBN exert their effects on the QMWS by different mechanisms. This finding suggests that the cannabinoids do not act via the endogenous opioid mechanisms.

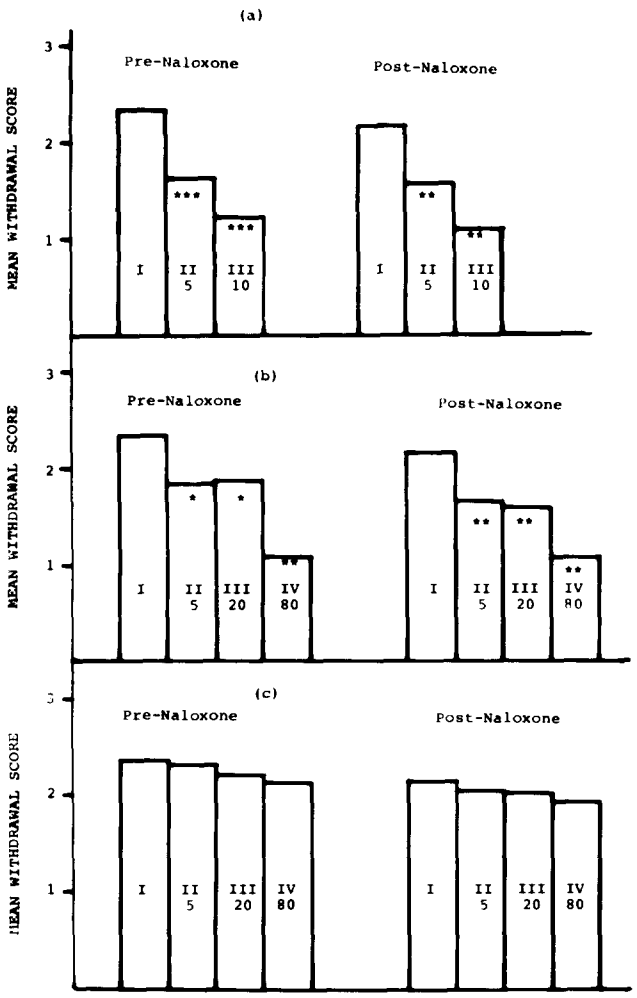

FIG. 1. The effect of three cannabinoids on the quasi morphine withdrawal syndrome (QMWS), before and after the administration of naloxone. The rats had been pre-treated with (a) Top: THC or vehicle, (b) Middle: CBN or vehicle, (c) Bottom: CBD or vehicle; The columns marked I represent the rats dosed IBMX plus vehicle; columns II to IV represent the rats dosed IBMX plus the dose indicated of the relative cannabinoid, i.e., 5, 10, 20 or 80 mg/kg. Significance levels are compared with the appropriate control (i.e., column I). $*p<0.05$, $**p<0.005$, $***p<0.0005$.

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