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Time Course of the Effects of Naturally Occurring Cannabinoids on Morphine Abstinence Syndrome

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BHARGAVA, H. N. *Time course of the effects of naturally occurring cannabinoids on morphine abstinence syndrome.* PHARMAC. BIOCHEM. BEHAV. 8(1) 7–11, 1978. – The effects of a single intraperitoneal injection (10 mg/kg) of Δ^9-tetrahydrocannabinol, Δ^8-tetrahydrocannabinol and 11-hydroxy-Δ^8-tetrahydrocannabinol on abstinence syndrome were investigated in mice rendered dependent on morphine by pellet implantation. In morphine dependent mice from which the pellets had been removed, Δ^9-tetrahydrocannabinol inhibited the naloxone-precipitated jumping response as evidenced by an increase in the ED_{50} of naloxone. This inhibition was evident for 24 hr, the most pronounced effect being produced between two to four hr after Δ^9-tetrahydrocannabinol administration. Withdrawal defecation was also inhibited for two hours. Similarly, in mice from which pellets were not removed, Δ^9-tetrahydrocannabinol suppressed the jumping response; however, the intensity of effect was less than when the pellets were removed. Δ^8-Tetrahydrocannabinol and 11-hydroxy-Δ^8-tetrahydrocannabinol were not effective in suppressing morphine abstinence syndrome two hr following their administration. The suppression of jumping response was specific, since, the vertical jumping behavior induced by coadministration of amphetamine and ℓ-dopa was not affected by cannabinoids. These results demonstrate that single injection of Δ^9-tetrahydrocannabinol is effective in controlling morphine abstinence syndrome for 24 hr, and that the drugs related to cannabinoids may show promise in narcotic detoxification.

Morphine abstinence Naloxone Δ^9-Tetrahydrocannabinol Δ^8-Tetrahydrocannabinol 11-Hydroxy-Δ^8-tetrahydrocannabinol Jumping behavior Amphetamine ℓ-Dopa

NARCOTIC addiction remains a medical problem in spite of considerable progress made to understand the biochemical mechanisms involved and various strategies developed for narcotic detoxification. Two chemotherapeutic approaches have been attempted. One includes the use of narcotic antagonists, which block the euphoria, sedation, and other effects of heroin and other narcotics. This should eventually overcome the addict's craving for heroin. Within this class naloxone [11] and naltrexone [18]. The latter is now being tested for treating heroin addicts. The disadvantages of using narcotic antagonists are their short duration of action, oral ineffectiveness (naloxone) and their ability to precipitate severe abstinence syndrome.

The second approach includes the narcotic substitution therapy. The drug most widely used is methadone, which serves as an orally active replacement for heroin [4,7]. Objections to various side effects of methadone, such as lessened libido [17], overdose potential and ability to produce physical dependence [15] makes the methadone treatment highly controversial and provides the impetus to look for alternate chemotherapeutic agents for detoxification and maintenance of heroin addicts. Propoxyphene napsylate, a narcotic and congener of methadone has been suggested [19,20] as a chemotherapeutic agent for narcotic detoxification. It is claimed that it not only possesses the full benefits of methadone therapy but also has advantages in that it produces minimal physical dependence. Propoxyphene has been shown to block narcotic withdrawal signs in animals [10] and in man [6,20]. Recently, it was shown that an orally administered suspension of propoxyphene napsylate suppressed the withdrawal jumping in a dose-dependent manner; however, its chronic administration in doses high enough to prevent withdrawal was associated with a high degree of toxicity [9].

An alternate chemotherapeutic agent Δ^9-tetrahydrocannabinol (Δ^9-THC) has been explored for its effect on morphine withdrawal. Morphine and Δ^9-THC share several pharmacological properties, e.g., analgesia, hypothermia and respiratory depression [14]. It was shown that wet shakes and defecation observed during antagonist-precipitated withdrawal in morphine dependent rats were suppressed by Δ^9-THC [8]. In our own laboratory, it was demonstrated that several cannabinoids, e.g., Δ^9-THC, Δ^8-THC, 11-hydroxy-Δ^8-THC, cannabidiol (CBD) and cannabinol (CBN), inhibited the naloxone-precipitated stereotyped jumping behavior, defecation and rearing behavior in morphine-dependent mice [1,2].

The present experiments were performed in order to

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TABLE 1

TIME COURSE OF EFFECT OF Δ^9-THC ON NALOXONE-PRECIPITATED JUMPING IN MORPHINE-DEPENDENT MICE*

Time after administration of vehicle or Δ^9-THC	Naloxone ED_{50}† μg/kg		Potency Ratio
	Vehicle	Δ^9-THC	
1	12.50(6.50–24.00)	118.92(75.75–186.70)	9.51(4.25–21.30)‡
2	8.51(4.59–15.76)	118.92(74.89–188.85)	13.98(6.50–30.06)‡
4	4.42(2.30–8.48)	50.00(26.02–96.10)	11.32(5.89–21.75)‡
8	19.84(10.33–38.09)	70.71(50.87–98.29)	3.56(1.91–6.67)‡
24	97.27(46.76–202.32)	456.46(268.51–775.98)	4.69(1.88–11.73)‡
48	1329.98(788.83–2242.35)	2015.87(1304.78–3114.52)	1.52(0.78–2.96)

*Mice were rendered dependent by morphine pellet implantation. The pellets were removed 72 hr later. Naloxone ED_{50}'s were determined at various times after a single injection of either the vehicle or Δ^9-THC(10 mg/kg, IP).

†The values in parentheses represent 95% confidence limits.

‡$p<0.05$ vs. vehicle control.

determine the duration of effects of Δ^9–THC, Δ^8–THC and 11-hydroxy-Δ^8–THC on morphine abstinence syndrome in morphine-dependent mice. In one set of studies the morphine pellets were removed from the animals, whereas, in the other they were left intact. Experiments have also been carried out to show the specificity of action of the cannabinoids studied.

METHOD

Male Swiss-Webster mice, weighing 25–30 g (Scientific Small Animals Company, Arlington Heights, IL), were housed eight or ten per cage, with food and water given ad lib, and in rooms with controlled temperature (23 ± 1°C), humidity 65 ± 2%), and light (lighted 06.00–18.00). The animals were rendered tolerant to, and dependent on, morphine by the subcutaneous (SC) implantation of a morphine pellet containing 75 mg of morphine base according to the method of Way *et al.* [21]. Since in our earlier work, it was demonstrated that CBD and CBN had only marginal activity and 20 mg/kg of Δ^9–THC showed abnormal behavior in some animals [2], in the present studies the effects of a single dose of 10 mg/kg of cannabinoids have been determined. Furthermore, since their molecular weights are very similar, a comparison at the same dose could be made. At 72 hr after the implantations, either the control vehicle (1% Tween 80 in isotonic saline) or cannabinoids (as a suspension in vehicle) in a dose of 10 mg/kg were administered intraperitoneally (IP), and the animals were divided into groups of 35 mice each for studying the effect on morphine abstinence on each time period. The mice were tested for up to 24 to 48 hr after the single administration. Morphine pellets were not removed from the mice. The abstinence was precipitated with naloxone HCl, which was injected SC at various times after the vehicle or the cannabinoid administration. An inverse relationship exists between the degree of morphine-induced dependence and the dose of naloxone needed to evoke the jumping response both in mice [21] and in rats [3]. Immediately after naloxone administration, the mice were placed on a circular platform and the number of mice jumping off the platform within a 15-min observation period was noted. Eight to ten mice were used for each of the three doses of naloxone. The dose-response curves were drawn by linear regression analysis and the dose of naloxone required to precipitate jumping in 50% of the mice (ED_{50}) was determined. The naloxone ED_{50}, potency ratio, their 95% confidence limits and the statistical test to establish significance were determined by the method of Litchfield and Wilcoxon [13]. Similar experiments were also carried out in animals from which the pellets had been removed. In these animals, the cannabinoid or the vehicle was administered immediately after the pellet removal.

Quantitative observations were also made on the defecation and rearing behavior exhibited during abstinence at various times after the cannabinoid administration. The numbers of fecal boli and rearings were counted in the control (vehicle-treated) and the cannabinoid treated group within a 15-min period following naloxone administration. The statistical significance was determined by the chi square test.

Test for Specificity of Cannabinoid Effect on Morphine Abstinence

It has been shown that in mice vertical jumping can be induced by administration of a combination of amphetamine and ℓ-dopa [12]. In order to test if the effect of cannabinoids on morphine abstinence jumping was specific or if it could inhibit jumping induced by amphetamine and ℓ-dopa, the following experiments were performed. It was earlier established that 11-hydroxy-Δ^8–THC given 30 min before naloxone administration significantly inhibited the stereotyped jumping response [2]. Sixteen mice were divided into two groups of 8 mice each. At 0 min one group received a suspension of 11-hydroxy-Δ^8–THC (5 mg/kg) in 1% Tween 80 in saline, while the other group received an equivalent volume of vehicle. At 15 min both the groups of mice received dℓ-amphetamine sulfate (4 mg/kg, IP) dissolved in physiologic saline. At 30 min both groups received an intraperitoneal injection of a suspension of ℓ-dopa (400 mg/kg) (2% carboxymethyl cellulose in saline). Immediately thereafter the mice were placed in wide mouth jars and the two groups were observed for an hour.

RESULTS

Effects of Δ^9–THC on Morphine Abstinence in Dependent Mice with Pellets Removed

Administration of Δ^9–THC (10 mg/kg) to morphine

TABLE 2

TIME COURSE OF EFFECTS OF Δ^9-THC (10 MG/KG,IP) ON WITHDRAWAL DEFECATION AND REARING BEHAVIOR IN MORPHINE DEPENDENT MICE*

Abstinence sign	Time after administration of vehicle or Δ^9-THC (hr)	No. of fecal boli or rearings			
		Vehicle	Δ^9-THC	χ^2	p
Defecation	2	43	10	6.85	0.03
	4	57	40	1.86	0.39
	6	60	52	2.37	0.31
	8	55	57	3.60	0.16
	24	58	64	3.35	0.18
Rearing	2	31	18	3.55	0.17
	4	31	12	1.46	0.48
	6	37	29	1.60	0.45
	8	33	35	1.33	0.51
	24	35	31	0.81	0.67

*Mice were rendered dependent on morphine by pellet implantation. The pellets were removed 72 hr later. The vehicle and Δ^9-THC treated groups (8 mice per group) were given an ED_{50} dose of naloxone (for jumping response) and observations were made for a 15-min period.

TABLE 3

TIME COURSE OF EFFECTS OF Δ^9-THC, Δ^8-THC AND 11-HYDROXY-Δ^8-THC ON NALOXONE-PRECIPITATED JUMPING BEHAVIOR IN MORPHINE-DEPENDENT MICE*

Time after administration of vehicle or cannabinoid (hr)	Naloxone ED_{50} μg/kg(95% confidence limits)						
	Vehicle	Δ^9-THC	Potency Ratio	Δ^8-THC	Potency Ratio	11-OH-Δ^8-THC	Potency Ratio
2	91.17 (53.95–154.08)	200.00 (118.34–338.00)	2.19 (1.04–4.60)†	89.09 (46.40–171.05	0.98 (0.44–2.20)	69.10 (40.89–116.78)	0.76 (0.36–1.60)
4	50.00 (29.41–85.00)	100.00 (58.80–169.00)	2.00 (0.98–4.20)†	35.36 (18.42–67.89)	0.71 (0.31–1.63)	50.00 (26.88–93.00)	1.00 (0.44–2.25)
6	23.40 (13.76–39.78)	53.40 (31.41–90.88)	2.28 (1.08–4.83)†	28.72 (13.61–60.60)	1.23 (0.50–3.01)	23.15 (12.44–43.06)	0.99 (0.44–2.23)
24	16.49 (7.82–34.79)	79.37 (51.53–122.12)	4.81 (2.05–11.30)†	23.15 (9.61–55.79)	1.40 (0.44–4.41)	21.91 (9.48–50.61)	1.32 (0.43–4.03)

*Mice were rendered dependent by morphine pellet implantation. Naloxone ED_{50}'s were determined at various times after a single injection of either the vehicle or the cannabinoid (10 mg/kg, IP). The pellets were not removed.
†$p<0.05$ vs. vehicle control.

dependent mice immediately after pellet removal suppressed the naloxone-induced abstinence jumping behavior for 24 hr. This was evident by increases in the dose of the antagonist required to elicit the jumping behavior. In an earlier study [2], it was shown that a dose of 10 mg/kg of Δ^9-THC increased the naloxone ED_{50} by 6-fold over the control values when the mice were challenged with the antagonist, 30 min after Δ^9-THC administration. At this time the withdrawal defecation and rearing behavior were also suppressed. As shown in Table 1, one hr after Δ^9-THC administration, a 10-fold increase in naloxone ED_{50} was noted. At 2 and 4 hr post Δ^9-THC administration 14- and 11-fold increases in naloxone ED_{50} over the control were noted. Thus, it appeared that the peak response of Δ^9-THC for inhibiting the jumping response was 2 to 4 hr. At 8 and 24 hr after a single injection of Δ^9-THC, a four and a five fold increase, respectively, in naloxone ED_{50} was noted. These increases seen at each time interval were significant ($p<0.05$). Forty-eight hr after the injection, the difference in naloxone ED_{50}'s of the Δ^9-THC-treated and the control group was not statistically significant. From this data, it is evident that a single injection of Δ^9-THC (10 mg/kg) was effective in suppressing the withdrawal jumping response for 24 hr. It is also of interest to note from Table 1, that the naloxone ED_{50} in the control animals appeared to decrease in the first four hr after the pellet removal. However, the values are not statistically significant. The naloxone ED_{50} values then increased rapidly at 24 and 48 hr after the pellet removal. A similar pattern of changes in ED_{50} values was also noted in animals injected with Δ^9-THC.

Withdrawal defecation was also inhibited by Δ^9-THC administration. As shown in Table 2, the number of fecal boli in Δ^9-THC-treated morphine-dependent mice was significantly smaller ($p<0.03$) for up to two hr after Δ^9-THC administration compared with the vehicle

injected dependent animals. No significant effect was observed at two or more hours after Δ^9-THC administration on the rearing behavior (Table 2).

Effect of Δ^9-THC, Δ^8-THC and 11-Hydroxy-Δ^8-THC on Morphine Abstinence in Dependent Mice with Pellets Intact

When Δ^9-THC was administered to mice 72 hr after pellet implantation with pellets intact, naloxone-induced jumping behavior was suppressed for 24 hr. The effect was, however, less pronounced when it was compared with that produced in mice from which the morphine pellets had been removed. These data depicted in Table 3, indicate that a 2-fold increase in naloxone ED_{50} was noted at 2, 4 and 6 hr after Δ^9-THC administration, whereas a 4,8-fold increase in naloxone ED_{50} was observed at 24 hr following Δ^9-THC.

Two hr after the administration of Δ^8-THC, and its 11-hydroxy derivative, the naloxone ED_{50}'s in the experimental and control groups were not significantly different. There was no indication of any delayed response either, since at all the times tasted, until 24 hr after the drug administration, the naloxone ED_{50}'s of treated groups and control groups remained identical (Table 3). The other abstinence signs, defecation and rearings, were unaffected at any of the time intervals tested by Δ^9-THC, Δ^8-THC and 11-hydroxy-Δ^8-THC, when the morphine pellets were not removed from the animals.

It should also be noted that the development of dependence was not maximal at 72 hr after the morphine pellets were implanted. This was evident by a 5-fold lower naloxone ED_{50} at 96 hr compared with 72 hr post pellet implantation.

Effect of 11-Hydroxy-Δ^8-Tetrahydrocannabinol on Jumping Induced by Amphetamine and ℓ-Dopa Combination

Pretreatment of mice with 11-hydroxy-Δ^8-THC in a dose that inhibited naloxone-induced jumping in morphine-dependent mice, did not inhibit the jumping and other behavior induced by combination of amphetamine and ℓ-dopa. Injection of 11-hydroxy-Δ^8-THC produced a very transient increase in activity followed by a slight decrease in the activity of the mice. Amphetamine administration produced hyperactivity in both the cannabinoid and vehicle injected animals. Within 2 min after ℓ-dopa injection, mice in experimental and control groups exhibited jumping behavior. When they were placed on a circular platform their jumping was so intense that handling became a problem. They were then placed in separate jars and observed for the vertical jumping behavior. There was no apparent difference in the two groups. The jumping continued for an hour in both the groups until the animals were completely exhausted.

DISCUSSION

The present studies indicate that single administration of Δ^9-THC is capable of blocking some of the signs of abstinence precipitated by naloxone in morphine-dependent mice. The stereotyped jumping behavior, which has been shown to be a highly characteristic sign of morphine abstinence in both mice [16,21] and rats [3,5], was inhibited significantly for 24 hr after a single injection of Δ^9-THC (10 mg/kg) as evidenced by the elevation in naloxone ED_{50} for the jumping response. The peak response occurred between 2 and 4 hr after Δ^9-THC administration at which time a 14-fold and an 11-fold increase, respectively, in naloxone ED_{50} were noted. Withdrawal defecation was suppressed significantly for two hr.

In our earlier studies, it was demonstrated that besides Δ^9-THC, Δ^8-THC, 11-hydroxy-Δ^8-THC, cannabidiol and cannabinol were also effective in inhibiting morphine abstinence syndrome, when the cannabinoids were administered 30 min before precipitating withdrawal with naloxone [2]. Among the cannabinoids tested cannabinol was the least active while Δ^9-THC was the most active on a molar basis. These cannabinoids were also active in suppressing the defecation and rearing behavior observed during withdrawal. In the present studies, when Δ^8-THC and its 11-hydroxy derivatives were administered two or more hr prior to naloxone challenge, a significant effect on morphine abstinence was not observed, indicating that both of these cannabinoids have shorter duration of action when compared with Δ^9-THC.

It is evident from these studies that in mice, the development of dependence on morphine was not maximal at 72 hr after morphine pellet implantation, since 96 hr after pellet implantation, the naloxone ED_{50} was 5 to 6 times lower than 72 hr post implantation. Since the naloxone ED_{50} for withdrawal jumping is inversely proportional to the degree of physical dependence [2,21], the 96 hr implanted mice were 5 times as dependent on morphine as the 72 hr implanted mice.

The degree of inhibition of morphine abstinence by Δ^9-THC was greater in morphine-dependent mice from which the pellets had been removed than in mice in which the pellets were left intact. This indicates that Δ^9-THC is more effective in suppressing morphine abstinence when it is given during the withdrawal phase than when it is given during the phase when the dependence is still developing.

The jumping syndrome in rodents can be elicited by drugs not related to narcotic analgesics [12,22], e.g., sodium 5-(1,3-dimethylbutyl)-5-ethylbarbiturate, naphthyloxyacetic acid, and combination of amphetamine and ℓ-dopa. It was of interest to find whether the suppression of naloxone-induced jumping by cannabinoids was specific or non-specific. The effect of a dose of 11-hydroxy-Δ^8-THC which suppressed the naloxone-induced jumping in morphine-dependent mice [2], was studied on jumping induced by amphetamine and ℓ-dopa combination [12]. It was found that 11-hydroxy-Δ^8-THC was ineffective in suppressing the jumping caused by amphetamine and ℓ-dopa combination. This observation would indicate that the cannabinoid effect on morphine abstinence is a specific effect.

In conclusion, it is evident that a single injection of Δ^9-THC has a long lasting inhibitory effect on morphine abstinence precipitated with naloxone. The disadvantages of methadone, propoxyphene and narcotic antagonists in the treatment of heroin abstinence, suggest the search for alternate chemotherapeutic agents. The chronic administration of Δ^9-THC has been shown not to be associated with development of any significant dependence liability as severe withdrawal phenomenon is not observed. Hence, the application of naturally occurring and/or synthetic cannabinoids may offer yet another approach for managing narcotic withdrawal syndrome.

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