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Short communication

TONIC ANALGESIC EFFECTS OF Δ^9-TETRAHYDROCANNABINOL AS MEASURED WITH THE FORMALIN TEST

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The analgesic effects of Δ^9-tetrahydrocannabinol (THC), the psychoactive component of marihuana, were tested using the formalin test. Rats were treated with either THC (5 mg/kg or 10 mg/kg) or a placebo by *gavage* 4 h before the formalin test for analgesia was initiated. THC produced a highly significant analgesic effect against both phasic pain and tonic pain. THC is discussed as a model for the development of new analgesics or as a suitable analgesic if used with another potentiating drug.

Tetrahydrocannabinol Analgesia Pain

1. Introduction

Several reports on the analgesic activity of marihuana or Δ^9-tetrahydrocannabinol (THC), the active component in marihuana, have suggested that THC has analgesic properties (cf. Buxbaum, 1972; Wilson and May, 1975). These findings have led to the study of THC and related compounds as potentiating agents in barbiturate action (Waser and Martin, 1976) and as analgesics for cancer pain (Noyes et al., 1975; Staquet et al., 1978). The results have, however, been mixed (Buxbaum, 1974; Dewey et al., 1969; Waser and Martin, 1976).

The formalin test introduced by Dubuisson and Dennis (1977) offers several important advantages over other methods of measuring analgesia. First of all, the pain stimulus is continuous over a period of an hour or more and it shows two distinct phases that appear to be a response to phasic pain immediately after the administration of the formalin and a response to tonic pain 20 or 30 min later. The response to the tonic pain probably bears a greater resemblance to clinical pain than responses to phasic pain introduced by other tests of pain and analgesia. The purpose of the present study was, therefore, to evaluate the analgesic effects of THC on phasic as well as tonic pain using the formalin test.

2. Materials and methods

Thirty male and female Holtzman albino rats (average body weight 265 ± 31 g) reared in our laboratory served as subjects. The lighting in the animal colony was regulated automatically to begin at 1900 h and terminate at 0700 h.

The (—)-trans-Δ^9-Tetrahydrocannabinol (THC), supplied by the Research Technology Branch of NIDA as a solution of 200 mg/ml in ethanol, was prepared for *gavage* by diluting this solution 1 : 20 in olive oil to produce a solution of 10 mg of THC in each mol of olive oil containing 5% ethanol. A placebo injection solution was prepared by making a solution of olive oil which contained 5% ethanol. The THC (5 mg/kg or 10 mg/kg) or the equivalent volume placebo solution was administered by *gavage* at 0900 h and the

animals were replaced in their home cages for 4 h. This procedure was used because administration by *gavage* is similar to oral administration studied in cancer pain tests and, in addition, it allows for normal absorption, metabolism, and distribution of the drug.

The formalin test was conducted 4 h after THC administration in Plexiglas observation chambers 22.8 cm square and 30.5 cm high. At the beginning of the analgesia tests, the rats were observed for a 5 min no pain baseline period and then 0.05 ml of 5% formalin was injected under the skin on the dorsal surface of one rear paw using a 25 gauge needle 16 mm in length. Although Dubuisson and Dennis (1977) used the front paw, the rear paw was used in these experiments because rats do not use their rear paws for grooming and other activities that interfere with rating pain. During the 1 h period that immediately followed the injection of the formalin, the rats were observed and rated according to a scale that is a slight modification of the scale used by Dubuisson and Dennis (1977). Pain was rated as 0 if there was no observable effect, 1 if the animal showed a slight limp or would not distribute weight equally on both rear feet, 2 if the animal lifted the injected foot off the floor but touched the floor often or held the foot loosely with only the toes touching the floor, 3 if the animal lifted the foot completely off the floor for 5 sec or longer and held the foot tightly against the abdomen, and 4 if the animal groomed the injected foot or lifted the foot and kicked. The animals were rated according to the above scale and the highest pain intensity rating observed in each 30 sec interval was assigned as the score for that interval. Six of the 30 sec intervals were averaged together to establish a score for 3 min blocks.

3. Results

The oral route of administration of THC proved to be highly effective as measured by hypothermia. There was no difference in initial body temperature between the control, 5 mg/kg THC, and the 10 mg/kg THC groups at 0900 h when the mean body temperature was 38.05° (S.E.M. = 0.1°C). By the beginning of the analgesia test 4 h later, however, there was a highly significant difference in body temperature measured by single classification analysis of variance ($F_{2,27} = 19.82$, $P < 0.01$) with the control group having a mean of 38.2° ± 0.1°C, 5 mg/kg THC group having a mean of 36.6 ± 0.5°C and the 10 mg/kg group having a mean of 34.4 ± 0.6°C. The ambient temperature was between 20 and 21°C.

Fig. 1 shows the results of THC on the pain intensity ratings for a 1 h period immediately following the injection of the formalin. These data were analyzed according to the analysis of variance model of Winer (1971) using an unweighted means solution for unequal group sizes. This analysis showed that the effect of THC was highly significant ($F_{2,27} = 18.98$, $P < 0.001$), there was a highly significant

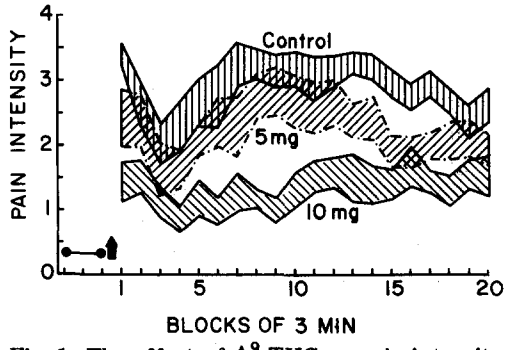

Fig. 1. The effect of Δ^9-THC on pain intensity ratings for 1 h after the injection of 0.05 ml of 5% formalin under the dorsal skin of one rear paw. The higher the numerical value of the pain intensity rating, the greater the pain response. The curves plotted represent the mean for each point plus and minus one standard error of the mean. The pain response of the control group is represented by the top line (n = 10), the response of the 5 mg/kg THC group is represented by the second line (n = 8), and the response of the 10 mg/kg THC group is represented by the bottom line (n = 12). The formalin was injected at the arrow and the line on the left represents the 5 min baseline period (no pain).

change in pain intensity ratings over time ($F_{19,513} = 3.579$, $P < 0.01$), and there was no significant interaction between drug dose and pain intensity with time ($F_{38,513} = 1.19$).

4. Discussion

The results presented in fig. 1 show that THC produces analgesia against both phasic and tonic pain that may be similar to some types of clinical pain. The analgesic effects of THC on tonic pain was still clearly evident even at the end of the one hour test. The doses required to produce the analgesic effect are, however, probably too high to be of therapeutic value because of the side effects observed at 15 to 20 mg given orally to humans (Noyes et al., 1975: Staquet et al., 1978). Because THC does not appear to have the addicting effect of some analgesics, it may serve as a model drug for further development of analgesics or THC may prove to have therapeutic value as an analgesic if it is used in conjunction with another analgesic or an analgesic potentiating agent.

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