

Permissive Role of Dopamine D₂ Receptors in the Hypothermia Induced by Δ^9 -Tetrahydrocannabinol in Rats

FELICE NAVA, GIOVANNA CARTA AND GIAN LUIGI GESSA

Department of Neuroscience B.B. Brodie, University of Cagliari and Neuroscience S.c.a.r.l., Cagliari, Italy

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NAVA, F., G. CARTA AND G. L. GESSA. *Permissive role of dopamine D₂ receptors in the hypothermia induced by Δ^9 -tetrahydrocannabinol*. PHARMACOL BIOCHEM BEHAV 66(1) 183–187, 2000.—Cannabinoids produce analgesia, hypomotility, catalepsy, cognitive deficits and positive reinforcement. Moreover, Δ^9 -tetrahydrocannabinol (Δ^9 -THC) and synthetic cannabinoids stimulate dopaminergic neurons and increase dopamine release in different brain areas. In order to clarify the role of endogenously released dopamine in the hypothermic response to cannabinoids, the effect of D₁ and D₂ dopamine receptor agonists and antagonists on Δ^9 -THC-induced hypothermia was studied in rats. Δ^9 -THC (2.5 and 5 mg/kg intraperitoneally [IP]) decreased body temperature in a dose-related manner. This effect was antagonized not only as expected by the CB₁ cannabinoid receptor antagonist SR 141716A (0.5 mg/kg, IP) but also, unexpectedly, by the dopaminergic D₂ receptor antagonists S(-)-sulpiride (5 and 10 mg/kg, IP) and S(-)-raclopride (1 and 3 mg/kg, IP). Conversely, the hypothermic effect of Δ^9 -tetrahydrocannabinol was potentiated by the D₂ dopamine receptor agonists (-)-quinpirole (0.025 and 0.500 mg/kg, SC) and (+)-bromocriptine (0.5 and 1 mg/kg, IP). In contrast, the Δ^9 -THC-induced hypothermic effect was not modified by either by the D₁ dopamine agonist SKF 38393 (10 mg/kg SC) or by the D₁ dopamine antagonist SCH 23390 (0.5 mg/kg SC). These results suggest that the D₂ dopamine receptors have a permissive role in the hypothermic action of cannabinoids. © 2000 Elsevier Science Inc.

Δ^9 -Tetrahydrocannabinol D₂ dopamine receptors CB₁ cannabinoid receptors Body temperature

CANNABINOIDS produce a large number of effects including analgesia (5,21), hypomotility (5,6), catalepsy (5,24), cognitive deficits (17) and positive reinforcement (13). Moreover, Δ^9 -tetrahydrocannabinol (Δ^9 -THC), the major psychoactive constituent of *Cannabis sativa*, has been shown to decrease body temperature by acting centrally (7,10–12,19). This effect is blocked by the CB₁ cannabinoid receptor antagonist SR 141716A, indicating a CB₁ cannabinoid receptor mediated response (5,19).

Evidence that cannabinoids also stimulate dopamine neurons (8,14) and increase dopamine release in different brain areas (2,3), has been reported, suggesting that endogenously released dopamine may play a role on the hypothermic response. Accordingly, previous observations have suggested that brain dopamine plays an important role in the central regulation of body temperature in rats (9,26,27). In fact, the D₂ dopamine receptor agonists (-)-quinpirole (4,18,26,27) and

(+)-bromocriptine (22) have been shown to reduce body temperature in rodents, an effect blocked by the D₂ dopamine receptor antagonists (4,29). On the other hand, the D₁ dopamine receptor agonist SKF 38393 has been shown to increase body temperature in rats (18).

The purpose of the present study was to examine the role of dopamine in the hypothermic effect induced by Δ^9 -THC. To this aim, the effects of the previously mentioned D₁ and D₂ dopamine receptor agonists and antagonists on Δ^9 -THC-induced hypothermia were analyzed.

METHOD

Animals

Male Sprague-Dawley rats weighing 125 to 150 g were used (Charles River, Calco, Como, Italy). Prior to experiments they were housed in group cages and kept at a temper-

ature of $22^\circ \pm 1^\circ\text{C}$ at 55% of humidity. Food and water were freely available and animals were maintained under an artificial 12/12 h light/dark schedule with light on from 0800 to 2000 h.

The experiments were carried out in accord to the recommendations of the declaration of Helsinki and to the European Communities Council Directive of 24 November 1986 (86/609/ECC).

Experimental Procedure

Different groups of rats (each $n = 6$) were treated with Δ^9 -THC, the CB_1 antagonist SR 141716A, and the D_2 dopamine agonists, as specified in the results.

Control rats received the proper vehicle. Each animal was used only once.

Rectal Temperature

Rectal temperature was measured using a digital laboratory thermometer (Physitemp, BAT-12). The probe was inserted into the animal's rectum to a constant depth of 4 cm and removed after each reading. Temperature was recorded before pretreatments, immediately prior to and 30, 60, 90, 120, and 150 min after drug treatments. The data reported are referred as a change in temperature from that recorded prior to drug treatment. In each group of rats rectal temperature was measured between 1000 and 1100 h at a room temperature of $22^\circ \pm 1^\circ\text{C}$.

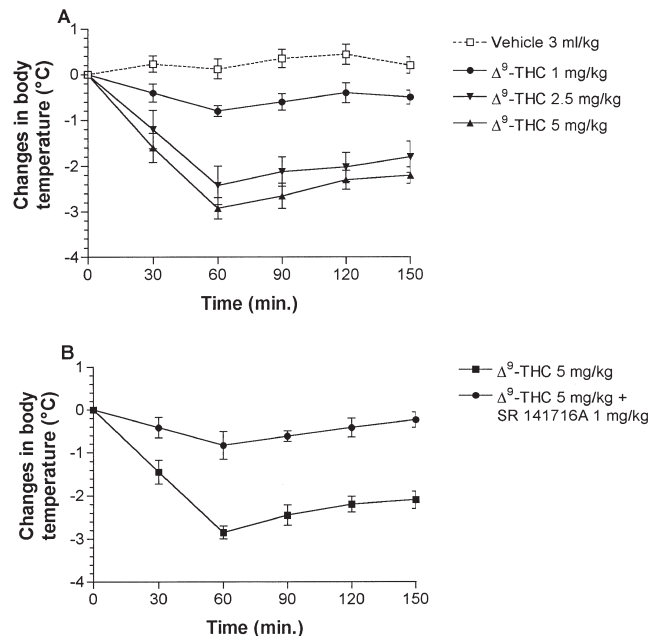


FIG. 1. Hypothermic effect induced by Δ^9 -THC (A) and reversal by SR 141716A (B). SR 141716A was given 20 min after Δ^9 -tetrahydrocannabinol. The Δ^9 -THC dose of 1 mg/kg had no effect. Data are expressed as a change in temperature from that recorded immediately prior to Δ^9 -THC or vehicle administration (at $t = 0$). (ANOVA main effect Δ^9 -THC 1 mg/kg $F(5, 30) = 2.70$; $p > 0.05$; ANOVA main effect Δ^9 -THC 2.5 mg/kg $F(5, 30) = 6.78$; $p < 0.001$; ANOVA main effect Δ^9 -THC 5 mg/kg $F(5, 30) = 21.24$; $p < 0.001$; ANOVA main effect Δ^9 -THC 5 mg/kg + SR 141716A $F(5, 30) = 2.18$; $p > 0.05$).

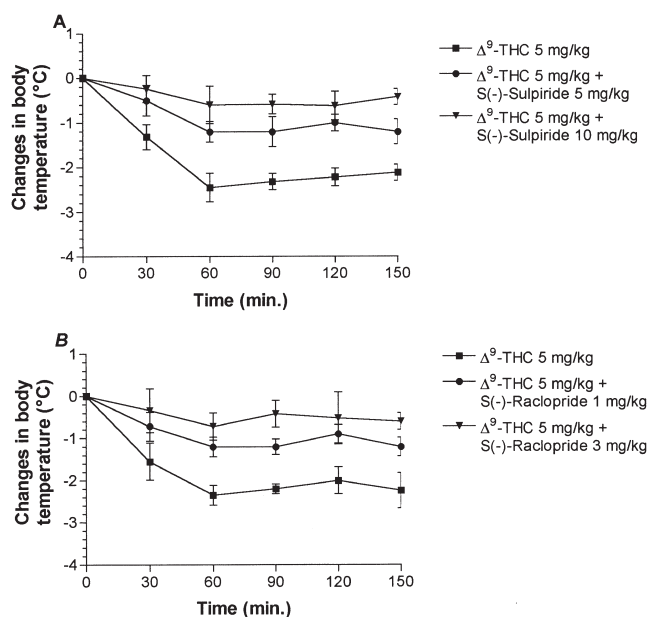


FIG. 2. Blockade of the hypothermic effects of Δ^9 -THC by S(-)-sulpiride (A), and S(-)-raclopride (B). D_2 dopamine antagonists were given 20 min after Δ^9 -THC. Data are expressed as a change in temperature from that recorded immediately prior to drug administration (at $t = 0$). (ANOVA main effect Δ^9 -THC 5 mg/kg + S(-)-sulpiride 5 mg/kg $F(5, 30) = 3.71$; $p > 0.05$; ANOVA main effect Δ^9 -THC 5 mg/kg + S(-)-sulpiride 10 mg/kg $F(5, 30) = 0.81$; $p > 0.05$; ANOVA main effect Δ^9 -THC 5 mg/kg + S(-)-raclopride 1 mg/kg $F(5, 30) = 4.26$; $p > 0.05$; ANOVA main effect Δ^9 -THC 5 mg/kg + S(-)-raclopride 3 mg/kg $F(5, 30) = 0.81$; $p > 0.05$).

Drugs

Δ^9 -Tetrahydrocannabinol (RBI, Italy) solutions were prepared from vials containing 10 mg of the drug in 1 ml of absolute ethanol. Vials were evaporated under nitrogen and the residue dissolved in two drops of Tween 80 and then diluted in saline. The specific CB_1 cannabinoid receptor antagonist SR 141716A (Sanofi Recherche, Montpellier, France) was dissolved in two drops of Tween 80 and then diluted in saline. The D_2 dopamine receptor antagonists S(-)-sulpiride (RBI, Italy) and S(-)-raclopride (RBI, Italy), the D_2 dopamine receptor agonists (-)-quinpirole (RBI, Italy) and (+)-bromocriptine (RBI, Italy), the D_1 dopamine agonist SKF 38393 (RBI, Italy) and the D_1 dopamine antagonist SCH 23390 (RBI, Italy) were dissolved in saline.

Δ^9 -Tetrahydrocannabinol, SR 141716A, S(-)-sulpiride and S(-)-raclopride were administered intraperitoneally (IP) in a volume of 3 ml/kg, while (-)-quinpirole, SKF 38393 and SCH 23390 were given subcutaneously (SC) in a volume of 2 ml/kg. Control rats were treated with vehicle used to dissolve the active ingredient.

Statistical Analysis of Data

When comparing pretreatment or post-treatment values plus Δ^9 -THC or vehicle, a ANOVA for repeated measures was used. When values were found to be significant ($p < 0.01$), the Student Newman-Keuls multi comparison test was used to determine differences between treatment groups and level of significance.

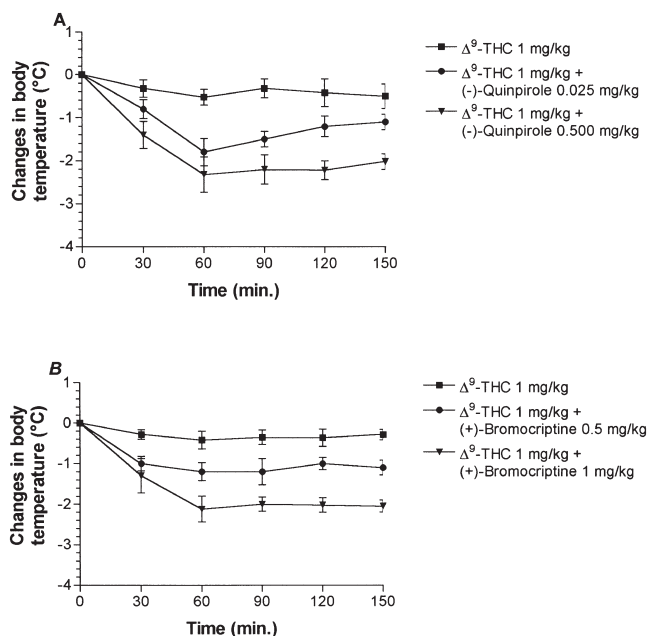


FIG. 3. Potentiation of the hypothermic effects of Δ^9 -tetrahydrocannabinol by (-)-quinpirole (A), and (+)-bromocriptine (B). The D₂ dopamine agonists were co-administered with Δ^9 -THC. Data are expressed as a change in temperature from that recorded immediately prior to Δ^9 -THC or vehicle administration (at $t = 0$). (ANOVA main effect Δ^9 -THC 1 mg/kg + (-)-quinpirole 0.025 mg/kg $F(5, 30) = 8.57$; $p < 0.001$; ANOVA main effect Δ^9 -THC 1 mg/kg + (-)-quinpirole 0.500 mg/kg $F(5, 30) = 10.19$; $p < 0.001$; ANOVA main effect Δ^9 -THC 1 mg/kg + (+)-bromocriptine 0.5 mg/kg $F(5, 30) = 5.28$; $p < 0.001$; ANOVA main effect Δ^9 -THC 1 mg/kg + (+)-bromocriptine 1 mg/kg $F(5, 30) = 43.13$; $p < 0.001$).

RESULTS

The administration of Δ^9 -THC caused a dose-dependent reduction in body temperature (Fig. 1). The maximum decrease obtained at doses of 2.5 and 5 mg/kg, respectively was 2.42 ± 0.42 and $2.92 \pm 0.24^\circ\text{C}$, and occurred 60 min after treatment. The dose of 1 mg/kg had no effect (Fig. 1). As expected, and consistent with previous results (19), the hypothermic response to Δ^9 -Tetrahydrocannabinol (5 mg/kg) was totally antagonized by the CB₁ cannabinoid receptor antagonist SR 141716A (0.5 mg/kg), given 20 min after the cannabinoid (Fig. 1). However, unexpectedly Δ^9 -Tetrahydrocannabinol effect was also antagonized by the D₂ dopamine receptor antagonist S(-)-sulpiride (5 and 10 mg/kg) and S(-)-raclopride (1 and 3 mg/kg), both given 20 min after cannabinoid, suggesting that the activation of D₂ dopamine receptors is necessary for Δ^9 -THC-induced hypothermia to occur (Fig. 2). To verify the above hypothesis the effect of the D₂ dopamine receptor agonist (-)-quinpirole or (+)-bromocriptine on Δ^9 -THC hypothermia, was investigated. As shown in Fig. 3, the administration of (-)-quinpirole (0.025 and 0.500 mg/kg) or (+)-bromocriptine (0.5 and 1 mg/kg), significantly potentiated the hypothermic effect of an ineffective dose of Δ^9 -THC (1 mg/kg).

The hypothermia produced by the combination of Δ^9 -THC with (-)-quinpirole or (+)-bromocriptine was totally antagonized by SR 141716A (0.5 mg/kg) (Fig. 4), S(-)-sulpiride (10 mg/kg) (Fig. 4) and S(-)-raclopride (3 mg/kg) (Fig. 4). When given alone at the doses reported above, the CB₁ cannabinoid

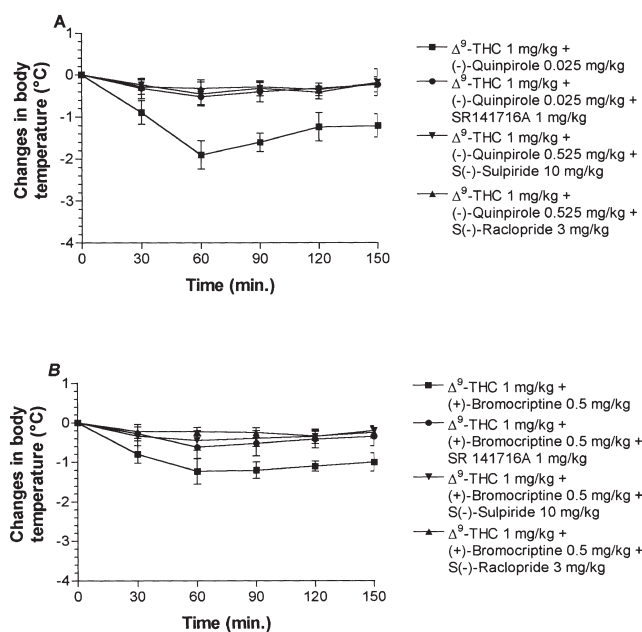


FIG. 4. Reversal by SR 141716A, S(-)-sulpiride or S(-)-raclopride of the hypothermic effect induced by the combination of Δ^9 -THC with (-)-quinpirole (A) or (+)-bromocriptine (B). Antagonists were given 20 min after Δ^9 -THC. Data are expressed as a change in temperature from that recorded immediately prior to drug administration (at $t = 0$). (ANOVA main effect Δ^9 -THC + (-)-quinpirole + SR 141716A $F(5, 30) = 0.95$; $p > 0.05$; ANOVA main effect Δ^9 -THC + (-)-quinpirole + S(-)-sulpiride $F(5, 30) = 0.65$; $p > 0.05$; ANOVA main effect Δ^9 -THC + (-)-quinpirole + S(-)-raclopride $F(5, 30) = 0.84$; $p > 0.05$; ANOVA main effect Δ^9 -THC + (+)-bromocriptine + SR 141716A $F(5, 30) = 0.91$; $p > 0.05$; ANOVA main effect Δ^9 -THC + (+)-bromocriptine + S(-)-sulpiride $F(5, 30) = 0.82$; $p > 0.05$; ANOVA main effect Δ^9 -THC + (+)-bromocriptine + S(-)-raclopride $F(5, 30) = 1.05$; $p > 0.05$).

antagonist, as well as the D₂ dopamine agonists and antagonists, did not significantly modify body temperature (data not shown).

In contrast to results obtained with the dopamine D₂ agonists and antagonists, the hypothermic effect of Δ^9 -THC was modified neither by the dopamine D₁ agonist SKF 38393 (10 mg/kg), nor by the dopamine D₁ antagonist SCH 23390 (0.5 mg/kg) (Fig. 5). These compounds, when given alone at the doses used, failed to modify significantly body temperature (data not shown).

DISCUSSION

The results of the present study confirm previous observations showing that Δ^9 -THC reduces body temperature (7,10–12,19) and that this effect is reversed by the CB₁ cannabinoid receptor antagonist SR 141716A (5,19). Moreover, our results indicate that Δ^9 -THC-induced hypothermia is antagonized by the D₂ dopamine receptor antagonists S(-)-sulpiride and S(-)-raclopride and, conversely, is potentiated by the D₂ dopamine receptor agonists (-)-quinpirole and (+)-bromocriptine. When given alone at doses that modify Δ^9 -THC action, the dopamine agonists and antagonists failed to modify body temperature, suggesting that the sole stimulation of the dopamine receptors is not sufficient to induce significant changes in rectal temperature. Moreover, the marked hypo-

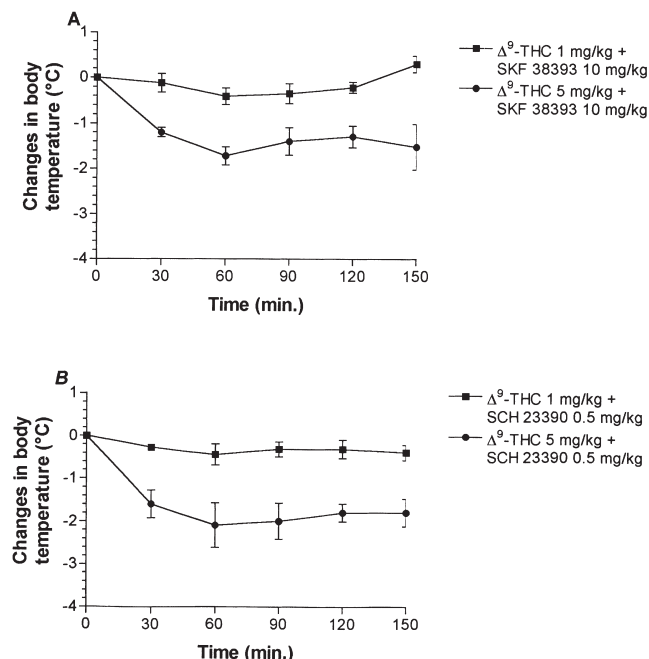


FIG. 5. Lack of effect by SKF 38393 (A) or SCH 23390 (B) on Δ^9 -THC hypothermic effects. The D_1 dopamine agonist or antagonist was given 20 min after Δ^9 -THC. Data are expressed as a change in temperature from that recorded immediately prior to drug administration (at $t = 0$). (ANOVA main effect Δ^9 -THC + SKF 38393 $F(5, 30) = 0.95$; $p > 0.05$; ANOVA main effect Δ^9 -THC + SCH 23390 $F(5, 30) = 1.05$; $p > 0.05$).

thermia produced by the combination of Δ^9 -THC and (-)-quinpirole or (+)-bromocriptine was antagonized both by the CB_1 cannabinoid receptor antagonist SR 141716A and the D_2 dopamine receptor antagonists S(-)-sulpiride and S(-)-raclopride, indicating that both receptors are implicated in Δ^9 -THC hypothermia.

These results suggest that the stimulation of the D_2 dopamine receptors enables hypothermia induced by Δ^9 -THC, and indicate that Δ^9 -THC response is mediated by the concomitant activation of both CB_1 cannabinoid and D_2 dopamine receptors, the latter being activated by dopamine endogenously released by Δ^9 -THC. On the other hand, the stimulation of either receptor alone is insufficient to produce the hypothermic response. Unlike D_2 dopamine receptors, D_1 dopamine receptors do not seem to be involved in the hypothermia induced by Δ^9 -THC. In fact, neither the D_1 dopamine

receptor agonist SKF 38393 nor the D_1 dopamine receptor antagonist SCH 23390 modified Δ^9 -THC-induced hypothermia. Taken together these findings suggest that the activation of D_2 but not of D_1 dopamine receptors are necessary for Δ^9 -THC-induced hypothermia to occur. Recently Giuffrida et al. (15) have provided evidence for an interaction between the endogenous cannabinoid anandamide and dopamine. They have shown that the activation of the D_2 dopamine receptors with (-)-quinpirole increases anandamide release in the striatum and that retreatment with SR 141716A potentiates (-)-quinpirole induced stimulation of motor activity. The two hypotheses are not alternative. Specifically, we hypothesized that Δ^9 -THC releases dopamine and the action of this neurotransmitter on dopamine D_2 receptors is essential for the actions induced by cannabinoids. Neither the brain site(s) where dopaminergic and cannabinoid interaction takes place, nor the mechanism involved in such interaction have yet been determined. Both CB_1 cannabinoid and D_2 dopamine receptors are present in hypothalamic structures controlling body temperature (1,20), suggesting that this brain area might be the site involved in cannabinoidergic and dopaminergic interaction.

Furthermore, the mechanism through which the stimulation of D_2 dopamine receptor stimulation enables the action of Δ^9 -THC is not clear. Because CB_1 cannabinoid and D_2 dopamine receptors may be coupled to an adenylate cyclase via pertussis toxin-sensitive G-protein (23,28) and may be co-localized in the same brain areas (23,28), it might be suggested that the concomitant activation of both receptors would result in a degree of cyclic AMP inhibition needed for eliciting Δ^9 -THC response. However, a recent observation by Glass and Felder (16) might offer an alternative explanation for the molecular mechanisms involved. In primary cultures of striatal neurons, these authors found that the concomitant stimulation of CB_1 cannabinoid and D_2 dopamine receptors resulted in the accumulation of cellular cyclic AMP, in contrast to the decrease normally observed with activation of either receptor alone. In line with this hypothesis we might suggest that in vivo Δ^9 -THC, by activating dopamine neurons (8,14) and releasing dopamine (2,3), might stimulate both CB_1 cannabinoid and D_2 dopamine receptors. The concurrent activation of both receptors might produce an accumulation of cellular cyclic AMP in neurons where these receptors are co-localized (25). However, our results do not exclude an involvement of other neurotransmitters such as serotonin in the hypothermic action of cannabinoids as suggested by different investigations (10,11,19).

Experiments in progress in our laboratory indicate that different Δ^9 -THC effects including amnesia and analgesia are also suppressed by the D_2 dopamine receptor antagonists, suggesting that D_2 dopamine receptors may play permissive a role in the actions of cannabinoids.

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