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SR 141716A, a cannabinoid receptor antagonist, produces hyperalgesia in untreated mice

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Abstract

Antinociceptive effects of cannabinoids are well documented. However, the physiological role of endogenous cannabinoids in nociception is unknown. We evaluated the effects of the cannabinoid receptor antagonist SR 141716A (*N*-piperidino-5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-4-methyl-3-pyrazolecarboxamide) on mouse hot plate latencies. Intrathecal injection of SR 141716A evoked a significant thermal hyperalgesia. These results suggest that the cannabinoid system tonically regulates thermal nociceptive thresholds. Furthermore, the absence of this regulation results in hyperalgesia suggesting that hypoactivity of this system may be involved in certain types of chronic pain.

Keywords: Cannabinoid; Hyperalgesia; Pain

Marijuana's mechanism of action has been the subject of much controversy. Recently, two G protein-coupled cannabinoid receptor subtypes were cloned (Matsuda et al., 1990; Munro et al., 1993). Activation of the cannabinoid receptor results in an inhibition of adenylyl cyclase activity (Howlett and Fleming, 1984), closing of certain Ca^{2+} channels (Mackie and Hille, 1992), and opening of certain K^+ channels (Deadwyler et al., 1993).

Cannabinoids induce antinociception when injected into areas associated with transmission of nociceptive information, e.g. spinal cord, dorsal raphe nucleus, and periaqueductal gray (Martin et al., 1995). Although these and other data indicate that exogenous cannabinoids increase nociceptive thresholds, the physiological role of the endogenous cannabinoid system in modulating tonic nociceptive thresholds has not been determined. The recent development of the cannabinoid receptor antagonist, SR 141716A (*N*-piperidino-5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-4-methyl-3-pyrazolecarboxamide), enables us to evaluate this important question. In the present study we evaluated whether the cannabinoid system tonically modulates thermal nociceptive thresholds.

Male Swiss-Webster mice (15–25 g, Harlan, Madison, WI, USA) were housed with a 12 h light/dark cycle and received food and water ad libitum. All procedures were approved by the Animal Care and Use Committee at the University of Minnesota. Baseline hot plate latencies (54°C, Harvard Hot-Plate Analgesia Meter, Edenbridge, KY, USA) were determined in triplicate by measuring the time for the animal to either lick its hind paw or jump from the hot plate surface. Average baseline latencies were 18.7 ± 0.7 s for the saline group and 18.6 ± 0.4 s for the SR 141716A group. Animals next received a 5 μl intrathecal injection of either saline or the cannabinoid receptor antagonist SR 141716A (0.005 fmol, a gift from Sanofi Recherché, France). Five minutes after injection, hot plate latencies were again recorded. The hot plate observer was blind to treatment allocations.

As illustrated in Fig. 1, animals receiving an intrathecal injection of SR 141716A demonstrated significant hyperalgesia when compared with animals receiving the saline vehicle (-6.34 ± 0.72 s vs. -1.17 ± 1.18 s, $P < 0.005$). This effect was transient, dose-related, and not associated with altered locomotor activity (unpublished observation). There were no other obvious differences between the two groups in their behaviors prior to or after the hot plate trial.

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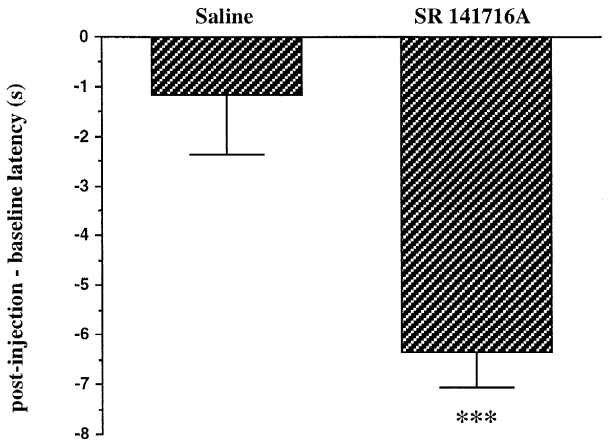

Fig. 1. Effect of SR 141716A or saline on hot plate latencies 5 min after intrathecal injection. After baseline latencies were recorded in triplicate, animals received an intrathecal injection of 0.005 fmol SR 141716A ($n = 34$) or saline ($n = 23$) in a 5 μl volume. Five minutes after drug administration, hot plate latencies were again recorded. Animals receiving an intrathecal injection of SR 141716A demonstrated hyperalgesia when compared with those receiving an intrathecal injection of saline ($P <$ 0.005, Student's two-tailed *t*-test).

The effect of SR 141716A is most likely mediated by its actions at the cannabinoid receptor for the following reasons. SR 141716A is selective for the cannabinoid receptor demonstrating a 100-fold higher affinity at the cannabinoid receptor as compared to more than 30 other receptors (Rinaldi-Carmona et al., 1994). Additionally, the K_d for SR 141716A has been reported to be 10 nM. The concentration which was injected in this study (0.005 fmol/5 μl, i.e., 1 pM) is a fraction of the K_d making it unlikely that the effects of SR 141716A are mediated by nonspecific actions at other receptors. These results suggest that the cannabinoid system tonically regulates thermal nociceptive thresholds. The absence of such regulation results in hyperalgesia.

Tonic activation of the cannabinoid system has been reported in other systems. SR 141716A reduces memory deficits in aged rats and mice as well as improves social recognition in adult rats (Terranove et al., 1996). The effects of SR 141716A may be due to the inhibition of the actions of tonically released endogenous cannabinoids. Alternatively, it is possible that SR 141716A acts as an inverse agonist to suppress spontaneous activity of the cannabinoid receptor at the G protein. However, such activity is not well documented for G protein-coupled receptors in vivo.

Many of the properties associated with the cannabinoid receptor are similar to those of opioid receptors. They are both seven transmembrane receptors coupled to G_i/G_o proteins. Activation at these receptors has been reported to lead to a decrease in cAMP levels, closing of certain Ca^{2+} channels, and opening of certain K^+ channels. Behaviorally, both compounds have been reported to result in antinociception in animals and analgesia in humans. However, the two systems diverge when it comes to tonic activation. Whereas our data supports a tonic activation of the cannabinoid system, the endogenous opioid system is inactive under tonic conditions. Thus, it is possible that some forms of opioid-resistant pain may be sensitive to treatment with cannabinoids. Furthermore, hypoactivity of the cannabinoid system may be involved in the etiology of certain types of pain.

Acknowledgements

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