Available online at www.sciencedirect.com
SCIENCE DIRECT
European Journal of Pharmacology 527 (2005) 172–174
www.elsevier.com/locate/ejphar

Rapid communication

Cannabinoid CB_2 receptor agonist activity in the hindpaw incision model of postoperative pain

Christopher J. LaBuda *, Michael Koblish, Patrick J. Little

Adolor Corporation, Department of Pharmacology, 700 Pennsylvania Drive, Exton, PA 19341, USA

Received 10 October 2005; accepted 18 October 2005

Abstract

The identification of peripherally expressed CB_2 receptors and reports that the selective activation of cannabinoid CB_2 receptors produces antinociception without traditional cannabinergic side effects suggests that selective cannabinoid CB_2 receptor agonists might be useful in the management of pain. In a rat hindpaw incision model, we examined the antiallodynic activity of the selective cannabinoid CB_2 receptor agonists AM1241 (3–30 mg/kg i.p.), GW405833 (3–30 mg/kg i.p.), and HU-308 (0.3–30 mg/kg i.p.). The rank order for efficacy in the hindpaw incision model following a dose of 10 mg/kg, i.p. was AM1241 > GW405833 = HU-308, and the selective cannabinoid CB_2 receptor antagonist, SR144528, reversed the antiallodynic effect of HU-308. Together, these data suggest that selective cannabinoid CB_2 receptor agonists might represent a new class of postoperative analgesics.

Keywords: Cannabinoid; Postoperative pain; Tactile allodynia

Selective activation of the cannabinoid CB_2 receptor produces antinociception in rodent models of arthritis, inflammation and neuropathy that is not accompanied by traditional cannabinoid-mediated side effects such as sedation, catalepsy, or hypothermia (Hanus et al., 1999; Ibrahim et al., 2003). Although the utility of selective cannabinoid CB_2 receptor agonists for the management of postoperative pain remains unclear, it was hypothesized that the selective activation of cannabinoid CB_2 receptors might produce antiallodynic activity in a rodent model of post-incisional pain.

All rodent housing conditions and experimental procedures were performed in accordance with the ethical guidelines of the IASP and the Adolor Corporation Institutional Animal Care and Use Committee. Incisional pain was produced by an incision in the plantar surface of the left hindpaw of male Sprague–Dawley rats (120–150 g, Harlan Laboratories, Columbus, OH) as described by Brennan et al. (1996). Twenty-four hours after hindpaw incision, animals received vehicle, (2-iodo-5-nitrophenyl)-[1-(1-methyl-piperidin-2-ylmethyl)-1H-indol-3-yl]-methanone (AM1241) (3, 10 and 30 mg/kg), 1-(2,3-Dichlorobenzoyl)-5-methoxy-2-methyl-(2-(morpholin-4-yl)ethyl)-1H-indole (GW405833) (3, 10 and 30 mg/kg), or {4-[4-(1,1-dimethylheptyl)-2,6-dimethoxy-phenyl]-6.6-dimethyl-bicyclo [3.1.1]hept-2-en-2-yl}-methanol (HU-308) (0.3, 3, 10 and 30 mg/kg). In a separate group of animals, vehicle or the cannabinoid CB_2 receptor antagonist *N*-[(1S)-endo-1,3,3-trimethyl bicycle [2.2.1] heptan-2-yl]-5-(4-chloro-3-methylphenyl)-1-(4-methylbenzyl)-pyrazole-3-carboxamide (SR144528) (3 mg/kg) was given 15 min before vehicle or HU-308 (30 mg/kg, i.p.). AM1241, GW405833, and SR144528 were synthesized at Adolor Corporation, and HU-308 was purchased from Cayman Chemical (Ann Arbor, MI). All compounds were dissolved in 5% ethanol, 1% cremophor and 94% sterile water for injection, and delivered i.p. in a volume of 1 ml/kg. Sixty minutes after cannabinoid CB_2 receptor agonist treatment, animals were tested for tactile hypersensitivity using von Frey monofilaments. Measurements of tactile sensitivity for each hindpaw were obtained using the up/down method as described previously (LaBuda and Little, 2005) with a series of seven von Frey monofilaments (1, 2, 4, 8, 10, 15 and 26 g).

There was a significant main effect of group for animals that received treatment with AM1241, GW405833, and HU-308

* Corresponding author. Tel.: +1 484 595 1972; fax: +1 484 595 1551.
E-mail address: clabuda@adolor.com (C.J. LaBuda).

0014-2999/$ - see front matter © 2005 Elsevier B.V. All rights reserved.
doi:10.1016/j.ejphar.2005.10.020

at 24 h after hindpaw incision or sham surgery (F 3,29=14.69, $P<0.0001$, F 3,20=6.31, $P<0.005$, and F 4,27=14.23, $P<0.0001$, respectively). As illustrated in Fig. 1, tactile allodynia resulting from hindpaw incision was significantly attenuated by the 10 and 30 mg/kg doses of AM1241, the 30 mg/kg dose of GW405833, and the 30 mg/kg dose of HU-308. The antiallodynic effect produced by a dose of 30 mg/kg of HU-308 was attenuated (99% antagonism) by the pretreatment with the selective cannabinoid CB_2 receptor antagonist SR144528 (inset Fig. 1).

There is only one study that systematically examined the analgesic activity of cannabinoids in the management of clinical postoperative pain, and in this study it was concluded that there was no analgesic activity for Δ^9-tetrahydrocannabinol in abdominal hysterectomy patients (Buggy et al., 2003). However, the administration of GW405833 (10 mg/kg, i.p.) to rats with a hindpaw incision produced a maximum percent reversal of mechanical hyperalgesia of 64% (Valenzano et al., 2005). The antiallodynic effect of GW405833 in the present experiment extends the results obtained from Valenzano et al. (2005) in the hindpaw incision model. Although it is unclear whether the selective activation of cannabinoid CB_2 receptors would have significant clinical analgesic activity following surgery, the results of the present study and the results from Valenzano et al. (2005) provide evidence that selective cannabinoid CB_2 receptor agonists show robust antinociceptive activity in preclinical models of incisional pain.

The magnitude of the antiallodynic effect produced by the administration of the selective cannabinoid CB_2 receptor agonists AM1241 (82-fold selective for the cannabinoid CB_2 receptor, Ibrahim et al., 2003), GW405833 (78-fold selective, Valenzano et al., 2005), and HU-308 (430-fold selective, Hanus et al., 1999) in the hindpaw incision model was similar to the analgesic effects reported in incisional or neuropathic pain models after the treatment with morphine and indomethacin (Hanus et al., 1999; Ibrahim et al., 2003; LaBuda and Little, 2005; Valenzano et al., 2005). In addition, the antiallodynic effect produced by the administration of HU-308 was blocked by pretreatment with SR144528, a selective cannabinoid CB_2 receptor antagonist (inset Fig. 1). These findings suggest that cannabinoid CB_2 receptor agonists devoid of central nervous system activity might be useful for the management of postoperative pain.

In the present experiment, the selective cannabinoid CB_2 receptor agonists, AM1241, GW405833, and HU-308 produced robust antiallodynic effects in the hindpaw incision model of postoperative pain. Although a central involvement of cannabinoid CB_2 receptor agonists cannot be excluded, it is most likely that cannabinoid CB_2 receptor agonists produce antiallodynic effects by inhibiting primary afferent fiber hyperactivity or by inhibiting the release of agents that act directly on nociceptors or primary afferent fibers (Ibrahim et al., 2003). These results provide support for the hypothesis that a cannabinoid-mediated analgesia can be achieved in the absence of psychoactive side effects and also support the development of cannabinoid CB_2 receptor agonists for the management of postoperative pain.

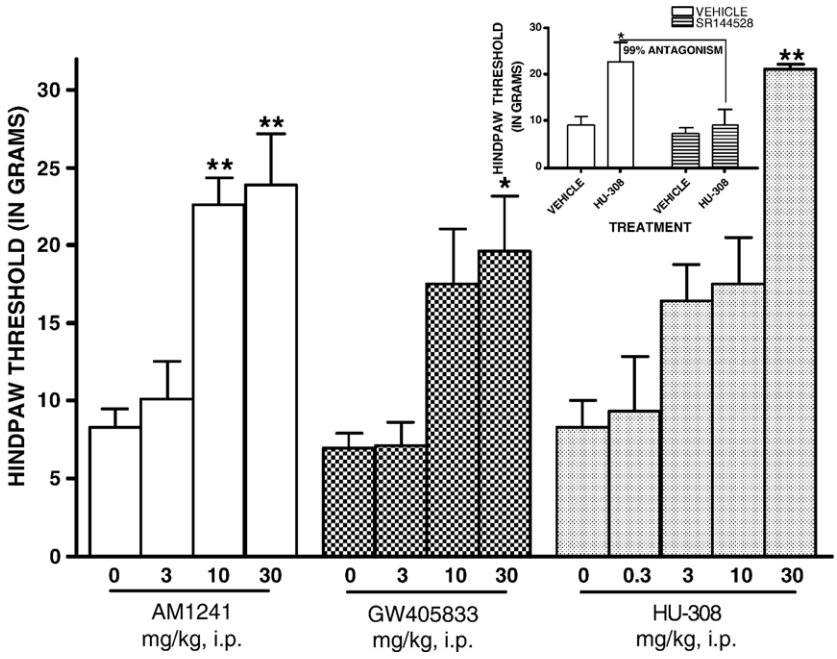

Fig. 1. Threshold to hindpaw tactile stimulation 24 h after surgical incision and following treatment with vehicle, AM1241, GW405833, or HU-308 (in mg/kg i.p.). Tactile sensitivity for the incised hindpaw after treatment with test compounds was analyzed using a one-way ANOVA for each compound followed by post hoc comparisons (Tukey test) for group differences. Statistical significance was set at $P<0.05$ for all analyses. The inset shows that the antiallodynic effect produced by a dose of 30 mg/kg of HU-308 was completely blocked (99% antagonism) by the pretreatment with the cannabinoid CB_2 receptor antagonist SR144528 (3 mg/kg i.p.). Data are plotted as the mean±SEM withdrawal threshold of the incised hindpaw. *$P<0.05$ compared to respective hindpaw incision, vehicle-treated animals; **$P<0.001$ compared to respective hindpaw incision, vehicle-treated animals.

References

Brennan, T.J., Vandermeulen, E.P., Gebhart, G.F., 1996. Characterization of a rat model of incisional pain. Pain 64, 493–501.

Buggy, D.J., Toogood, L., Maric, S., Sharpe, P., Lambert, D.G., Rowbotham, D. J., 2003. Lack of analgesic efficacy of oral δ-9-tetrahydrocannabinol in postoperative pain. Pain 106, 169–172.

Hanus, L., Breuer, A., Tchilibon, S., Shiloah, S., Goldenberg, D., Horowitz, M., Pertwee, R.G., Ross, R.A., Mechoulam, R., Fride, E., 1999. HU-308: a specific agonist for CB_2, a peripheral cannabinoid receptor. Proc. Natl. Acad. Sci. U. S. A. 96, 14228–14233.

Ibrahim, M.M., Deng, H., Zvonok, A., Cockayne, D.A., Kwan, J., Mata, H.P., Vanderah, T.W., Lai, J., Porreca, F., Makriyannia, A., Malan, T.P., 2003. Activation of CB2 cannabinoid receptors by AM1241 inhibits experimental neuropathic pain: pain inhibition by receptors not present in the CNS. Proc. Natl. Acad. Sci. U. S. A. 100, 10529–10533.

LaBuda, C.J., Little, P.J., 2005. Pharmacological evaluation of the selective spinal nerve ligation model of neuropathic pain in the rat. J. Neurosci. Methods 144, 175–181.

Valenzano, K.J., Tafesse, L., Lee, G., Harrison, J.E., Boulet, J.M., Gottshall, S. L., Mark, L., Pearson, M.S., Miller, W., Shan, S., Rabadi, L., Rotshteyn, Y., Chaffer, S.M., Turchin, P.I., Elsemore, D.A., Toth, M., Koetzner, L., Whiteside, G.T., 2005. Pharmacological and pharmacokinetic characterization of the cannabinoid receptor 2 agonist, GW405833, utilizing rodent models of acute and chronic pain, anxiety, ataxia and catalepsy. Neuropharmacology 48, 658–672.