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RESEARCH PAPER

The μ-opioid receptor agonist morphine, but not agonists at δ- or κ-opioid receptors, induces peripheral antinociception mediated by cannabinoid receptors

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Background and purpose: Although participation of opioids in antinociception induced by cannabinoids has been documented, there is little information regarding the participation of cannabinoids in the antinociceptive mechanisms of opioids. The aim of the present study was to determine whether endocannabinoids could be involved in peripheral antinociception induced by activation of μ-, δ- and κ-opioid receptors.
Experimental approach: Nociceptive thresholds to mechanical stimulation of rat paws treated with intraplantar prostaglandin E_2 (PGE_2, 2 μg) to induce hyperalgesia were measured 3 h after injection using an algesimetric apparatus. Opioid agonists morphine (200 μg), (+)-4-[(alphaR)-alpha-((2S,5R)-4-Allyl-2,5-dimethyl-1-piperazinyl)-3-methoxybenzyl]-*N*,*N*-diethylbenzamide (SNC80) (80 μg), bremazocine (50 μg); cannabinoid receptor antagonists *N*-(piperidin-1-yl)-5-(4-iodophenyl)-1-(2,4-dichlorophenyl)-4-methyl-1*H*-pyrazole-3-carboxamide (AM251) (20–80 μg), 6-iodo-2-methyl-1-[2-(4-morpholinyl)ethyl]-1*H*-indol-3-yl(4-methoxyphenyl) methanone (AM630) (12.5–100 μg); and an inhibitor of methyl arachidonyl fluorophosphonate (MAFP) (1–4 μg) were also injected in the paw.
Key results: The CB_1-selective cannabinoid receptor antagonist AM251 completely reversed the peripheral antinociception induced by morphine in a dose-dependent manner. In contrast, the CB_2-selective cannabinoid receptor antagonist AM630 elicited partial antagonism of this effect. In addition, the administration of the fatty acid amide hydrolase inhibitor, MAFP, enhanced the antinociception induced by morphine. The cannabinoid receptor antagonists AM251 and AM630 did not modify the antinociceptive effect of SNC80 or bremazocine. The antagonists alone did not cause any hyperalgesic or antinociceptive effect.
Conclusions and implications: Our results provide evidence for the involvement of endocannabinoids, in the peripheral antinociception induced by the μ-opioid receptor agonist morphine. The release of cannabinoids appears not to be involved in the peripheral antinociceptive effect induced by κ- and δ-opioid receptor agonists.
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Keywords: Morphine; SNC80; bremazocine; CB_1 receptor; CB_2 receptor; peripheral antinociception

Abbreviations: AM251, *N*-(piperidin-1-yl)-5-(4-iodophenyl)-1-(2,4-dichlorophenyl)-4-methyl-1*H*-pyrazole-3-carboxamide; AM630, 6-iodo-2-methyl-1-[2-(4-morpholinyl)ethyl]-1*H*-indol-3-yl(4-methoxyphenyl) methanone; MAFP, methyl arachidonyl fluorophosphonate/(5Z,8Z,11Z,14Z)-5,8,11,14-eicosatetraenyl-methyl ester phosphonofluoridic acid; PGE_2, prostaglandin E_2; SNC80, (+)-4-[(alphaR)-alpha-((2S,5R)-4-Allyl-2,5-dimethyl-1-piperazinyl)-3-methoxybenzyl]-*N*,*N*-diethylbenzamide

Introduction

Opioids are the drugs of choice for treating severe pain, despite the development of tolerance and dependence (Bhargava, 1994). They produce their pharmacological effects by acting mainly through three types of opioid receptors, namely μ, δ and κ (Singh *et al*., 1997). Cannabinoid receptor agonists also produce pain relief in a variety of animal models (Richardson, 2000). Two types of cannabinoid receptors have been identified. CB_1 receptors are expressed primarily in central and peripheral neurons and CB_2 receptors, mainly in immune cells (Pertwee, 2001, 2006;

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Howlett *et al*., 2002; Alexander *et al*., 2008). CB_2 receptor expression in rat microglial cells (Carrier *et al*., 2004), in cerebral granule cells (Skaper *et al*., 1996), in mast cells (Samson *et al*., 2003) and in adult rat retina (Lu *et al*., 2000) has also been demonstrated. In the periphery, both receptors participate in pain control (Malan *et al*., 2001; Rice *et al*., 2002). In addition, receptors for opioids and cannabinoids are coupled to similar intracellular signalling mechanisms, mainly to a decrease in cAMP production through the activation of G_i proteins (Bidaut-Russell *et al*., 1990; Childers, 1991).

Since the discovery that opioids and cannabinoids produce not only several similar biochemical effects but also similar pharmacological effects, the interaction between these two classes of drugs has been extensively studied (Manzaneres *et al*., 1999). Many studies have indicated that cannabinoids can enhance the antinociceptive property of opioids. For example, the effects of morphine have been found to be enhanced by crude *cannabis* extracts (Ghosh and Bhattacharya, 1979). Synergism occurs at subeffective or submaximal doses of cannabinoid or opioid agonists and these effects are blocked by cannabinoid receptor (CB_1) and opioid receptor antagonists (Reche *et al*., 1996; Smith *et al*., 1998). In addition, several studies have suggested that endogenous opioids might be involved in the regulation of pain control by cannabinoids. For example, intrathecally administered Δ^9-tetrahydrocannabinol (THC) has been shown to release endogenous opioid peptides (Pugh *et al*., 1996). Additionally, the cannabinoids, Δ^9-THC and levonantradol appear to enhance the antinociceptive effect of morphine by releasing dynorphin A and dynorphin B, respectively (Welch and Eads, 1999). Moreover, a number of studies have indicated that opioid receptor antagonists might block cannabinoid-induced antinociception (Cox and Welch, 2004).

Anandamide, an endocannabinoid, is produced following intracellular cleavage of *N*-arachidonyl-phosphatidylethanolamine by phospholipase D and shows preferential affinity for CB_1 receptors (Howlett *et al*., 2002). It is synthesized on demand instead of being stored in synaptic vesicles and is hydrolyzed to arachidonic acid and ethanolamine by a membrane bound enzyme named fatty acid amide hydrolase (FAAH) (Hohmann and Suplita, 2006). Mice lacking the FAAH gene exhibited enhanced antinociceptive behaviour, following administration of exogenous anandamide (Cravatt *et al*., 2001). One inhibitor of FAAH is methyl arachidonyl fluorophosphonate (MAFP) and this compound reacts irreversibly with FAAH (Deutsch *et al*., 1997) and thus enhances the responses induced by endocannabinoids (Ho and Randall, 2007).

The role of opioids in antinociception induced by cannabinoids has been observed; however, no information exists regarding the participation of cannabinoids in the antinociceptive mechanisms of opioids. Therefore, the aim of the present study was to determine whether endogenous cannabinoids could be involved in peripheral antinociception induced by activation of μ-, δ- and κ-opioid receptors through the use of cannabinoid receptor antagonists and a FAAH inhibitor.

Methods

Animals

All animal procedures and protocols were approved by the Ethics Committee on Animal Experimentation (CETEA) of the Federal University of Minas Gerais (UFMG).

The experiments were performed on 180–220 g male Wistar rats ($N=5$ per group) from the CEBIO-UFMG (The Animal Centre of the University of Minas Gerais). The rats were housed in a temperature-controlled room (23 ± 1 °C) on an automatic 12-h light/dark cycle (0600–1800 hours of light phase). All testing was carried out during the light phase (0800–1500 hours). Food and water were freely available until the onset of the experiments.

Measurement of the hyperalgesia

After manual restraint, rats were s.c. injected with prostaglandin E_2 (PGE_2, 2 μg) into the plantar surface of its hindpaw and measured by the paw pressure test described by Randall and Selitto (1957). An analgesimeter (Ugo-Basile, Comerio, Italy) with a cone-shaped paw-presser with a rounded tip was used to apply a linearly increasing force to the rat's right hindpaw. The weight in grams required to elicit nociceptive responses, such as paw flexion or struggling, was determined as the nociceptive threshold. A cutoff value of 300 g was used to prevent damage to the paws. The nociceptive threshold was measured in the right paw and determined by the average of three consecutive trials recorded before (zero time) and 3 h after PGE_2 injection (peak of hyperalgesic effect). The results are presented as the difference between these two averages (Δ of nociceptive threshold) and expressed as grams. To reduce stress, the rats were habituated to the apparatus 1 day before the experiments.

Experimental protocol

(+)-4-[(alphaR)-alpha-((2S,5R)-4-Allyl-2,5-dimethyl-1-piperazinyl)-3-methoxybenzyl]-*N*,*N*-diethylbenzamide (SNC80), morphine and bremazocine were given s.c. in the right hindpaw 1.5, 2 and 2.75 h after local injection of PGE_2. Dose–response curves were determined for all opioid receptor agonists to determine effective doses for this study (data not shown). In the protocol used to determine whether the drugs were acting outside the injected paw, PGE_2 was injected into both hindpaws, whereas morphine, SNC80 or bremazocine were administered into the left paw (data not shown).

N-(piperidin-1-yl)-5-(4-iodophenyl)-1-(2,4-dichlorophenyl)-4-methyl-1*H*-pyrazole-3-carboxamide (AM251) and 6-iodo-2-methyl-1-[2-(4-morpholinyl)ethyl]-1*H*-indol-3-yl(4-methoxyphenyl) methanone (AM630) were given s.c. 15 min before the measurement of hyperalgesia (3 h).

The nociceptive threshold was always measured in the right hindpaw. The protocol above was assessed in pilot experiments to determine the best moment for the injection of each substance.

Statistical analysis

Data were analysed statistically by one-way ANOVA with *post hoc* Bonferroni's test for multiple comparisons. Probabilities less than 5% ($P<0.05$) were considered to be statistically significant.

Materials

The following drugs and chemicals were used: PGE_2 (Sigma, St Louis, MO, USA), morphine (Merck, Darmstadt, Germany), SNC80 (Tocris, Ellisville, MO, USA), bremazocine (RBI, Natick, MA, USA), AM251 (Tocris), AM630 (Tocris) and MAFP (Tocris). The drugs were dissolved as follows: PGE_2 (ethanol 2%), morphine, SNC80 (dimethyl sulphoxide (DMSO) 8%), bremazocine (saline), AM251 (DMSO 12%), AM630 (DMSO 12%), MAFP (ethanol 3.2%), and injected in a volume of 100 μl per paw, with the exception of the AM251, AM630 and MAFP, which were injected in a volume of 50 μl per paw.

Results

Antagonism of morphine-induced antinociception by AM251

The intraplantar injection of the CB_1 receptor antagonist AM251 (20, 40 and 80 μg) inhibited the morphine-induced peripheral antinociception (200 μg per paw) in a dose-dependent manner (Figure 1a). The highest dose of AM251, given without PGE_2 or without morphine, did not induce hyperalgesia or antihyperalgesic effects (Figure 1b).

Antagonism of morphine-induced antinociception by AM630

The CB_2 receptor antagonist AM630 (12.5, 25 and 50 μg) elicited partial antagonism of the peripheral antinociceptive effect of morphine (200 μg per paw; Figure 2a). Partial blockade was obtained even when using higher doses (100 μg per paw). This antagonist did not significantly modify the nociceptive threshold in control animals or induce any overt behavioural effect (Figure 2b).

Effect of AM251 and AM630 on SNC80- or bremazocine-induced antinociception

As shown in Figure 3a, neither AM251 (80 μg per paw) nor AM630 (50 μg per paw) reduced the peripheral antinociceptive effect of SNC80 (80 μg per paw). AM251 (80 μg per paw) and AM630 (50 μg per paw) did not modify the peripheral antinociception of bremazocine (50 μg per paw; Figure 3b).

Increase of morphine-induced antinociception by MAFP

As shown in Figure 4, the administration of MAFP (1, 2 and 4 μg per paw) progressively enhanced the antinociception induced by a low dose of morphine (50 μg per paw). However, MAFP alone did not induce any effect.

Discussion

The interaction between cannabinoids and opioids has been extensively studied and evidence exists that cannabinoid-induced antinociception may, to some extent, depend on the release of opioid peptides (Reche *et al.*, 1996). Because

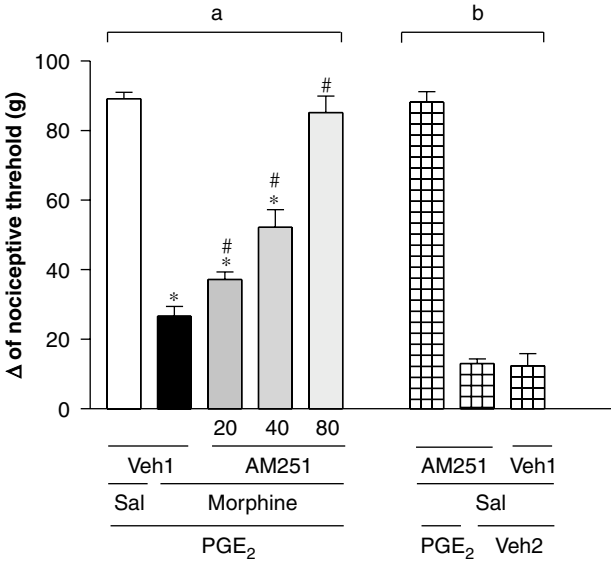

Figure 1 Antagonism induced by intraplantar administration of AM251 of the peripheral antinociception produced by morphine in the hyperalgesic paw (PGE_2, 2 μg). AM251 (20–80 μg) was administered 45 min after morphine (200 μg per paw) (**a**). This antagonist did not significantly modify the nociceptive threshold in control animals (**b**). Each column represents the mean ± s.e.mean for five rats per group. *, #indicate significant differences compared with PGE_2 + Sal + Veh1- and PGE_2 + morphine + Veh1-injected groups, respectively (ANOVA + Bonferroni's test; $F = 60{,}9$; df = 4; $P < 0.0001$). Veh1, vehicle1 (DMSO 12% in saline); Veh2, vehicle2 (ethanol 2% in saline); Sal, saline. AM251, *N*-(piperidin-1-yl)-5-(4-iodophenyl)-1-(2,4-dichlorophenyl)-4-methyl-1*H*-pyrazole-3-carboxamide; DMSO, dimethyl sulphoxide; PGE_2, prostaglandin E_2.

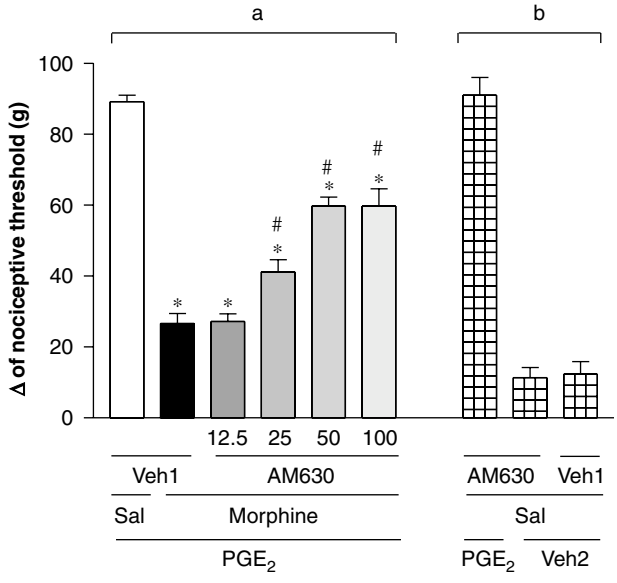

Figure 2 Antagonism induced by intraplantar administration of AM630 on the peripheral antinociception produced by morphine in the hyperalgesic paw (PGE_2, 2 μg). AM630 (12.5–100 μg) was administered 45 min after morphine (200 μg per paw) (**a**). Given alone, this antagonist did not induce hyperalgesia or antihyperalgesic effects (**b**). Each column represents the mean ± s.e.mean for five rats per group. *, #indicate significant differences compared with PGE_2 + Sal + Veh1- and PGE_2 + morphine + Veh1-injected groups, respectively (ANOVA + Bonferroni's test; $F = 60{,}0$; df = 5; $P < 0.0001$). Veh1, vehicle1 (DMSO 12% in saline); Veh2, vehicle2 (ethanol 2% in saline); Sal, saline. AM630, 6-iodo-2-methyl-1-[2-(4-morpholinyl)ethyl]-1*H*-indol-3-yl(4-methoxyphenyl) methanone; DMSO, dimethyl sulphoxide; PGE_2, prostaglandin E_2.

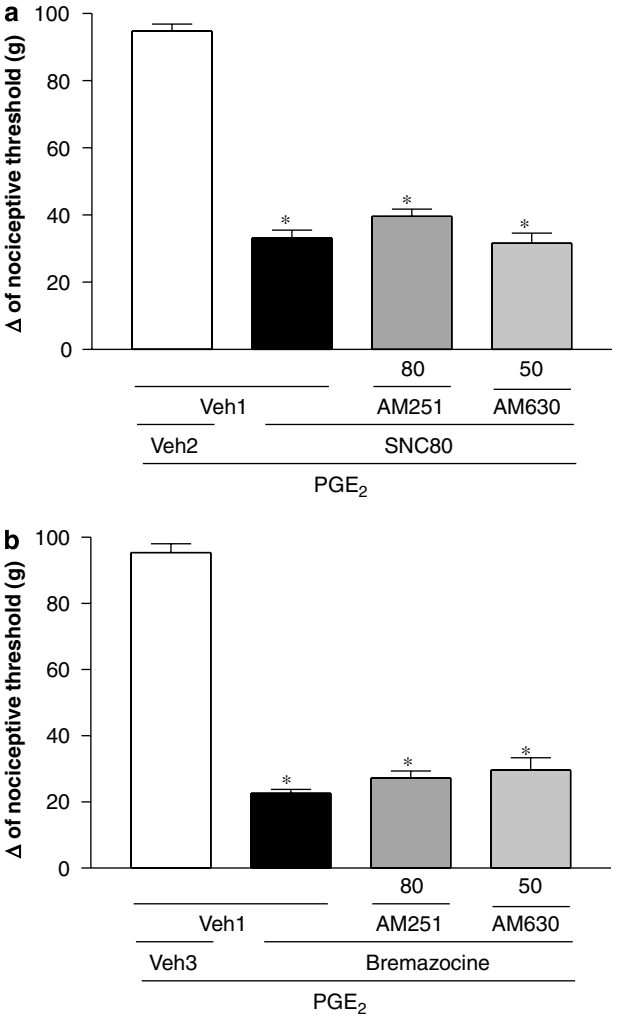

Figure 3 Effect of intraplantar administration of AM251 and AM630 on the peripheral antinociception produced by SNC80 (**a**) or bremazocine (**b**) in the hyperalgesic paw (PGE_2, 2 μg). AM251 (80 μg) or AM630 (50 μg) were administered 1:15 h after SNC80 (80 μg per paw) or at the same time as bremazocine (50 μg per paw). Each column represents the mean ± s.e.mean for five rats per group. *indicate significant differences compared with PGE_2 + Veh1 + Veh2- and PGE_2 + Veh1 + SNC80/bremazocine-injected groups, respectively (ANOVA + Bonferroni's test; $F = 153,9$; df = 3; $P < 0.0001$ (**a**) and $F = 176.5$; df = 3, $P < 0.0001$ (**b**)). Veh1, vehicle1 (DMSO 12% in saline); Veh2, vehicle2 (DMSO 8% in saline); Veh 3, vehicle 3 (saline). AM251, *N*-(piperidin-1-yl)-5-(4-iodophenyl)-1-(2,4-dichlorophenyl)-4-methyl-1*H*-pyrazole-3-carboxamide; AM630, 6-iodo-2-methyl-1-[2-(4-morpholinyl)ethyl]-1*H*-indol-3-yl(4-methoxyphenyl) methanone; DMSO, dimethyl sulphoxide; PGE_2, prostaglandin E_2; SNC80, (+)-4-[(alphaR)-alpha-((2S,5R)-4-Allyl-2,5-dimethyl-1-piperazinyl)-3-methoxybenzyl]-*N*,*N*-diethylbenzamide.

little is known of the participation of endogenous cannabinoids in the analgesic mechanism of opioids, we have used here AM251 (a CB_1 receptor antagonist) and AM630 (CB_2 receptor antagonist) to characterize the role of endocannabinoids in peripheral antinociception induced by opioids.

Initially, the ability of the μ-, δ- and κ-opioid agonists, morphine (200 μg per paw), SNC80 (80 μg per paw) and bremazocine (50 μg per paw), respectively, to induce peripheral antinociception in the rat paw PGE_2-induced hyperalgesia test was investigated. It is important to emphasize that these doses did not cause any central antinociceptive effect (data not shown).

Our results demonstrated that AM251 was able to prevent the peripheral antinociception induced by morphine, in a dose-dependent manner. AM251 is a potent CB_1 receptor antagonist, 306-fold selective over CB_2 receptors (Gatley *et al*., 1997; Lan *et al*., 1999). The participation of CB_1 receptors in peripheral antinociception has been related in various studies (Rice *et al*., 2002). Additionally, intraplantar administration of CB_1 agonist WIN55212-2 attenuated the development of carrageenan-evoked mechanical hyperalgesia and allodynia (Nackley *et al*., 2003). Recently, it was showed that by targeting CB_1 receptors expressed on the peripheral axons of primary sensory neurons, substantial analgesia can be achieved in somatic and visceral pain, as well as in inflammatory and neuropathic pain (Agarwal *et al*., 2007). Moreover, one study provided strong evidence that peripheral CB_1 receptors, presumed to be located on the peripheral endings of A- and C- fibre primary afferents, are able to modulate the transmission of innocuous and noxious somatosensory information from the periphery to the spinal cord (Kelly *et al*., 2003).

Many studies have shown that cannabinoids enhance the antinociception of morphine through the release of endogenous opioid peptides. For example, the cannabinoid Δ^9-THC increased morphine antinociception by releasing dynorphin A (Welch and Eads, 1999). Another study demonstrated that naloxone blocked the synergistic antinociception produced by low oral doses of Δ^9-THC and morphine, indicating the involvement of the μ-opioid receptor in this effect (Cichewicz *et al*., 1999). Recently, it was suggested that CB_1- and μ-opioid receptors form heterodimers (Rios *et al*., 2006). Heterodimer formation is needed for the function of certain G-protein-coupled receptors, for example, the $GABA_B$ receptor (Ong and Kerr, 2000).

The CB_2 receptor antagonist AM630 partially blocked the peripheral antinociception induced by morphine. AM630 is a CB_2-selective ligand that behaves as an antagonist/inverse agonist at CB_2 receptors and is 165-fold selective over CB_1 receptors (Ross *et al*., 1999). The CB_2 receptor is primarily located on immune cells in the periphery (Galiègue *et al*., 1995) and studies have demonstrated the presence of CB_2 receptors in a number of brain regions, contrary to the prevailing view that they are restricted to peripheral tissues (Sickle *et al*., 2005; Gong *et al*., 2006; Onaivi *et al*., 2006). These receptors have not been found on peripheral neurons, suggesting that the activation of CB_2 receptors produces antinociception indirectly, by causing the release of mediators from non-neuronal cells that alter the responsiveness of primary afferent neurons to noxious stimuli. One cell type that might mediate the actions of CB_2 receptor-selective agonists is the keratinocyte, which has been reported to express CB_2 receptors (Casanova *et al*., 2003) and to contain endogenous opioid peptides (Kauser *et al*., 2003). Antinociception produced by CB_2 receptor-selective agonists may be mediated by the stimulation of β-endorphin release from cells with these receptors. The β-endorphin thus released

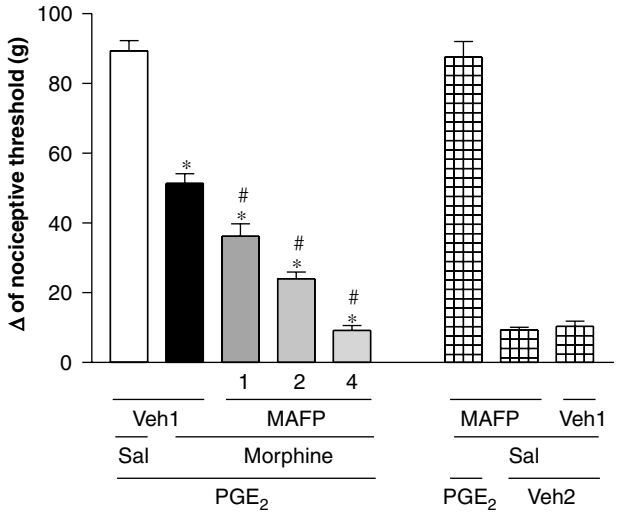

Figure 4 Potentiation of morphine-induced antinociception by MAFP in the hyperalgesic paw (PGE_2, 2 μg). MAFP (1, 2 and 4 μg) was administered at the same time as morphine (50 μg per paw). MAFP given alone (4 μg) did not induce any nociceptive effect. Each column represents the mean ± s.e.mean for five rats per group. *, #indicate a significant differences compared with PGE_2 + Veh1 + Sal- and PGE_2 + Veh1 + morphine-injected groups, respectively (ANOVA + Bonferroni's test; $F = 137.3$; df = 4; $P < 0.0001$). Veh1, vehicle1 (DMSO 3.2% in saline); Veh2, vehicle 2 (ethanol 2% in saline); Sal, saline. DMSO, dimethyl sulphoxide; MAFP, methyl arachidonyl fluorophosphonate; PGE_2, prostaglandin E_2.

appears to act at μ-opioid receptors, probably on the terminals of primary afferent neurons, to produce peripheral antinociception (Ibrahim *et al*., 2005). Another study has shown that intraplantar administration of the CB_2 receptor agonist, AM1241, reduces thermal nociception. Moreover, the antinociceptive actions of systemic AM1241 were blocked by injection of AM630 into the paw where the thermal stimulus was applied. These findings demonstrate the local, peripheral nature of the antinociception mediated through CB_2 receptors (Malan *et al*., 2001). Additionally, local peripheral activation of CB_2 receptors attenuates innocuous and noxious mechanically evoked responses of spinal wide dynamic range neurons in models of acute inflammatory and neuropathic pain (Elmes *et al*., 2004). Also, inhibitory effects of anandamide in rats with hindpaw inflammation were blocked by the co-injection of the CB_2 receptor antagonist SR144528. These data indicate that, under these conditions, the inhibitory effects of anandamide are mediated predominantly by peripheral CB_2 receptors (Sokal *et al*., 2003). There are no studies demonstrating the participation of CB_2 receptors in the effects of opioids.

To confirm the participation of endocannabinoids in the peripheral antinociceptive actions of morphine, we used MAFP, an irreversible inhibitor of FAAH, the enzyme responsible for hydrolysis and inactivation of the endocannabinoid anandamide. The current results demonstrated that administration of MAFP enhanced the peripheral antinociception produced by a low dose of morphine (50 μg per paw), suggesting that activation of μ-opioid receptors induced the release of endocannabinoids. Anandamide is an agonist at CB_1 and CB_2 receptors, but has greater affinity for CB_1 receptors (Howlett *et al*., 2002) and the present work showed that the antinociceptive effect of morphine was completely reversed by the CB_1 receptor antagonist AM251 and only partially reversed by the CB_2 receptor antagonist AM630. It has been proposed that anandamide is rapidly inactivated by a re-uptake system consisting of the anandamide membrane transporter, which transports anandamide into cell where it is hydrolyzed (Di Marzo *et al*., 1994). Although FAAH appears to be the enzyme primarily responsible for the hydrolysis of anandamide, another acid amidase has been identified that is also capable of hydrolyzing anandamide (Ueda *et al*., 2001). Notably, the compound MAFP, which is often used to inhibit FAAH, has been found to be a potent inhibitor of monoacylglycerol lipase activity (Dinh *et al*., 2002). The crucial role of FAAH and monoacylglycerol lipase in the inactivation of anandamide suggests that inhibitors of these enzymes could be utilized to enhance endocannabinoid activity (Ho and Randall, 2007). The endocannabinoids involved in pain modulation have been identified directly using microdialysis and liquid and/or gas chromatography mass spectrometry (Cravatt *et al*., 2001; Cravatt and Lichtman, 2002) and indirectly by administration of pharmacological agents that regulate endocannabinoid uptake or degradation (Hohmann and Suplita, 2006). The present study focused on the indirect approach. Nevertheless, the direct measurement of endocannabinoid levels in paw tissue would have been very desirable and should be the subject of future work. Additionally, MAFP affects activities of $cPLA_2$, $iPLA_2$ and COX (Huang *et al*., 1994, 1996), but it binds irreversibly and with greater affinity to anandamide amidase than it does to other amide hydrolytic enzymes or to the cannabinoid receptor CB_1 (Deutsch *et al*., 1997). Also, intrathecal administration of MAFP dose-dependently prevented thermal hyperalgesia induced by intraplantar carragenan, as well as formalin-induced flinching (Lucas *et al*., 2005). Moreover, the co-injection of AM251 with MAFP in the formalin test completely reversed the MAFP-induced antinociception, indicating that this effect is mediated by CB_1 receptors (Ates *et al*., 2003). Our data showed that, in the experimental model utilized, MAFP alone did not alter the hyperalgesia induced by PGE_2. On the other hand, the FAAH inhibitor URB597 significantly attenuated mechanically evoked responses of spinal neurons in sham-operated rats. In contrast, in neuropathic rats, the same intraplantar dose of URB597 had no effect, although a higher dose attenuated responses of spinal neurons, without increasing the levels of endocannabinoids (Jhaveri *et al*., 2006). These authors suggested that the contribution of FAAH to endocannabinoid metabolism is altered in models of neuropathic pain.

In contrast to morphine, AM251 and AM630 did not exert an effect on peripheral antinociception induced by SNC80 or bremazocine at effective doses. On the other hand, some studies have demonstrated that intrathecally administered cannabinoids evoke the release of endogenous opioids that stimulate δ- and κ-opioid receptors to produce antinociception (Welch, 1993; Pugh *et al*., 1996). Other studies have shown that μ-receptors and, preferentially, κ-receptors, but not δ-receptors, are involved in the antinociceptive action of Δ^9-THC (Reche *et al*., 1996). There are no studies on the

participation of cannabinoids in the outcome of activation of κ- and δ-opioid receptors.

In conclusion, the present data showed, for the first time, that the antinociceptive effects of agonists at the μ- but not at the κ- or δ-opioid receptors were blocked by CB_1 and, at least in part, CB_2 receptor antagonists, suggesting that activation of these CB receptors by endocannabinoids contributes to the analgesic effects of opioid analgesics in a model of inflammatory hyperalgesia. However, more work needs to be carried out to elucidate this new interaction between opioids and cannabinoids.

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Conflict of interest

The authors state no conflict of interest.

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