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Study of the involvement of K^+ channels in the peripheral antinociception of the κ-opioid receptor agonist bremazocine

Luiz H. Amarante, Daniela P. Alves, Igor D.G. Duarte*

Department of Pharmacology, Institute of Biological Sciences, Universidade Federal de Minas Gerais (UFMG), Av. Antônio Carlos 6627, Belo Horizonte, MG, 31.270-100, Brazil

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Abstract

The involvement of the nitric oxide (NO)/cyclic GMP pathway in the molecular mechanisms of antinociceptive drugs like morphine has been previously shown by our group. Additionally, it is known that the desensitisation of nociceptors by K^+ channel opening should be the final target for several analgesic drugs including nitric oxide donors and exogenous μ-opioid receptor agonists. In our previous study, we demonstrated that bremazocine, a κ-opioid receptor agonist, induces peripheral antinociception by activating nitric oxide/cyclic GMP pathway. In the current study, we assessed whether bremazocine is capable to activate K^+ channels eliciting antinociception. Bremazocine (20, 40 and 50 μg) dose-dependently reversed the hyperalgesia induced in the rat paw by local injection of carrageenan (250 μg) or prostaglandin E_2 (2 μg), measured by the paw pressure test. Using the selective κ-opioid receptor antagonist nor-binaltorphimine (Nor-BNI, 200 μg/paw), it was confirmed that bremazocine (50 μg/paw) acts specifically on the κ-opioid receptors present at peripheral sites. Prior treatment with the ATP-sensitive K^+ channel blockers glibenclamide (40, 80 and 160 μg) and tolbutamide (40, 80 and 160 μg) did not antagonise the antinociceptive effect of bremazocine (50 μg). The same results were obtained when we used prostaglandin E_2 (2 μg) as the hyperalgesic stimulus. The supposed participation of other types of K^+ channels was tested using the Ca^{2+}-activated K^+ channel blockers dequalinium (12.5, 25 and 50 μg) and charybdotoxin (0.5, 1 and 2 μg) and different types of the non-selective K^+ channel blockers tetraethylammonium (25, 50 and 100 μg) and 4-aminopyridine (10, 25 and 50 μg). None of the K^+ channel blockers reversed the antinociceptive effect of bremazocine. On the basis of these results, we suggest that K^+ channels are not involved in the peripheral antinociceptive effect of bremazocine, although this opioid receptor agonist induces nitric oxide/cGMP pathway activation.

Keywords: Bremazocine; κ-opioid receptor; Potassium channel; Peripheral antinociception; Carrageenan

1. Introduction

A growing number of experimental and clinical studies has demonstrated a relationship between opioid receptor activation and potassium channels (K^+ channels) (Werz and Macdonald, 1983b; Fürst, 1999). These channels have been found in almost all excitable and non-excitable cells. They exhibit basically inhibitory currents regulating neuronal excitability (Rudy, 1988). Because of this property, K^+ channels have been associated with several physiological processes, including neuronal desensitisation and analgesia (Kuriyama et al., 1995; Garcia et al., 1997). The activation of K^+ flow through the neuronal cytoplasmic membranes is often suggested as the final molecular mechanism of the opioid morphine (Ocaña et al., 1990; Rodrigues and Duarte, 2000) and the non-opioid analgesic drug metamizol (Alves and Duarte, 2002).

On the other hand, there is evidence that morphine-induced antinociception can be significantly reduced by local administration of the nitric oxide (NO) synthesis and guanilatecyclase inhibitors L-NIO (*N*-5-(iminoethyl)-L-ornithine) and methylene blue, suggesting that NO/cGMP activation at the peripheral and central level plays a role in antinociception induced by this μ-opioid receptor agonist (Duarte et al., 1990; Duarte and Ferreira, 1992).

Recently, Soares et al. (2000) and Soares and Duarte (2001) suggested a link between the activation of the NO/cGMP pathway and the opening of ATP-sensitive K^+ channels, since the sulphonylureas glibenclamide and tolbutamide

* Corresponding author. Tel./fax: +55-31-3499-2695.
E-mail address: dimitri@mono.icb.ufmg.br (I.D.G. Duarte).

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were able to block the antinociceptive effect of sodium nitroprusside and dibutyryl cyclic GMP.

Taken together, these data suggest that the μ-opioid receptor agonist morphine produces a peripheral antinociceptive action through the activation of the NO/cGMP pathway followed by the opening of ATP-sensitive K^+ channels. Since we have previously reported that the κ-opioid receptor agonist bremazocine induces peripheral antinociception by activating the NO/cGMP pathway (Amarante and Duarte, 2002), we decided to extend our observations by studying the possible participation of K^+ channels using the paw pressure test in rats.

2. Materials and methods

2.1. Animals

Male Wistar rats weighing 180–250 g from the Animal House of the Institute of Biological Sciences, Federal University of Minas Gerais, Brazil, were used for the experiments. The animals were housed in a temperature-controlled room (23±1 °C) on an automatic 12 h light/dark cycle (6:00 a.m. to 6:00 p.m.). All tests were conducted during the light phase (8:00 a.m. to 2:00 p.m.). Food and water were freely available until the beginning of the experiments. Naive animals were used throughout.

2.2. Measurement of hyperalgesia

Subcutaneous administration of a carrageenan suspension (250 μg) or prostaglandin E_2 (2 μg) into the hind paw elicited hyperalgesia which was measured by the pressure test described by Randall and Selitto (1957). This method is approved by Ethics Committee on Animal Experimentation (CETEA/UFMG). We used an analgesimeter (Ugo-Basile, Italy) with a cone-shaped paw-presser with a rounded tip, which applies a linearly increasing force to the plantar surface of the paw. The weight in grams required to elicit the nociceptive response of paw flexion was defined as the nociceptive threshold. A cut-off value of 300 g was used to prevent damage to the paws. The nociceptive threshold was always measured in the right hind paw and determined by the average of three consecutive trials recorded before (zero time) and 3 h after carrageenan or prostaglandin E_2 injection. The results were calculated by the difference between these two averages (Δ of nociceptive threshold).

2.3. Experimental protocol

All drugs were administered subcutaneously into the right hind paw and the nociceptive threshold was measured in this same paw, except in the protocol used to determine whether bremazocine was acting at central sites. In this protocol, carrageenan was injected into both hind paws, bremazocine was administered into the left or right paw, and the nociceptive threshold was measured in the right hind paw. Bremazocine was always administered 15 min before the measurements of nociceptive threshold and other drugs were administered before bremazocine injection at the following times: (a) nor-binaltorphimine (Nor-BNI), glibenclamide and tolbutamide: 5 min; (b) 4-aminopyridine, tetraethylammonium, dequalinium and charybdotoxin: 15 min. The moment of administration was based on pilot studies or on Ortiz et al. (2002).

2.4. Drugs

Carrageenan (Sigma, USA), prostaglandin E_2 (Sigma), (±)-bremazocine hydrochloride (RBI, USA), nor-binaltorphimine (Sigma), 4-aminopyridine (Sigma) and tetraethylammonium (Sigma) were dissolved in physiological saline. Glibenclamide (Sigma) and tolbutamide (ICN, USA) were dissolved in Tween 80 (1% in saline). Charybdotoxin (Sigma) was dissolved in demineralized water and dequalinium (Calbiochem-Novabiochem, USA) was dissolved in dimethyl sulfoxide (DMSO, 10% in saline). Carrageenan, prostaglandin E_2, bremazocine and vehicles were injected in a volume of 100 μl/paw and the other drugs in a volume of 50 μl/paw. For acidic or alkaline solutions the pH was adjusted to approximately 7.4.

2.5. Statistical analysis

Statistical analysis was carried out by one-way analysis of variance (ANOVA) followed by Bonferroni's test for multiple comparisons. Probabilities of less than 5% ($P<0.05$) were considered to be statistically significant.

3. Results

3.1. Peripheral antinociceptive effect of bremazocine

The administration of bremazocine (20, 40 and 50 μg) into the right hindpaw antagonised the hyperalgesic effect of carrageenan (250 μg/paw) in a dose-dependent manner (Fig. 1). ED_{50} (30.1 μg) was calculated for a log dose response (same figure, above). The possibility of a central or systemic effect for bremazocine (50 μg) was excluded since its administration into the left paw did not elicit antihyperalgesia in the right paw (data not shown).

3.2. Antagonism of bremazocine-induced antinociception by nor-binaltorphimine

Fig. 2 shows that the peripheral antinociceptive effect of bremazocine (50 μg) was antagonised by local administration of the selective κ-opioid receptor antagonist (Song and Takemori, 1990), Nor-BNI (200 μg).

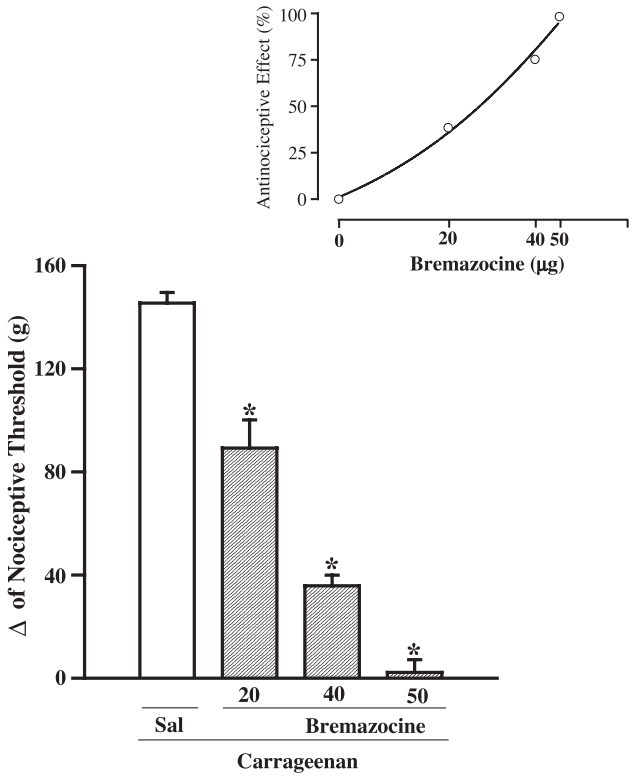

Fig. 1. Effect of bremazocine on the nociceptive threshold in carrageenan-induced hyperalgesia in rats. Bremazocine (20, 40 and 50 μg) was administered intraplantarly 2 h and 45 min after local administration of 100 μl of a carrageenan suspension (250 μg). The figure above is a log dose–response curve (ED_{50}=30.1 μg). Each column represents the mean±S.E.M. (n=5–7). * Indicates a significant difference from the carrageenan+saline (Sal) control group (P<0.05, ANOVA+Bonferroni's test).

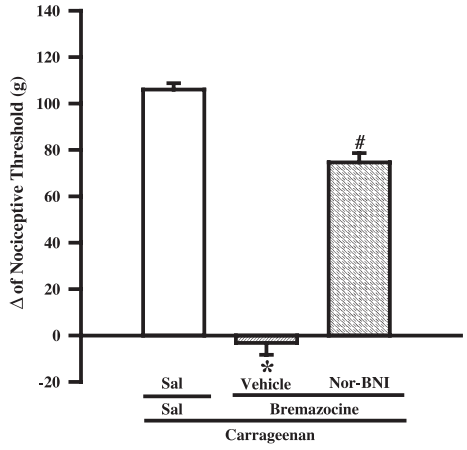

Fig. 2. Antagonism induced by intraplantar administration of Nor-BNI against peripheral antinociception produced by bremazocine in the hyperalgesic paw. Nor-binaltorphimine (200 μg) was administered 5 min before bremazocine (50 μg). Each column represents the mean±S.E.M. (n=5). * and # indicate, respectively, a significant difference from the carrageenan+vehicle+vehicle control group and carrageenan+vehicle+bremazocine group (P<0.05, ANOVA+Bonferroni's test).

3.3. Effect of glibenclamide and tolbutamide on bremazocine-induced antinociception

This experiment showed that the sulfonylureas glibenclamide (40, 80 and 160 μg) and tolbutamide (40, 80 and 160 μg), potent blockers to ATP-sensitive K^+ channels, had no effect on the ability of bremazocine (50 μg) to induce antinociception (Fig. 3). The same result was obtained when prostaglandin E_2 (2 μg) was used to induce hyperalgesia in the rat paw (data not shown). None of the sulphonylureas tested significantly modified the nociceptive threshold in control animals or induced any overt behavioral effect at the doses used (not shown).

3.4. Effect of dequalinium and charybdotoxin on bremazocine-induced antinociception

Intraplantar injection of the blockers of the small conductance Ca^{2+}-activated K^+ channels dequalinium (12.5, 25 and 50 μg) or large conductance Ca^{2+}-activated K^+ channels charybdotoxin (0.5, 1 and 2 μg) had no significant effect on bremazocine-induced antinociception (50 μg), as shown in Fig. 4A and B, respectively. When administered alone, dequalinium and charybdotoxin were not able to induce any hyperalgesic or antinociceptive effect.

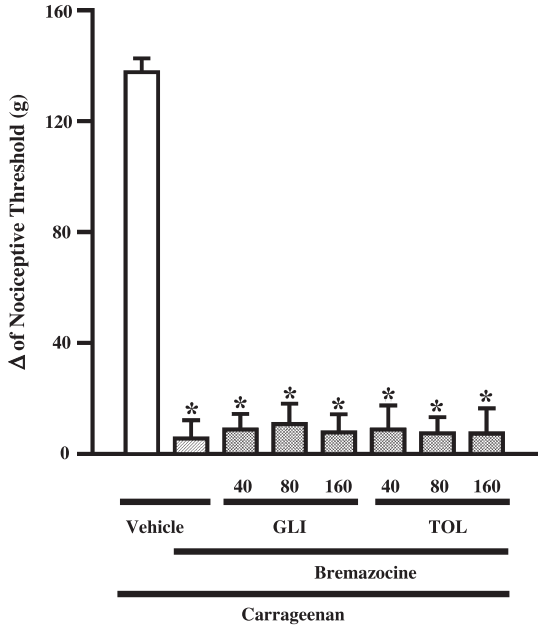

Fig. 3. Effect of intraplantar administration of glibenclamide (GLI) and tolbutamide (TOL) on the peripheral antinociception produced by bremazocine in the hyperalgesic paw. Glibenclamide (40, 80 and 160 μg) and tolbutamide (40, 80 and 160 μg) were administered 5 min before bremazocine injection (50 μg). Each column represents the mean±S.E.M. (n=5–7). * Indicates a significant difference from the carrageenan+vehicle+saline (Sal) control group (P<0.05, ANOVA+Bonferroni's test). No significant statistical difference was found between carrageenan+glibenclamide+bremazocine or carrageenan+tolbutamide+bremazocine and carrageenan+vehicle+bremazocine-injected control.

3.5. Effect of 4-aminopyridine and tetraethylammonium on bremazocine-induced antinociception

Non-selective blockers of the K^+ channels 4-aminopyridine (10, 25 and 50 μg) and tetraethylammomium (25, 50 and 100 μg) also failed to significantly counteract the antinociceptive effect of bremazocine (Fig. 5). Tetraethylammonium and 4-aminopyridine were not able to significantly modified the nociceptive threshold in control animals or induced any overt behavioral effect at the doses used (data not shown).

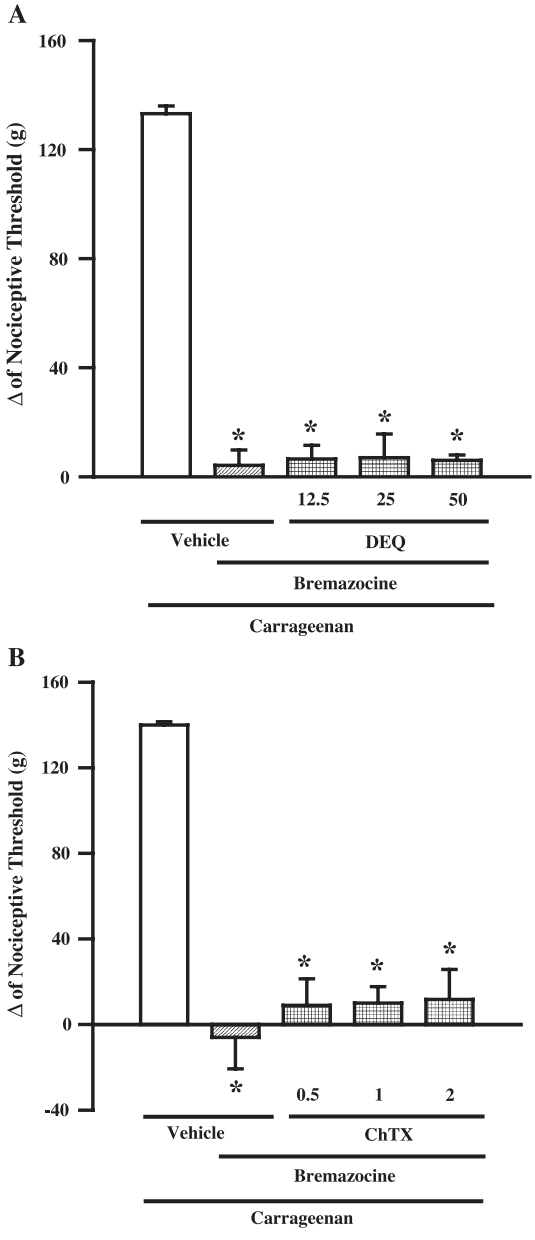

Fig. 4. Effect of intraplantar administration of dequalinium (DEQ, panel A) and charybdotoxin (ChTX, panel B) on the peripheral antinociception produced by bremazocine in the hyperalgesic paw. Dequalinium (12.5, 25 and 50 μg) and charybdotoxin (0.5, 1 and 2 μg) were administered 15 min before bremazocine (50 μg). Each column represents the mean±S.E.M. (n=5–6). * Indicates a significant difference from the carrageenan+vehicle+saline (Sal) control group (P<0.05, ANOVA+Bonferroni's test). No significant statistical difference was found between carrageenan+dequalinium+bremazocine or carrageenan+charybdotoxin+bremazocine and carrageenan+vehicle+bremazocine-injected control.

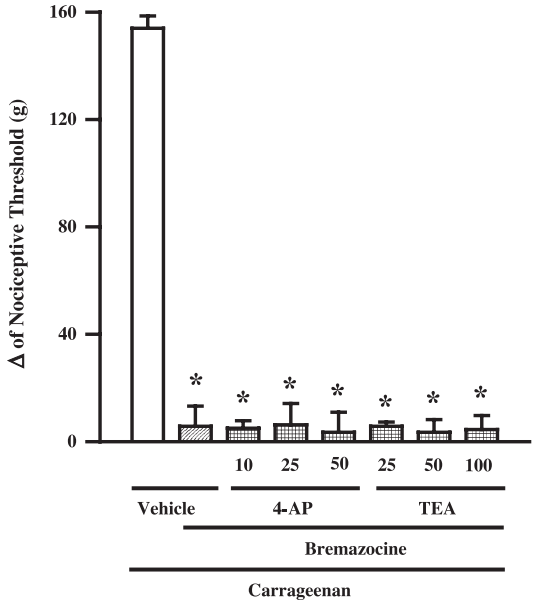

Fig. 5. Effect of intraplantar administration of 4-aminopyridine (4-AP) and tetraethylammonium (TEA) on the peripheral antinociception produced by bremazocine in the hyperalgesic paw. 4-Aminopyridine (10, 25 and 50 μg) and tetraethylammonium (25, 50 and 100 μg) were administered 15 min before bremazocine (50 μg). Each column represents the mean±S.E.M. (n=4). * Indicates a significant difference from the carrageenan+vehicle+saline (Sal) control group (P<0.05, ANOVA+Bonferroni's test). No significant statistical difference was found between carrageenan+4-aminopyridine+bremazocine or carrageenan+tetraethylammonium+bremazocine and carrageenan+vehicle+bremazocine-injected control.

4. Discussion

Bremazocine is a benzomorphan analogue that evokes a potent and long-lasting antinociceptive effect in animal models of studies of pain (Römer et al., 1980).

In the present investigation, we observed peripheral antinociception with bremazocine (ED_{50}=30.1 μg) measured in the paw pressure test described in methods. The antinociceptive effect was not due to a systemic or a central action since the administration of bremazocine (50 μg) into the contralateral paw was inactive.

Bremazocine has properties which justify its classification as a κ-opioid receptor agonist (Römer et al., 1980; Horan et al., 1991; Ko et al., 1999). In the present study, we successfully reversed the antinociceptive effect of bremazocine by local injection of nor-binaltorphimine, a specific κ-opioid receptor antagonist, showing that bremazocine seems to act exclusively on the κ-opioid receptor.

Stimulation of μ-, δ- and κ-opioid receptors decreases neuronal Ca^{2+} influx and Ca^{2+}-dependent action potentials (Werz and Macdonald, 1983a, 1985) and induces antinoci-

ception (Porreca et al., 1984). The effect of μ and δ stimulants on Ca^{2+} fluxes is secondary to the opening of neuronal K^+ channels (Werz and Macdonald, 1983b).

The capacity of μ-opioid receptor agonist morphine to induce antinociception was inhibited by ATP-sensitive K^+ channels blockers (Ocaña et al., 1990; Rodrigues and Duarte, 2000). ATP-sensitive K^+ channels blockers also decreased the antinociception evoked by [D-Pen (2.5)] enkephalin, a δ-opioid receptor agonist (Picolo et al., 2003), but did not reversed the antinociceptive effect of U50,488H (*trans*-3,4-dichloro-*N*-methyl-*N*-[2-(1-pyrrolidinyl)-cyclohexyl]-benzeneacetamide), a κ-opioid receptor agonist (Ocaña and Baeyens, 1993; Picolo et al., 2003).

In our study, the ATP-sensitive K^+ channel blockers glibenclamide and tolbutamide did not antagonise the antinociceptive effect of the κ-opioid receptor agonist bremazocine. It is interesting to note that the same doses of these blockers were able to reverse the antinociception induced by morphine (Rodrigues and Duarte, 2000) and dipyrone (Alves and Duarte, 2002). We have previously shown that bremazocine elicits peripheral antinociception by activating the NO/cGMP pathway (Amarante and Duarte, 2002) and it is known that the effects of NO/cGMP could be ranged by concentration in the tissue (MacAndrew et al., 1997; Sousa and Prado, 2001). Moreover, the lack of antagonism by sulphonylureas of the antinociceptive effect of bremazocine was also evident when a lower dose of this drug (20 μg/paw) was used with glibenclamide (data not shown).

The capacity of carrageenan to release several inflammatory mediators (Vinegar et al., 1969) could be the reason why sulfonylureas failed to reverse the antinociceptive effect of bremazocine on the inflammatory tissue. Although this possibility cannot be totally excluded, we did not observe any effect of glibenclamide or tolbutamide on bremazocine antinociception even though we induced hyperalgesia in the rat paw by injection of prostaglandin E_2 (2 μg), an agent that directly sensitises the peripheral nociceptor without releasing hyperalgesic mediators (data not shown).

In the view of these results, we suggest that, even though bremazocine is capable to stimulate local generation of NO and cGMP, there is no evidence for the involvement of ATP-sensitive K^+ channels in the peripheral antihyperalgesic effect of bremazocine, independently of the hyperalgesic stimulus or bremazocine concentration used.

A possible participation of others types of K^+ channels was tested. Injection of dequalinium and charybdotoxin, respectively specific blockers of small-conductance Ca^{2+}-activated K^+ channels (Dunn, 1994) and large-conductance Ca^{2+}-activated K^+ channels (Miller et al., 1985), did not reverse the effect of bremazocine either. 4-Aminopyridine and tetraethylammonium are drugs that non-selectively block different types of K^+ channels, including Ca^{2+}-activated and voltage-dependent K^+ channels (Cook and Quast, 1990). Our data show no significant effect of these drugs on antinociception induced by bremazocine. The doses of these ineffective blockers were those used by Ortiz et al. (2002) in a study about the involvement of K^+ channels in the antinociceptive effect of diclofenac.

Thus, the data presented here do not support the participation of any type of K^+ channels in bremazocine-induced antinociception. The lack of K^+ channel blocker antagonism against bremazocine antinociception was reasonable explained since bremazocine is a selective κ-opioid receptor stimulant (Römer et al., 1980) and the activation of these receptors does not open K^+ channels in neurons (Millan, 1990). Although some studies have reported that κ-opioid receptor agonist U50,488H produces antinociception by activation of G-protein-coupled inwardly rectifying K^+ channels, named GIRK (Ulens et al., 1999; Ikeda et al., 2000), other authors have demonstrated that κ-opioid receptor agonists U50,488H and U69593 (5α,7α,8β-(+)-*N*-methyl-*N*-[7-(1-pyrrolidinyl)-1-oxaspiro [4,5] dec-8-yl]-benzeneacetamide) induce antinociception that was not antagonised by K^+ channel blockers (Ocaña and Baeyens, 1993; Ocaña et al., 1993; Picolo et al., 2003). This apparent discrepancy could be explained by the heterogeneity of κ-opioid receptors (Horan et al., 1991, 1993; Horan and Porreca, 1993). It is known that U50,488H acts on the κ_1-opioid receptor (Kolesnikov et al., 1996), while bremazocine presents high affinity for κ_2-opioid receptor (Wan Fan et al., 2002). Additionally, Ulens et al. (1999) suggested that the action of κ-opioid receptor ligants on the GIRK channels could be dose-dependent.

Further experiments are needed to investigate how bremazocine could induce antinociception via NO/cGMP activation (Amarante and Duarte, 2002) without activating K^+ channels.

Acknowledgements

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