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δ-Opioid receptor agonist SNC80 induces peripheral antinociception via activation of ATP-sensitive K^+ channels

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Abstract

We investigated the effect of several K^+ channel blockers on the antinociception induced by δ-opioid receptor agonist SNC80 using the paw pressure test, in which pain sensitivity is increased by an intraplantar injection (2 μg) of prostaglandin E_2 (PGE_2). Administration of SNC80 (20, 40 and 80 μg/paw) caused a decrease in the hyperalgesia induced by PGE_2, in a dose-dependent manner. The possibility of higher dose of SNC80 (80 μg) causing a central or systemic effect was excluded since administration of the drug into the contralateral paw did not elicit antinociception in the right paw. Specific blockers of ATP-sensitive K^+ channels, glibenclamide (20, 40 and 80 μg/paw) and tolbutamide (40, 80 and 160 μg/paw), antagonized the peripheral antinociception induced by SNC80 (80 μg). On the other hand, charybdotoxin (2 μg/paw), a large-conductance blocker of Ca^{2+}-activated K^+ channels, and dequalinium (50 μg/paw), a small conductance selective blocker of Ca^{2+}-activated K^+ channels, did not modify the effect of SNC80. This effect also remained unaffected by intraplantar administration of the voltage-dependent K^+ channel blockers tetraethylammonium (30 μg/paw) and 4-aminopyridine (10 μg/paw), and of a non-specific K^+ channel blocker, cesium (500 μg/paw). This study provides evidence that the peripheral antinociceptive effect of SNC80 result from the activation of ATP-sensitive K^+ channels, and the other K^+ channels are not involved.

Keywords: SNC80; δ-Opioid receptor agonist; K^+ channel; Peripheral antinociception; PGE_2

1. Introduction

The δ opioid receptor is a target for analgesic drug development, since agonists acting on this receptor elicit effective antinociception in animal models of pain and appear to show a limited ability to produce many of the non-therapeutic side effects primarily associated with a μ receptor-acting opiate analgesic such as morphine (Rapaka and Porreca, 1991). Potential advantages of δ opioid receptor agonists include the production of analgesia with a reduction or absence in the development of physical dependence (Cowan et al., 1988), reduced constipation (Sheldon et al., 1990), and reduced respiratory depression (Cheng et al., 1993).

Supporting evidence for δ-opioid receptor-mediated antinociception was provided by the introduction of pharmacological agonists and antagonists with greater selectivity for the δ-opioid receptor. SNC80 was developed as a highly selective δ-opioid receptor agonist (Calderon et al., 1994) and produces an effective, antinociceptive response after systemic administration (Bilsky et al., 1995). Other specific agonists for this receptor such as DPDPE (Mosberg et al., 1983), deltorphins (Erspamer et al., 1989; Kreil et al., 1989), and BW373U86 (Chang et al., 1993) also demonstrated that the δ-opioid receptor was capable of mediating antinociception. According to the North et al. (1987) the δ-opioid receptor belong to the K^+ channel coupled receptor family which produce analgesia by opening K^+ channels in the central nervous system (Wild et al., 1991).

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Although it has been experimentally demonstrated that the δ-opioid receptor agonist induces analgesia, there is only minimal information about its mechanisms, specially those related to peripheral antinociception. Therefore, the aim of the present study was to determine whether specific and non-specific K^+ channel blockers have any effect on the peripheral antinociception induced by SNC80. For this purpose, we tested the effects of glibenclamide and tolbutamide, sulphonylureas that specifically block ATP-sensitive K^+ channels (Edwards and Weston, 1993); charybdotoxin, a large-conductance blocker of Ca^{2+}-activated K^+ channels (Miller et al., 1985); dequalinium, a selective small conductance blocker of Ca^{2+}-activated K^+ channels (Dunn, 1994); non-selective voltage-dependent K^+ channel blockers, 4-aminopyridine and tetraethylammonium, and cesium, a non-specific K^+ channel blocker (Cook and Quast, 1990).

2. Materials and methods

2.1. Animals

The experiments were performed on 180–220 g male Wistar rats (from CEBIO-UFMG). The animals were housed in a temperature-controlled room (23±1 °C) on an automatic 12-h light/dark cycle (06:00–18:00 h). All tests were conducted during the light phase (08:00–15:00 h). Food and water were freely available until the beginning of the experiments.

2.2. Measurement of the hyperalgesia

Hyperalgesia was induced by subcutaneous injection of PGE_2 (2 μg) into the plantar surface of the hind paw. The hyperalgesia was measured according to the paw pressure test described by Randall and Sellito (1957). An analgesimeter was used (Ugo-Basile, Italy) with a cone-shaped paw-presser with a rounded tip which applies a linearly increasing force to the hind paw. The weight in grams (g) required to elicit a nociceptive response such as paw flexion was determined as the nociceptive threshold. A cut-off value of 300 g was used to prevent damage to the paws. The nociceptive threshold was measured in the right paw and determined as the average of the three consecutive trials recorded before and 3 h after PGE_2 injection. The threshold was calculated as the difference between these two averages (Δ of nociceptive threshold) and is expressed in grams.

2.3. Drug administration

The drug used as a hyperalgesic agent was PGE_2 (Sigma, USA), and SNC80 (Tocris, USA) was used as the δ-opioid receptor agonist. BNTX (Tocris, USA) and naltriben (Tocris, USA) were used as δ_1 and δ_2 opioid receptor antagonists, respectively. The K^+ channel blockers were glibenclamide (Sigma), tolbutamide (ICN Biomedicals, USA), tetraethylammonium chloride (Sigma), 4-aminopyridine (Sigma), dequalinium chloride (Calbiochem, USA), charybdotoxin (Sigma) and cesium (Mitsuma's Pure Chemicals, Japan). SNC80 and PGE_2 were dissolved in isotonic saline and injected in a volume of 100 μl/paw. The opioid receptor antagonists were dissolved in isotonic saline and injected in a volume of 50 μl/paw. The K^+ channel blockers were dissolved in demineralized water, with the exception of the sulphonylureas, which were dissolved in tween 80 vehicle (2% in saline), immediately before use and injected in a volume of 50 μl/paw.

2.4. Experimental protocol

SNC80 was administered subcutaneously in the right hind paw 90 min after local injection of PGE_2. In the protocol used to determine whether SNC80 was acting outside the injected paw, PGE_2 was injected into both hind paws, while SNC80 was administered 90 min later into left paw. The nociceptive threshold was always measured in the right hind paw. The opioid receptor antagonists were administered 45 min after SNC80. The K^+ channel blockers, 4-aminopiridine and tetraethylammonium, were administered 30 min before SNC80. Other K^+ channel blockers were injected 5 min before SNC80 (based in Ortiz et al., 2002).

2.5. Statistical analysis

The data were analyzed statistically by one-way analysis of variance (ANOVA) with post-hoc Bonferroni's test for multiple comparisons. Probabilities less than 5% ($P<0.05$) were considered to be statistically significant.

3. Results

3.1. Antinociceptive effect of SNC80

The administration of SNC80 (20, 40 and 80 μg) into the right hind paw produced an antinociceptive response against the hyperalgesia induced by prior local injection of PGE_2 (2 μg/paw) in a dose-dependent manner (Fig. 1). SNC80 at a dose of 80 μg, when administered into the left paw, did not produce an antinociceptive effect in the right paw, whereas SNC80 at a dose of 240 μg, when injected into the left paw, induced a potent antinociceptive effect in the contralateral paw (Fig. 2).

3.2. Effect of BNTX and naltriben on SNC80-induced antinociception

The BNTX (10 μg/paw)–Naltriben (5 μg/paw) combination completely antagonized the peripheral antinoci-

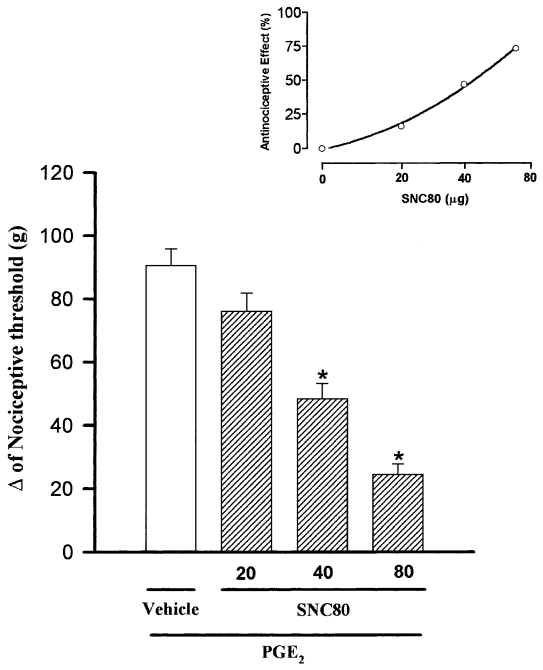

Fig. 1. Effect of SNC80 on the nociceptive threshold in PGE_2-induced hyperalgesia in rats. SNC80 (20, 40, 80 μg) was administered 90 min after local administration of 100 μl of PGE_2 (2 μg). The antinociceptive response was measured in the paw pressure test as described in Section 2. The figure above is a log dose-response curve (ED_{50}=48.3 μg). Each column represents the mean±S.E.M. (n=5). *Indicates a significant difference from the PGE_2+vehicle-injected control (P<0.05, ANOVA+Bonferroni's test).

ception induced by SNC80 (80 μg) (Fig. 3). These drugs do not induce hyperalgesia or antinociception by themselves.

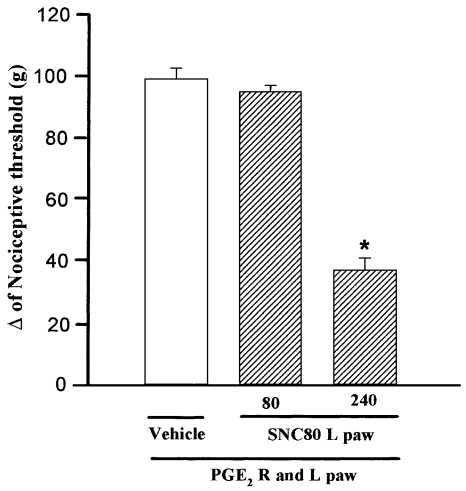

Fig. 2. Exclusion of outside paw antinociceptive effect of SNC80. SNC80 (μg) was administered into the left (L) paw 90 min after PGE_2 (2 μg) administration into both hind paws, right (R) and left (L). The antinociceptive response of the right (R) hind paw was measured by the paw pressure test as described in Materials and methods. Each column represents the mean±S.E.M. (n=5). *Indicates a significant difference from the PGE_2+vehicle-injected control (P<0.05, ANOVA+Bonferroni's test).

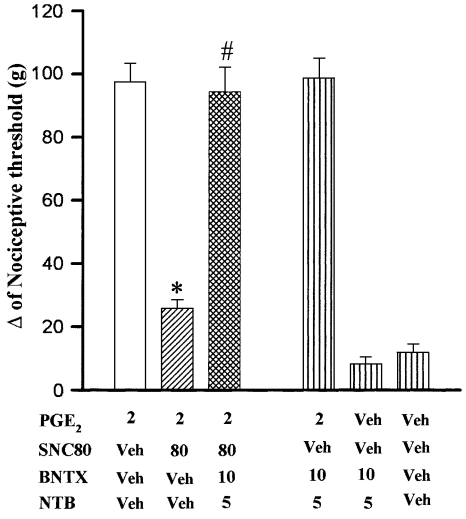

Fig. 3. Complete antagonism induced by intraplantar administration of BNTX–naltriben combination of the peripheral antinociception produced by SNC80 in hyperalgesic paws (PGE_2, 2 μg). BNTX–naltriben combination (μg/paw) was administered 45 min after SNC80 (80 μg/paw). Each column represents the mean±S.E.M. (n=5). * and # indicate a significant difference compared to (PGE_2+Veh+Veh) and (PGE_2+SNC80+Veh)-injected controls, respectively (P<0.05, ANOVA+Bonferroni's test). Veh=vehicle.

3.3. Antagonism of SNC80-induced antinociception by glibenclamide and tolbutamide

Glibenclamide (20, 40 and 80 μg/paw) significantly reduced the SNC80-induced peripheral antinociception (80 μg/paw) in a dose-dependent manner (Fig. 4). As shown in Fig. 5, the other sulphonylurea tested, tolbutamide, at doses of 40, 80 and 160 μg/paw also significantly inhibited the

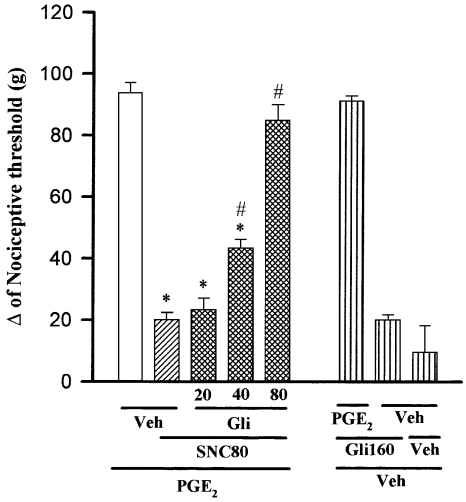

Fig. 4. Antagonism induced by intraplantar administration of glibenclamide of the peripheral antinociception produced by SNC80 in hyperalgesic paws (PGE_2, 2 μg). Glibenclamide (μg) was administered 5 min before SNC80 (80 μg/paw). Each column represents the mean±S.E.M. (n=5). * and # indicate a significant difference compared to (PGE_2+vehicle+vehicle) and (PGE_2+vehicle+SNC80)-injected controls, respectively (P<0.05, ANOVA+Bonferroni's test).

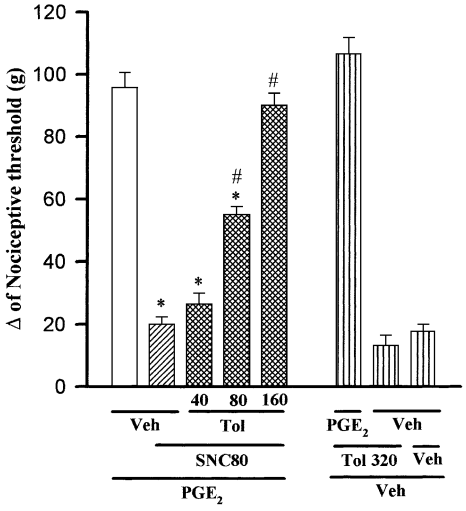

Fig. 5. Antagonism induced by intraplantar administration of tolbutamide of the peripheral antinociception produced by SNC80 in hyperalgesic paws (PGE_2, 2 μg). Tolbutamide (μg) was administered 5 min before SNC80 (80 μg/paw). Each column represents the mean±S.E.M. (n=5). * and # indicate a significant difference compared to (PGE_2+vehicle+vehicle) and (PGE_2+vehicle+SNC80)-injected controls, respectively (P<0.05, ANOVA+Bonferroni's test).

SNC80-induced antinociceptive effect. Neither of the sulphonylurea tested significantly modified the nociceptive threshold in control animals nor did they induce any overt behavioural effect.

3.4. Effect of tetraethylammonium, 4-aminopyridine, dequalinium, charybdotoxin and cesium on SNC80-induced antinociception

Tetraethylammonium (30 μg) and 4-aminopyridine (10 μg) injected into the paw did not significantly reduce the peripheral antinociception induced by SNC80 (Fig. 6A). Dequalinium (50 μg), charybdotoxin (2 μg) and cesium (500 μg) also failed to significantly counteract the antinociception induced by SNC80 (Fig. 6B). These drugs do not induce hyperalgesia or antinociception by themselves (not shown).

4. Discussion

In view of the scarce information about the analgesic mechanism of δ-opioid receptor agonists, the present work had the objective of determining whether potassium channels are involved in the peripheral antinociception of SNC80, a δ-opioid receptor agonist (Bilsky et al., 1995).

Initially, we tested the ability of SNC80 to induce peripheral antinociception. Our data showed that SNC80 produced a dose-dependent peripheral antinociceptive effect in the rat paw PGE_2-induced hyperalgesia test. These results are in agreement with a previous study that demonstrated that a locally administered δ-opioid agonist can produce an antinociceptive effect by interacting with peripheral opioid receptors (Nozaki-Taguchi and Yamamoto, 1998). Also, Herz (1995) demonstrated that opioids are able to inhibit nociception arising from inflamed tissue by local peripheral activation of μ, δ and κ receptors, presumably located in the terminal region of the sensory nerves.

In order to exclude the possibility that SNC80, at a dose of 80 μg/paw, produced antinociception by acting at sites outside the paw, we used the strategy of evaluating the efficacy of ipsi versus contralateral paw administration. We chose this strategy because the route and site of injection would be the same. PGE_2 was injected into both hind paws, thus creating the same tissue conditions and equal possibility that the agents tested would reach sites outside the injected paw. Remembering that the nociceptive threshold was always measured in the right paw, SNC80

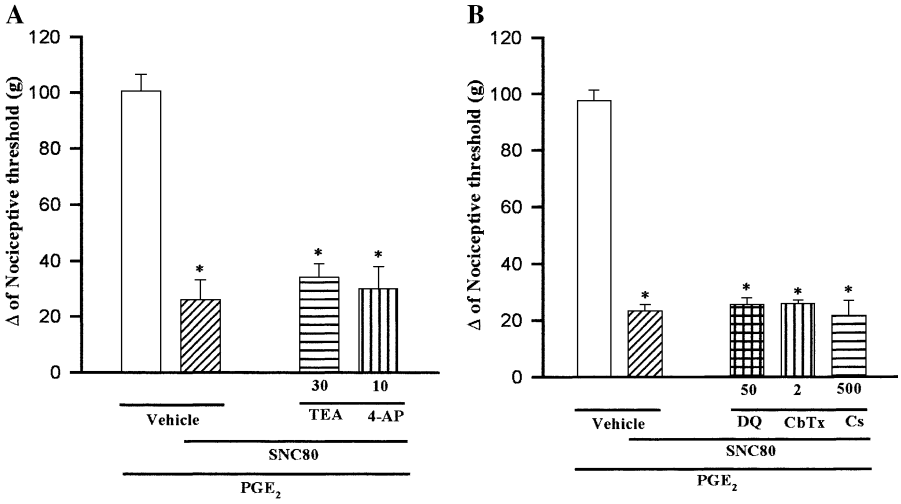

Fig. 6. Effect of intraplantar administration of (A) tetraethylammonium (TEA) and 4-aminopyridine (4-AP); (B) dequalinium (DQ), charybdotoxin (CbTx) and cesium (Cs) on the peripheral antinociception produced by SNC80 in the hyperalgesic paw. TEA and 4-AP (μg) were administered 30 min before SNC80 (80 μg). Other blockers were administered 5 min before SNC80 (80 μg). Each column represents the mean±S.E.M. (n=5). *Indicates a significant difference from the PGE_2+vehicle+vehicle control group (P<0.05, ANOVA+Bonferroni's test).

at dose of 80 μg was ineffective when administered into the contralateral paw. However, when the dose of SNC80 was increased to 240 μg a significant increase in the nociceptive threshold was observed, as measured in the hyperalgesic contralateral paw. This experiment showed that SNC80 had no central or systemic effects at the dose used in the present study (80 μg/paw).

In order to confirm the involvement of the δ opioid receptor in the peripheral antinociception induced by SNC80, BNTX and Naltriben were used in the present study. It was observed that BNTX and naltriben, separately administered in maximum doses, partially blocked the peripheral antinociceptive effect of SNC80 (not shown), but were able to completely revert this effect when combined, suggesting a complementary participation of both receptors.

Our results demonstrated that the sulphonylureas glibenclamide and tolbutamide could prevent the peripheral antinociceptive effect induced by SNC80 in a dose-dependent manner. Sensitivity to sulphonylureas is commonly used to characterize the ATP-sensitive K^+ channels (Babenco et al., 1998). These drugs specifically block ATP-sensitive K^+ channels, with no effect on Ca^{2+}-activated K^+ channels or voltage-dependent K^+ channels (Amoroso et al., 1990; Nichols and Lederer, 1991; Edwards and Weston, 1993). In 2000, Rodrigues and Duarte demonstrated that ATP-sensitive K^+ channels play an important role in μ-opioid analgesia. It has also been demonstrated that glibenclamide reverses the effect of the δ-opioid agonist DPDPE in arrhythmic rats (Maslov et al., 2001). It is important to emphasize that the sulphonylureas tested did not cause any hyperalgesic or antinociceptive effect when administered alone (see Results).

In contrast, voltage dependent K^+ channel blockers, tetraethylammonium and 4-aminopyridine, did not exhibit any effect in the peripheral antinociception induced by SNC80. Ocaña et al. (1995), while studying the central antinociceptive effect of morphine and fentanyl, Rodrigues and Duarte (2000), in a study of the peripheral antinociceptive action of morphine and Soares et al. (2000), in a study of the mechanism of peripheral antinociceptive action of sodium nitroprusside also observed that these blockers failed in reverse the action of the antinociceptive substances tested. On the other hand, in recent experiments our group demonstrated that both TEA and 4-AP (same dose and time as those used for SNC80) reverted the peripheral antinociceptive effect elicited by GABA-B agonist baclofen (not published). These data are supported by those of Ocaña and Baeyens (1993) who reported that these two blockers had been able to block baclofen-induced antinociception in mice. The blockers utilized in the present study did not cause any hyperalgesic or antinociceptive effect.

Dequalinium, a selective blocker of small conductance Ca^{2+}-activated K^+ channels (Castle et al., 1993; Dunn, 1994) and charybdotoxin, a blocker of large conductance Ca^{2+}-activated K^+ channels (Mackinnon and Miller, 1988) also failed to antagonize the peripheral antinociceptive effect induced by SNC80. These drugs do not induce hyperalgesia or antinociception by themselves.

Alves et al. (2004) demonstrated that NS1619, a specific opener of large conductance Ca^{2+}-activated K^+ channels, did not produce antinociceptive action in hyperalgesia induced by PGE_2, suggesting that these channels were not involved in this effect. In contrast, Ortiz et al. (2002) studying the involvement of K^+ channels in the antinociceptive action of diclofenac in the formalin test demonstrated that charybdotoxin reverted the effect of diclofenac.

Similarly with the results using Ca^{2+}-activated K^+ channel blockers, cesium did not have any effect in the peripheral antinociception induced by SNC80. Also, Alves and Duarte (2002) observed that cesium did not exhibit any effect in the peripheral antinociception induced by dipirone.

In conclusion, our results support the suggestion that the peripheral antinociceptive effect of SNC80 is associated with ATP-sensitive K^+ channels activation and also that other K^+ channels do not appear to be involved in this effect.

Acknowledgements

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