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Activity of nicorandil, a nicotinamide derivative with a nitrate group, in the experimental model of pain induced by formaldehyde in mice

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ABSTRACT

Nicorandil (2-nicotinamide ethyl nitrate), an antianginal drug characterized by the coupling of nicotinamide with a nitric oxide (NO) donor, activates guanylyl cyclase and opens ATP-dependent K^+ channels. In the present study, we investigated the effects induced by per os (p.o.) administration of nicorandil (12.5, 25 or 50 mg/kg) or equimolar doses (corresponding to the highest dose of nicorandil) of N-(2-hydroxyethyl) nicotinamide (NHN), its main metabolite, or nicotinamide in the model of nociceptive response induced by formaldehyde in mice. Nicorandil, but not NHN or nicotinamide, inhibited the second phase of the nociceptive response. This activity was observed when nicorandil was administered between 30 and 120 min before the injection of formaldehyde. Ipsilateral intraplantar injection of nicorandil (125, 250 or 500 μg/paw) did not inhibit the nociceptive response. After p.o. administration of nicorandil (50 mg/kg), peak plasma concentrations of this compound and NHN were observed 0.63 and 4 h later, respectively. Nicotinamide concentrations were not increased after administration of nicorandil. 1H-[1,2,4]oxadiazolo[4,3-a]quinoxalin-1-one (ODQ; 1 or 2 mg/kg), a guanylyl cyclase inhibitor, partially attenuated the antinociceptive activity of nicorandil. However, this activity was not changed by glibenclamide (30 or 60 mg/kg), an inhibitor of ATP-dependent K^+ channels. In conclusion, we demonstrated the antinociceptive activity of nicorandil in a model of pain that exhibits both a nociceptive and an inflammatory profile. This activity is not mediated by nicotinamide or NHN. The coupling of an NO-donor to nicotinamide results in a compound with an increased potency. The NO–cGMP pathway, but not ATP-dependent K^+ channels, partially mediates the antinociceptive activity of nicorandil.

1. Introduction

Discovering new functions of drugs already used in the clinic is among the different and important strategies that have been promoted to optimize the development of new and safe pharmacotherapies, with lower costs and in a shorter period of time (Ashburn and Thor, 2004). B vitamins, traditionally used to correct nutritional deficiencies, exhibit analgesic and anti-inflammatory properties when administered in patients with neuropathic disorders (Jörg et al., 1988), premenstrual tension (Wyatt et al., 1999) and carpal tunnel syndrome (Folkers et al., 1984) and are useful in migraine prophylaxis (Boehnke et al., 2004; Schoenen et al., 1998). Expectedly, B vitamins, including thiamine, pyridoxine and riboflavin, also induce effects in different experimental models of pain and inflammation (Bertollo et al., 2006; Bartoszyk and Wild, 1990; França et al., 2001; Zimmermann et al., 1990). In addition, another member of the B vitamin family, nicotinamide, suppresses arthritis and inhibits the phagocytic generation of reactive oxygen species in an experimental model of arthritis (Miesel et al., 1995), the paw edema and mechanical allodynia induced by carrageenan and the nociceptive response induced by formaldehyde and heat in rodents (Godin et al., 2011).

Nicorandil, a nicotinamide nitrate derivative (2-nicotinamide ethyl nitrate; Fig. 1), is a nitric oxide (NO) donor approved for the treatment of patients with angina pectoris (El-Moselby et al., 2009; Frampton et al., 1992). In addition to releasing NO, nicorandil may be converted in vivo to N-(2-hydroxyethyl)-nicotinamide (NHN, Fig. 1), the main metabolite (César et al., 2011; Frydman et al., 1989), and also nicotinamide (Frydman et al., 1989). NO-donors have been used to treat patients with angina due to their vasodilator properties, but it has been acknowledged that an intrinsic analgesic activity associated with the release of NO is also involved (Ferreira et al., 1992; Soares et al., 2000). It has been demonstrated that NO-donors induce antinociceptive and anti-hyperalgesic effects in different experimental models of pain,

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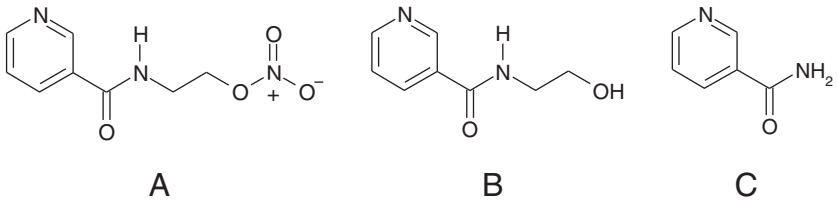

Fig. 1. Chemical structures of nicorandil (A), NHN (B) and nicotinamide (C).

although this activity depends on the local concentration of NO and its location (Duarte et al., 1990; Soares et al., 2000; Sousa and Prado, 2001). The demonstration of the antinociceptive and anti-hyperalgesic activities of NO donors contributed to the search for new compounds with fewer side effects and greater efficacy such as the NO-releasing steroidal and non-steroidal anti-inflammatory drugs (Galassi et al., 2006; Keeble and Moore, 2002). Regarding nicorandil, it has been shown that its central administration, while not inducing antinociception per se, exacerbates the antinociceptive effect induced by morphine, fentanyl, bethanechol and clonidine in experimental models of nociceptive pain induced by heat in rats (Asano et al., 2000; Yamazumi et al., 2001).

In the present study, we investigated the effects induced by systemic administration of nicorandil in the experimental model of pain induced by formaldehyde in mice, a model that exhibits both a nociceptive and an inflammatory profile. We also investigated whether the activity of nicorandil is mediated by biotransformation to nicotinamide or NHN and involves activation of guanylyl cyclase and ATP-dependent potassium channels.

2. Materials and methods

2.1. Animals

Male Swiss mice (25–30 g) were used and had free access to food and water. The animals were kept in a room with 12 h light–dark cycle and temperature of 27 °C, which corresponds to the thermoneutral zone for rodents, for at least 3 days before the experiment to allow acclimatization. This study was approved by the Ethics Committee on Animal Experimentation of the Federal University of Minas Gerais (Protocol 131/11) and all experiments were conducted according to the ethical guidelines for investigation of experimental pain in conscious animals (Zimmermann, 1986).

2.2. Drugs

Nicorandil and NHN, both with purity >99.0%, were synthesized at the Department of Chemistry, Federal University of Minas Gerais. Nicotinamide, glibenclamide, 1H-[1,2,4]oxadiazolo[4,3-a]quinoxalin-1-one (ODQ), and dipyrone sodium were purchased from Sigma, USA. Phenobarbital was purchased from Aventis Pharma, Brazil. Nicotinamide and dipyrone solutions were prepared in saline. The suspensions of nicorandil, NHN and phenobarbital for per os (p.o.) administration were prepared in carboxymethylcellulose (CMC; 0.5% w/v in saline). The suspension of nicorandil for local administration (intraplantar, i.pl.) was prepared in 2% dimethyl sulfoxide (DMSO). The suspensions of glibenclamide and ODQ were prepared in 1% CMC and 4% DMSO, respectively. The solutions of formaldehyde (0.92 or 1.84%) were prepared in saline. All solutions or suspensions were prepared immediately before each experiment.

2.3. Evaluation of the nociceptive response induced by formaldehyde

On the experiment day, the animals were placed under glass funnels (18 cm diameter and 14 cm high) about 30 min before injection of formaldehyde to allow acclimatization. Formaldehyde (0.92%, 20 μl) was injected subcutaneously (s.c.) into the dorsal surface of the right hindpaw of the animals. In the protocol used to investigate the effect induced by local injection of nicorandil or dipyrone, a volume of 10 μl of 1.84% formaldehyde solution was used. The amount of time that the animal licked the injected paw was measured 0–5 min and 15–30 min after the injection of formaldehyde, corresponding to the first and second phases of the nociceptive response, respectively (Tjølsen et al., 1992).

In most of the protocols, nicorandil was administered p.o. 60 min before the injection of formaldehyde. However, in one protocol aimed to assess the duration of its effect, nicorandil was administered at different times (30, 60, 120, 180 or 240 min) before the administration of formaldehyde. NHN and nicotinamide were administered p.o. 60 min before the injection of formaldehyde. ODQ (intraperitoneal, i.p.) and glibenclamide (p.o.) were administered 30 and 60 min, respectively, before nicorandil. To investigate the effects induced by local injection of nicorandil or dipyrone, these drugs were administered i.pl. 20 min before the injection of formaldehyde. The animals were carefully monitored during the interval between administration of nicorandil and injection of formaldehyde to evaluate whether the local injection of nicorandil could induce a behavior indicative of discomfort.

2.4. Evaluation of the motor activity

A rota-rod apparatus was used to evaluate the motor activity of the animals. The animals were trained on the apparatus for 3 days before the experiment. On the experimental day, the animals were placed on the rota-rod (14 rpm) and the time they spent on it was measured. The cut-off time was 2 min. After determination of the baseline values, the animals were treated with nicorandil (50 mg/kg, p.o.) or phenobarbital (40 mg/kg, p.o.) and 60 min later they were again tested in the apparatus.

2.5. Quantification of nicorandil, NHN and nicotinamide in plasma by liquid chromatography–electrospray ionization tandem mass spectrometry (LC–ESI-MS/MS)

The methods used for the quantification of nicorandil, NHN and nicotinamide were developed and validated by César et al. (2011). The mobile phase consisted of methanol and aqueous ammonium acetate containing 2 mM formic acid 0.03% (v/v) (33:67 v/v) in the flow rate of 1 ml/min. The injection volume was 50 μl. The linear ranges of concentrations were: 25–75 μg/ml (nicorandil), 25–50 μg/ml (NHN) and 25–10 μg/ml (nicotinamide).

For the pharmacokinetic study, we used animals submitted to food restriction for 6 h. Nicorandil was administered p.o. at a dose of 50 mg/kg to 44 animals. At different times (5, 15, 30 and 45 min, 1, 2, 3, 4, 6, 8 and 10 h) after administration of nicorandil, a group of four animals were euthanized by decapitation after anesthesia by halothane. Twelve additional animals received an injection of vehicle. These animals, in groups of four, were euthanized immediately before and 30 and 60 min after injection of the vehicle. A blood sample from each animal was collected in a heparinized tube and immediately

centrifuged at 14,000 rpm for 10 min. Then, the plasma samples were transferred to plastic tubes and stored at −70 °C until analysis.

2.6. Statistical analysis

Two or three observers, that were not aware of the treatments, evaluated the nociceptive behavior in the different experimental protocols. Results were expressed as mean ± standard error of mean. Data were analyzed by one-way ANOVA, followed by Newman–Keuls test or Student's t test. For dose–response curves one-way ANOVA and subsequent linear regression ANOVA were performed. A $p < 0.05$ was considered significant.

3. Results

3.1. Effects induced by p.o. administration of nicorandil or equimolar doses of NHN or nicotinamide on the nociceptive response induced by formaldehyde

Nicorandil, at the dose of 50 mg/kg, inhibited the second phase of nociceptive response induced by formaldehyde. However, equimolar doses of nicotinamide or the metabolite NHN (Fig. 2) did not inhibit this response. The effects induced by lower doses of nicorandil (12.5 and 25 mg/kg) were also evaluated. Although the dose of 25 mg/kg partially inhibited the nociceptive response, this reduction was not statistically significant (Fig. 2).

To investigate whether the inhibition of the nociceptive behavior induced by nicorandil is not the result of a motor impairment, we evaluated the effect induced by the drug on the performance of the animals on the rota-rod apparatus. Nicorandil (50 mg/kg) did not alter the time mice spent in the apparatus, while phenobarbital (40 mg/kg) markedly reduced this parameter (data not shown).

To assess the duration of the effect induced by nicorandil and also to evaluate if there is a relation between the antinociceptive effect induced by the drug and its pharmacokinetic profile, a protocol in which the drug was administered at different times before the administration of formaldehyde was carried out. Nicorandil inhibited the first phase of the nociceptive response only when administered 30 min prior to administration of the nociceptive stimulus. The second phase of the nociceptive response induced by formaldehyde was inhibited when nicorandil was given 30, 60 or 120 min before. On the other hand, the administration of nicorandil 3 or 4 h before the administration of formaldehyde did not inhibit the nociceptive response (Fig. 3).

3.2. Plasma concentrations of nicorandil, NHN and nicotinamide after p.o. administration of nicorandil

After administration of nicorandil (50 mg/kg), peak plasma concentrations of the drug and its primary metabolite, NHN, were found 0.63 and 4 h, respectively (Fig. 4). The plasma concentrations

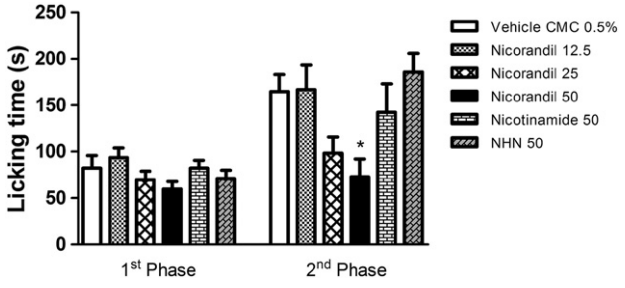

Fig. 2. Effect induced by nicorandil (12.5, 25 or 50 mg/kg, p.o., −60 min) or a dose of nicotinamide or NHN (equimolar to 50 mg/kg of nicorandil, p.o., −60 min) on the nociceptive response induced by formaldehyde. n = 6–8. * indicates statistically significant difference compared to the vehicle treated group ($p < 0.05$).

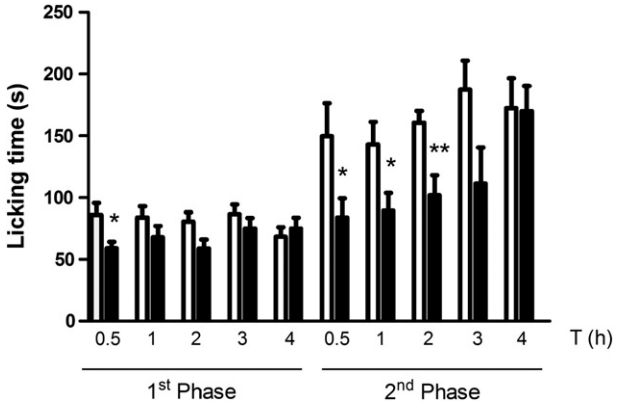

Fig. 3. Effect induced by nicorandil (50 mg/kg, p.o.) administered at different times (−0.5, −1, −2, −3 or −4 h) on the nociceptive response induced by formaldehyde. * and ** indicate statistically significant difference compared to the vehicle treated group at the respective times ($p < 0.05$ and $p < 0.01$, respectively). n = 6–8.

of nicorandil between 30 and 120 min after its administration ranged from 20 to 25 μg/ml. As the drug induced an antinociceptive effect when administered 30 to 120 min before the injection of formaldehyde, this effect was associated with the highest plasma concentrations of nicorandil. On the other hand, the concentrations of nicotinamide ranged between 1.4 and 3.3 μg/ml after administration of nicorandil and did not differ from that observed in the plasma of untreated animals.

From the analysis of the results presented in Fig. 4, some pharmacokinetic parameters were calculated for nicorandil and NHN. These parameters included maximum plasma concentration, time to reach maximum concentration (T_{max}) and elimination half-life ($T_{1/2}$) and are shown in Table 1.

3.3. Effect induced by i.pl. administration of nicorandil on the nociceptive response induced by formaldehyde

To evaluate whether the antinociceptive effect induced by nicorandil could be the result of an action at the peripheral site where the noxious stimulus was injected, the drug was administered via the i.pl. route at the doses of 125, 250 or 500 μg/paw, 20 min before the injection of formaldehyde. The i.pl. administration of nicorandil failed to inhibit the nociceptive response induced by formaldehyde (Fig. 5). The animals were carefully monitored during the interval between i.pl. administration of nicorandil or vehicle and the injection of formaldehyde, leading to the conclusion that the i.pl. injection of nicorandil, per se, does not induce a behavior indicative of discomfort (licking or shaking the injected paw). The nociceptive response induced by formaldehyde may be inhibited by the local action of drugs, as confirmed by the demonstration that previous (20 min) ipsilateral, but not contralateral, administration of dipyrone (200 μg/paw) inhibited this response (data not shown).

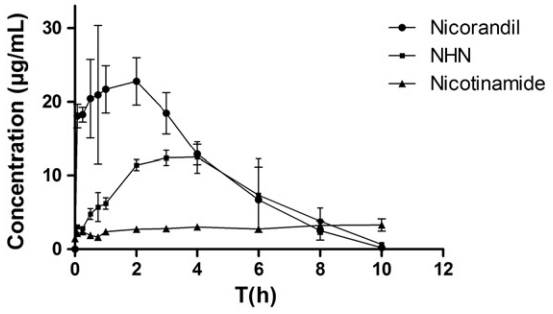

Fig. 4. Plasma concentrations of nicorandil, NHN and nicotinamide observed after administration of nicorandil (50 mg/kg, p.o.). n = 4 at each point.

Table 1
Maximum concentration, time for maximum concentration (T_{max}) and elimination half-life ($T_{1/2}$) of nicorandil and NHN after p.o. administration of nicorandil (50 mg/kg).

	Maximum concentration (μg/ml)	T_{max} (h)	$T_{1/2}$ (h)
Nicorandil	30.92 ± 9.64	0.63 ± 0.32	1.06 ± 0.48
NHN	16.82 ± 3.63	4.00 ± 1.41	1.45 ± 0.50

3.4. Effects induced by glibenclamide or ODQ on the antinociceptive activity of nicorandil

The administration of glibenclamide (30 or 60 mg/kg; p.o.), 60 min before the p.o. administration of nicorandil (50 mg/kg), did not affect its antinociceptive activity (Fig. 6). On the other hand, the antinociceptive activity of nicorandil (50 mg/kg) was partially attenuated in the animals previously (30 min) treated with ODQ (2 mg/kg; i.p.) (Fig. 7).

4. Discussion

Central administration of nicorandil, while not inducing antinociception per se, exacerbates the antinociceptive effect induced by morphine, fentanyl, bethanechol and clonidine in rodents (Asano et al., 2000; Yamazumi et al., 2001). In the present study, we demonstrated that systemic administration of nicorandil per se induces an antinociceptive effect in an experimental model of pain that exhibits both a nociceptive and an inflammatory profile. The nociception induced by formaldehyde results from the fast activation of the transient receptor potential channels $TRPA_1$ (McNamara et al., 2007) and $TRPV_1$ (Tian et al., 2009) and also the inflammation following the tissue damage (Hunskaar and Hole, 1987; TjøLsen et al., 1992). Excepting the protocol in which the administration occurred 30 min before formaldehyde, nicorandil inhibited only the second phase of the nociceptive response. Thus, its profile resembles more that of anti-inflammatory drugs such as indomethacin (Morgan et al., 1992) and diclofenac (León-Reyes et al., 2009). It is unlikely that the inhibitory effect induced by nicorandil on the nociceptive behavior results from muscle relaxing effect or motor incoordination, as the drug did not reduce the time that the animals spent in the rota-rod.

As nicorandil represents a coupling of nicotinamide with an NO donor, some suggestions may be put forward to explain its antinociceptive activity. These include (1) an indirect antinociceptive effect induced by nicotinamide, a compound that exhibits antinociceptive activity (Godin et al., 2011) and can be formed from nicorandil in vivo (Frydman et al., 1989); (2) an indirect antinociceptive effect induced by NHN, the nicorandil main metabolite (Frydman et al., 1989; César et al., 2011); (3) an indirect antinociceptive effect induced by NO, as nicorandil has the ability to release NO (Lefer and Lefer, 1988; Sakai et al., 2000) and NO donor drugs exhibit antinociceptive activity (Duarte et al., 1990; Sousa and Prado, 2001); (4) an antinociceptive effect induced directly by nicorandil; and (5) an antinociceptive effect resulting from a combination of two or more of the suggested mechanisms.

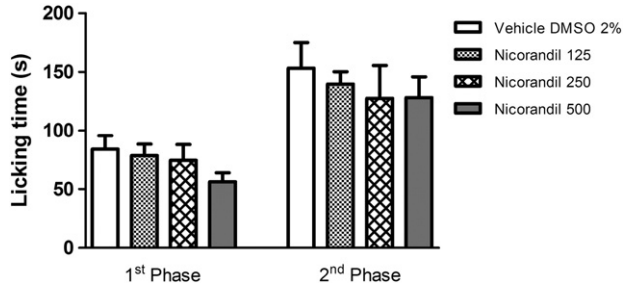

Fig. 5. Effect induced by ipsi or contralateral administration of nicorandil (125, 250 or 500 μg/paw, i.pl., −20 min) of the nociceptive response induced by formaldehyde. n = 6–7.

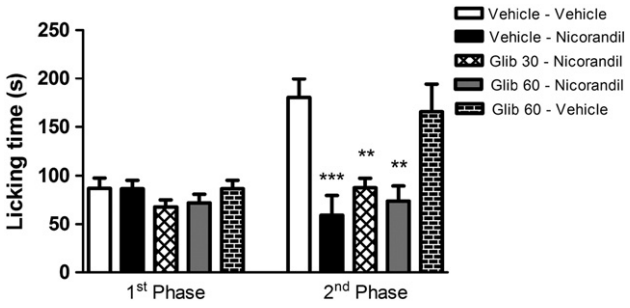

Fig. 6. Effect induced by nicorandil (50 mg/kg, p.o., −60 min) on the nociceptive response induced by formaldehyde in animals previously (60 min) treated with vehicle or glibenclamide (30 or 60 mg/kg, p.o.). ** and *** indicate statistically significant difference compared to vehicle treated group ($p < 0.01$ and $p < 0.001$, respectively). n = 7–8.

The first suggestion, i.e., the antinociceptive activity of nicorandil resulting from the action of nicotinamide, is unlikely as it was not associated with an increase of the plasma concentrations of the last compound. Furthermore, equimolar doses of nicotinamide did not induce an antinociceptive effect. Previously, using the same experimental model, we demonstrated that nicotinamide, at the dose of 1000 mg/kg, but not at the doses of 125, 250 or 500 mg/kg, exhibited antinociceptive activity (Godin et al., 2011). As nicorandil induced an antinociceptive effect at the dose of 50 mg/kg, its potency is about 34 times higher than that of nicotinamide.

Regarding the second suggestion, i.e., the antinociceptive activity of nicorandil resulting from the action of NHN, the results of the present study also indicate that it is highly unlikely. Equimolar doses of NHN did not induce an antinociceptive effect and there is also a mismatch between its plasma concentrations after nicorandil administration and the antinociceptive effect induced by the last drug. The highest concentrations of NHN were observed between 3 and 5 h after nicorandil administration while this last drug only inhibited the nociceptive response when administered between 30 and 120 min before the injection of formaldehyde.

The third suggestion, an indirect antinociceptive effect resulting from the action of NO, may also be put forward to explain the activity of nicorandil. The results of the present study provided mixed cues. Assuming that the formation of NHN is paralleled with the formation of NO, once again, a mismatch is observed between the antinociceptive activity and formation of NO. On the other hand, the previous administration of ODQ, an inhibitor of guanylyl cyclase, partially attenuates the antinociceptive activity of nicorandil. It has been shown that this enzyme catalyses the formation of cGMP, a signaling molecule that mediates many effects induce by NO (Duarte et al., 1990; Jain et al., 2001).

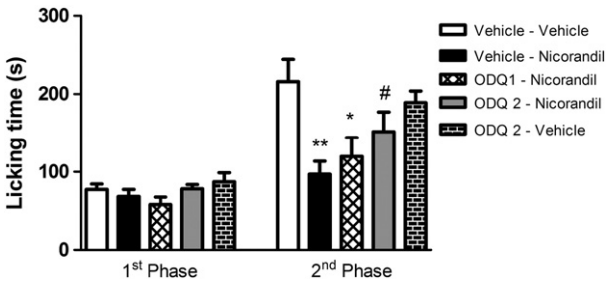

Fig. 7. Effect induced by nicorandil (50 mg/kg, p.o., −60 min) on the nociceptive response induced by formaldehyde in animals previously (30 min) treated with vehicle or ODQ (1 or 2 mg/kg, i.p.). * and ** indicate statistically significant difference compared to vehicle–vehicle treated group ($p < 0.05$ and $p < 0.01$, respectively). # indicates statistically significant difference compared to vehicle–nicorandil treated group ($p < 0.05$). n = 7–8.

The fourth suggestion is an effect induced directly by nicorandil. This possibility is likely, not only because the main metabolites of nicorandil do not exhibit antinociceptive activity (NHN and nicotinamide) or have a partial role (NO), but also because there is a good relationship between the effect induced by nicorandil and its plasma concentrations, that were maximal between 60 and 120 min, declining thereafter. Coincidentally, nicorandil induced an antinociceptive effect when administered 30 to 120 min before injection of formaldehyde, and this effect was reduced or absent when the drug was administered 3 or 4 h before the noxious stimulus. The pharmacokinetic profile of nicorandil in mice is similar to that observed in rats. T_{max} values for mice and rats (César et al., 2011) were 0.63 and 0.46 h, respectively. Moreover, the values of $T_{1/2}$ for mice and rats (César et al., 2011) were 1.1 and 1.9 h, respectively.

We also investigated whether the antinociceptive effect induced by nicorandil could be the result of an action at the peripheral site where the noxious stimulus was injected. Some NO donors induce an antinociceptive effect by activating peripheral mechanisms. Topical application of nitroglycerin to the paw attenuates the mechanical hyperalgesia induced by i.pl. injection of prostaglandin E_2 (PGE_2) and reduces the neurogenic inflammatory edema induced by electrical stimulation in rats (Ferreira et al., 1992). Furthermore, intra-articular or i.pl. administration of sodium nitroprusside induces an antinociceptive effect in a model of arthritis induced by zymosan (Rocha et al., 2002) and attenuates the hyperalgesia induced by i.pl. injection of PGE_2 (Alves et al., 2004a) in rats, respectively. As i.pl. injection of nicorandil failed to induce an antinociceptive effect, its activity after p.o. administration may be the result of an action at other sites. Although differences in animal species and experimental models used may help to explain the different results, there is evidence that nicorandil, despite being an NO donor, exhibits many differences when compared to other drugs that also release NO, particularly organic nitrates.

Regarding the cardiovascular actions of nicorandil, those that have been investigated more extensively, it is concluded that this drug exhibits important differences when compared to the traditional organic nitrates, possibly due to its ability of opening potassium channels, an activity that appears to be linked to the nicotinamide portion of the molecule (Edwards and Weston, 1990; Taira, 1987).Greenberg et al. (1991), investigating the effects induced by nicorandil and traditional organic nitrates (nitroglycerin, isosorbide dinitrate, 2-isosorbide mononitrate, 5-isosorbide mononitrate), demonstrated that nicorandil relaxes different canine blood vessels equieffectively with the traditional organic nitrates but with smaller maximal increases in cGMP. These results indicate that despite being less efficient as an activator of guanylyl cyclase when compared to the traditional organic nitrates, the vasodilator activity of nicorandil is not reduced. In addition, depending on the rat vascular bed analyzed, the vasodilator activity of nicorandil may be associated with activation of guanylyl cyclase or opening of potassium channels. However, in porcine artery preparations, the vasodilator effect is associated with the two mechanisms simultaneously (Borg et al., 1991). These results indicate the complexity of mechanistic pathways associated with the vasodilator activity of nicorandil, a drug that, in spite of being an NO donor, differs markedly in relation to the traditional organic nitrates.

In spite of differences related to vascular beds, oxygen levels and nature of contracting agonists used (Dumas et al., 1996; Pérez-Vizcaíno et al., 1998; Cogolludo et al., 1999), the vasodilation induced by nicorandil is usually mediated by activation of soluble guanylyl cyclase and opening of ATP-dependent potassium channels. Thus, we investigated whether these putative biochemical mechanisms could also contribute to the antinociceptive activity of nicorandil. To accomplish this objective, we investigated whether glibenclamide, an ATP-dependent potassium channel blocker (Alves et al., 2004b), and ODQ, a guanylyl cyclase inhibitor (Boulton et al., 1995; Garthwaite et al., 1995), could affect the antinociceptive activity of nicorandil. It is known that the antinociceptive activity of various drugs, coupled or not with NO donors, is reversed by guanylyl cyclase inhibitors and ATP-dependent potassium channel blockers (Duarte and Ferreira, 1992; Duarte et al., 1992; Ferreira et al., 1991; Prado et al., 2002).

Previous administration of ODQ partially attenuated the antinociceptive effect induced by nicorandil. However, glibenclamide failed to affect the antinociceptive activity of nicorandil. It is unlikely that the doses of glibenclamide used in the present study were low, as Ortiz (2011) have shown that much lower doses of glibenclamide (3 or 10 mg/kg) inhibit the antinociceptive effect induced by diclofenac (30 mg/kg) in the model of nociceptive response induced by formaldehyde. Altogether, these results indicate that the activity of nicorandil in the model used in the present study partially involves the activation of guanylyl cyclase, but not ATP-dependent potassium channels. They also provide support to the suggestion that besides the ODQ- and glibenclamide-sensitive mechanisms, other mechanisms mediate the antinociceptive effects induced by nicorandil.

In conclusion, systemic administration of nicorandil induces an antinociceptive effect in an experimental model of pain that exhibits both a nociceptive and an inflammatory profile. Considering pharmacokinetic data and pharmacological activity, it is highly unlikely that the antinociceptive activity of nicorandil is mediated by nicotinamide or NHN. The partial involvement of guanylyl cyclase, but not ATP-dependent potassium channels, is suggested. The demonstration of the antinociceptive activity of nicorandil may contribute to raise the interest in the clinical evaluation of its usefulness in the treatment of patients with painful disorders and, ultimately, result in a new drug repositioning.

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