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Nicotinic acid induces antinociceptive and anti-inflammatory effects in different experimental models

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ABSTRACT

Although in vitro studies have shown that nicotinic acid inhibits some aspects of the inflammatory response, a reduced number of in vivo studies have investigated this activity. To the best of our knowledge, the effects induced by nicotinic acid in models of nociceptive and inflammatory pain are not known. Per os (p.o.) administration of nicotinic acid (250, 500 or 1000 mg/kg, −1 h) inhibited the first and the second phases of the nociceptive response induced by formalin in mice. Nicotinic acid (250 or 500 mg/kg, −1 and 3 h) also inhibited the mechanical allodynia induced by carrageenan in rats, a model of inflammatory pain. However, in a model of nociceptive pain, exposure of mice to a hot-plate, nicotinic acid was devoid of activity. In addition to inhibiting the nociceptive response in models of inflammatory pain, nicotinic acid (250 or 500 mg/kg, p.o., −1 and 3 h) inhibited paw edema induced by carrageenan in mice and rats. Picolinic acid (62.5 or 125 mg/kg, p.o., −1 h), a nicotinic acid isomer, inhibited both phases of the nociceptive response induced by formalin, but not paw edema induced by carrageenan in mice. The other nicotinic acid isomer, isonicotinic acid, was devoid of activity in these two models. In conclusion, our results represent the first demonstration of the activity of nicotinic acid in experimental models of nociceptive and inflammatory pain and also provide further support to its anti-inflammatory activity. It is unlikely that conversion to nicotinamide represents an important mechanism to explain the antinociceptive and anti-inflammatory activities of nicotinic acid. The demonstration of new activities of nicotinic acid, a drug that has already been approved for clinical use and presents a positive safety record, may contribute to raise the interest in conducting clinical trials to investigate its usefulness in the treatment of painful and inflammatory diseases.

1. Introduction

Nicotinic acid, a member of the vitamin B family, was identified as the precursor in the synthesis of nicotinamide adenine dinucleotide (NAD^+) and its analog nicotinamide adenine dinucleotide phosphate ($NADP^+$) (Ijichi et al., 1966). These coenzymes participate in several metabolic pathways and cell signaling (Bogan and Brenner, 2008; Pollak et al., 2007). In addition to being a nutrient, Altschul et al. (1955) demonstrated that high doses of nicotinic acid decrease plasma concentrations of cholesterol. Nicotinic acid is the oldest drug used in the treatment of dyslipidemia and induces favorable changes in some lipid parameters: reduction of the concentrations of total cholesterol, triglycerides, very low density lipoprotein, low density lipoprotein and increase of the concentration of high density lipoprotein (Carlson, 2005; Wierzbicki, 2011).

In addition to inducing favorable changes in lipid metabolism, nicotinic acid exhibits antioxidant and anti-inflammatory properties that may also contribute to its efficacy in the treatment of atherosclerotic cardiovascular disease (Tavintharan et al., 2011). Nicotinic acid inhibits the production of reactive oxygen species and inflammatory mediators induced by different stimuli in cultured human endothelial cells (Ganji et al., 2009; Tavintharan et al., 2009). These mediators promote chemotaxis and adhesion of monocytes involved in the formation of the atherosclerotic plaque. Ganji et al. (2009) also showed that nicotinic acid inhibits low density lipoprotein oxidation and increases the concentrations of NADPH and glutathione, which inhibit the production of free radicals. Moreover, it has been shown that nicotinic acid inhibits the production of atherogenic chemokines and upregulates the atheroprotective adiponectin in adipocytes (Digby et al., 2010).

Although many in vitro studies have provided results showing that nicotinic acid inhibits some aspects of the inflammatory response independently of its effects on lipid metabolism, few in vivo studies have been carried out to investigate this property. Wang et al. (1990) showed that nicotinic acid attenuates bleomycin-induced accumulation of inflammatory cells in the lungs of hamsters. In addition, it has been shown that nicotinic acid markedly attenuates NFκB activation and inflammatory cytokine gene expression in lung

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tissues of endotoxemic rats and, more importantly, reduces lung damage and improves survival (Kwon et al., 2011).

To the best of our knowledge, the effects induced by nicotinic acid in models of nociceptive and inflammatory pain have not been investigated. Evaluating the effects induced by nicotinic acid in experimental models of pain and inflammation is warranted as there is evidence from in vitro studies indicating that this drug also presents anti-inflammatory activity (Digby et al., 2010; Ganji et al., 2009). In addition, studies aiming to reposition existing drugs for new indications is a widely justified trend that is increasing steadily in recent years (Ashburn and Thor, 2004) and it has been shown that many drugs that were originally approved for the treatment of patients with dyslipidemias exhibit anti-inflammatory and antinociceptive activities (Barsante et al., 2005; Garcia et al., 2011; Oliveira et al., 2007).

We have recently demonstrated the antinociceptive and anti-inflammatory activities of nicotinamide in such models (Godin et al., 2011). As nicotinic acid may be converted to nicotinamide in vivo (Collins and Chaykin, 1972; Petrack et al., 1966), it would be interesting to investigate whether both compounds share these activities and thus provide information that could contribute to expand their use in the treatment of painful or inflammatory conditions. Regarding the nicotinic acid isomers, picolinic and isonicotinic acids, Heyliger et al. (1998) showed that systemic administration of picolinic acid in mice induces antinociceptive effect in experimental models of thermal nociceptive pain. Similarly to the experimental approach we used in our previous study (Godin et al., 2011), we also investigated the effects induced by nicotinic acid isomers, picolinic and isonicotinic acids (Fig. 1), to establish whether the change of the lateral chain position in the pyridine ring could result in compounds with different activities.

2. Materials and methods

2.1. Animals

Female Swiss mice (24–28 g) and Wistar rats (200–250 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. The temperature of 27 °C was used because the thermoneutral zone for mice and rats ranges between 26 and 34 °C, temperatures that markedly differ from that of standard laboratory environments which could be stressful and affect many aspects of physiology and behavior (Gaskill et al., 2009; Gordon, 1990). All experiments were approved by the Ethics Committee on Animal Experimentation of the Federal University of Minas Gerais and carried out according to the ethical guidelines for investigation of experimental pain in conscious animals (Zimmermann, 1983).

2.2. Drugs

Suspensions of nicotinic acid (Sigma, USA), isonicotinic acid (Sigma-Aldrich, Germany), picolinic acid (Sigma-Aldrich, Germany), dexamethasone 21-phosphate disodium salt (Sigma, USA), dipyrone (Sanofi Aventis, Brazil) and phenobarbital (Aventis Pharma, Brasil) were prepared in 0.5% carboxymethylcellulose sodium salt (Sigma, USA) suspension in saline immediately before the experiments. Suspensions were administered per os (p.o.) in a volume of 12 ml/kg. λ–carrageenan (Sigma, USA) suspension and formaldehyde (Sigma, USA) solution were prepared in saline.

Fig. 1. Chemical structures of nicotinic acid and its isomers, picolinic and isonicotinic acids.

2.3. Evaluation of the nociceptive response induced by formalin in mice

One hour after p.o. administration of nicotinic, isonicotinic or picolinic acids, a volume of 20 μl of formalin (2.5%, corresponding to 0.92% formaldehyde) was injected via the subcutaneous (s.c.) route into the dorsum of the right hind paw. Each mouse was placed under a transparent glass funnel (18 cm diameter, 15 cm-high) and the amount of time that the animal licked the injected paw was determined between 0 and 5 min (first phase) and 15 and 30 min (second phase) after the injection of formalin.

2.4. Evaluation of the nociceptive response of mice in the hot-plate model

We selected the plate temperature of 50 °C to evaluate the effect induced by nicotinic acid in this model of nociceptive pain. This temperature was chosen as a higher temperature (54 °C) reduces the probability of detecting an antinociceptive effect in this experimental model (Godin et al., 2011). One hour after treatment with nicotinic acid or dipyrone (positive control), each animal was placed on the hot-plate. The latency to lick one of the hind paws or to jump off the plate was determined. The animal was removed from the hot-plate immediately after the response. The cut-off time was 50 s to avoid tissue damage.

2.5. Evaluation of the edema induced by carrageenan in rats or mice

A plethysmometer (Model 7140, Ugo Basile, Italy) was used to measure paw volume. Before administration of any drug, the basal volume of the right hind paw was measured. After determination of the basal paw volume, the animals were divided into the experimental groups in such a way that the mean volumes of the different groups were similar. Carrageenan was injected via the intraplantar (i.pl.) route in rats (500 μg, 50 μl) or mice (600 μg, 30 μl). Considering that (a) the paw volume was measured at 2, 4 and 6 h later, (b) the half-life of nicotinic acid is about 1 h (Petrack et al., 1966) and (c) preliminary results indicated that only one dose of nicotinic acid did not markedly inhibit the response evaluated, we administered two doses of nicotinic acid, 1 h before and 3 h after carrageenan. Similar protocol was used for isonicotinic and picolinic acids. The results were presented as the paw volume changes in relation to the basal values.

2.6. Evaluation of mechanical allodynia induced by carrageenan in rats

Mechanical allodynia was measured with a 40 mN nylon filament (Sorri, Brazil) as previously described (Souza et al., 2002). Briefly, the rats were kept individually in Perspex boxes (20×20 cm with 18 cm-high walls) whose floor was a metal grid through which the filament was pressed on the plantar surface of the right hind paw with the strength just necessary to cause it to bend for approximately 1 s. The number of withdrawal reflexes was determined in a trial of 10 touches for each rat. The basal withdrawal frequency was determined before administration of any drug. Once the basal withdrawal frequency was determined, the animals were divided into the experimental groups in such a way that the mean withdrawal frequencies of the different groups were similar. The withdrawal frequency was determined at 2, 4 and 6 h after injection of the inflammatory stimulus. Nicotinic acid was administered 1 h before and 3 h after carrageenan.

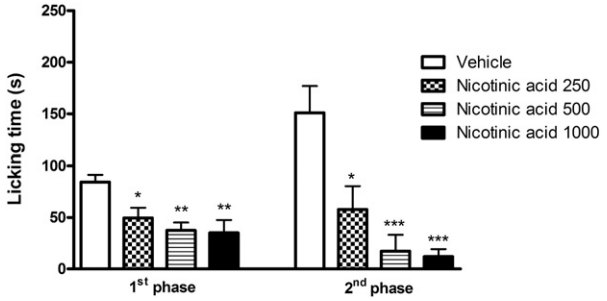

Fig. 2. Effect induced by nicotinic acid (250, 500 or 1000 mg/kg, p.o., −1 h) on the nociceptive response induced by formalin (2.5%; 20 μl; s.c.) in mice. *, ** and *** significantly different from vehicle ($p<0.05$, $p<0.01$ and $p<0.001$, respectively). n = 8.

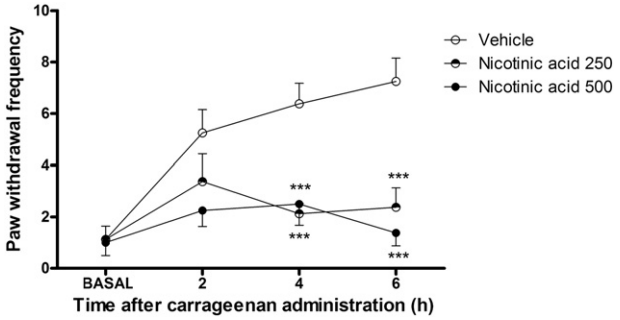

Fig. 4. Effect induced by nicotinic acid (250 or 500 mg/kg, p.o., −1 h and 3 h) on the mechanical allodynia induced by carrageenan (500 μg, 50 μl, i.pl.) in rats. *** significantly different from vehicle ($p<0.001$). n = 8.

2.7. Evaluation of the motor activity of mice

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 nicotinic or picolinic acids or phenobarbital (positive control) and 1 h later they were again tested in the apparatus. In another protocol, we evaluated the effect induced by two administrations of nicotinic acid to validate the results observed in the model of mechanical allodynia. The first administration occurred 3 h before the first evaluation of the motor activity. The second administration occurred 1 h after the first evaluation of the motor activity. After the second administration, the motor activity was evaluated at 1 and 3 h.

2.8. Data collection and statistical analysis

Two observers evaluated the nociceptive behavior and edema in the different experimental protocols. The observers were not aware of the treatments and registered the nociceptive behavior or edema of animals from the different experimental groups within each protocol. The results were presented as mean ± standard error mean (S.E.M.) and analyzed by one-way analysis of variance followed by Newman–Keuls post-hoc test when the main effect was significant. A $P<0.05$ was considered significant. Statistical analysis was conducted using GraphPrism 5.0 for Windows.

3. Results

Nicotinic acid, at the doses of 250, 500 or 1000 mg/kg, inhibited both phases of the nociceptive response induced by formalin in mice (Fig. 2). As the doses of 500 and 1000 mg/kg induced similar effects, we chose the doses of 250 or 500 mg/kg for subsequent experiments. Nicotinic acid (250 or 500 mg/kg) did not increase the latency for the nociceptive response of mice in the hot-plate model (Fig. 3). However, the latency for the nociceptive response was increased after treatment of the animals with dipyrone (500 mg/kg). Nicotinic acid (250 or 500 mg/kg) also inhibited the mechanical allodynia induced by carrageenan in rats (Fig. 4).

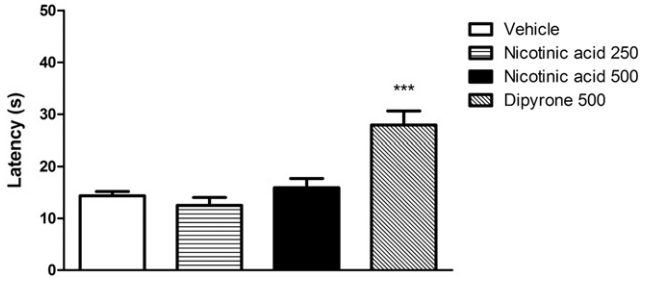

Fig. 3. Effect induced by nicotinic acid (250 or 500 mg/kg, p.o., −1 h) or dipyrone (500 mg/kg, p.o., −1 h) on the nociceptive response induced by heat (hot plate model, 50 °C). *** Significantly different from vehicle ($p<0.001$). n = 10.

To validate the results observed in the nociceptive models, we investigated the effects induced by nicotinic acid on the motor coordination of the animals. Single (−1 h) or double (−1 h and 3 h) doses of nicotinic acid (500 mg/kg) did not alter the time mice spent in the rota-rod apparatus. The positive control, phenobarbital (50 mg/kg) markedly inhibited the performance of the animals (Table 1).

In addition to inhibiting the nociceptive response, nicotinic acid (250 or 500 mg/kg) also inhibited the paw edema induced by Carrageenan in mice (Fig. 5). Aiming to verify whether this inhibition also occurs in other species, we observed that nicotinamide (250 or 500 mg/kg) also reduces the inflammatory edema in rats (Fig. 6). In both species, the inhibitory effect induced by nicotinic acid on carrageenan-induced edema was more marked on the late phase of the response.

Next, we investigated whether the nicotinic acid isomers, isonicotinic and picolinic acids, also exhibit similar activities. Isonicotinic acid (250 or 500 mg/kg) did not inhibit the nociceptive response induced by formalin in mice (Fig. 7). However, when we evaluated the effects induced by picolinic acid (250 or 500 mg/kg), we observed lethality similarly to what was observed for picolinamide in our previous study (Godin et al., 2011). Therefore, the doses were reduced to 62.5 or 125 mg/kg. Information in the literature about the lethal dose of the picolinic acid was not found. Picolinic acid (125 mg/kg) inhibited both phases of the nociceptive response induced by formalin in mice (Fig. 8).

To validate the antinociceptive activity of picolinic acid, we investigated its effect on the motor coordination of mice. Picolinic acid (125 mg/kg) did not alter the time mice spent in the rota-rod apparatus (Table 1).

Table 1
Effect induced by nicotinic acid (500 mg/kg, p.o., −1 h or −1 h and 3 h), picolinic acid (125 mg/kg, p.o., −1 h) or phenobarbital (50 mg/kg, p.o., −1 h) on the time spent by mice on the rota-rod.

Treatment	Time spent on the rotating rod (s)			
	Baseline	1 h		
Vehicle	120 ± 0	119 ± 1		
Nicotinic acid 500	120 ± 0	120 ± 0		
Picolinic acid 125	120 ± 0	120 ± 0		
Phenobarbital 50	120 ± 0	14 ± 2[a]		
	Baseline	2 h	4 h	6 h
Vehicle	119 ± 1	120 ± 0	119 ± 1	120 ± 0
Nicotinic acid 500	120 ± 0	120 ± 0	120 ± 0	120 ± 0

[a] Significantly different from respective vehicle-treated group at the same time point ($P<0.001$). n = 8.

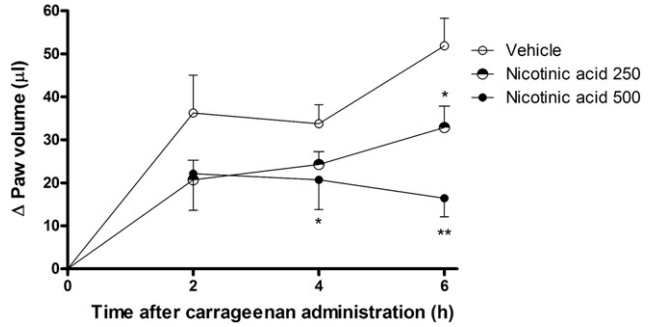

Fig. 5. Effect induced by nicotinic acid (250 or 500 mg/kg, p.o., −1 h and 3 h) on the edema induced by carrageenan in mice. The mean basal paw volumes of the groups treated with vehicle, nicotinic acid 250 and nicotinic acid 500 were 114±2, 111±2 and 113±2 μl, respectively. * and ** significantly different from vehicle ($p<0.05$ and $p<0.01$, respectively). n=8.

In addition to investigating the effects induced by isonicotinic and picolinic acids on the nociceptive response induced by formalin, we evaluated their effects in a model of inflammatory edema in mice. These compounds did not inhibit the paw edema induced by Carrageenan. The positive control, dexamethasone (10 mg/kg), markedly inhibited the paw edema at 2, 4 and 6 h (Figs. 9 and 10).

4. Discussion

Initially, we investigated the effect induced by nicotinic acid in the model of nociceptive response induced by formalin in mice. Widely used, this is an experimental model of continuous pain that results from tissue injury and consequent inflammation and also activation by formaldehyde of transient receptor potential (TRP) channels, specifically TRPA1 (McNamara et al., 2007) and TRPV1 (Tian et al., 2009), in nociceptors. The formalin pain model is useful to screen candidates for analgesic compounds as it encompasses inflammatory, neurogenic and central mechanisms of nociception (Tjolsen et al., 1992). Although nicotinic acid inhibited both phases of the nociceptive response induced by formalin, the second phase was inhibited to a greater extent indicating a profile similar to that of anti-inflammatory drugs (Hunskaar and Hole, 1987). The anti-inflammatory profile was further supported by the inhibition of the mechanical allodynia and edema induced by i.pl. injection of carrageenan, responses that result from the local production of a variety of inflammatory mediators (Cunha et al., 2000; Handy and Moore, 1998; Salvemini et al., 1996; Vinegar et al., 1987), and lack of effect on the nociceptive response induced by heat in the hot-plate model, an immediate response due to direct activation of heat-sensitive channels of the TRP family (Vriens et al., 2011).

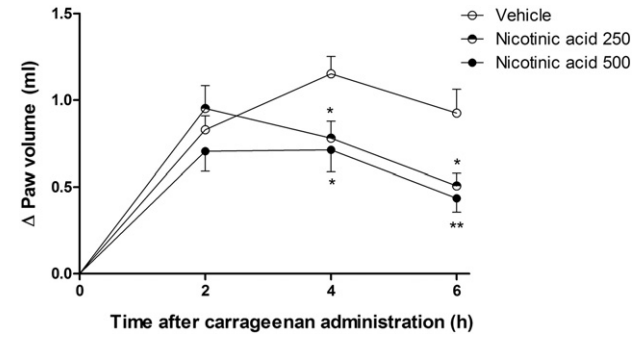

Fig. 6. Effect induced by nicotinic acid (250 or 500 mg/kg, p.o., −1 h and 3 h) on the edema induced by carrageenan in rats. The mean basal paw volumes of the groups treated with vehicle, nicotinic acid 250 and nicotinic acid 500 were 1.17±0.07, 1.18±0.05 and 1.18±0.04 ml, respectively. * and ** significantly different from vehicle ($p<0.05$ and $p<0.01$, respectively). n=6.

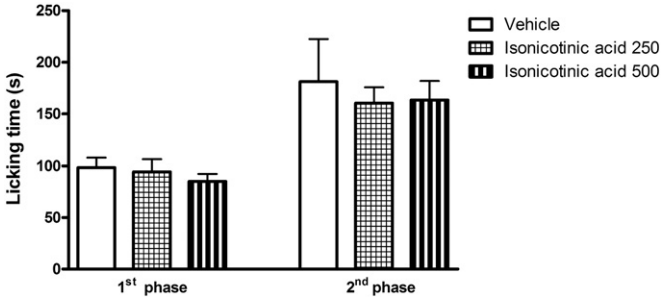

Fig. 7. Effect induced by isonicotinic acid (250 or 500 mg/kg, p.o., −1 h) on the nociceptive response induced by formalin (2.5%; 20 μl; s.c.) in mice. n=8.

Regarding the inhibition induced by nicotinic acid on the nociceptive behavior in the experimental models of pain, it is highly unlikely that it is the result of motor incoordination or muscle relaxing effect, as the time that the animals spent in the rota-rod was not altered. Such validation is important as it has been demonstrated that nicotinic acid inhibits seizures induced by pentylenetetrazole or kynurenine, suggesting a central depressant effect (Lapin, 1981).

The mechanisms that contribute to the anti-inflammatory profile of nicotinic acid in the experimental models of inflammatory pain and edema are not clear. However, it has been shown that nicotinic acid decreases the activation of NF-κB (Crowley et al., 2000; Ganji et al., 2009; Kwon et al., 2011; Tavintharan et al., 2009), a transcription factor that regulates the production of many inflammatory mediators (Lawrence, 2009; Lentsch and Ward, 1999) that are clearly involved in the nociceptive response induced by formalin (Chichorro et al., 2004; Tjolsen et al., 1992) and in the allodynia and edema induced by carrageenan (Chen et al., 1994; Nakamura et al., 1996; Salvemini et al., 1996; Tonussi and Ferreira, 1994). Importantly, many inflammatory stimuli activate NF-κB (Sum and Anderson, 2002) and it has been recently demonstrated that transgenic mice that overexpress a protein (IκB) that inhibits the NF-κB pathway exhibit a reduced nociceptive response induced by formalin (Fu et al., 2007). Moreover, the first and second phases of the nociceptive response induced by formalin are inhibited in NF-κB-deficient mice (Niederberger et al., 2007). More direct evidence that nicotinic acid may inhibit the production of inflammatory cytokines was recently provided by Kwon et al. (2011) who demonstrated that high doses of this compound reduce the serum concentrations of tumor necrosis factor (TNF)-α and interleukin (IL)-6 in endotoxemic rats.

Recently, it has been shown that nicotinic acid is a ligand to GPR109A receptor, a member of G-protein-coupled receptors that are targets for endogenous hydroxy-carboxylic acid metabolites (for a review see Offermanns et al., 2011; Tunaru et al., 2003). The GPR109A was initially identified in adipocytes and its role in the mediation of the anti-lipolytic and lipid-lowering effects of nicotinic acid in vivo was demonstrated (Tunaru et al., 2003). Additional studies

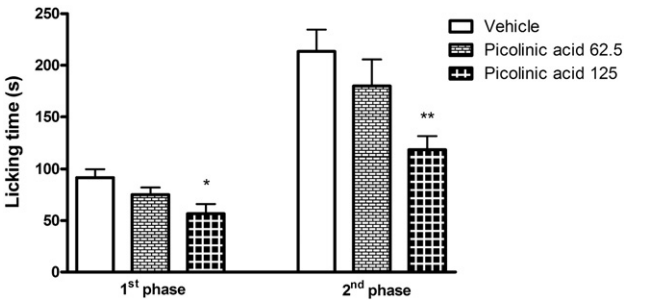

Fig. 8. Effect induced by picolinic acid (62.5 or 125 mg/kg, p.o., −1 h) on the nociceptive response induced by formalin (2.5%; 20 μl; s.c.) in mice. * and ** significantly different from vehicle ($p<0.05$ and $p<0.01$, respectively). n=8.

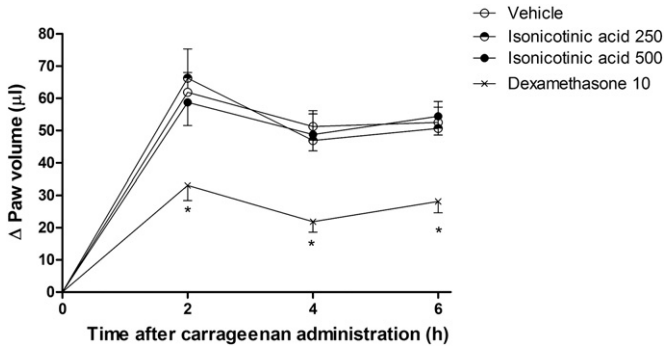

Fig. 9. Effect induced by isonicotinic acid (250 or 500 mg/kg, p.o., −1 h and 3 h) on the edema induced by carrageenan in mice. The mean basal paw volumes of the groups treated with vehicle, isonicotinic acid 250, isonicotinic acid 500 and dexamethasone 10 were 94±3, 95±5, 97±4 e 93±5 μl, respectively. * significantly different from vehicle ($p<0.05$). n=8.

demonstrated that this receptor is also present in macrophages and neutrophils (Knowles et al., 2006; Kostylina et al., 2008), cells that have important roles in many aspects of the inflammatory response. However, the role of GPR109A in mediating the antinociceptive and anti-inflammatory activities of nicotinic acid has not been objectively investigated as antagonists for this receptor or GPR109A deficient animals are still not available.

As nicotinic acid may be converted to nicotinamide (Collins and Chaykin, 1972; Petrack et al., 1966), a compound that induces marked effects in experimental models of nociceptive and inflammatory pain (Godin et al., 2011), it could be suggested that such conversion could play an important role in the antinociceptive and anti-inflammatory activities of nicotinic acid. However, if such conversion plays a role, it is minor, as the doses of nicotinamide that induce antinociceptive and anti-inflammatory effects in the experimental models used in our studies are higher than those of nicotinic acid. In the formalin model, nicotinic acid at the dose of 250 mg/kg markedly inhibited the nociceptive response (present study), while a dose of 500 mg/kg of nicotinamide was ineffective (Godin et al., 2011).

The evaluation of the effects induced by the isomers of nicotinic acid on the nociceptive response induced by formalin and the paw edema induced by carrageenan demonstrated how the position of the acid side chain attached to the pyridine ring can influence the activities of the nicotinic acid isomers. Physical–chemical analysis demonstrated that these isomers differ in their steric and electrostatic interactions (Seliger et al., 2006) which may contribute to different biological activities, such as the lethality induced by higher doses of picolinic acid, the isomer that possess the side chain in the *ortho* position of pyridine ring, and the lack of activity of isonicotinic acid, the isomer that possess the side chain in the *para* position of pyridine ring, in the models of nociceptive response induced by formalin and paw edema induced by carrageenan.

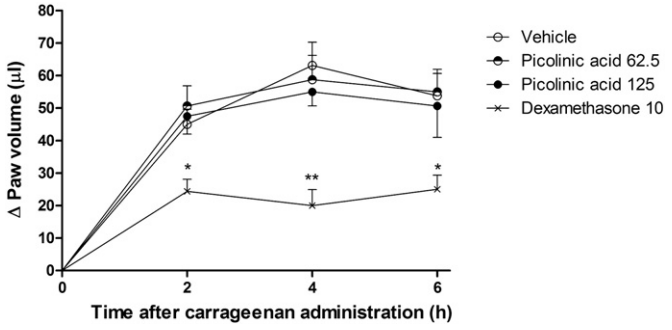

Fig. 10. Effect induced by picolinic acid (62.5 or 125 mg/kg, p.o., −1 h and 3 h) on the edema induced by carrageenan in mice. The mean basal paw volumes of the groups treated with vehicle, picolinic acid 62.5, picolinic acid 125 and dexamethasone 10 were 106±3, 104±3, 105±2, 107±4 μl, respectively. * and ** significantly different from vehicle ($p<0.05$ and $p<0.01$, respectively). n=8.

If the side chain in the para position of the pyridine ring (isonicotinic acid) leads to the loss of antinociceptive and anti-inflammatory activities, the side chain in the ortho position (picolinic acid) results in a drug with a different profile. Picolinic acid inhibited both the first and second phases of the nociceptive response induced by formalin, an activity that was not associated with motor incoordination. Our results do not represent the first demonstration of the antinociceptive activity of picolinic acid. Heyliger et al. (1998) had already demonstrated that picolinic acid induces antinociceptive effect in the hot-plate and tail flick models. As picolinic acid did not inhibit paw edema induced by carrageenan, it is possible that its antinociceptive activity is associated mainly with the inhibition of nociceptive processing in the central nervous system. Interestingly, it has been demonstrated that picolinic acid inhibits the activation of spinal interneurons induced by glutamate (Tonohiro et al., 1990), an important mediator of the spinal nociceptive processing (Bleakman et al., 2006; Larsson, 2009).

In conclusion, our results represent the first demonstration of the activity of nicotinic acid in different experimental models of nociceptive and inflammatory pain and also provide further support to its anti-inflammatory activity. It is highly unlikely that conversion to nicotinamide represents an important mechanism to explain the antinociceptive and anti-inflammatory activities of nicotinic acid. The acid side chain in the *meta* position is important for its activity, as the isomers with the chain in the *ortho* (picolinic acid) and *para* (isonicotinic acid) positions exhibit reduced or absent activity in the experimental models evaluated. The demonstration of new activities of nicotinic acid, a drug that has already been approved for clinical use and exhibits a positive safety record, clearly exemplifies the importance of promoting drug repositioning, a strategy that has raised great interest in the last years due mainly to the sustained high attrition rate and costs in attempts to bring new drugs to the market. Altogether, the results may contribute to raise the interest in conducting clinical trials to investigate the usefulness of nicotinic acid in the treatment of painful and inflammatory diseases.

Acknowledgments

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