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Blockade of the antinociception induced by diclofenac, but not of indomethacin, by sulfonylureas and biguanides

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ABSTRACT

There is evidence that administration of sulfonylureas, such as glibenclamide and tolbutamide, blocks diclofenac-induced antinociception, suggesting that diclofenac activates ATP-sensitive K^+ channels. However, there is no evidence for the interaction between diclofenac and other hypoglycemic drugs, such as the biguanides metformin or phenformin. Therefore, this work was undertaken to determine whether two sulfonylureas, glibenclamide and glipizide, as well as two biguanides, metformin and phenformin, have any effect on the systemic antinociception that is induced by diclofenac and indomethacin using the rat formalin test as an animal model. Systemic injections of diclofenac (10 to 30 mg/kg) and indomethacin (10 to 30 mg/kg) produced dose-dependent antinociception during the second phase of the test. Systemic pretreatment with glibenclamide (3 and 10 mg/kg), glipizide (3 and 10 mg/kg), metformin (100 and 180 mg/kg) or phenformin (100 and 180 mg/kg) blocked diclofenac-induced systemic antinociception in the second phase of the test ($P<0.05$). In contrast, pretreatment with glibenclamide, glipizide, metformin or phenformin did not block indomethacin-induced systemic antinociception ($P>0.05$). These data suggest that diclofenac, but not indomethacin, activated K^+ channels and metformin and phenformin-dependent mechanisms, which resulted in systemic antinociceptive effects in the rat formalin test.

1. Introduction

It is well known that insulin resistance is associated with obesity, especially in patients with metabolic syndrome and patients with type 2 diabetes mellitus (Campbell, 2009). When left unmanaged, these diseases can result in hyperglycemia, which, over time, can lead to serious damage in many organ systems, especially the nervous and cardiovascular systems (Campbell, 2009; Guastella and Mick, 2009). Treatment of chronic diabetes includes the use of drugs to lower blood sugar and drugs to treat its complications (Campbell, 2009; Guastella and Mick, 2009). Sulfonylurea molecules and biguanides are widely used to lower blood sugar in the therapeutic management of type 2 diabetes (Aziz et al., 2010). Glibenclamide, a potent second-generation sulfonylurea, has been widely used to manage non-insulin dependent diabetes mellitus throughout the world (Wysowski et al., 2003). Glibenclamide improves glucose tolerance predominantly by augmenting insulin secretion (Luzi and Pozza, 1997). At cellular level, glibenclamide acts to inhibit ATP-sensitive K^+ channels (Edwards and Weston, 1993). In contrast, biguanides such as metformin and phenformin are mainly insulin-sensitizing agents that exhibit potent antihyperglycemic properties. Biguanides suppress hepatic gluconeogenesis and increase peripheral tissue insulin sensitivity. Biguanides activate 5′AMP-activated protein kinase (AMPK) in hepatocytes, thereby reducing the activity of acetyl-CoA carboxylase, which results in reduced lipogenic transcription factor levels as well as inhibition of hepatic gluconeogenesis (Zhou et al., 2001; Lochhead et al., 2000). Recently, it was shown that phenformin, but not metformin, inhibits several ATP-sensitive K^+ channels in vascular and non-vascular smooth muscle (Kir6.1/SUR2B and Kir6.2/SUR2B) and in pancreatic beta cells (Kir6.2/SUR1) (Aziz et al., 2010). This drug has also been reported to exhibit other mechanisms of action, such as enhanced secretion of β-endorphins, activation of the Cl^-/HCO^{-3} exchanger, attenuation of the agonist-stimulated $[Ca^{2+}]i$ response, activation of α_1-adrenoceptors, release of noradrenalin and activation of K^+ efflux through 4-AP-sensitive voltage-dependent K^+ channels (Bhalla et al., 1996; Peuler, 1999; Lee and Peuler, 2001; Lutz et al., 2001; Cheng et al., 2006).

Diclofenac is a non-steroidal anti-inflammatory drug (NSAID) that exhibits potent analgesic and anti-inflammatory properties. Diclofenac administered orally, rectally or intramuscularly has shown clinical efficacy in patients with rheumatoid arthritis, osteoarthritis, ankylosing spondylitis and other inflammatory conditions (Todd and Sorkin, 1988). It is known that diclofenac as well as other nonselective NSAIDs are able to impair prostaglandin synthesis by inhibiting the cyclooxygenase isozymes COX-1 and COX-2 in injured tissues and in the central nervous system (Todd and Sorkin, 1988; Vane and Botting,

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1996; Warner et al., 1999). However, there is evidence that diclofenac exhibits additional prostaglandin-independent properties that mediate its antinociceptive effects. For instance, local administration of glibenclamide has been shown to block the peripheral antinociceptive effects of diclofenac in rats (Ortiz et al., 2002, 2003; Alves et al., 2004), suggesting a possible role for ATP-sensitive K^+ channels in its antinociceptive effects at the peripheral level. Likewise, the antinociceptive effects of oral diclofenac were abolished by local or spinal administration of either L-NAME or glibenclamide (Ortiz et al., 2008). These results suggest that oral diclofenac achieves sufficient concentrations to induce antinociceptive effects involving the nitric oxide-ATP-sensitive K^+ channel pathway locally and in the spine. Finally, systemically delivered glibenclamide has been shown to reverse the antinociceptive and antihyperalgesic effects that are produced by systemic administration of diclofenac, suggesting that K^+ channels participate in these effects (Ortiz and Castañeda-Hernández, 2006; León-Reyes et al., 2009). Currently, the interaction between diclofenac and other hypoglycemic drugs such as biguanides, thiazolidinediones and insulin remains elusive. Therefore, this work was undertaken to determine whether the systemic antinociception that is induced by diclofenac and indomethacin is sensitive to two sulfonylureas, glibenclamide and glipizide, and two biguanides, metformin and phenformin.

2. Material and methods

2.1. Animals

Male Wistar rats aged 7 to 9 weeks (weight 180 to 220 g) were used in this study and were obtained from our internal breeding facilities. Animals had free access to food and drinking water before experiments. Efforts were made to minimize animal suffering and to reduce the number of animals used in this study. Rats were only used once. At the end of the experiments, the rats were sacrificed in a CO_2 chamber. All experiments followed the Guidelines on Ethical Standards for Investigation of Experimental Pain in Animals (Zimmermann, 1983), and the protocol was approved by the Institutional Animal Care and Use Committee (UAEH).

2.2. Drugs

Diclofenac, glibenclamide, glipizide, indomethacin, metformin and phenformin were purchased from Sigma (St. Louis, MO, USA). Glibenclamide and glipizide were dissolved in 20 to 40% DMSO solution. Indomethacin was dissolved in Tween 20 and buffer solution (sodium hydroxide and monobasic potassium phosphate). Diclofenac, metformin and phenformin were dissolved in saline.

2.3. Measurement of antinociceptive activity

Pain and antinociception were measured using the formalin test, which has been previously described (Ortiz et al., 2002, 2003; Ortiz and Castañeda-Hernández, 2008). Briefly, 50 µl of diluted formalin (1%) was injected subcutaneously (s.c.) into the dorsal surface of the right hind paw, and the resulting flinching behavior was considered to be an expression of nociception. The number of flinches was plotted as a function of time, and these curves were biphasic. The initial acute phase of the curve (0 to 10 min) was followed by a short quiescent period and then by a prolonged tonic response (15 to 60 min). The area under the biphasic curve was estimated, and a significant reduction in area was interpreted as antinociception.

2.4. Effect of hypoglycemic drugs on NSAID-induced antinociception

Rats received an intraperitoneal injection (1 mL) of vehicle or increasing doses of either diclofenac (10 to 30 mg/kg) or indomethacin (10 to 30 mg/kg), which was given 60 min before formalin injection into the paw. To determine whether the systemic antinociception that was induced by diclofenac or indomethacin was mediated by either ATP-sensitive K^+ channels or biguanide-induced mechanisms, rats that were given diclofenac (30 mg/kg, i.p.) or indomethacin (30 mg/kg, i.p.) were also pretreated with vehicle or with glibenclamide (1 to 10 mg/kg, s.c.), glipizide (1 to 10 mg/kg, s.c.), metformin (30 to 180 mg/kg, s.c.) or phenformin (30 to 180 mg/kg, s.c.) 70 min before the formalin injection, and the effect on antinociception was assessed. Drugs were injected in a volume of 1 mL. Doses and timing of hypoglycemic and analgesic systemic administration were selected based on previous reports and on pilot experiments in our laboratory. Rats in every group were observed and tested for possible side effects such as a reduction in righting, stepping, and corneal reflexes.

2.5. Motor coordination test and blood glucose determination

Effects of the highest tested dose of each drug as well as of drug combinations were assessed. Independent groups, each containing 8 to 10 rats, were examined for motor coordination and blood glucose levels before and after administration of diclofenac (30 mg/kg), indomethacin (30 mg/kg), glibenclamide (10 mg/kg), glipizide (10 mg/kg), metformin (180 mg/kg), phenformin (180 mg/kg), diclofenac (30 mg/kg) + glibenclamide (10 mg/kg), diclofenac (30 mg/kg) + glipizide (10 mg/kg), diclofenac (30 mg/kg) + metformin (180 mg/kg), diclofenac (30 mg/kg) + phenformin (180 mg/kg), indomethacin (30 mg/kg) + glibenclamide (10 mg/kg), indomethacin (30 mg/kg) + glipizide (10 mg/kg), indomethacin (30 mg/kg) + metformin (180 mg/kg), indomethacin (30 mg/kg) + phenformin (180 mg/kg) or vehicle (1 mL). Animals were placed on a cylinder (7 cm in diameter) rotating at a speed of 20 rpm. Rats were trained to walk on the cylinder in 3 consecutive sessions; on the fourth session, they received drug or vehicle treatment at time 0, and the amount of time spent walking during a 2-min period was recorded at 1, 2 and 3 h after treatment. Likewise, blood glucose levels were measured from the tail vein with the MediSense Optium glucose meter (Abbott, UK) before as well as 1, 2 and 3 h after drug administration.

2.6. Data analysis and statistics

All experimental results are represented as the mean ± SEM for 8 to 10 animals per group. Curves were constructed by plotting the number of flinches as a function of time. The area under curve (AUC), which is an expression of the duration and intensity of the effect, was calculated using the trapezoidal rule. Reduction in the number of flinches or in the AUC of the second phase was reported; we did not observe any effect of treatment on the first phase of this curve. One-way analysis of variance (ANOVA) followed by Tukey's test was used to analyze differences between treatments. Differences were considered to reach statistical significance when $P<0.05$.

3. Results

3.1. Systemic antinociceptive effects of diclofenac and indomethacin

Formalin administration resulted in a typical pattern of flinching behavior. The first phase of flinching began immediately after formalin administration and then diminished gradually over approximately 10 min (phase one). The second phase began approximately 15 min after administration and lasted until 1 h post-administration (phase two). Systemic administration of diclofenac or indomethacin produced a dose-dependent reduction in flinching behavior after formalin injection (Fig. 1). Diclofenac and indomethacin significantly reduced the number of flinches during phase two ($P<0.05$) but not during phase one ($P>0.05$, data not shown). There was no observed

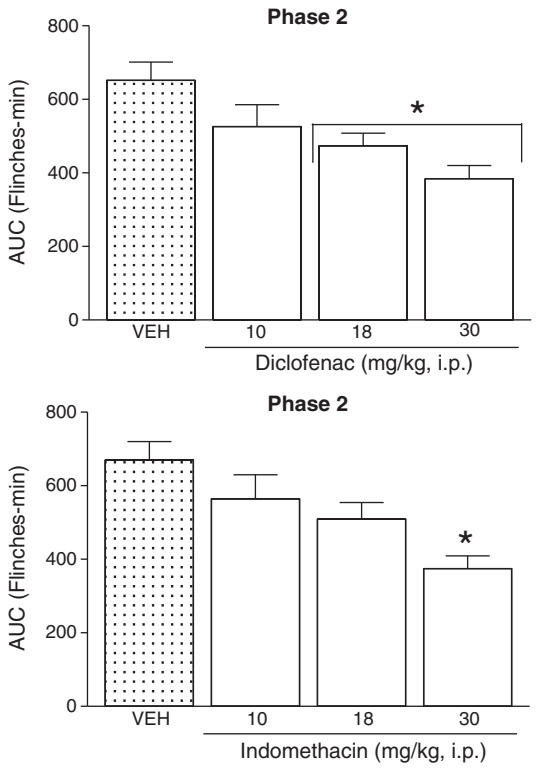

Fig. 1. Systemic antinociceptive effects of diclofenac and indomethacin in the 1% formalin test. Rats were pretreated with an i.p. injection of vehicle (VEH), diclofenac or indomethacin before the formalin injection. Data are expressed as the area under the curve (AUC) for the number of flinches plotted as a function of time in the second phase. Each point corresponds to the mean ± SEM for 8 to 10 animals. *Significantly different from vehicle group ($P<0.05$) as determined by one-way analysis of variance followed by Tukey's test.

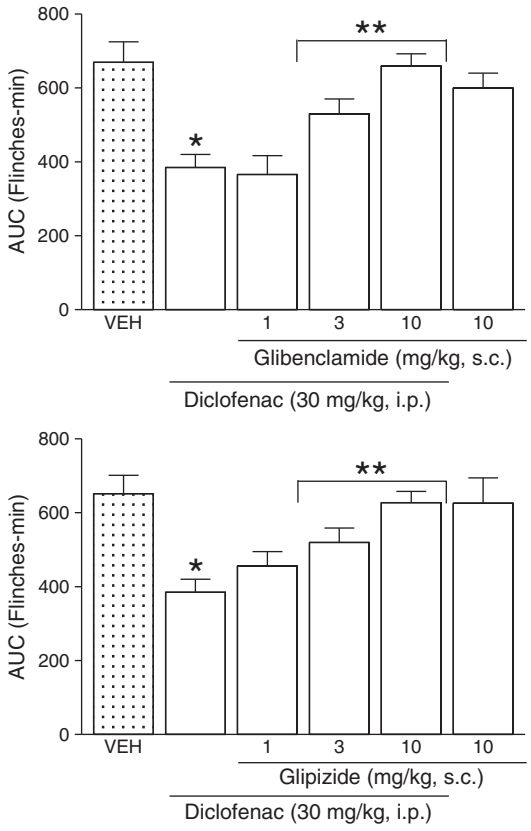

Fig. 2. Effect of two ATP-sensitive K^+ channel inhibitors, glibenclamide and glipizide, on diclofenac-induced systemic antinociception during the second phase of the formalin test. Rats were pretreated with an injection of glibenclamide or glipizide plus diclofenac. Data are expressed as the area under the curve (AUC) for the number of flinches plotted as a function of time in the second phase. Bars represent the mean ± SEM for 8 to 10 animals. *Significantly different from the vehicle group ($P<0.05$) and **significantly different from the diclofenac group ($P<0.05$), as determined by one-way analysis of variance followed by Tukey's test.

reduction in the assessed reflexes in either the control or treated groups.

3.2. Effect of sulfonylureas on antinociception induced by diclofenac and indomethacin

Systemic pretreatment with two ATP-sensitive K^+ channel inhibitors, glibenclamide or glipizide, blocked diclofenac-induced antinociception ($P<0.05$) but not indomethacin-induced antinociception ($P>0.05$) (Figs. 2 and 3). Given alone, the ATP-sensitive K^+ channel inhibitors did not affect formalin-induced nociceptive behavior ($P>0.05$) (Figs. 2 and 3).

3.3. Effect of biguanides on antinociception induced by diclofenac and indomethacin

Systemic pretreatment with two biguanides, metformin and phenformin, blocked diclofenac-induced antinociception ($P<0.05$) (Fig. 4) but not indomethacin-induced antinociception ($P>0.05$) (Fig. 5). Given alone, the biguanides did not affect formalin-induced nociceptive behavior ($P>0.05$) (Figs. 4 and 5).

3.4. Effect of hypoglycemic and analgesic drugs on motor coordination and blood glucose levels

Systemic treatment with diclofenac, indomethacin, glibenclamide, glipizide, metformin or combinations of these drugs did not alter motor coordination in these rats (Table 1) ($P>0.05$). However, phenformin alone or in combination with either diclofenac or indomethacin significantly altered motor coordination in these rats (Table 1) ($P<0.05$). Systemic administration of diclofenac, indomethacin or metformin did not significantly reduce blood glucose levels in these animals (Table 2) ($P>0.05$). However, systemic administration of glibenclamide, glipizide, phenformin or combinations of these drugs significantly altered blood glucose levels in these rats (Table 2) ($P<0.05$).

4. Discussion

4.1. Effect of sulfonylureas on antinociception induced by diclofenac and indomethacin

Molecules from the sulfonylurea chemical family, as well as biguanides, such as metformin and phenformin, are widely used in the therapeutic management of type 2 diabetes. Glibenclamide and glipizide improve glucose tolerance predominantly by augmenting insulin secretion. At a cellular level, sulfonylureas act to inhibit the ATP-sensitive K^+ channels (Edwards and Weston, 1993). In the present work, systemic administration of glibenclamide or glipizide decreased diclofenac-induced antinociceptive effects in rats. This result is consistent with previous results from our group in which we show that systemic, spinal or peripheral administration of glibenclamide is able to block the effects of diclofenac treatment (Ortiz et al., 2002; 2003; 2008; Ortiz and Castañeda-Hernández, 2006; León-Reyes et al., 2009). In addition, treatment with sulfonylureas alone and in combination with diclofenac significantly reduced blood glucose levels compared to treatment with diclofenac alone in this study. However, treatment with sulfonylureas alone or in combination with diclofenac did not alter motor coordination in these rats. Therefore,

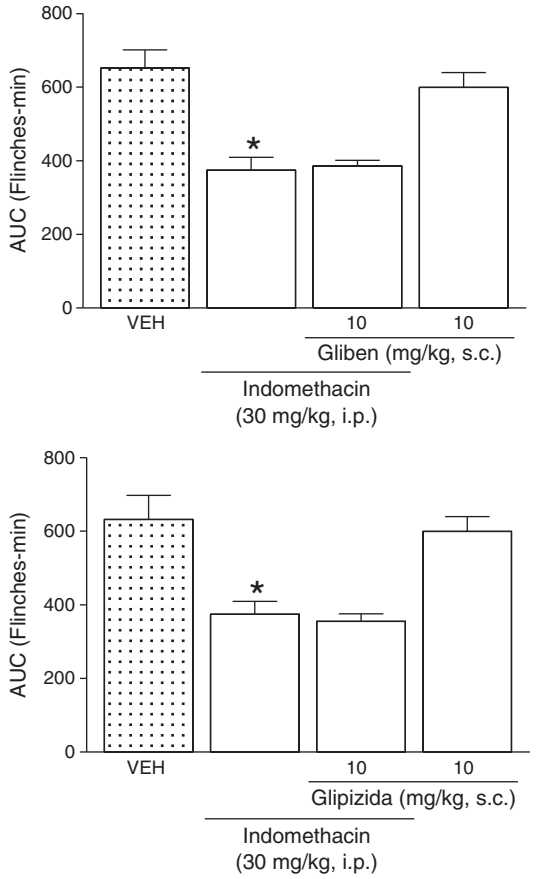

Fig. 3. Effect of two ATP-sensitive K^+ channel inhibitors, glibenclamide and glipizide, on indomethacin-induced systemic antinociception during the second phase of the formalin test. Rats were pretreated with an injection of glibenclamide or glipizide plus indomethacin. Data are expressed as the area under the curve (AUC) for the number of flinches plotted as a function of time in the second phase. Bars represent the mean ± SEM for 8 to 10 animals. *Significantly different from the vehicle group ($P<0.05$) as determined by one-way analysis of variance followed by Tukey's test.

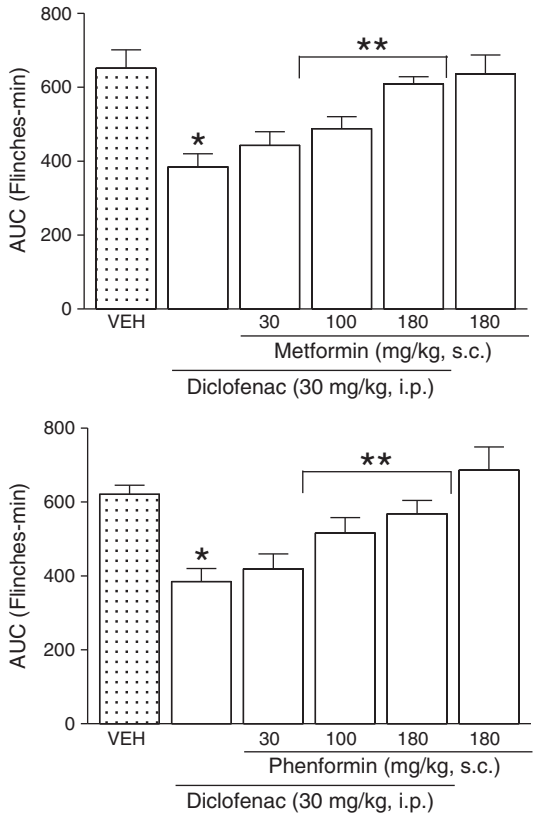

Fig. 4. Effect of two biguanides, metformin and phenformin, on diclofenac-induced systemic antinociception during the second phase of the formalin test. Rats were pretreated with an injection of metformin or phenformin plus diclofenac. Data are expressed as the area under the curve (AUC) for the number of flinches plotted as a function of time in the second phase. Bars represent the mean ± SEM for 8 to 10 animals. *Significantly different from the vehicle group ($P<0.05$) and **significantly different from the diclofenac group ($P<0.05$) as determined by one-way analysis of variance followed by Tukey's test.

blockade of diclofenac-induced antinociception by sulfonylureas does not seem to appear as a result of a hypoglycemic effect or of motor alteration. Furthermore, data suggest that this blockage was a result of ATP-sensitive K^+ channel inhibition.

In contrast, K^+ channel activation does not appear to be involved in the systemic effects of indomethacin-induced antinociception because neither glibenclamide nor glipizide was able to inhibit systemic antinociception induced by indomethacin treatment. Our results are in agreement with previous results from our group in which we demonstrated that peripheral administration of glibenclamide or tolbutamide was not sufficient to block the effects of indomethacin (Ortiz et al., 2002; Gil-Flores et al., 2010). The inability of sulfonylureas to block indomethacin-induced antinociception does not appear to be a result of a hypoglycemic effect because sulfonylureas in combination with indomethacin did not alter motor coordination in these rats.

4.2. Effect of metformin and phenformin on antinociception induced by diclofenac

In the present study, systemic administration of a biguanide, metformin, was able to reverse diclofenac-induced antinociception. This effect was not a result of changes in motor coordination or to a decrease of blood glucose levels because administration of metformin in combination with diclofenac did not significantly alter these two variables. Therefore, it is possible that diclofenac activates metformin-dependent pathways at a systemic level. Previous investigations have demonstrated that biguanide administration leads to the activation of α_1-adrenoceptors and the release of noradrenalin (Lee and Peuler, 2001; Lutz et al., 2001). Therefore, it is possible that metformin administration also leads to the activation of noradrenergic pathways to reverse the antinociceptive effects induced by diclofenac. However, this is not consistent with our current data because noradrenergic pathways were not activated by metformin to increase formalin-induced nociception in the absence of diclofenac (see Fig. 4). Previous investigations have also demonstrated that metformin is able to activate K^+ efflux through 4-AP-sensitive voltage-dependent K^+ channels, to enhance β-endorphin secretion and to attenuate the agonist-stimulated $[Ca^{2+}]i$ response (Bhalla et al., 1996; Peuler, 1999; Cheng et al., 2006). It is likely that these mechanisms would be able to produce neuronal inhibition (increasing the diclofenac-induced antinociception) (North, 1989; Tseng, 2001; Castañeda-Hernández et al., 2005) instead of neuronal excitability. Therefore, these studies suggest that these mechanisms are not directly involved in diclofenac-induced antinociception, which is supported by previous findings from our group in which treatment with a combination of individually ineffective doses of diclofenac and pinacidil produced an antinociceptive effect in the formalin test. In addition, pinacidil enhanced the efficacy of diclofenac through the activation of K^+ channels (Castañeda-Hernández et al., 2005). Alternatively, it is possible that the blockade of diclofenac-induced antinociception by metformin results from the activation of the Cl^-/HCO^{-3} exchanger to disrupt the equilibrium between intracellular and extracellular Cl^- and to enhance Cl^- efflux through Cl^- channels, thereby causing depolarization (Lutz et al., 2001). However, this is not consistent with our

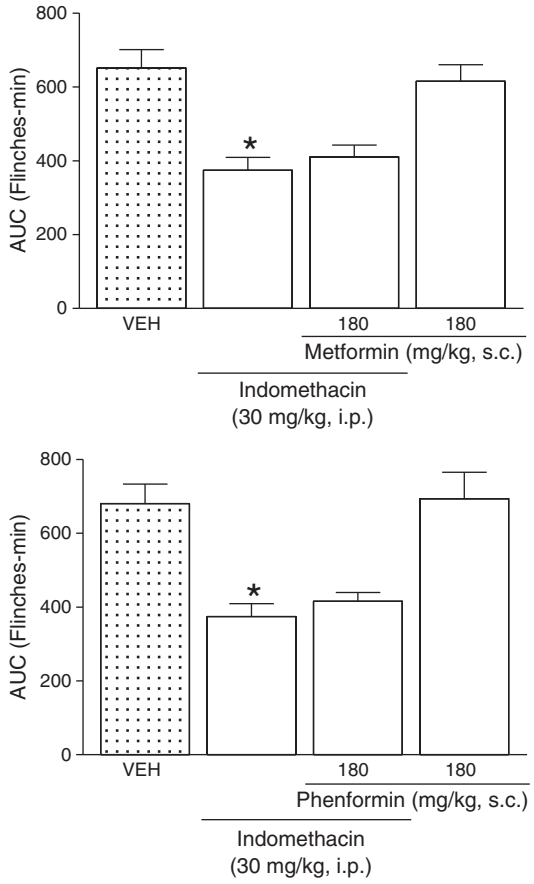

Fig. 5. Effect of two biguanides, metformin and phenformin, on the indomethacin-induced systemic antinociception during the second phase of the formalin test. Rats were pretreated with an injection of metformin or phenformin plus indomethacin. Data are expressed as the area under the curve (AUC) for the number of flinches plotted as a function of time in the second phase. Bars represent the mean ± SEM for 8 to 10 animals. *Significantly different from the vehicle group ($P<0.05$) as determined by one-way analysis of variance followed by Tukey's test.

current data because formalin-induced nociception was not augmented when metformin was administered in the absence of diclofenac (see Fig. 4). The exact mechanisms by which metformin reverses diclofenac-induced antinociception should be further addressed in future experiments.

Phenformin administration was also able to block diclofenac-induced systemic antinociception. It is possible that this effect was due to altered motor coordination or decreased blood glucose levels because administration of phenformin in combination with diclofenac significantly altered these two variables. However, if this were true, indomethacin-induced systemic antinociception should have also been reversed by phenformin (see Fig. 5). Whether changes in motor coordination and blood glucose levels had an effect on the phenformin-induced reversal of diclofenac-induced antinociception should be investigated further. Recently, phenformin but not metformin was shown to block ATP-sensitive K^+ channels (Aziz et al., 2010). Therefore, we suggest that the phenformin-induced reversal of diclofenac-induced antinociception resulted from the blockade of potassium channels, similar to sulfonylureas. However, future experiments should be performed to determine the exact mechanism by which phenformin reverses the antinociceptive effects produced by diclofenac in rats.

Table 1
Effect of the analgesics, hypoglycemic and their combinations on the motor coordination in the rats.

	Time after the drug administration		
	1 h	2 h	3 h
Control	117.5 ± 1.3	119.4 ± 0.6	118.1 ± 0.9
Diclofenac 30 mg/kg	118.8 ± 1.3	116.7 ± 3.3	118.3 ± 1.7
Indomethacin 30 mg/kg	117.5 ± 1.7	120.0 ± 0.0	118.8 ± 1.7
Glibenclamide 10 mg/kg	117.5 ± 1.4	117.5 ± 2.5	117.5 ± 2.5
Glipizide 10 mg/kg	116.4 ± 2.4	117.5 ± 1.3	120.0 ± 0.0
Metformin 180 mg/kg	117.5 ± 1.4	118.8 ± 1.3	118.8 ± 1.3
Phenformin 180 mg/kg	80.6 ± 4.6*	66.7 ± 4.3*	36.1 ± 7.0*
Diclofenac + glibenclamide	117.1 ± 1.3	118.8 ± 1.3	119.0 ± 0.7
Diclofenac + glipizide	116.3 ± 2.4	112.5 ± 6.0	116.3 ± 2.4
Diclofenac + metformin	120.0 ± 0.0	118.8 ± 1.3	120.0 ± 0.0
Diclofenac + phenformin	106.5 ± 5.4	88.5 ± 5.6*	94.5 ± 7.7*
Indomethacin + glibenclamide	117.5 ± 1.4	118.8 ± 1.3	117.5 ± 2.5
Indomethacin + glipizide	119.0 ± 0.7	116.3 ± 2.4	118.8 ± 1.3
Indomethacin + metformin	116.3 ± 2.4	117.5 ± 1.4	119.0 ± 0.7
Indomethacin + phenformin	84.4 ± 5.9	51.5 ± 7.0*	30.0 ± 6.4*

Rats were pretreated with vehicle (VEH) or the different drugs before the rotarod test. All the animals walked during a 120 seconds period at the basal time (0-min). Data are expressed as seconds. Each point corresponds to the mean ± SEM of 8–10 animals. *Significantly different from control group ($P<0.05$) as determined by one way analysis of variance followed by Tukey's test.

Table 2
Effect of the analgesics, hypoglycemics and their combinations on the blood glucose in the rats.

	Time after the drug administration		
	1 h	2 h	3 h
Control	82.8 ± 5.3	93.5 ± 4.3	88.8 ± 5.7
Diclofenac 30 mg/kg	93.5 ± 5.1	85.4 ± 4.4	82.7 ± 3.6
Indomethacin 30 mg/kg	75.0 ± 4.0	71.0 ± 5.0	79.5 ± 12.5
Glibenclamide 10 mg/kg	43.0 ± 3.0*	32.5 ± 4.5*	47.0 ± 6.0*
Glipizide 10 mg/kg	47.8 ± 3.4*	36.3 ± 5.3*	38.8 ± 5.2*
Metformin 180 mg/kg	67.0 ± 4.0	64.0 ± 1.0	68.0 ± 13.0
Phenformin 180 mg/kg	75.3 ± 3.1	64.7 ± 5.1	31.1 ± 2.3*
Diclofenac + glibenclamide	46.9 ± 3.4*	46.5 ± 4.9*	48.2 ± 4.9*
Diclofenac + glipizide	30.5 ± 1.5*	33.0 ± 9.0*	48.5 ± 3.5*
Diclofenac + metformin	70.0 ± 1.0	66.5 ± 7.5	73.5 ± 6.5
Diclofenac + phenformin	78.6 ± 3.3	59.4 ± 4.9*	51.1 ± 7.5*
Indomethacin + glibenclamide	39.5 ± 8.5*	52.0 ± 12.0*	53.5 ± 3.5*
Indomethacin + glipizide	65.2 ± 3.0	66.2 ± 4.2	49.4 ± 2.5*
Indomethacin + metformin	86.0 ± 4.0	57.5 ± 9.5*	58.5 ± 10.5*
Indomethacin + phenformin	59.5 ± 2.1*	37.4 ± 2.9*	30.8 ± 2.9*

Rats were pretreated with vehicle or the different drugs before the blood glucose determination. Data are expressed as mg/dL. At the basal time (0-min), animals had normal blood glucose levels (mean ± SEM of 84.9 ± 3.3 mg/dL). Each point corresponds to the mean ± SEM of 8–10 animals. *Significantly different from control group ($P<0.05$) as determined by one way analysis of variance followed by Tukey's test.

4.3. Effect of metformin and phenformin on antinociception induced by indomethacin

In the current study, metformin and phenformin were not able to block indomethacin-induced systemic antinociceptive effects, suggesting a lack of involvement of metformin or phenformin-dependent mechanisms in the activity of indomethacin. Here, administration of indomethacin in combination with metformin significantly modified blood glucose levels but did not alter motor coordination, unlike administration of indomethacin in combination with phenformin, which significantly modified both blood glucose levels and motor coordination. Whether metformin or phenformin-dependent mechanisms affect indomethacin-induced antinociception should be investigated further.

By themselves, neither sulfonylureas nor biguanides affected formalin-induced nociception, thus excluding the possibility that the inhibition of diclofenac-induced antinociception is a result of the hyperalgesic or nociceptive effects of these hypoglycemic drugs. The inability to modify flinching behavior by different modulators (sulfonylureas and biguanides) at concentrations that are sufficient to prevent antinociception may also indicate that K^+ channels and

biguanide-dependent mechanisms that are involved in the modulation of pain at systemic level are not tonically activated.

Metformin has become one of the most widely prescribed antihyperglycemic agents (Wysowski et al., 2003). Cardiovascular disease, impaired glucose tolerance, metabolic syndrome and polycystic ovary syndrome are now recognized as complications from the insulin resistance syndrome, and there is growing interest in using metformin to manage these common metabolic disorders (Wysocki and Wierusz-Wysocka, 2010). There is evidence that one potential drawback to metformin is the development of lactic acidosis (Lalau, 2010). Acidosis is observed in patients with renal alteration and is where metformin accumulates. In addition, there are reports that metformin-induced lactic acidosis occurs after the concomitant treatment with indomethacin (Chan et al., 1998). Renal failure associated with NSAID treatment is transient and is often reversible upon drug withdrawal. However, the severity increases in patients with other risk factors such as diabetes and heart failure (Harirforoosh and Jamali, 2009). In the present study, we did not measure renal function in animals treated with a combination of NSAIDs and biguanides; however, we did observe that metformin and phenformin significantly modify diclofenac-induced antinociceptive effects. Therefore, treatment with biguanides in combination with diclofenac should be carefully considered. Furthermore, in the future, we plan to evaluate the effect of these NSAID-hypoglycemic drug therapies in diabetic rats.

In summary, the results from this study demonstrated that the interaction between sulfonylureas or biguanides and diclofenac, but not indomethacin, resulted in reduced analgesic efficacy. Clinical studies are warranted to establish the relevance of these interactions.

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