Involvement of the L-arginine/Nitric Oxide/Cyclic GMP/K_{ATP} Channel Pathway and PPARγ Receptors in the Peripheral Antinociceptive Effect of Carbamazepine

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ABSTRACT

Carbamazepine has been shown to exert analgesic effects in clinical and experimental pain situation. This study was conducted to evaluate its potential peripheral antinociceptive effects and the possible involvement of L-arginine/NO/cGMP/K_{ATP} channel pathway and PPARγ receptors in an animal model of pain. The antinociceptive effect induced by intraplantar administration of carbamazepine (100–1 000 µg/paw) was assessed using the formalin test in rats. To evaluate the involvement of L-arginine/NO/cGMP/K_{ATP} channel pathway in the antinociceptive action of carbamazepine, rats were pre-treated intraplantarlly with L-arginine (a nitric oxide precursor, 100 and 200 µg/paw), L-NAME (NOS inhibitor, 50 and 100 µg/paw), methylene blue (guanylyl cyclase inhibitor, 100 and 200 µg/paw), glibenclamide (K_{ATP} channel blocker, 100 and 200 µg/paw), and diazoxide (400 µg/paw). Moreover, to investigate the possible involvement of PPARγ receptors, pioglitazone (10 µg/paw; a PPARγ agonist) alone or in combination with GW9662 (3 µg/paw; a PPARγ antagonist) were pre-treated with carbamazepine. The local ipsilateral, but not contralateral, administration of carbamazepine into the hind paw produced dose-related analgesia during both early and late phases of formalin test. Moreover, pre-treatment with L-NAME, methylene blue, and glibenclamide dose-dependently prevented carbamazepine (300 µg/paw)-induced antinociception in both phases of the test. In addition, administration of L-arginine and diazoxide before the sub-effective dose of carbamazepine (100 µg/paw) produced an antinociceptive effect. Also, antinociception induced by carbamazepine plus pioglitazone (10 µg/paw) was blocked by GW-9662 in both phases of the test. In conclusion, carbamazepine induced a peripheral antinociceptive effect through PPARγ receptors and L-arginine/NO/cGMP/K_{ATP} channel pathway, with potential for a new topical analgesic drug.

Introduction

Research on new analgesic drugs is very important and interesting in improving patient health. Current drugs include nonsteroidal anti-inflammatory drugs and opioids have several side effects [1]. On the other hand, many patients are not satisfied with their pain care. So, the discovery of new compounds that specially exert their analgesic effect in the periphery could be a way to avoid major side effects.

Anticonvulsant drugs produce multiple pharmacological actions [2]. It has been reported that these drugs have some analgesic activity independent from their psychotropic effect [3]. Carbamazepine, an anticonvulsant drugs, is one of the therapeutic choices

to treat neuropathic pain. However, the systemic use of carbamazepine is often limited by its adverse effects such as somnolence, and hematological abnormalities [4]. In this regard, Vuckovic et al. (2006) reported that carbamazepine produces local peripheral analgesic in animal models [5].

Nitric oxide (NO) has different physiological roles in the nervous system [6, 7]. Evidence has revealed that changing in NO signaling significantly affect nociceptive transmission [8]. NO is produced from L-arginine by the catalytic action of NO synthase (NOS). The effects of NO may be mediated directly, and in most instances by the subsequently generated second messenger molecule guanosine 3′5′ cyclic monophosphate (cGMP). Furthermore, it has been reported that different types of K^+ channels can be activated by NO per se or through cGMP [9]. On the other hand, activation of K^+ channels results in a decrease in neurotransmitter release [10]. A growing line of data indicates that the L-arginine/NO/cGMP/K_{ATP} channels pathway has a significant effect on the peripheral analgesic properties of many drugs [7, 11, 12].

Evidence has shown that NO is involved in some pharmacological actions of carbamazepine [13]. In this regard, Ficarra et al. (2013) showed that carbamazepine is able to increase the release of NO derived molecules from RBC [14]. Moreover, it has been shown that carbamazepine inhibits LPS-induced microglial inducible NOS expression through the down-regulation of Akt activation, and thus may play a pivotal role of anti-neuroinflammation [15].

Peroxisome proliferator-activated receptors (PPARs) are ligand-dependent activated nuclear receptors which widely expressed in adipose tissue, immune cells, neurons, and glia of the peripheral nervous system, and modulate the inflammatory process and pain [16]. In previous reports, we showed the role of PPARγ receptors in animal models of pain [17, 18]. On the other hand, Turpin et al. (2013) indicated that carbamazepine may alter adipose tissue development and metabolism through PPARγ receptors in mice cells [19].

Considering the studies mentioned above, the objective of the present study was to obtain data that would support our suggestion that the L-arginine/NO/cyclic GMP pathway and PPARγ receptors are involved in the peripheral analgesic effect of carbamazepine.

Materials and Methods

Animals

We used male Wistar rats weighing 130–160 g (Ahvaz Jundishapur University of Medical Sciences, Ahvaz, Iran). Rats were housed under standard conditions with unrestricted access to food and water and a constant temperature (24 ± 1°C) under a 12-h light/dark cycle. All procedures were performed in accordance with the Declaration of the NIH Guide for Care and Use of Laboratory Animals (No. 80–23, revised 1978), and approved by the Animal Care Committee at Dezful University of Medical Sciences (IR.DUMS.REC.1397.010).

Drugs

L-arginine hydrochloride (NO synthase (NOS) substrate), L-NAME (non-selective inhibitor of NO synthase), and diazoxide (an ATP-sensitive K + channel opener) were obtained from Sigma–Aldrich (St. Louis, Missouri, USA). Methylene blue (NOS and guanylyl cyclase inhibitor) was provided by Merck. Glibenclamide (ATP-sensitive K + channel inhibitor) and carbamazepine were kindly donated by Darupakhsh and Abidi Pharmaceutical Co. (Tehran, Iran), respectively. Pioglitazone (a PPARγ agonist) and GW-9662 (a PPARγ antagonist) were purchased from Osveh Pharmaceutical Co, and Tocris Bioscience, respectively. All drugs were dissolved or suspended in normal saline (0.9 % NaCl) and buffered to a pH of 7.3. Drug concentrations were freshly prepared in such a way that the necessary dose could be injected in a volume of 50 µL/paw by the intraplantar (i.pl.) route. Doses and drug administration schedules (▶ **Fig. 1**) were selected based on previous reports and also our experience in the laboratory [7, 11, 17, 20].

Formalin test

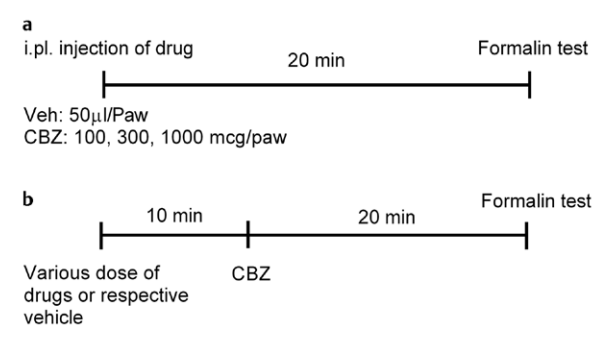
Rats were injected 50 µL of 2.5 % formalin solution (in normal saline) into the subplantar region of the right hind paw using a 30 G needle. Immediately after formalin injection, the animals were placed in a chamber and the number of flinches (an elevation and shrinking back of the injected paw) of the hind paw was recorded every 5 min for a total of 60 min. The first 5 min after formalin administration was considered as the early phase (neurogenic phase) and the period between 15 and 60 min as the late phase (inflammatory phase) [21].

Peripheral antinociceptive effect of carbamazepine

The rats were given 50 µL/paw of either carbamazepine (100, 300, and 1 000 µg/paw) or normal saline into the subplantar region of right hind paw 20 min before formalin injection into the ipsilateral paw. Moreover, to investigate whether carbamazepine acts locally, the maximum dose of carbamazepine was administered to the left (contralateral) hind paw 20 min before injection of formalin into the right paw, and the corresponding response on nociceptive behaviors was assessed [7].

Involvement of the L-arginine/NO pathway

For this, rats were pretreated with L-arginine, a nitric oxide precursor (100 and 200 µg/paw) and after 10 min they received sub-



▶ **Fig. 1** Timeline of the experimental schedule in the formalin test. **a** Rats were received a single i.pl. dose carbamazepine (CBZ; 100–1 000 µg/paw) or vehicle (Veh), and were tested for antinociceptive effect using the formalin test 20 min after the drug administration. **b** In further experiments, 10 min before administration of carbamazepine (100 or 300 µg/paw; i.pl.) animals were pre-treated with increasing doses of L-arginine, L-NAME, methylene blue, glibenclamide, diazoxide, and GW-9662 and then tested on the formalin assay after 20 min.

effective dose carbamazepine (100 µg/paw) or its vehicle and nociceptive responses were evaluated 20 min later using the formalin test. In another set of experiments, we investigated the effect of the combined administration of carbamazepine (300 µg/paw) with L-NAME (50 and 100 µg/paw, a non-selective NO synthase inhibitor) [22].

Involvement of the cGMP pathway

To evaluate the role of cGMP in the local antinociceptive effect of carbamazepine, animals were pre-treated with methylene blue (100 and 200 µg/paw), or vehicle, 10 min before the effective dose of carbamazepine (300 µg/paw), and nociceptive responses were assessed 20 min later using the formalin test.

Involvement of K_{ATP} channel pathway

To determine the role of K_{ATP} channel in the local antinociceptive effect of carbamazepine, rats were pretreated with glibenclamide, a K_{ATP} channel inhibitor (100 and 200 µg/paw) and after 10 min they received an effective dose of carbamazepine (300 µg/paw) or its vehicle and formalin test was done 20 min later. In another set of experiments, we investigated the effect of the combined administration of sub-effective dose carbamazepine (100 µg/paw) with diazoxide (400 µg/paw, K_{ATP} channel opener) [7, 23].

Involvement of PPARγ receptors

In order to clarify the role of PPARγ receptors in the analgesic effect of carbamazepine, rats were pre-treated with the combination of sub-effective doses of pioglitazone (10 µg/paw, PPARγ receptor agonist) plus carbamazepine (100 µg/paw) [18]. In addition, GW-9662 (3 µg/paw, a PPARγ receptor antagonist) was given 10 min before the combined regimen and flinching behavior was recorded 20 min later by formalin assay.

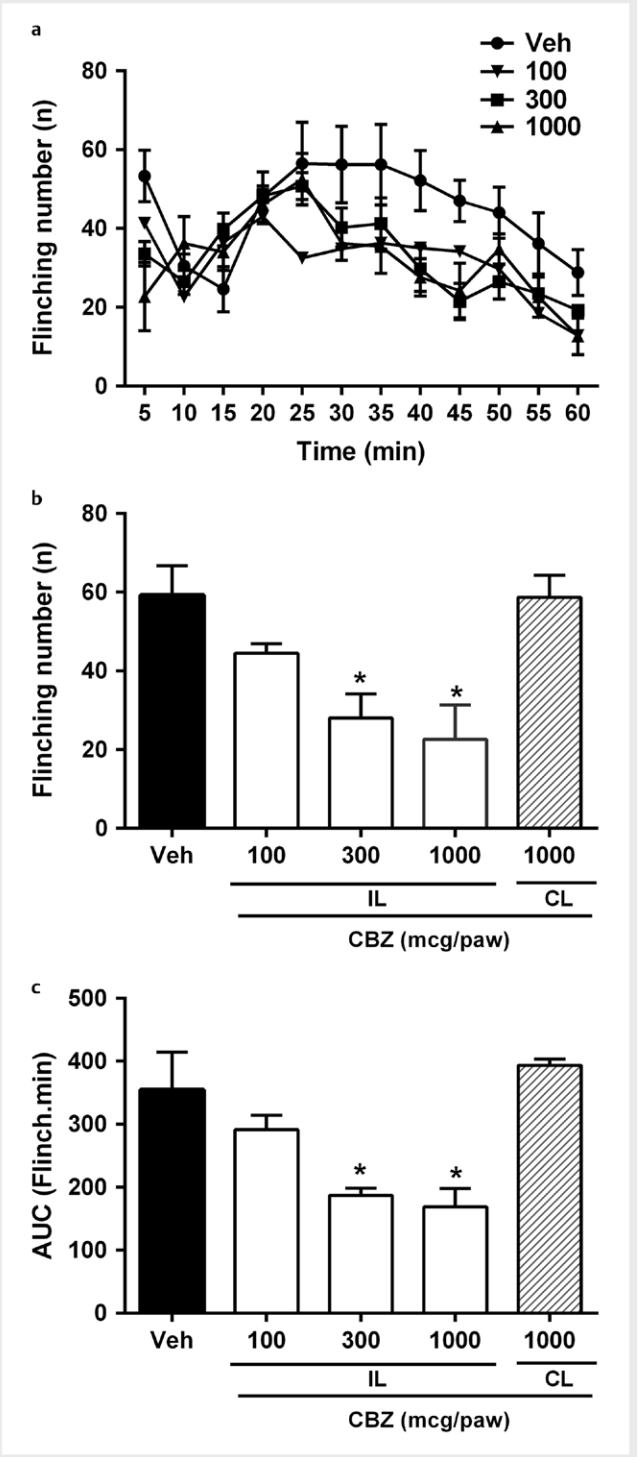
Statistical analysis

All data are expressed as means ± SEM for 6–8 animals per group. The area under the number of flinches versus time curve (AUC) was calculated by using the trapezoidal rule. Percentage of maximum possible effect (%MPE) was computed using the following formula: %MPE = (No. of flinches, saline control–No. of flinches, test drug)/(No. of flinches, saline control) × 100. The effective dose 50 (ED_{50}; the dose of carbamazepine reducing the nociceptive response by 50 % relative to the control value) values were measured by linear regression from individual experiments using GraphPad software (GraphPad Prism 7.05, San Diego, California, USA). For multiple comparisons of dose-response experiments, one-way ANOVA followed by Tukey's post hoc test were used. Statistical difference was considered significant at $P < 0.05$.

Results

Peripheral antinociceptive effect of carbamazepine

Formalin injection into the hind paw produced a typical pattern of flinching behavior characterized by a biphasic time-course (▶ **Fig. 2a**). Local ipsilateral, but not contralateral administration of carbamazepine reduced in a dose-dependent manner formalin-induced nociceptive behavior during both early ($F(4, 18) = 7.02$, $P < 0.01$; ▶ **Fig. 2b**)

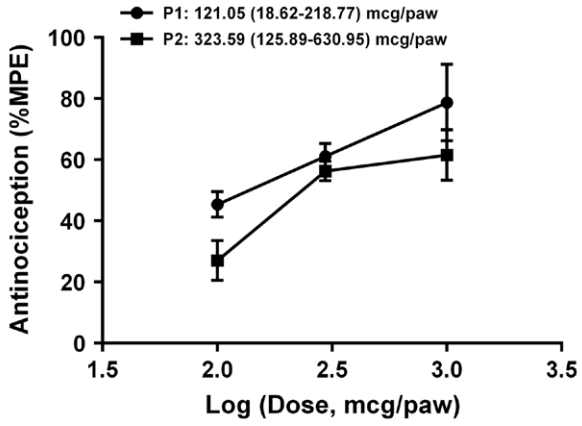


▶ **Fig. 2** Time course of local antinociceptive effect of carbamazepine (CBZ) in the formalin test **a**. Rats were pre-treated with carbamazepine or vehicle (Veh) into either the right (ipsilateral, IL) or left (contralateral, CL) paw, before formalin injection. Dose-response relationship obtained after peripheral administration of carbamazepine during early **b** and late phases **c** of the formalin test. Data are expressed as the area under the number of flinches against time curve (AUC). Bars are the means ± S.E.M. for 6–8 animals. * $P < 0.05$ and ** $P < 0.01$ compared to animals treated with vehicle (Veh), as determined by one-way ANOVA followed by Tukey's test.

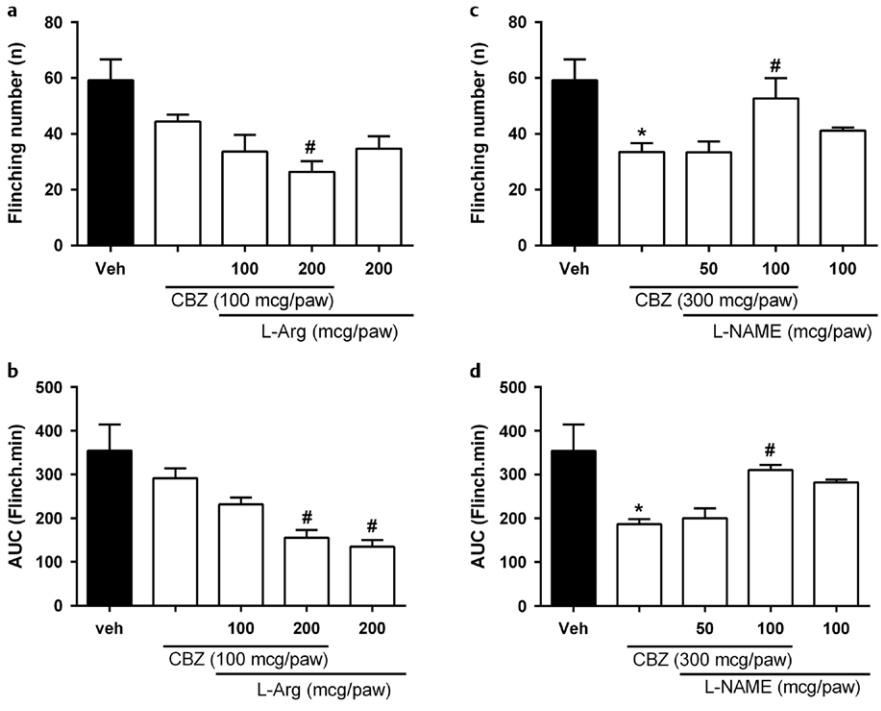
and late ($F(4, 21) = 8.01$, $P < 0.01$; ▶ **Fig. 2c**) phases of the test, suggesting that the response was exerted by local mechanisms. The calculated ED_{50} values for these effects were 121.05 (18.62–218.77) and 323.59 (125.89–630.95) µg/paw for early and late phases, respectively (▶ **Fig. 3**). Based on these results, dose 100 µg/paw and 300 µg/paw carbamazepine was considered as sub-effective and effective dose, respectively, and selected for subsequent experiments to elucidate whether the antinociceptive effect of carbamazepine was mediated by the peripheral L-arginine/NO/cGMP/K_{ATP} channel pathway and PPARγ receptor.

Involvement of the L-arginine/NO pathway in the peripheral antinociceptive effect of carbamazepine in the formalin test

▶ **Figure 4a, b** showed that intraplantar administration of L-arginine (200 µg/paw) in combination with sub-effective dose of carbamazepine (100 µg/paw) produced peripheral antinociception in early ($F(4, 22) = 5.24$, $P < 0.01$) and late ($F(4, 17) = 5.87$, $P < 0.01$) phases of formalin test, respectively. On the other hand, the antinociceptive effect of carbamazepine (300 µg/paw) was antagonized by L-NAME (50 and 100 µg/paw) in a dose-dependent manner in early ($F(4, 18) = 3.04$, $P < 0.05$; ▶ **Fig. 4c**) and late ($F(4, 20) = 4.61$, $P < 0.01$; ▶ **Fig. 4d**) phases. In addition, L-NAME did not induce hyperalgesia or antinociception when used alone.



▶ **Fig. 3** Effects of intraplantar carbamazepine (100–1 000 mcg/paw) against the early (P1) and late (P2) phases of formalin-induced flinching behaviour in rats. The total number of flinches of the injured hind paw was measured in the early phase (circles; 0–5 min) and late phase (squares; 15–60 min) after intraplantar injection of formalin. Each point represents the mean ± SEM for 6–8 animals. Values of effective dose 50 (with 95 % confidence limits) are presented in the figure. %MPE, percentage of maximum possible effect.



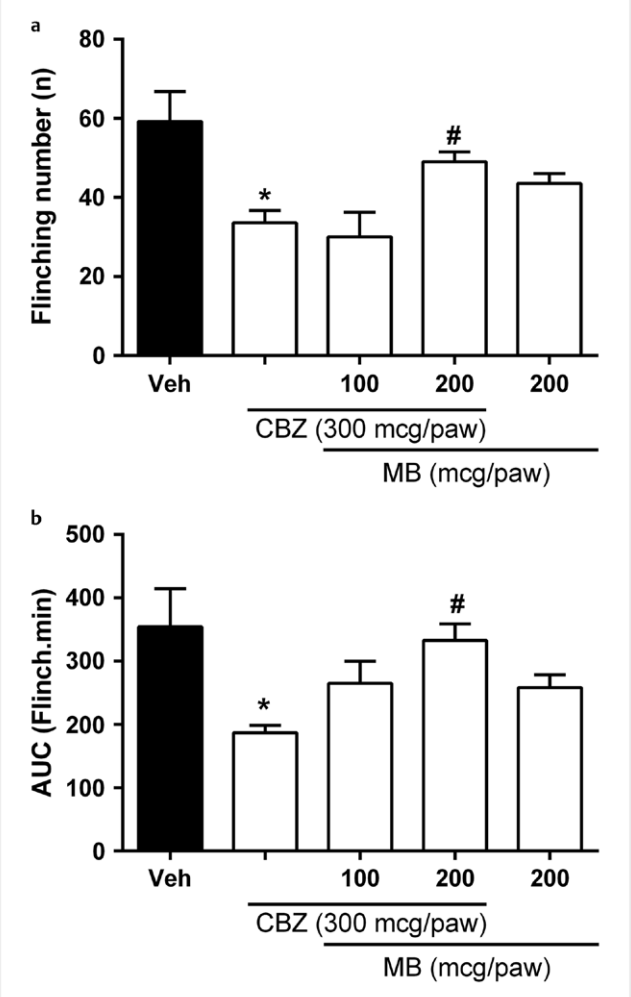
▶ **Fig. 4** Evaluation of the involvement of the L-arginine–NO pathway in the carbamazepine (CBZ) antinociceptive effect in the formalin test. The effect of pretreatment with L-arginine (100 and 200 mcg/paw, i.p.l.) on antinociceptive effect of carbamazepine in early and late phases of formalin test is shown in panels **a** and **b**, respectively. The effect of pretreatment with L-NAME (50 and 100 mcg/paw, i.p.l.) on the antinociceptive effect of carbamazepine in the early and late phases is shown in panels **c** and **d**, respectively. Values are expressed as mean ± S.E.M. (n = 6–8). * $P < 0.05$ compared to animals treated with vehicle (Veh), # $P < 0.05$ compared to animals treated with CBZ alone, as determined by one-way ANOVA followed by Tukey's test.

Involvement of guanylyl cyclase in the peripheral antinociceptive effect of carbamazepine in the formalin test

The local administration of methylene blue was not able to significantly modify formalin-induced flinching behavior. However, it attenuated the antinociceptive effect of carbamazepine (300 µg/paw) in a dose-dependent way (100 and 200 µg/paw) in early ($F(4, 21) = 5.05$, $P < 0.01$; ▶ **Fig. 5a**) and late ($F(4, 20) = 3.29$, $P < 0.05$; ▶ **Fig. 5b**) phase of the formalin test.

Involvement of K_{ATP} channels in the peripheral antinociceptive effect of carbamazepine in the formalin test

Local glibenclamide did not produce any significant changes in pain behavior. However, it reversed dose-dependently (100 and 200 µg/paw) the antinociception produced by carbamazepine during the early ($F(4, 20) = 5.7$, $P < 0.01$; ▶ **Fig. 6a**) and late ($F(4, 24) = 3.03$, $P < 0.05$; ▶ **Fig. 6b**) phase of the formalin test. Moreover, local diazoxide (400 µg/paw) in combination with sub-effective dose of carbamazepine (100 µg/paw) produced peripheral antinociception in early ($F(3, 18) = 9.16$, $P < 0.01$; ▶ **Fig. 6c**) and late ($F(3, 19) = 6.72$, $P < 0.01$; ▶ **Fig. 6d**) phases of formalin test.



▶ **Fig. 5** Evaluation of the involvement of guanylyl cyclase in the carbamazepine (CBZ) antinociceptive effect in the formalin test. The effect of pretreatment with methylene blue (100 and 200 mcg/paw, i.pl.) on antinociceptive effect of carbamazepine in early and late phases of formalin test is shown in panels **a** and **b**, respectively. Values are expressed as mean ± S.E.M. (n = 6–8). * $P < 0.05$ compared to animals treated with vehicle (Veh), # $P < 0.05$ compared to animals treated with CBZ alone, as determined by one-way ANOVA followed by Tukey's test.

Involvement of PPARγ receptors in the peripheral antinociceptive effect of carbamazepine in the formalin test

As shown in ▶ **Fig. 7**, local administration of sub-effective dose of pioglitazone (10 µg/paw) significantly potentiated the antinociceptive effects of effect of carbamazepine during the early ($F(4, 21) = 7.37$, $P < 0.01$; ▶ **Fig. 7a**) and late ($F(4, 23) = 3.79$, $P < 0.05$; ▶ **Fig. 7b**) phase of the formalin test, respectively. However, GW-9662 (3 µg/paw) significantly antagonized the antinociceptive effects of carbamazepine (100 µg/paw) in combination with pioglitazone (10 µg/paw) during both phases of the formalin test.

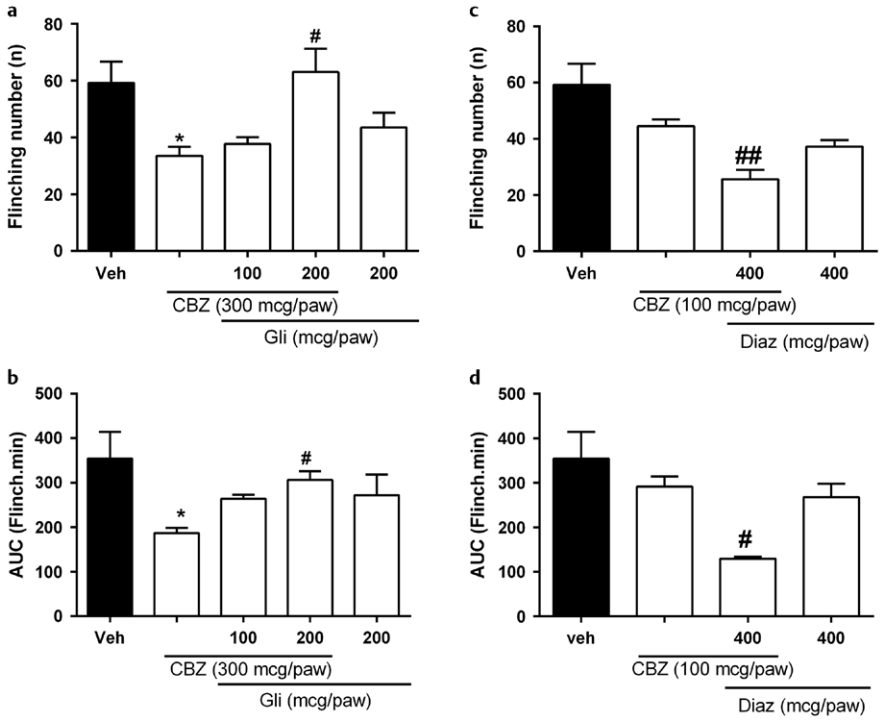
Discussion and Conclusions

Our results indicated that carbamazepine had a dose-dependent peripheral antinociceptive effect against both phases of formalin assay. Furthermore, we demonstrated for the first time the possible involvement of the L-arginine/NO/cGMP/K_{ATP} channels pathway and PPARγ in the peripheral antinociceptive action of carbamazepine in both phases of formalin test in rats.

During formalin test two phases of the response are observed: an early phase (neurogenic) observed immediately after injection and lasting for 0–5 min and a late phase (inflammatory) 15–60 min after injection [21]. It has been shown that the early phase results from a direct effect of formalin on nociceptors, whereas the late phase is mediated by a combination of peripheral input and spinal cord sensitization [24]. In our study, the intraplantar administration of carbamazepine dose-dependently attenuated both phases of formalin-induced nociceptive behavior. However, this effect was a local and, was not due to a systemic effect, because carbamazepine (1 000 µg/paw) administered into the contralateral paw was not effective.

Our observations confirm previous results that local administration of carbamazepine induces an antinociceptive effect in inflammatory mechanical hyperalgesia model in the rat (Vuckovic et al., 2006). Moreover, Kohli et al. (2016) reported that carbamazepine produced analgesia in thermal and mechanical hyperalgesia in neuropathic pain models [25].

Nitric oxide (NO) acts as a neuronal messenger in the central and peripheral nervous systems and is involved in various biological events [26]. The role of NO in pain is complex. In this regard, Kawabata et al. (1994) reported that peripheral NO may play a dual role in nociceptive modulation as assessed by the formalin test in the mouse [27]. In the present study, we reported that L-arginine (a nitric oxide precursor) produce peripheral antinociception in the formalin test. On the other hand, we demonstrated that L-arginine potentiated the antinociceptive effect of carbamazepine. Furthermore, to evaluate that the effect of carbamazepine is dependent on L-arginine/NO pathway activation, we performed experiments



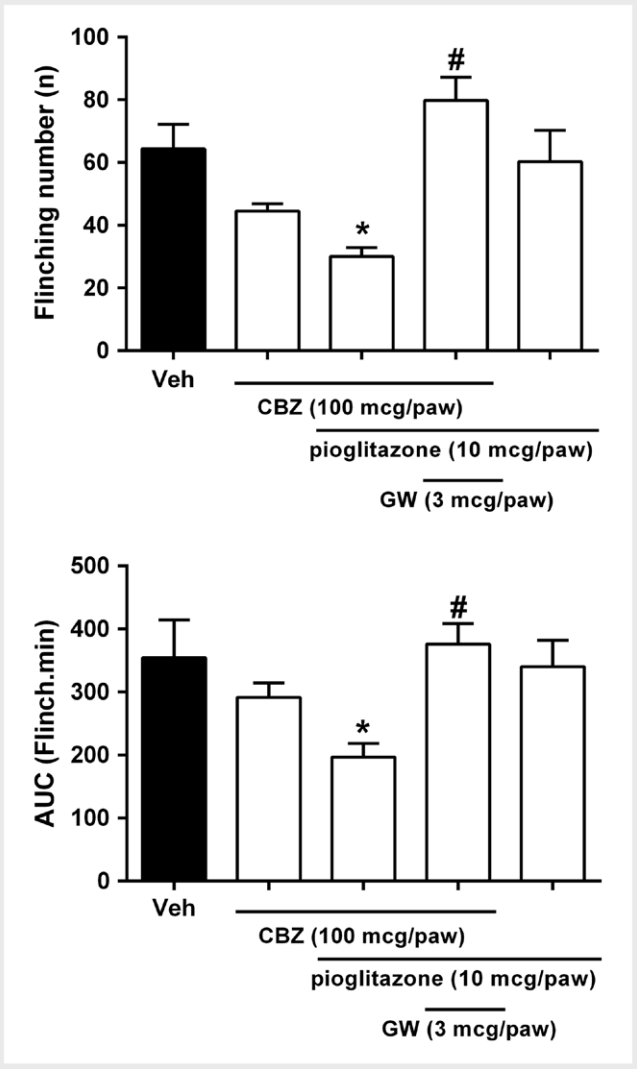
▶ **Fig. 6** Evaluation of the involvement of K_{ATP} channels in the carbamazepine (CBZ) antinociceptive effect in the formalin test. The effect of pre-treatment with glibenclamide (100 and 200 mcg/paw, i.pl.) on antinociceptive effect of carbamazepine in early and late phases of formalin test is shown in panels **a** and **b**, respectively. The effect of pretreatment with diazoxide (400 mcg/paw, i.pl.) on the antinociceptive effect of carbamazepine in the early and late phases is shown in panels **c** and **d**, respectively. Values are expressed as mean ± S.E.M. (n = 6–8). * $P < 0.05$ compared to animals treated with vehicle (Veh), # $P < 0.05$ and ## $P < 0.01$ compared to animals treated with CBZ alone, as determined by one-way ANOVA followed by Tukey's test.

based on NO synthesis. Results showed that carbamazepine-induced peripheral antinociception attenuated after intraplantar administration of L-NAME (a non selective inhibitor of the NOS) in a dose-dependent manner. In this regard, it has been shown that carbamazepine is able to increase the release of NO from erythrocytes [14]. In addition, Wang et al. (2014) reported that carbamazepine inhibits LPS-induced microglial inducible NOS expression [15]. Furthermore, several studies have determined that the L-arginine/NO pathway plays an important role in the peripheral analgesic effect of several drugs in the formalin test [7, 28, 29].

The effect of NO may be mediated by locally produced NO directly, and often by the subsequent generation of cGMP. Functionally, activation of guanylyl cyclase (GC) by NO increases cGMP level in the cell, and consequently produces antinociception [30]. In the present work, we observed that the pre-treatment with methylene blue (a GC inhibitor), which results in a decrease in cGMP, reversed dose-dependently local antinociception caused by carbamazepine. This result showed the role of cGMP in the antinociception mechanism of carbamazepine.

On the other hand, the peripheral analgesic activity of the NO/cGMP pathway may result from the activation of K_{ATP} channels. Accordingly, some studies indicate that different types of K^+ channels in several tissues can be activated by NO and cGMP [9, 31]. The results presented here reveal that the modulation of K_{ATP} channels may change the antinociceptive effect of carbamazepine. Local administration of glibenclamide significantly reduced, and diazoxide increased the antinociceptive effect of carbamazepine, suggesting that antinociceptive effect of carbamazepine is also dependent on K_{ATP} channels in peripheral sites, and probably stimulated by NO/cGMP pathway. These observations are in agreement with our previous studies and several reports showing the role of K_{ATP} channel in the analgesic effect of drugs [7, 32, 33]. Moreover, Zhou et al. (2014) showed that carbamazepine modulates K_{ATP} channels effect in cell culture [34].

At the present work, we also attempted to investigate the role of PPARγ receptors in the local antinociceptive effects of carbamazepine as a target for pain modulation. Accordingly, carbamazepine was co-administered with pioglitazone and GW-9662. The results showed that combined administration of local carbamazepine with pioglitazone at low doses which showed a sub-effective response produced synergistic analgesia in rat formalin assay. However, GW-9662 reversed the anti-nociceptive action of carbamazepine combined with a low dose of pioglitazone. So, it can be suggested that peripheral PPARγ receptors have a possible role in the antinociceptive effect of local carbamazepine. Daynes and Jones (2002) reported that PPARγ receptors activation attenuates pro-inflammatory cytokines and the inflammatory mediators [35]. In addition, it has been shown that PPARγ receptors are present in the subcutaneous



▶ **Fig. 7** Evaluation of the involvement of PPARγ receptors in the carbamazepine (CBZ) antinociceptive effect in the formalin test. Rats were pretreated with the combination of sub-effective doses of pioglitazone plus carbamazepine (100 µg/paw) in early and late phases of formalin test in panels **a** and **b**, respectively. Also, GW-9662 was given 10 min before the combination therapy, and flinching behavior was recorded 20 min later by formalin assay. Values are expressed as mean ± S.E.M. (n = 6–8). * $P < 0.05$ compared to animals treated with vehicle (Veh), # $P < 0.05$ compared to animals treated with CBZ + pioglitazone, as determined by one-way ANOVA followed by Tukey's test.

tissue of rat that can produce anti-inflammation by PPARγ agonists [36]. Moreover, we previously reported that the role of PPARγ receptors in the antinociceptive effects of some drugs [17, 18]. On the other hand, Turpin et al. (2013) indicated that carbamazepine may alter cell metabolism through PPARγ receptors in mice cells [19].

In conclusion, results show that local carbamazepine was able to produce analgesia in both phases of the formalin test. Moreover, we have shown for the first time that the analgesic activity of carbamazepine is probably mediated through the L-arginine/NO/cGMP/K_{ATP} channels signaling pathway and PPARγ receptors. Taken together, to confirm the local analgesic effect of carbamazepine, clinical studies on pain by a topical application are warranted.

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Conflict of Interest

The authors declare that there is no conflict of interest associated with this work.

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