

The Analgesic and Anxiolytic Activity of Resveratrol Mediated by Different Sub-Types of α -Adrenoceptors of Anterior Cingulate Cortex Following Neuropathic Pain in Male Rats

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ABSTRACT

Background & Objective: The mechanism of analgesic and anxiolytic activity of resveratrol in neuropathic pain conditions remains obscure. The present study was conducted to examine whether the analgesic and anxiolytic activities of resveratrol are associated with α_1 - and α_2 -adrenoceptors of the anterior cingulate cortex (ACC), which is a key area of the cortex in the pain process, following neuropathic pain in rats.

Materials & Methods: Neuropathic pain was created by chronic constriction injury (CCI) of the sciatic nerve. Male Wistar rats were assigned to the sham, CCI, CCI+resveratrol (40 μ g/5 μ L), CCI+resveratrol+prazosin (α_1 -adrenoceptor antagonist, 30 μ g/5 μ L), and CCI+resveratrol-Yohimbine (α_2 -adrenoceptor antagonist, 30 μ g/5 μ L) groups. The rats received intra-ACC injection of the drug on the day of CCI and for 6 days post-CCI on a daily basis. Cold allodynia (using acetone test) and anxiety (using elevated plus maze, EPM) were examined on days 2, 4, and 6 following CCI.

Results: CCI model significantly increased cold allodynia and anxiety. Resveratrol significantly decreased cold allodynia. Prazosin induced no significant changes in allodynia as compared with the CCI+resveratrol treated group. But the animals in this group had no significant difference from the day before the surgery or compared with the sham group. Prazosin significantly decreased entries into open arms. Additionally, yohimbine significantly increased cold allodynia as compared with the CCI+resveratrol treated group. However, it induced no significant changes in the EPM parameters. Our findings also demonstrated a significant correlation between allodynia and anxiety in CCI rats.

Conclusion: It is suggested that the mechanism of analgesic and anxiolytic activities of resveratrol in the ACC of rats is different, and is mediated through α_2 - and α_1 -adrenoceptors, respectively.

Keywords: Allodynia, Anxiety, Anterior cingulate cortex, α -adrenoceptors, Rat, Resveratrol



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Introduction

Peripheral or central nerve damage can induce neuropathic pain (1,2). Common abnormal signs of neuropathic pain are hyperalgesia (exaggerated pain perception in response to noxious), allodynia (pain perception in response to non-noxious stimuli) and psychological disorders such as anxiety (3,4). In most of the pharmacological studies along with neuropathic pain management, the effects of different compounds on these behavioral parameters are investigated (5). Nowadays, conventional analgesics and existing treatments only partially alleviate the neuropathic pain, due to its unknown underlying mechanism(s). Moreover, it is suggested that α -adrenoceptors critically

contribute to the process of pain development (6). These receptors are widely distributed in the central nervous system (7). Several pharmacological studies have originally reported that the administration of α -adrenoceptor agonists can attenuate the hypersensitivity that follows neuropathic pain (7-9). For example, Roh *et al.* (2008) indicated that the intrathecal injection of clonidine (α_2 adrenoceptor agonist, 20 μ g/rat) induces anti-hyperalgesic and anti-allodynic effects in the chronic constriction injury (CCI) model of the rats with sciatic nerve (10). Additionally, Liang *et al.* (2017) revealed that the intrathecal administration of dexmedetomidine attenuated mechanical allodynia and

thermal hyperalgesia in the CCI model of the sciatic nerve in Sprague-Dawley rats (11). Similarly, Chia *et al.* (2020) revealed that the administration of zerumbone (the main bioactive compound, a wild ginger plant species) have anti-allodynia and anti-hyperalgesia effects via activation of α - and β -adrenoceptors in the CCI-induced neuropathic pain mouse model (12). Therefore, it is suggested that α -adrenoceptors have an important role in the processing of pain information in the central nervous system. Here, we focus on the α_1 - and α_2 -adrenoceptors of the anterior cingulate cortex (ACC). Accumulating evidence indicates that the ACC is the most important cortical circuit related to pain information processing (13). Xie *et al.* reported that the delivery of repetitive noxious laser to the rat's hind paw induced extracellular activity in the ACC in the rats (14). Additionally, in humans, surgical cinglectomy suppressed responses to noxious stimuli (15). Hence, the activity of neurons in the ACC is associated with pain perception. Resveratrol (3,5,4'-trihydroxystilbene), which is a natural polyphenolic compound, is found in certain fruits and vegetables including red grapes (16). Pharmacological studies have demonstrated that resveratrol possesses diverse properties, including anti-oxidant, anti-carcinogenic, anti-inflammatory, cell growth-modulatory, and analgesic and anti-nociceptive effects (16-19). Although, the analgesic effects of resveratrol have been well documented, the underlying mechanism of its analgesic and anxiolytic activities is far from clear. Here, we concentrate on the interaction effects of resveratrol with α_1 - and α_2 -adrenoceptors of the ACC following neuropathic pain among male rats. Indeed, the present study, is aimed to explore whether analgesic or anxiolytic activities of resveratrol are mediated by α_1 - and α_2 -adrenoceptors of ACC following neuropathic pain.

Materials and Methods

Animals

The experiments were carried out on adult male Wistar rats (weight 180 ± 20 g, $n = 6/\text{group}$). The animals were purchased from breeding colony of Baqiatallah University of Medical Sciences, Tehran, Iran. The animals were housed in the animal house of Baqiyatallah University of Medical Sciences under a 12-hour light/dark cycle (6 am lights on–6 pm lights off) in a temperature-controlled room ($22 \pm 2^\circ\text{C}$ and humidity: $60 \pm 5\%$) with food and water available ad libitum. All the experiments were conducted in agreement with the codes of National Institutes of Health Guide for Care and Use of Laboratory Animals. The Ethics Committee of the Baqiatallah University approved this animal study (Ethical code: IR.BMSU.REC.1396.750).

Drugs and Chemicals

Resveratrol was acquired from Sigma–Aldrich Inc. (St Louis, MO, USA). Prazosin and Yohimbine were purchased from Iran Daru Pharmaceutical Company. The drug was dissolved in physiological saline (0.9%).

Experimental Protocol

In the present study, rats were randomly divided into 5 groups. These groups were as follows: (Group 1: sham-operated group); (Group 2: CCI group); (Group 3: CCI+ Resveratrol group); (Group 4: CCI+ Resveratrol + Prazosin group); and (Group 5: CCI+ Resveratrol + Yohimbine group). Resveratrol ($40 \mu\text{g}/5 \mu\text{L}$) applied intra-ACC daily from days 1 to 6 after surgery ($n=6$ rats per group). Co-injection Resveratrol and Prazosin (as α_1 -adrenoceptor antagonist, $30 \mu\text{g}/5 \mu\text{L}$) or Yohimbine (as α_2 -adrenoceptor antagonist, $30 \mu\text{g}/5 \mu\text{L}$) was also applied daily from days 1 to 6 post-surgery. The behavioral evaluation was carried out 1 day prior to CCI surgery (day -1), and on days 2, 4, and 6 post-surgery (20), at 30 min after drugs injection.

Drugs Injection

For intra-ACC injections of normal saline (control), Resveratrol, Prazosin and Yohimbine, a guide cannula (stainless steel 28-gauge) was implanted into the right ACC, contra-lateral to nerve injury, (AP 1.5 mm from bregma, ML ± 0.6 mm from midline, DV 1.5 mm beneath the surface of the skull), using stereotaxic frame (21). A $5.0 \mu\text{L}$ Hamilton syringe with a 33-gaugeneedle was used to inject $5 \mu\text{L}$ of chemical and drugs. The syringe was left in place for 3 min to ensure diffusion of the injected.

Neuropathic Pain Model (CCI Model)

The left sciatic nerve was tightly ligated to produce the CCI model of neuropathic pain, as previously introduced by Bennett and Xie (22). The rats were anesthetized with chloral hydrate ($350 \text{ mg}/\text{kg}$, i.p). The left sciatic nerve (body section of nerve about 1 cm) was exposed and 4 loose ligatures (4/0 cat-gut) were tied around the nerve, about 1 mm apart, until a brief twitch in the hind limb was observed. The muscle and the adjacent fascia and skin were closed with sutures. A sham operation was performed by exposing, but not ligating the sciatic nerve.

Cold Allodynia (Acetone Test)

To quantify cold sensitivity, the number of paw withdrawal responses (PWR, as a positive response) was evaluated after application of acetone drop to the plantar surface of the left hind paw (injured side) (23). Briefly, the rat was placed under a transparent Plexiglas chamber with a metal mesh floor and an acetone drop was applied to the plantar surface of the hind paw, using a syringe. The acetone drop was applied 5 times (total trials=5, every 5 min) to the left hind paw. The frequency of PWR was expressed as the percentage and calculated as follows: $(\text{Number of positive responses} \times 100) / (\text{Number of total trials})$.

Anxiety-like Behaviors (EPM)

The elevated plus maze is a cross-shaped platform which consists of 2 open and 2 closed arms. All the arms communicate through a central zone. The rats were placed on the central zone of the maze, facing an

open arm for 5 min. Their movements on the maze were controlled for a 5 min period by camera. The percentage of time spent in open arms and the percentage of entries into open arms were used as indices of anxious behaviors. A decrease in the time spent in the open arms and the number of entries into open arms indicated anxiety (24).

Statistical Analysis

All the data were presented as mean ± standard error of the mean (SEM). Analyses were performed in SPSS 24 (SPSS Inc., Chicago, Ill. USA). Differences in the measured parameters among the 4 groups were analyzed using one-way analysis of variance (ANOVA), followed by Tukey’s post-hoc test. Additionally, the data were evaluated using two-way ANOVA to determine the day × group interaction. Pearson linear regression analysis (variables; frequency of PWR and open arm entries) was also performed between sham and neuropathic group. The differences were considered to be significant at $p < 0.05$.

Results

Effects of Resveratrol and Its Interaction with $\alpha_{1,2}$ -adrenoceptors on Cold Allodynia

The frequency of PWR in CCI rats was significantly higher after the neuropathic surgery as compared to before the surgery (Figure 1). Cold allodynia was significantly increased from 2 days up to 6 days after the neuropathic surgery [Figure 1, ($*P < 0.05$ on Day 2)

and ($**P < 0.01$ on Days 4 and 6)]. Additionally, intra-ACC injection of resveratrol significantly decreased the frequency of PWR as compared with the CCI group [Figure 1, ($###P < 0.001$ on Day 4) and ($##P < 0.01$ on Day 6)] (it indicated analgesic activity of Resveratrol). There was no significant difference in PWR between the CCI+ resveratrol and CCI+ resveratrol +prazosin groups. The co-injection of resveratrol and prazosin had no significant effect on the frequency of PWR as compared with the CCI+ resveratrol group. Surprisingly, co-injection of resveratrol and yohimbine significantly increased the frequency of PWR from days 4 to 6 post-surgery as compared with the CCI+ resveratrol group (Figure 1, $^^^P < 0.001$ and $^P < 0.05$; respectively) (that is Yohimbine suppressed analgesic effect of Resveratrol). Two-way ANOVA (days × groups) analysis confirmed significant effects of groups ($P = 0.001$), and days ($P = 0.001$), as well as interaction between both of the factors ($P = 0.002$).

Effects of Resveratrol and Its Interaction with $\alpha_{1,2}$ -adrenoceptors on Anxiety-Like Behaviors

In the EPM test, the percentage of entries into open arms decreased on day 6 in CCI rats compared to the sham group; moreover, the percentage of time spent into open arms decreased on all the experimental days after neuropathy in CCI rats as compared with the sham group (Figure 2).

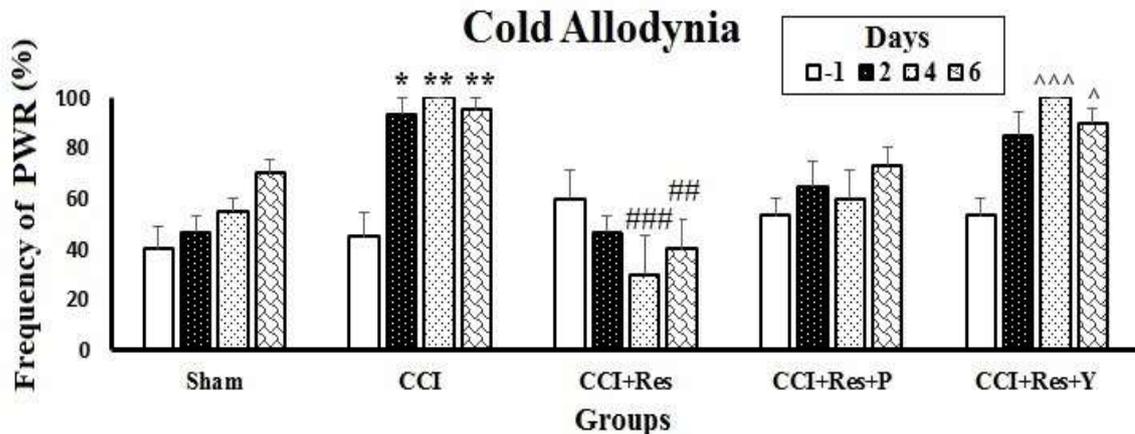


Figure 1. Effects of Resveratrol and its interaction with α_{1} and α_{2} -adrenoceptors on cold allodynia were evaluated. Frequency of paw withdrawal response (PWR) to acetone stimulation was assessed on ipsilateral hind paws of experimental groups, at day -1 (baseline), and days 2, 4, and 6 post-neuropathy. Differences in measured parameters among 4 groups were analyzed using Two- and One-way analysis of variance (ANOVA), followed by the Tukey’s post-hoc test. CCI; chronic constriction injury, CCI+Res; chronic constriction injury+ Resveratrol, CCI+ Res +P; chronic constriction injury+ Resveratrol + Prazosin, CCI+ Res +Y; chronic constriction injury+ Resveratrol + Yohimbine.

*denote a significant difference with sham animals or day -1 (baseline) in each group; # denote a significant difference with CCI animals at the same day. ^ denote a significant difference with CCI+Resveratrol animals at the same day.

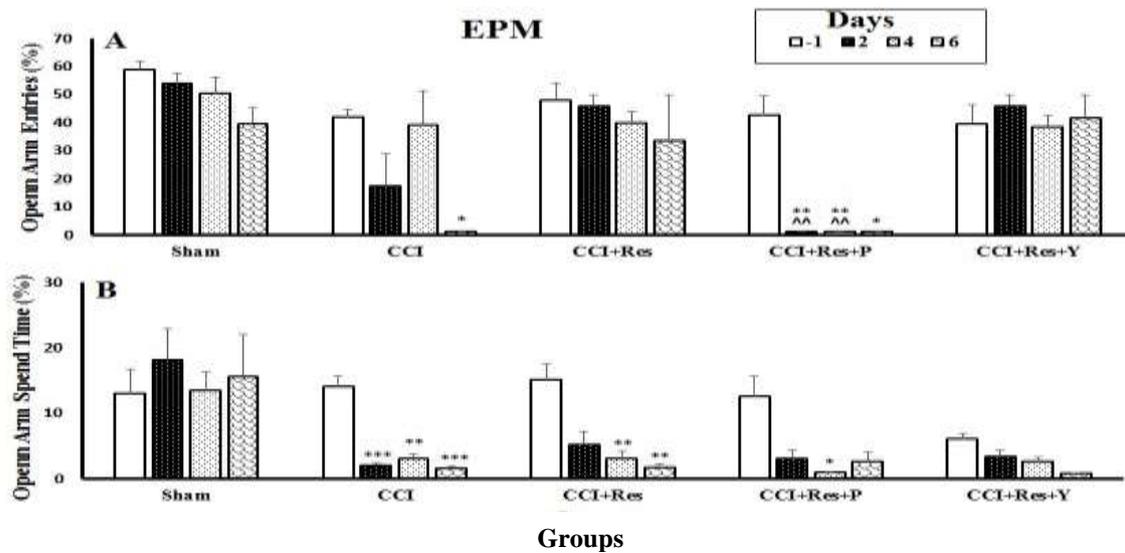


Figure 2. Effects of Resveratrol and its interaction with $\alpha 1$ and 2-adrenoceptors evaluated on anxiety-like behaviors at days -1 (baseline) and 6 post-neuropathy. Percentage of open arms entries (A) and spent time in open arms (B) were evaluated as anxiety indices. Differences in measured parameters were analyzed using two- and one-way analysis of variance (ANOVA), followed by the Tukey’s post-hoc test. CCI; chronic constriction injury, CCI+Res; chronic constriction injury+ Resveratrol, CCI+ Res +P; chronic constriction injury+ Resveratrol + Prazosin, CCI+ Res +Y; chronic constriction injury+ Resveratrol + Yohimbine.

* denote a significant difference with sham animals or day -1 (baseline) in each group; ^ denote a significant difference with CCI+Res animals.

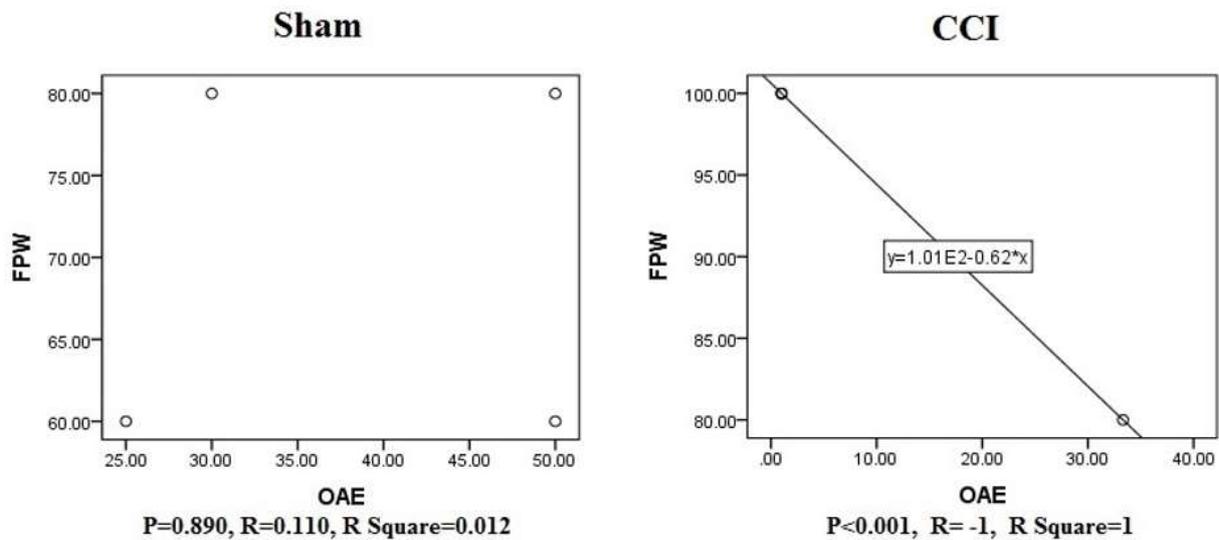


Figure 3. Correlation between allodynia (frequency of paw withdrawal, FPW) and anxiety (open arms entries, OAE) were evaluated in the sham and CCI (neuropathy animals) groups. Data extracted from 6 days after CCI injury. Only significant correlation between allodynia (FPW) and open arm entries was observed in CCI rats. No significant correlation between these parameters was observed in sham-operated rats. The corresponding Pearson correlation (R), R Square, and P-values as determined by regression analysis are indicated below each corresponding panel.

A decline in the percentage of entries into open arms or time spent in open arms displayed increased anxiety. Moreover, intra-ACC injection of resveratrol could not induce a significant alteration in entries into open arms of EPM as compared with the CCI group. However, this increase was not different as compared to before

CCI surgery (day -1) in CCI+ resveratrol group, which is indicated the anxiolytic effects of resveratrol (Figure 2a). In addition, the co-injection of resveratrol and prazosin significantly decreased only the parameter of entries into open arms (increased anxiety) as compared with the CCI+ resveratrol group on days 2 and 4 post-

surgery (Figure 2, $^{**}P<0.01$). Moreover, there was no significant difference in either of the evaluated parameters of EPM between the CCI+ resveratrol and CCI+ resveratrol +yohimbine groups (Figure 2a). Generally, the co-injection of resveratrol with prazosin or yohimbine did not induce a significant alteration in the percentage of time spent in open arms as compared with the CCI+ resveratrol or CCI groups. The present findings also demonstrated a significant correlation was observed between allodynia (PWR) and anxiety (open arm entries) among the CCI rats (Figure 3; $R_{\text{Square CCI}}=1$). No significant correlation was observed between these parameters in sham-operated rats (Figure 3; $R_{\text{Square Sham}}=0.012$). Finally, two-way ANOVA (days \times groups) analysis confirmed the significant effects of groups ($P=0.001$), and days ($P=0.001$), as well as interaction between both of the factors ($P=0.002$).

Discussion

In the current study, neuropathic pain was induced by tying 4 loose ligatures around the left-side sciatic nerve (CCI model) and a marked cold allodynia was observed in the ipsilateral-hind paw of the animals, which is a hypersensitivity index in the pain pathways, up to 6 days after CCI. No cold allodynia and anxious behavior was observed in the sham-operated rats. Experimental CCI surgery is widely used as a neuropathic pain model that involved in explaining the underlying mechanisms of neuropathic pain (25). Several reports have shown that this different neuropathy model causes allodynia (3,26-29). For example, Abbaszadeh *et al.* demonstrated that the CCI model markedly caused hyperalgesia and allodynia 21 days post-CCI (30). Moreover, in the present study the CCI was found to induce anxiety-like behaviors in the rats, using EPM test. In support of the presents study, Roeska *et al.* revealed that anxiety-like behaviors markedly increased in the CCI-operated rats (31). In the EPM test, two parameters, including open arms entry and time spent in open arms, were measured as index of anxious behaviors. Indeed, a decline in the open arm entries or open arm time spent indicated increased anxious behaviors in the animal. Anxious behaviors in the EPM are easily assessed and quantified by an observer. The EPM is well-known animal behavioral test and is widely used to evaluate the effects of pharmacological agents and help understand the neuropathic pain mechanism (32). We also demonstrated the significant correlation between allodynia and anxiety (open arm entries) in the CCI rats. No significant correlation was observed between these parameters in the sham-operated rats. Moreover, the present results revealed that intra-ACC injection of resveratrol, as a potent antioxidant, diminished the

allodynic activity and anxious behavior (increased percentage of open arms entries parameter in the EPM test, anxiolytic effects) associated with the neuropathic pain. These findings were in accordance with those of previous reports, which have shown the analgesic and anxiolytic effects of resveratrol in the different neuropathy models (33,34). For example, Yin *et al.* (2013) revealed that the intrathecal administration of resveratrol decreased pain sensitivity in the CCI-induced neuropathic model (35). Similarly, Xu *et al.* (2018) reported the analgesic effects of the intraperitoneal administration of resveratrol (daily for 14 consecutive days) following CCI surgery (36). In the present study, it is important to note that, the open arms entries parameter was not significantly altered in the CCI group in any of the days of the experiment. Therefore, the present results could suggest that the intra-ACC injection of resveratrol reduced anxious behaviors in the EPM in CCI-operated animals. In our study, we also observed that resveratrol produced no significant alterations in the percentage of spent time of animals in open arms, as another index of anxious behavior, compared with CCI group. It is well accepted that ACC is an important cortical area responsible for process of pain perception (37). Therefore, we selected this area of the brain to investigate the mechanism of analgesic and anxiolytic activity of resveratrol in neuropathic pain. The underlying mechanism(s) of analgesic and anxiolytic activity of resveratrol in neuropathic pain is far from clear. Therefore, one of the main goals of the present study was to investigate the mechanism of analgesic and anxiolytic activity of resveratrol. It is well accepted that α -adrenoceptors are an important therapeutic target for pain (6). Antidepressants, as the first-line drugs for the treatment of neuropathic pain, inhibit NE and serotonin transporters, and lead to increased norepinephrine levels in the synaptic space (38). In the cortex, pyramidal neurons in many areas of the cortex such as ACC receive a great number of adrenergic inputs from the locus cerulean (39). Koga *et al.* (2020) reported that the application of NE can induce both pre- and post-synaptic amplification in ACC neurons (39). They also revealed that activation of locus cerulean projection to the ACC increased excitatory transmission in vitro and produced behavioral sensitization for mechanical stimulation (39). Therefore, adrenoceptors significantly contribute to the processing of pain information during neuropathic pain. In the present study, the findings demonstrated that the mechanism of analgesic and anxiolytic activities of resveratrol in the ACC were mediated by different subtypes of receptors. Only concomitant injection of yohimbine with resveratrol significantly suppressed the

analgesic activity of resveratrol. Indeed, resveratrol seemed to have failed to reduce cold allodynia in the presence of the α_2 -adrenoceptor antagonist in the ACC. Furthermore, concomitant injection of only prazosin with resveratrol significantly attenuated the anxiolytic activity of resveratrol. In fact, resveratrol seems to have failed to increase entries to open arms of EPM in the presence of the α_1 -adrenoceptor antagonist in the ACC.

Conclusion

The results of the present study revealed that resveratrol exhibited analgesic and anxiolytic effects in the CCI-operated rats. Furthermore, our data have shown that the analgesic and anxiolytic activities of resveratrol were mediated by α_2 - and α_1 -adrenoceptors in the ACC, respectively. The present study suggests that the mechanism of analgesic and anxiolytic activities of resveratrol in the ACC of rat are different, which are mediated through different subtypes of α -adrenoceptors. Our limitation of the present research was lack of determination of the anti-oxidant activity of resveratrol. Further researches are needed to explain the pharmacologic properties of resveratrol in the treatment of the neuropathic pain symptoms.

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Conflict of Interest

Authors declared no conflict of interest.

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