The Involvement of Peripheral $\alpha_2$-Adrenoceptors in the Antihyperalgesic Effect of Oxcarbazepine in a Rat Model of Inflammatory Pain

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BACKGROUND: We studied whether peripheral $\alpha_2$-adrenergic receptors are involved in the antihyperalgesic effects of oxcarbazepine by examining the effects of yohimbine (selective $\alpha_2$-adrenoceptor antagonist), BRL 44408 (selective $\alpha_{2A}$-adrenoceptor antagonist), MK-912 (selective $\alpha_{2C}$-adrenoceptor antagonist), and clonidine ($\alpha_2$-adrenoceptor agonist) on the antihyperalgesic effect of oxcarbazepine in the rat model of inflammatory pain.

METHODS: Rats were intraplantarly (i.pl.) injected with the proinflammatory compound concanavalin A (Con A). A paw-pressure test was used to determine: 1) the development of hyperalgesia induced by Con A; 2) the effects of oxcarbazepine (i.pl.) on Con A-induced hyperalgesia; and 3) the effects of i.pl. yohimbine, BRL 44408, MK-912 and clonidine on the oxcarbazepine antihyperalgesia.

RESULTS: Both oxcarbazepine (1000–3000 nmol/paw; i.pl.) and clonidine (1.9–7.5 nmol/paw; i.pl.) produced a significant dose-dependent reduction of the paw inflammatory hyperalgesia induced by Con A. Yohimbine (260 and 520 nmol/paw; i.pl.; BRL 44408 (100 and 200 nmol/paw; i.pl.) and MK-912 (10 and 20 nmol/paw; i.pl.) significantly depressed the antihyperalgesic effects of oxcarbazepine (2000 nmol/paw; i.pl.) in a dose-dependent manner. The effects of antagonists were due to local effects since they were not observed after administration into the contralateral hindpaw. Oxcarbazepine and clonidine administered jointly in fixed-dose fractions of the ED$_{50}$ (1/4, 1/2, and 3/4) caused significant and dose-dependent reduction of hyperalgesia induced by Con A. Isobolographic analysis revealed an additive antihyperalgesic effect.

CONCLUSIONS: Our results indicate that the peripheral $\alpha_{2A}$ and $\alpha_{2C}$-adrenoceptors could be involved in the antihyperalgesic effects of oxcarbazepine in a rat model of inflammatory hyperalgesia.

(Oxcarbazepine, an anticonvulsant drug developed as a carbamazepine derivative, has been used in neuropathic pain treatment (1). Recently, it has been reported to be effective in animal pain inflammation models after systemic (2-5) and local peripheral administration (6). However, the sites and mechanisms of analgesic actions of oxcarbazepine are not completely known. Besides its ability to suppress neural conductance of pain impulses (7), some evidence indicates that receptor-mediated mechanisms may also be involved in the analgesic action of oxcarbazepine. We have previously shown that systemic oxcarbazepine reversed the mechanical hyperalgesia of an inflamed rat paw, and that this effect is mediated via $\alpha_2$-adrenoceptors (5). Adrenergic $\alpha_2$ receptors are implicated in pain modulation at both peripheral and central sites of the pain processing system (8-10). At peripheral sites, $\alpha_2$-adrenoceptors are located at both sympathetic postganglionic and primary afferent fibers (11), and mediate the contribution of the sympathetic nerve system to hyperalgesia and analgesia after tissue injury and inflammation (10,12). There are sparse data regarding the effects of activation of different subtypes of $\alpha_2$-adrenoceptors on peripheral pain modulation (13). Peripheral $\alpha_{2A}$-adrenoceptors mediate antinoceception induced by $\alpha_2$-adrenoceptor agonist after nerve injury (14) and contribute to antihyperalgesia induced by transcutaneous nerve stimulation (15). In inflammatory pain models, hyperalgesia was proposed to be mediated by $\alpha_{2B}$-adrenoceptors and analgesia by $\alpha_{2C}$-adrenoceptors (11,16).)
After systemic administration of oxcarbazepine, the interaction with α2-adrenoceptors in producing analgesia may happen at both central and/or peripheral sites of the pain processing system; thus the site of interaction between anticonvulsive and α2-adrenoceptors remains unclear.

Our purpose in the present experiments was to examine the involvement of peripheral α2-adrenergic receptors in oxcarbazepine antihyperalgesia by examining the effects of yohimbine (selective α2-adrenoceptor antagonist), BRL 44408 (selective α2A-adrenoceptor antagonist), MK-912 (selective α2C-adrenoceptor antagonist), and clonidine (α2-adrenoceptor agonist) on the antihyperalgesic effect of oxcarbazepine in the rat model of inflammatory pain.

METHODS

Animals

Experiments were performed on 180–220 g male Wistar rats (Military Farm, Belgrade, Serbia) and were approved by the Institutional Animal Care and Use Committee. The animals were housed in groups of four in home cages (42.5 × 27 × 19 cm³) and maintained on a 12 h light–dark cycle at 22°C ± 1°C. Food and water were freely available, except during the experimental procedure. Before experimental manipulation, the animals were given at least 3 days to adapt to the laboratory. All experiments were performed at the same time of day between 8:00 and 16:00 h to avoid diurnal variation in behavioral tests. All experimental groups consisted of 6–8 rats.

Paw-Pressure Test

The antihyperalgesic activity was determined by a modified paw-pressure test (3,17). The apparatus (Hugo Sachs Elektronik, March-Hugstetten, Germany) was used to evaluate the force exerted by rat hindpaws to determine right/left differences. The rat was placed with its hindpaws on two transducer platforms and pushed slowly and smoothly downwards with the investigator’s hand, so that the force (pressure) was applied simultaneously to both paws. The pressure is applied until one of the paws exceeds the trigger level set at 100 g. At this point, the apparatus produces an audible click and the measurement is stopped automatically. It was obvious that the rats use the uninflamed paw as the weight-bearing limb while sparing the inflamed paw. Therefore, drugs with the potential to reduce the difference between pressures applied to the uninflamed (noninjected) versus inflamed (injected) paw are recognized as those with antihyperalgesic (antiallodynic) activity. The forces applied on the paws are read on the displays, and the difference (d) is calculated as: d = force (g) applied on uninflamed paw – force (g) applied on inflamed paw. Measurements were repeated three times at each time point, and the average d for each rat was used for further calculations. The observer was blinded to the drug treatment received by the animals.

In the first experiment, we retested the peripheral antihyperalgesic effect of oxcarbazepine (Fig. 1A). The anticonvulsive compound and proinflammatory compound concanavalin A (Con A) (3,18) were co-administered intraplantarly (i.pl.), into the right hindpaw, after obtaining predrug d (Fig. 1A). Post-drug d was measured at 90, 150, 210, 270, and 330 min after drug administration. Control animals received the same volume of Con A (i.pl.) dissolved in the same vehicle (Fig. 1B).

Force differences are expressed as a percent antihyperalgesic activity (%AA) and calculated according to the following formula:

\[
\%AA = \frac{[(control\ group\ average\ d - test\ group\ average\ d)] \times 100}{control\ group\ average\ d} (3,5).
\]

If the test group average d was more than control group average d, a value of 0% AA was assigned.

Dose-response curves were analyzed using linear regression. The ED50 (the dose that was expected to result in 50% AA) with 95% confidence limits were estimated from corresponding log dose-response curves (19). A test for parallelism was used to compare the slopes of the log dose-response curves (19).

In the second set of experiments, the influence of yohimbine, BRL 44408 and MK-912 on the peripheral antihyperalgesic actions of oxcarbazepine were tested. The antagonists were co-administered with oxcarbazepine and Con A (i.pl.), into the right hindpaw (Fig. 1C). The comparative group of animals received the same volume of Con A with anticonvulsive drug (Fig. 1A). To exclude the possible systemic effect of i.pl. injected antagonists, in separate groups of animals the highest tested dose of each antagonist was given contralaterally (into the uninflamed hindpaw) immediately before the Con A with oxcarbazepine in the other paw, and tested in inhibiting the antihyperalgesic effect of anticonvulsive (Fig. 1D). Finally, the effects of co-administration of the highest dose of each antagonist used with Con A (Fig. 1E) were evaluated and compared with the effect of Con A alone (Fig. 1B).

The percent inhibition (%I) of the antihyperalgesic effect by antagonist treatment was expressed as follows:

\[
%I = 100 - \left[\frac{(%AA \text{ with antagonist}}{%AA \text{ without antagonist}}\right] \times 100 (3).
\]

Isobolographic Analysis

In the final experiment, the interaction between oxcarbazepine with clonidine was evaluated by co-administration of fixed proportions of the anticonvulsive with clonidine, and performing an isobolographic analysis (20). At first, an ED50 value of each drug has to be obtained from the corresponding log dose-response curves. Therefore, we examined the effect of clonidine using the same procedure as when testing oxcarbazepine...
The comparative group of animals received the same volume of Con A (i.pl.) dissolved in the same vehicle instead of clonidine (Fig. 1B). In the next step, clonidine and oxcarbazepine were co-administered at fixed-dose fractions of the ED50 (1/4 ED50 OXCARBAZEPINE/1/4 ED50 CLONIDINE, 1/2 ED50 OXCARBAZEPINE/1/2 ED50 CLONIDINE and 3/4 ED50 OXCARBAZEPINE/3/4 ED50 CLONIDINE). Clonidine, oxcarbazepine, and Con A were co-administered i.pl. into the right hindpaw (Fig. 1G). The comparative group of animals received the same volume of Con A (i.pl.) dissolved in the same vehicle instead of drug combinations (Fig. 1B). For the drug mixture, experimental ED50 (ED50 mix) and its associated 95% confidence intervals were determined by linear regression analysis of the log dose-response curve and compared with a theoretical additive ED50 (ED50 add) obtained from the calculation: ED50 add = f × ED50 OXCARBAZEPINE + (1 - f) × ED50 CLONIDINE, where f denotes a fraction of the corresponding ED50 in drug mixture (in our study, f = 0.5). In this equation, ED50 add is the total dose, and the variance of ED50 add was calculated as: Var ED50 add = f^2 × Var ED50 OXCARBAZEPINE + (1 - f)^2 × Var ED50 CLONIDINE. From these variances, confidence intervals were calculated and resolved according to the ratio of the individual drug in the combination. Supraadditivity is defined as the effect of a drug combination that is higher and statistically different (ED50 significantly lower) than the theoretical calculated equieffective action of a drug combination with the same proportions. When the drug combination gives an experimental ED50 not statistically different from the theoretical calculated ED50, the combination has an additive effect (20).

Additionally, to describe a magnitude of interaction, an interaction index (γ) was calculated as:

\[ \gamma = \frac{ED_{50} \text{ OXCARBAZEPINE combined with CLONIDINE}}{ED_{50} \text{ OXCARBAZEPINE given alone}} + \frac{ED_{50} \text{ CLONIDINE combined with OXCARBAZEPINE}}{ED_{50} \text{ CLONIDINE given alone}} \]

(21). An interaction index is a quantitative marker for the drug combination that indicates the changed potency of the combination. Values near 1 indicate additive interaction, values more than 1 imply an antagonistic interaction and values <1 indicate a synergistic interaction (21).

**Drug Administration**

Oxcarbazepine (Novartis Pharma AD, Basel, Switzerland), Con A, yohimbine hydrochloride, BRL 44408 maleate, MK-912 hydrate, and clonidine hydrochloride (all from Sigma-Aldrich Chemie, Germany) were co-administered at fixed-dose fractions of the ED50.

**Figure 1.** Experimental protocol used in the evaluation of: antihyperalgesic effects of oxcarbazepine (OXC) coadministered with concanavalin A (Con A) into the right hindpaw (A), hyperalgesia induced by injection of Con A into the right hindpaw (B), the influence of yohimbine (YOH) or BRL 44408 or MK-912 co-administered with Con A + OXC into the right hindpaw on the antihyperalgesic effects of OXC (C), the influence of YOH or BRL 44408 or MK-912 injected into the left (contralateral) hindpaw on the antihyperalgesic effects of OXC (D), the influence of YOH or BRL 44408 or MK-912 on Con A-induced hyperalgesia (E), the antihyperalgesic effects of clonidine (CLON) co-administered with Con A into the right hindpaw (F), the influence of CLON co-administered with Con A + OXC into the right hindpaw on the antihyperalgesic effects of OXC (G).
dissolved or suspended in a vehicle containing 50% polyethylene glycol 400 (PEG 400) and 50% saline, and sonicated for 15 min for proper distribution. Con A was used in a fixed dose of 0.8 mg/paw. All substances were injected i.pl. in a final volume of 0.1 mL/paw, using 1-mL syringe and 24-guage (0.55 × 25 mm) needle. Through all experiments, the left hind-paw was injected immediately before the right one.

**Statistical Analysis**

All computations were done according to Tallarida and Murray (19), Dawson-Saunders and Trapp (22),...
and Tallarida (20, 21). Differences between corresponding means were verified by using Student’s t-test or analysis of variance (one-way ANOVA), followed by Tukey’s HSD test. The difference between theoretical ED50 and experimental ED50 was examined by Student’s t-test. A P value of < 0.05 was considered statistically significant.

RESULTS
Effects of Intraplantar Oxcarbazepine and Clonidine in the Paw-Pressure Test

The co-administration of oxcarbazepine (1000–3000 nmol/paw; i.pl.) or clonidine (1.9–7.5 nmol/paw; i.pl.) with Con A produced a significant dose-dependent reduction in differences in forces exerted by inflamed and uninflamed rat hindpaw in a modified paw-pressure test used (Figs. 2A, B and 4A). The peak effects of the most doses tested of both oxcarbazepine and clonidine occurred 150 min after the i.pl. administration. The antihyperalgesic effect of oxcarbazepine lasted up to 270 min. The duration of the antihyperalgesic effect of clonidine was 210 min. The corresponding ED50 values are presented in Table 1.

Slopes of the log dose-response curves are 66.0 ± 6.0 and 38.4 ± 8.4 for oxcarbazepine and clonidine, respectively (P > 0.05, test for parallelism; not shown).

The Influence of α-Adrenoceptor Antagonists on the Effects of Oxcarbazepine in the Paw-Pressure Test

Co-administration of yohimbine (260 and 520 nmol/paw; i.pl.), BRL 44408 (100 and 200 nmol/paw; i.pl.), and MK-912 (10 and 20 nmol/paw; i.pl.) with oxcarbazepine into the rat hindpaw significantly decreased the antihyperalgesic effect of oxcarbazepine in a dose-dependent manner (Figs. 3A–C). The maximum inhibitory effects of yohimbine on oxcarbazepine-induced antinociception were achieved 90–150 min after administration, and the corresponding values were 48% for the dose of yohimbine of 260 nmol/paw (i.pl), and 100% for 520 nmol/paw (i.pl.) (not shown). For BRL 44408, the maximal inhibition of oxcarbazepine antihyperalgesia were 61% and 100% for the doses of 100 nmol/paw (i.pl.) and 200 nmol/paw (i.pl.), respectively (not shown). The maximum inhibitory effects of MK-912 on the antihyperalgesic effect of oxcarbazepine were

Table 1. ED50 ± SEM Values (nmol) with 95% Confidence Limits and Interaction Index (γ) Obtained 90 Minutes (Oxcarbazepine + Clonidine) or 150 Minutes (Oxcarbazepine, Clonidine) After Intraplantarly Drugs Administration

<table>
<thead>
<tr>
<th>Drugs</th>
<th>ED50 ± SEM (confidence limits)</th>
<th>ED50 add †</th>
<th>ED50 mix ‡</th>
<th>γ §</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oxcarbazepine</td>
<td>2725.9 ± 149.6 (1356.6–5477.2)</td>
<td></td>
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<td></td>
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<tr>
<td>Clonidine</td>
<td>5.8 ± 1.0 (0.6–54.3)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oxcarbazepine + Clonidine (total dose)</td>
<td>1365.9 ± 74.8 (1009.2–1702.6)</td>
<td>1362.7 ± 39.3 (962.055–1930.2)</td>
<td>1.0</td>
<td></td>
</tr>
</tbody>
</table>

* ED50 = effective dose required to produce 50% antihyperalgesic activity.
† ED50 add = theoretical additive ED50 for drug mixture.
‡ ED50 mix = experimental ED50 for drug mixture.
§ γ = ED50 OXCARBAZEPINE COMBINED WITH CLONIDINE/ED50 OXCARBAZEPINE GIVEN ALONE + ED50 CLONIDINE COMBINED WITH OXCARBAZEPINE/ED50 CLONIDINE GIVEN ALONE. Values near 1 indicate additive interaction, values more than 1 imply an antagonistic interaction and values less than 1 indicate a synergistic interaction (Tallarida et al. 21).

Figure 4. (A) Log dose-response curves for oxcarbazepine (OXC), clonidine (CLON), and oxcarbazepine-clonidine combination (OXC + CLON) for antihyperalgesia at the time of peak effects in the paw-pressure test. Data are expressed as a percent antihyperalgesic activity (%AA). Each point represents the mean ± SEM of %AA obtained in 6–8 animals. (B) Isobologram for the OXC-CLON combination in a paw-pressure test. The ED50 values (obtained at the time of peak effects) for each drug are plotted at the axes. The straight line connecting the each ED50 value is the theoretical additive line, and the point in this line is the ED50 add (theoretical additive ED50). There is no significant difference (P > 0.05; t-test) between the ED50 add and the ED50 mix (experimental ED50 for drug mixture), indicating an additive drug interaction for combination tested.
achieved 90–150 min after administration, and the corresponding values were 66% for the dose of MK-912 of 10 nmol/paw (i.pl) and 100% for 20 nmol/paw (i.pl.) (not shown). The effects of antagonists were due to local action, since they were not observed after injection of the highest doses used into the contralateral hindpaw (Figs. 3A–C).

Peripheral co-administration of higher dose of each antagonist with Con A failed to produce any significant effect on Con A-induced hyperalgesia (P > 0.05, Student’s t-test, data not shown).

The Influence of i.pl. Clonidine on the Effects of Oxcarbazepine in the Paw-Pressure Test

Oxcarbazepine-clonidine fixed-dose combination of the ED 50 (1/4, 1/2, and 3/4) of each drug caused significant and dose-dependent reduction of the hyperalgesia induced by Con A in a paw-pressure test in rats (Figs. 2C and 4A). The peak effects of drug combination occurred at 90 min after i.pl. administration and lasted up to 210 min. The corresponding ED 50 mix and the ED 50 add values are presented in Table 1. The t-test applied to the potency ratio between the ED 50 mix and the ED 50 add reveals that there is no significant difference; thus, this combination presents an additive interaction. A graphic illustration on the isobologram (Fig. 4B) shows that the confidence intervals of these two points does overlap and the interaction index value equals 1, confirming an additive interaction (Table 1).

DISCUSSION

In this study, peripherally applied oxcarbazepine caused a dose-dependent, significant reduction of the hyperalgesia induced by Con A in a paw-pressure test in rats. This effect is consistent with the results of our previous study in which we demonstrated local peripheral antihyperalgesia induced by oxcarbazepine in the same model of pain (6). In both studies, i.pl. injected doses of oxcarbazepine (1000–3000 nmol/paw = 0.25–0.76 mg/rat; corresponds to 1.25–3.80 mg/kg; i.pl.) were 10–32 times lower than the lowest effective systemic dose applied intraperitoneally (40 mg/kg) (3,5), supporting a local versus systemic effect. A peripheral site of action of oxcarbazepine has also been suggested by Ichikawa et al. (23), who showed that oxcarbazepine inhibits the generation of high-frequency firing in cutaneous afferent nerve fibers.

Our experiments have also demonstrated that peripheral yohimbine (260 and 520 nmol/paw; i.pl.) significantly decreased the antihyperalgesic effects of oxcarbazepine. As yohimbine does not discriminate between α 2 -adrenoceptor subtypes, further experiments in which BRL 44408 (100 and 200 nmol/paw; i.pl.) and MK-912 (10 and 20 nmol/paw; i.pl.) suppressed oxcarbazepine antihyperalgesia showed that both α 2A - and α 2C -adrenoceptors may play a significant role in the mechanism of antinociceptive action of oxcarbazepine. As these effects were not shown after administration of the highest dose of each antagonist into the contralateral (noninflamed) hindpaw, the systemic effects of antagonists due to absorption from the site of injection are excluded.

The finding that the peripheral α 2A - and α 2C -adrenoceptors are involved in oxcarbazepine antihyperalgesia could be interpreted in two ways: oxcarbazepine may act on α 2-adrenoceptors 1) directly or 2) indirectly, by influencing endogenous noradrenergic system to produce antinociception.

There are no available data on the binding properties of oxcarbazepine to α 2-adrenoceptors. However, its parent drug, carbamazepine, does not have any binding affinity to α 2-adrenergic receptors (24). There is also a lack of data on the ability of oxcarbazepine to release noradrenaline from noradrenergic neurons. There is evidence that carbamazepine could activate catecholaminergic neurons located in the central nervous system (25,26). Because of the similarities with carbamazepine in the structure and the mechanisms of action (27,28), an indirect interaction of oxcarbazepine with noradrenaline-containing neurons is thus possible. At peripheral sites of pain processing, noradrenaline is released from postganglionic sympathetic nerve fibers (29). The data on its effects on pain transmission and modulation at these sites are controversial. In a paw-pressure test in rats, Khasar et al. (11) demonstrated a dose-dependent hyperalgesia induced by noradrenaline when co-injected with calcium ionophore into the rat hindpaw, and a lack of hyperalgesia, when co-injected with prostaglandin E 2. In contrast, Binder et al. (12) showed that noradrenaline, injected i.pl. into the inflamed rat paw, produces a dose-dependent antinociception in a paw-pressure test. Moreover, this effect was reversed by yohimbine. The authors concluded that peripheral α 2-adrenoceptors are involved in the antinociceptive action of noradrenaline. Therefore, the suppression of the antihyperalgesic effect of oxcarbazepine by peripheral α 2-adrenoceptors antagonists observed in our study could be explained by its indirect interaction with peripheral α 2-adrenoceptors, which is mediated by endogenous noradrenaline.

In the present study, peripheral α 2-adrenoceptor antagonists per se injected into the inflamed paw lacked effects on the inflammatory hyperalgesia. Similar studies with local peripheral administration of antagonists also showed no effect of peripheral yohimbine (11) or BRL 44408 (11,14) on existing hyperalgesia.

The local antihyperalgesic effect of clonidine (1.9–7.5 nmol/paw; i.pl.) observed in this study is in agreement with the findings of several studies, which have all demonstrated peripheral clonidine analgesia in various models of inflammatory pain in rats (11,16,30,31), as well as in humans (32). In the study of Khasar et al. (11), i.pl. clonidine (1–10 ng/paw = 0.0004–0.004 nmol/paw) inhibited prostaglandin E 2-induced hyperalgesia, as determined by using the paw-pressure test in rats. In the same model of hyperalgesia, Aley and Levine (16) have also demonstrated...
the antinociceptive effect of intradermally administered clonidine (100 ng/paw = 0.43 nmol/paw). Buerkle et al. (31) observed the thermal and mechanical antinociceptive action of intraarticular clonidine (1–30 μg/knee = 4.3–130.4 nmol/knee) in rats. In all cited studies, clonidine induced antinociception in doses comparable with those used in our study. Moreover, the doses of clonidine we used were up to nine times lower than the lowest effective systemic dose determined in our previous study (0.02 mg/kg; i.p.) (5). From all these data, it is likely that the antihyperalgesic effects of clonidine observed in this study were due to its local peripheral action.

In the present study, the additive interaction between oxcarbazepine and clonidine after local peripheral administration in the rat model of inflammatory hyperalgesia is revealed. In our previous study (5), the interaction between those two drugs administered systemically resulted in supra-additivity.

The properties of a system that defines a pharmacologic interaction between two classes of drugs are likely complicated. The type of drug interaction between two drugs may be explained by altering the kinetics of each other or at various levels of drug action (at membrane, by acting on a common membrane to alter the actions of the other drug at its target site; or at a physiologic level, at which the separate drug systems interact with respect to a common end-point e.g., hyperalgesia) (33). If fundamentally different mechanisms jointly contribute to the observed actions of two drugs on a given effect, it is likely that co-administration will result in synergistic interaction (34). The supra-additive interaction between oxcarbazepine and clonidine given systemically (5) could be explained by different and complementary mechanisms of action of two drugs: systemic clonidine acts as an α2-adrenergic agonist in producing analgesia (35,36) whereas systemic oxcarbazepine, besides the activation of α2-adrenergic receptors (5), may also activate adenosine (3) and γ-aminobutyric acid type A receptors (37) and suppresses neural conductance of pain impulses most probably due to blockade of ion currents (8). The additive interaction observed in this study might be explained by the common target of the drugs in producing local peripheral analgesia; local peripheral clonidine acts as α2A and α2C-adrenergic agonist (11,14,16) and oxcarbazepine also involves α2A and α2C-adrenoceptors in producing analgesia. Although we have previously shown that the antihyperalgesic effect of local peripheral oxcarbazepine is also mediated by adenosine A1-receptors (6), if we consider the findings of Aley and Levine (16) who suggested that peripheral A1 adenosine and α2 adrenergic receptors are attached in a receptor complex and signal via a common second messenger, our finding of the additive interaction between oxcarbazepine and clonidine is still not surprising.

In conclusion, the results of the present study indicate that peripheral adrenergic α2A and α2C-adrenoceptors may play a significant role in the antihyperalgesic effects of oxcarbazepine. Co-administration of oxcarbazepine with clonidine results in an additive anti-hyperalgesic effect. Better understanding of the mechanisms of peripheral antinociceptive action of oxcarbazepine could help in generating new local pain treatments.

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