Cukurova Medical Journal
ÇUKUROVA ÜNİVERSİTESİ TIP FAKÜLTESİ

Cukurova Med J 2024;49(2):415-423
DOI: 10.17826/cumj.1429753

RESEARCH

Antinociceptive effect of bupropion on visceral pain and its mechanism of action

Bupropionun visseral ağrı üzerindeki antinosiseptif etkisi ve etki mekanizması

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Abstract

Purpose: Bupropion is an antidepressant that inhibits noradrenaline and dopamine reuptake. In the current scientific literature, there is limited information regarding the effects of bupropion on pain, predominantly derived from somatic pain studies. This study aims to investigate the impact of bupropion for the first time in visceral pain induced by colorectal distension, a pure visceral pain model, and to reveal the role of various receptors involved in pain control in this effect.

Materials and Methods: Male Sprague-Dawley rats were used in the study. Visceral pain was assessed by colorectal distension-induced visceromotor response. Bupropion is administered gastrically at 5, 10, 20, and 40 mg/kg doses. The mechanism of action of bupropion at the spinal cord level was investigated by intrathecal administration of antagonists of α1 and α2 adrenoceptors (prazosin and yohimbine), D1 and D2 dopamine (SCH 23390 and sulpiride) and opioid receptors (naloxone) 10 minutes before bupropion's effective dose.

Results: Bupropion showed significant antinociceptive effects at 20 and 40 mg/kg intragastric doses; no difference was found between these two doses. Intrathecally administered yohimbine (30 µg/rats), sulpiride (30 µg/rats, i.t.), and naloxone (2.5 µg/rats) diminished the antinociceptive effect of bupropion. Prazosin and SCH 23390 did not alter bupropion's effect.

Conclusion: The findings show the antinociceptive effect of bupropion in visceral pain, and adrenergic, dopaminergic, and opioidergic receptors in the spinal cord play a role in this effect.

Keywords:. Antidepressant, Bupropion, visceral, pain, visceromotor.

Öz

Amaç: Bupropion, noradrenalin ve dopamin geri alımını inhibe eden bir antidepresandır. Bilimsel literatürde, bupropionun ağrı üzerindeki etkilerine ilişkin sınırlı bilgi bulunmaktadır ve bu bilgiler ağırlıklı olarak somatik ağrı çalışmalarından elde edilmiştir. Bu çalışmanın amacı, ilk kez olarak pür viseral ağrı modeli olan kolorektal distansiyon ile indüklenen viseral ağrıda bupropionun etkisini araştırmak ve bu etkide ağrı kontrolünde rol alan çeşitli reseptörlerin rolünü ortaya koymaktır.

Gereç ve Yöntem: Çalışmada erkek Sprague-Dawley sıçanlar kullanıldı. Viseral ağrı, kolorektal distansiyon ile indüklenen viseromotor yanıt ile değerlendirildi. Bupropion 5, 10, 20, 40 mg/kg dozlarında gastrik olarak uygulandı. Bupropionun omurilik seviyesindeki etki mekanizması, α1 ve α2 adrenoseptörlerinin, D1 ve D2 dopamin ve opioid reseptörlerinin antagonistlerinin bupropionun etkili dozundan 10 dakika önce intratekal olarak uygulanmasıyla araştırıldı.

Bulgular: Bupropion 20 ve 40 mg/kg intragastrik dozlarda anlamlı antinosiseptif etki göstermiş, bu iki doz arasında fark bulunmamıştır. İntratekal olarak uygulanan yohimbin (30 µg/sıçan), sülpirid (30 µg/ sıçan, i.t.) ve nalokson (2,5 µg/sıçan) bupropionun antinosiseptif etkisini azaltmıştır. Prazosin ve SCH 23390 bupropionun etkisini değiştirmemiştir.

Sonuç: Bulgular bupropionun visseral ağrıda antinosiseptif etkisini ve bu etkide omurilikteki adrenerjik, dopaminerjik ve opioiderjik reseptörlerin rol oynadığını göstermektedir.

Anahtar kelimeler: Antidepresan, Bupropion, viiseral, ağrı, viseromotor.

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Received: 02.02.2024 Accepted: 18.05.2024

INTRODUCTION

Antidepressants are becoming more widely used in the treatment of pain. These drugs' analgesic effects are known to be independent of their antidepressant effects[1]. Antidepressants' antinociceptive impact is attributed to mechanisms such as increasing monoamine concentration in the synaptic gap, antagonism of NMDA receptors, sodium channel blockade, calcium channel blockade, and suppression of proinflammatory cytokine production[2,3].

Visceral pain is caused by internal organs and deep tissues. The clinical and neurophysiological properties of visceral pain differ from somatic pain. Visceral pain is a diffuse and weak localized sensation reflected in other regions and often associated with autonomous and emotional reactions[4]. Visceral pain is still significant in clinical practice and pre-clinical research because of these characteristics.

Bupropion (BPR) is an antidepressant that inhibits noradrenaline and dopamine reuptake but does not affect serotonin reuptake. For this reason, BPR does not induce the same adverse effects as SSRI medicines, such as sedation, sexual dysfunction, and weight gain[5]. Somatic pain models were mostly used in studies on the relationship between BPR and pain. In the experimental visceral pain model, there is only one study on this subject[6]. In that study, pain was created with acetic acid and the antinociceptive effect of BPR was investigated. There is no literature study on the mechanism of the antinociceptive effect of BPR in visceral pain and the temporal relationship of this effect.

This study aimed to investigate the effect of BPR on colorectal distension (CRD) induced visceral pain, the temporal relationship, and the mechanism of this effect**.**

MATERIALS AND METHODS

All experiments were approved by the Ondokuz University Institutional Animal Care and Use Committee dated 14/07/2020 and numbered 2020/25 and abided by the guidelines of the Committee for Research and Ethical Issues of the International Association for the Study of Pain.

Animals

Sprague-Dawley rats (male, 275–320 g) were used, and all rats were obtained from "Laboratory Animals Application and Research Center" (Ondokuz University, Turkey). During the study, all rats were kept in separate cages in their natural environment (22 ± 1°C on a 12-h alternating light-dark cycle) in the mentioned university research laboratory, and the experiments were conducted in the same institutions. The number of animals to be used was 7 for each group due to the power analysis performed in the G-Power (v3.1) software regarding the pain study by Marinho et al.[7]. A total of 126 rats were used in this study. After the experiments were completed, cervical dislocation was applied to all animals.

Surgical procedures

Surgical applications were performed under aseptic conditions under ketamine and chlorpromazine anesthesia (100 mg/kg ketamine and 0,75 mg/kg chlorpromazine; intraperitoneal). Enamel-coated water-insoluble Nickel/Chrome (80 mm diameter) wire electrodes were fixed to the left external oblique muscles of rats using a fine-tipped syringe needle. For bipolar recording, two electrodes are placed with 10 mm spacing. A cannula made from a 0,4 ch feeding catheter (Bıçakçılar, Turkey) is placed in the stomach for intragastrical drug administration. Furthermore, for the administration of various antagonists, an 8.5 cm sterile polyethylene-10 tube catheter was advanced backward to the level of lumbar enlargement, as previously described in another study from our laboratory[8]. The rats were kept in separate cages for seven days after the surgical procedures to allow them to recover. To get used to the experimental environment, the rats were seated in Bollman cages in the experimental laboratory for 2 hours every day during this period.

Experimental visceral pain model

The colorectal distention model (CRD), which has been shown to imitate human pain, was used in this study[9]. All the trials were performed after 8 hours of night fasting. An inflatable colorectal pressure device was created by connecting a latex balloon to the 7 cm end of the feeding tube with a thread. CRD balloon was lubricated with ultrasound gel and was placed into the anal channel and secured with a medical plaster tape to the rats' tails. The rats were housed in Bollman cages for the duration of the trials.

Bipolar electrodes were placed into the external oblique muscle of rats. The EMG was recorded as the rats' visceromotor response (VMR) to the painful stimulus. A bioamplifier (ML132, ADInstruments,

Australia) was used to enhance the EMG signals, which were then digitalized using the Labchart application (Lab Chart version 7.3.7, AD Instruments). CRD was applied according to the standard pressure procedure. The average EMG responses against the 80-mmHg pressure in the 3 CRD series before the intragastric (i.g.) BPR application was accepted as a baseline record. Stable distension was induced every 10 minutes following BPR or saline treatment. The second stage of the investigation, effect mechanism studies, was planned. Various receptor antagonists were administered intrathecally (i.t.) 10 minutes before BPR, and the same experimental protocol was repeated.

The VMRs were obtained by finding the difference between the integrals of the EMG activities during the 20-second periods before and during the CRD application calculated in the Labchart program. The percentage of control used to indicate the VMR (% control), where the mean predrug responses to 80 mmHg are expressed as a percentage (100%). Using the area under the curve (AUC) of the time-response function in Excel, the overall impact of any therapy was calculated. The AUC was calculated from the post-drug response time plot normalized to the baseline response (100%), plotted against time using the trapezoidal rule (AUC = response × 90 min), a technique for substantially calculating the definite integral.

Drugs

Bupropion hydrochloride (Zyban™ tablet, GlaxoSmithKline Co., Turkey), naloxone hydrochloride (Tocris Bioscience, Bristol, UK), prazosin hydrochloride (Tocris Bioscience, Bristol, UK), yohimbine hydrochloride (Tocris Bioscience, Bristol, UK), SCH 23390 hydrochloride (Tocris Bioscience, Bristol, UK), sulpiride (Tocris Bioscience, Bristol, UK) were used. For intrathecal injection, yohimbine and sulpiride were dissolved in DMSO. Prazosin, SCH 23390 and naloxone were dissolved in saline. All intrathecal drug injections were applied at a volume of 5µl. The doses of the drugs used were determined based on reference studies[10–12]. Based on power analysis, seven animals were randomly selected for each group in dose-response and mechanism studies.

Statistical analysis

All data are expressed as a mean ± standard error. GraphPad Prism (version 8.0.1) software was used to conduct the statistical analysis. Following confirmation of normal distribution, one-way ANOVA and Tukey-Kramer post hoc test were used to compare the AUC values of the groups. Repeated measures of ANOVA and Tukey-Kramer post hoc test were used in the analyses to investigate the time-dependent effect of drugs. $p < 0.05$ was considered statistically significant.

RESULTS

As the control group, intragastric (i.g.) administration of saline had no effect on CRD-induced VMR. BPR was applied in different groups at 5, 10, 20, and 40 mg/kg doses (n = 7 in each group). Doses of 5 and 10 mg/kg of the drug did not cause an effect on VMR compared to saline administered control group. However, higher doses of BPR (20 and 40 mg/kg, i.g.) lead to a statistically significant antinociceptive effect on visceral pain ($P < 0.001$), as represented in Figure 1. The antinociceptive effect of BPR started from the 10th minute in both doses. Effect of 20 mg/kg dose continued until 60th minutes. However, highest dose (40 mg/kg) was effective even at the end of the experimental period (Fig. 1A). There was no significant difference between the AUC values of both doses (Fig 1B). For this reason, the dose of 20 mg/kg was selected as an effective dose to investigate the mechanism of the antinociceptive action of BPR.

α1 adrenoceptor (α1AR) antagonist prazosin (30 µg/rats, i.t.) did not alter BPR's antinociceptive effects for 90 minutes ($P = 0.9988$) as indicated in Fig. 2A and Fig. 2B. This dose of prazosin did not affect visceral pain when it applied intrathecally alone. In the control group, saline, solvent of both, did not alter VMR. When α2 adrenoceptor (α2AR) antagonist yohimbine was applied intrathecally (30 µg/rats, i.t.) 10 minutes before BPR significantly reduced the antinociceptive effect of its ($P < 0.001$), as represented in Fig. 3B. This reducing effect of yohimbine started from the 10th minute. It continued until the 80th minute (Fig. 3A). When the dose of yohimbine was doubled in the new group of animals, the reducing effect of yohimbine similar to the previous dose was observed. These two groups did not significantly differ from one another ($P > 0.9999$) (Fig. 3B). Doses of 30 and 60 µg/rat of yohimbine did not cause an effect on VMR compared to the control group when applied intrathecally alone. In the control group, saline (solvent of BPR, 2 ml/rat, i.g.) and DMSO (solvent of yohimbine, 5 µl/rat, i.t.) did not affect VMR.

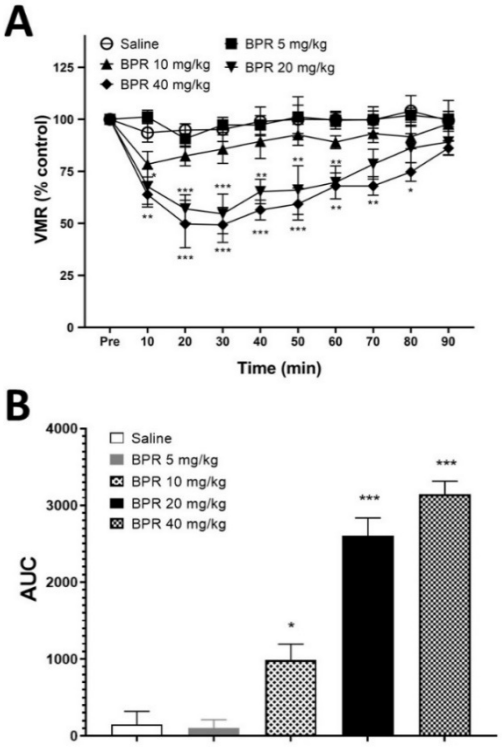

Figure 1. The effect of intragastric administration of bupropion at various doses (5-40 mg/kg) on visceromotor response. A) % control visceromotor responses over time in groups after bupropion administration. B) Area under the curve (AUC) presentation of data (n=7) ,

*P < 0.05, ** P < 0.01, *** P < 0.001; compared to the "saline" administered control group. BPR: Bupropion, VMR: Visceromotor response, AUC: Area under the curve

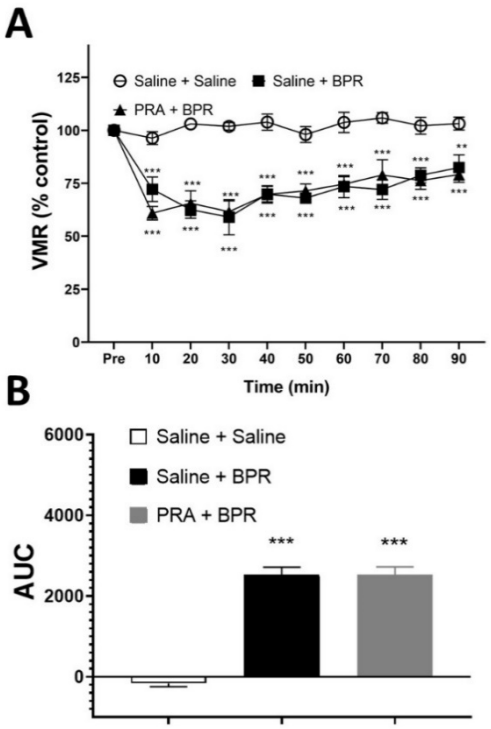

Figure 2. Effects of α1-adrenoceptor antagonist prazosin on the antinociceptive effect of bupropion. A: % control visceromotor responses over time in groups after bupropion administration. B: Area under the curve (AUC) presentation of data. Pretreatment with prazosin or saline before bupropion did not alter the antinociceptive effect of bupropion (n=7).

P < 0.05, **P < 0.01, ***P < 0.001. BPR: Bupropion, PRA: Prazosin, VMR: Visceromotor response, AUC: Area under the curve.

When given 10 minutes before BPR, dopamine 1 receptor antagonist SCH 23390 (25 μg/rat i.t.) did not affect the antinociceptive effect of BPR for 90 minutes ($P = 0.9684$) as represented in Fig. 4A and Fig.4B. VMR has not changed when SCH 23390 is given alone and in the control group.

Sulpiride (30 μg/kg, i.t.), which was applied intrathecally before the effective dose of BPR, significantly reduced the antinociceptive effect of BPR ($P < 0.001$). But like yohimbine, sulpiride could not completely block it. This reducing effect of sulpiride started from the 10th minute. It continued until the 80th minute (Fig. 5A). When the dose of sulpiride was doubled (60 μg/kg, i.t.) in the new group of animals, the reducing effect of sulpiride similar to the previous dose was observed. These two groups did not significantly differ from one another (P = 0.6326) (Fig. 5B). When these doses of sulpiride were applied alone did not cause an effect on VMR compared to the control group. In the control group, saline (solvent of BPR, 2 ml/rat, i.g.) and DMSO (solvent of sulpiride, 5 μl/rat, i.t.) did not affect VMR.

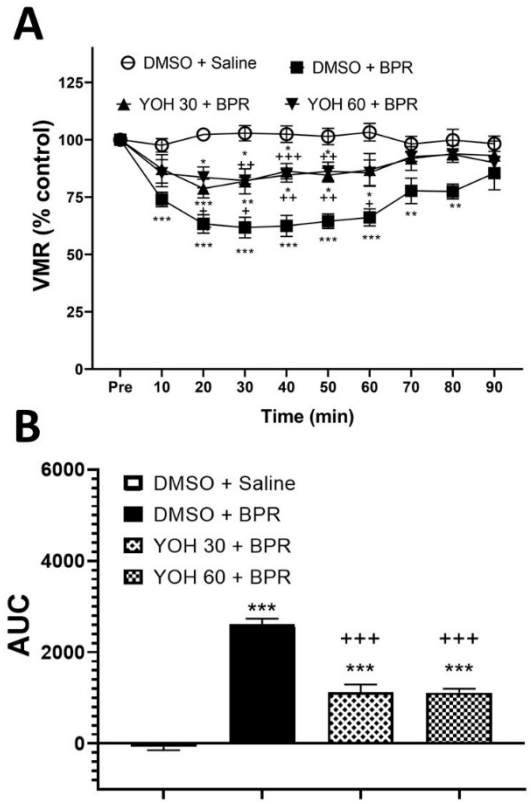

Figure 3. Effects of α2-adrenoceptor antagonist yohimbine on the antinociceptive effect of bupropion. A: % control visceromotor responses over time in groups after bupropion administration. B: Area under the curve (AUC) presentation of data. Pretreatment with yohimbine (30 and 60 µg/rat i.t.) 10 minutes before bupropion administration inhibited the antinociceptive effect of bupropion (n=7)

P < 0.05, **P < 0.01, ***P < 0.001; compared to the "DMSO + saline" administered control. + P < 0.05, ++ P < 0.01, +++ P < 0.001; compared to the "DMSO + bupropion" group. BPR: Bupropion, YOH: Yohimbine, VMR: Visceromotor response, AUC: Area under the curve.

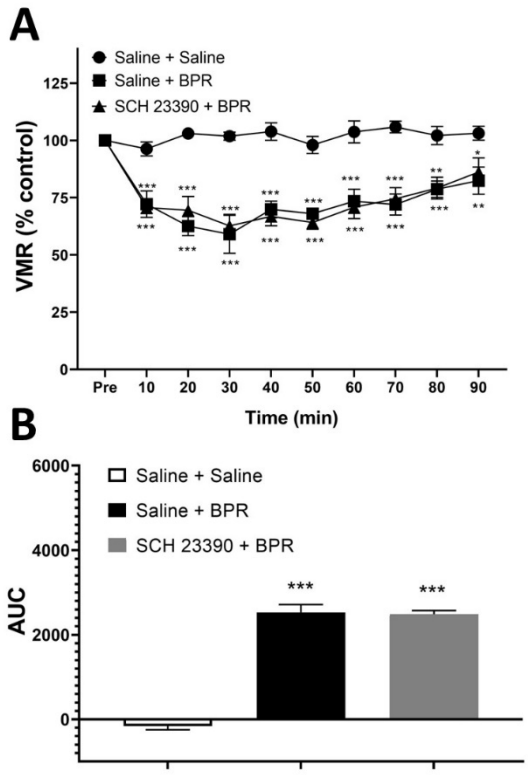

Figure 4. Effects of D1 receptor antagonist SCH 23390 on the antinociceptive effect of bupropion. A: % control visceromotor responses over time in groups after bupropion administration. B: Area under the curve (AUC) presentation of data. Pretreatment with SCH 23390 or saline 10 min before bupropion did not change the antinociceptive effect of bupropion (n=7).

p < 0.05, **P < 0.01, ***P < 0.001; BPR: Bupropion, VMR: Visceromotor response, AUC: Area under the curve.

In the preliminary studies, the dose of non-selective opioid agonist morphine, which has a similar effect with BPR on VMR, had been found to be 1 µg/rat, i.t. (5µL volume). Naloxone (2,5 µg/rat, i.t.) completely prevented the effect of morphine in this dose. Examining how opioid receptors contribute to BPR's antinociceptive effects, naloxone was applied 10 minutes before BPR. Naloxone reduced the antinociceptive effect of BPR starting from 20th minutes (P < 0,001). This effect persisted until the end of the experimental period (Fig. 6). Naloxone, which reduces the antinociceptive effect of BPR, did not change VMR when applied alone. In the control group, saline, solvent of both, did not alter VMR.

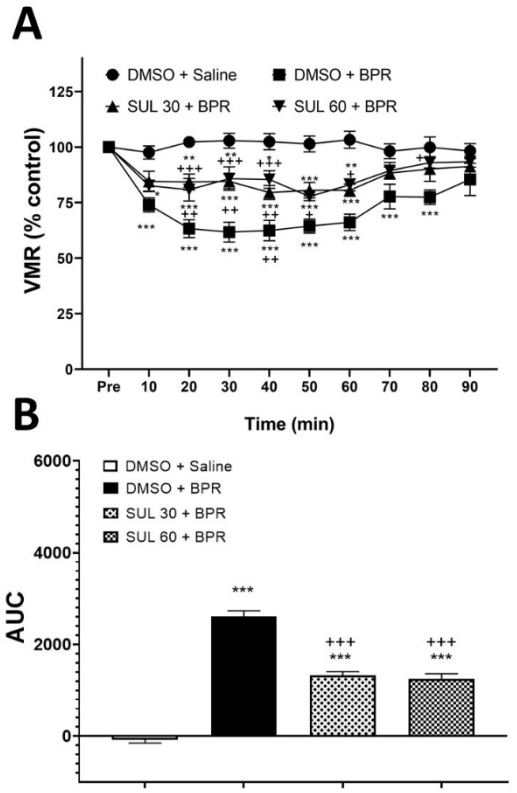

Figure 5. Effects of D2 receptor antagonist sulpiride on the antinociceptive effect of bupropion. A: % control visceromotor responses over time in groups after bupropion administration. B: Area under the curve (AUC) presentation of data. Pretreatment with sulpiride (30 and 60 µg/rat i.t.) 10 minutes before bupropion administration inhibited the antinociceptive effect of bupropion (n=7).

P < 0.05, **P < 0.01, ***P < 0.001; compared to the "DMSO + saline" administered control group. + P < 0.05, ++ P < 0.01, +++ P < 0.001; compared to the "DMSO + bupropion" group. BPR: Bupropion, SUL: Sulpiride, VMR: Visceromotor response, AUC: Area under the curve.

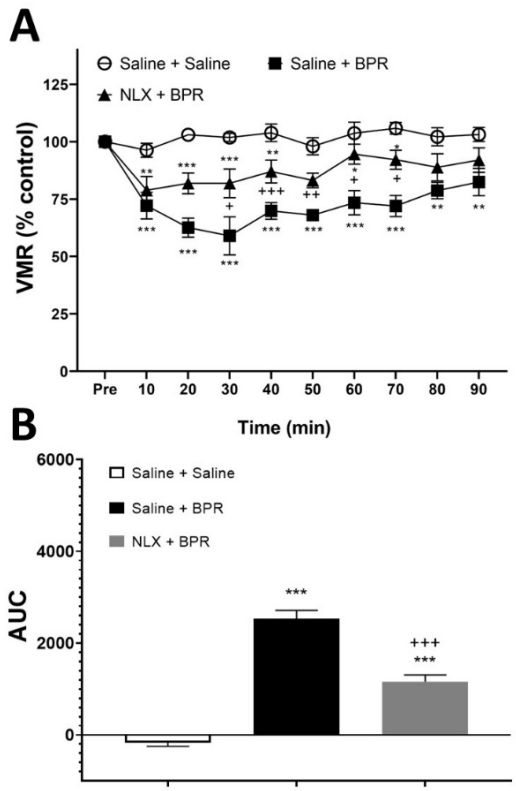

Figure 6. Effects of opioid receptor antagonist naloxone on the antinociceptive effect of bupropion. A: % control visceromotor responses over time in groups after bupropion administration. B: Area under the curve (AUC) presentation of data. Pretreatment with naloxone 10 minutes before bupropion administration inhibited the antinociceptive effect of bupropion (n=7).

P < 0.05, **P < 0.01, ***P < 0.001; compared to the "saline + saline" administered control group + P < 0.05, ++ P < 0.01, +++ P < 0.001; compared to the "saline + bupropion" group. BPR: Bupropion, NLX: Naloxone, VMR: Visceromotor response, AUC: Area under the curve

DISCUSSION

With this research, the effect of bupropion on visceral pain and the possible mechanisms of this effect were investigated. Bupropion has a significant antinociceptive effect at 20 and 40 mg/kg doses. This antinociceptive effect was partially rejected by α2AR antagonist, dopamine D2 receptor antagonist and non-selective opioid receptor antagonist. However, the α1AR antagonist and dopamine D1 receptor antagonist did not alter the antinociceptive effect of bupropion.

BPR has shown antinociceptive effects in experimental thermal, inflammatory, and neuropathic pain models [6,10,13-16]. However, in the visceral pain model, there was only one study investigating the effect of bupropion. In this reference study, the impact of bupropion in the acetic acid writhing test in mice was observed between only 40-50 minutes after bupropion injection[6]. Until our study, no

research in the literature shows the effects of bupropion in the visceral pain created with CRD. Nonetheless, this study is different from the previous studies due to features that show when the analgesic effect of bupropion started, how long it took, and when the effect reached the highest level. This difference in our study stems from the fact that the pain response can be measured at 10-minute intervals with the CRD model and this process can be repeated for a long time.

Antidepressants that inhibit the reuptake of neurotransmitters have been shown to have antinociceptive effects[17]. BPR acts mainly by inhibiting the intake of dopamine and noradrenaline and slightly increasing the release of these neurotransmitters. As a result, BPR has an effect on increasing the concentration of noradrenaline and dopamine in the synaptic cleft[18]. For this reason, the second part of our research was based on the hypothesis that these neurotransmitter receptors may contribute to bupropion's antinociceptive impact.

It is known that both α adrenoceptor types are widely expressed at the spinal cord level[19]. It is shown by immunohistochemical methods that dorsal root ganglia primary afferent neurons lack the catecholamine synthesis-related enzymes, but which includes monoamine oxidase, which oversees metabolism[20].

Based on previous studies, it is clear that α1 adrenoceptors have a role in the neurophysiological mechanism of pain in some experimental models. Contrary to this, it is seen that these receptors do not have a role in some experimental models[21-23]. Prazosin is an α1AR antagonist widely used in pain research to examine the involvement of α1AR. Research on which prazosin is applied intrathecally in both pain and non-pain studies shows that the dose we use (30 μg/rats, i.t.) is effective and sufficient[11,23,24]. However, in our research, prazosin did not change the antinociceptive effect of bupropion. Therefore, it seems that α1ARs did not contribute to bupropion's antinociceptive action.

α2 adrenoceptors are frequently studied in visceral pain induced by CRD. Noradrenaline and various selective α2AR agonists applied intrathecally have shown antinociceptive effects in visceral pain created by CRD. This antinociceptive effect is lost when agonists are combined with the α2AR antagonist yohimbine at a dose of 30 μg/rats i.t.[25]. However, in our study, the same dose of yohimbine partially rejected BPR's antinociceptive effect. When the yohimbine dose was doubled, similar results were found. With these findings, it is clear that α2AR is involved in the antinociceptive effect of BPR in visceral pain, but these receptors are not responsible for the entire effect.

It is known that D2 dopamine receptors have a stronger association with pain than D1 receptors[26-28]. Shimizu et al. showed that the pain they produced by applying substance P decreased with dopamine D2 receptor antagonist sulpiride and did not change with SCH 23390 (D1 receptor antagonist)[27]. Pretreatment with 25 μg/rats i.t. dose of SCH 23390, which completely reversed the effects of its agonist[12], did not affect the antinociceptive effect of BPR in our study. In addition, sulpiride reduced the antinociceptive effect of BPR. But, like yohimbine, sulpiride could not completely eliminate the effect of BPR.

It is thought that the dopaminergic system and visceral pain are relatively less related, but on the contrary, some studies show this relationship. In a study on this subject, it was shown that the antinociceptive effect of levodopa in acetic-acid induced visceral pain was inhibited by sulpiride but not changed by SCH 23390[27]. In a more recent study, levodopa and quinpirole (D2 receptor agonist) showed an antinociceptive effect in CRD-induced Hoshino et al. showed that the antinociceptive effect of BPR in nerve ligation-induced neuropathic pain is dose-dependently inhibited by the α2AR antagonist idazoxan and the D2 antagonist sulpiride[10]. In that study, 30 μg/rats doses of both antagonists completely blocked the antinociceptive effect of BPR. Conversely, in our study, α2AR and D2 antagonists partially reversed the effect of BPR. Possible reasons for this difference are the using different pain models and the systemic application of BPR instead of local. Visceral pain, and their effects are inhibited by the serotonin antagonist[29]. This finding shows the role of D2 receptors in visceral pain, as in our study.

The role of opioids, which are one of the most essential components of the endogenous analgesia system, has been frequently investigated in similar pain studies. There are also many studies showing the participation of opioids in the antinociceptive mechanism of antidepressants that inhibit the reuptake of neurotransmitters[30-32]. There are conflicts in the literature about the appropriate dose of naloxone to be used in investigating the mechanism

of action. Therefore, we determined the dose of naloxone, which completely inhibits the opioid agonist, and showed antinociception similar to the effective BPR dose in this study. 2.5 μg/rats dose of naloxone completely blocked the antinociception of morphine but partially blocked the effect of BPR. In conclusion, it is understood that opioid receptors have a partial role in the antinociceptive effect of BPR in visceral pain. However, this study does not reveal how BPR affects the opioidergic system. There is insufficient data on the interaction of BPR with opioids. It has been shown that α2AR agonists and opioids have synergistic analgesic effects[33]. Similarly, Ulger et al. showed that the antinociceptive effect of clonidine and dexmedetomidine was abolished by the opioid antagonist in visceral pain[34]. These previous findings offer an opportunity to discuss the interaction between BPR and the opioidergic system.

The results obtained with this study reveal that BPR has an antinociceptive effect in visceral pain and that α2AR, dopamine (D2), and opioid receptors are involved in this action. The findings of our study, in which we evaluated the effect of BPR, a widely prescribed medicine, on pain and the mechanism of this action, will make significant contributions to the literature. In addition, these data contain essential information that should be considered during the use of BPR in non-pain indications. Some of the antagonists used reduced the antinociceptive effect of BPR, which helped to elucidate the possible mechanisms. However, the fact that these antagonists did not completely abolish the effect of bupropion suggests that further studies on the mechanism of action of bupropion are necessary.

The most important limitation of the study is that the mechanism of action of the drug was examined only through receptors in the spinal cord. However, the study was designed this way because this is where pain modulation mainly takes place. The fact that the antagonists we used could not reverse the drug's effect alone suggests that other receptors may be involved in the mechanism of action of BPR or that the combination of antagonists we used may achieve this. In this respect, the relationship of bupropion with nicotinic receptors appears to be a potential area of research[35]. In addition, molecular methods should reveal how dopamine, noradrenaline and opioid receptors are involved in the antinociceptive effect of bupropion and how they interact with each other.

Author Contributions: Concept/Design : İY, AB; Data acquisition: İY, ÖDS; Data analysis and interpretation: AB, İY; Drafting manuscript: İY; Critical revision of manuscript: AB, ÖDS; Final approval and accountability: İY, ÖDS, AB; Technical or material support: İY, ÖDS, AB; Supervision: AB; Securing funding (if available): n/a.
Ethical Approval: This study was approved by Ondokuz Mayis University Animal Experiments Ethics Committee with the acceptance number 2020/25 on 14/07/2020.
Peer-review: Externally peer-reviewed.
Conflict of Interest: Authors declared no conflict of interest.
Financial Disclosure: This research was funded by Ondokuz University Research Fund (PYO.TIP.1904.20.012).

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