Behavioural Brain Research 412 (2021) 113439

Contents lists available at ScienceDirect

Behavioural Brain Research

journal homepage: www.elsevier.com/locate/bbr

Blockade of the kinin B_1 receptor counteracts the depressive-like behaviour and mechanical allodynia in ovariectomised mice

Izaque de Souza Maciel [a,b,d,*,1], Vanessa Machado Azevedo [b], Patricia Oliboni [b,c], Maria Martha Campos [a,b,c]

[a] Programa de Pós-graduação em Medicina e Ciências da Saúde, Escola de Medicina, Pontifícia Universidade Católica do Rio Grande do Sul, Porto Alegre, RS, Brazil
[b] Centro de Pesquisa em Toxicologia e Farmacologia, Escola de Ciências da Saúde e da Vida, Pontifícia Universidade Católica do Rio Grande do Sul, Porto Alegre, RS, Brazil
[c] Programa de Pós-graduação em Odontologia, Escola de Ciências da Saúde e da Vida, Pontifícia Universidade Católica do Rio Grande do Sul, Porto Alegre, RS, Brazil
[d] Escola de Medicina de Ribeirão Preto, Universidade de São Paulo, Ribeirão Preto, SP, Brazil

ARTICLE INFO

Keywords:
Ovariectomy
Depressive-like behaviour
Nociception
Kinin
B_1receptor

ABSTRACT

Menopause is related to a decline in ovarian oestrogen production, affecting the perception of the somatosensory stimuli, changing the immune-inflammatory systems, and triggering depressive symptoms. It has been demonstrated that the inhibition of the kinin B_1 and B_2 receptors (B_1R and B_2R) prevented the depressive-like behaviour and the mechanical allodynia that was induced by immune-inflammatory mediators in mice. However, there is no evidence regarding the role of the kinin receptors in the depressive-like and nociceptive behaviour in female mice that were subjected to bilateral ovariectomy (OVX). This study has shown that the OVX mice developed time-related mechanical allodynia, together with an increased immobility time as indicative of depression. Both of these changes were reduced by the genetic deletion of B_1R, or by the pharmacological blockade of the selective kinin B_1R antagonist R-715 (acute, i.p.). The genetic deletion or the pharmacological inhibition of B_2R (HOE 140, i.p.) did not prevent the OVX-elicited behavioural changes. The data has suggested a particular modulation of kinin B_1R in the nociceptive and depressive-like behaviour in the OVX mice. The selective inhibition of the B_1R receptor may be a new pharmacological target for treating pain and depression symptoms in women during the perimenopause/menopause period.

1. Introduction

In women, the ageing process is linked to the onset of the perimenopause/menopause period, which occurs approximately at the age of 45−55. It is related to a progressive decrease in the circulating levels of the gonadal hormones [1–3]. These hormonal changes include an increase in the serum levels of the follicle-stimulating hormone (FSH), which is associated with diminished oestradiol and inhibin B [3]. This oestrogen decrease is associated with several physical and psychological symptoms [2,4–6]. Some of these symptoms especially occur during the perimenopause period. Some such examples are vasomotor alterations, sleep disturbances, depression, sexual dysfunctions, cognitive impairment, and joint pain. A range of these alterations can accompany women for the rest of their lives [7]. The most effective therapeutic option to treat menopausal symptoms remains hormone replacement therapy (HRT). All the same, HRT increases some risks, such as postmenopausal breast cancer, thrombosis, an increase of cardiovascular disease, and stroke [3,8,9].

Besides the importance of oestrogen receptors (ERs) in mediating the sexual growth and differentiation in women, these receptors are widespread in the central nervous system (CNS) [10]. The activation of these ERs in the CNS regulates mood, alertness, cerebral blood flow, and neurotransmitter activity [2]. Previous clinical evidence has shown that one of the most prevalent symptoms during perimenopause/menopause

Abbreviations: OVX, ovariectomised mice; TST, tail suspension test; PWT, paw withdrawal threshold; FSH, follicle-stimulating hormone; HRT, hormone replacement therapy; ER, oestrogen receptors; MD, major depression; BK, bradykinin; CNS, central nervous system; LPS, lipopolysaccharide; TNF, tumour necrosis factor; CSF, cerebrospinal fluid; ACE, angiotensin-converting enzyme; ROS, reactive oxygen species.

* Corresponding author at: School of Medicine of Ribeirão Preto, University of São Paulo, Avenida do Café s/n, 14040-903, Ribeirão Preto, SP, Brazil.
E-mail address: izaque.de@uef.fi (I. de Souza Maciel).
[1] Current affiliation: Faculty of Health Sciences, A.I. Virtanen Institute for Molecular Sciences, University of Eastern Finland, Kuopio, Finland.

https://doi.org/10.1016/j.bbr.2021.113439
Received 1 September 2020; Received in revised form 31 May 2021; Accepted 25 June 2021
Available online 29 June 2021
0166-4328/© 2021 Elsevier B.V. All rights reserved.

is chronic pain [3,11,12]. Furthermore, the ERs regulate the immune systems and the inflammatory mediators [13,14].

Major depressive (MD) disorder affects more than 350 million people globally, and the prevalence is higher in women than in men [15,16]. Notably, the data from clinical studies has indicated that perimenopause is a critical period for the development of MD signs [4]. In treating MD symptoms, the currently available antidepressant therapy shows mixed results in its effectiveness. In addition, many patients discontinue the therapy because of the variable side effects of the antidepressants [17]. Preclinical studies have shown that OVX rats or mice developed depressive-like behaviour and nociception changes, both of which were counteracted by an oestradiol treatment [18–20]. Despite that, these HRT adverse effects cannot be disregarded [8]. As a result, to treat menopause-associated MD and pain symptoms, the development of new approaches is essential.

Over the past few years, kinin receptors have been associated with a series of pathophysiological conditions [21–24]. The biological effects of kinins are mediated via the activation of two metabotropic receptors, namely, B_1R and B_2R. While B_2R is constitutively expressed in several tissues and is preferably activated by bradykinin (BK), the B_1R receptor is weakly expressed under physiological conditions but is upregulated in traumatic and immune-inflammatory conditions [25,26]. The activation of B_1R is modulated by the kinin metabolites and it contributes to chronic allodynia and hyperalgesia, which are associated with the production of the inflammatory cytokines [27,28]. The activation of B_1R has also been implicated in some central nervous system (CNS) conditions, such as Alzheimer's disease, epilepsy, and bipolar disorder [29–31]. Furthermore, our previous work has shown that B_1R participated in the depressive-like behaviour that was induced by the systemic administration of *E. coli* lipopolysaccharide (LPS) in mice [22]. Such an effect seemed to be related to an increase in the TNF levels and the microglia activation in the brains of the mice [22].

When considering the impact of an ovarian oestrogen depletion on MD, pain, and the immune-inflammatory system [4,14], this study has hypothesised that the kinin receptors may participate in the OVX-induced behavioural changes in rodents [20]. The researchers have also postulated that kinin receptor inhibition might attenuate the behavioural changes in OVX mice. This current study has assessed the effects of the pharmacological and genetic inhibition of B_1R and B_2R on mechanical nociception and the depressive-like behaviour in OVX female mice.

2. Materials and methods

2.1. Animals

The experiments were conducted when using four different adult female mice (8 weeks of age, at 25–30 g), namely, Swiss and the C57BL6 wild type (WT), together with B_1, and B_2 receptor knockout mice (B_1 -/- and B_2 -/-, UNIFESP-EPM). The animals were housed under standard conditions of light, temperature, and humidity (12 h light-dark cycle, 22 ± 1 °C, under 60–80 % humidity), with food and water provided ad libitum. The Swiss and the C57/BL6 mice were obtained from the Central Animal Facility at the Universidade Federal de Pelotas (UFPEL, Brazil). The B_1 and B_2 receptor knockout mice were obtained from the Animal Facility at the Department of Biophysics, Universidade Federal de São Paulo (UNIFESP-EPM, São Paulo, Brazil). All of the procedures were conducted in accordance with the Brazilian Council for Animal Experimentation (COBEA) guidelines, which comply with international laws and policies for the investigation of experimental pain in conscious animals. The protocols were approved by the local Ethical Committee (protocol number CEUA-PUCRS 12/00,290). Every effort was made to minimise the animal's suffering and with an aim to reduce the number of animals used. The experiments were conducted between 08:00−17:00 (during the light phase of the 24 -h cycle), with randomisation of the experimental groups.

2.2. Ovariectomy surgical procedure

The surgical procedure was conducted as previously described in the literature [18,19], with minor modifications. Briefly, the animals were anaesthetised by an intraperitoneal (i.p.) injection of ketamine (50 mg/kg) and xylazine (5 mg/kg). After the onset of anaesthesia, the lumbar dorsal was shaved. The exposed skin was prepared for aseptic surgery by a povidone-iodine (10 %) scrub, followed by a sterile saline wipe. The ovary was resected bilaterally at 8 weeks of age, with a one to two cm incision in the skin in the midline on the lumbar vertebral line. The ovary was pulled through a small opening in the musculature. A ligature was placed around the exposed ovary and an initial segment of the fallopian tube was removed (OVX group). The skin and muscle incision were then sutured (4−0 non-absorbable). The Sham group underwent the same procedure as the OVX group but without the resection of the ovaries and the initial segment of the fallopian tube. The behavioural tests were initiated after a period of recovery of 7 days.

2.3. Measurement of the uterine weight

Uterine atrophy is indicative of the success of ovariectomy surgical model [18]. After the battery of behavioural tests, all of the animals of both the OVX and Sham groups were euthanised by a deep inhalation of isoflurane. The uterus of each animal was resected quickly without the periovarian fat and was immediately weighted. The values were expressed in mg.

2.4. Mechanical allodynia

The measurement of the mechanical paw withdrawal threshold (PWT) was carried out when using the up-down paradigm, as described in the literature [32,33], with minor modifications. The mice were individually acclimatised for one hour in elevated clear plexiglass boxes, with a wire mesh floor to allow for access to the right hind paw plantar surface. Von Frey filaments of increasing stiffness (0.02–10 g) were applied to the right hind paw plantar surface of the animals, with a pressure that was high enough to bend the filament. The tests were initiated with a 0.4 g filament. The absence of a paw lifting after 5 s led to the use of the next filament with an increased weight, whereas a paw lifting indicated a positive response, which led to the use of the next weaker filament. This paradigm continued for a total of 6 measurements, including the one before the first paw-lifting response had been made, or until four consecutives positive (assigned a score of 0.030) or four successive negatives (assigned a score of 6.76) responses occurred. The mechanical paw withdrawal threshold response was then calculated as described previously [34], using the following formula:

$$\text{Threshold } 50\ \% = \log \text{ of the last filament used} - (\text{K. mean})$$

where K was the constant based on the Dixon Table, and mean referred to the mean difference (in log units) between the stimuli (for the mice, 0.44). The paw withdrawal threshold was expressed in grams (g) and was evaluated before (baseline) and 7, 14, 21, and 28 days after the surgical procedure. A significant decrease in the paw withdrawal threshold when compared to the baseline values was considered as mechanical allodynia.

2.5. Tail suspension test

According to the methodology as was described initially [35], the study used the tail-suspension test (TST) to assess the depressive-like behaviour. At different time-points, following the ovariectomy surgical procedure (7, 14, 21, and 28 days), the animals were suspended 50 cm above the floor by using adhesive tape that was placed approximately 1 cm from the tip of the tail. The mice were exposed to the TST, 30 min after the PWT test. The time during which mice remained immobile was

quantified in seconds for 6 min [22].

2.6. Open-field locomotor activity

The locomotor activity was assessed in the open-field arena at 7, 14, 21, and 28 days, after the ovariectomy surgical procedure. The experiments were conducted 30 min after the TST in a sound-attenuated room, under low-intensity light. The mice were individually placed in the centre of an acrylic box (40 × 60 × 50 cm), with the floor divided into nine squares. The number of squares that were crossed with the four paws was registered for 6 min [22].

2.7. Pharmacological treatments

To assess the involvement of the B_1 and B_2 receptors on the behavioural changes that were induced by the ovariectomy surgery, the animals were pre-treated with the selective B_1 receptor antagonist R-715 (0.5 mg/kg; i.p.) and the selective B_2 receptor antagonist Hoe-140 (50 nmol/kg; i.p.). The positive and negative control groups were treated with pregabalin (30 mg/kg; i.p.), or saline (0.9 %; i.p.), respectively. All of the treatments were administered 30 min before the behaviour PWT test. The doses and the treatment schedules were determined based on the previous literature, or on the pilot experiments [22,28,36].

2.8. Drugs and reagents

The following drugs and reagents were used: the B_1 receptor antagonist R-715 was kindly provided by Dr Fernand Gobeil (Department of Pharmacology, University of Sherbrooke, QC, Canada) and the B_2R antagonist Hoe-140 was of the commercial source (Bachem, USA; #4,043,056). Ketamine (Cristália), Xylazine (Syntec), 10 % povidone-iodine, and pregabalin (Lyrica®) were obtained from Pfizer (UK). All of the drugs were diluted in sterile saline immediately before the injection (NaCl 0.9 %) solutions.

2.9. Statistical analysis

The results are presented as the mean ± SEM. The statistical analyses were performed by One-Way or Two-Way Analysis of Variance (ANOVA), followed by Bonferroni's post hoc test, or by using the unpaired Student *t* test. *P*-values less than 0.05 ($p < 0.05$) were considered significant. All of the tests were performed when using GraphPad Prism Software version 8.0 (San Diego, USA).

3. Results

3.1. The ovariectomised mice showed mechanical allodynia and depressive-like behaviour

Initially, the researchers characterised the behavioural changes that were induced by the menopause surgical model (Fig. 1A). The ovariectomised Swiss mice (OVX group) showed mechanical allodynia, which was characterised by a significant reduction in the right hind PWT (OVX = F (1, 20) = 42.72, p = 0.0001, N = 11 by group; at 7, 14, and 21 days, respectively; Fig. 1B). On the 28th day after the surgical procedure, there were no significant differences between the groups (OVX x Sham, P = 0.49; Fig. 1B). The same group of mice demonstrated a significant increase in immobility time in the TST (OVX = F (1, 40) = 31.20, p =

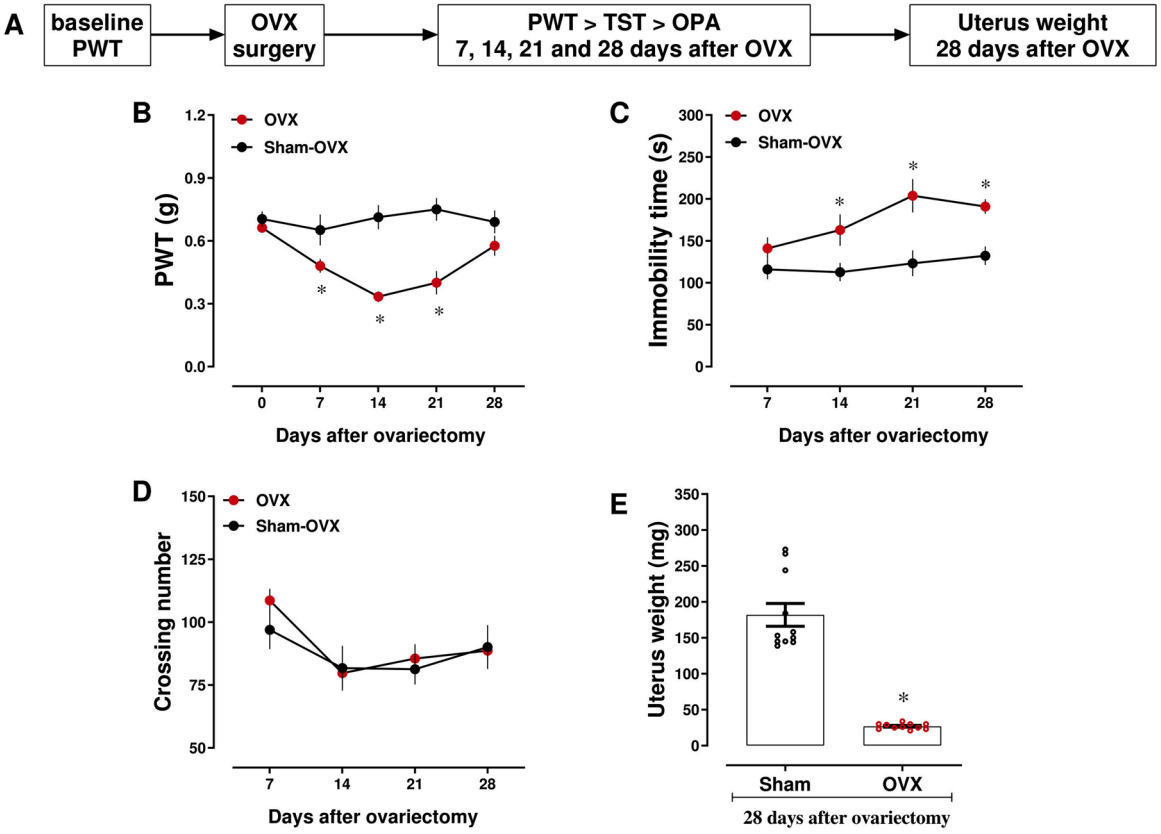

Fig. 1. Time-related behaviour effect after ovariectomy in mice. (A) Timeline of the experimental approach. The effects of ovariectomy at 7, 14, 21, and 28 days: (B) Mechanical threshold, as analysed by using the von Frey test; (C) Immobility time in the tail suspension test; (D) Crossing number in the open-field arena test, and (E) Uterus weight (mg), after 28 days of surgery. Each point or column represents the mean ± SEM of 11 animals per group. *P < 0.05 shows a significant difference from the Sham Swiss group; Two-Way (repeated-measure) ANOVA (time x OVX), followed by Bonferroni's post hoc test, or the Student's t-test). PWT = paw withdrawal threshold; TST = tail suspension test; OPA = open-field arena; OVX = ovariectomy.

0.001, n = 11 by group; at 14, 21, and 28 days after the surgery, Fig. 1C). The locomotor activity, which was assessed in the open-field arena, was not significantly altered (OVX = F (1, 40) = 0.49, p = 0.48, N = 11 by group; Fig. 1D). Finally, confirming the surgical procedure, the uterine weight of the OVX group was significantly lower than that of the Sham group (t = 9.72, df = 20; p = 0.0001, Fig. 1E), according to the evaluation at 28 days after surgery. Based on these results, the next experiments were conducted 21 days after the ovariectomy surgical procedure.

3.2. The B_1 receptor antagonist R-715 attenuated the mechanical nociceptive and depressive-like behaviour in the ovariectomised mice

At the next step, the study essayed the effects of an effective dose of pregabalin and the B_1 receptor antagonist peptide for kinin R-715 in mechanical allodynia (von Frey filaments test) and the immobility time in the TST (Fig. 2A). The results showed that the ovariectomised Swiss mice displayed a significant decrease in the PWT, when measured at 21 days, following the surgical procedure (OVX = F (1, 42) = 29.43, p = 0.0001, N = 13; Fig. 2B). The acute treatment with pregabalin (30 mg/kg; i.p.; 30 min. before the behaviour test), or with the B_1R antagonist R-715 (0.5 mg/kg, i.p.; 30 min. before the behaviour test), significantly inhibited the mechanical allodynia that was induced by the ovariectomy procedure (interaction = F (3, 42) = 12.51, p = 0.0001, N = 7–13; Fig. 2B). Only the treatment with R-715 significantly reduced the TST immobility time (F (3, 41) = 26.84, p = 0.0001, N = 7–13; Fig. 2C) in the ovariectomised female mice. Both of these pharmacological treatments were not able to reverse the decrement of uterus weight in the ovariectomised mice (p = 0.99, N = 7–13; Fig. 2D).

3.3. The B_1 receptor knockout mouse was protected from the behavioural changes elicited by the ovariectomy

To confirm the role of the B_1 receptor for kinin in the mechanical allodynia and depressive-like behaviour that was induced by the ovariectomy, the B_1 receptor knockout female mouse (KOB_1) was used (Fig. 3A). The results showed that the ovariectomised C57BL6 mice (WT) displayed a significant decrease in the PWT value when measured at 21 days, following the surgical procedure (OVX = F (1, 42) = 14.02, p = 0.0005, N = 10; Fig. 3B). Both the KOB_1 mice that were submitted to the ovariectomy procedure (OVX-KOB_1 group) and the OVX-WT mice that were treated with R-715 (0.5 mg/kg; i.p., 30 min. before the behaviour test) significantly exhibited an inhibition of the mechanical allodynia induced by the ovariectomy procedure (interaction = F (4, 42) = 10.19, p = 0.0001, N = 8–10; Fig. 3B). Relevantly, both the OVX-KOB_1 group and the OVX-WT group that were treated with R-715 had a significant decrease of the immobility time in the TST (F (4, 39) = 9.0, p = 0.0001, N = 8–10; Fig. 3C). Either the pharmacological treatment with the B_1 receptor antagonist, or the gene deletion, were unable to reverse the decrease of uterus weight in the ovariectomised mice (p < 0.05; N = 8–10, Fig. 3D).

3.4. The pharmacological inhibition or gene deletion of the B_2 receptor failed to protect against the behavioural changes that were induced by the ovariectomy

The present study also investigated the participation of the kinin B_2 receptor in the behavioural changes as elicited by the ovariectomy surgery (Fig. 4A). The B_2 receptor knockout mouse (KOB_2) and the selective B_2 receptor antagonist Hoe-140 (50 nmol/kg; i.p., 30 min before the behaviour test) were used. Similarly, the OVX-WT group and the KOB_2 female mice that were submitted to ovariectomy (OVX-KOB_2 group) developed mechanical allodynia when measured at 21 days, following the surgical procedure (OVX = F (1, 33) = 129.2, p = 0.0001, N = 6–9; Fig. 4B). The OVX-KOB_2 group, and the OVX-WT group that were treated with Hoe-140, did not prevent the mechanical allodynia that was induced by the ovariectomy surgery (interaction; F (4, 33) = 17.84, p = 0.99; N = 6–9; Fig. 4B). Furthermore, both the OVX-KOB_2 group and the OVX-WT group that were treated with Hoe-140 did not present a reduction of the immobility time in the TST (F (4, 32) = 18.30, p = 0.99, N = 6–9; Fig. 4C). Either the pharmacological treatment with the B_2 receptor antagonist or the gene deletion were unable to reverse the decrement of uterus weight in the ovariectomised mice (p < 0.05, N = 6–9; Fig. 4D).

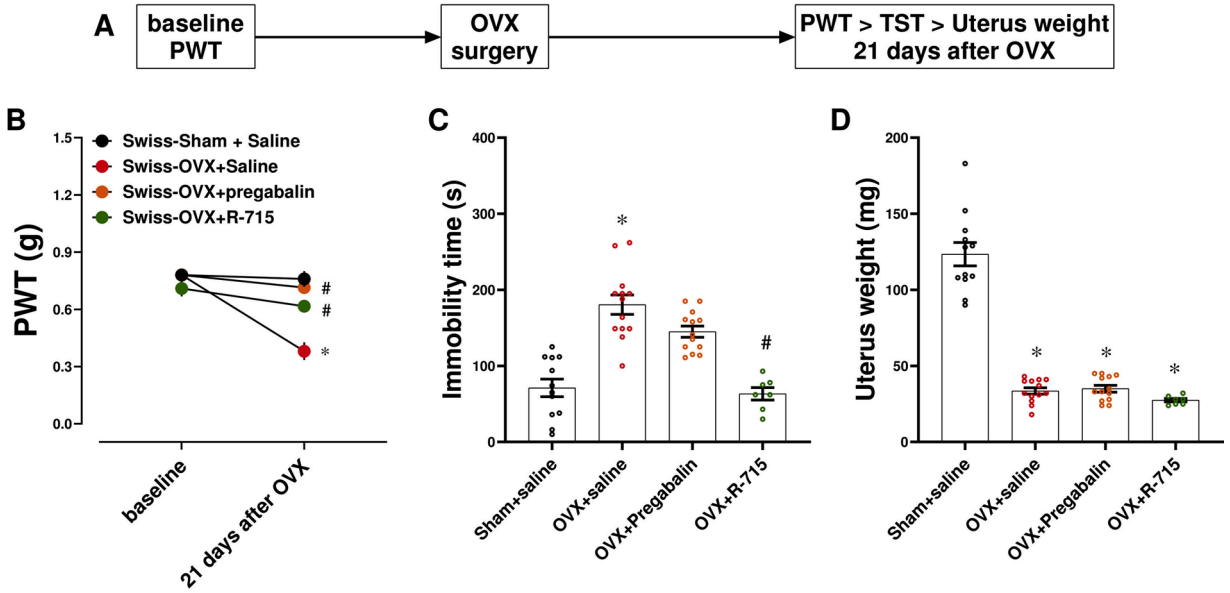

Fig. 2. Evaluation of the acute treatment with the B_1 antagonist in the ovariectomised Swiss mice. (A) Timeline of the experimental approach. The effects of ovariectomy surgery at 21 days. (B) Mechanical threshold, as analysed by using the von Frey test, (C) Immobility time in the tail suspension test, and (D) Uterus weight (mg). The effects of the treatment with pregabalin (30 mg/kg), or R-715 (0.5 mg/kg); both by i.p., injected 30 min before behavioural tests. Each column represents the mean ± SEM of 7-13 animals per group. *P < 0.05 shows a significant difference from the Sham Swiss group; #P < 0.05 shows a significant difference from the OVX Swiss group; One or Two-Way (repeated-measure) ANOVA (time x OVX + treatment), followed by Bonferroni's post hoc test. PWT = paw withdrawal threshold; TST = tail suspension test; OVX = ovariectomy.

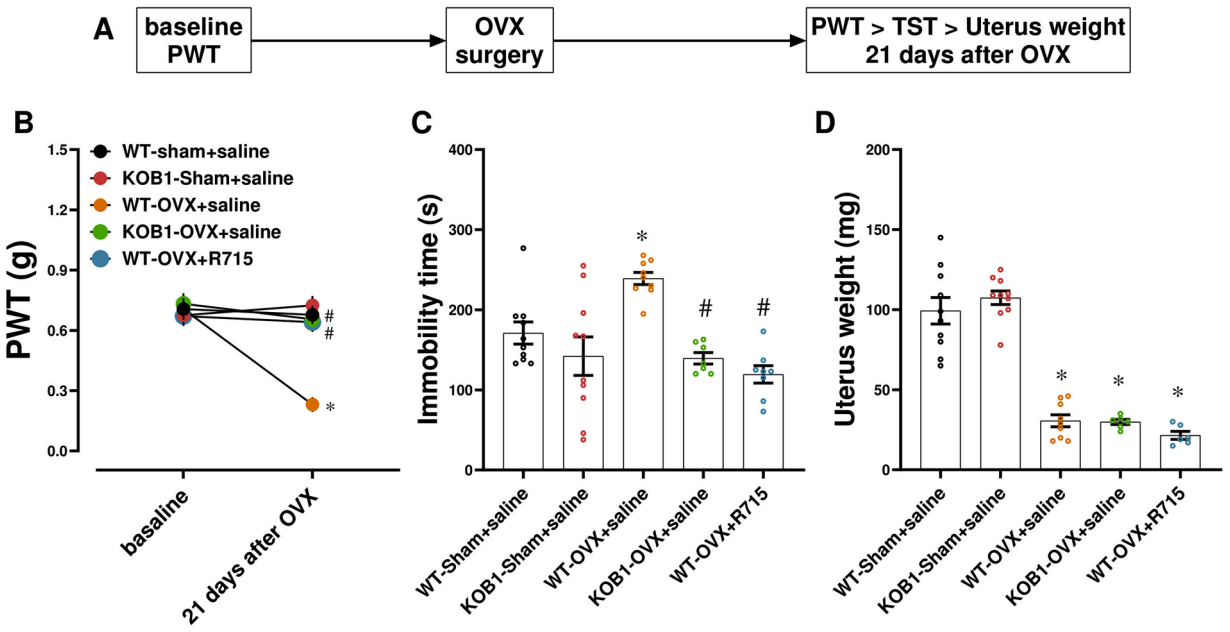

Fig. 3. The B_1 receptor showed a protective effect against mechanical allodynia or the depressive-like behaviour in the ovariectomised mice. (A) Timeline of the experimental approach. The effects of ovariectomy surgery at 21 days for the C57BL6-WT or KOB_1 female mice. (B) Mechanical threshold, as analysed by using the von Frey test, (C) Immobility time in tail suspension test, and (D) Uterus weight (mg). The effects of the treatment with R-715 (0.5 mg/kg; i.p., 30 min before the behaviour test). Each column represents the mean ± SEM of 8-10 animals per group. *P < 0.05 shows a significant difference from the Sham WT group; #P < 0.05 shows a significant difference from the OVX WT group; One or Two-Way (repeated-measure) ANOVA (time x OVX + treatment, followed by Bonferroni's post hoc test. PWT = paw withdrawal threshold; TST = tail suspension test; OVX = ovariectomy.

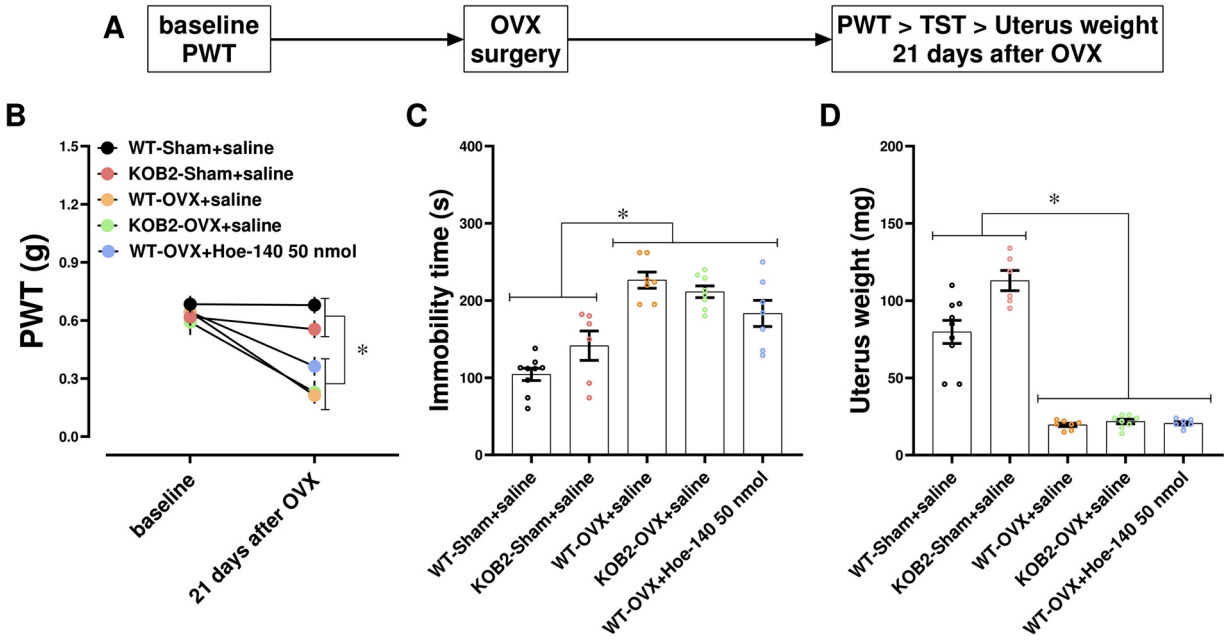

Fig. 4. The B_2 receptor failed to inhibit mechanical allodynia or the depressive-like behaviour in the ovariectomised mice. (A) Timeline of the experimental approach. The effects of ovariectomy surgery after 21 days for the C57BL6-WT or KOB_2 mice. (B) Mechanical threshold, as analysed by using the von Frey test, (C) Immobility time in the tail suspension test, and (D) Uterus weight (mg). The effects of the treatment with Hoe-140 (50 nmol/kg; i.p., 30 min before the behaviour test). Each column represents the mean ± SEM of 6-9 animals per group. *P < 0.05 shows a significant difference from the WT-Sham + saline or the KOB2-Sham + saline group. One or Two-Way (repeated-measure) ANOVA (time x OVX + treatment), followed by Bonferroni's post hoc test. PWT = paw withdrawal threshold; TST = tail suspension test; OVX = ovariectomy.

4. Discussion

The present study has described the participation of the bradykinin receptors on the depressive-like behaviour and mechanical allodynia that were triggered by a preclinical model of menopause in mice. Both the pharmacological inhibition and the genetic deletion of the B_1 receptor mitigated the ovariectomy-induced behavioural changes. Neither the pharmacological or the genetic inhibition of the B_2 receptor for kinin attenuated the bilateral ovariectomy-induced mechanical hypernociception and the increase in immobility time. The data has indicated

a specificity for the B_1 receptor subtype for bradykinin in the OVX-induced mechanical allodynia and depressant-like behaviour. This specificity has suggested a potential pharmacological target to treat pain and the symptoms of major depression in women during the menopause period.

During the perimenopause/menopause period, an increase in depression and pain symptoms is associated with a decrease of ovarian hormones [37]. In preclinical studies, the decline of ovarian hormones by the bilateral ablation of ovaries has induced mechanical allodynia and thermal hyperalgesia, with an increase of immobility time in the FST or TST [18–20,38]. Corroborating previous data, it was observed that the bilateral ovariectomy significantly decreased the uterine weight, being an indirect indicator of oestrogen decrease [18,20]. Uterine atrophy was associated with mechanical allodynia at 7, 14, and 21 days after surgery, with a significant increase in immobility time in the TST at 14, 21, and 28 days. The locomotor activity had no significant changes when compared with the Sham group, indicating that an increase of immobility time in the TST was not due to motor impairment. This study has, therefore, assumed that a depletion of the ovarian hormone levels facilitated the development of mechanical allodynia and the acute coping behaviour (helplessness state) in the female mice.

Clinical and preclinical studies have demonstrated the relationship between a decrease in the ovarian hormones and an increase in the pro-inflammatory markers when associated with molecular mechanisms of pain perception and the symptoms of major depression [39–41]. Examples of such markers are interleukin-1 (IL-1), interleukin-6 (IL-6), and tumour necrosis factor-α (TNF-α) [39,42]. Certain researchers have postulated that the pro-inflammatory cytokines, by activating the B_1 kinin receptor, elicit mechanical nociception and the acute coping behaviour in mice [22,43]. Such mechanisms are associated with an increased expression of B_1R in the peripheral (e.g. terminal nerves) and central (e.g. hippocampus and cortex) nervous system structures, both of which are related to allodynia and major depression [22,26,43–45]. This evidence is similar to the results from the present study, wherein pregabalin (positive control) and the B_1R antagonist R-715 effectively inhibited mechanical allodynia in the OVX mice. Notably, only R-715 was able to decrease the immobility time in the TST. On the other hand, for the ovariectomised mice, the selective B_2R antagonist HOE-140 failed to prevent an increase of mechanical nociception or immobility time. Additionally, the B_1R knockout mice were unresponsive to the OVX-induced mechanical allodynia and the increased immobility time, while the B_2R knockout mice were responsive. Thus, in the ovariectomised mice, this decrease in the ovarian hormones may increase the B_1R expression/activity and modulate the nociception and depressive-like behaviour.

In humans and rodents, post-ovariectomy oestrogen reduction is associated with an increase of the systemic and central immune-inflammatory mediators [41]. In the ovariectomised mice, the 17 beta-oestradiol treatment significantly inhibited the LPS-induced increase in the microglia activation [46]. In a previous study by the same researchers, the systemic LPS injection induced an increase in the immobility time in the TST, and significantly increased the TNF levels in the whole brain, serum, and cerebrospinal fluid (CSF). These increases preceded an acute elevation of the B_1R mRNA expression in the hippocampus and cortex [22]. The acute systemic treatment with the B_1R antagonists decreased the microglia activation in the hippocampus. In addition, the LPS-treated TNF P55 knockout mice displayed no depressive-like behaviour, or an increase in the B_1R expression [22]. Together, this data has suggested that 17 beta-oestradiol and the selective B_1R antagonist (R-715) may be acting via similar mechanisms to protect against the behavioural changes and the molecular alterations, as modulated by the increasing TNF levels. Accordingly, clinical and preclinical data suggest that a decrease of ovarian hormones induces: (I) an alteration of the angiotensin-converting enzyme (ACE) activity, (II) an increase in oxidative stress, and (III) an increase of the pro-inflammatory cytokines [47–49], which leads to an increased production of kinin, receptor activation, and/or upregulation [41,50].

In a clinical study, hormone replacement therapy (HRT), as administered in hypertensive postmenopausal women, decreased the serum levels of ACE activity and increased the plasma levels of angiotensin II (ANG II) and bradykinin [47]. The cultured primary hypothalamic neurons of the mice that were treated with ANG II showed a significant increase in the B_1R expression, an increase of oxidative stress, and the proinflammatory cytokines, which were prevented by a pre-treatment with the B_1R antagonist (R-715) [51]. Hence, HRT may facilitate the kinin-kallikrein system and the B_1R activity.

A reduction of the oestrogen levels has been associated with an increased reactive oxygen species (ROS) [52–54]. In preclinical studies, an increase of ROS induced the upregulation of B_1R in the brain of a rat model with insulin resistance [49]. This increase of B_1R activity led to downstream pathways, which involved an increase of nitric oxide (NO), glutamate, and substance P (SP) [49]. The ovariectomised mice demonstrated an increase of nitric oxide (NO) in the hippocampus. An acute treatment with the non-selective NO synthase inhibitor (L-NAME) significantly decreased the immobility time of the OVX mice in the FST [19]. Consequently, these decreasing ovarian hormones may increase the B_1R activity via oxidative stress and the pro-inflammatory cytokines [19,49].

When comprehended together, this data has suggested that the antagonists of the kinin receptors could be a new pharmacological approach to treat pain and major depression symptoms during the menopause period. Having said that, it is not clear how the ovarian hormones modulate the B_1R expression or activity. Further investigation is needed to address the direct role of the ovarian hormones on the kinin-kallikrein system when related to major depression.

5. Conclusion

In conclusion, this study has shown the specificity of B_1R on the mechanical nociception and depressive-like behaviour in female mice when submitted to ovariectomy. To the best of the authors' knowledge, this is the first evidence that the pharmacological or genetic inhibition of B_1R has prevented the behavioural changes that were induced by the surgical menopause model in female mice. The inhibition of B_1R could be a new pharmacological target to treat pain and major depression during the perimenopause/menopause period.

Author contributions

ISM designed the study, performed the experiments, collected, analysed, and interpreted the data, as well as writing the manuscript draft. VMA and PO performed the experiments, collected, and analysed the data. MMC designed the study, analysed and interpreted the data, and wrote the manuscript.

Funding

This work was supported by grants from the Brazilian Research Agency (CAPES), the National Council for Scientific and Technological Development (CNPq), the Fundação de Amparo à Pesquisa do Estado do Rio Grande do Sul (FAPERGS), and the FINEP Research Grant "Implantação, Modernização e Qualificação de Estrutura de Pesquisa da PUCRS" (PUCRS INFRA) # 01.11.0014−00. M.M.C. (304,042/2018−8) is a researcher career awardee of the CNPq, Brazil.

Author statement

Izaque de Sousa Maciel designed the study, performed the experiments, collected, analysed, and interpreted the data, as well as writing the manuscript draft. **Vanessa Machado Azevedo** and **Patricia Oliboni** performed the experiments, collected, and analysed the data. **Maria Martha Campos** designed the study, analysed and interpreted the data,

and wrote the manuscript. All the authors read and approved the final version to be published in the Behavioural Brain Research.

Declaration of Competing Interest

The authors declare that there are no conflicts of interest.

Acknowledgments

The authors would like to thank Dr Plinio C. Casaratto (University of Helsinki) and Dr Luma Melo (Indiana University) for their critical review of the manuscript draft.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.bbr.2021.113439.

References

[1] M. Steiner, E. Dunn, L. Born, Hormones and mood: from menarche to menopause and beyond, J. Affect. Disord. 74 (2003) 67–83.
[2] E. O'Connell, Mood, energy, cognition, and physical complaints: a mind/body approach to symptom management during the climacteric, J. Obstet. Gynecol. Neonatal Nurs. 34 (2005) 274–279, https://doi.org/10.1177/0884217505274589.
[3] S.R. Davis, I. Lambrinoudaki, M. Lumsden, G.D. Mishra, L. Pal, M. Rees, N. Santoro, T. Simoncini, Menopause, Nat. Rev. Dis. Primers 1 (2015) 1–19, https://doi.org/10.1038/nrdp.2015.4.
[4] J.T. Bromberger, H.M. Kravitz, Mood and menopause: findings from the Study of Women's Health Across the Nation (SWAN) over 10 years, Obstet. Gynecol. Clin. North Am. 38 (2011) 609–625, https://doi.org/10.1016/j.ogc.2011.05.011.
[5] J.L. Gordon, S.S. Girdler, Hormone replacement therapy in the treatment of perimenopausal depression, Curr. Psychiatry Rep. 16 (2014) 517, https://doi.org/10.1007/s11920-014-0517-1.
[6] N. Chidi-Ogbolu, K. Baar, Effect of Estrogen on musculoskeletal performance and injury risk, Front. Physiol. 9 (2019) 1834, https://doi.org/10.3389/fphys.2018.01834.
[7] S.M. McKinlay, D.J. Brambilla, J.G. Posner, The normal menopause transition, Maturitas 61 (2008) 4–16.
[8] J.E. Rossouw, G.L. Anderson, R.L. Prentice, A.Z. LaCroix, C. Kooperberg, M. L. Stefanick, R.D. Jackson, S.A.A. Beresford, B.V. Howard, K.C. Johnson, J. M. Kotchen, J. Ockene, Writing Group for the Women's Health Initiative Investigators, Risks and benefits of estrogen plus progestin in healthy postmenopausal women: principal results from the Women's Health Initiative randomized controlled trial, JAMA 288 (2002) 321–333.
[9] T. Deli, M. Orosz, A. Jakab, Hormone replacement therapy in Cancer survivors – review of the literature, Pathol. Oncol. Res. 26 (2020) 63–78, https://doi.org/10.1007/s12253-018-00569-x.
[10] M. Jia, K. Dahlman-Wright, J.-Å. Gustafsson, Estrogen receptor alpha and beta in health and disease, Best Pract. Res. Clin. Endocrinol. Metab. 29 (2015) 557–568, https://doi.org/10.1016/j.beem.2015.04.008.
[11] J.E. Blümel, P. Chedraui, G. Baron, E. Belzares, A. Bencosme, A. Calle, L. Danckers, M.T. Espinoza, D. Flores, G. Gomez, J.A. Hernandez-Bueno, H. Izaguirre, P. Leon-Leon, S. Lima, E. Mezones-Holguin, A. Monterrosa, D. Mostajo, D. Navarro, E. Ojeda, W. Onatra, M. Royer, E. Soto, K. Tserotas, M.S. Vallejo, Collaborative Group for Research of the Climacteric in Latin America (REDLINC), Menopausal symptoms appear before the menopause and persist 5 years beyond: a detailed analysis of a multinational study, Climacteric 15 (2012) 542–551, https://doi.org/10.3109/13697137.2012.658462.
[12] J.E. Blümel, S. Palacios, D. Legorreta, M.S. Vallejo, S. Sarra, Is fibromyalgia part of the climacteric syndrome? Maturitas 73 (2012) 87–93, https://doi.org/10.1016/j.maturitas.2012.06.001.
[13] M. Perelló, A. Giovambattista, D. Castrogiovanni, R.C. Gaillard, E. Spinedi, Modulatory role of the ovarian function in neuroimmunoendocrine axis activity, Neuroimmunomodulation 18 (2011) 19–27, https://doi.org/10.1159/000314608.
[14] M.R. Gubbels Bupp, Sex, the aging immune system, and chronic disease, Cell. Immunol. 294 (2015) 102–110, https://doi.org/10.1016/j.cellimm.2015.02.002.
[15] J.M. Cyranowski, E. Frank, E. Young, M.K. Shear, Adolescent onset of the gender difference in lifetime rates of major depression: a theoretical model, Arch. Gen. Psychiatry 57 (2000) 21–27, https://doi.org/10.1001/archpsyc.57.1.21.
[16] A.J. Baxter, K.M. Scott, A.J. Ferrari, R.E. Norman, T. Vos, H.A. Whiteford, Challenging the myth of an "epidemic" of common mental disorders: trends in the global prevalence of anxiety and depression between 1990 and 2010, Depress. Anxiety 31 (2014) 506–516, https://doi.org/10.1002/da.22230.
[17] A. Fekadu, S.C. Wooderson, K. Markopoulo, C. Donaldson, A. Papadopoulos, A. J. Cleare, What happens to patients with treatment-resistant depression? A systematic review of medium to long term outcome studies, J. Affect. Disord. 116 (2009) 4–11, https://doi.org/10.1016/j.jad.2008.10.014.
[18] N. Bekku, H. Yoshimura, Animal model of menopausal depressive-like state in female mice: prolongation of immobility time in the forced swimming test following ovariectomy, Psychopharmacology (Berl.) 183 (2005) 300–307, https://doi.org/10.1007/s00213-005-0179-0.
[19] P. Heydarpour, M. Salehi-Sadaghiani, M. Javadi-Paydar, R. Rahimian, G. Fakhfouri, M. Khosravi, S. Khoshkish, M.H. Gharedaghi, M. Ghasemi, A. R. Dehpour, Estradiol reduces depressive-like behavior through inhibiting nitric oxide/cyclic GMP pathway in ovariectomized mice, Horm. Behav. 63 (2013) 361–369, https://doi.org/10.1016/j.yhbeh.2012.12.005.
[20] L.-H. Li, Z.-C. Wang, J. Yu, Y.-Q. Zhang, Ovariectomy results in variable changes in nociception, mood and depression in adult female rats, PLoS One 9 (2014) e94312, https://doi.org/10.1371/journal.pone.0094312.
[21] J.B. Calixto, R. Medeiros, E.S. Fernandes, J. Ferreira, D.A. Cabrini, M.M. Campos, Kinin B1 receptors: key G-protein-coupled receptors and their role in inflammatory and painful processes, Br. J. Pharmacol. 143 (2004) 803–818, https://doi.org/10.1038/sj.bjp.0706012.
[22] A.F. Viana, I.S. Maciel, F.N. Dornelles, C.P. Figueiredo, J.M. Siqueira, M. M. Campos, J.B. Calixto, Kinin B1 receptors mediate depression-like behavior response in stressed mice treated with systemic E. Coli lipopolysaccharide, J. Neuroinflammation 7 (2010) 98, https://doi.org/10.1186/1742-2094-7-98.
[23] R.C. Dutra, A.F. Bento, D.F.P. Leite, M.N. Manjavachi, R. Marcon, M.A. Bicca, J. B. Pesquero, J.B. Calixto, The role of kinin B1 and B2 receptors in the persistent pain induced by experimental autoimmune encephalomyelitis (EAE) in mice: evidence for the involvement of astrocytes, Neurobiol. Dis. 54 (2013) 82–93, https://doi.org/10.1016/j.nbd.2013.02.007.
[24] R. Marcon, R.F. Claudino, R.C. Dutra, A.F. Bento, E.C. Schmidt, Z.L. Bouzon, R. Sordi, R.L.T. Morais, J.B. Pesquero, J.B. Calixto, Exacerbation of DSS-induced colitis in mice lacking kinin B(1) receptors through compensatory up-regulation of kinin B(2) receptors: the role of tight junctions and intestinal homeostasis, Br. J. Pharmacol. 168 (2013) 389–402, https://doi.org/10.1111/j.1476-5381.2012.02136.x.
[25] L.M.F. Leeb-Lundberg, F. Marceau, W. Müller-Esterl, D.J. Pettibone, B.L. Zuraw, International union of pharmacology. XLV. Classification of the kinin receptor family: from molecular mechanisms to pathophysiological consequences, Pharmacol. Rev. 57 (2005) 27–77, https://doi.org/10.1124/pr.57.1.2.
[26] M.M. Campos, P.C. Leal, R.A. Yunes, J.B. Calixto, Non-peptide antagonists for kinin B1 receptors: new insights into their therapeutic potential for the management of inflammation and pain, Trends Pharmacol. Sci. 27 (2006) 646–651, https://doi.org/10.1016/j.tips.2006.10.007.
[27] J. Ferreira, M.M. Campos, R. Araújo, M. Bader, J.B. Pesquero, J.B. Calixto, The use of kinin B1 and B2 receptor knockout mice and selective antagonists to characterize the nociceptive responses caused by kinins at the spinal level, Neuropharmacology 43 (2002) 1188–1197, https://doi.org/10.1016/s0028-3908(02)00311-8.
[28] R. Costa, E.M. Motta, R.C. Dutra, M.N. Manjavachi, A.F. Bento, F.R. Malinsky, J. B. Pesquero, J.B. Calixto, Anti-nociceptive effect of kinin B and B receptor antagonists on peripheral neuropathy induced by paclitaxel in mice, Br. J. Pharmacol. 164 (2011) 681–693, https://doi.org/10.1111/j.1476-5381.2011.01408.x.
[29] B. Ongali, F. Hellal, D. Rodi, M. Plotkine, C. Marchand-Verrecchia, D. Pruneau, R. Couture, Autoradiographic Analysis of Mouse Brain Kinin B1 and B2 Receptors after Closed Head Trauma and Ability of Anatibant Mesylate to Cross the Blood–Brain Barrier, J. Neurotrauma 23 (2006) 696–707, https://doi.org/10.1089/neu.2006.23.696.
[30] R.D.S. Prediger, R. Medeiros, P. Pandolfo, F.S. Duarte, G.F. Passos, J.B. Pesquero, M.M. Campos, J.B. Calixto, R.N. Takahashi, Genetic deletion or antagonism of kinin B(1) and B(2) receptors improves cognitive deficits in a mouse model of Alzheimer's disease, Neuroscience 151 (2008) 631–643, https://doi.org/10.1016/j.neuroscience.2007.11.009.
[31] Y.M. Naaldijk, M.C. Bittencourt, U. Sack, H. Ulrich, Kinins and microglial responses in bipolar disorder: a neuroinflammation hypothesis, Biol. Chem. 397 (2016), https://doi.org/10.1515/hsz-2015-0257.
[32] S.R. Chaplan, F.W. Bach, J.W. Pogrel, J.M. Chung, T.L. Yaksh, Quantitative assessment of tactile allodynia in the rat paw, J. Neurosci. Methods 53 (1994) 55–63.
[33] C.P. Klein, N.D.M. Sperotto, I.S. Maciel, C.E. Leite, A.H. Souza, M.M. Campos, Effects of D-series resolvins on behavioral and neurochemical changes in a fibromyalgia-like model in mice, Neuropharmacology 86 (2014) 57–66, https://doi.org/10.1016/j.neuropharm.2014.05.043.
[34] W.J. Dixon, Efficient analysis of experimental observations, Annu. Rev. Pharmacol. Toxicol. 20 (1980) 441–462, https://doi.org/10.1146/annurev.pa.20.040180.002301.
[35] L. Steru, R. Chermat, B. Thierry, P. Simon, The tail suspension test: a new method for screening antidepressants in mice, Psychopharmacology (Berl.) 85 (1985) 367–370.
[36] N.L.M. Quintão, G.F. Passos, R. Medeiros, A.F. Paszcuk, F.L. Motta, J.B. Pesquero, M.M. Campos, J.B. Calixto, Neuropathic pain-like behavior after brachial plexus avulsion in mice: the relevance of kinin B1 and B2 receptors, J. Neurosci. 28 (2008) 2856–2863, https://doi.org/10.1523/JNEUROSCI.4389-07.2008.
[37] A.H. Clayton, P.T. Ninan, Depression or menopause? Presentation and management of major depressive disorder in perimenopausal and postmenopausal women, Prim. Care Companion J. Clin. Psychiatry (2010), https://doi.org/10.4088/PCC.08r00747blu.
[38] S.F. da, S. Moreira, E.A. Nunes, J. Kuo, I.C. de Macedo, A. Muchale, C. de Oliveira, V.L. Scarabelot, P.R. Marques Filho, L.F. Medeiros, W. Caumo, I.L.S. Torres, Hypoestrogenism alters mood: ketamine reverses depressive-like behavior induced by ovariectomy in rats, Pharmacol. Rep. 68 (2016) 109–115, https://doi.org/10.1016/j.pharep.2015.06.009.

[39] V. Benedusi, C. Meda, S. Della Torre, G. Monteleone, E. Vegeto, A. Maggi, A lack of ovarian function increases neuroinflammation in aged mice, Endocrinology 153 (2012) 2777–2788, https://doi.org/10.1210/en.2011-1925.
[40] K.-Y. Shivers, N. Amador, L. Abrams, D. Hunter, S. Jenab, V. Quiñones-Jenab, Estrogen alters baseline and inflammatory-induced cytokine levels independent from hypothalamic–pituitary–adrenal axis activity, Cytokine 72 (2015) 121–129, https://doi.org/10.1016/j.cyto.2015.01.007.
[41] A. Au, A. Feher, L. McPhee, A. Jessa, S. Oh, G. Einstein, Estrogens, inflammation and cognition, Front. Neuroendocrinol. 40 (2016) 87–100, https://doi.org/10.1016/j.yfrne.2016.01.002.
[42] A. Stubelius, A. Andersson, U. Islander, H. Carlsten, Ovarian hormones in innate inflammation, Immunobiology 222 (2017) 878–883, https://doi.org/10.1016/j.imbio.2017.05.007.
[43] I. Brusco, A.B. Justino, C.R. Silva, S. Fischer, T.M. Cunha, R. Scussel, R. A. Machado-de-Ávila, J. Ferreira, S.M. Oliveira, Kinins and their B1 and B2 receptors are involved in fibromyalgia-like pain symptoms in mice, Biochem. Pharmacol. 168 (2019) 119–132, https://doi.org/10.1016/j.bcp.2019.06.023.
[44] J.B. Calixto, D.A. Cabrini, J. Ferreira, M.M. Campos, Kinins in pain and inflammation, Pain 87 (2000) 1–5, https://doi.org/10.1016/s0304-3959(00)00335-3.
[45] J. Sheng, S. Liu, Y. Wang, R. Cui, X. Zhang, The link between depression and chronic pain: neural mechanisms in the brain, Neural Plast. 2017 (2017) 9724371, https://doi.org/10.1155/2017/9724371.
[46] E. Vegeto, S. Belcredito, S. Etteri, S. Ghisletti, A. Brusadelli, C. Meda, A. Krust, S. Dupont, P. Ciana, P. Chambon, A. Maggi, Estrogen receptor- mediates the brain antiinflammatory activity of estradiol, Proc. Natl. Acad. Sci. 100 (2003) 9614–9619, https://doi.org/10.1073/pnas.1531957100.
[47] M. Umeda, S. Ichikawa, T. Kanda, H. Sumino, I. Kobayashi, Hormone replacement therapy increases plasma level of angiotensin II in postmenopausal hypertensive women, Am. J. Hypertens. 14 (2001) 206–211, https://doi.org/10.1016/s0895-7061(00)01253-x.
[48] E.G. Erdös, F. Tan, R.A. Skidgel, Angiotensin I-converting enzyme inhibitors are allosteric enhancers of kinin B1 and B2 receptor function, Hypertension 55 (2010) 214–220, https://doi.org/10.1161/HYPERTENSIONAHA.109.144600.
[49] J.P. Dias, H.D.B. Gariépy, B. Ongali, R. Couture, Brain kinin B1 receptor is upregulated by the oxidative stress and its activation leads to stereotypic nociceptive behavior in insulin-resistant rats, Peptides 69 (2015) 118–126, https://doi.org/10.1016/j.peptides.2015.04.022.
[50] A. Nokkari, H. Abou-El-Hassan, Y. Mechref, S. Mondello, M.S. Kindy, A.A. Jaffa, F. Kobeissy, Implication of the Kallikrein-Kinin system in neurological disorders: quest for potential biomarkers and mechanisms, Prog. Neurobiol. 165–167 (2018) 26–50, https://doi.org/10.1016/j.pneurobio.2018.01.003.
[51] R.U. Parekh, J. Robidoux, S. Sriramula, Kinin B1 Receptor Blockade Prevents Angiotensin II-induced Neuroinflammation and Oxidative Stress in Primary Hypothalamic Neurons, Cell. Mol. Neurobiol. 40 (2020) 845–857, https://doi.org/10.1007/s10571-019-00778-1.
[52] I. Eren, M. Naziroğlu, A. Demirdaş, O. Celik, A.C. Uğuz, A. Altunbaşak, I. Ozmen, E. Uz, Venlafaxine modulates depression-induced oxidative stress in brain and medulla of rat, Neurochem. Res. 32 (2007) 497–505, https://doi.org/10.1007/s11064-006-9258-9.
[53] S.B. Doshi, A. Agarwal, The role of oxidative stress in menopause, J. Midlife Health 4 (2013) 140–146, https://doi.org/10.4103/0976-7800.118990.
[54] M.J. Ramírez-Expósito, E. Sánchez-López, C. Cueto-Ureña, B. Dueñas, P. Carrera-González, J. Navarro-Cecilia, M.D. Mayas, J.M. Arias de Saavedra, R. Sánchez-Agesta, J.M. Martínez-Martos, Circulating oxidative stress parameters in pre- and post-menopausal healthy women and in women suffering from breast cancer treated or not with neoadjuvant chemotherapy, Exp. Gerontol. 58 (2014) 34–42, https://doi.org/10.1016/j.exger.2014.07.006.