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Effect of Pregabalin and Gabapentin on Nociceptive Behaviors Induced by Spinal Nerve Ligation

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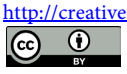


Abstract

Pain is defined as an unpleasant sensory and emotional experience, associated with actual or potential tissue damage. According to its neurobiological mechanism, pain is classified into nociceptive, inflammatory, dysfunctional, and neuropathic. Neuropathic pain (NP) is caused by a lesion or disease of the somatosensory nervous system. Both pregabalin and gabapentin are pharmaceuticals used as validation drugs in experimental models of NP. Pregabalin was shown to produce significant antihyperalgesic and antiallodynic effects. Gabapentin is used as a reference compound for new analgesics and reduces tactile allodynia in rats. The aim of this work is to evaluate pregabalin and gabapentin effects on nociceptive behaviors induced by spinal nerve ligation (SNL). Female Wistar rats of 140 - 160 g were used, divided into five groups: Naive, SHAM, SNL rats treated with saline solution, SNL rats treated with pregabalin 30 mg/kg p.o., SNL rats treated with gabapentin 300 mg/kg p.o. Nociceptive behaviors were determined by the up and down method. In the establishment of SNL-induced allodynic behavior, a reduction in paw withdrawal threshold was observed in the time course, which was present from day 1 and it was maintained for 28 days post-ligation. With the administration of pregabalin and gabapentin, anti-allodynic behavior was observed in the time course and in the areas under the curve (AUC) of the time course of anti-allodynic behavior, significant difference was observed between pregabalin, and gabapentin groups compared to vehicle with a value of $p < 0.0001$. The results showed pregabalin and gabapentin induce an antinociceptive effect in rats subjected to SNL.

Keywords

Tactile Allodynia, Neuropathic Pain, Pregabalin, Gabapentin

1. Introduction

The International Association for the Study of Pain (IASP) defines neuropathic pain as "pain caused by a lesion or disease of the somatosensory nervous system" [1], both in the central and peripheral nervous system, affecting the neuromodulatory mechanisms of the nociceptive transmission pathways. Neuropathic pain is classified as central, originating from damage to the brain or spinal cord, or peripheral, originating from damage to the peripheral nerve, plexus, dorsal root ganglion or root [2]. Currently, the use of gabapentin, pregabalin and tricyclic antidepressants as first line treatment for neuropathic pain is recommended with a strong degree of evidence [3]. They are indicated in the treatment of neuropathic pain in adults. Gabapentin increases the concentration of the neurotransmitter of γ-aminobutyric acid (GABA) in the brain. GABA acts as a calming agent and balances nerve activity by preventing rapid and repeated nerve discharges [4], on the other hand pregabalin is an analog of GABA, structurally related to gabapentin. It binds to the auxiliary subunit of voltage-dependent calcium channels, reducing calcium entry into nerve endings and, consequently, decreasing the release of excitatory neurotransmitters [5]. In the case of pregabalin (PGB) it has been shown to produce significant antihyperalgesic and antiallodynic effects in experimental animal models of neuropathic pain [6], gabapentin (GBP) is also used as a drug in neuropathic pain models and as a reference compound for new analgesics [7]. In addition, other authors suggest that it improves nerve remyelination after chronic constriction of the sciatic nerve (CCI), a model of neuropathic pain [8]; these drugs reduce tactile allodynia in rodents [9] [10] and are effective in 50% - 60% of treated patients, so the aim of this study was to determine the effect of pregabalin and gabapentin on nociceptive behaviors induced by spinal nerve ligation.

2. Materials and Methods

2.1. Drugs

Pregabalin (Ultra Laboratorios Mexico), was dissolved in saline solution (0.9%) for administration in a volume of 4 ml/kg at a dose of (30 mg/kg p.o.).

Gabapentin (Laboratorio AMSA Mexico) was dissolved in saline solution (0.9%) for administration in a volume of 4 ml/kg at a dose of (300 mg/kg p.o.).

2.2. Animals

Female Wistar rats weighing (6 - 7 weeks, 140 - 160 g) since L5/L6 spinal nerve ligation produces tactile allodynia in male and female Wistar rats, and there is no difference in the manifestation of neuropathic pain between both [11]. The

rats were maintained under controlled environmental conditions of temperature (21˚C ± 1˚C) and 12:12 light-dark cycles, with access to purified water and food on demand throughout the experimental phase.

All experiments were performed according to international guidelines on ethical aspects of experimental pain research in animals [12], the Mexican standard NOM-062-1999, 2002. This project was tested by the Internal Committee for the Use and Care of Laboratory Animals (CICUAL 03-2019).

2.3. Measurement of Antiallodynic Activity

For the induction of experimental neuropathic pain, the spinal nerve ligation (SNL) model described by Kim and Chung in 1992 [13] was used. Generally, rats were anesthetized with a mixture of ketamine (50 mg/kg, i.p.) and xylazine (10 mg/kg, i.p.) and a dorsal midline incision was made at the iliac crests 0.5 cm in the cephalic direction and 1 cm in the caudal direction. Subsequently, an incision was made in the spinal muscle, (1 cm in cephalic direction and 0.5 cm in caudal direction) the transverse process of the lumbar vertebra L6 was located and removed. The L5 and L6 spinal nerves were exposed and ligated with 6-0 silk suture. For sham-operated rats (SHAM), the nerves were exposed, but not ligated. Rats not demonstrating allodynia were not further studied. These represented less than 5% of the animals used.

The animals were then transferred to plastic crates on wire mesh for 30 to 45 min for habituation. Tactile allodynia was measured according to the method of Chaplan [14] (Stoelting, Wood Dale, IL, USA). This test consisted of applying mechanical pressure by means of calibrated filaments (0.008 g to 300 g) on the medial area of the plantar region of the left (ipsilateral) hind paw. The evaluation started with the (2 g) filament and pressure was maintained for at least 8 seconds. When the rat withdrew the paw before the pressure, it was considered as a positive response of allodynia and the evaluation was continued with the following filament of lower grammage, the rats that did not withdraw the paw before the pressure; were considered as a negative response of allodynia and the evaluation was continued with the following filament of higher grammage, only 6 responses were counted, which started from the first change from negative to positive.

Tactile allodynia was considered present when 50% of the paw withdrawal threshold was less than 4 grams of force. The 50% withdrawal threshold was determined using the up and down method [15]. The evaluation of allodynia with the administration of drugs was evaluated from (time 0) followed by the administration of the corresponding drugs, 30 min later and every hour thereafter, at hour 4 the animals were transferred to their box and climbed on the wire mesh 30 minutes before 6 hours to continue with the evaluation until 6 h were reached.

2.4. Study Design

Rats received vehicle (saline) or doses of pregabalin (30 mg/kg p.o.) or gabapen-

tin (300 mg/kg p.o.). Doses were selected based on studies by Pineda-Farias *et al.* 2017 [16].

3. Static Analysis

Behavioral results were presented as the mean ± standard error (SEM) of 6 animals per group (n = 6). The 50% withdrawal threshold was plotted as a function of time. Subsequently, the area under the curve (ABC) of each time course was determined using the trapezoid method and the mean ± SEM of each group was plotted. The anti-allodynic effect was expressed as the percentage of maximum possible effect (%MPE) of the ABCs of each individual rat with the following: Equation (1):

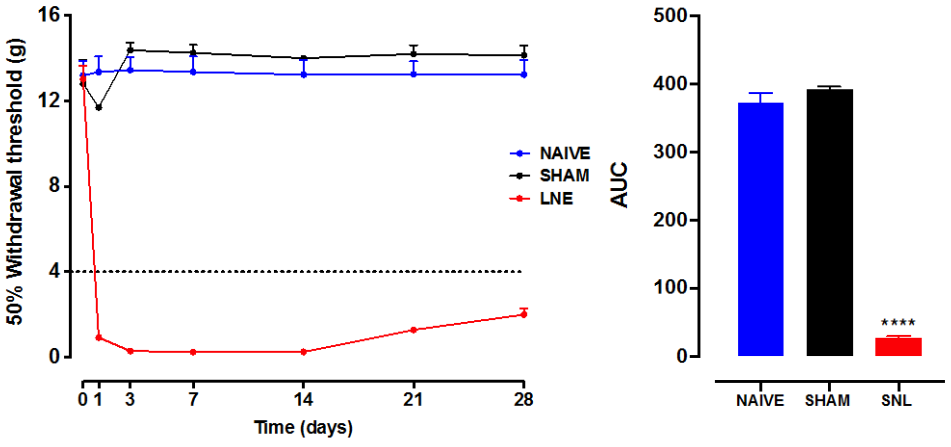
$$\%\text{MPE} = \frac{\text{AUC}_{\text{Compound}} - \text{AUC}_{\text{Vehicle}}}{\text{AUC}_{\text{Vehicle}} - \text{AUC}_{\text{Sham}}} \times 100 \quad (1)$$

To determine differences between groups, one-way or two-way analysis of variance (ANOVA) followed by Dunnett's test was performed. For all cases, a P value less than 0.05 was considered significant. All analyses and graphs were performed with the statistical program GraphPad Prism 8.0 (GraphPad Inc. San Diego, CA).

4. Results

4.1. Standardization of the Spinal Nerve Ligation (SNL) Model

The results showed in the time course of the establishment of allodynic behavior induced by spinal nerve ligation, a reduction of the paw withdrawal threshold, which occurred from day 1 and was maintained for 28 days post-ligation (**Figure 1(A)**). The area under the curve showed a significant difference between the



(A) (B)

Figure 1. Time course of the establishment of tactile allodynic behaviour induced by spinal nerve ligation (SNL). Each value is expressed as mean ± SEM. Time course of tactile allodynia showed a reduction in the paw withdrawal threshold of LNE rats. (A) The area under the curve the bars represent mean ± SEM (n = 6). ****p < 0.0001 vs. NAÏVE and SHAM groups, as determined by ANOVA (B).

NAIVE and SHAM groups compared to the SNL group, with a value with a P value of <0.05. The NAIVE group compared to SHAM showed no significant difference. SNL group, with a value of $P < 0.05$, however the NAIVE group compared to SHAM showed no significant difference, as determined by ANOVA followed by Tukey's test (Figure 1(B)). Based on these data, it was decided to perform the pharmacological treatment with the drugs and/or vehicle 14 days post-ligation of the spinal nerves.

4.2. Effects of Pregabalin and Gabapentin

In the time course of administration of pregabalin as positive controls at a dose of 30 mg/kg and gabapentin at a dose of 300 mg/kg, antiallodynic behavior of both drugs was observed (Figure 2(A)).

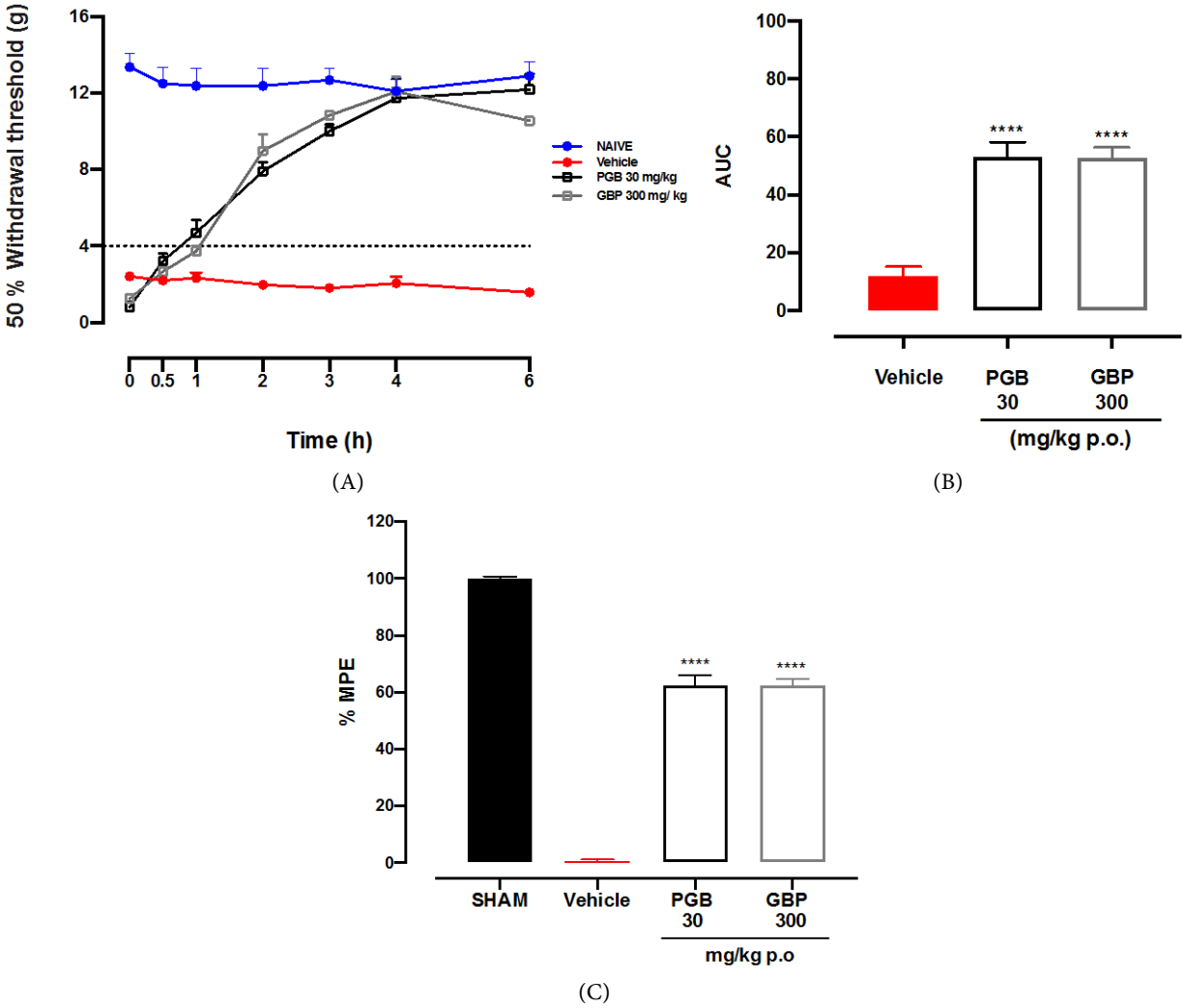


Figure 2. Treatment with pregabalin and gabapentin after spinal nerve ligation. Each value is expressed as mean ± SEM. Time course antinociceptive effect of pregabalin (PGB) and gabapentin (GBP) in rats submitted to spinal nerve ligation (A), Orally administered doses of pregabalin and gabapentin, represented as area under the curve, **** represents the statistically significant dose with respect to the vehicle control group (saline) $p < 0.0001$ (B). Data are expressed as percentage of activity against allodynia, considering the maximum possible effect (%MPE). Bars represent mean ± SEM (n = 6). ****$p < 0.0001$ vs. vehicle group, as determined by ANOVA (C).

In the areas under the curve, a significant difference was observed between the pregabalin, and gabapentin groups compared to vehicle ($P < 0.0001$), determined by ANOVA followed by Dunnett's test (**Figure 2(B)**).

To evaluate the effect of pregabalin and gabapentin, the results were expressed as the percentage of maximum possible effect (%MPE) of the areas under the curve of each individual rat. The administration of pregabalin at a dose of 30 mg/kg and gabapentin at a dose of 300 mg/kg orally, generated a significant antiallodynic effect decreasing allodynia, at 62.51% and 62.39% respectively **(Figure 2(C)**).

5. Discussion

The main objective of this project was to evaluate effect of pregabalin and gabapentin in rats with neuropathic pain induced by spinal nerve ligation. This experimental model was used to obtain pharmacological evidence of pregabalin and gabapentin and determine their on SNL-induced nociceptive behavior and was shown to reduce paw withdrawal threshold in the tactile allodynia test by the up and down method. In addition, this study showed that sham-operated rats (SHAM) group had no significant difference compared to the healthy rats (NAIVE) group. However, a reduction of the withdrawal threshold occurred on day 1 post-surgery in the sham-operated rats, but on day 2 post-surgery the threshold increased and was maintained until day 28. This resembles other rodent models of neuropathic pain using sham surgery control procedures that cause deep tissue damage expecting sham surgeries to induce potentially long-lasting post-surgical pain, however a persistent improvement in pain avoidance behavior after sham surgeries has been demonstrated for models of neuropathic pain [17] [18].

On the other hand, gabapentinoids bind to the $\alpha 2\text{-}\delta$ subunit of voltage-activated calcium channels [19], are primarily anticonvulsant drugs and have been shown to be clinically effective in neuropathic pain conditions [20] [21].

It is known so far that the most accepted mechanism of action is a complex synergy between increased GABA synthesis and NMDA receptor antagonism, however, the identification of specific binding at the $\alpha 2\text{-}\delta$ subunit of voltage-dependent calcium channels (VDCC) [22], suggested that the antinociceptive action of gabapentinoids was mediated by an attenuation of Ca^{2+} channel influx into cells [23]. In addition, it has been manifested in the reduction of the release of neurotransmitters such as glutamate, substance P, and norepinephrine [24] [25].

In vivo, gabapentinoids inhibit the hyperactivity of wide dynamic range neurons of the dorsal horn in different models of neuropathic pain, which may be involved in the decrease of excitatory amino acid release [26] [27].

Likewise, other studies have shown that gabapentin inhibits the formalin-induced increase in spinal aspartate and glutamate release in a chronic constriction injury model of neuropathic pain [28].

In addition, gabapentin, pregabalin are administered long-term in conditions

such as epilepsy [29], neuropathic pain [30] and fibromyalgia [31].

However, in this study we administered pregabalin and gabapentin in a model of neuropathic pain induced by spinal nerve ligation, and evaluated their effect by observing that the administration of pregabalin and gabapentin increased the withdrawal threshold in rats with spinal nerve ligation, We also analyzed the percentage of maximum possible effect represented as (%MPE), observing that pregabalin generated a significant antiallodynic effect decreasing allodynia in 62.51% and gabapentin in 62.39%. This demonstrates its antinociceptive effects on the behaviors induced by nerve lesion.

Therefore, it is considered that the analgesic action of pregabalin and gabapentin is highly related because they share the specific and high affinity binding site of high affinity $\alpha 2\text{-}\delta$ (calcium channel protein) of voltage-activated calcium channels, or Cav$\alpha 2\text{-}\delta$ located especially in the synapses inducing a decrease in the release of neurotransmitters in the synapses [32].

6. Conclusion

According to the findings shown in the present study, it can be inferred that both gabapentin and pregabalin administered orally attenuate the nociceptive behavior manifested in a rat model of neuropathic pain by reducing the tactile allodynia induced by spinal nerve ligation. In this study after 2 hours of administration of both drugs the increased paw withdrawal threshold was maintained until the 6 hours test. It demonstrates the antihyperalgesic efficacy of gabapentinoids. The present study confirms that oral administration of gabapentinoids could contribute to improving neuropathic pain in rats. Furthermore, these molecules may be useful for all those processes in which the nervous system is involved.

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Conflicts of Interest

There is no conflict of interest in this study.

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