Pharmacology, Biochemistry and Behavior 94 (2009) 51–55

Contents lists available at ScienceDirect

Pharmacology, Biochemistry and Behavior

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

Systemic amitriptyline administration does not prevent the increased thermal response induced by paradoxical sleep deprivation

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ARTICLE INFO

Article history:
Received 27 January 2009
Received in revised form 3 June 2009
Accepted 12 July 2009
Available online 17 July 2009

Keywords:
Sleep deprivation
Pain
Antidepressants

ABSTRACT

Sleep deprivation has been associated with hyperalgesia in humans and in animal models. The tricyclic antidepressant amitriptyline is used as an analgesic drug in patients and in animal models of chronic pain, including that associated with spinal nerve injury. Pain hypersensitivity following paradoxical sleep deprivation (PSD) and that following peripheral nerve injury seem to share common spinal mechanisms. Accordingly, we evaluated the effects of amitriptyline (acutely and chronically administered) on the increased thermal response observed in PSD rats (72 or 96 h). Rats were evaluated for thermal sensitivity using a hot plate (52 °C or 46 °C) at 1 or 24 h after the last administration of the drug. Following the hot plate test, motor behavior was analyzed in an open field arena for a period of 5 min. Paw withdrawal latency response to temperatures of 46 °C and 52 °C was significantly lower in PSD and in 24-hour post-PSD rats than in controls and it was not modified by amitriptyline (3, 10 and 30 mg/kg). Analgesic effects and reduced motor behavior were only observed in control groups. Overall, these findings indicate that a period of PSD can influence pain modulatory mechanisms, and that amitriptyline action is insufficient to reduce PSD-enhanced thermal sensitivity.

1. Introduction

Increased pain sensitivity is frequently reported after periods of sleep deprivation. Currently, prevalent lifestyles often result in sleep restriction in humans; the paradoxical sleep/rapid eye movement (PS/REM) phase is the most affected, since it occurs in the second half of the night. Paradoxical sleep deprivation (PSD) can induce hyperalgesia (Roehrs et al., 2006). Sleep disturbances such as sleepiness and insomnia are also common in patients with chronic pain (Zgierska et al., 2007; Ohayon, 2005; Smith and Haythornthwaite, 2004).

A bidirectional relationship between sleep and pain has also been reported in animal studies. Pain-related behavioral responses of male rats subjected to 72 h of PSD were significantly increased when challenged with noxious mechanical, thermal, and electrical stimuli (Onen et al., 2001). Rats with peripheral neuropathy induced by sciatic nerve constriction also exhibit a poor quality of sleep with reduced sleep efficiency (Andersen and Tufik, 2003), highlighting the influence of painful conditions on sleep patterns. Hence, the relationship between poor sleep and pain seems to be reciprocal and may explain why some pathological conditions that result in a reduction of sleep can also lead to a hyperalgesic state, impairing the therapeutic effects of some analgesic compounds. In fact, PSD also reduces morphine antinociception (Nascimento et al., 2007). Paradoxical sleep deprivation produces changes in several neurotransmitter systems, and it is believed that modulation of pain and sleep–wake regulation share common neurotransmitters such as the central serotonergic and noradrenergic systems (Foo and Mason, 2003). However, the basic mechanisms governing sleep-induced alterations in pain sensitivity are unknown.

The analgesic properties of antidepressant drugs have been known for more than 40 years (Paolo et al., 1960). Antidepressants are typically used for different types of neuropathic pain such as fibromyalgia (Arnold, 2007; O'Malley et al., 2000), postherpetic neuralgia (Zin et al., 2008), central post-stroke pain (Frese et al., 2006; Hansson, 2004), spinal cord injury pain (Baastrup and Finnerup, 2008; Rintala et al., 2007) and diabetic neuropathic pain (Kajdasz et al., 2007; Wong et al., 2007; Raskin et al., 2006) when classical analgesics such as non-steroidal anti-inflammatory drugs (NSAIDs) and opiates fail to alleviate pain. In most of these cases, tricyclic antidepressants (TCAs) are the first choice for treatment (Saarto and Wiffen, 2007; Sindrup et al., 2005). In animal neuropathic pain models such as sciatic nerve injury (Mochizucki, 2004), chronic constriction injury (Bomholt et al., 2005) and segmental spinal nerve ligation (Wei et al., 2007), chronic (7 days) administration of amitriptyline, a tricyclic antidepressant also decreases sensitivity to noxious test stimulation (McCarson et al., 2005). This analgesic effect occurs through amitriptyline's ability to inhibit the presynaptic reuptake of the biogenic amines serotonin and noradrenalin, as well

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doi:10.1016/j.pbb.2009.07.005

as through other mechanisms including N-methyl-D-aspartate receptor and ion channel blockade.

Recent studies have demonstrated that similar spinal mechanisms involving nitric oxide and the mGluR5 contribute to mechanical noxious stimuli hypersensitivity following both peripheral nerve injury and PSD. These results suggest that the same descending facilitatory or disinhibitory pathways are involved in mechanical hypersensitivity in sleep-deprived and in nerve-injured animals (Wei et al., 2007). Similarly, Wei and collaborators found that normal pain sensitivity and sleep deprivation-induced hypersensitivity were reduced by intrathecal administration of a 5-HT1A receptor antagonist (WAY-100635), a 5-HT2C receptor antagonist (RS-102221), and a 5-HT1A receptor agonist (8-OHDPAT) (Wei et al., 2008). These results suggest that spinal cord serotonergic receptors play a role in pain hypersensitivity of PSD rats.

Since the pain hypersensitivity induced by PSD and peripheral nerve injury seem to share common mechanisms and since serotonergic selective drugs reduce the pain hypersensitivity of PSD rats, amitriptyline (an effective analgesic drug in chronic pain models) is expected to prevent pain-related behavior following PSD. The purpose of this study was to investigate the effects of amitriptyline on increased responses to thermal noxious stimuli exhibited by animals exposed to different periods of PSD.

2. Materials and methods

2.1. Animals

Adult male Wistar rats (300–350 g) from our own colony were used. The animals were housed in cages with free access to food and water in a room under controlled light/dark cycle conditions (12 h light/12 h dark; lights on at 6:00 a.m.) and ambient temperature (23 ± 1 °C).

2.2. Paradoxical sleep deprivation

PSD was achieved using the flower pot technique. Rats were housed individually in tanks and placed on single narrow circular platforms (6.5 cm diameter) surrounded by water up to 1 cm beneath the surface. When the animal enters the paradoxical sleep phase, it falls into the water due to muscle atonia, and awakens. With this technique, paradoxical sleep is completely eliminated during the four-day period. Furthermore, slow wave sleep is also reduced; this, however does not lead to rebound sleep (Machado et al., 2004; Maloney et al., 2000). The control group was maintained individually in cages in the same room and conditions for the same period of time as the experimental group. The animals were provided with food and water ad libitum. All animal studies were conducted in accordance with principles and procedures approved by the Animal Care Committee of the Universidade do Estado do Rio de Janeiro.

2.3. Hot plate test

The hot plate test was used to measure changes in nociceptive threshold upon thermal stimulation, following the procedure described by Eddy and Leimbach (1953). The animals were placed above a hot plate unit (Letica Scientific Instruments, Barcelona, Spain) warmed to 52 °C or 46 °C that allowed the activation of different nociceptive fibers (C and Aδ) (May et al., 2005; Yeomans et al., 1996). The experiments were videotaped and evaluated by two independent, blind observers. The results represent the mean latency of removing one of the hindpaws from the hot apparatus (in seconds). To avoid paw damage, a cutoff of 30 s was established.

2.4. Open field test

The open field test was conducted as previously described (Broadhurst, 1957). The open field arena (60 × 60 cm) was divided into 16 equal squares. The animals were placed at the corner of the arena and allowed to explore for 5 min. The exploratory behavior was videotaped and evaluated by two independent, blind observers who assessed the number of crossed squares.

2.5. Experimental design

Amitriptyline (3, 10, and 30 mg/kg, Laboratto-Brasil) or saline was administered i.p. for 11 days. This amitriptyline dosing regimen was selected on the basis of a previous work showing that this induces behavioral and neurochemical changes in rats (McCarson et al., 2005). In the last 3 or 4 days of treatment, animals (separate groups, $n = 7$/group) were subjected to 72 or 96 h of PSD, respectively, or maintained in their home cages. Subsequently thermal sensitivity was evaluated 1 or 24 h after the last drug administration using the hot plate test (52 °C or 46 °C). In order to determine whether the highest withdrawal latencies were due to decreased locomotor activity or to an analgesic effect, the number of squares crossed during a 5 min period in an open field arena was counted immediately following the hot plate test. An additional experiment ($n = 14$, 7/group) was conducted with a single dose of amitriptyline after 96 h of PSD, followed by the hot plate test (52 °C) 1 h after acute administration.

2.6. Statistics

Data are expressed as means ± S.E.M. Statistical analyses were performed using GraphPad Prism 5.00 (GraphPad Software, Inc., USA). One-way analysis of variance (ANOVA) was used for the comparisons of the data among the doses studied followed by the Newman–Keuls test for post hoc comparison. Differences between control and PSD groups for each dose were determined by Student's unpaired two-tailed t-test. p-values less than 0.05 were considered significant.

3. Results

3.1. Thermal stimulus after 96 and 72 h of PSD

3.1.1. Noxious temperature at 52 °C

Chronic administration of amitriptyline significantly increased the latency of withdrawal from a 52 °C noxious stimulus in control animals ($F_{[3,26]} = 22.53$, $p < 0.05$) with a potent analgesic effect induced by the 30 mg/kg dose (+184%, $p < 0.001$, Newman–Keuls test, post hoc comparisons). However, no significant antinociceptive responses were observed in the 96-hour PSD group at any dose ($F_{[3,26]} = 2.818$, $p > 0.05$) (Fig. 1A).

A significant difference was observed between control and PSD animals treated with saline (−37%, $p < 0.05$), 3 mg/kg (−32%, $p < 0.05$), 10 mg/kg (−41%, $p < 0.05$), or 30 mg/kg (−67%, $p < 0.001$) of amitriptyline (Fig. 1A).

After a single-dose administration of amitriptyline, an analgesic effect in response to a 52 °C thermal noxious stimulus was not observed for any dose in control animals ($F_{[3,21]} = 0.5159$, $p > 0.05$) or PSD rats ($F_{[3,21]} = 1.076$, $p > 0.05$). However, differences observed between control and PSD groups treated with saline (−32%, $p < 0.05$) were also detected upon treatment with 3 mg/kg (−37%, $p < 0.05$), 10 mg/kg (−35%, $p < 0.05$), or 30 mg/kg (−47%, $p < 0.05$) of amitriptyline (Table 1).

In the 72-hour PSD study, significant differences between control and PSD animals in both saline- (−37%, $p < 0.05$) and 10 mg/kg-treated groups (−64%, $p < 0.05$) were observed although an apparent difference was observed between control animals treated with saline

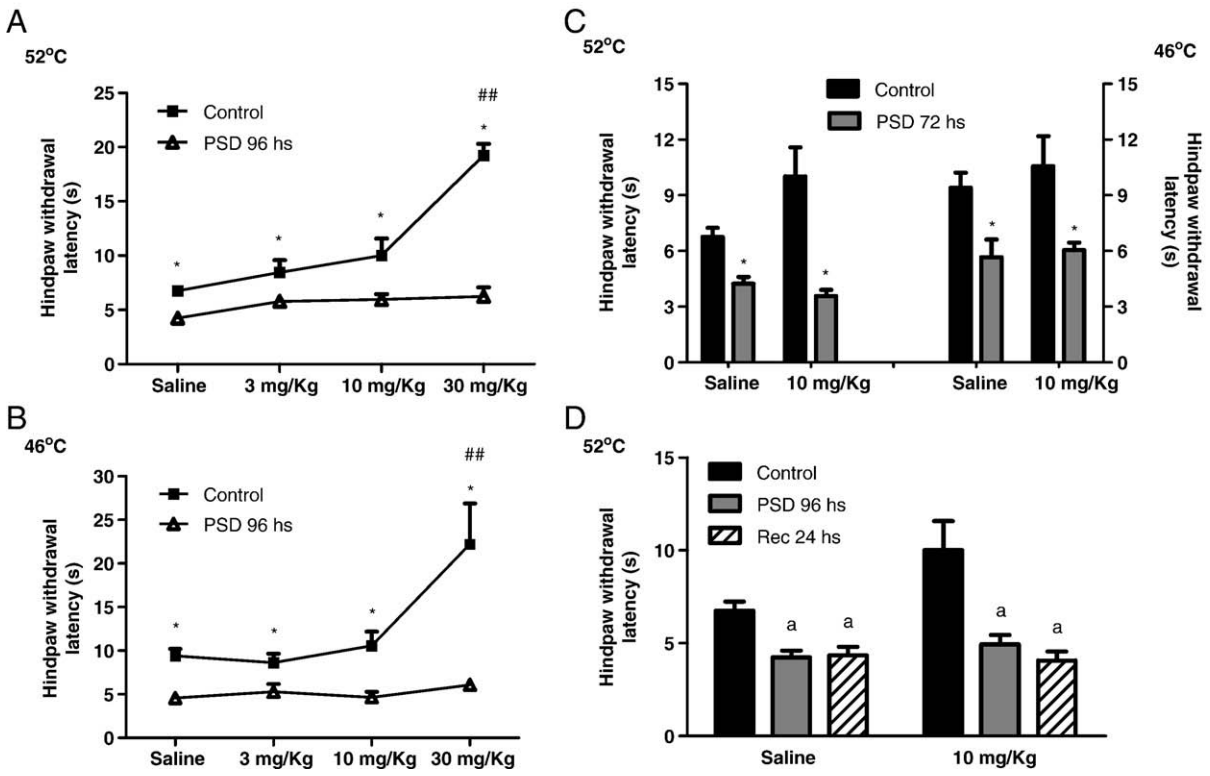

Fig. 1. Effects of chronic amitriptyline treatment on increased thermal response induced by PSD. Hindpaw withdrawal latency (s) in response to (A) 52 °C and (B) 46 °C thermal stimulation as a measure of thermal response after 96 h or (C) 72 h of PSD. (D) Hindpaw withdrawal latency (s) in response to 52 °C in control, PSD, and sleep-recovered rats. Data are presented as mean ± SEM. Seven animals were included in each group. $^{\#\#}p<0.05$ *vs.* saline, 3 mg/kg and 10 mg/kg groups (one-way ANOVA followed by Newman–Keuls test); $^{*}p<0.05$ *vs.* respective control groups (unpaired *t*-test); $^{a}p<0.05$ *vs.* control group (one-way ANOVA followed by Newman–Keuls test).

and those treated with 10 mg/kg of amitriptyline, Student's unpaired *t*-test did not reveal a statistical difference (+48%, $p>0.05$). A similar result was observed for PSD animals, in which the chronic treatment of 10 mg/kg amitriptyline did not significantly alter the hindpaw withdrawal latency as compared to saline treatment (−15%, $p>0.05$) (Fig. 1C).

3.1.2. Noxious temperature at 46 °C

A similar profile was seen when the thermal noxious stimulus was set to 46 °C. With the 30 mg/kg dose, a significant effect of chronic treatment of amitriptyline was observed in control animals ($F_{[3,22]}=8.990$, $p<0.05$) (+135%, $p<0.001$), but not in the 96 h of the PSD group ($F_{[3,21]}=1.182$, $p>0.01$) (Fig. 1B). The significant difference between control and PSD animals treated with saline (−51%, $p<0.05$) was also present when they were treated with 3 mg/kg (−38%, $p<0.05$), 10 mg/kg (−56%, $p<0.05$) or 30 mg/kg (−68%, $p<0.05$) of amitriptyline (Fig. 1B).

There was no significant difference between the control animals treated with saline or 10 mg/kg amitriptyline (+12%, $p>0.05$) and in the 72-hour PSD animals treated with saline or 10 mg/kg amitriptyline (+6%, $p>0.05$) (Student's unpaired *t*-test, $p<0.05$). A significant difference between control and 72-hour PSD rats treated with saline (−40%, $p<0.05$) or 10 mg/kg of drug (−43%, $p<0.05$) was observed (Fig. 1C).

Table 1
Effects of acute amitriptyline treatment on the hindpaw withdrawal latency in control and PSD (96 h) rats.

Groups	Saline	Amitriptyline, i.p.		
		3 mg/kg	10 mg/kg	30 mg/kg
Control	5.59 ± 0.41	6.56 ± 0.78	5.62 ± 0.47	6.24 ± 0.83
PSD	3.75 ± 0.30[a]	4.08 ± 0.31[a]	3.61 ± 0.40[a]	3.29 ± 0.31[a]

Results do not show a dose–response effect for amitriptyline in control or PSD animals, although a decrease on the hindpaw withdrawal latencies induced by PSD *vs.* control was observed in all doses evaluated. Thermal stimulation set at 52 °C. Data are shown as mean (s) ± S.E.M., $p<0.05$.
[a] Unpaired *t*-test between control and PSD rats.

3.2. Thermal stimulus 24 h after PSD

After 24 h of sleep recovery, significant differences among control, PSD, and sleep-recovered rats were observed ($F_{[2,19]}=10.78$, $p<0.05$). Post hoc comparisons (Newman–Keuls test) revealed decreased thermal response in PSD animals compared with the control group (−37%, $p<0.05$); 24 h of sleep recovery did not reverse this decrease (−36%, $p<0.05$). Even with chronic treatment of 10 mg/kg amitriptyline, a difference was detected (−51%, $p<0.05$), and there was no significant alteration after 24 h of sleep recovery (−59%, $p<0.05$) ($F_{[2,19]}=9.93$, $p<0.05$) (Fig. 1D). A Student's unpaired *t*-test between groups treated with amitriptyline and their respective saline groups showed that hindpaw withdrawal latencies were not significantly different.

3.3. Locomotor activity in an open field arena

Chronic treatment with amitriptyline reduced the locomotor activity of the controls ($F_{[3,23]}=6.40$, $p<0.05$), but not for PSD animals ($F_{[3,20]}=0.59$, $p>0.05$). This reduction was observed for the 10 mg/kg (−45%, $p<0.05$) and 30 mg/kg doses (−52%, $p<0.05$) (post hoc comparisons — Newman–Keuls test) (Fig. 2).

4. Discussion

The results obtained in this work demonstrate a reduction in the threshold for paw withdrawal induced by thermal noxious stimulation after 72 and 96 h of paradoxical sleep deprivation; this reduction

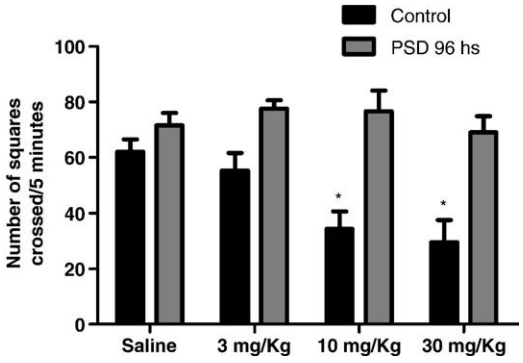

Fig. 2. Effects of chronic amitriptyline treatment on the locomotor activity of control and PSD animals. Data are presented as mean ± SEM. Seven animals were included in each group. *$p<0.05$ *vs.* saline and 3 mg/kg (one-way ANOVA followed by Newman–Keuls test).

persisted after 24 h of sleep recovery. The reduced threshold for noxious stimulation was not dependent on a specific nociceptive fiber since it was observed when the animals were exposed to 46 °C and 52 °C stimuli. To investigate whether the hyperalgesia seen after PSD might involve the same mechanisms as neuropathic pain, amitriptyline, a drug used to reduce neuropathic pain was administered to rats before and during PSD; however, amitriptyline did not significantly influence the withdrawal response of PSD animals.

The present findings are in accord with previous reports that indicate an increase in thermal responsiveness after PSD (Nascimento et al., 2007; May et al., 2005; Kundermann et al., 2004; Onen et al., 2001) and stand in contrast to studies in which changes in latencies after sleep deprivation were not observed (Dametto et al., 2002; Arima et al., 2001). It should be noted that these various studies were conducted using different periods of sleep deprivation and distinct intensities and types of noxious stimuli; these differences could explain the divergence among results.

The alterations in nociceptive thresholds seem to be influenced by the period of sleep deprivation to which the animal is submitted. Two days of PSD have been described as sufficient to modify mechanical sensitivity, but not thermal sensitivity (Wei et al., 2007), while 3 days of PSD appears to alter mechanical, electrical, and thermal sensitivity, but not chemical sensitivity (Onen et al., 2001). In the present work, the animals showed hypersensitivity to thermal noxious stimuli after 3 days of PSD; and this effect was also confirmed after 4 days of PSD. Additionally PSD animals challenged with 46 °C or 52 °C thermal stimuli showed a decrease in thresholds, this was also detected when the hot plate was set at 50 °C (Nascimento et al., 2007). We conclude from our results that hindpaw withdrawal responses evoked by stimulation of nociceptive C and A-delta fibers were facilitated in PSD rats.

We found that 24 h of sleep recovery after 4 days of sleep deprivation did not restore the thermal response thresholds. In fact, an earlier study demonstrated that nociceptive thresholds only return to basal values after 96 h of sleep rebound in 4-day PSD rats (Hicks et al., 1979). However, a return to basal values in 24 h has been described for animals deprived of paradoxical sleep for 3 days (Onen et al., 2000).

During and after paradoxical sleep deprivation, a range of neurochemical changes has been shown to occur; some of these are likely involved in the processing of pain. These neurochemical changes occur in various neurotransmitter systems including the serotonergic system (Machado et al., 2008; Senthilvelan et al., 2006). Serotonin has a well-known central pain inhibitory effect, and this neurotransmitter is likely involved in the pain hypersensitivity associated with sleep deprivation (Foo and Mason, 2003).

The analgesic effect of antidepressants is achieved with lower doses and reduced time of administration when compared to their antidepressant effects (for review, see Sindrup et al., 2005). In the present study, we did not observe an analgesic dose–response effect when control and PSD animals were acutely given amitriptyline; however, an effect was observed for control animals after 11 days of chronic administration. Our results are in accord with previous studies indicating that 7 days of desipramine administration is needed to potentiate opioidergic analgesia (Gordon et al., 1993), with a 3-day administration or a single dose showing no effect (Levine et al., 1986).

The efficacy of systemically administered amitriptyline, given, as an analgesic drug in the hot plate test in partial sciatic nerve ligation-injured rats has been previously reported (McCarson et al., 2005). Amitriptyline also has analgesic properties in other nociceptive contexts, such as persistent pain as demonstrated by the rat formalin test and mechanical hyperalgesia in nerve-injured animals (Bomholt et al., 2005). However, some studies reported a non-analgesic effect of amitriptyline in the rat tail withdrawal test (Korzeniewska-Rybicka and Plaznik, 1998; Bomholt et al., 2005) and acetic acid test (Casas et al., 1995). Although the neural basis of the observed reactions in these tests is poorly understood, the formalin and mechanical test responses have been considered to be complex behaviors and the rat tail withdrawal and acetic acid test responses to be spinal reflexes (for review, see Le Bars et al., 2001). Taking these differences into consideration the varying effects of amitriptyline administration on analgesia suggest that supraspinally organized responses to a noxious stimulus may be more sensitive than spinal responses to increased monoaminergic function following TCA administration. In the current work, a potent analgesic effect was observed in control groups for the 30 mg/kg amitriptyline dose, but it was not observed in PSD rats. Decreased motor activity was observed in control groups for the 10 and 30 mg/kg amitriptyline doses (Fig. 2); however, this cannot explain the potent analgesic effect observed only for the 30 mg/kg amitriptyline dose.

A decrease in paradoxical sleep that occurs early during treatment with amitriptyline and gradually diminishes during long-term treatment has been described (Wilson and Argyropoulos, 2005). However, in the current work, control group rats receiving amitriptyline for 11 days without PSD did not present reduced latency of hindpaw withdrawal when compared with the control group that received only saline (Fig. 1A and B). The same was observed in the PSD groups. Therefore, even if amitriptyline decreased paradoxical sleep it did not measurably affect thermal pain sensitivity.

Since it has been suggested that mechanical hypersensitivity following PSD and peripheral nerve injury share common spinal mechanisms (Wei et al., 2007) and since serotonergic antagonists and agonist drugs reduce pain hypersensitivity (Wei et al., 2008) amitriptyline is expected to prevent the hyperalgesia induced by PSD. In the present work, we did not observe an analgesic effect of amitriptyline in 72 and 96-hour sleep-deprived rats exposed to a noxious thermal stimulus. The results described by Wei and collaborators were observed after intrathecal administration of the drug. In those studies, the drug was observed to act on 5-HT1A and 5-HT2C receptors, which play a significant role in serotoninergic pain regulation at the spinal cord level, while amitriptyline has been associated with a supraspinal modulation of pain (McCarson et al., 2005). We conclude from our results that amitriptyline action is insufficient to change the increased thermal response induced by PSD. Furthermore, the lack of an analgesic effect of amitriptyline likely implies that effectors downstream of the central serotoninergic pain pathway are altered after paradoxical sleep deprivation. In this manner, the sleep disturbances common in patients with chronic pain, may interfere with the effect of amitriptyline, reducing its efficacy.

Acknowledgements

This work was supported by grants from Fundação de Amparo à Pesquisa do Estado do Rio de Janeiro (FAPERJ) and Universidade do Estado do Rio de Janeiro (UERJ).

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