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Nicotine and fluoxetine induce arousing effects on sleep–wake cycle in antidepressive doses: A possible mechanism of antidepressant-like effects of nicotine

Gonzalo Vázquez-Palacios [a,*], Marisela Hernández-González [c], Miguel-Ángel Guevara Pérez [c], Herlinda Bonilla-Jaime [b]

[a] Academy of Biology, College of Science and Technology, Universidad Autónoma de la Ciudad de México-San Lorenzo Tezonco, Av. Prolongación San Isidro 151, Col. San Lorenzo Tezonco, Deleg., Iztapalapa, CP 09790, México

[b] Behavioral and Reproductive Biology Laboratory, Department of Reproductive Biology, Universidad Autónoma Metropolitana-Iztapalapa, Mexico City, CP 09340, México

[c] Instituto de Neurociencias, Universidad de Guadalajara, Francisco de Quevedo 180, Col. Arcos Vallarta, CP 44130, Guadalajara, Jalisco, México

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ABSTRACT

A number of studies have reported an association between smoking and depression, and several reports suggest that nicotine (NIC) may act as an antidepressant. The present study was designed to determine whether the effects of NIC on sleep–wake patterns in rats are similar to those of the antidepressant fluoxetine (FLX), a selective serotonin reuptake inhibitor. Male rats were chronically implanted with a standard set of electrodes for sleep recording. We compared the effects of antidepressive doses of NIC, FLX and the combination of both drugs on sleep–wake pattern in rats subjected to one day, one week and two weeks of administration, as well as after the withdrawal of the two-week treatment. The changes observed in our study in an 8-h sleep recording period during one day, one week and two weeks of NIC administration are very similar to those observed in the rats that received FLX, which led to a decrease in both slow wave sleep II and rapid eye movement (REM) sleep as a consequence of an increase in wakefulness. In addition, all treatments also induced a significant lengthening of REM sleep latency onset. These data suggest that the antidepressant-like action of NIC could be caused by its arousing properties.

1. Introduction

Both preclinical and clinical studies have suggested that nicotine (NIC) and related compounds may have therapeutic value for treating a wide range of neuropsychiatric disorders (Vazquez-Palacios and Bonilla-Jaime, 2004; Newhouse et al., 2004; Romanelli et al., 2007). Converging lines of evidence indicate a strong relationship between major depression, neuronal acetylcholine nicotinic receptors (nAChRs) and NIC (for review: see Bertrand, 2005; Quattrocki et al., 2000; Vazquez-Palacios and Bonilla-Jaime, 2004). The direct link between NIC and depression is suggested primarily by the fact that transdermal NIC patch treatment has improved mood in non-smoking depressed patients (Salin-Pascual et al., 1996). In addition, a growing number of findings in animal models of depression have recently shown that NIC and some nicotinic ligands also have antidepressant properties (Buckley et al., 2004; Ferguson et al., 2000; Semba et al., 1998; Nakamura and Tanaka, 2001; Tizabi et al., 1999; Vazquez-Palacios et al., 2004, 2005). It has been shown that most antidepressant drugs are associated with changes in sleep architecture, notably the delayed onset of rapid eye movement (REM) sleep and a reduced amount of REM sleep (Wilson and Argyropoulos, 2005). Because the majority of antidepressants, irrespective of their chemical classes, suppress REM sleep, it has been hypothesized that the improvement in symptoms of depression is related to sleep deprivation, especially the deprivation of REM sleep (Vogel et al., 1990; Thase, 1998; Giedke and Schwärzler, 2002; Berger et al., 2003). For instance, the effects on sleep of fluoxetine (FLX), a potent selective serotonin reuptake inhibitor (SSRI), have been studied extensively in both normal volunteers and depressed patients. Insomnia and other "activating" side effects occur in depressed patients treated with FLX (Beasley et al., 1992; Armitage and Sussman, 1997). This effective antidepressant medication is a potent suppressor of REM sleep (Kerkhofs et al., 1990; Gillin et al., 1997; Nicholson and Pascoe, 1988; Vasar et al., 1994). A similar result has been observed in animals (Pastel and Fernstrom, 1987; Bakalian and Fernstrom, 1990; Gao et al., 1992). Changes in sleep and, especially, REM sleep, in depressive patients have been attributed to an increased ratio of cholinergic to aminergic neurotransmission in critical central synapses (see Adrien, 2002). Given that these neurotransmitter systems are primarily involved in regulating sleep and wakefulness, it is believed that they represent common neurobiological substrates that underlie the impairment of the regulation of both mood and the sleep–wakefulness cycle (Adrien, 2002).

* Corresponding author. Tel.: +52 525 8501901x14510.
E-mail address: gvp@xanum.uam.mx (G. Vázquez-Palacios).

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However, there is also contradictory evidence as to the role of NIC in sleep regulation, as early reports failed to detect any effect of NIC on sleep (George et al., 1964). In contrast, when administered intravenously (Domino and Yamamoto, 1965), subcutaneously (Jewet and Norton, 1966), or into the medial pontine reticular formation (Velazquez-Moctezuma et al., 1990), NIC actually increased REM sleep in cats. Similarly, research conducted with humans has yielded inconsistent results. Several studies have shown that transdermal NIC induced a decrease in total sleep time, sleep efficiency and REM sleep, as well as an increase in wakefulness (Gillin et al., 1994; Salin-Pascual et al., 1999; Vazquez et al., 1996; Page et al., 2006). In the present study, we compared the effects of antidepressive doses of NIC, FLX and the combination of both drugs on sleep–wake pattern in rats, according to the forced swim test (Vazquez-Palacios et al., 2004, 2005), with the objective of determining whether the effects of NIC are similar to those of FLX, a SSRI and currently the most widely-used antidepressant.

2. Methods

In this study, sleep–wakefulness patterns in rats were monitored after one day, one week and two weeks of administration, as well as after the withdrawal of the two-week treatment with NIC, FLX and the combination of FLX plus NIC. Adult male Wistar rats (250–300 g at the beginning of the experiment) from our vivarium were chronically implanted with a standard set of electrodes for electroencephalogram (EEG) and electromyogram (EMG) recording under deep anesthesia [Ketamine (100 mg/ml): 0.25 ml plus xilacine (20 mg/ml): 0.05 ml plus acepromazine (0.2 mg/ml) 0.1 ml plus 0.6 ml of saline to obtain a 1 ml cocktail, ip] and aseptic conditions. Once anesthesized, the animals were injected with xylocaine (2%) in the dorsal part of the cranium to complete the local anesthesia. All electrodes were then soldered to the connectors of a plug that was permanently fixed to the skull with acrylic cement. At the end of the surgical procedure, each animal received an ip injection of 0.3 ml of penicillin and all appropriate antiseptic measures were taken to prevent infection. At that point, the animals were placed individually in transparent plastic cages (recording chambers) containing sawdust bedding. All animals were kept in the same sound-attenuated room and maintained on a 12-h alternating light–dark schedule (lights on 0900 h) and at a controlled temperature (23 ± 1 °C). Food and water were available *ad libitum* throughout the study. Following a post-surgical recovery period of at least 7 days, all animals were habituated for 3 days by being allowed to move freely around the recording chamber with their slip rings and cable-connectors attached. EEG and EMG were recorded continuously for 8 h during the light period (the sleep period in rats) of the 12-h light/12-h dark cycle, beginning at approximately 0900 h. Animals were randomly assigned to one of the following experimental groups ($n = 10$): saline control (CON), NIC, FLX and FLX + NIC. The same CON group was used for all treatments. Sleep recordings were obtained during 8 h after one day, one week and two weeks of administration, as well as after withdrawal from the two-week treatment period (7 days after completing the two-week treatment). In order to determine the possible effects on the sleep–wake cycle, four distinct states of vigilance were established, based on the visual scoring of records according to Takeuchi's (1970) criteria. The behavioral states of wakefulness (W), slow wave sleep I (SWS I), slow wave sleep II (SWS II) and REM sleep were scored in successive 10-s epochs. These sleep–wake measures provided the following dependent variables that were quantified for each 8-h recording session: total time of sleep–wakefulness stages; their frequency, duration and latencies; and sleep efficiency (percentage of total sleep time during the recording period) (Vazquez-Palacios and Velazquez-Moctezuma, 2000). Brief awakenings (less than 30 s) during SWS I, SWS II or REM sleep were counted as the total number of awakenings. Statistical analysis was conducted using Kruskal–Wallis analysis of variance (ANOVA) and significant sources of variance were identified using the Dunn post-hoc test. A level of $p \leq 0.05$ was considered significant in all tests.

2.1. Drugs

–(–) Nicotine bitartrate was dissolved in a saline solution, while FLX–HCL was dissolved in distilled H_2O. All drugs were administered subcutaneously in a volume equivalent to 0.2 ml. Doses were calculated on mg/kg of salt and prepared fresh each morning. The dose tested for each drug was as follows: NIC bitartrate at 0.4 mg/kg body weight/day (0.14 mg/kg body weight/day of nicotine base), and FLX–HCl at 5 mg/kg body weight/day (4.47 mg/kg body weight/day of FLX base). NIC was injected 10 min prior to sleep recording, while the FLX–HCl injections were given 30 min before the start of sleep recording. The combination of FLX + NIC was administered using the same doses and at the above mentioned times prior to sleep recording. The control rats received a 0.9% saline solution as the vehicle (same volume and route of administration). Both the NIC and FLX doses were selected based on reports in the literature and our own previous studies that had demonstrated antidepressive effectiveness in the forced swim test (Detke et al., 1995; Tizabi et al., 1999; Vazquez-Palacios et al., 2004, 2005).

Also relevant is the fact that no increase of general locomotor activity has been reported at these doses (Tizabi et al., 1999; Detke et al., 1995). All animals were treated in strict accordance with both the NIH Guidelines and Mexico's Official Norms (NOM-062-ZOO-1999) for the Care and Use of Laboratory Animals.

3. Results

3.1. One day of treatment

Our results indicate that NIC induces sleep–wake changes similar to those found in the FLX group in that it increases wakefulness and decreases both SWS II and REM sleep. Sleep time decreased in all experimental treatments as indicated by total sleep time, and sleep was also less efficient (Fig. 1). With regard to REM sleep latency onset, a significant increment was observed under all treatments (Fig. 2). Fig. 1 shows the effects of all treatments on the total time of the different sleep stages. In the 8-h recording sessions, sleep–wake patterns after one day of NIC administration were characterized by a significant increment in the duration of W [+78%] with a consequent significant decrease in the total time of both SWS II [−50%] and REM sleep [−63.15%] (Fig. 1A). These changes, induced by one day of NIC treatment, led to decreased sleep efficiency (Table 1). The greater amount of time spent in W resulted from an increase in the average duration of each episode (Table 1), while the reduction in both SWS II [−52.18%] and REM sleep [−69.84%] occurred due to a significant reduction in the number of episodes. NIC also induced a significant lengthening of REM sleep latency onset (Fig. 2A).

One day of FLX administration induced effects in the sleep–wake architecture similar to those of NIC during the entire recording period (Fig. 1A). Overall amounts of W increased following of one day of FLX treatment [+56.69%] with a concomitant decrease in SWS II [−33.83%] and REM sleep [−61.47%]. These changes led to decreased sleep efficiency (Table 1). One day of FLX administration increased the total duration of W through an increase in the duration of each episode (Table 1), though in this case the number of episodes remained unchanged. In contrast to W, the duration of SWS II diminished due to a reduction in the number of episodes, though the duration of each single episode increased. Overall amounts of REM sleep also decreased via a reduced number of episodes, but the average duration of each REM sleep episode remained unchanged (Table 1). With regard to REM sleep latency onset, a significant