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Antidepressant-like effects of the acute and chronic administration of nicotine in the rat forced swimming test and its interaction with flouxetine

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Abstract

An antidepressant action of nicotine (NIC) has recently been suggested. Flouxetine, a selective serotonin reuptake inhibitor, is currently the most widely used antidepressant. In the present study, we analyzed the effects of the administration of NIC, fluoxetine (FLX), and the combination of both drugs given acutely, subchronically, and chronically as well as 7 days after chronic administration of these drugs on the forced swim test. Results showed that NIC induced a significant reduction of the time in immobility during the forced swim test (antidepressant effect), with a concomitant increase in swimming activity (serotonergic activation), after acute administration. These effects remain the same after subchronic and chronic administration. FLX failed to induce any effect after acute administration but did induce a significant decrease of immobility and an increase of swimming after subchronic administration. The effect of the chronic administration was significantly larger compared to subchronic administration. The combination of both drugs induced a larger effect than that observed after a single administration but only after subchronic treatment. No effect was observed after the end of the 7-day treatments. Data suggest that NIC has an antidepressant action that is expressed faster than FLX but remains the same later. Thus, cholinergic–serotonergic interactions could play an important role in the treatment of depression.

Keywords: Antidepressant; Depression; Nicotine; Fluoxetine; Forced swimming test; Porsolt test; Selective serotonin uptake inhibitor

1. Introduction

A number of studies have recently reported a clinical association between smoking and depression (for review, see Picciotto et al., 2000; Quattrocki et al., 2000). Epidemiological studies indicate a high incidence of cigarette smoking among depressed individuals (Breslau et al. 1998; Covey, 1999; Kendler et al., 1993). Although the neurobiological basis of this association is not clear, it has been suggested that smoking is a self-medication effort made by the depressed individual to alleviate some symptoms of depression by using nicotine (NIC) (Breslauet et al., 1998; Lerman et al., 1996; Markou et al., 1998). In addition, various reports suggest that NIC, the main psychoactive component of tobacco, may act as an antidepressant (Gilbert, 1996; Glassman, 1993; Salin-Pascual and Drucker-Colin, 1998). Recent studies in animal models of depression suggest that NIC may have antidepressant effects (Djuríc et al., 1999; Ferguson et al., 2000; Martínez-González et al., 2002; Semba et al., 1998; Tizabi et al., 1999, 2000).

Most of the treatments currently employed as antidepressants improve serotonergic transmission (Blier and Montigny, 1998; Blier et al., 1987). There is growing evidence for a bidirectional relationship between NIC and the serotonergic system (see Seth et al., 2002, for review).

On the other hand, The forced swimming test (FST) is a behavioral test that has been widely used as a screening method for antidepressant activity (Lucki, 1997; Porsolt et al., 1977, 1978; see Borsini and Meli, 1988, for a review). In brief, this test links time of immobility with antidepressant activity. It has recently been reported that a modification of the scoring procedure allows swimming and climbing to be measured; these behaviors are claimed to be selectively associated with serotonergic or noradrenergic activity, respectively (Detke et al., 1995; Lucki, 1997).

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Thus, it is possible that the suggested antidepressant effect of NIC involves serotonergic transmission. In the present study, we analyzed the effects of acute and chronic administration of NIC, fluoxetine (FLX; an antidepressant with serotonergic activity), and a combination of both drugs on rats submitted to the FST.

2. Materials and methods

Adult male Wistar rats ($N = 160$; 250–300 g at the start of the experiment) from our own vivarium were used in this experiment. Subjects (Ss) were kept in a room with a 12:12 light–dark cycle (lights on at 9 a.m.) and controlled temperature. Ss were housed in groups (5 per cage), with free access to food and water. All the experimental procedures were done following the Principles of Laboratory Animal Care issued by the National Institute of Health.

Ss were randomly assigned to the following groups and treatments ($n = 10$ in each group):

Acute treatment—Group A1: One subcutaneous injection of NIC bitartrate (0.4 mg/kg bw) in a volume of 0.2 ml of saline solution. NIC injection was given 10 min before the start of the 5-min FST. Group A2: One subcutaneous injection of FLX HCl (5 mg/kg bw) in a volume of 0.2 ml of distilled water. FLX injection was given 40 min before the start of the 5-min FST. Group A3: Acute administration of combined FLX and NIC. Drugs were administered in combination using the same dose and at the times mentioned above. Group A4: control. Ss received one subcutaneous injection of 0.2 ml of saline, 20 min before the 5-min FST.

Subchronic treatment—Group B1: Ss received subcutaneous NIC administration for 7 days. Group B2: Ss received subcutaneous administration of FLX for 7 days. Group B3: Ss received subcutaneous administration of both drugs for 7 days. Group B4 (Control): Ss received subcutaneous injection of saline for 7 days. The 5-min FST was done on the last day of treatment for all of the subchronic groups.

Chronic administration—Group C1: Ss received subcutaneous NIC injections for 14 days. Group C2: Ss received subcutaneous FLX injections for 14 days. Group C3: Ss received subcutaneous injections of both drugs for 14 days. Group C4 (Control): Ss received subcutaneous injection of saline for 14 days. The 5-min FST was done on the last day of treatment for all of the chronic groups.

Postchronic withdrawal—Group D1: Ss received subcutaneous administration of NIC for 14 days and were submitted to the FST 7 days after termination of the treatment. Group D2: Ss received subcutaneous administration of FLX for 14 days and were submitted to the FST 7 days after termination of the treatment. Group D3: Ss received subcutaneous administration of FLX/NIC for 14 days and were submitted to the FST 7 days after termination of the treatment. Group D4: Ss received subcutaneous injections of saline for 14 days and were submitted to the FST 7 days after termination of the injections.

Drug doses were chosen based on previous reports (Detke et al., 1997; Tizabi et al., 1999).

2.1. FST

The test was done by placing a rat in a glass cylinder (46 cm high × 20 cm in diameter) containing a 30-cm water column (24 ± 1 °C temperature). Water was replaced between every trial. Two swimming sessions were conducted: an initial 15-min pretest, followed by a 5-min test 24 h later. Test sessions were video taped for scoring. A time-sampling technique was employed to score several behaviors during a single viewing. This method has previously been described and shown to be reliable and valid for detecting the effects of different antidepressant drugs (Detke et al., 1995). At the end of each 5-s period during the 5 min test, the scorer rated the rat's behavior as one of the following behavioral categories: (1) immobility—floating passively in the water and only making slight movements to keep its head above the water line (Porsolt et al., 1977); (2) swimming—making active swimming motions, more than necessary to merely keep the head above water (i.e., moving around in the cylinder); and (3) climbing—making active movements with forepaws in and out of the water, usually directed against the walls. An experienced rater who was blind to the treatment conditions did all of the behavior scoring. Scores for each behavior were expressed as total behavioral counts per 5-min session. The number of counts represents the number of times that a specified behavior of immobility, swimming, or climbing was detected following the different treatments.

Statistical analysis was done using an ANOVA, followed, when significant, by the Dunn post hoc test.

3. Results

Fig. 1 shows the effects of acute treatments on the FST. NIC decreased immobility ($F = 19.7659$, $df = 3$, $P < .0002$; Dunn $P < .01$) and increased swimming ($F = 21.23$, $df = 3$, $P < .001$; Dunn $P < .01$), without modifying the levels of climbing behavior ($F = 5.01$, $df = 3$, $P < .17$). FLX administration did not induce any significant change when compared to the control group. The combined FLX/NIC treatment induced a significant reduction of immobility behavior (Dunn $P < .01$) with an increase in swimming (Dunn $P < .01$). The effects observed after the administration of both drugs was similar to that observed after the administration of NIC.

The effects of subchronic administrations on the FST are shown in Fig. 2. NIC administration decreased immobility ($F = 26.81$, $df = 3$, $P < .0001$; Dunn $P < .01$) and increased swimming ($F = 29.27$, $df = 3$, $P < .001$; Dunn $P < .01$), with-

RESULTS

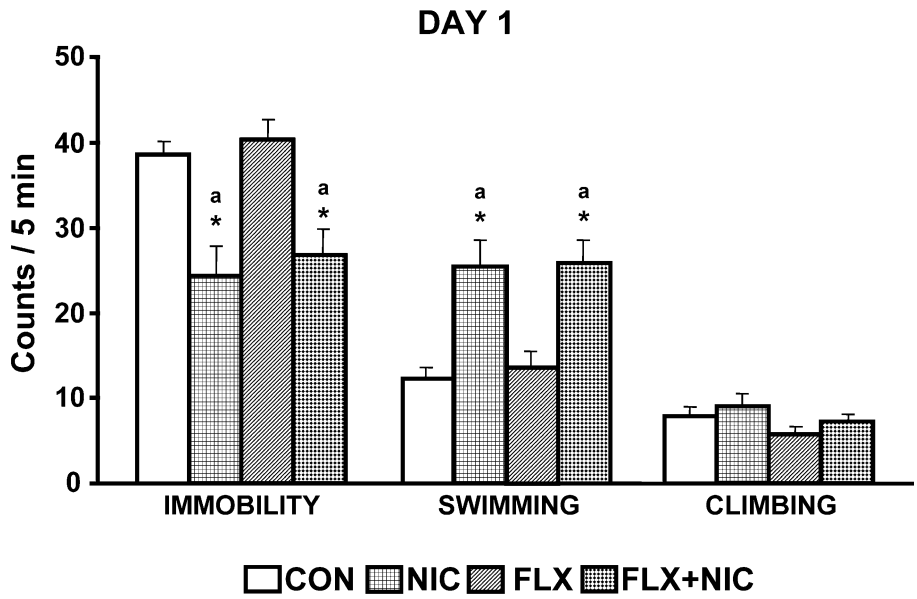

Fig. 1. Amount of immobility, swimming, and climbing behaviors in rats when sampled every 5 s during the 5-min period of the FST. Bars represent the mean number of counts over the 5-min period of the test (± S.E.M.). Acute (1 day) administration of saline (CON); NIC (0.4 mg/kg/day); FLX (5 mg/kg/day); and the combination of FLX and NIC (FLX + NIC). For each group, $n = 10$. ANOVA followed by the Dunn test. The symbol (*) signifies $P < .01$ compared to their respective control. The symbol (a) signifies $P < .01$ compared to their respective FLX group.

out modifying the levels of climbing behavior ($F = 5.92$, $df = 3$, $P < .12$). FLX administration for 7 days also decreased immobility (Dunn $P < .01$) and increased swimming (Dunn $P < .01$), without affecting climbing. The combined FLX/NIC treatment also reduced immobility (Dunn $P < .01$) and increased swimming (Dunn $P < .01$). The effect of the combination of drugs was significantly stronger when compared to the effects obtained after the individual administration of NIC or FLX ($P < .05$ vs. both NIC and FLX.).

Fig. 3 shows the effects on the FST of 14 days of treatment. The effect of NIC was similar to that obtained after the acute and the subchronic administration. Immobility decreased ($F = 24.98$, $df = 3$, $P < .001$; Dunn $P < .05$) and swimming increased ($F = 29.52$, $df = 3$, $P < .001$; Dunn

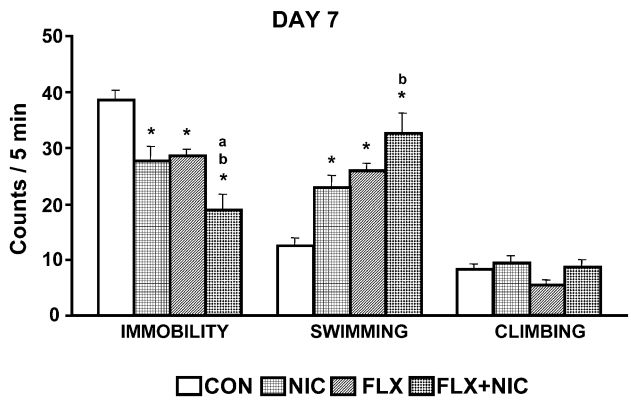

Fig. 2. Amount of immobility, swimming, and climbing behaviors in rats when sampled every 5 s during the 5-min period of the FST. Bars represent the mean number of counts over the 5-min period of the test (± S.E.M.). Subchronic (7 days) administration of saline (CON); NIC (0.4 mg/kg/day); FLX (5 mg/kg/day); and the combination of FLX and NIC (FLX + NIC). For each group, $n = 10$. ANOVA followed by the Dunn test. The symbol (*) signifies $P < .01$ compared to control. The symbol (a) signifies $P < .01$ compared to FLX. The symbol (b) signifies $P < .01$ compared to NIC.

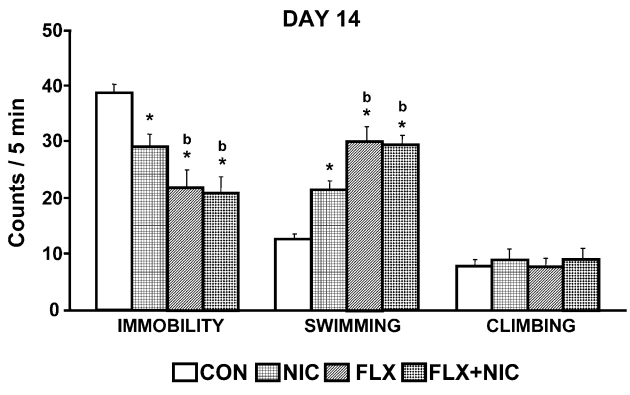

Fig. 3. Amount of immobility, swimming, and climbing behaviors in rats when sampled every 5 s during the 5-min period of the FST. Bars represent the mean number of counts over the 5-min period of the test (± S.E.M.). Chronic (14 days) administration of saline (CON); NIC (0.4 mg/kg/day); FLX (5 mg/kg/day); and the combination of FLX and NIC (FLX + NIC). For each group, $n = 10$. ANOVA followed by the Dunn test. The symbol (*) signifies $P < .01$ compared to control. The symbol (b) signifies $P < .01$ compared to NIC.

$P < .01$), while climbing was not affected. FLX administration induced a larger effect than that observed after the subchronic treatment. FLX reduced immobility (Dunn $P < .01$) and increased swimming (Dunn $P < .01$), without affecting climbing. The combined administration of FLX/NIC also showed a similar effect to that observed after 7 days of treatment, with a reduction of immobility (Dunn $P < .01$) and an increase of swimming (Dunn $P < .01$).

When Ss were submitted to the FST 7 days after the termination of the treatments, no significant differences were observed when compared to their respective controls.

4. Discussion

The present study provides new evidence for the antidepressant-like behavioral effects of NIC. Assuming that the FST is a reliable tool to detect antidepressant activity, the present results show that NIC has an antidepressant effect that can be observed following its acute administration. This antidepressant action did not increase after repeated administration. Inasmuch as NIC modified swimming levels in the FST, it could be assumed that its effects have a serotonergic component that is also present from the first administration (Detke et al., 1995, 1997; Page et al., 1999). The effect of NIC on swimming remains the same after 7 and 14 days of treatment and disappears when the treatment is suspended.

FLX seems to require repeated administration to start showing its effects on immobility in the FST. Its maximum effect was reached after 14 days of treatment, returning to control levels after 7 days of the end of the treatment. Interestingly, only after 7 days of treatment, the combined administration of FLX and NIC seem to have a synergistic effect that incidentally was not observed at any other moment.

The present results are consistent with preliminary clinical reports showing an antidepressant effect of NIC when it was applied transdermally (Salin-Pascual et al., 1995). NIC exhibited antidepressant-like activity in the FST when it was administered to Flinders Sensitive Line rats (Tizabi et al., 1999). Flinders rats have been selectively bred for cholinergic supersensitivity, and they have been proposed as an animal model of depression (Overstreet, 1986) In addition, chronic NIC exposure induced a significant reduction in the number of escape failures in the learned helplessness paradigm (Semba et al., 1998). These results were supported by Ferguson et al. (2000) who reported that SIB-1508Y, a selective agonist of the nicotinic receptors, was able to reverse the escape deficit in the learned helplessness model. Furthermore, chronic NIC treatment reduced alcohol consumption in rats neonatally treated with clomipramine (Martínez-González et al., 2002). Neonatal treatment with clomipramine has been proposed as a method to induce depressive-like behavior when the animals reach adulthood (Vogel et al., 1990).

NIC–serotonin interactions have been repeatedly demonstrated (for review, see Seth et al., 2002). NIC induced a concentration-dependent increase in the release of serotonin from rat midbrain slices, which was accompanied by both increases and decreases of firing rates of neurons located in the dorsal raphe nucleus (DRN) (Mihailescu et al., 1998). Serotonin release was much higher during the decrease in firing rates, which suggests an action of NIC on presynaptic receptors of serotonin neurons (Mihailescu et al., 1998). In anaesthetized rats, systemic administration of NIC induced a transient inhibition of most neurons recorded in the DRN. This inhibition was blocked by a selective 5-HT_{1A} receptor antagonist, WAY 1000635, indicating that NIC might influence serotonin receptors (Engberg et al., 2000).

It is possible that NIC and FLX have a synergistic effect only at 7 days of treatment, because at that moment, the effect of FLX is barely getting stronger, and the serotonergic component of the NIC administration can exert an action. On the contrary, at 14 days of treatment, the effect of FLX is so strong that the addition of NIC has no significance.

It has been reported that chronic, but not acute, administration of selective serotonin reuptake inhibitors, such as FLX, induces antidepressant effects in the FST (Kelly and Leonard, 1994). Experiments using in vivo microdialisis have reported that a single injection of FLX induces only a transient increase of extracellular serotonin, while repeated administration significantly increases base line levels of serotonin (Kreiss and Lucki, 1995; Rutter et al., 1994). In addition, the chronic administration of FLX seems to also induce an increased desensitization of the $5HT_{1A}$ receptors (Li et al., 1996; Raap et al., 1999). Furthermore, the serotonergic 5-HT_{1A} receptor is particularly important in mediating NIC-induced behaviors (File et al., 2000). Because NIC alters 5-HT neurotransmission, it has been suggested that NIC modulates the expression of 5-HT_{1A} receptors located in certain cortical and limbic regions involved in the etiology of depression (Kennedy et al., 2001; Kenny et al., 2001; Mayberg et al., 2000; Stockmeier, 1997). These data support the notion that NIC administration can have a positive influence on the antidepressant treatment with serotonergic agents.

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