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NICOTINE POTENTIATES THE ANTIDEPRESSANT EFFECTS OF IMIPRAMINE AND SERTRALINE

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ABSTRACT

Clinical observations suggest the involvement of nicotinic acetylcholine receptors (nAChRs) in depressive illness. There is no clear cut evidence that nicotine produces an antidepressant effect. The antidepressant effect was assessed by the forced swimming test using male albino mice. Nicotine (1.2 mg/kg *s.c.*) given 15 min. before the test exerted no effect on immobility. Given 30 min before the test, imipramine and sertraline (each 20 mg/ kg *i.p.*) produced a significant decrease in immobility; coadministration of nicotine (1.2 mg/ kg, 15 min before the test) to either imipramine or sertraline-treated mice resulted in an enhancement in anti-immobility effect. The study further investigated the effect of nicotine, alone and in combination with either imipramine or sertraline on sucrose consumption in mice exposed to 3-weeks application of stressors. There was a reversal of anhedonia 3 weeks after i.p. administration of the antidepressant drugs given alone, and this reversal was enhanced when nicotine was co-administered with them.

Key words: **Nicotine – Antidepressant – Imipramine – Sertraline.**

INTRODUCTION

Depression is treated with the use of drugs that inhibit the reuptake and/or metabolism of biogenic amines (Skolnick, 1999). Imipramine hydrochloride is a tricyclic antidepressant that inhibits norepinephrine and serotonin uptake by brain synaptosomes (Mukherjee *et al.*, 2004). Sertraline hydrochloride is a selective serotonin reuptake inhibitor (SSRI) antidepressant blocking specifically neuronal sites involved in the reuptake of serotonin increasing the amount of this neurotransmitter in synaptic cleft (Cryan *et al.*,2004). Converging lines of evidence indicate that nicotinic acetylcholine receptors (nAChRs) are involved in major depression. As pointed by Elgoyhen *et al.*(2001), epidemiological findings suggest that depressive symptoms occur more often in smokers than nonsmokers, and that depressed patients are less likely to cease smoking. In addition, depressed smokers are being more dependent on cigarettes, and the cessation of smoking is often followed by a depressive episode (Wonnacott, 1997). Finally, smokers with a history of major depressive episodes are more likely to relapse than smokers with no history of depression (Wonnacott *et al.*, 2000). Furthermore, nicotine patches can improve the mood of depressed patients (Anderson *et al.*, 2000). Based on these observations, it has been postulated that nAChRs are involved in the etiology of major depression. Also,it has been hypothesized that nicotine produces antidepressant effects, and that smokers 'self-medicate' the underlying depressive illness with nicotine, and/or depressive symptoms produced by nicotine withdrawal (Markou *et al.*, 1998). Other pharmacological lines of evidence indicate that the antidepressant drug, bupropion, antagonizes neuronal nAChRs (Paterson and Nordberg, 2000), and has also been used as the treatment for smoking cessation (Pittaluga *et al.*, 1999). Another hypothesis that appears at face value, is based on findings indicating that most clinically effective antidepressants antagonize nAChRs (Popik *et al.*, 2003). This latter hypothesis assumes that the common final pathway for the antidepressant effects is the inhibition of nAChRs (Picciotto *et al.*, 2002). The present study was planned to investigate the effect of nicotine on the antidepressant actions of imipramine (IMI) and sertraline (SERT) using the forced swimming test in mice. Additionally the study was extended to investigate the effect of 3-weeks administration of nicotine with either antidepressant in the 3-weeks application of stressors as a model of anhedonia that has a similar and predictive validity simulating depression in humans (Willner *et al.*, 1987).

MATERIALS AND METHODS

Materials

Drugs: Imipramine hydrochloride (IMI) (Sigma Aldrich Chemicals Co.MO,USA), Sertraline hydrochloride (SERT) (Pfizer,USA), Nicotine hydrogen bitartrate (N) (Sigma Aldrich Chemicals Co.MO,USA). They were dissolved in sterile saline and administered in a volume not exceeding 10 ml/kg. Doses of N, IMI and SERT were selected according to Popik *et al.*, 2003; Mukherjee *et al.*, 2004 and Cryan *et al.*,2004, respectively.

Animals

Male albino mice, (30-35 g) were used allover the experiment..The animals were housed in standard laboratory conditions under a 12 h light/dark cycle, light on at 6 a.m., at a controlled temperature (21±2°C) , with free access to standard food pellets and tap water.

Methods and animal treatment:

The forced swimming test (FST): It is used to test the behavioral despair in rodents (Solberg et al., 1999) and considered as a way to measure "fighting spirit" of mice. In the first 2 min., the animal was allowed to adjust to the new conditions, then, the immobility time that alternated with conditions of enhanced motor activity was measured. Immobility time was measured with a stopwatch for the next 4 minutes (Porsolt *et al*., 1977). Mice were removed from their cages and placed individually in glass cylinders (diameter 15 cm) containing water (22-24°C) at a depth of 14-16 cm so that they could not escape and could not touch the bottom. The animals were placed in the cylinders for observation in a 6-min test swim. Two swimming sessions were conducted : an initial 15-min pretest followed 24 h later by a 6-min test. The duration of immobility during the last 4 min. of the 6 min. test was measured. The mouse was considered as immobile when it stopped struggling and moved only to remain floating on the water, keeping its head above water. Shorter immobility time is an indicator of the stronger antidepressant effect of the tested substance (Urani *et al*., 2001).

Mice were divided into 6 groups (each group=12 mice) and treated as follow:

Group 1: Control [they were treated with two consecutive injections of saline before carrying out the test; 15 min. (*s.c.*) and 30 min.(*i.p.*)]

Group 2: Nicotine (N)-treated group (1.2 mg/kg *s.c.*, 15 min. before the test)

Group 3: Imipramine(IMI)-treated group (20 mg/kg *i.p.*, 30 min. before the test)

Group 4: Sertraline (SERT)-treated group (20 mg/kg *i.p.*, 30 min. before the test)

Group 5: N+IMI treated group: (IMI (20 mg/kg *i.p.*) 30 min before the test then N (1.2 mg/kg *s.c.)* 15 min. before the test)

Group 6: N+SERT treated group (SERT (20 mg/kg *i.p.*) 30 min before the test then N (*1.2 mg/kg s.c.)* 15 min. before the test)

The shorter (15 min) interval between nicotine administration and the test was due to the short half-life of nicotine (Mathieu-Kia *et al*., 2002).

Three-weeks application of stressors procedure:

It was adopted from Willner *et al.* (1987) and Solberg *et al.* (1999). The protocol consisted of the following stressors applied for 3 weeks without treatment to induce anhedonia simulating human depression in mice:

a) 16-h water deprivation (water bottles were removed from the cages during this time)

b) 5 min.-tail suspension (animals were held upside down by their tail with metal tongs)

c) 1-to2-h restraint (animals were placed in a 50 ml conical tube with breathing holes)

d) 30-45 min. paired housing (the mouse was placed in the cage of another mouse of the stress group, each week the home cage mouse was alternated)

e) Soiled cage: 100 ml (16-18°C) water was poured into the cage

f) 5-min forced swim in cold water (16-18°C)

Each week, the stressors were presented in a different order and given at different times of the day.

The development of anhedonia in mice was tested by sucrose test. The stressed animals consumed less sucrose when they become anhedonic comparing to the control group. Preliminary data have shown that control mice prefer a 2% sucrose solution over regular un-sweetened water (pilot study). Once each week, animals were given bottles of both water and 2% sucrose for a 1-h period, this occurs 6 hours after lights out (because the pilot study revealed that mice consumed more water during their active period), thereby, enhancing the chance of seeing a difference in sucrose consumption. After 1-hour, both bottles were removed and total sucrose consumption was calculated.

After exposure for 3 weeks stressors, the mice were divided into 6 groups (each group=12 mice) with daily administration of saline or drugs for another 3 weeks as follows: :

Group 1: Control (saline-treated *i.p.*)

Group 2: Nicotine (N)-treated group (1.2 mg/kg/day *s.c.*)

Group 3: Imipramine(IMI)-treated group (20 mg/kg/day *i.p.*)

Group 4: Sertraline (SERT)-treated group (20 mg/kg/day *i.p.*)

Group 5: N+IMI treated group (IMI 20 mg/kg/day, *i.p.* & N 1.2 mg/kg/day, *s.c.*)

Group 6: N+SERT treated group (SERT 20 mg/kg/day, *i.p.*& N 1.2 mg/kg*/day, s.c.)*

Statistical analysis:

Data of forced swimming test and of sucrose consumption in the anhedonic model were statistically analysed using one-way ANOVA followed by Dunnett's test. $P<0.05$ was used as a criterion of significance.

RESULTS

Figure (1): Effects of N, IMI, SERT and their combination on the duration of immobility of male albino mice.

Data are presented as mean ±SD
*** = significant different from control (saline-treated) group.**
 # = significant different from nicotine treated group.
$ = significant different from IMI or SERT treated groups.

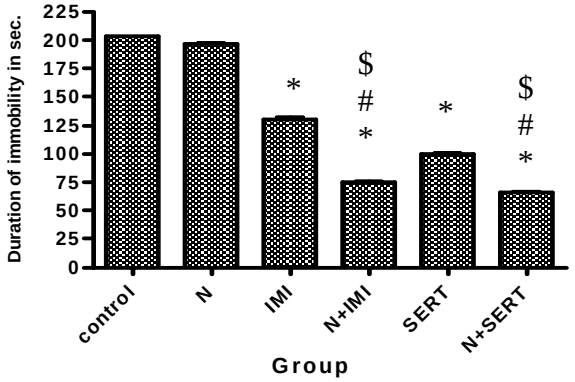


Figure (1): the results revealed significant effect of either IMI or SERT treatment compared to the control group (130±0.2 and 100±0.2 versus 205±0.1 sec.) with a decrease –36.6% and -51.3%, respectively. Nicotine given s.c. before the test did not significantly influence the immobility (199±0.1 verus 205±0.1 sec.) with a decrease –2.9%. Co-treatment of nicotine with either IMI or SERT produced significant effects on immobility (75±0.2 and 65±0.2 versus 205±0.1 sec.) with decrease of –63.4% and – 68.3%, respectively.

Figure (2) The influence of exposure to three-weeks application of stressors on sucrose consumption of male albino mice.

Data are presented as mean ±SD
*** = significant different from control (saline-treated) group.**
 # = significant different from group exposed to 3-weeks application of stressors without treatment.
$ = significant different from IMI or SERT treated groups.

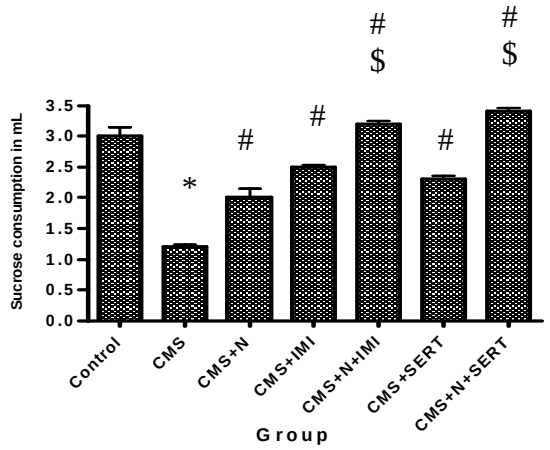


Figure (2): demonstrated the reversal of anhedonia after 3 weeks *i.p.* administration of either nicotine (N), imipramine (IMI) or sertraline (SERT). Each antidepressant was administered either alone or in combination with nicotine to male albino mice continuously exposed to 3-weeks application of stressors. In comparison to the control saline-injected group, the stressed group was associated with a decrease (-56.67%) in sucrose consumption(1.3±0.1 versus 3±0.5 mL). This decrease was reversed in the nicotine, IMI, SERT treated groups to – 33.33%; -16.67% and -20% respectively of the control group level (2±0.2; 2.5±0.1 and 2.4±0.3 versus 3 ±0.5 mL). In the groups treated with the combined regimen of drugs, the decrease was significantly reversed to be +10% and +11.76% respectively of the control group (3.3±0.1 and 3.4±0.1 versus 3 ±0.5 mL).

DISCUSSION

In the present study, nicotine was inactive in the forced swimming test , however there was an increase in the antidepressant activity of IMI and SERT when given in combination to nicotine. Additionally, there was a reversal of model of anhedonia when nicotine given alone or in combination with IMI or SERT. These results are in agreement with results of Popik *et al.* (2003), who demonstrated a potentiation of antidepressant-like action of imipramine by nicotine in a screening test in mice. Popik et al. (2005) reported that treatment of rats with nicotine for 2 weeks produced behavioral and neurochemical manifestations characteristic of antidepressant like actions. It potentiated apomorphine-induced hyperactivity, regarded as a characteristic effect of antidepressants (Spyraki and Fibiger, 1981).The potentiating effect of antidepressant action of either IMI or SERT by nicotine in the forced swimming test could be contributed to the stimulation of nicotinic cholinergic receptors at the beginning of therapy with antidepressants that can result in a decrease of the ß-adrenoceptors density (Popik *et al.*, 2005). This phenomenon of down regulation of β-adrenoceptors by 2-weeks administration of nicotine was demonstrated by the study of Pipok *et al.* (2005). On the other hand, the model of anhedonia produced an increase in the expression of pre- and post-synaptic dopamine D2 receptors in the nucleus accumbens (Ainworth *et al.*, 1998). Dmasma *et al.* (1989) reported that chronic treatment with nicotine produced adaptation of the dopaminergic system by increasing the extracellular concentrations of dopamine in mesolimbic areas. This is most likely due to the fact that activation of pre-synaptic nicotinic acetylcholine receptors evoked the vesicular release of dopamine and regulated the release of dopamine via the dopamine transporters (Drew *et al.*, 2000). Nicotine induced slow adaptation of β-adrenoceptors and enhanced release of norepinehrine through stimulation of acetylcholine receptors in brain cortices in rats (Rao *et al.*, 2003). Similar to that, imipramine and sertraline increased the availability of synaptic norepinephrine and serotonin by

inhibiting their reuptake (Amtage *et al*., 2004). The concentrations of serotonin (5-HT), norepinephrine (NE) and dopamine (DA) in the brain are critical for mood and motivational processes, and the distributions in these monoamine systems are considered to be responsible for mood instability and depression (Vetulani and Nalepa, 2000). Nicotinic acetyl-choline receptors are located mainly presynaptically and modulated the release of a variety of neurotransmitters including acetyl choline (Ach) itself, DA, NE and 5-HT (Toth *et al*., 1992). Combined administration of nicotine and IMI or SERT may result in the significant increase in the concentrations of monoamines and/or prolongation of their presence in synaptic cleft as a consequence of enhanced monoamine release. (Popik *et al*., 2003).The behavioral outcome of antidepressant action in this study is demonstrated as a decrease in immobility time in the forced swimming test in the tested groups. These results can suggest that the antidepressant like effect of nicotine is detected only with co-administration of monoamine reuptake inhibitors. In support, Ribeiro et al. (1993), found that s.c. injection of nicotine increased 5-HT concentration in the frontal cortex of anesthetized rats for the first 15 min. after nicotine injection; and in the presence of fluoxetine (SSRI). In conclusion, nicotine potentiates the antidepressant effects of either imipramine or sertraline as evidenced by the reduction in the immobility time of the forced swimming test and the reversal of anhedonia in mice exposed to 3-weeks application of stressors.

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