NICOTINE DISPLAYS ANTIDEPRESSANT ACTIVITY DURING THE RAT FORCED SWIMMING TEST

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Abstract: *Nicotine addiction is frequent in people with mood disorders; however the mechanisms involved in nicotine action are not well understood, despite numerous electrophysiological, pharmacological and behavioural studies. The present study investigates the antidepressant effect of nicotine on 30 male Wistar rats divided into three groups: nicotine, nicotine plus mecamylamine and control. The rats were exposed after substance administration to the forced swimming test, the most predictive and widely used animal test for antidepressant action. The results showed a significant increase in swimming activity, a reduction of immobility activity and a delay in immobility latency. The effects of nicotine were blocked by mecamylamine administration. The study demonstrates that acute nicotine administration induces the activation of serotonergic neurons, acting as an antidepressant pharmacological agent.*

Cuvinte cheie: *testul înotului forțat, mecamilamină, nicotină, serotonină*

Rezumat: *Dependența de nicotină este frecvent întâlnită la pacienții cu tulburări de dispoziție, totuși mecanismele implicate în acțiunea nicotinei sunt încă insuficient cunoscute, în ciuda numeroaselor studii de electrofiziologie, farmacologie și comportament din literatură. Studiul prezent investighează efectul antidepresiv al nicotinei pe un număr de 30 de șobolani Wistar, împărțiți în trei loturi: nicotină, nicotina plus mecamilamină și control. După administrarea substanțelor, animalele au fost expuse testului de înot forțat, cel mai răspândit și mai predictiv test utilizat pentru demonstrarea efectelor antidepresive la animal. Rezultatele demonstrează o creștere semnificativă a timpului de înot, o reducere a imobilității și o creștere a latenței imobilității. Efectele induse de nicotină au fost inhibate în situația administrării mecamilaminei. Studiul prezent demonstrează că administrarea acută a nicotinei conduce la activarea neuronilor serotonergici și acționează ca un agent farmacologic antidepresiv.*

INTRODUCTION

Tobacco smoking is probably the most widespread and persistent addiction in humans and is driven by nicotine in tobacco smoke.

Over the last several decades, numerous studies have investigated the molecular genetics, pharmacology, electrophysiology and behaviour in nicotine reinforcement.

Although several treatments have been designed for smoking cessation, smoking motivations like the ability to control symptoms of anxiety and depression or the desire to control appetite are not fully understood in terms of functional mechanisms.(1)

Serotonin (5-HT) neurons are located mainly in the raphe nuclei of the brain stem and provide the majority of 5-HT innervations to the forebrain.

Their function is associated to wide spectrum of actions in the nervous system by modulating neural development, synaptic plasticity, pain sensation, rhythm, food intake and a variety of behaviours.(2-4)

It has been proposed that perturbation of the 5-HT level in the brain contributes to depression and anxiety.(5,6) Several lines of evidence suggest that forebrain 5-HT contributes to acute and chronic nicotine exposure.

Nicotine increases the firing rate of neurons located in the raphe nuclei and leads to a rise in extracellular 5-HT in some regions of the forebrain.(7,8)

Direct administration of nicotine to the dorsal raphe nuclei (DRN) demonstrated clear anxiolytic effects (9).

Certain studies point nicotine to be involved in the onset of depression secondary to the suppression of 5-HT transporters (10) and the inhibition of 5-HT_3 receptors.(11)

The forced swimming test (FST) is a common behavioural test for assessing depression in rodents and testing the efficiency of anti-depressant drugs. Despite some limitations, the FST is currently the most widely used preclinical in-vivo test of antidepressant efficacy.(12,13)

PURPOSE

The aim of the current study is to investigate the effects of nicotine acute administration on a rat model of depression, involving the forced swimming test.

To validate the behavioural effects of nicotine, mecamylamine hydrochloride, a noncompetitive nicotinic acetylcholine receptor antagonist was also administered.

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METHODS

The study was conducted in accordance with the guiding principles for biomedical research involving animals as stated by the European Communities Council Directive 86/609/EEC and carried out with approval of the local ethics committee for animal research of "Carol Davila" University of Medicine and Pharmacy (Bucharest, Romania).

Substances. Nicotine and mecamylamine hydrochloride were obtained from Sigma-Aldrich Gmbh, Munich, Germany. Both agents were administered through intraperitoneal (i.p.) injection. A 0.15 mg/kg dose was used for nicotine.

For mecamylamine hydrochloride a 2 mg/kg dose was used (dissolved as base, 167.29 g per mole).

Animals and treatments. Adult male Wistar rats (aged 14 weeks, body weight 291 ± 31 g, n=30), housed in individual cages, floored with wood shavings, in a room with constant temperature (23°C) and 12-h light-dark cycle (lights on at 07:00 h), with free access to rat chow and water ad libitum, were randomly allocated into three experimental groups: nicotine group (NIC) (N=10) – treated with nicotine i.p. injection; nicotine and mecamylamine group (MEC) (N=10) – in which mecamylamine was administered, rats were placed back into home cages for 10 min before receiving the nicotine dose; control group (N=10) received only saline i.p. injection.

Behavioural tests. The (Porsolt) forced swim test, also known as the behavioural despair test, was used to test for depression-like behaviour. The FST apparatus consists of a glass cylinder (30 cm diameter, 45 cm tall) filled with water to a depth of 20 cm and maintained at a temperature of 23-25°C.

Animals are subjected to two trials in the FST apparatus. The first trial lasts 15 minutes. Then, after 24-hours, a second trial is performed that lasts 5 minutes. The second trial represents the actual testing, the investigated drugs being administered 30 minutes prior to the trial. An automated video-tracking software system (Ethovision 3.0, Noldus, Leesburg, VA) simultaneously analyzes the behavioral response of the animal in real-time.

During the trial, behavioural responses are separated into 3 categories: immobility, swimming, climbing (14). Measurements of the behavioural response are tabulated in 10 1-min bins.

Statistical analysis. Differences between measurements were compared by the Wilcoxon's matched pairs signed-rank test using SPSS software (version 11.0, SPSS Inc., Chicago, IL). If not otherwise indicated, results are presented as mean ± SD. Significant differences were considered if $p < .05$.

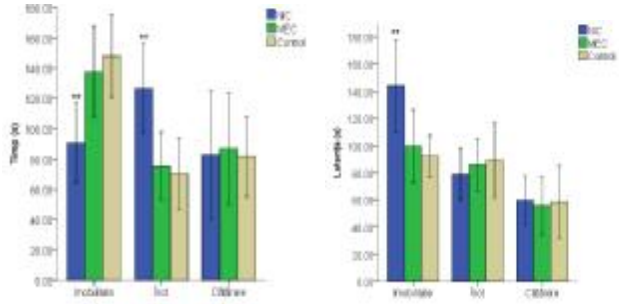
RESULTS

The administration of nicotine demonstrates a significant reduction of immobility (90.7 ± 13.1 s, $p < .001$) compared to the control (147.9 ± 13.5 s) and MEC (137.6 ± 15.1 s) groups ; and an increase in swimming activity (126.6 ± 14.6 s, $p < .001$) compared to control (70.4 ± 11.8 s) and MEC (75.4 ± 11.1 s) groups (figure no. 1).

No significant differences were noticed between MEC and control group, for the measurements of immobility and swimming, as well as between the three groups while quantifying climbing activity.

While measuring the latencies of different activities during the FST, a significant delay was noticed for nicotine (144.0 ± 16.9 s, $p < .001$) compared to control (92.0 ± 7.6 s) and MEC (99.5 ± 13.4 s) groups.

Figure no 1. Effects on immobility, swimming and climbing in the forced swimming test in the nicotine (NIC), nicotine plus mecamylamine (MEC) and control groups ** p < .001 vs. control and MEC groups



DISCUSSIONS

Animal behaviour during FST has been divided into three categories: climbing has been associated to noradrenergic neurotransmission, enhancement of 5-HT neurotransmission is expressed during swimming, and immobility as a marker of behavioural despair.(15,16)

In the present study the administration of nicotine demonstrates a significant increase in serotonergic activity by increasing swimming activity and reducing immobility. The effect is consolidated by the results obtained from the MEC group, which demonstrate the reversal of the effects elicited by nicotine under mecamylamine receptor blockade. A second finding of the present study demonstrates a significant increase in the latency of immobility under nicotine administration, which is also reverted by mecamylamine coadministration. A nonsignificant difference could be noticed between the MEC and the control groups during the FST. This difference might be explained by the incomplete antagonist effect of mecamylamine on the nicotinic receptors, as the α7 nicotinic acetylcholine receptors are not blocked by mecamylamine.

Our results are in accordance with previously published studies that demonstrate that nicotinic effects are mediated by 5-HT1A receptors showing that nicotine can have anxiolytic and antidepressant actions.(17) Studies done on rat midbrain slices demonstrated an increase in DRN neurons firing rates after the administration of nicotine, but the effects were blocked by mecamylamine administration.(8) However, there are still controversies in the understanding of nicotine action on the 5-HT systems. For instance, a paradoxical situation is the activation of the 5-HT system both by exposure to nicotine and by withdrawal from it. Endogenous activation of several 5-HT receptors appears to contribute to nicotine withdrawal syndromes including anxiety (18,19) and place aversion.(20) Another paradoxical situation is that although nicotine administration demonstrates antidepressant effects, as it results from our study but also from the literature (21), long term administration of nicotine is associated with pro-inflammatory processes and increased oxidative stress leading to the development of depressive disorders.(22)

A limitation of the current study is that nicotine administration is associated to locomotor stimulation, mediated probably by activation of postsynaptic dopamine receptors in the nucleus accumbens.(23,24) Therefore a cumulative locomotor effect due to dopamine system stimulation is hard to exclude. The antidepressant effects of nicotine during the forced swimming test might be enhanced through the effect of nicotine on dopaminergic neurons (25), however this effect could be responsible for the reduction of immobility but not for the increase in swimming activity.(26)

CONCLUSIONS

The results of this study show that acute nicotine administration increases swimming activity during the forced swimming test in rats, presumably by stimulating the serotonergic neurons. The concomitant administration of mecamylamine eliminates the effects induced by nicotine. Acute administration of nicotine demonstrates clear antidepressant effects, however further studies are needed to fully understand the pharmacological and behavioural action of nicotine.

REFERENCES

1. Picciotto MR, Mineur YS. Molecules and circuits involved in nicotine addiction: The many faces of smoking. Neuropharmacology; 2013.
2. Sodhi MS, Sanders-Bush E. Serotonin and brain development. Int Rev Neurobiol. 2004;59:111-174.
3. Jacobs BL, Azmitia EC. Structure and function of the brain serotonin system. Physiol Rev. 1992;72(1):165-229.
4. Nastase A, Ioan S, Braga RI, Zagrean L, Moldovan M. Coffee drinking enhances the analgesic effect of cigarette smoking. Neuroreport. 2007;18(9):921-924.
5. Middlemiss DN, Price GW, Watson JM. Serotonergic targets in depression. Curr Opin Pharmacol. 2002;2(1):18-22.
6. Naughton M, Mulrooney JB, Leonard BE. A review of the role of serotonin receptors in psychiatric disorders. Hum Psychopharmacol. 2000;15(6):397-415.
7. Mihailescu S, Guzman-Marin R, Dominguez MC, Drucker-Colin R. Mechanisms of nicotine actions on dorsal raphe serotoninergic neurons. Eur J Pharmacol. 2002;452(1):77-82.
8. Mihailescu S, Palomero-Rivero M, Meade-Huerta P, Maza-Flores A, Drucker-Colin R. Effects of nicotine and mecamylamine on rat dorsal raphe neurons. Eur J Pharmacol. 1998;360(1):31-36.
9. Cheeta S, Irvine EE, Kenny PJ, File SE. The dorsal raphe nucleus is a crucial structure mediating nicotine's anxiolytic effects and the development of tolerance and withdrawal responses. Psychopharmacology (Berl). 2001;155(1):78-85.
10. Xu Z, Seidler FJ, Ali SF, Slikker W, Jr., Slotkin TA. Fetal and adolescent nicotine administration: effects on CNS serotonergic systems. Brain Res. 2001;914(1-2):166-178.
11. Breitinger HG, Geetha N, Hess GP. Inhibition of the serotonin 5-HT3 receptor by nicotine, cocaine, and fluoxetine investigated by rapid chemical kinetic techniques. Biochemistry. 2001;40(28):8419-8429.
12. Cryan JF, Markou A, Lucki I. Assessing antidepressant activity in rodents: recent developments and future needs. Trends Pharmacol Sci. 2002;23(5):238-245.
13. Lucki I. The forced swimming test as a model for core and component behavioral effects of antidepressant drugs. Behav Pharmacol. 1997;8(6-7):523-532.
14. Porsolt RD, Brossard G, Hautbois C, Roux S. Rodent models of depression: forced swimming and tail suspension behavioral despair tests in rats and mice. Curr Protoc Neurosci; Chapter 8:Unit; 2001.
15. Detke MJ, Rickels M, Lucki I. Active behaviors in the rat forced swimming test differentially produced by serotonergic and noradrenergic antidepressants. Psychopharmacology (Berl). 1995;121(1):66-72.
16. Detke MJ, Lucki I. Detection of serotonergic and noradrenergic antidepressants in the rat forced swimming test: the effects of water depth. Behav Brain Res. 1996;73(1-2):43-46.
17. Seth P, Cheeta S, Tucci S, File SE. Nicotinic--serotonergic interactions in brain and behaviour. Pharmacol Biochem Behav. 2002;71(4):795-805.
18. West R, Hajek P, McNeill A. Effect of buspirone on cigarette withdrawal symptoms and short-term abstinence rates in a smokers clinic. Psychopharmacology (Berl). 1991;104(1):91-96.
19. Hilleman DE, Mohiuddin SM, Del Core MG, Sketch MH, Sr. Effect of buspirone on withdrawal symptoms associated with smoking cessation. Arch Intern Med. 1992;152(2):350-352.
20. Suzuki T, Ise Y, Tsuda M, Maeda J, Misawa M. Mecamylamine-precipitated nicotine-withdrawal aversion in rats. Eur J Pharmacol. 1996;314(3):281-284.
21. Caldirola D, Dacco S, Grassi M, Citterio A, Menotti R, Cavedini P, et al. Effects of cigarette smoking on neuropsychological performance in mood disorders: a comparison between smoking and nonsmoking inpatients. J Clin Psychiatry 2013; 74(2):e130-e136.
22. Nunes SO, Vargas HO, Prado E, Barbosa DS, de Melo LP, Moylan S, et al. The shared role of oxidative stress and inflammation in major depressive disorder and nicotine dependence. Neurosci Biobehav Rev; 2013.
23. Benwell ME, Balfour DJ. The effects of acute and repeated nicotine treatment on nucleus accumbens dopamine and locomotor activity. Br J Pharmacol. 1992;105(4):849-856.
24. Clarke PB, Fu DS, Jakubovic A, Fibiger HC. Evidence that mesolimbic dopaminergic activation underlies the locomotor stimulant action of nicotine in rats. J Pharmacol Exp Ther. 1988;246(2):701-708.
25. Borsini F, Lecci A, Mancinelli A, d'Aranno V, Meli A. Stimulation of dopamine D-2 but not D-1 receptors reduces immobility time of rats in the forced swimming test: implication for antidepressant activity. Eur J Pharmacol. 1988;148(3):301-307.
26. Perona MT, Waters S, Hall FS, Sora I, Lesch KP, Murphy DL, et al. Animal models of depression in dopamine, serotonin, and norepinephrine transporter knockout mice: prominent effects of dopamine transporter deletions. Behav Pharmacol. 2008;19(5-6):566-574.