Nicotine Influences the Motor Performance of Immature Rats in Two Different Sensorimotor Tasks

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Received March 25, 2011; Accepted July 1, 2011.

Key words: Nicotine – Motor performance – Sensorimotor test – Rat behaviour

Abstract: The aim of this study was to assess the effect of nicotine on motor performance of immature (12-day-old) rats. We used two sensorimotor tasks (surface righting response and negative geotaxis test) to evaluate the influence of nicotine on animal's motor activity in course of 24 hours. Animals were treated intraperitoneally with two different nicotine doses (0.5 mg/kg and 1.0 mg/kg) and tested in four sessions (1 minute, 10 minutes, 1 hour and 24 hours after the injection). We concluded that nicotine significantly influences the motor behaviour in 12-day-old rats and this effect is dose dependent.

This study was supported by grants GAČR 305/09/P136 and MSM 00216 208 16.

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Introduction

Nicotine is the principal alkaloid present in cigarette smoke and in recent decades this alkaloid has attracted the interest of many researcher groups because of its possible neuroprotective potential (Riljak et al., 2007; Shin et al., 2007; Ferrea and Winterer, 2009). Previously we demonstrated that nicotine is capable to influence the rat seizure susceptibility (Riljak et al., 2010), to ameliorate the neuronal damage caused by kainic acid administration (Riljak et al., 2007), to influence the density of NADPH-diaphorase positive cells in hippocampus (Riljak et al., 2006), and to change the EEG pattern and behaviour of experimental animals (Hralová et al., 2010). These findings bring about the question what dose of nicotine, used as pretreatment to excitotoxin administration or to other challenging condition (e.g. hypoxia) has the minimal side effects and is still effective to ameliorate the consequences of such conditions. Adverse effects of nicotine represent mainly: the loose of posture control and pathological breathing pattern (Hralová et al., 2010). The question therefore was how long after the administration is the drug able to influence the motor performance of young rats and whether the motor response is dose related. In the view of data mentioned above, the aim of this study was to assess the effect of nicotine, administered in different doses on motor performance of immature 12-day-old rats. Two relatively simple sensorimotor tasks were used to evaluate the influence of nicotine on animal's motor response in the course of 24 hours.

Material and Methods

Animals

Male Wistar rats (of our own breed) 12 days old were used in our experiments. Animals were housed at a constant temperature (23 ± 1 °C) and relative humidity (60%) with a fixed 12 h light/dark cycle and pups where kept together with their mothers. Mothers have been fed with food and water *ad libitum*. On the testing day animals were transported into the experimental room and pups were separated from their mother. The cage was placed on a heating pad maintained at 34 °C (nest temperature). Animals were weighed, marked and randomly assigned into three groups, treated with two different doses of nicotine and with equal volume of saline. All experiments were carried out in accordance with the European Communities Council Directive (86/609/EEC) and in agreement with the guidelines of the Animal Protection Law of the Czech Republic.

Statistics

Motor performance data were subjected to nonparametric tests. To compare the differences in motor performances between four subsequent sessions in particular groups the Friedman test followed by Wilcoxon signed rank test were used. To compare the differences between the different doses of nicotine and appropriate control groups within a given session, Kruskal-Wallis test and the Mann-Whitney test were used.

Drugs and experimental groups
All drugs were applied intraperitoneally. The solutions were freshly prepared for each experiment. The recalculated volume per body mass was same for both nicotine (Sigma) concentrations (1 ml of solution/kg of body mass).

Animals were assigned into following experimental group (each group consisted of 10 animals):

1. animals treated with 0.5 mg/kg of nicotine,
2. animals treated with 1.0 mg/kg of nicotine,
3. animals treated with the equal volumes of normal saline solution.

Motor performance procedures
In the study two modified sensorimotor tests described by other authors (Kubová et al., 1999; Mikulecká and Mareš, 2002) were used: surface righting response and negative geotaxis. In the first test pups were individually placed in a supine position on the desk and the time to righting was recorded. Animals were tested for a maximum of 60 seconds. In the second test animals were placed individually on an inclined (30°) surface with the head facing downwards. The ability (and time) of animal to turn for 180° was recorded. Animals were tested for a maximum of 60 seconds. Each test was performed 3 times in close succession. Both of the tests were performed immediately after the drug or saline administration, and after 10 minutes, 1 hour and 24 hours after the injection.

Results

Surface righting
Nicotine in dose 1 mg/kg significantly extended the latency to the surface righting response in the very first tested interval compared to saline treated group. We detected the prolonged latency to surface righting response one hour after administration of 0.5 mg/kg nicotine. Statistical analysis of each particular group in time revealed, that administration of higher (1.0 mg/kg) nicotine bolus leaded to shortening of latencies to the surface righting response in time course (measurement in first minute significantly differs from measurement in 10 minutes, 1 hour and after 24 hours). There were no statistically significant changes in vehicle treated group.

Negative geotaxis
Nicotine influenced the time of turning in the negative geotaxis response only in the last measured session (24 hours after nicotine treatment). Statistical analysis of each particular group in time revealed significant differences between the first and the last session, the second and last session and the third and last session (lower nicotine concentration). Higher concentration of nicotine caused the statistically significant difference between the third and the last session. There were no statistically significant changes in vehicle treated group.

Discussion

The present data demonstrate that nicotine influences significantly the motor performance of immature rats in both used sensorimotor tasks. Administration of nicotine is associated with broad range of physiological and behavioural processes such as brain cortex excitability (Riljak et al., 2010), cognitive, neuromuscular and autonomic functions (Riljak and Langmeier, 2005). Moreover in recent years nicotine has been promoted to ameliorate the consequences of processes such as aging and neurodegeneration (Carrasco et al., 2006; Redolat et al., 2009; Aleisa et al., 2010). Nicotine pretreatment has been repeatedly demonstrated as powerful factor protecting neuronal cells from effects of hypoxia and excitatory amino acids-induced changes in the central nervous system (Kim et al., 2000; Riljak and Langmeier, 2005; Khwaja et al., 2007). In our experimental design we tried to test the influence of a single dose of nicotine (doses have been chosen according to our previous experiments and according to well documented literature evidence) on the motor performance of immature rats, with the aim to elucidate possible dose dependent effects in the course of time. Presented results showed clearly that nicotine in concentration 1 mg/kg acutely influenced (prolonged) the surface righting response nearly immediately after drug injection (session 1 min). Later on (session 10 min, 1 hour, 24 hour) the effect of nicotine

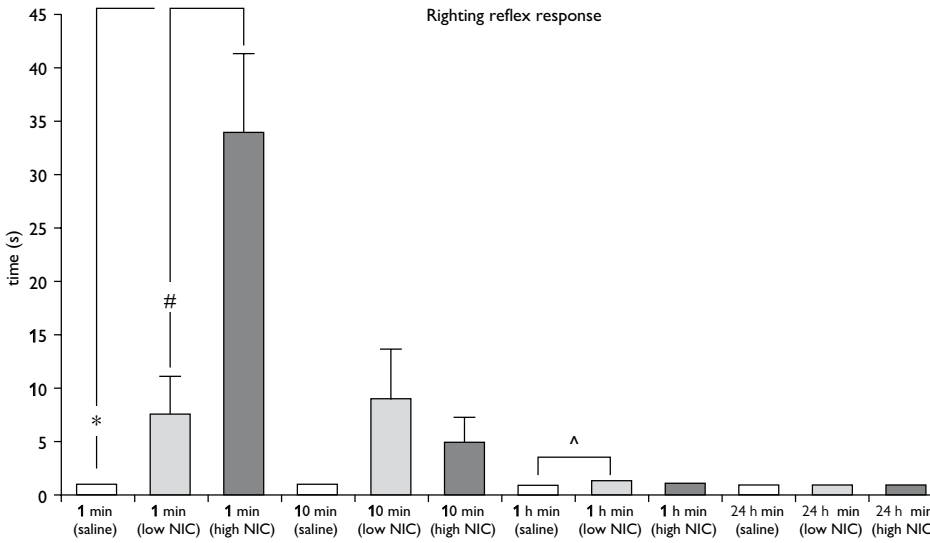

Figure 1 – Latency to surface righting at four different intervals (1 minute, 10 minutes, 1 hour and 24 hours after nicotine or vehicle administration. Low NIC – nicotine administered in dose 0.5 mg/kg of body mass, high NIC – nicotine administered in dose 1.0 mg/kg of body mass. Ordinate: latencies in seconds. (*) and (#) and (^) signalize the significant difference between particular columns. For (*) p≤0.01, for (#) p≤0.01 and for (^) p≤0.05.

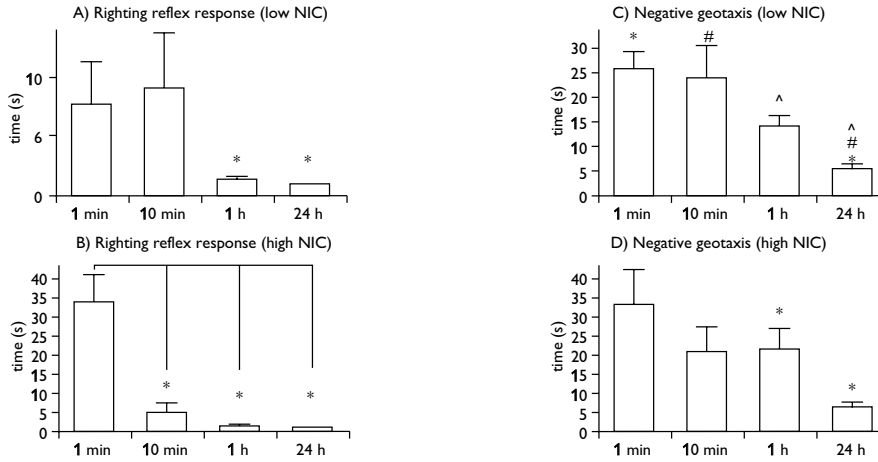

Figure 2 – A: Latency to surface righting. Statistical comparison within the experimental group treated with 0.5 mg/kg of nicotine (low NIC). (*) signalize significant difference between the 3rd and 4th session (1 hour vs. 24 hours). For (*) p≤0.1. B: Latency to surface righting. Statistical comparison within the experimental group treated with 1 mg/kg of nicotine (high NIC). (*) signalize significant difference between the 1st session and the remaining sessions. For (*) p≤0.1. C: Negative geotaxis response. Statistical comparison within the experimental group treated with 0.5 mg/kg of nicotine (low NIC). (*) and (#) and (^) signalize the significant difference between particular columns. For (*) p≤0.05, for (#) p≤0.1 and for (^) p≤0.1. D: Negative geotaxis response. Statistical comparison within the experimental group treated with 1 mg/kg of nicotine (high NIC). (*) signalize the significant difference between particular columns. For (*) p≤0.05.

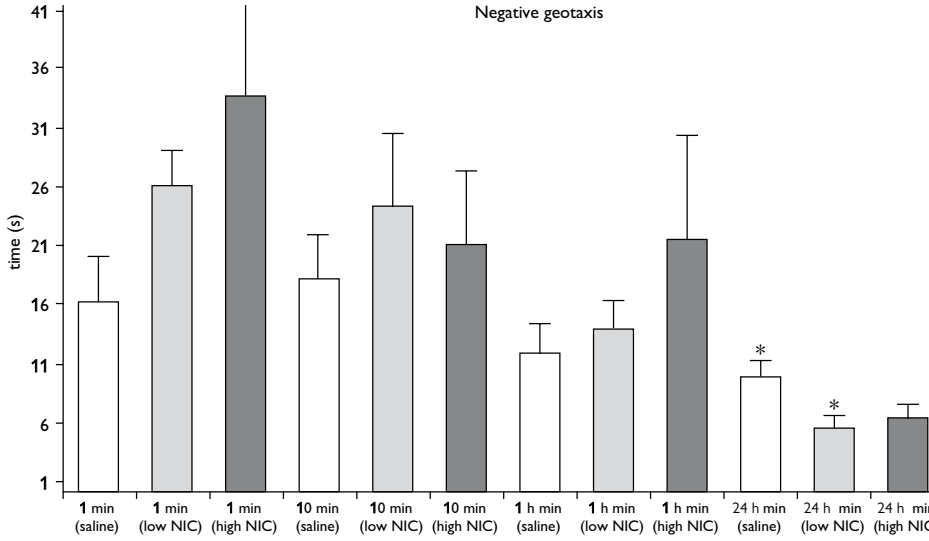

Figure 3 – Negative geotaxis response at four different intervals (1 minute, 10 minutes, 1 hour and 24 hours after nicotine or vehicle administration. Low NIC – nicotine administered in dose 0.5 mg/kg of body mass, high NIC – nicotine administered in dose 1.0 mg/kg of body mass. Ordinate: latencies in seconds. (*) signalize the significant difference between particular columns. For (*) p≤0.01.

was not pronounced. As showed on Figures 1 and 2, the duration of righting response shortened and comparison of the session at the very first minute with all the remaining sessions showed significantly prolonged reaction. The test of negative geotaxis brought very similar results (Figures 2 and 3) – the tendency to decrease the time needed for righting from supine position significantly shorter 24 hours after the injection when compared with measurements performed closer to nicotine administration. This effect was expressed also when only 0.5 mg/kg of nicotine was used. Our results suggest, that the effect of nicotine (given acutely) on motor performance is rapid but disappears in 24 hours. It can be explained by a rapid nicotine resorption and fast nicotine metabolism. Interestingly the shortening of time necessary for turning on the incline desk in last experimental session (24 hours after nicotine administration) after injection of 0.5 mg/kg of nicotine was observed. This effect could be partially explained by the process of learning – data, that nicotine enhance such processes are already present in literature (Carrasco et al., 2006; Raybuck and Gould, 2010). On the other hand results obtained from the second test (righting response) did not confirm this learning paradigm. Very important appears also the ontogenetic aspect and immature central nervous system in animals tested in this experimental design. It is possible to conclude that nicotine significantly influences the motor behaviour of 12-day-old rats and this effect is dose dependent.

References

Aleisa, A. M., Helal, G., Alhaider, I. A., Alzoubi, K. H., Srivareerat, M., Tran, T. T., Al-Rejaie, S. S., Alkadhi, K. A. (2010) Acute nicotine treatment prevents REM sleep deprivation-induced learning and memory impairment in rat. *Hippocampus* doi: 10.1002/hipo.20806. (Epub ahead of print)

Carrasco, C., Vicens, P., Redolat, R. (2006) Neuroprotective effects of behavioural training and nicotine on age-related deficits in spatial learning. *Behav. Pharmacol.* **17**, 441–452.

Ferrea, S., Winterer, G. (2009) Neuroprotective and neurotoxic effects of nicotine. *Pharmacopsychiatry* **42**, 255–265.

Hralová, M., Marešová, D., Riljak, V. (2010) Effect of the single-dose of nicotine-administration on the brain bioelectrical activity and on behaviour in immature 12-day-old rats. *Prague Med. Rep.* **111**, 182–190.

Khwaja, M., McCormack, A., McIntosh, J. M., Di Monte, D. A., Quik, M. (2007) Nicotine partially protects against paraquat-induced nigrostriatal damage in mice; link to alpha6beta2* nAChRs. *J. Neurochem.* **100**, 180–190.

Kim, H. C., Jhoo, W. K., Ko, K. H., Kim, W. K., Bing, G., Kwon, M. S., Shin, E. J., Suh, J. H., Lee, Y. G., Lee, D. W. (2000) Prolonged exposure to cigarette smoke blocks the neurotoxicity induced by kainic acid in rats. *Life Sci.* **66**, 317–326.

Kubová, H., Mikulecká, A., Haugvicová, R., Mareš, P. (1999) The benzodiazepine receptor partial agonist Ro 19-8022 suppresses generalized seizures without impairing motor functions in developing rats. *Naunyn Schmiedebergs Arch. Pharmacol.* **360**, 565–574.

Mikulecká, A., Mareš, P. (2002) NMDA receptor antagonists impair motor performance in immature rats. *Psychopharmacology (Berl.)* **162**, 364–372.

Raybuck, J. D., Gould, T. J. (2010) The role of nicotinic acetylcholine receptors in the medial prefrontal cortex and hippocampus in trace fear conditioning. *Neurobiol. Learn. Mem.* **94**, 353–363.

Redolat, R., Pérez-Martínez, A., Carrasco, M. C., Mesa, P. (2009) Individual differences in novelty-seeking and behavioral responses to nicotine: a review of animal studies. *Curr. Drug Abuse Rev.* **2**, 230–242.

Riljak, V., Langmeier, M. (2005) Nicotine an efficient tool of the neurobiological research today, the tool of treatment tomorrow? *Prague Med. Rep.* **106**, 329–348.

Riljak, V., Milotová, M., Jandová, K., Marešová, D., Pokorný, J., Trojan, S., Langmeier, M. (2006) Changes in the number of nitrergic neurons in rats hippocampus following nicotine administration. *Prague Med. Rep.* **107**, 117–124.

Riljak, V., Milotová, M., Jandová, K., Pokorný, J., Langmeier, M. (2007) Morphological changes in the hippocampus following nicotine and kainic acid administration. *Physiol. Res.* **56**, 641–649.

Riljak, V., Marešová, D., Pokorný, J. (2010) Nicotine effects on rat seizures susceptibility and hippocampal neuronal degeneration. *Neuro Endocrinol. Lett.* **31**, 792–795.

Shin, E. J., Chae, J. S., Jung, M. E., Bing, G., Ko, K. H., Kim, W. K., Wie, M. B., Cheon, M. A., Nah, S. Y., Kim, H. C. (2007) Repeated intracerebroventricular infusion of nicotine prevents kainate-induced neurotoxicity by activating the alpha7 nicotinic acetylcholine receptor. *Epilepsy Res.* **73**, 292–298.