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The effects of dopaminergic drugs in the dorsal hippocampus of mice in the nicotine-induced anxiogenic-like response

Mohammad Nasehi [a], Fatemeh Mafi [b], Shahrbanoo Oryan [b], Sima Nasri [b], Mohammad Reza Zarrindast [c,d,e,f,*]

[a] Department of Biology, Faculty of Basic Sciences, Islamic Azad University, Garmsar Branch, Semnan, Iran
[b] Science Faculty, Department of Biology, Payam Noor University of Tehran, Tehran, Iran
[c] Institute for Cognitive Science Studies, Tehran, Iran
[d] Department of Physiology, Iran University of Medical Sciences, Tehran, Iran
[e] Department of Pharmacology and Iranian National Center for Addiction Studies, School of Medicine, Tehran University of Medical Sciences, Tehran, Iran
[f] Institute for Studies in Theoretical Physics and Mathematics, School of Cognitive Sciences, Tehran, Iran

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ABSTRACT

Rationale: Nicotine, an active alkaloid of tobacco has an acetylcholine property that alters anxiety-like behaviors in rodents. Moreover, several investigations suggest that the mesolimbic/cortical dopamine systems to be involved in the drugs affecting anxiety. The dopaminergic modulation of acetylcholine synaptic transmission has also been also suggested by different studies. Furthermore, modulation of such behaviors in rodents may be mediated through the dorsal hippocampus.
Objectives: In the present study, a possible role of the dorsal hippocampal acetylcholine receptor mechanism in nicotine's influence on anxiogenic-like responses has been investigated.
Methods: During test sessions, the hole-board was used to investigate the effects of SCH23390, sulpiride, SKF38393 and quipirole on nicotine response in mice.
Results: Intraperitoneal (i.p.) administration of nicotine (0.5 mg/kg) decreased the number of head dips but had no effect on other behaviors. Intra-dorsal hippocampal injections of ineffective doses of SCH23390 (SCH; 0.125 and 0.25 μg/mouse) or sulpiride (SUL; 0.5 and 0.75 μg/mouse) reversed head dips induced by nicotine but did not impact other exploratory behaviors. Furthermore, co-administration of ineffective doses of SKF38393 (SKF; 4 μg/mouse, dorsal hippocampus) or quipirole (QUI; 0.5 μg/mouse) in conjunction with an ineffective dose of nicotine (0.25 mg/kg, i.p.) decreased head dips induced by nicotine, but were otherwise ineffective.
Conclusion: These results may indicate a modulatory effect for the dorsal hippocampus dopamine receptors (D_1 and D_2) on an anxiogenic-like response induced by nicotine.

1. Introduction

Worldwide, nicotine is one of the most popular addictive drugs known to cause numerous pharmacological effects within both the central and peripheral nervous systems (Benowitz, 1988; Le Foll and Goldberg, 2009; Stolerman, 1988). In rodents, nicotine may have different effects on anxiety (anxiolytic, anxiogenic or no effect), all of which are dependent upon the species, strain, dose, route of administration, experimental paradigm or number of research trials conducted (Chae et al., 2008; Cheeta et al., 2001; File et al., 1998b; O'Neill and Brioni, 1994; Zarrindast et al., 2000; Zarrindast et al., 2008). Many of the drug's effects are due to its ability to interact with various neurotransmitters (Balfour, 1982), such as its direct excitatory action on the zona compacta neurons within the substantia nigra in the rat (Lichtensteiger et al., 1982), as well as increasing the release of dopamine (DA) from the limbic system (Imperato et al., 1986) and striatal slices (Lichtensteiger et al., 1982). Moreover, DA is one of the most active neuromodulators involved in the states of fear and anxiety (Feenstra et al., 1995). In fact, alterations in DA transmission occur following exposure to a wide variety of acute stressors (Goldstein et al., 1996).

On the other hand, it has been suggested that the dorsal hippocampus plays a role in anxiety, consistent with the importance of the hippocampus in various neurobiological theories of anxiety (LeDoux, 2000). The hippocampus is massively interconnected with the septum, and has important connections with the locus coeruleus, raphe nuclei, hypothalamus, amygdala and medial frontal cortex; areas that are involved in anxiety (Amaral, 2002). Furthermore, dopaminergic system(s) may regulate hippocampal cholinergic function. Considering the involvement of the dorsal hippocampus (Bannerman et al., 2003) and DA receptor (Corrigall et al., 1992) in the

* Corresponding author at: Department of Pharmacology, School of Medicine, Tehran University of Medical Sciences, Tehran, Iran, P.O.Box 13145–784. Tel./fax: +98 21 66402569.
E-mail address: zarinmr@ams.ac.ir (M.R. Zarrindast).

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modulation of anxiety-like behaviors; therefore, in the present study, the possible involvement of the dorsal hippocampal D_1 and D_2 dopaminergic receptors in nicotine's anxiogenic-like effect have been investigated with the use of the hole-board task.

2. Materials and methods

2.1. Animals

Male albino NMRI mice (Pasteur Institute, Tehran, Iran) weighing 25–30 g at the time of surgery were used. Animals were kept in an animal house with a 12 h light: dark cycle at a controlled temperature (22 ± 2 °C). Animals were housed in groups of ten in Plexiglass cages where food and water were available ad libitum. A total of ten animals were used in each group and each animal was used only once. Behavioral experiments were performed during the light phase of the light:dark cycle. Animal treatment and maintenance were conducted in accordance with the Principles of Laboratory Animal Care (NIH publication No. 85–23, revised 1985) and with the Animal Care and Use Guidelines of Tehran University of Medical Sciences.

2.2. Cannulae guide implantation

Mice were anesthetized with intraperitoneal (i.p.) injections of ketamine hydrochloride (50 mg/kg) plus xylazine (5 mg/kg) and placed in a stereotaxic apparatus. The skin was incised and the skull was cleaned. The 22-gauge guide cannulae were placed (bilaterally) 1 mm above the intended injection site according to the atlas of Paxinos and Franklin (Paxinos and Franklin, 2001). Stereotaxic coordinates for the dorsal hippocampus were: AP − 2 mm from the bregma; L ± 1.6 from the sagittal suture and V − 1.5 mm from the skull surface. The cannulae were secured with dental acrylic. Stainless steel stylets (27-gauge) were inserted into the guide cannulae to keep them free from debris. All animals were allowed a 1 week recovery period from surgery and the effects of the anesthetic agents prior to being used in the experiments.

2.3. Intra-dorsal hippocampus injections

For drug infusions, the animals were gently restrained by hand and the stylets were removed from the guide cannulae and replaced by 27-gauge injection needles (1 mm below the tip of the guide cannulae). Animals manually received a total volume of 1 μl/mouse (0.5 μl/side) over 60 s. Injection needles were left in place for an additional 60 s to facilitate diffusion.

2.4. Drugs

The following drugs were used in the experiments: nicotine hydrogen tartrate (Sigma, Poole, Dorset, UK), SCH23390 [SCH; R(1)-chloro-8-hydroxy-3-methyl-1-phenyl2,3,4,5-tetrahydro-1 H-3-enzazepine hydrochloride; Tocris, UK], sulpiride (SUL; Sigma Chemical Co., St. Louis, CA, USA), SKF38393 (SKF) and quinpirole (QUI; Sigma Chemical Co., St. Louis, CA, USA). SCH, SKF and QUI were dissolved in sterile 0.9% saline. SUL was dissolved in a minimal volume of diluted acetic acid (1 drop of 5 μl; pH 6.3), increased to a volume of 5 ml with 0.9% physiological saline and then diluted to the required volume with a 0.9% w/v NaCl solution. Nicotine was dissolved in sterile saline with subsequent adjustment of the pH to 7.2 with NaOH (0.1 N solutions). The drugs were injected in a volume of 0.5 μl/side of the dorsal hippocampus (1 μl/mouse). The total drug doses were expressed as μg/mouse.

2.5. Apparatus and behavioral test

The hole-board test, as a simple method for examining the response of an animal to an unfamiliar environment, was first introduced by Boissier and Simon (Boissier and Simon, 1962). This test has been used to evaluate emotional behavior, anxiety and/or responses to stress in animals (Rodriguez Echandia, 1987). Different behaviors which can be observed and measured in this test allow for a comprehensive description of the animal's behavior. The hole-board apparatus (Borj Sanat Co, Tehran, Iran) consisted of grey Perspex panels (40 cm × 40 cm, 2.2 cm thick) with 16 equidistant holes, 3 cm in diameter, in the floor constructed as previously described (Vinade et al., 2003). The board was positioned 15 cm above a table. Animals were placed singly in the center of the board away from the observer and head-dip numbers were recorded by photocells arranged below the holes over a 5 min period. Furthermore, locomotor activity was measured by an observer blinded to the treatments measured during the testing phase. For this purpose, the ground area hole-boards were divided into four equal sized squares. Locomotion was measured as the number of locomotor activity crossings from one square to another. Other behavioral performances such as latency to the first head-dipping, rearing, grooming and defecation were manually recorded by the observer during the test period. Data for rearing, grooming and defecation have not been shown in all experiments.

2.6. Drug treatments

2.6.1. Experiment 1: effects of nicotine on exploratory behaviors

Four groups of mice received saline (1 ml/kg) or nicotine (0.1, 0.25 and 0.5 mg/kg) and the hole-board test session was performed 30 min later. For all experiments, number of head dips, latency to the first head-dipping, locomotor activity, rearing, grooming and defecation were measured as previously described.

2.6.2. Experiment 2: effects of SCH on nicotine response

Eight groups of animals received saline (1 μl/mouse) or SCH (0.125, 0.5 and 0.5 μg/mouse, intra- dorsal hippocampus) 5 min before testing in the animals that were treated with either saline (1 ml/kg, i.p.) or nicotine (0.5 mg/kg, i.p.) 30 min before testing.

2.6.3. Experiment 3: effects of SUL on nicotine response

Eight groups of animals received saline (1 μl/mouse) or SUL (0.25, 0.5 and 0.75 μg/mouse, intra- dorsal hippocampus) 5 min before testing in the animals that were treated with either saline (1 ml/kg, i.p.) or nicotine (0.5 mg/kg, i.p.) 30 min before testing.

2.6.4. Experiment 4: effect of SKF and QUI on nicotine response

Six groups of mice received saline (1 μl/mouse, intra- dorsal hippocampus), SKF (4 μg/mouse, intra- dorsal hippocampus) and QUI (0.5 μg/mouse, intra- dorsal hippocampus) 5 min before testing in the animals that were treated with saline (1 ml/kg, i.p.) or nicotine (0.5 mg/kg, i.p.) 30 min before testing.

2.7. Statistical analysis

Data were presented as mean ± S.E.M. One-way repeated measure of analysis of variance (ANOVA) followed by Dunnett's test were used for statistical evaluation. $P<0.05$ was considered significant.

3. Results

3.1. Histology

Fig. 1 illustrates the approximate point of the drug injections in the dorsal hippocampus from animals (A). The histological results were plotted on representative sections taken from the mice brain atlas of (Paxinos and Franklin, 2001) (B). A total number of 343 animals were implanted into the dorsal hippocampus, but only the data from 280 animals with correct cannulae implants were included in the statistical analyses.

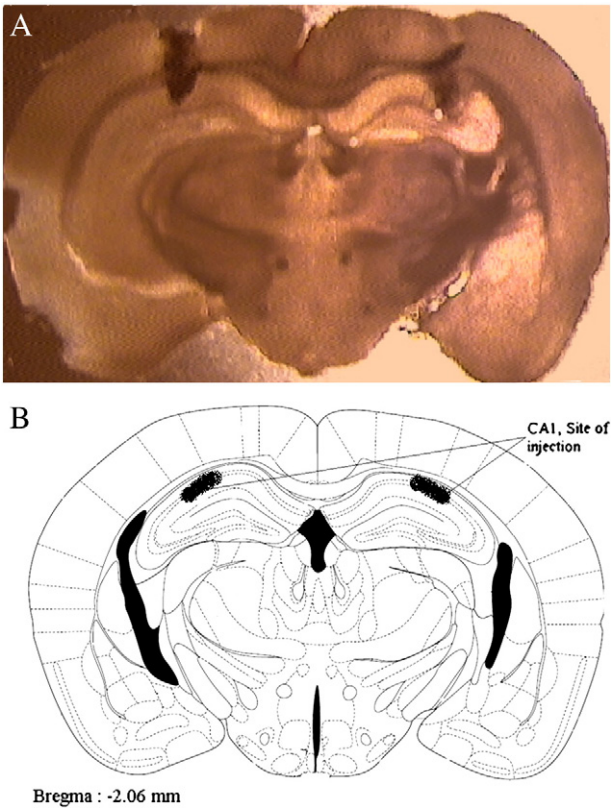

Fig. 1. A. The location of the injection cannulae tips in the dorsal hippocampus regions for all mice included in the data analyses. B. Verified section of dorsal hippocampus was taken from the mouse brain in stereotaxic coordinates (Paxinos and Franklin, 2001).

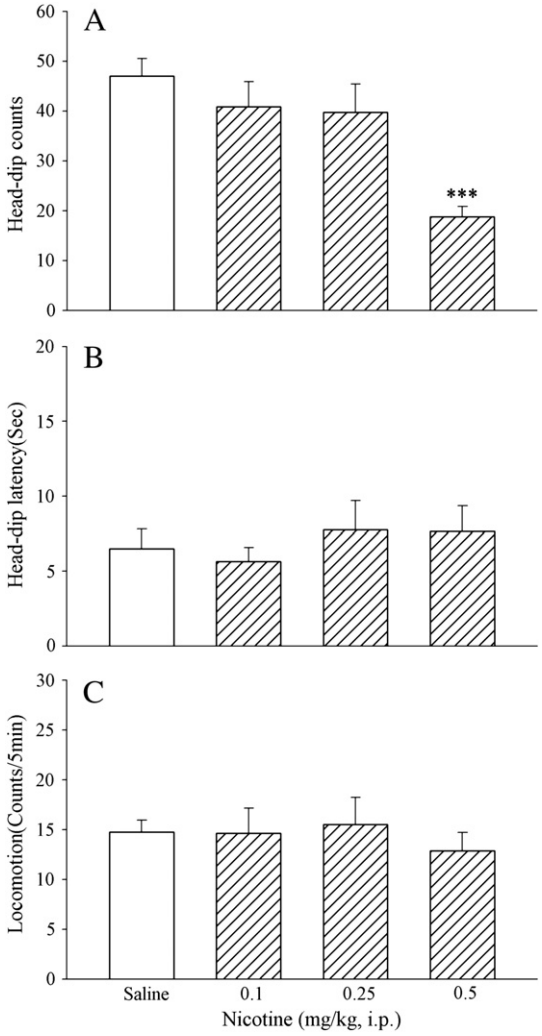

Fig. 2. The effects of nicotine and saline on exploratory behaviors. Different doses of nicotine (0.125, 0.25 and 0.5 mg/kg, i.p.) or saline (10 ml/kg, i.p.) were injected 30 min before testing and exploratory behaviors including head dips (panel A), latency to the first head-dipping (panel B) and locomotor activity (panel C) were examined. Each bar represents mean ± S.E.M. ***P<0.001, compared to the saline group.

3.2. Effects of nicotine on exploratory behaviors

One-way ANOVA and post hoc analysis revealed that nicotine (0.5 mg/kg) decreased head dips [$F(3, 28) = 8.2$, $P<0.001$], but had no effect on latency to the first head-dipping [$F(3, 28) = 0.43$, $P>0.05$], locomotor activity [$F(3, 28) = 0.26$, $P>0.05$], rearing [$F(3, 28) = 0.17$, $P>0.05$], grooming [$F(3, 28) = 1.77$, $P>0.05$] and defecation [$F(3, 28) = 0.14$, $P>0.05$] (Fig. 2).

3.3. Effects of SCH on nicotine response

One-way ANOVA and post hoc analysis revealed that SCH (0.5 μg/mouse) decreased head dips [$F(3, 28) = 3.64$, $P<0.05$] and defecation [$F(3, 28) = 4.2$, $P<0.05$], but was ineffective on latency to the first head-dipping [$F(3, 28) = 0.54$, $P>0.05$], locomotor activity [$F(3, 28) = 0.84$, $P>0.05$], rearing [$F(3, 28) = 0.34$, $P>0.05$] and grooming [$F(3, 28) = 0.34$, $P>0.05$] (Fig. 3; left panel).

According to one-way ANOVA and post hoc analysis, all doses of SCH (0.125, 0.25 and 0.5 μg/mouse) reversed the nicotine influence on head dips [$F(3, 28) = 8.80$, $P<0.01$]. SCH administered at a dose of 0.5 μg/mouse were shown to decrease latency to the first head-dipping [$F(3, 28) = 3.04$, $P<0.05$] and increase locomotor activity [$F(3, 28) = 1.73$, $P<0.05$] when combined with nicotine. No change was seen with the nicotine response in terms of rearing [$F(3, 28) = 2.21$, $P>0.05$], grooming [$F(3, 28) = 0.61$, $P>0.05$] and defecation [$F(3, 28) = 0.41$, $P>0.05$] (Fig. 3; right panel).

3.4. Effects of SUL on nicotine response

One-way ANOVA and post hoc analysis revealed that SUL did not alter head dips [$F(4, 35) = 0.76$, $P>0.05$], latency to the first head-dipping [$F(4, 35) = 0.24$, $P>0.05$], locomotor activity [$F(4, 35) = 0.83$, $P>0.05$], rearing [$F(4, 35) = 0.12$, $P>0.05$], grooming [$F(4, 35) = 1.33$, $P>0.05$] and defecation [$F(4, 35) = 1.22$, $P>0.05$] (Fig. 4; left panel).

SUL (0.5 and 0.75 μg/mouse) reversed the nicotine influence on head dips [$F(4, 35) = 4.3$, $P<0.01$], but did not change latency to the first head-dipping [$F(4, 35) = 1.04$, $P>0.05$], locomotor activity [$F(4, 35) = 0.5$, $P>0.05$], rearing [$F(4, 35) = 1.3$, $P>0.05$], grooming [$F(4, 35) = 1.25$, $P>0.05$] and defecation [$F(4, 35) = 0.60$, $P>0.05$] (Fig. 4; right panel).

3.5. Effects of SKF and QUI on nicotine response

According to one-way ANOVA and post hoc analysis, ineffective doses of SKF (4 μg/mouse, intra- dorsal hippocampus) and QUI (0.25 μg/mouse, intra- dorsal hippocampus) decreased head dips [$F(5, 42) = 7.99$, $P<0.001$] but were ineffective on latency to the first head-dipping [$F(5, 42) = 0.93$, $P>0.05$], locomotor activity [$F(5, 42) = 0.79$, $P>0.05$], rearing [$F(5, 42) = 1.33$, $P>0.05$], grooming [$F(5, 42) = 0.97$, $P>0.05$] and defecation [$F(4, 42) = 0.91$, $P>0.05$] which was induced by nicotine (0.25 mg/mouse, i.p.) (Fig. 5).

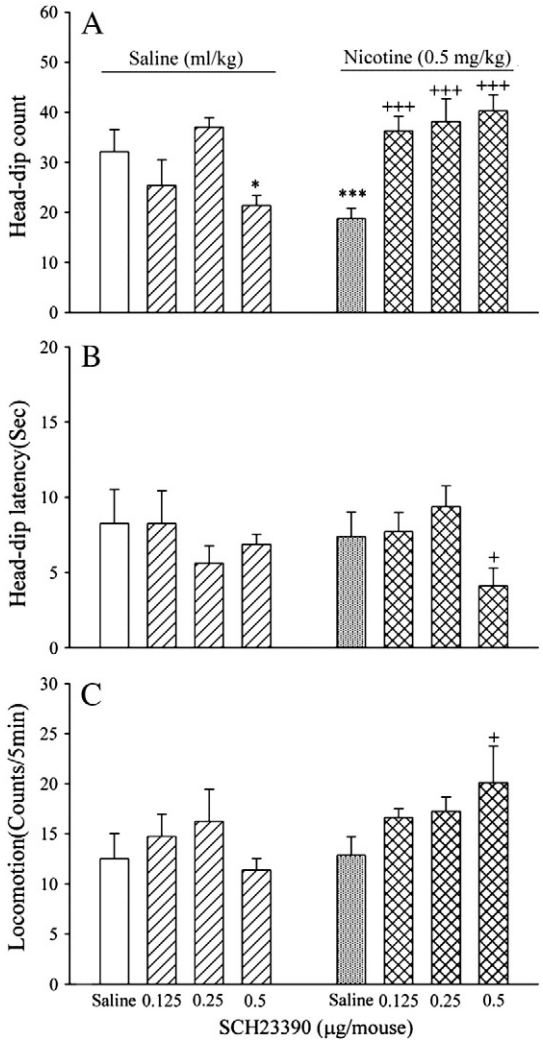

Fig. 3. The effects of pre-test administration of SCH (0.125, 0.25 and 0.5 μg/mouse, intra-dorsal hippocampus) or saline (1 μl/mouse, intra- dorsal hippocampus) on animals treated under the influence of saline (10 ml/kg, i.p.; left panel) or nicotine (0.5 mg/kg, i.p.; right panel) on exploratory behaviors. Each bar represents mean ± S.E.M. *P<0.05 and ***P<0.001 when compared to the saline/saline group. +P<0.05, +++P<0.001 when compared to the nicotine/saline group.

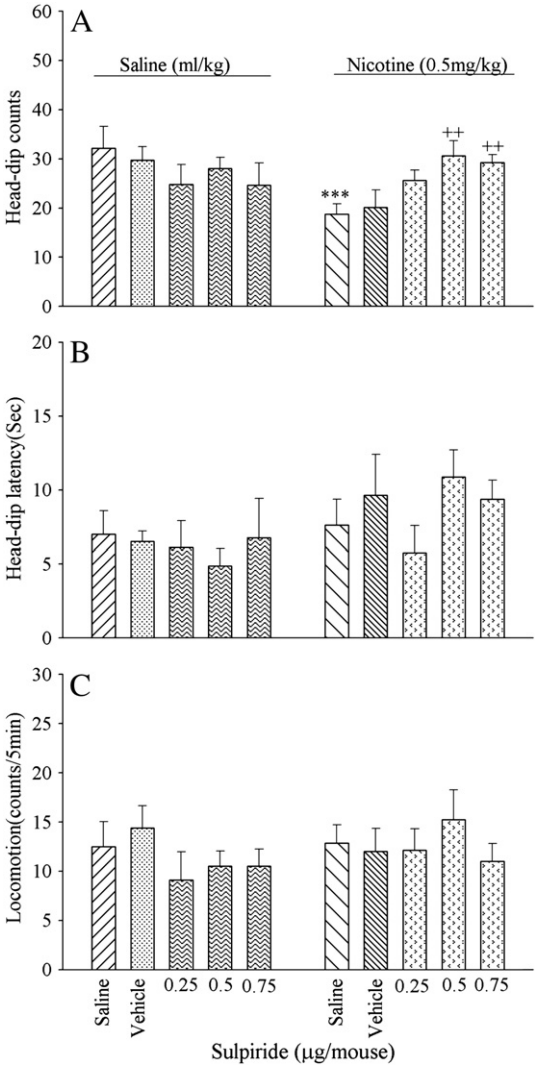

Fig. 4. The effects of pre-test administration of SUL (0.25, 0.5 and 0.75 μg/mouse, intra-dorsal hippocampus) or saline (1 μl/mouse, intra- dorsal hippocampus) on animals treated under the influence of saline (10 ml/kg, i.p.; left panel) or nicotine (0.5 mg/kg, i.p.; right panel) on exploratory behaviors. Each bar represents mean ± S.E.M. ***P<0.001 when compared to the saline/saline group. ++P<0.01 when compared to the nicotine/saline group.

4. Discussion

In the present study, the effects of the dorsal hippocampus dopaminergic system on anxiety-related behaviors induced by nicotine in mice have been investigated. The hole-board, which is one of the numerous tests for the identification of anxiolytic or anxiogenic-like drug effects (Rodriguez Echandia, 1987) was used in the test sessions. However, anxiety-like behaviors were not confirmed in a different test.

4.1. The effects of nicotine upon anxiety like-behavior

Our present data indicated that intraperitoneal administration of nicotine (0.5 mg/kg) decreased the number of head dips but not other parameters, suggesting possible anxiogenic-like behaviors. This is in agreement with our previous report showing that nicotine induced an anxiogenic-like response (Zarrindast et al., 2000). On the other hand, a number of researchers have shown that both nicotine and a nicotine receptor agonist, lobeline, have exhibited anxiolytic-like properties on the plus-maze test, whereas cytisine had no impact on anxiety-like behavior in CD1 mice (Brioni et al., 1993). Moreover, in some investigations an anxiolytic-like response with lower doses (0.01, 0.05 and 0.1 mg/kg) of nicotine was observed, while the higher drug doses (0.5, 0.8 and 1 mg/kg) induced an anxiogenic-like effect (Ouagazzal et al., 1999; Zarrindast et al., 2010). Nicotine may play a modulatory role in the brain through its receptor sites (Role and Berg, 1996). Nicotinic agonists primarily act indirectly via nAChRs located on or near nerve terminals where they mediate the calcium-dependent release of neurotransmitters, including: DA, norepinephrine, glutamate, GABA and acetylcholine (O'Neill and Brioni, 1994). However, the exact pharmacology of the drug's effects has not been completely understood and possibly could be due to either the release of acetylcholine and/or other neurotransmitters. It has been shown that nAChRs are involved in DA release by nicotine (Zoli et al., 2002). Furthermore, the hippocampal cholinergic system has been proposed to be involved in the modulation of anxiety-like behavior (File et al., 1998a). There is also evidence indicating that cholinergic activation may induce anxiolytic-like behavior (Brioni et al., 1993). Moreover, nAChRs are of the superfamily of ligand-gated ion channels, which act on both the pre- and post-synaptic subtypes of nAChRs (Poorthuis et al., 2009). These receptors are present in many areas of the brain, including the hippocampus (Tizabi et al., 2002). Activation of nAChRs has been shown to modulate many systems associated with stress

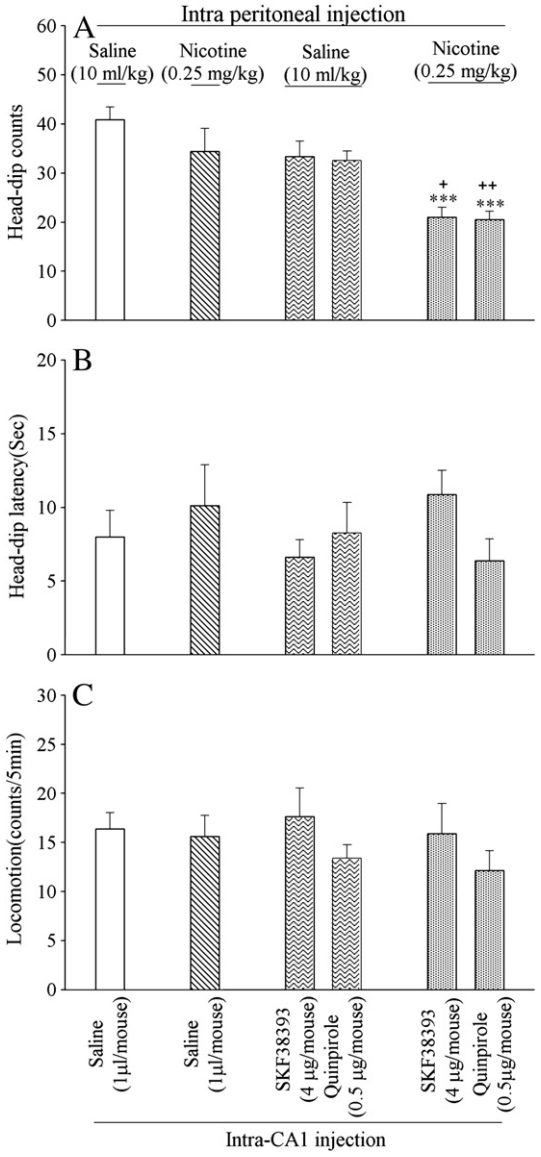

Fig. 5. Effects of pre-test administration of SKF (4 µg/mouse, intra- dorsal hippocampus), QUI (0.5 µg/mouse, intra- dorsal hippocampus) or saline (1 µl/mouse, intra-dorsal hippocampus) on animals trained under the influence of saline (10 ml/kg, i.p.; left panel) or nicotine (0.25 mg/kg, i.p.; right panel) on exploratory behaviors. Each bar represents mean ± S.E.M. ***P<0.001 when compared to the saline/saline group. +P<0.05 when compared to the respective groups.

response that include stress hormone pathways, monoaminergic transmission and release of classical neurotransmitters throughout the brain (Picciotto et al., 2002). The regulation of DA release by acetylcholine has also been shown (Tizabi et al., 2002), which may modulate anxiety-like behavior in mice (Rodgers et al., 1994). In conclusion the several influences of nAChRs in brain sites may be involved in different response of nicotine.

4.2. The effects of dopaminergic system of dorsal hippocampus upon anxiogenic-like behavior induced by nicotine

Considerable evidence suggests that the hippocampus is important for the regulation of anxiety; it is likely that mesoaccumbens or mesocortical DA projections are involved in this effect. Possibly, hippocampal–prefrontal cortex-nucleus accumbens afferents forms part of a neural network that control anxiety expression (Timothy et al., 1999). However, the combination of several lines of evidence suggests that the mesolimbic/cortical DA systems seem to be involved in drugs affecting anxiety (Cabib et al., 1988; Deutch et al., 1985; Dunn, 1988; Imperato et al., 1990; Louilot et al., 1986; Puglisi-Allegra et al., 1991; Reinhard et al., 1982). DA exerts its action through different receptor subtypes: D_1-like (D_1 and D_5) and D_2-like (D_2, D_3 and D_4) (Sealfon and Olanow, 2000).

In the present experiments, ineffective doses of a DA D_1 receptor antagonist (SCH23390) and DA D_2 receptor antagonist (sulpiride) decreased the anxiogenic response caused by nicotine by increasing head dips, but they did not alter latency to the first head-dipping, locomotor activity, grooming, rearing and defecation in the hole-board task, showing involvement of D1 and D2 receptor mechanism in anxiogenic-like effect of nicotine. Single administration of a higher dose of SCH (0.5 µg/mouse) induced anxiogenic-like behaviors. This may indicate that under normal circumstances, the dopaminergic system in dorsal hippocampus exerts a physiological influence on anxiety-like behavior through the DA D_1 receptor which is in agreement with our recent study in the hole-bored task (Nasehi et al., 2010). Other studies have assessed the involvement of DA receptor mechanisms and dopaminergic drugs in animal models of anxiety (Davis et al., 1993; Forestiero et al., 2006; Garcia et al., 2005; Greba and Kokkinidis, 2000; Inoue et al., 2000; Reis et al., 2004; Rodgers et al., 1994; Shah et al., 2004). An investigation showed that low dose of a dopaminergic drug, bupropion had no effect but high dose of drug induced anxiogenic-like behaviors in the hole-board task (Redolat et al., 2005).

The present data indicated that co-administration of ineffective doses of SKF (4 µg/mouse) or QUI (0.5 µg/mouse) with an ineffective dose of nicotine (0.25 mg/kg) increased anxiogenic-like behaviors induced by nicotine and it may further support that nicotine-induced anxiogenic-like behaviors is mediated through the D_1 and D_2 receptors mechanism(s). In agreement with our results, histochemical studies showed that nAChRs are present on dopamine nerve terminals (Hill et al., 1993; Jones et al., 2001) and the activity of presynaptic nAChRs may regulate action potential-dependent striatal dopamine release (Grady et al., 2001; Johnson et al., 2000; Marshall et al., 1997). The nicotinic influence can control dopamine release in the striatum and can be modulated by acetylcholinesterase inhibitors that are used to treat Alzheimer's disease. Furthermore, some researchers showed that nicotine receptors are highly expressed in the areas such as ventral tegmentum and substantia nigra which modulate the release of dopamine in the nigrostriatal pathway (Cui et al., 2003). There is the possibility that these receptors modulate dopamine release in the amygdala in a similar manner.

In agreement with our data a study showed that the decreased anxiety and increased levels of nicotine-stimulated dopamine release was observed in the beta 3 null mutants (Cui et al., 2003). In contrast, there is other investigation indicating that deletion of the alpha 4 nicotinic subunit decreases nicotine-stimulated dopamine release (Salminen et al., 2004) and resulted in an increase in anxiety (Ross et al., 2000). Some data also show that mice expressing the Leucine/Serine mutation in the alpha 4 subunit demonstrate increased anxiety and decreased expression of dopaminergic neurons (Labarca et al., 2001), which likely results in a decrease in dopamine release in vivo. The DA receptor system is also implicated in other effects of nicotine, including the reinforcing effects of the drug (Corrigall et al., 1992). Nicotine can also desensitize preterminal nAChRs on GABAergic neurons in the VTA, resulting in disinhibition and a consequent increase in DA cell firing (Mansvelder et al., 2002; Wooltorton et al., 2003). In conclusion our data may show that anxiogenic-like effect of nicotine is due to increase in the tone of dopamine receptor mechanism.

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References

Amaral DG. The primate amygdala and the neurobiology of social behavior: implications for understanding social anxiety. Biol Psychiatry 2002;51:11–7.

Balfour DJ. The effects of nicotine on brain neurotransmitter systems. Pharmacol Ther 1982;16:269–82.

Bannerman DM, Grubb M, Deacon RM, Yee BK, Feldon J, Rawlins JN. Ventral hippocampal lesions affect anxiety but not spatial learning. Behav Brain Res 2003;139:197–213.

Benowitz NL. Drug therapy. Pharmacologic aspects of cigarette smoking and nicotine addition. N Engl J Med 1988;319:1318–30.

Boissier JR, Simon P. The exploration reaction in the mouse. Preliminary note. Therapie 1962;17:1225–32.

Brioni JD, O'Neill AB, Kim DJ, Decker MW. Nicotinic receptor agonists exhibit anxiolytic-like effects on the elevated plus-maze test. Eur J Pharmacol 1993;238:1–8.

Cabib S, Kempf E, Schleef C, Oliverio A, Puglisi-Allegra S. Effects of immobilization stress on dopamine and its metabolites in different brain areas of the mouse: role of genotype and stress duration. Brain Res 1988;441:153–60.

Chae Y, Yeom M, Han JH, Park HJ, Hahm DH, Shim I, et al. Effect of acupuncture on anxiety-like behavior during nicotine withdrawal and relevant mechanisms. Neurosci Lett 2008;430:98-102.

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. Psychopharmacol Berl 2001;155:78–85.

Corrigall WA, Franklin KB, Coen KM, Clarke PB. The mesolimbic dopaminergic system is implicated in the reinforcing effects of nicotine. Psychopharmacol Berl 1992;107: 285–9.

Cui C, Booker TK, Allen RS, Grady SR, Whiteaker P, Marks MJ, et al. The beta3 nicotinic receptor subunit: a component of alpha-conotoxin MII-binding nicotinic acetylcholine receptors that modulate dopamine release and related behaviors. J Neurosci 2003;23:11045–53.

Davis M, Falls WA, Campeau S, Kim M. Fear-potentiated startle: a neural and pharmacological analysis. Behav Brain Res 1993;58:175–98.

Deutch AY, Tam SY, Roth RH. Footshock and conditioned stress increase 3,4-dihydroxyphenylacetic acid (DOPAC) in the ventral tegmental area but not substantia nigra. Brain Res 1985;333:143–6.

Dunn AJ. Stress-related activation of cerebral dopaminergic systems. Ann NY Acad Sci 1988;537:188–205.

Feenstra MG, Botterblom MH, van Uum JF. Novelty-induced increase in dopamine release in the rat prefrontal cortex in vivo: inhibition by diazepam. Neurosci Lett 1995;189:81–4.

File SE, Gonzalez LE, Andrews N. Endogenous acetylcholine in the dorsal hippocampus reduces anxiety through actions on nicotinic and muscarinic1 receptors. Behav Neurosci 1998a;112:352–9.

File SE, Kenny PJ, Ouagazzal AM. Bimodal modulation by nicotine of anxiety in the social interaction test: role of the dorsal hippocampus. Behav Neurosci 1998b;112: 1423–9.

Forestiero D, Manfrim CM, Guimaraes FS, de Oliveira RM. Anxiolytic-like effects induced by nitric oxide synthase inhibitors microinjected into the medial amygdala of rats. Psychopharmacol Berl 2006;184:166–72.

Garcia AM, Martinez R, Brandao ML, Morato S. Effects of apomorphine on rat behavior in the elevated plus-maze. Physiol Behav 2005;85:440–7.

Goldstein LE, Rasmusson AM, Bunney BS, Roth RH. Role of the amygdala in the coordination of behavioral, neuroendocrine, and prefrontal cortical monoamine responses to psychological stress in the rat. J Neurosci 1996;16:4787–98.

Grady SR, Meinerz NM, Cao J, Reynolds AM, Picciotto MR, Changeux JP, et al. Nicotinic agonists stimulate acetylcholine release from mouse interpeduncular nucleus: a function mediated by a different nAChR than dopamine release from striatum. J Neurochem 2001;76:258–68.

Greba Q, Kokkinidis L. Peripheral and intraamygdalar administration of the dopamine D1 receptor antagonist SCH 23390 blocks fear-potentiated startle but not shock reactivity or the shock sensitization of acoustic startle. Behav Neurosci 2000;114: 262–72.

Hill Jr JA, Zoli M, Bourgeois JP, Changeux JP. Immunocytochemical localization of a neuronal nicotinic receptor: the beta 2-subunit. J Neurosci 1993;13:1551–68.

Imperato A, Mulas A, Di Chiara G. Nicotine preferentially stimulates dopamine release in the limbic system of freely moving rats. Eur J Pharmacol 1986;132:337–8.

Imperato A, Puglisi-Allegra S, Zocchi A, Scrocco MG, Casolini P, Angelucci L. Stress activation of limbic and cortical dopamine release is prevented by ICS 205–930 but not by diazepam. Eur J Pharmacol 1990;175:211–4.

Inoue T, Izumi T, Maki Y, Muraki I, Koyama T. Effect of the dopamine D(1/5) antagonist SCH 23390 on the acquisition of conditioned fear. Pharmacol Biochem Behav 2000;66:573–8.

Johnson JH, Zhao C, James JR, Rosecrans JA. Individual variability of dopamine release from nucleus accumbens induced by nicotine. Brain Res Bull 2000;51:249–53.

Jones IW, Bolam JP, Wonnacott S. Presynaptic localisation of the nicotinic acetylcholine receptor beta2 subunit immunoreactivity in rat nigrostriatal dopaminergic neurones. J Comp Neurol 2001;439:235–47.

Labarca C, Schwarz J, Deshpande P, Schwarz S, Nowak MW, Fonck C, et al. Point mutant mice with hypersensitive alpha 4 nicotinic receptors show dopaminergic deficits and increased anxiety. Proc Natl Acad Sci USA 2001;98:2786–91.

Le Foll B, Goldberg SR. Effects of nicotine in experimental animals and humans: an update on addictive properties. Handb Exp Pharmacol 2009:335–67.

LeDoux JE. Emotion circuits in the brain. Annu Rev Neurosci 2000;23:155–84.

Lichtensteiger W, Hefti F, Felix D, Huwyler T, Melamed E, Schlumpf M. Stimulation of nigrostriatal dopamine neurones by nicotine. Neuropharmacology 1982;21:963–8.

Louilot A, Le Moal M, Simon H. Differential reactivity of dopaminergic neurons in the nucleus accumbens in response to different behavioral situations. An in vivo voltammetric study in free moving rats. Brain Res 1986;397:395–400.

Mansvelder HD, Keath JR, McGehee DS. Synaptic mechanisms underlie nicotine-induced excitability of brain reward areas. Neuron 2002;33:905–19.

Marshall DL, Redfern PH, Wonnacott S. Presynaptic nicotinic modulation of dopamine release in the three ascending pathways studied by in vivo microdialysis: comparison of naive and chronic nicotine-treated rats. J Neurochem 1997;68: 1511–9.

Nasehi M, Piri M, Nouri M, Farzin D, Nayer-Nouri T, Zarrindast MR. Involvement of dopamine D1/D2 receptors on harmane-induced amnesia in the step-down passive avoidance test. Eur J Pharmacol 2010;634:77–83.

O'Neill AB, Brioni JD. Benzodiazepine receptor mediation of the anxiolytic-like effect of (−)-nicotine in mice. Pharmacol Biochem Behav 1994;49:755–7.

Ouagazzal AM, Kenny PJ, File SE. Stimulation of nicotinic receptors in the lateral septal nucleus increases anxiety. Eur J Neurosci 1999;11:3957–62.

Paxinos G, Franklin KBJ. The mouse brain in stereotaxic coordinates. 2nd. Academic Press; 2001.

Picciotto MR, Brunzell DH, Caldarone BJ. Effect of nicotine and nicotinic receptors on anxiety and depression. NeuroReport 2002;13:1097–106.

Poorthuis RB, Goriounova NA, Couey JJ, Mansvelder HD. Nicotinic actions on neuronal networks for cognition: general principles and long-term consequences. Biochem Pharmacol 2009;78:668–76.

Puglisi-Allegra S, Imperato A, Angelucci L, Cabib S. Acute stress induces time-dependent responses in dopamine mesolimbic system. Brain Res 1991;554:217–22.

Redolat R, Gomez MC, Vicens P, Carrasco MC. Bupropion effects on aggressiveness and anxiety in OF1 male mice. Psychopharmacol Berl 2005;177:418–27.

Reinhard Jr JF, Bannon MJ, Roth RH. Acceleration by stress of dopamine synthesis and metabolism in prefrontal cortex: antagonism by diazepam. Naunyn Schmiedebergs Arch Pharmacol 1982;318:374–7.

Reis FL, Masson S, de Oliveira AR, Brandao ML. Dopaminergic mechanisms in the conditioned and unconditioned fear as assessed by the two-way avoidance and light switch-off tests. Pharmacol Biochem Behav 2004;79:359–65.

Rodgers RJ, Nikulina EM, Cole JC. Dopamine D1 and D2 receptor ligands modulate the behaviour of mice in the elevated plus-maze. Pharmacol Biochem Behav 1994;49: 985–95.

Rodriguez Echandia EL, Broitman ST, Foscolo MR. Effect of the chronic ingestion of chlorimipramine and desipramine on the hole board response to acute stresses in male rats. Pharmacol Biochem Behav 1987;26:207–10.

Role LW, Berg DK. Nicotinic receptors in the development and modulation of CNS synapses. Neuron 1996;16:1077–85.

Ross SA, Wong JY, Clifford JJ, Kinsella A, Massalas JS, Horne MK, et al. Phenotypic characterization of an alpha 4 neuronal nicotinic acetylcholine receptor subunit knock-out mouse. J Neurosci 2000;20:6431–41.

Salminen O, Murphy KL, McIntosh JM, Drago J, Marks MJ, Collins AC, et al. Subunit composition and pharmacology of two classes of striatal presynaptic nicotinic acetylcholine receptors mediating dopamine release in mice. Mol Pharmacol 2004;65:1526–35.

Sealfon SC, Olanow CW. Dopamine receptors: from structure to behavior. Trends Neurosci 2000;23:S34–40.

Shah AA, Sjovold T, Treit D. Selective antagonism of medial prefrontal cortex D4 receptors decreases fear-related behaviour in rats. Eur J Neurosci 2004;19:3393–7.

Stolerman IP. Characterization of central nicotinic receptors by studies on the nicotine cue and conditioned taste aversion in rats. Pharmacol Biochem Behav 1988;30: 235–42.

Timothy C, Costall B, Smythe JW. Effects of SCH23390 and raclopride on anxiety-like behavior in rats tested in the black-white box. Pharmacol Biochem Behav 1999;62: 323–7.

Tizabi Y, Copeland Jr RL, Louis VA, Taylor RE. Effects of combined systemic alcohol and central nicotine administration into ventral tegmental area on dopamine release in the nucleus accumbens. Alcohol Clin Exp Res 2002;26:394–9.

Vinade ER, Schmidt AP, Frizzo ME, Izquierdo I, Elisabetsky E, Souza DO. Chronically administered guanosine is anticonvulsant, amnesic and anxiolytic in mice. Brain Res 2003;977:97-102.

Wooltorton JR, Pidoplichko VI, Broide RS, Dani JA. Differential desensitization and distribution of nicotinic acetylcholine receptor subtypes in midbrain dopamine areas. J Neurosci 2003;23:3176–85.

Zarrindast MR, Homayoun H, Babaie A, Etminani A, Gharib B. Involvement of adrenergic and cholinergic systems in nicotine-induced anxiogenesis in mice. Eur J Pharmacol 2000;407:145–58.

Zarrindast MR, Naghdi-Sedeh N, Nasehi M, Sahraei H, Bahrami F, Asadi F. The effects of dopaminergic drugs in the ventral hippocampus of rats in the nicotine-induced anxiogenic-like response. Neurosci Lett 2010;475:156–60.

Zarrindast MR, Solati J, Oryan S, Parivar K. Effect of intra-amygdala injection of nicotine and GABA receptor agents on anxiety-like behaviour in rats. Pharmacology 2008;82:276–84.

Zoli M, Moretti M, Zanardi A, McIntosh JM, Clementi F, Gotti C. Identification of the nicotinic receptor subtypes expressed on dopaminergic terminals in the rat striatum. J Neurosci 2002;22:8785–9.