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Intra-accumbal and Peripheral administration of nicotine reduces the side-effects of Inescapable Stress

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ABSTRACT

Background: The mesolimbic dopaminergic system plays an important role in controlling the effects of stress. Here, the role of nicotinic receptors in the nucleus accumbens, one of the most important parts of the mesolimbic system in reducing the effects of stress in mice has been studied.

Methods: Bilateral intra-accumbal (shell of nucleus accumbens; sNA) cannulation was performed carefully. Animals were allocated randomly into nine groups and received nicotine intra-peritoneally (IP; 0.25, .05, and 1 ml/Kg) and intra-accumbally (sNA; 1, 5 and 10 µg/mouse), respectively. 30 minutes later saline and nicotine injection, the animal received an electric shock stress from the soles of the feet for 60 seconds. The body, brain and adrenal glands weight, food and water consumption and anorexia time were evaluated.

Results: The results showed that IP administration of 1 mg/Kg nicotine (IP Nic 1) and intra-accumbal injection of 1 and 5 µg/mouse nicotine (NAc Nic 1 and 5) lead to weight loss. Although, intra-sNA injection of nicotine couldn't improve the food consumption, but the significant increases in food intake were observed in the IP Nic 1. The water intake increased and the brain weight decreased dose-dependently by rises of nicotine dose. The weight of the adrenal gland was significantly raised in IP Nic groups. Anorexia (decreased appetite), decreased or increased depending on the nicotine dose.

Conclusion: We conclude that intra-accumbal nicotine administration reduces the signs of stress in a dose dependent manner, which probably is associated with the role of nicotinic acetylcholine receptors.

INTRODUCTION

Stress is a reaction alongside a perceived threat (real or imaginary) to physical, mental, emotional and spiritual health, leading to a series of physiological responses and adaptations. In other words, any environmental or mental factors that make life difficult to animate can be considered as stress and stimulant that disturbs homeostasis of the body, called stressor (Tilbrook *et al*., 2000; Dalooei *et al*., 2016).

The activation of the Hypothalamic-Pituitary-Adrenal axis (HPA axis) and increasing the level of Adrenocorticotropic hormone (ACTH) level, is one of the homeostatic mechanisms observed in all types of stress in laboratory animals (Ailing *et al*., 2008). The longstanding release of stress hormones raises the risk of metabolic and neuropsychiatric disorders such as diabetes, anxiety, depression, and schizophrenia (Mohammadi *et al*., 2017). Thus, understanding the mechanisms implicated in brain responses to stress is the most important key to inhibit stress and its side effects. Studies have shown that the NAc (a part of the ventral striatum), Plays a vital role in reward, reinforcement and motivational aspects of behaviors toward addiction. This nucleus is involved in reward aspects of the addictive substance, psychological dependence, and withdrawal syndromes. The core and shell of NAc (cNAc, sNAc), have different functions. Addictive drugs increase dopamine release in the sNAc.

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Dopamine is the most studied neurotransmitter and play a crucial role in the pathophysiology of neuropsychiatric disorders such as anxiety, depression, and schizophrenia (Javadpour and Mohammadi, 2015; Noori-Daloii *et al*., 2015; Javadpour and Mohammadi, 2016). It has been suggested that the sNAc may be related to stimulus-reward associations which can be changed by addictive drugs. The cNAc, which secretes hormones include dopamine, glutamate, and serotonin, has a critical role in models of drug-seeking behavior such as Pavlovian approach (Chiari *et al*., 1999; Ambroggi *et al*., 2011). Nicotine is an agonist of nicotinic acetylcholine receptors and is existent in the range of 2–7 µg/kg of different comestible plants. By way of nicotine binds to these receptors, the intracellular cation is augmented and the cell becomes depolarized. Nicotine could cause enlarged dopamine circulation through systematic activity on ionotropic receptors of dopamine, GABA and the arrivals of glutamatergic neurons (G Hunter, 2012). Nicotine is a robust base, which rapidly absorbed crossways respiratory tract, skin, and oral mucosa and spreads the brain through a vein spreading in 8 seconds (Benowitz *et al*., 1991). Furthermore, nicotine is the most psychoactive complexes in tobacco (BLISS and AILION, 1969; Betz, 1990; Bidzseranova *et al*., 1992; Blokland *et al*., 1999) and its pharmacological effects are due to encouraging the release of numerous neurotransmitters (Bombig *et al*., 2003). It has been demonstrated that smoking decreases anxiety due to nicotine withdrawal (Bon and Garthwaite, 2003). Long-lasting stimulation of the sympathetic nervous system by nicotine upsurges metabolic percentage and the uptake of brown fat and results in weight loss (Betz, 1990). Nicotine could be used to treat various diseases (Bidzseranova and Varga *et al*., 1992). It has been shown that acute systemic administration of nicotine improves the memory and cognitive performance (Boscarino *et al*., 2011). Likewise, it increases dynamic activity and food associated conditions-reflex. In this study, we evaluated the effects of peripheral and intra-accumbal injection of nicotine on metabolic and behavioral responses to inescapable stress in male NMRI mice.

MATERIALS AND METHODS

Animals

Fifty-four adult NMRI male mice (25-35 grams, the Pasteur Institute, Tehran, Iran) were used throughout the study and randomly allocated to 9 groups (6 for each group including: negative control group; control^{-}, without any intervention), two Positive control groups (control IP^{+} and control NAc^{+}, receiving 1 ml/mouse and 10 µg/mouse saline, respectively), three intra-peritoneal groups (IP nic, receiving 0.25, 0.5 and 1 mg/kg nicotine) and three intra-accumbal groups (NAc nic, getting 1, 5 and 10 µg/mouse nicotine). The animals were housed six per cage (22 ± 2 °C with a 12/12 h light/dark cycle) with ad libitum food and water available. All experiments were done in accordance with standard ethical guidelines and were approved by the local ethical committee (Baqiyatallah University of Medical Sciences, Use and Care of Animals Committee, 87/211-2015).

Drugs

The nicotine [(-)-Nicotine ditartrate] was purchased from Tocris Bioscience (Cat. No. 3546) and dissolved in sterile saline before use and injected into the sNAc (1, 5 and 10 µg/mouse) or peritoneum (0.25, 0.5 and 1 mg/kg).

Stress induction

Stress box is a Plexiglas device with 9 compartments. The Holes in each compartment and their transparent walls allow animals to communicate with each other. The floor of the device consists of stainless steel rods that connect to an electroshock device (ESD) with adjustable voltage, frequency and time.

Experimental design

After an adaptation period (seven days), animals received nicotine in experimental groups (IP Nic and NAc Nic) and saline in control^{+} groups (control IP^{+} and control NAc^{+}), before stress induction. Animals were placed in stress box 20 minutes before exposure to stress. Electric foot shock (voltage of 60 volts and frequency of 10 hertz for 60 seconds) was applied to animals daily for 7 consecutive days except for two unpredictable days. After a 10-minute rest, the animals were returned to their cage and time interval between their return and the beginning of feeding was measured and declared as anorexia. Moreover, the weight of animals and water and food intake were measured. In groups undergoing surgery, experiments were started after the recovery period of 5 to 7 days.

Surgical procedures

To inoculate nicotine or saline into the nucleus accumbens, the animals were anesthetized by IP injection of ketamine (50–75 mg/kg) and diazepam (5–7 mg/kg). A stainless steel guide cannula (Gauge 21) was located within the sNAc (the stereotaxic coordinates were AP: 1.56 mm, ML: +/- 0.5 mm, DV: 7 mm from bregma, Fig1).

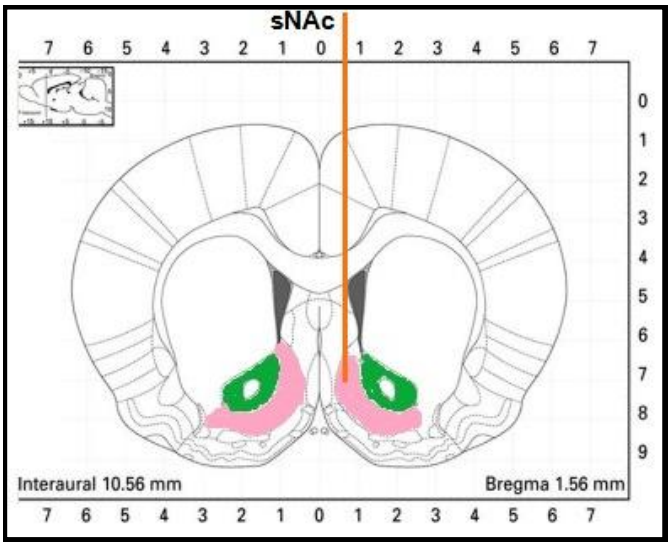


Fig. 1: Location of the guide cannula in the sNAc (green: core and ink: shell).

Inoculation into the sNAc was achieved by a stainless steel injection cannula (Gauge 30) which was connected to a 5 µL Hamilton syringe by an elastic cannula. At the end of the experiments, animals were anesthetized with ketamine (100 mg/kg) and their adrenal glands and brains were removed, fixed using 4% formalin and their weights were determined.

Data analysis

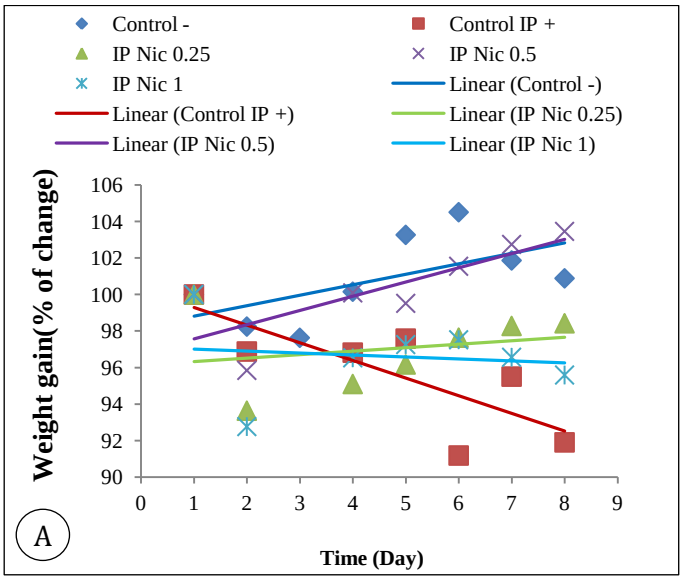
Data were presented as mean ± standard error of mean (SEM) and analyzed using one-way analysis of variance (Bidzseranova and Varga *et al.*) followed by an LSD test to analyze changes in the brain's and the adrenal gland's weight and Repeated Measures ANOVA to analyze changes in body weight, water and food intake. $P < 0.05$ was measured as an indication of a significant difference. In all data analysis, when the statistically significant difference was 0.05 ($P < 0.05$), the power analysis was among 0.6 to 0.64. Also, when the statistically significant differences were 0.01 and 0.001 ($P < 0.01$ and $P < 0.001$), the power analysis were among 0.7 to 0.72 and 0.81 to 0.86, respectively. In insignificant status, the power analysis was lower than 0.08.

RESULTS

Effects of IP administration of nicotine

Effects of IP administration of nicotine on body weight and food intake

Control^{-} and IP Nic 0.25 and 0.5 mg/kg groups showed weight gain, whereas control IP^{+} and the IP Nic 1 groups showed weight loss (Fig2 A). The animals of control^{-}, control IP^{+}, and IP Nic 0.5 groups showed increased food intake. The highest increase was observed in the IP Nic 1 and the lower one was observed in the stressed group received 0.25 mg/kg nicotine (IP Nic 0.25, $P<0.0001$, Fig. 2 B).



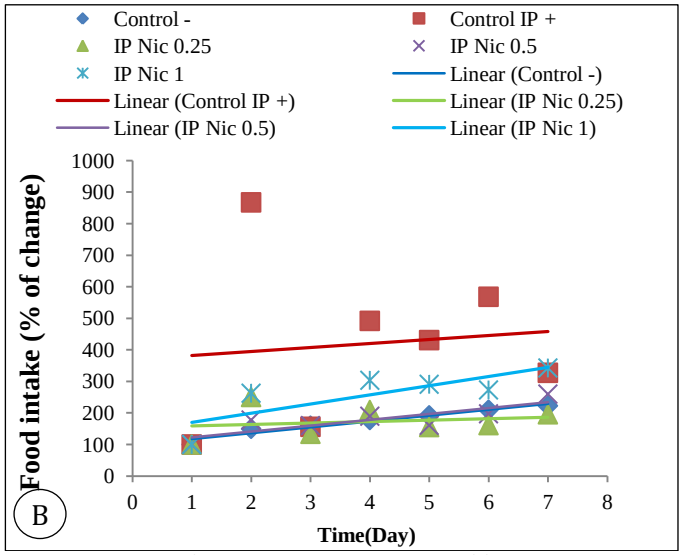
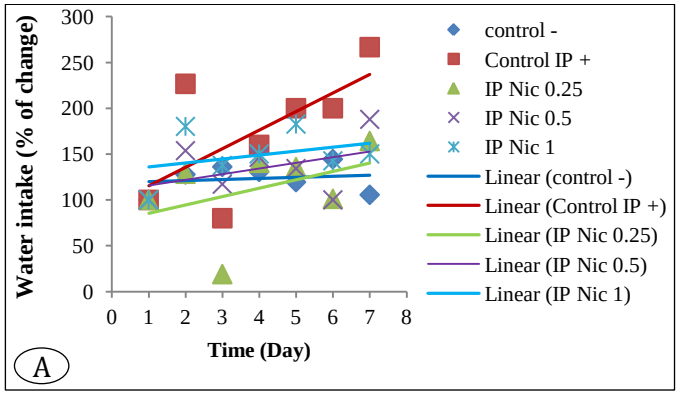


Fig. 2: The average of body weight (A) and amount of food intake (B) in mice under stress with and without nicotine injection ($P<0.0001$, for food intake and weight changes).

Effects of IP administration of nicotine on brain weight and water intake

The results showed that the amount of water intake depends on the dose of nicotine and exposure to stress (Fig3 A). Water intake increased dose-dependently by rises of nicotine dose. The average brain weight in the control IP^{+} and groups received nicotine decreased significantly compared with control group ($P <0.0001$, Fig3 B).



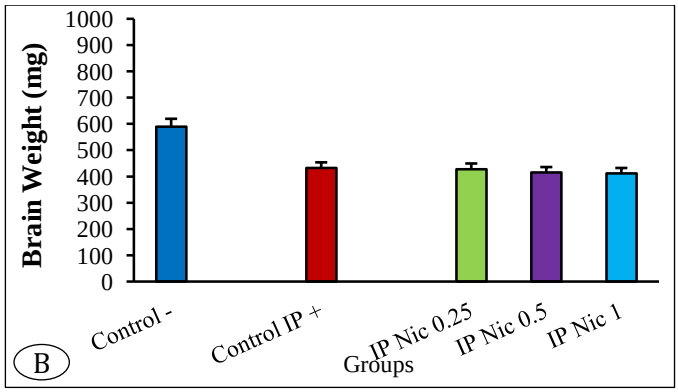


Fig. 3: The amount of water intake (A) and average brain weight (B). ($P<0.0001$, for brain weight and water intake).

Effects of IP administration of nicotine on adrenal glands weight and anorexia

The average weight of the adrenal glands in the IP group received 1mg/kg nicotine (IP Nic 1) was significantly more than the control^{-} group (P<0.05, Fig. 4A). Control^{-} and IP groups received 0.25 mg/kg nicotine (IP Nic 0.25) showed decreased anorexia (increased appetite, Fig. 4B). Anorexia was increased in IP groups received 0.5 and 1 mg/kg nicotine (IP Nic 0.5 and 1). The results showed that the appetite depends on the severity and duration of stress and the dose of nicotine.

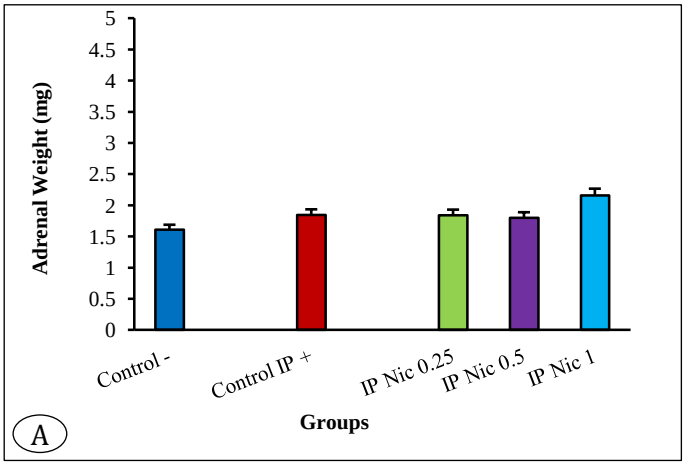


Fig. 4: The average adrenal gland weight (A) and anorexia (B) in the positive and negative control groups and stressed groups received different doses of nicotine (P<0.05 for adrenal weight (*) and P<0.0001 for anorexia).

Effects of bilateral sNA injection of nicotine

Effects of bilateral injection of nicotine in sNA on body weight and food intake

The animals of control^{-}, control NAc^{+}, and sNA groups received 10 µg/mouse nicotine (NAc Nic 10) showed weight gain and groups received 1 and 5 µg/mouse nicotine (NAc Nic 1 and 5) presented weight loss (Fig5 A). Control^{-} group displayed the higher rate of food intake than other groups; on the other hand, intra-sNA injection of nicotine couldn't improve the food consumption in mice which have been exposed to inescapable stress (Fig. 5 B). It seems that the body weight and food intake depend on the dose of nicotine and exposure to stress.

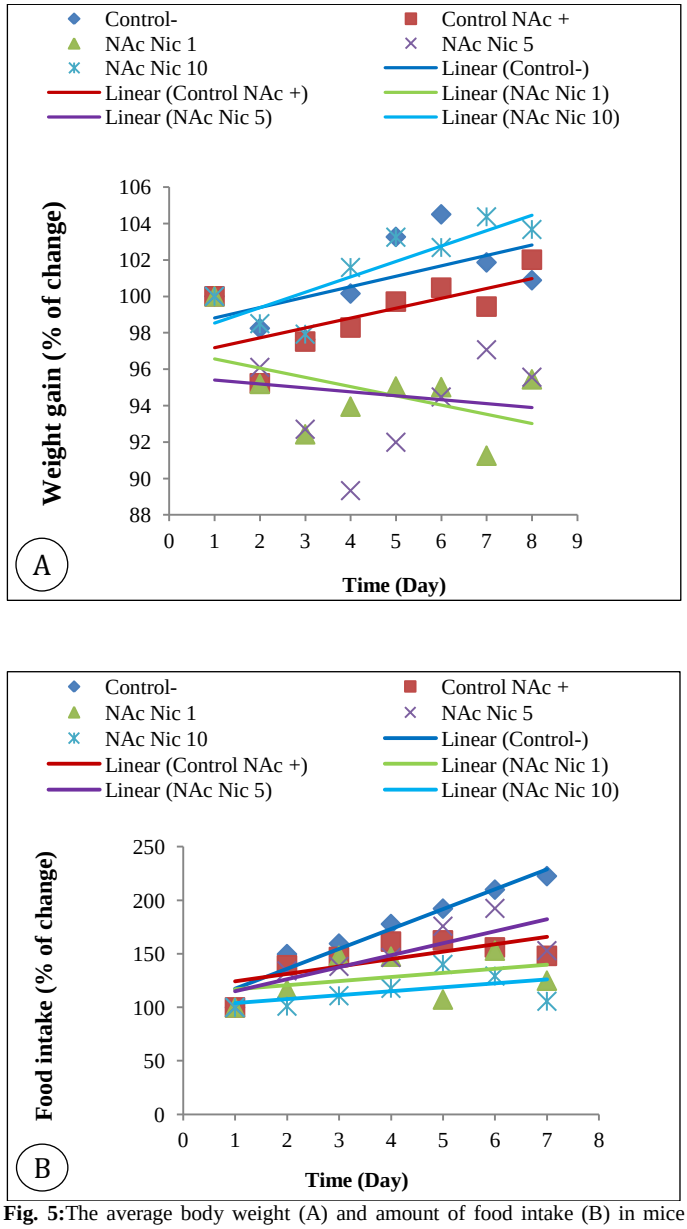
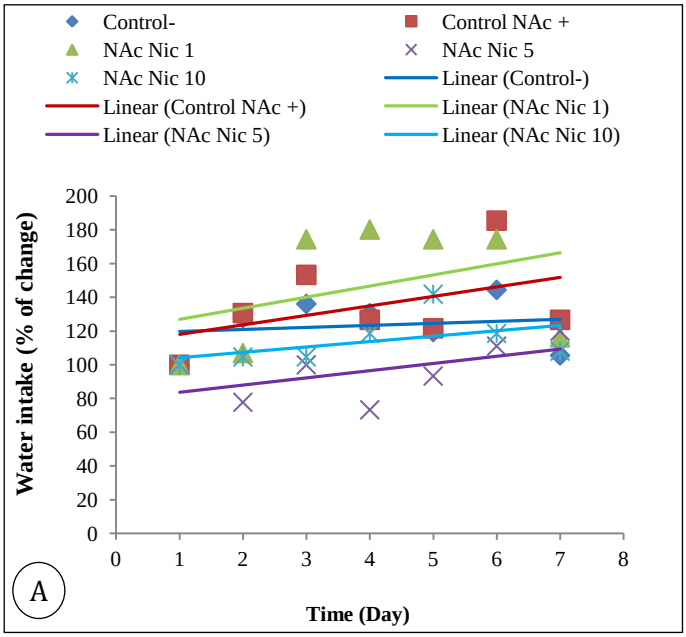


Fig. 5: The average body weight (A) and amount of food intake (B) in mice under stress with and without intra-accumbal injection of nicotine. (P<0.0001, for weight changes and food intake)**.**

Effects of bilateral injection of nicotine in sNA on brain weight and water intake

According to the results, the amount of water intake was increased in all groups and the lowest one was seen in control^{-} group (Fig6 A). An increase in the average brain of weight following bilateral injection of nicotine in the sNA in animals of

the control NAc^{+} group was significantly higher than control ($P<0.05$). The average of brain weight was decreased in a group with an injection of 10 µg/mouse nicotine (NAc Nic 10) ($P<0.05$, Fig. 6 B).



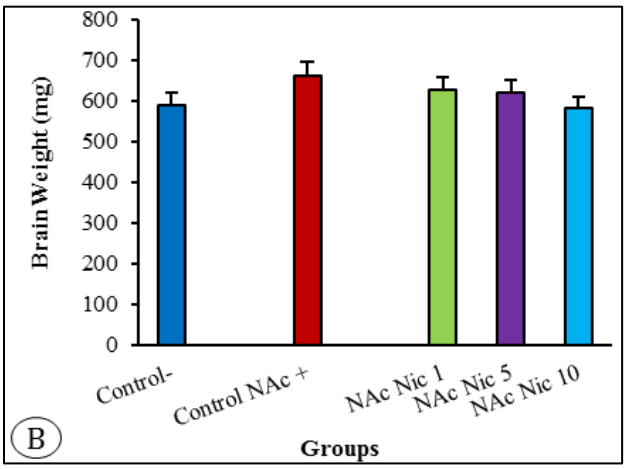
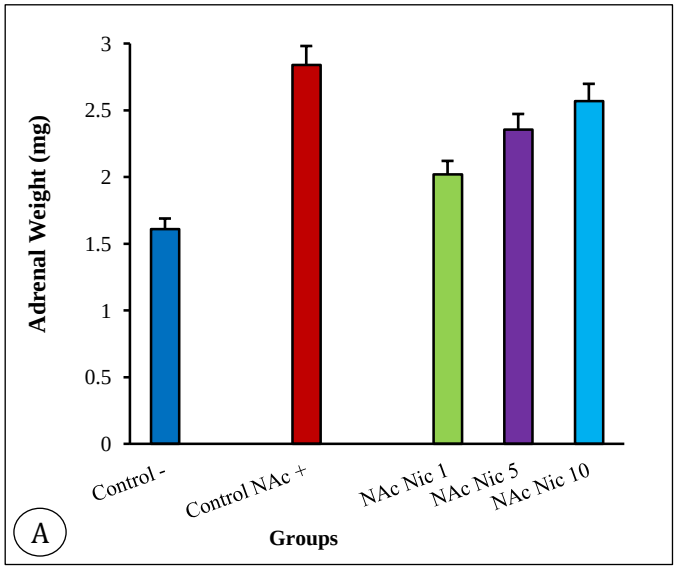


Fig. 6: The amount of water intake (A) and average brain weight (B). ($P<0.0001$, for water intake and brain weight).

Bilateral injection of nicotine in sNA on adrenal gland weight and anorexia

The sNA group received 1 µg/mouse nicotine (NAc Nic 1), showed a significant decrease in average weight of adrenal glands compared with the control NAc^{+} group (Fig7 A). The stressed group (NAc Nic 1) showed more increase in anorexia (decreased appetite) than control NAc^{+} and NAc Nic 10. The NAc Nic 5 and control^{-} groups showed decreased anorexia (Fig7 B). The results showed that the craving to food intake depends on the dose of nicotine and whether the animals are underneath stress or not.



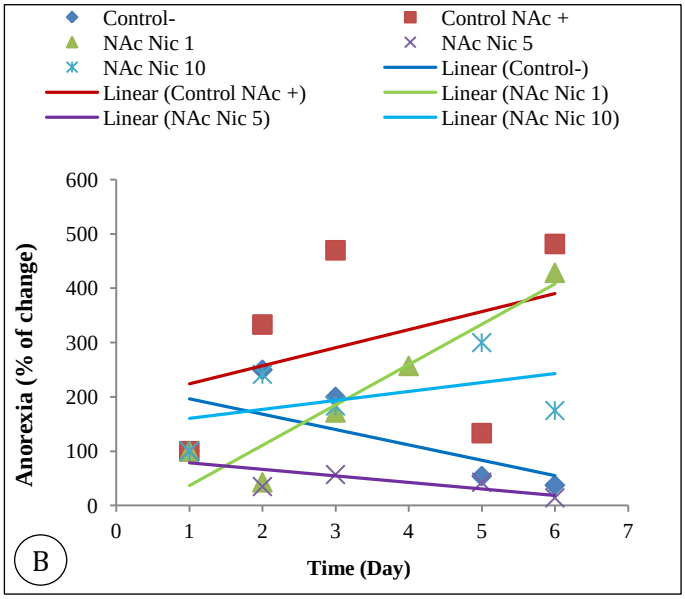


Fig. 7: The average f adrenal gland weight (A) and anorexia (B) in positive and negative control groups and stressed groups received intra-hippocampal different doses of nicotine. ($P<0.05$ (*) and $P<0.001$ (***) for adrenal weight and $P<0.0001$ for anorexia)**.**

DISCUSSION

In the present study, we have assessed the stimulation of nicotinic acetylcholine receptors in the nucleus accumbens and its consequence on inescapable stress responses in mice. In line with previous studies, our results have shown that inescapable stress causes widespread alterations in animal performance, including reduced body weight loss, brain weight, food intake, increased anorexia and water intake and adrenal gland weight (McEwen, 2007; Colomer *et al*., 2010; G Hunter, 2012; Guérineau *et al*., 2012; Lutfy *et al*., 2012). It would be renowned that according to preceding studies, stress stimulates HPA axis and upsurges secretion of epinephrine and glucocorticoids from the central and cortical parts of the adrenal gland, respectively (McEwen, 2007;

Hunter *et al*., 2010). It has been reported that the reduced level of dopamine in the nucleus accumbens recovers the animal's ability to acquire used to stress following inescapable stress (Dubrovsky, 2005; Viveros *et al*., 2007; Colomer and Olivos-Oré *et al*., 2010; Hunter and Bloss *et al*., 2010). Various parts of reward system are involved in the variation of stress responses and the nucleus accumbens as a main parts of this reward system, acting a vital role in inhibiting the effects of stress (Zhao *et al*., 2007). In the present study, the stimulation of nicotinic receptors in the nucleus accumbens induced different responses indicating the influence of the cholinergic system in the nucleus accumbens. Our study has expressed that inescapable stress decreases brain weight which is in agreement with other studies (McEwen, 2007). It is well known that stress reduces intracellular cytoskeleton of neurons in different parts of the brain. Research showed that the size of the amygdala and hippocampus are decreased in chronic stress, which is related to glucocorticoids secreted by the adrenal gland. In immobilization stress, the number of dendritic spines, dendrites, and synapses established in the amygdala and prefrontal cortex are decreased in rats. fMRI studies in humans have shown that the volume and size of active regions in hippocampus and amygdala are reduced in individuals with chronic stress. Numerous studies have shown the high density of glucocorticoid and mineralocorticoid receptors in different areas of the cerebral cortex, especially prefrontal cortex and different areas of the limbic system, such as hippocampus and amygdala. So impressionability of these areas of high concentration of glucocorticoid hormones in chronic stress conditions is much higher than other areas in the nervous system (McEwen, 2007). The present study has demonstrated an increase in adrenal gland weight of stressed animals. Previous investigations presented the sensitivity of both central and peripheral parts of the adrenal gland to stress stimulations. In stress conditions, activation of HPA axis and release of ACTH hormone affect adrenal gland cells, especially zona fasciculata and lead to an increase in number and size of glucocorticoid hormone-secreting cells (McEwen, 1998). On the other hand, stress can stimulate sympathetic nervous system and increase the size and activity of Chromaffin cells in the adrenal gland (Miller and O'Callaghan, 2002). Reduced feeding activity, increased water intake and subsequent weight loss has also been observed in our project which is consistent with preceding research (Müller *et al*., 2000; Miller and O'Callaghan, 2002; Myers and Rinaman, 2002; Amouei *et al*., 2016). Our analysis presented that nicotine in doses of 0.25 and 0.5 mg/kg decreased anorexia and in doses of 1mg /kg increased it. Moreover, it has been revealed that 0.25 and 0.5 mg/kg nicotine inhibited the effect of stress on weight loss and 1mg/kg nicotine reinforced this effect. It means that peripheral administration of nicotine may have double effects in human and animal models as some doses causes anorexia and others have appetite stimulating effects (Le Novere and Changeux, 1995; Cao *et al*., 2010; Hunter and Bloss *et al*., 2010; Niehaus *et al*., 2010). It seems that the influences of nicotine in inhibiting unwanted psychological complications of stress are more important than its influences on metabolic and physical aspects of stress and this may have a role in the etiology of smoking. Leao and colleagues (2012) showed that sensitivity induced by stress reinforces drug-seeking behavior caused by nicotine and reduces the CREB protein (cAMP response element-binding protein) in nucleus accumbens, which indicate the interaction of stress and nicotine in mental performance (Leão *et al*., 2012). No studies to our knowledge have yet been conducted regarding the interaction between nicotine and stress in regulating brain volume. In our study stimulation of nicotinic acetylcholine receptors in the nucleus accumbens by nicotine, prevents increased brain weight caused by stress. We have also demonstrated that administration of saline into the nucleus accumbens of stressed rats causes increased brain weight, which is inconsistent with previous findings of the effect of stress on reduced size and volume of neurons in the brain (McEwen, 2007). Therefore, increased brain weight in animals receiving saline into nucleus accumbens should be considered in future studies. In our study, injection of nicotine into the nucleus accumbens reduced stress-induced adrenal gland hypertrophy in a dose-dependent manner. The effect of nicotine on the size of the adrenal glands and increased level of the glucocorticoid hormones has been proven.

CONCLUSION

Stimulation of nicotinic receptors in the nucleus accumbens may inhibit the effects of stress in a dose-dependent manner which is indicated by parameters such as weight changes in the brain and adrenal gland as well as metabolic and behavioral responses. We found that IP administration of 1 mg/Kg nicotine (IP Nic 1) and intra-accumbal injection of 1 and 5 µg/mouse nicotine (NAc Nic 1 and 5) lead to weight loss. Although, intra-sNA injection of nicotine couldn't improve the food consumption, but the significant increases in food intake were observed in the IP Nic 1. The water intake increased and the brain weight decreased dose-dependently by rises of nicotine dose. The weight of the adrenal gland was significantly raised in IP Nic groups. Anorexia (decreased appetite), decreased or increased depending on the nicotine dose. Altogether, we conclude that intra-accumbal nicotine administration reduces the signs of stress in a dose dependent manner, which probably is associated with the role of nicotinic acetylcholine receptors. Future research with a focus on molecular and cellular changes caused by stress should be done to understand the mechanisms responsible for the inhibitory effects of nicotine on stress.

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Conflict of Interests: There are no conflicts of interest.

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