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Antidepressant-like effects of nicotine and transcranial magnetic stimulation in the olfactory bulbectomy rat model of depression

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Abstract

In this study, we compared the depression-like symptoms induced by olfactory bulbectomy (OBX) in the two inbred Wistar and Long Evans rat strains. We also analyzed the self-regulated oral intake of nicotine in these strains and the effect of nicotine on the depression-like symptoms of olfactory bulbectomy. Furthermore, we compared the antidepressant-like effects of nicotine on Wistar rats to those of transcranial magnetic stimulation (TMS), which has emerged as a therapeutic alternative for depression management.

Our results show that Wistar rats develop depression-like symptoms, demonstrated by the forced swim test (FST), four weeks after OBX. However, we cannot observe these symptoms in bulbectomized Long Evans rats. Our results suggest that there are some innate differences in susceptibility to stress between these two rat strains.

In Wistar rats, voluntary oral nicotine intake (1.2 mg/kg/day for 14 days) as well as nicotine administered as a single daily i.p. injection (1.5 mg/kg/day for 14 days) decrease the depression-like symptoms of OBX. Daily transcranial magnetic stimulation (TMS; 60 Hz and 0.7 mT for two hours per day for 14 days) also decreases depression-like symptoms but is less effective than nicotine.

In conclusion, our results support the idea that there are possible innate differences for depression susceptibility and that nicotine and TMS may be useful in the treatment of this syndrome.

Keywords

models of depression; olfactory bulbectomy; nicotine; self-medication; forced swim test; transcranial magnetic stimulation

1. Introduction

There are mainly three effective treatments for depression: drug treatment, psychotherapy and electroconvulsive therapy. It has been shown that the lifetime prevalence of depression in

smokers is directly correlated with the degree of nicotine dependence [3,4]. Nicotine patch can improve mood in non-smoking depressed patients [9,23–25], while smoking cessation frequently precipitates depressive symptoms that are reversed upon relapse to smoking [17, 29].

Based on these observations, a self-medication hypothesis could be envisioned, in which smoking alleviates some symptoms of depression through the actions of nicotine, the primary psychoactive component in tobacco [16,31]. Behavioral studies in rodents have shown that chronic nicotine administration has antidepressant-like effects through its actions on specific subtypes of the nicotinic acetylcholine receptor [5,7,27]. However, little is known about the antidepressant-like effects of freely-consumed nicotine in animals, a mode of intake that more clearly resembles nicotine self-administration in humans.

Over the past decade, transcranial magnetic stimulation (TMS) of the dorsolateral prefrontal cortex has been established as a much less invasive alternative to electroconvulsive therapy [20] as treatment of depressive symptoms, but presently no comparison has been made between nicotine and TMS on depression.

The olfactory bulbectomy (OBX) rat model is considered to be one of the best animal models of depression because of its complex constellation of behavioral, neurochemical, neuroendocrine and neuroimmune alterations; similar to those reported in patients with major depression [11,12,33]. OBX has been shown to be sensitive to chronic, but not acute, administration of clinically efficacious antidepressants [6,33]. In addition, this model does not rely on selectively bred animals and can therefore provide a method to investigate the interaction between genetic susceptibility and environmental factors in different inbred strains of rats.

In the present study, we compared the susceptibility to develop depression-like symptoms after OBX in the two inbred Wistar and Long Evans rat strains using the forced swim test (FST). We also analyzed the effect of voluntary oral intake of nicotine on these symptoms and compared the efficacy of orally ingested to i.p. injected nicotine on OBX. Finally, we compared the antidepressant-like effects of i.p. injected nicotine and TMS.

2. Materials and methods

2.1. Animals

Sixty-day-old male Wistar and Long Evans rats (200 – 250 g) were used in this study. Animals were individually housed under standard colony conditions: 12:12 light/dark cycle, (lights on at 7:00 am), controlled room temperature ($22 \pm 1^\circ\text{C}$) with free access to food and water. Rats were acclimated to these conditions for one week prior to experimentation. All studies were conducted in accordance with the Principles and Procedures described by the National Institutes of Health Guide for the Care and Use of Laboratory Animals and in accordance with the Local Committee of the Universidad Nacional Autonoma de Mexico.

2.2. Olfactory bulbectomy; Surgical Procedure

OBX was performed under anesthesia induced by 3% halothane and was maintained at 1%. A cranial window with the posterior edge at 5.2 mm anterior to Bregma was created in the frontal bone. Olfactory bulbs were cut and aspirated, taking care not to damage the frontal cortex. After the operation, bleeding was controlled by plugging the holes with haemostatic sponge (Gelfoam, Pharmacia & Upjohn Company, Michigan, USA). The Sham operation was performed similarly, except that bulbs were left intact. Following surgery, rats were returned to their home cage and animals were observed but not handled. To prevent infection, animals were given 1,200,000 IU/kg of benzathine G penicillin (Novartis, Mexico DF, Mexico) by

intramuscular injection after surgery. A two week recovery period was allowed after the surgical procedure. All animals were sacrificed at the end of the study and only rats with a complete removal of the olfactory bulbs and with no damage to the frontal cortex were included for data analysis.

2.3. Open field; Locomotor Activity

In sequence to differentiate the effects of nicotine on swimming test from a general locomotor effect, each animal was placed individually into the center of the apparatus (circle made of wood, 80 cm in diameter) [36], the number of squares-crosses made by the animal (with all four paws) during 3 min observation period was recorded as the locomotor activity. All open field tests were performed between 10 am and 1 pm.

2.4. Forced swim test

This test was performed under standard conditions as Porsolt et al, 1997 described previously. Rats were placed in a cylindrical tank (height: 40 cm, diameter: 18 cm) filled with water at 25° C (water depth to 30 cm). Animals were removed and returned to their home cages after 15 min in water. 24 hours later, rats were placed in the same cylinder under the same conditions. The total duration of immobility was measured for a five-min period. A rat was considered immobile when it remained floating passively in the water [18] with only respiratory movements.

The amount of time spent floating was recorded and was considered to be an index of depressive-like behavior. All forced swim tests were performed between 10 am and 1 pm.

2.5. Transcranial magnetic field stimulation

Animals were placed in plastic cylindrical cages designed to keep them immobile while receiving magnetic stimulation to their heads. Each coil consisted of 1000 turns of enamelled copper wire (7cm diameter) contained in plastic boxes (10.5 × 10.5 × 3.5 cm). A pair of Helmholtz coils (selected to minimize electric field effects) generated the fields (Dhan 1000 (tm); Magnetoterapia S.A. de C.V., Mexico D.F., Mexico). The stimulation consisted of an oscillatory magnetic field in the form of a sinusoidal wave with a frequency of 60 Hz and amplitude of 0.7 mT applied for two hours in the morning and two hours in the afternoon during 14 days. The distance between each coil and the midpoint of the head was approximately six cm.

2.6. Effects of nicotine self-administration on OBX-induced depression in rats evaluated by the forced swim test

For individual fluid intake measurement Wistar and Long Evans rats were single-housed. Every home cage was equipped with two drinking bottles and rats had access to fluid *ad libitum*. For a 15-day period, 16 – 24 animals of each strain were randomly assigned to two experimental groups: a) Nicotine group; one bottle was filled with nicotine (30 mg/l in deionized water) [8] and the other one with deionized water or b) Control group; both bottles were filled with deionized water. During the following 15-day period, rats from each group were subjected to surgery and separated into Sham and bulbectomized animals (N= 8 – 12). During this period (postsurgery recovery), animals from each group consumed only deionized water in both drinking bottles. During the last 15-day period, rats of each group had access to one bottle filled with deionized water and other with nicotine. Fluid intake was recorded daily and animals were weighed weekly.

After these three 15-day periods, animals were subject to open field test followed by forced swim test [31].

2.7. Effect of i.p. injected nicotine or TMS on forced swim test in rats with olfactory bulbectomy

For this experiment 20 Wistar rats were divided as follows: a) OBX + Vehicle (deionized water); b) OBX + Nicotine; c) OBX + Mock TMS, which involved placing the animals in the same TMS cage for the same period of time, but without any stimulation; d) OBX + TMS.

Two weeks after surgery drug treatment began, nicotine was administered chronically once daily for 14 days at dose of 1.5 mg/kg body weight i.p. (dissolved in deionized water and prepared freshly each morning) [32] and TMS was applied for 14 days, either on its own or combined with olfactory bulbectomy. The animals were subjected to open field test followed by forced swim test on the 14th day of chronic nicotine administration.

2.8. Statistical analysis

Differences in immobility times and fluid intake (water vs. nicotine) were compared using the non-parametric Kruskal-Wallis one-way ANOVA on ranks test. Multiple pairwise comparison between the different groups was evaluated using Dunn's method. A significant level was considered when $P < 0.05$.

When comparing result from the TMS experiments, differences of treatment (Vehicle, Mock TMS, Nicotine, TMS) in rats were analyzed by one-way ANOVA followed by Bonferroni-corrected post hoc test to determine the source of significance. The level of statistical significance was set at 0.05. Data are presented as mean $\pm$ S.E.M. StatView 5 (SAS Institute Inc, Cary, NC, USA) was used to do all analyses.

3. Results

3.1 Effects of OBX on Wistar and Long Evans rats

We evaluated the time that rats spent immobile in the FST. Wistar rats tended to stay less time immobile than Long Evans rats (73.3 ± 1.3 s/5 min vs. 105.9 ± 7.5 , respectively; $Q = 3.93$, $P < 0.05$). Moreover, swimming behaviour was less homogeneous in Long Evans (Median immobility time 97.5 s/5 min, range: 69–150 s/5 min) than in Wistar rats (Median immobility time 74 s/5 min, range: 70–90 s/5 min). Four weeks after OBX, the time Wistar rats spent immobile was increased (94.6 ± 4.6 s/5 min; $Q = 3.09$, $P < 0.05$) with respect to pre-surgery and Sham (72.5 ± 1.7 s/5 min) values. In contrast, Long Evans did not show increases in immobility after OBX (96.6 ± 15.6 ; $P = 0.182$) or Sham (78.2 ± 2.6 ; $P = 0.182$) surgeries. A higher variability in the time Long Evans rats spent immobile was still observed after surgeries (Figure 1).

3.2 Nicotine alleviates the depression-like symptoms of OBX in Wistar rats

We analyzed the effect of oral self-administration of nicotine on immobility in FST in OBX animals. In Long Evans rats, which did not show increased immobility in FST after OBX, nicotine intake did not have a significant effect on this test after Sham (61.1 ± 4.3 s/5 min vs. 87.3 ± 12.8 s/5 min water-only; $P = 0.165$) or OBX surgeries (77.7 ± 8.5 s/5 min vs. 78.2 ± 2.6 s/5 min water-only; $P = 0.165$). In Wistar rats, nicotine intake decreased the amount of time OBX rats spent immobile (63.2 ± 9.7 s/5 min vs. 94.6 ± 4.6 s/5 min water-only; $Q = 3.136$; $P < 0.05$). However, nicotine intake did not have an effect on the time sham-operated Wistar animals spent immobile (47 ± 7.2 s/5 min vs. 72.5 ± 1.7 s/5 min water-only; $Q = 2.138$; $P > 0.05$).

3.3 Nicotine intake does not increase after surgeries

Prior to OBX or Sham surgeries, Wistar rats showed greater nicotine intake than Long Evans rats (1.64 ± 0.06 mg/kg/day vs. 1.22 ± 0.06 mg/kg/day, $Q = 6.4$, $P < 0.05$). Rats were then

separated into different groups and were subject to surgery. After a four-week period, nicotine consumption was reassessed.

In the group of Wistar rats where Sham surgery was performed, animals decreased their nicotine intake by 30% after surgery (1.08 ± 0.07 mg/kg/day vs. 1.6 ± 0.09 mg/kg/day pre-surgery; $Q=3.4$; $P<0.05$). Nicotine intake was decreased by 25% in the group of Wistar rats where OBX surgery was performed (1.2 ± 0.05 mg/kg/day vs. 1.7 ± 0.08 mg/kg/day pre-surgery; $Q=3.1$; $P<0.05$). There were no statistically significant differences in nicotine intake between animals subject to either type of surgery (Table).

Long Evans rats also decreased their nicotine intake by 55% after Sham surgery (0.45 ± 0.04 mg/kg/day vs. 0.99 ± 0.09 pre-surgery; $Q=5.2$; $P<0.05$). After OBX, Long Evans rats showed no significant differences in nicotine intake with respect to pre-surgery intake (1.2 ± 0.05 mg/kg/day vs. 1.3 ± 0.08 ; $Q=1.5$; $P=0.112$), but they showed a significant higher intake when compared to sham-operated animals ($Q=10.3$; $P<0.05$) (Table). Total fluid intake among all different experimental groups was not significantly different (Table).

3.4 Comparison of antidepressant effects of nicotine and TMS

Because our results showed an anti-depressant effect of nicotine when administered as a voluntarily-ingested oral solution, we decided to evaluate the effect of a single i.p. injection of nicotine on OBX, to have a tighter control over nicotine dosage. Furthermore, we compared this effect to TMS, which has arisen as an alternate therapy for major depression. Nicotine administered as a single, daily i.p. injection (1.5 mg/kg/day for 15 days) decreased the immobility time in OBX Wistar rats (63 ± 2.7 s/5 min vs. 160.8 ± 22.4 s/5 min in vehicle-injected group; $F_{(1,16)} = 3.03$, $P < 0.0001$). TMS also decreased the immobility time in OBX Wistar rats (106.2 ± 8.6 s/5 min) when compared to OBX animals subject to the same procedure under the TMS apparatus without exposing them to a magnetic field (OBX+Mock TMS group: 163.6 ± 11.2 s/5 min; $F_{(1,16)} = 15.60$, $P < 0.0001$). Nicotine had a stronger effect than TMS on immobility time in OBX animals ($F_{(1,16)} = 3.03$, $P < 0.0001$) (Fig. 2). There were no significant differences between the OBX+Vehicle vs. OBX+Mock TMS groups ($F_{(1,16)} = 3.03$, $P = 0.7272$). The effect of nicotine or TMS on OBX rats vs. Vehicle or Mock TMS, decrease the locomotor activity ($F_{(1,16)} = 15.60$, $P < 0.0001$) (Fig. 2).

4. Discussion

The aim of this study was to compare the depression-like state induced by OBX in two different inbred rat strains and to evaluate the anti-depressant effect of nicotine in this model. We observe innate differences in susceptibility to develop depression-like symptoms after OBX between Wistar and Long Evans rats.

While Wistar rats started developing depression-like symptoms two weeks after OBX, assessed by an increased time of immobility in the FST, Long Evans rats did not show significant increases immobility, even 4 weeks after OBX. These results suggest that either Long Evans rats are more resilient to OBX-induced depression or that the FST is not a good test to show depression-like symptoms correlated to OBX in this inbred strain. This latter possibility could also be supported by the fact that swimming behavior of Long Evans rats in FST is more variable than Wistar rats' behavior. Also, Long Evans rats tend to spend more time immobile in the FST at baseline than Wistar rats. Higher baseline immobility and variability could mask differences between OBX- and Sham-Long Evans rats, making this strain a poor model of depression under these conditions.

In Wistar rats, nicotine intake decreased the immobility time in the FST after OBX. An antidepressant-like effect of nicotine has been previously reported in rats [34] and other rodents

using models that induce depression-like behavior, such as chronic mild stress and learned helplessness [5,7,27]. To the best of our knowledge, this is the first description of an anti-depressant effect of nicotine when self-administered as an oral solution.

Nevertheless, nicotine intake decreased in these animals after the surgical procedures, both Sham and OBX, and no significant differences in nicotine intake were observed between Sham and OBX Wistar rats. Thus, although Wistar rats showed higher rates of nicotine consumption than Long Evans rats, we could not observe a self-medicating effect for nicotine intake.

The nicotine intake differences between Wistar, which showed higher rates of consumption, and Long Evans rats could also be related to intrinsic phenotypic variability between these two strains, as it was observed in depression post-OBX. We also observed increased locomotor activity in Wistar rats in the open field test. The nature of this variability, whether there are intrinsic differences in susceptibility to stress or differences in baseline locomotor activity, remains to be elucidated [1]. Our studies were in agreement with previous studies that have shown similar differences in mobility between inbred strains [14,19,35].

Interestingly, there was no preference for nicotine compared to water at baseline in any of the two inbred strains we tested. It is possible, however, that the lack of preference reflects a limitation in fluid intake, such that rats first drink nicotine up to a physiological threshold, but still need to drink fluid for hydration. Previous studies have shown that both animals and humans can titrate nicotine dosage intake precisely [8,26], thus it is possible that our experimental animals ingested nicotine up to certain level. It should be noted that even though the rats did not prefer nicotine to water at baseline, all animals showed a significant intake of the drug.

In both strains, nicotine intake decreased after animals were subject to the Sham surgical procedure. In Wistar rats, nicotine consumption was also decreased after OBX, but we observed no significant differences in nicotine intake between animals subject to the different surgeries. In contrast, Sham Long Evans rats showed a major decrease in nicotine intake, but showed no differences in intake after OBX.

Because Sham animals had been exposed to nicotine before surgery and nicotine intake was reevaluated four weeks after surgery, the differences in nicotine intake could be due to sensory adaptation; i.e., rats tend to reject the bitter flavor of nicotine once they are familiar with it. A higher susceptibility to the stress caused by the Sham operation in Long Evans rats could further reduce nicotine intake. This could also indicate that there is not a self-medicating driving force behind nicotine intake, at least under these conditions. On the other hand, OBX in Long Evans rats could change the gustatory preference and thus preclude the negative effect of the surgery on nicotine intake[30]. In contrast, the higher rates of nicotine intake in Wistar rats, observed under all conditions, could suggest a high intrinsic preference for nicotine in this strain.

Interestingly, there does not seem to be a correlation between the amount of nicotine consumed and the antidepressant-like effects observed in the FST. Comparing nicotine-induced decreases in immobility within strain and surgery groups, the size of the effect was not different across groups. This suggests that the effect of nicotine was not related to the absolute amount of nicotine ingested, but rather that it varies in relation to intrinsic susceptibility. This is similar to what is observed in human subjects, where self-reported feelings of nicotine liking vary greatly between individuals [2,28].

After showing that nicotine had an anti-depressant-like effect when voluntarily ingested, we decided to evaluate the effect of a single, daily i.p. injection of this drug on the depression-like symptoms induced by OBX in Wistar rats, to compare the efficacy of these two methods of nicotine administration. We further compared the effect of nicotine to the anti-depressant like

effects of TMS, because it is well known that the OBX-rodent model responds well to other anti-depressant therapies [15,21], and we wanted to test the effect of TMS, which has emerged as an alternative to electroconvulsive therapy for the treatment of human depression [13]. Moreover, repetitive TMS reduces immobility time in the FST, which further supports an antidepressant effect for this therapy [22].

Injected nicotine was as effective as orally ingested nicotine in decreasing immobility in the FST in OBX Wistar rats. Our results also show that chronic stimulation with TMS (2 × 2 hours per day for 15 days) decreased the immobility time but that the effect of nicotine was greater, suggesting a more efficient anti-depressant efficacy for this drug than TMS. Furthermore, injected nicotine and TMS attenuated the hyperactivity associated with OBX as shown by other antidepressant substances [10].

Finally, it can be suggested that TMS had more modest antidepressant properties than nicotine, and both approaches may provide an alternative for the treatment of depressive symptoms.

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Figure 1. Effects of OBX on Wistar and Long Evans rats

(A, B) Immobility time in the FST from animals exposed to water only. Prior to surgery, Wistar rats tended to stay less time immobile than Long Evans rats in the FST (** in B denotes $P < 0.05$ vs. pre-surgery Wistar rats). Four weeks after OBX, the time Wistar rats spent immobile was increased with respect to pre-surgery and sham procedures (* in A denotes $P < 0.05$ vs. presurgery). Voluntary nicotine intake decreased the immobility time in OBX-Wistar rats (* in C denotes $P < 0.05$ vs. water-only). In Long Evans rats, OBX did not have significant effects on the immobility time in the FST.

Figure 2. Comparison of antidepressant effects of nicotine and TMS

A) Injected nicotine and TMS decreased the immobility time in the FST of OBX-Wistar rats. Nicotine showed a stronger anti-depressant effect than TMS. (+ denotes $P < 0.0001$ vs. Vehicle and TMS; ** denotes $P < 0.0001$ vs. Mock TMS). B) Injected nicotine and TMS decreased the hyperactivity of OBX-Wistar rats, evaluated by the open field test. (* denotes $P < 0.0001$ vs. Vehicle; ** denotes $P < 0.0001$ vs. Mock TMS).

Table 1
Nicotine consumption pre and post surgery

At baseline Wistar showed higher nicotine intake than Long Evans rats (* $P < 0.05$). Animals were then separated into different surgical treatment groups. Wistar rats decreased their nicotine intake after sham or OBX surgeries, with respect to pre-surgical intake (** $P < 0.05$). Long Evans rats also decreased their nicotine intake after the sham procedure, compared to pre-surgery levels (** $P < 0.05$). However, OBX surgery did not have significant effects on nicotine intake, when compared to pre-surgery levels, although OBX-Long Evans rats showed higher levels of nicotine intake when compared to sham-operated animals (**** $P < 0.05$).

			Long Evans	Wistar
Baseline	Total Fluid Intake	Water only group (ml/day)	44.12 ± 1.16 (N=16)	43.34 ± 2.06 (N=16)
		Water+Nicotine group (ml/day)	38.79 ± 1.76 (N=28)	42.1 ± 1.1 (N=24)
	Nicotine intake	ml/day	13.42 ± 0.68	17.21 ± 0.65
		mg/kg/day	1.22 ± 0.06	1.64 ± 0.06 *
Pre Sham	Total Fluid Intake	Water only group (ml/day)	42.15 ± 1.07 (n=8)	43.7 ± 1.96 (n=8)
		Water+Nicotine group (ml/day)	39.01 ± 1.05 (n=10)	43 ± 1.09 (n=8)
	Nicotine intake	ml/day	10.66 ± 0.97	18.29 ± 1.06
		mg/kg/day	0.99 ± 0.09	1.56 ± .09
Post Sham	Total Fluid Intake	Water only group (ml/day)	39.64 ± 1.65 (n=8)	44 ± 1.26 (n=8)
		Water+Nicotine group (ml/day)	40.78 ± 1.9 (n=10)	42.7 ± 1.84 (n=8)
	Nicotine intake	ml/day	6.21 ± 0.49	17.21 ± 1.14
		mg/kg/day	0.45 ± 0.04 ***	1.08 ± 0.07 **
Pre OBX	Total Fluid Intake	Water only group (ml/day)	41.15 ± 1.18 (n=8)	41.78 ± 1.93 (n=8)
		Water+Nicotine group (ml/day)	39.86 ± 1.56 (n=18)	42.0 ± 1.72 (n=16)
	Nicotine intake	ml/day	14.97 ± 0.89	16.68 ± 0.81
		mg/kg/day	1.35 ± 0.08	1.67 ± .08
Post OBX	Total Fluid Intake	Water only group (ml/day)	39.51 ± 1.22 (n=8)	40.69 ± 1.4 (n=8)
		Water+Nicotine group (ml/day)	41.8 ± 1.64 (n=18)	42.9 ± 1.38 (n=16)
	Nicotine intake	ml/day	17.53 ± 0.71	17.92 ± 0.77
		mg/kg/day	1.24 ± 0.05 ****	1.25 ± 0.05 **