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Pharmacology, Biochemistry and Behavior 72 (2002) 355–364

PHARMACOLOGY BIOCHEMISTRY AND BEHAVIOR

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Effects of nicotine on alcohol intake in a rat model of depression

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Received 19 June 2001; received in revised form 31 October 2001; accepted 21 November 2001

Abstract

Clinical studies suggest that depression facilitates alcohol abuse. Depressed individuals also have increased rates of smoking, and it has been suggested that nicotine may improve depression. It is therefore possible that nicotine may reduce alcohol use in depression. To investigate this potential relationship, we evaluated alcohol intake in an animal model of depression, which consists of administering clomipramine (CLI), a preferential serotonin reuptake inhibitor, to neonatal rats. This pharmacological manipulation produces adult depression-like behaviors, such as reduced aggressiveness, decreased pleasure seeking, diminished sexual activity, increased locomotor activity and increased REM sleep. In this study, we found that CLI rats exhibited significantly higher locomotor activity, lower aggressiveness and higher alcohol intake than control rats. Chronic administration of a low dose of nicotine (0.25 mg/kg/day) or a sham operation did not modify these behaviors. However, chronic administration of nicotine at a higher dose (1.5 mg/kg/day) significantly increased aggressive behavior and reduced alcohol intake in CLI rats. The effect of nicotine on alcohol intake lasted at least 1 month after cessation of nicotine administration. These results indicate that nicotine reverted some depression signs and reduced alcohol self-administration in the CLI model of depression.

Keywords: Alcohol; Depression; Nicotine; Animal model

1. Introduction

Depression and substance abuse are highly prevalent in the general population and often co-occur within the same individual (Lejoyeux et al., 2000; Modesto-Lowe and Kranzler, 1999; Swendsen and Merikangas, 2000). Many community studies have revealed significant co-morbidity between depression and alcoholism (Clark et al., 1997; Kessler et al., 1996; Maier and Merikangas, 1996; Penick et al., 1994; Pomerleau et al., 1997; Regier et al., 1990; Rodgers et al., 2000; Roy et al., 1991; Spak et al., 2000). Furthermore, depressed patients exhibit a tendency to consume increased amounts of alcohol in comparison to never-depressed patients (Dixit and Crum, 2000; Pettinati et al., 1997; Roy et al., 1991).

Animal models have been developed to study neurobiology and treatment of depression and substance abuse. One commonly used method to produce rats with behavioral changes consistent with human depression is to inject neonatal rats with antidepressant medications (Hilakivi and Hilakivi, 1987; Vogel and Vogel, 1982; Vogel et al., 1990a). For example, neonatal rats treated with clomipramine (CLI), a preferential serotonin reuptake inhibitor, exhibit behavioral abnormalities resembling endogenous depression (Vogel et al., 1990a), including reduced aggressiveness (Vijayakumar and Meti, 1999; Vogel et al., 1988), decreased pleasure seeking (Vogel et al., 1990b), diminished sexual activity (Bonilla-Jaime et al., 1998; Neill et al., 1990; Velazquez-Moctezuma et al., 1993; Vogel et al., 1996), shortened REM sleep onset latency and more REM sleep periods (Frank and Heller, 1997; Vogel et al., 1990c) —

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0091-3057/02/$ – see front matter
PII: S0091-3057(01)00772-9

behaviors typically observed in depressed patients (DSM-IV, 1994; Mann, 1999). CLI rats also exhibit locomotor hyperactivity, which may be analogous to the agitation found in human depression (Hartley et al., 1990). Behavioral abnormalities in these rats (sexual, aggressive and motor) begin to normalize after treatments known to alleviate depression in humans (imipramine; REM sleep deprivation) (Vogel et al., 1990a).

A positive association between depression and voluntary alcohol intake has been suggested in animal models of both depression (Dwyer and Rosenwasser, 1998; Hilakivi et al., 1984; Paré et al., 1999) and alcoholism (Ciccocioppo et al., 1999; Overstreet et al., 1992). In fact, neonatal CLI treatment increases voluntary alcohol consumption (10% alcohol vol/vol) of adult rats (Dwyer and Rosenwasser, 1998; Hilakivi et al., 1984). Similar findings were obtained in the Wistar–Kyoto rat strain, which represents another animal model that reveals depressive behavior (Paré and Redei, 1993; Paré et al., 1999).

Epidemiological studies also reveal a high incidence of cigarette smoking among depressed individuals (Balfour and Ridley, 2000; Benowitz, 1999; Covey, 1999; Fergusson et al., 1996; Glassman et al., 1990). Moreover, individuals with a history of depression have a much harder time giving up smoking than nondepressed individuals, presumably due to the occurrence of severe withdrawal symptoms (Carton et al., 1994; Covey, 1999; Stage et al., 1996). A few authors have suggested that most of these individuals may be smoking in an attempt to self-medicate against depression (Breslau et al., 1998; Lerman et al., 1996; Markou et al., 1998). Actually, human (Salín-Pascual and Drucker-Colín, 1998; Salín-Pascual et al., 1995, 1996) and animal studies (Djuric et al., 1999; Semba et al., 1998; Tizabi et al., 1999) suggest that nicotine may have antidepressant effects. For example, Salín-Pascual et al. (1995, 1996) demonstrated that transdermal nicotine administration improved mood, as determined by the Hamilton Rating Scale for Depression, in nonsmoking patients with major depression.

Taken together, these data suggest that depression is a contributing factor in the development of excessive alcohol and tobacco uses and that nicotine may act as an antidepressant drug. We hypothesized that nicotine may decrease alcohol preference in depressed subjects.

The influence of nicotine on alcohol intake in animals with experimentally induced depression has not been characterized. Therefore, we sought to determine if the chronic administration of nicotine reduces alcohol consumption in the CLI-induced depression model in rats (Vogel et al., 1990a). Because it is well established that neonatal CLI treatment results in increased locomotor activity and reduced aggressive behavior in adulthood, these behaviors were evaluated to verify the efficacy of CLI administration, and to examine potential antidepressant-like effects of nicotine.

2. Methods

2.1. Drugs

The following compounds were used: CLI hydrochloride (Sigma, St. Louis, MO, USA), (−)nicotine hydrogen tartrate salt (Sigma), alcohol (JT Baker, Mexico City) and saline (NaCl 0.9% in sterile water; Baxter, Mexico City).

2.2. Subjects

We used 146 neonatal male Long–Evans rats, which were housed four/five per cage with their mothers and treated with CLI (CLI group) or vehicle (saline, control group). All pups within a litter received the same treatment. From Postnatal Day 8, each pup belonging to the CLI group received subcutaneous injections of CLI (30 mg/kg/day, 100 μl, suspended in saline) in the back, between the shoulder blades. Rats in the control group received injections of saline (same volume and route of administration). The injections were given once daily at 10:00 am until rats were 21 days old. At 28 days of age, pups were separated from their mothers and housed in groups of four per cage until the age of 3 months. Rats were housed individually for approximately 3 weeks before the implementation of any experimental testing. During this period, rats had free access to food and water and were maintained on a 12:12 light–dark cycle (lights on 8:00 am). The ambient temperature was maintained at 22–24 °C.

2.3. Nicotine treatment

Nicotine was infused at a constant rate of 0.25 or 1.5 mg/kg/day (free base) for 4 weeks by osmotic minipumps (Alzet model 2ML4; ALZA, Palo Alto, CA, USA). Nicotine was dissolved in saline, and pH was adjusted to 7.4 by adding a small quantity of NaOH. Before implantation, each pump was primed for 12 h in saline. Rats were anesthesized by inhalation of halothane in oxygen (5% halothane for 3 min, then 1–2% halothane as required when the rat was implanted). The minipump was subcutaneously implanted in the dorsal thoracic area by making a small incision, inserting the pump and closing the incision with suture. Four weeks following the implantation of pumps, rats were anesthesized with halothane and the pumps were removed.

2.4. Alcohol schedule

Rats were exposed to alcohol (10% vol/vol) solution as their only drinking fluid for 7 days. Upon the completion of this period, rats had free choice between tap water and 10% alcohol solution in two plastic graduated drinking tubes (100 ml capacity) for 4 weeks. Alcohol was diluted (10% vol/vol) with regular tap water. Water and alcohol

intakes were scored daily at 10:00 am, when the tubes also were filled with fresh beverages. The positions (right/left) of the alcohol tube and the water tube were alternated to compensate for any position preference by the rat. Alcohol consumption was determined by calculating grams of alcohol consumed per kilograms of body weight. Data were averaged across the 7 days of the week. Body weight was also measured weekly.

2.5. Apparatus and equipment

Locomotor activity was measured in a black box [$42 \times 42 \times 20$ (h) cm] with 32 photocells. One wall of this box had a row of 16 photocells mounted 11.5 cm from the floor, and an adjacent wall had a similar row, mounted 0.5 cm from the floor. Photocells were 2.6 cm apart from each other. The number of photocells crossings during 10 min determined locomotion.

Aggressive behavior was assessed in a Plexiglas chamber [$25.5 \times 30 \times 28$ (h) cm] with a floor made up of 15 stainless steel rods (diameter: 7 mm), 2 cm apart from each other. A stimulator (Grass Model S88; Quincy, MA, USA) was connected to the floor rods to deliver an electric stimulus (1.33 mA, 0.5 s duration). Rats were tested in pairs. Each pair consisted of one CLI and one control rat. Prior to testing, all rats were paired by body weight to rule out size differences, which could affect the expression of the behavior. The same pairings of rats were maintained throughout the experiments. Tests were carried out daily for 4 days. On the first day, pairs of rats were placed in the chamber for 12 min for habituation. On Days 2–4, the sessions started with a 2-min habituation period followed by 10 min during which electrical stimuli were delivered at 10-s intervals. Two evaluators scored the behaviors simultaneously, each evaluator observing one of the rats. Rats were identified by a black mark placed on the tail of one of the rats. Observers were blind to the treatment condition of the animals. Offensive and defensive behaviors were scored according to the system of Miczec and Barry (1976). Offensive behaviors consisted of offensive upright posture (the dominant rat towered over the submissive rat), offensive crouch (the animal turned its flank towards the subordinate), mounting behavior and leaping toward the other rat in response to the stimuli. The defensive behaviors scored included defensive upright posture (the submissive rat reared on its hindfeet, with the head positioned at an upward angle), submissive crouch (freezing in a motionless crouching position) and supine position in submission to the dominant rat (ventral surface of the body facing the opponent). Average numbers of individual offensive behaviors of each group across the test days are presented.

All behavioral testings were conducted during the dark phase of the light/dark cycle in a quiet and ventilated room under dim red light illumination. Separated groups of rats were used for all experiments.

2.6. Procedure

2.6.1. Experiment 1: effects of nicotine on locomotor activity and aggressive behavior

Prior to treatment, both control and CLI rats were evaluated for locomotor activity, and then, 2 days after, for aggressive behavior. One day after evaluation of aggressive behavior, both control and CLI rats were randomly allocated to the following groups: sham (control, $n=8$; CLI, $n=8$), low nicotine dose (0.25 mg/kg/day; control, $n=8$; CLI, $n=8$) and high nicotine dose (1.5 mg/kg/day; control, $n=8$; CLI, $n=8$). Sham-operated rats underwent the entire surgical procedure, but they did not receive the pump. Minipumps were not implanted in the sham group since it has been shown that the presence of the minipump alone does not change the basal parameters of several behaviors studied, including T-maze, open field and novel water maze performance (Doucette et al., 2000). Three weeks following surgery, rats were again tested for locomotor activity and aggressive behavior. Therefore, a total of approximately 4 weeks elapsed between evaluations.

2.6.2. Experiment 2: effects of nicotine on alcohol intake

Controls and CLI adult rats were randomly allocated to the following groups: sham (control, $n=10$; CLI, $n=10$), low nicotine dose (0.25 mg/kg/day; control, $n=10$; CLI, $n=9$) and high nicotine dose (1.5 mg/kg/day; control, $n=8$; CLI, $n=8$). Rats were anesthesized with halothane and implanted with miniosmotic pumps containing nicotine. The sham group underwent the surgical procedure, but without implantation of the minipump. Immediately after the surgery, all animals were returned to their home cages where they were exposed to the alcohol treatment schedule.

2.6.3. Experiment 3: duration of the nicotine effect on alcohol intake

We employed the same method as in Experiment 2, but rats were not exposed to the alcohol treatment schedule until they had 4 weeks of treatment with nicotine. Rats were randomly allocated to the following groups: sham (control, $n=10$; CLI, $n=10$), low nicotine dose (0.25 mg/kg/day; control, $n=5$; CLI, $n=6$) and high nicotine dose (1.5 mg/kg/day; control, $n=5$; CLI, $n=7$). Four weeks following surgery, rats were anesthesized with halothane and the pumps were removed. Immediately after the removal of the pump, rats were exposed to alcohol schedule.

2.7. Data analysis

All results are expressed as means ± S.E.M. For locomotor activity, aggressive behavior and alcohol intake scores were compared by repeated measures ANOVA (General Linear Model, SPSS X; SPSS, Chicago, IL, USA) between-subjects factor as were group (control, CLI) and nicotine dose (0, 0.25 and 1.5 mg/kg/day). Comparisons between individual groups were made with

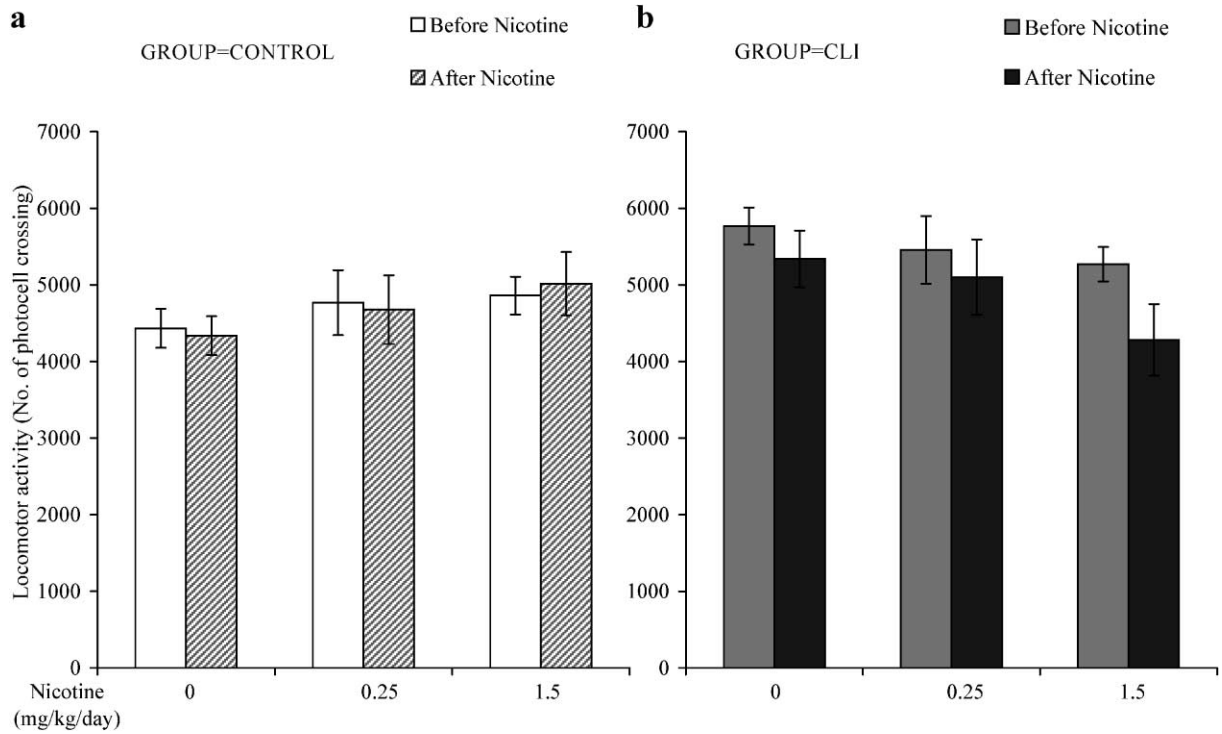

Fig. 1. Change in the baseline of locomotor activity in control (a) and CLI (b) rats after nicotine infusion (0.25, 1.5 mg/kg/day) and sham operation (0 mg/kg/day). Values indicate mean of total photocell crossings ± S.E.M. across 10 min. Eight animals per group are shown.

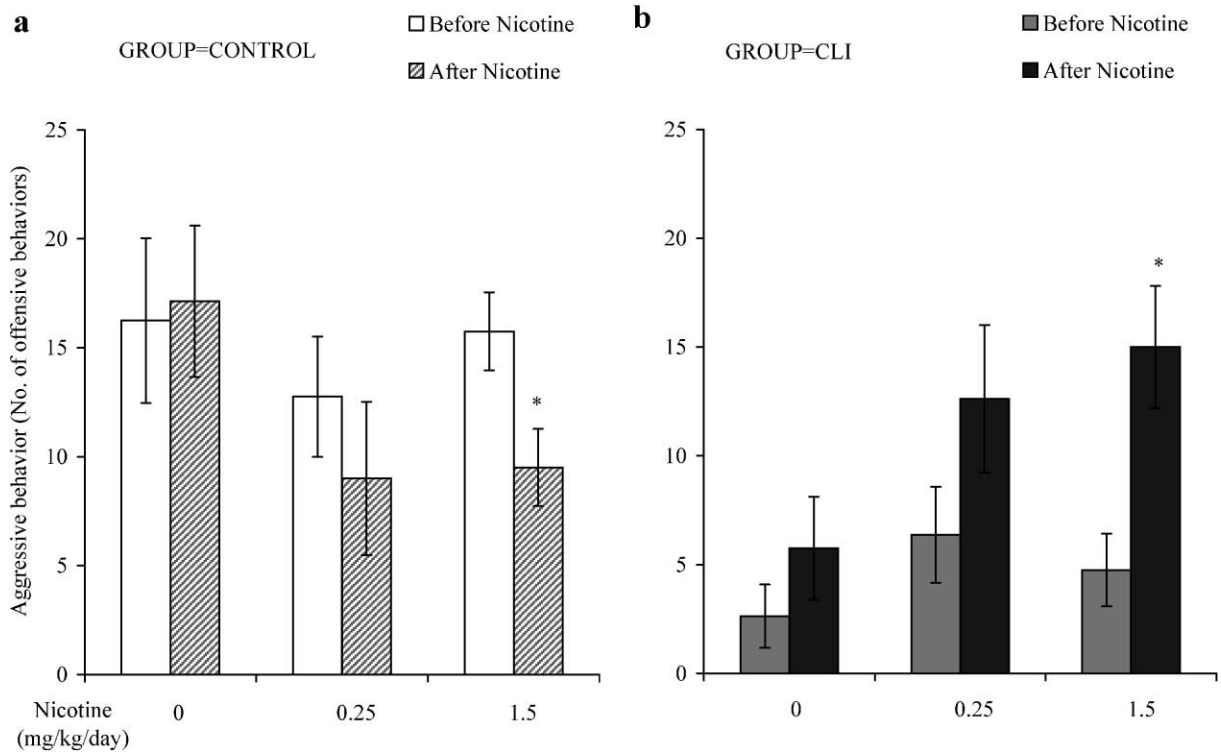

Fig. 2. Change in the baseline of aggressive behavior in control (a) and CLI (b) rats after nicotine infusion (0.25, 1.5 mg/kg/day) and sham operation (0 mg/kg/day). Values indicate mean of number of individual offensive behaviors ± S.E.M. Eight animals per group are shown. * $P < .05$ compares Before Nicotine vs. After Nicotine.

Fisher's post hoc tests. Differences were considered significant at $P < .05$.

3. Results

3.1. Locomotor activity after 4 weeks of nicotine treatment

At 3 months of age, CLI rats were significantly more active than control rats [$F(1,46) = 4.96$, $P < .05$] (see Fig. 1). Neither nicotine administration at low (0.25 mg/kg/day) and high (1.5 mg/kg/day) doses nor sham operation modified locomotor activity in CLI or control animals [$F(5,42) = 0.539$] (see Fig. 1). Nicotine at the higher dose produced a decrease on locomotor activity in the CLI group, although this difference was not statistically significant.

3.2. Aggressive behavior after 4 weeks of nicotine treatment

CLI rats exhibited significantly fewer offensive behaviors than control rats [$F(1,46) = 7.77$, $P < 0.01$] (see Fig. 2). Unlike the sham operation, nicotine administration at the higher dose (1.5 mg/kg/day) produced a significant increase in the number of offensive behaviors in the CLI group and a significant decrease in offensive behaviors in the control group [$F(5,42) = 4.70$, $P < .05$] (see Fig. 2). The effects of the low nicotine dose (0.25 mg/kg/day) were similar to those of the higher dose, but did not achieve statistical significance.

3.3. Alcohol intake during 4 weeks of nicotine treatment

In sham-operated group, CLI rats ingested more alcohol than control rats during the period when alcohol solution was their only choice [$F(1,18) = 5.85$, $P < .01$] (see Figs. 3 and 4). During the free-choice period, when the animals could choose to drink water or alcohol, alcohol consumption was significantly higher in the CLI group [$F(1,18) = 11.3$, $P < .01$] (see Figs. 3 and 4). Alcohol intake by the control and CLI groups did not vary across the free-choice period.

When nicotine and alcohol were administered simultaneously (Experiment 2), a significant decrease in alcohol intake in the CLI group for both nicotine doses (0.25 and 1.5 mg/kg/day) was observed during the period that alcohol solution was their only drinking fluid [$F(2,24) = 7.52$, $P < .01$] (see Fig. 3). During the free-choice period, alcohol

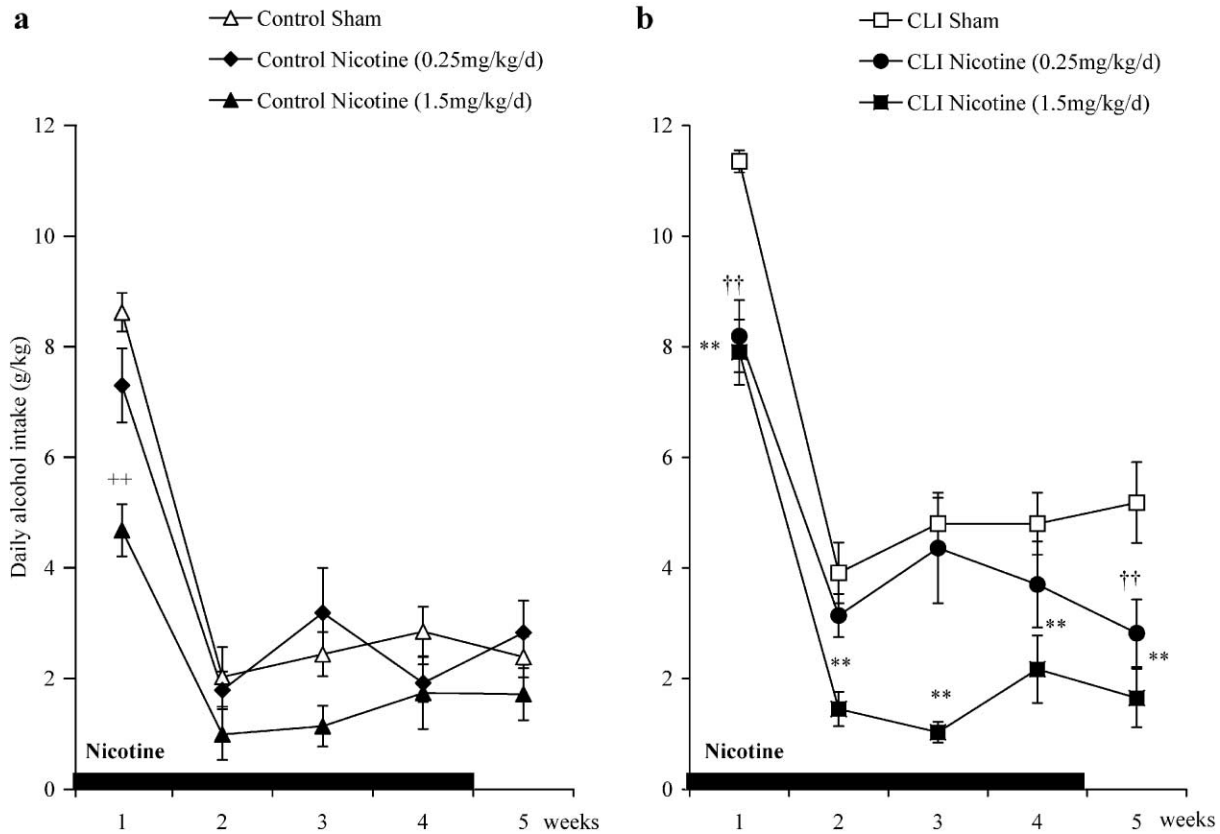

Fig. 3. Alcohol intake in control (a) and CLI (b) rats during chronic treatment with nicotine (Weeks 1–4) and subsequent nicotine withdrawal (Week 5). During the first week, alcohol solution was their only choice. From the second week, they had the option to ingest water and/or alcohol. The values are expressed as grams of alcohol consumed per kilogram of body weight. Mean daily alcohol intake ± S.E.M. of 8–10 animals is given in each week. $^{++}P < .01$ compares Control Sham vs. Control Nicotine (1.5 mg/kg/day); $^{\dagger\dagger}P < .01$ compares CLI Sham vs. CLI Nicotine (0.25 mg/kg/day); $**P < .01$ compares CLI Sham vs. CLI Nicotine (1.5 mg/kg/day).

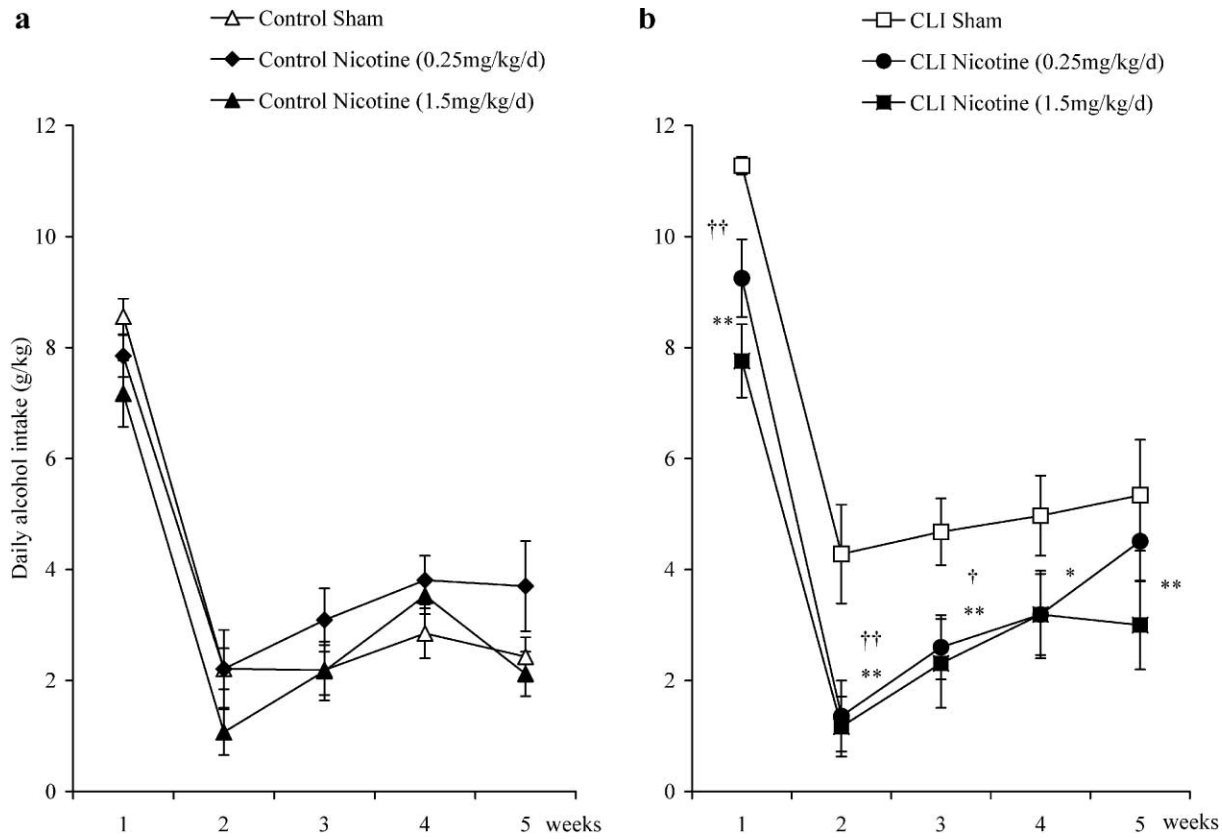

Fig. 4. Alcohol intake following 4 weeks of chronic nicotine administration at a low dose (0.25 mg/kg/day) and a high dose (1.5 mg/kg/day) by osmotic minipumps vs. sham-operated control (a) and CLI (b) rats. During the first week, alcohol solution was their only choice. From the second week, they had the option to ingest water and/or alcohol. The values are expressed as grams of alcohol consumed per kilograms of body weight. Mean daily alcohol intake ± S.E.M. of 5–10 animals is given. $^{\dagger}P<.05$, $^{\dagger\dagger}P<.01$ compare CLI Sham vs. CLI Nicotine (0.25 mg/kg/day); $*P<.05$, $**P<.01$ compare CLI Sham vs. CLI Nicotine (1.5 mg/kg/day).

consumption by CLI rats was significantly lower for the high dose of nicotine (1.5 mg/kg/day) [$F(2,24)=3.36$, $P<.01$]. With the low nicotine dose (0.25 mg/kg/day), there was a trend for a decrease in alcohol consumption, but this became statistically significant only during the fourth week [$F(2,24)=3.80$, $P<.05$] (see Fig. 3). In the control group given the higher nicotine dose, a trend for reduced alcohol consumption was observed. It was significant only when alcohol solution was their only choice [$F(2,25)=4.6$, $P<.01$], whereas the low nicotine dose (0.25 mg/kg/day) did not produce significant changes at any time [$F(2,25)=0.41$] (see Fig. 3).

3.4. Alcohol intake following 4 weeks of nicotine treatment

In Experiment 3, both control and CLI rats were exposed to alcohol after 4 weeks of treatment with nicotine at either 0.25 or 1.5 mg/kg/day. In control animals, there was no difference in alcohol consumption between sham animals and nicotine-treated animals [$F(2,17)=1.67$] (see Fig. 4).

In the CLI group, alcohol consumption was significantly lower in animals pretreated with both nicotine doses (0.25 and 1.5 mg/kg/day) during all times [$F(2,20)=7.4$, $P<.05$] (see Fig. 4), with only two exceptions; during Weeks 3 and 4 of free choice, animals given the lower dose of nicotine did not show significant differences compared with sham CLI rats.

4. Discussion

The results of this study suggest that chronic nicotine treatment reduced alcohol consumption in a rat model of depression. In our experiments, neonatal treatment with CLI produced the basic criteria for experimental depression reported previously for the CLI model, including significantly decreased aggressiveness associated with higher locomotor activity (Vogel et al., 1990a) and increased intake of alcohol (Dwyer and Rosenwasser, 1998; Hilakivi et al., 1984).

In CLI animals, nicotine administration at high dose (1.5 mg/kg/day) produced a significant increase in aggressive behavior, which may represent a manifestation of antidepressant-like actions of nicotine. Nicotine has been demonstrated to possess some antidepressant-like activity. Results obtained in our laboratory showed that nicotine applied transdermally improves mood in patients with major depression (Salín-Pascual and Drucker-Colín, 1998;

Salín-Pascual et al., 1995, 1996). Animal models of depression suggest that nicotine can have long-term antidepressant-like properties. For example, Flinders Sensitive Line rats selectively bred for their hyperresponsiveness to cholinergic stimulation and developed as an animal model of depression showed exaggerated immobility in the forced swimming test. Acute or chronic administration of nicotine significantly improved the performance of these rats in the forced swimming test (Tizabi et al., 1999). Another animal model of depression is the learned helplessness paradigm in rats that show escape failures. Chronic nicotine exposure induced a significant reduction in the number of escape failures in these rats (Semba et al., 1998).

We found that alcohol intake was significantly higher in CLI rats than in controls, both when only alcohol was available to drink, as well as during the free-choice period when the animals were allowed to choose alcohol or water. These results are in agreement with those reported by Hilakivi et al. (1984) and Dwyer and Rosenwasser (1998), which indicated that depressed animals manifested an increase in their appetite for alcohol, very much like depressed humans.

With simultaneous nicotine administration and alcohol exposure, both absolute and relative alcohol intakes in CLI rats were significantly reduced by the higher dose of nicotine (1.5 mg/kg/day). When rats were exposed to alcohol after a treatment with nicotine for 4 weeks, CLI rats exhibited significantly lower alcohol consumption that was dependent on the dose of nicotine used as a pretreatment. In contrast, nicotine pretreatment did not significantly alter alcohol intake in control animals. These results suggest that in CLI animals, nicotine may have sensitizing effects upon the mechanisms that antagonize alcohol intake.

One potential explanation for these results is that the mesolimbic dopamine system is a common target of nicotine and alcohol (Koob, 1999; Koob et al., 1998; Pich et al., 1997). Both alcohol and nicotine appear to enhance dopamine release in the nucleus accumbens (Blomqvist et al., 1993; Di Chiara and Imperato, 1988; Kiianmaa et al., 2000). Nicotine directly stimulates dopaminergic neurons of the ventro tegmental area (VTA), which leads to an increase in dopamine release in the nucleus accumbens (Nisell et al., 1994). In addition, alcohol also seems to increase dopamine release when applied into the nucleus accumbens through projections that stimulate VTA dopaminergic neurons, a process mediated by nicotinic receptors (Ericson et al., 1999). Taking into account these mechanisms of action, and the fact that chronic nicotine exposure leads to desensitization of nicotine receptors (Marks et al., 1983, 1993), one may speculate that nicotine blocks the receptors and/or mechanisms linked to alcohol action in the nucleus accumbens, while sensitizing the VTA-dependent dopamine release mechanisms. Alternatively, nicotine may simply increase dopamine release up to a level that reduces the need for alcohol intake.

Another potential neurochemical target system involved in depression and the effects of antidepressants is the serotonergic system. Serotonin reuptake blockers are commonly used in the treatment of depression (Gorman and Kent, 1999). Rats with CLI-induced depression have lower serotonin levels in the frontal cortex, hippocampus, brainstem, septum and hypothalamus (Feenstra et al., 1996; Vijayakumar and Meti, 1999). Similarly, alcohol-preferring rats have reduced serotonergic activity in the forebrain (Zhou et al., 1994a,b). Both alcohol and nicotine stimulate the serotonergic system. For example, nicotine has been shown to increase dorsal raphe neuron firing rate, while simultaneously augmenting serotonin release in vitro (Li et al., 1998; Mihailescu et al., 1998). In addition, serotonin release has been demonstrated to increase following nicotine administration in several others structures, such as hypothalamus, hippocampus, cortex, striatum and cerebellum (Miyata et al., 1999; Quattrocki et al., 2000; Summers and Giacobini, 1995; Ribeiro et al. 1993; Takada et al., 1995; Takahashi et al., 1998; Yang et al., 1999; Yu and Wecker, 1994). Likewise, alcohol administration increases serotonin release in the nucleus accumbens (Yoshimoto et al., 1992). Conversely, serotonin reuptake blockers reduce alcohol intake in alcohol-preferring rats (Maurel et al., 1999; Zhou et al., 1998). These data provide an additional or alternative explanation for the nicotine-induced decrease in alcohol intake in CLI rats shown in this study. It could be suggested that nicotine-induced serotonin release decreases the need for alcohol intake. It is possible that the dopamine and serotonin effects are complementary.

Clinical studies have demonstrated a linkage between alcohol and nicotine intake. Alcoholism is 10 times more common among smokers than nonsmokers (DiFranza and Guerrera, 1990). Likewise, more than 80% of alcoholics are also smokers (Batel et al., 1995). Experimental studies have provided conflicting results concerning the influence of systemic administration nicotine on alcohol consumption. For example, there are some studies demonstrating that nicotine administration increases alcohol consumption (Le et al., 2000; Olausson et al., 2001; Potthoff et al., 1983), whereas opposite results were observed by Dyr et al. (1999). In the former studies, alcohol intake was measured in animals exposed to chronic treatment with nicotine, whereas the latter study tested the acute effects of nicotine on alcohol consumption. Our findings rather support that nicotine reduces alcohol intake. However, these discrepancies may be a result of the experimental paradigm used. For example, Potthoff et al. (1983) administered nicotine 3.4 mg/day in rats that had already been induced to drink, whereas we used lower doses of nicotine (0.25 and 1.5 mg/kg/day) in rats that had never been exposed to alcohol. Regarding the study by Dyr et al. (1999) they used low nicotine doses (0.1 and 0.6 mg/kg). Likewise, Clark et al. (2001) studied the effect of nicotine by chronic continuous infusion on the operant self-administration of alcohol (at doses similar to those employed in our study and higher) and demonstrated an

increase in the behavior to obtain alcohol in the rats receiving 2.5 mg/kg/day compared with the controls. However, the amount of alcohol consumed did not show any significant changes. Söderpalm et al. (2000) suggest that nicotine, under certain circumstances, substitutes for alcohol, thus leading to a decrease in alcohol intake. In our study, the rats were treated with CLI during the neonatal period. It is, therefore, very likely that the brains of these rats are different from the nontreated rats, resulting in differing effects of nicotine on alcohol intake.

In conclusion, the present study indicates that nicotine decreases alcohol intake in CLI-treated rats. It is possible that this effect is the result of an improvement in depression, which is suggested by the increase in aggressiveness in the CLI rats. If this is true, then it is conceivable that nicotine could be considered as an antidepressant drug with potential capabilities for preventing depression-induced alcohol preference. It would be interesting to determine whether antidepressant drugs would have effects similar to nicotine in this model.

Acknowledgments

The authors wish to thank Dr. Ruth M. Benca and Dr. William H. Obermeyer for their helpful comments on the manuscript, and Mr. Manuel Zárate for the care of the animals. This work was supported by DGAPA IN207396 and Fideicomiso UNAM to R.D.-C. D.M.-G. is recipient of a scholarship from the Consejo Nacional de Ciencia y Tecnología (CONACYT) and DGEP-UNAM.

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