Progress in Neuro-Psychopharmacology & Biological Psychiatry 33 (2009) 398–402

Contents lists available at ScienceDirect

Progress in Neuro-Psychopharmacology & Biological Psychiatry

journal homepage: www.elsevier.com/locate/pnpbp

Antidepressant-like effects of nicotine and reduced nicotinic receptor binding in the Fawn-Hooded rat, an animal model of co-morbid depression and alcoholism

Yousef Tizabi [a,*], Bruk Getachew [a,1], Amir H. Rezvani [b], Sheketha R. Hauser [a,1], David H. Overstreet [c]

[a] Department of Pharmacology, Howard University College of Medicine, Washington, DC 20059, United States
[b] Department of Psychiatry and Behavioral Sciences, Duke University Medical Center, Durham, NC 27710, United States
[c] Department of Psychiatry, University of North Carolina, Chapel Hill, NC 27599, United States

ARTICLE INFO

Article history:
Received 23 May 2008
Received in revised form 20 August 2008
Accepted 14 September 2008
Available online 19 September 2008

Keywords:
Alcohol intake
Depressive-like behavior
FH rat model
Nicotine
Nicotinic receptors

ABSTRACT

A strong positive association between depression and alcoholism is evident in epidemiological studies. Curiously, the incidence of smoking (nicotine intake) is also very high among depressed individuals. Because neuronal nicotinic receptors have been implicated in mood regulation as well as in reinforcing effects of alcohol, it was of interest to determine whether inherent changes in these receptors may be manifested in an animal model that expresses both depressive-like characteristics and high alcohol intake. Thus, Fawn-Hooded (FH) rats along with their control ACI rats were used to measure the density of the high affinity nicotinic receptor in discrete brain regions. Furthermore, the effects of acute and chronic nicotine on depressive-like characteristics of FH rats were also evaluated. Measurements of [^{3}H]cytisine binding (selective for $\alpha4\beta2$ nicotinic receptor subtype) revealed a reduction in these receptors only in the striatum of FH rats, a result very similar to that observed in selectively-bred alcohol-preferring (P) rats. Administration of nicotine acutely (0.4 mg/kg, sc) resulted in a significant reduction of immobility in the forced swim test (FST) in FH rats only, implying an antidepressant-like effect of nicotine. Another group of FH rats were administered 0.4 mg/kg nicotine (daily, sc) for 14 days and their behavior in the FST was evaluated 22–24 h after the last injection. In this case, nicotine also had a significant antidepressant-like effect in FH rats suggesting no tolerance to nicotine had occurred. The effects of nicotine on FST behavior are very similar to those observed in Flinders Sensitive Line rats, a putative animal model of depression. Together, these findings provide additional evidence for antidepressant-like effects of nicotine and strengthen the postulated association between striatal nicotinic receptors and high alcohol intake. Thus, nicotinic receptors could be suitable targets for the development of novel pharmacotherapy for treatment of depression and possibly alcoholism.

1. Introduction

Although significant progress in the pharmacotherapy of depression has been achieved in the past decades, the refractory cases, delays in response and side effects associated with current medications are among major medical challenges. Similarly, therapeutic approaches in treatment of alcoholism are far from ideal and are often complicated by the prevalent co-morbid occurrence of depression. Thus, understanding the biological substrates that could contribute to such co-morbidity may offer novel pharmacotherapy. Interestingly, Fawn-Hooded (FH) rats show both high alcohol intake and depressive characteristics (Rezvani et al., 2002, 2007), rendering them a suitable animal model to investigate neurobiological substrates of co-morbid alcohol-depression condition. The FH/Wjd strain voluntarily consumes high amounts of alcohol (Rezvani et al., 1990, 2002), shows innate exaggerated immobility in the forced swim test (Rezvani et al., 2002), and exhibits elevated corticosterone levels that are normalized with antidepressant treatment (Aulakh et al., 1993). These differences are observed not only in reference to other strains of rats, such as Wistar and Sprague–Dawley, but also in reference to other inbred strains, including the FH/Har and ACI strains (Overstreet et al., 1999).

Curiously, the incidence of smoking (nicotine intake) is very high among both alcoholics (Meyerhoff et al., 2006) and depressed individuals (see reviews: Glassman, 1993, Quattrocki et al., 2000). Whereas the reinforcing effects of nicotine may contribute to its simultaneous intake with alcohol (Tizabi et al., 2002, 2007), the postulated antidepressant effects of nicotine may contribute to its use in depressed individuals. It has been observed that chronic administration of nicotine or selective nicotinic agonist in the learned helplessness paradigm in rats may alleviate the depressive symptoms in these rats (Semba et al., 1998, Ferguson et al., 2000). We have demonstrated that acute or chronic intermittent administration of nicotine in Flinders Sensitive Line (FSL) rats, an animal model of depression (Overstreet et al., 2005a), alleviates their depressive

Abbreviations: FH, fawn-hooded; FRL, Flinders Resistant Line; FSL, Flinders Sensitive Line; FST, forced swim test; NP, non-preferring; P, alcohol-preferring.

* Corresponding author. Department of Pharmacology, College of Medicine, 520 W Street N.W., Howard University, Washington, DC 20059, United States. Tel.: +1 202 806 9719; fax: +1 202 806 4453.
E-mail address: ytizabi@howard.edu (Y. Tizabi).
[1] Current address: Department of Psychiatry, Indiana University, Indianapolis, IN, USA.

0278-5846/$ – see front matter © 2008 Elsevier Inc. All rights reserved.
doi:10.1016/j.pnpbp.2008.09.010

symptoms as determined by reduction of their immobility in the forced swim test (FST) (Tizabi et al., 1999). Similar results were obtained by Djuric et al. (1999) following chronic oral intake of nicotine in FSL rats. We also observed that FSL rats had higher nicotinic receptor densities in several brain regions (as determined by [^{3}H]cytisine binding in tissue homogenate) compared to their control, the Flinders Resistant Line (FRL) rats (Tizabi et al., 1999). Moreover, the antidepressant effects of nicotine in FSL rats could be blocked by pretreatment with the non-selective nicotinic receptor antagonist mecamylamine, strengthening the argument that the antidepressant effects of nicotine are mediated through nicotinic receptors (Tizabi et al., 2000).

A role for central nicotinic receptors in the reinforcing effects of alcohol has also been suggested by several animal studies. Thus, administration of mecamylamine either systemically (Blomqvist et al., 1996; Lê et al., 2000) or into the ventral tegmental area of rats (Ericson et al., 1998) markedly reduced ethanol intake and preference (see also Soderpalm et al., 2000; Lof et al., 2007) as well as ethanol-induced dopamine release in the nucleus accumbens (Tizabi et al., 2002, 2007, Ericson et al., 2008). Moreover, several clinical studies have reported a decrease in alcohol reinforcing effects following mecamylamine administration (Blomqvist et al., 2002; Chi and de Wit, 2003). Interestingly, alcohol-preferring (P) rats show a reduction of the high affinity nicotinic receptors in the striatum (Tizabi et al., 2001), which is in contrast to the increased number of these receptors seen in FSL rats. In this study we sought to determine whether high affinity nicotinic receptor densities in FH rats would resemble those of P or FSL rats. Moreover, it was of relevance to investigate whether nicotine may also act as an antidepressant in this strain.

2. Materials and methods

2.1. Animals and housing

The Fawn-Hooded FH/Wjd (FH) and ACI/N (ACI) rats which serve as control model for FH rats were randomly selected from the breeding colonies maintained by brother–sister mating at the Center for Alcohol Studies at the University of North Carolina at Chapel Hill. As mentioned above, the inbred ACI/N strain drinks very little alcohol voluntarily and therefore is an ideal control for the inbred FH/Wjd rats (Li and Lumeng, 1984; Overstreet et al., 1999).

Adult male rats of approximately 80 days old and weighing 300–350 g were maintained in groups of 2–3 in plastic cages in a temperature (22 °C) and humidity (50%) controlled room with free access to food and water and a reversed 12:12 light:dark cycle (lights on at 1900 h). The reversal of time cycle was to allow convenient measurement of the behavior during active (dark) phase of the light cycle. The treatment and care of the animals were carried out under an experimental protocol in accordance with NIH guidelines as approved by the Institutional Animal Care and Use Committee.

2.2. Forced swim test (FST)

Although the forced swim test was originally developed to test the efficacy of antidepressants, this test is also commonly used to assess the helplessness or depressive-like behavior in rodents, particularly those of inbred strains (Porsolt et al., 1977; Detke et al., 1995; Lucki, 1997; Tizabi et al., 1999; Rezvani et al., 2002; Overstreet et al., 2005a, 2008). This test was conducted in a cylindrical tank 60 cm tall and 18 cm diameter, containing enough 25 °C water so that the rat could not touch the bottom with its hind paws. The animal was placed in the water (20 min after the injection for acute studies, 20–24 h after the last injection for the chronic studies) and the amount of time it was immobile was recorded over a single 5 min period by an experienced observer blind to treatment condition. Immediately after the test the animal was dried and returned to its home cage. It should be mentioned that many studies using the forced swim test (FST) for screening the antidepressant efficacy of a compound subject the rats to 15 min "pretest" where the rats are exposed to inescapable water tank as during the 5 min actual test. This pre-exposure in actuality induces the learned helplessness in that 24 h later the rats manifest significant amount of immobility against which potential antidepressants are evaluated. However, FH rats are genetically selected for their manifestation of the behavioral despair and have been inbred through many generations whereby they may be considered an inbred animal model of behavioral despair as reflected in their exaggerated immobility in the FST compared to their control the ACI rats. Thus, the efficacy of an antidepressant may be evaluated in these animals without the need for pretest. This modified test has been used repeatedly in our laboratory (e.g., Tizabi et al., 1999; Rezvani et al., 2002; Overstreet et al., 2005a,b, 2008; Getachew et al., 2008).

Table 1
[^{3}H]Cytisine binding (fmol/mg protein) in discrete brain regions of ACI and FH rats.

Strain		
Region	ACI	FH
Frontal cortex	33.7 ± 1.2	31.9 ± 1.3
Striatum	44.0 ± 3.0	31.8 ± 2.4*
Hippocampus	28.9 ± 2.2	32.0 ± 1.9
Midbrain	52.1 ± 2.9	48.6 ± 3.3
Colliculi	31.5 ± 3.1	28.1 ± 2.1
Cortex	32.5 ± 2.5	35.9 ± 2.9
Cerebellum	10.1 ± 0.62	10.2 ± 0.91

Values are mean ± SEM, $n = 8$/group.
*$p < 0.05$ compared to ACI.

Since the biological half-life of nicotine is approximately 90 min, it is unlikely that any nicotine would be present in the body 20–24 h after the last nicotine injection when the animals were tested following chronic nicotine administration. Although, the major nicotine metabolite cotinine may still be present in the plasma due to much longer half-life of this compound, it is unlikely that the behavioral effects could be attributed to cotinine as it is well established the major behavioral effects observed following nicotine administration are attributed to nicotine itself and not its metabolite cotinine (James et al., 1998; Benowitz, 2008; Pehrson et al., 2008).

2.3. Locomotor activity (LCA) monitoring

In order to exclude the possibility that the differential effect of nicotine in the FST in the FH and ACI lines could be attributed to any non-specific locomotor effects of nicotine, we evaluated the acute effects of nicotine in an open field locomotor activity test. In this test, 20 min after nicotine injection the rats were placed in a monitoring box (60 × 60 cm) that was divided in 16 squares (10 × 10 cm each) and the number of squares crossed was scored over a 5 min period.

2.4. Drug administration

For acute studies, -(−)nicotine bitartrate (Sigma, St. Louis, US) was dissolved in saline and was administered subcutaneously (0.1 ml/100 g.b.w.). The nicotine dose was adjusted such that 0.4 mg/kg nicotine base was injected. The animals were tested 20 min after a single injection. For chronic studies, 0.4 mg/kg nicotine was administered (sc) once daily for 14 consecutive days. In chronic treatments, the swim test was performed 20–24 h after the last injection. Controls were administered isotonic saline (0.1 ml/100 g. b.w.).

2.5. Tissue collection

Following their adaptation to the housing environment for one week, 8 FH rats and 8 age-matched ACI rats were decapitated between 10 AM and 2:00 PM. The order of killing was alternated between the groups. Brains were quickly removed and frozen on dry ice and stored at −80 °C until dissected and assayed for receptor density.