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Alcohol reverses depressive and pronociceptive effects of chronic stress in mice with enhanced activity of the opioid system

Mariusz Sacharczuk[1]*, Grzegorz Juszczak[2], Artur H. Swiergiel[3,4], Kazimierz Jaszczak[1], Andrzej W. Lipkowski[5], and Bogdan Sadowski[2]

[1]Department of Molecular Cytogenetic and [2]Department of Animal Behaviour, Institute of Genetics and Animal Breeding, Polish Academy of Sciences, Jastrzębiec, Wólka Kosowska, Poland, *Email: m.sacharczuk@ighz.pl; [3]Department of Animal Physiology, University of Gdansk, Poland; [4]Department of Pharmacology, Toxicology and Neuroscience, Shreveport, LA, USA; [5]Neuropeptide Laboratory, M. Mossakowski Medical Research Centre, Polish Academy of Sciences, Warsaw, Poland

The role of the opioid system in mediating effects of alcoholism and stress in depression is far from clear. We studied, therefore, the effects of chronic mild stress (CMS) and alcohol drinking on depression-like behavior and nociception in lines of mice selected for high (HA) or low (LA) swim stress-induced analgesia. Compared to the LA mice, the HA animals display up-regulation of opioid receptor system function and depression-like behavior in tail suspension test (TST). We report now that alcohol reverses depressive and pronociceptive effect of CMS in HA mice. In contrast, in LA mice CMS does not affect nociception or behavior in TST and the animals are not susceptible to alcohol under CMS. The results suggest that opioid system activity may determine the effects of alcohol on behavior under stress and, therefore, link predispositions to depression and to alcoholism.

Key words: chronic mild stress, alcohol intake, depression-like behavior, nociception, opioid system, selected mouse lines

INTRODUCTION

The coexistence of alcohol abuse and depression has been widely recognized but the relationship between alcohol and depression is still unclear. Depressive symptoms observed in alcoholics may be induced by alcohol or may be alcohol-independent (Preuss et al. 2002, Olgiati et al. 2007). Furthermore, alcoholism and depression may be precipitated by chronic stress and both disorders depend on complex gene-environment interactions (Gordis 1997, Heath et al. 2002, Langbehn et al. 2003, Barr et al. 2004, Scherrer et al. 2005).

One of the major genetic mechanisms involved in the coexistence of alcoholism and depression may be congenital differences in activity of the opioid system. It has been reported that activity of the opioid system appears diminished in depressed humans and in animal models of depression, and that it can be normalized by treatment with antidepressants (Przewlocki et al. 1985, Extein and Gold 1993, Kosten et al. 1998, Weiss et al. 2001, Torrens et al. 2005, Dean et al. 2006). Another frequently described feature of depression in which the opioid system may play an important role is an increased pain vulnerability (Lautenbacher et al. 1994).

Therefore, in a multifactorial experimental model we attempted to assess the role of alcohol × stress × genotype (opioid system) interaction in mediating depressive behavior. Two mouse lines that have been selectively bred for high (HA) or low (LA) swim stress-induced analgesia (SSIA) provided genetic factor. These lines differ in basal nociception and the magnitude of SSIA (Panocka et al. 1986b). The breeding has up-regulated opioid system receptors in HA mice and down-regulated this system in LA mice (Panocka et al. 1986a, 1991, Kest et al. 1993, 1999, Sadowski and Panocka 1993, Lutfy et al. 1994, Mogil et al. 1994, 1996).

Correspondence should be addressed to M. Sacharczuk, Email: m.sacharczuk@ighz.pl

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In a recent study we found that chronic mild stress (CMS) increased alcohol intake in LA mice with low opioid system activity but not in HA mice with the enhanced activity of the system (Sacharczuk et al. 2008). Stress-induced alcohol drinking appeared in LA mice almost immediately after exposure to stress and persisted throughout the next 6 weeks of stress (Figs 1, 2). We concluded that CMS imposed on individuals with genetically determined low opioid activity may favour the development of alcohol abuse (Sacharczuk et al. 2008).

Presently we describe the effects of alcohol × stress × opioid system interaction on nociception assessed on a hot plate and on depression-like behavior determined in a tail suspension test (TST).

METHODS

Subjects

Swiss-Webster male mice were obtained from the colony maintained in the Institute of Genetics and Animal Breeding of the Polish Academy of Sciences in Jastrzebiec. The animals were selectively bred for 70 generations for high (the HA line) and low (the LA line) SSIA. The selection protocol for the HA and LA lines was described previously (Panocka et al. 1986b). Briefly, outbred mice of either sex, 2 min after completion of 3-min swimming in 20°C water, were screened for the latency of a nociceptive reflex on a 56°C hot plate (HP).

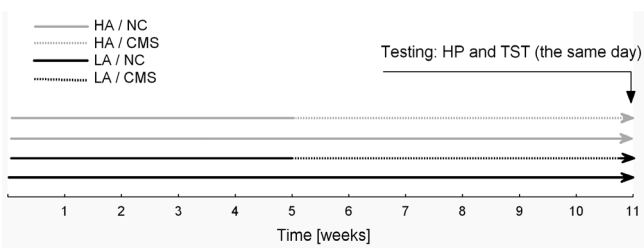

Fig. 1. Scheme of the experiment. In order to evaluate the effect of alcohol consumption under NC and CMS, mice of each line were randomly assigned to four groups: two without and two with access to alcohol. One group of each pair was maintained without stressing (NC conditions) throughout the entire 11-week experiment, whereas the other group of each pair was exposed to stress conditions (CMS conditions) throughout the second part of the experiment (weeks 6 through 11). Each group consisted of 10 mice. Open field test was performed five days before beginning of the experiment.

The animals displaying the longest (50–60 s) and the shortest (<10 s) post-swim latencies of the hind paw flick or lick response were selected as progenitors of the HA and the LA lines. A similar procedure was repeated in each offspring generation, but only the mice displaying the longest and the shortest post-swim hot plate latencies were mated to maintain the lines.

After weaning, mice were housed in groups, 4–5 same-sex siblings per cage, at ambient temperature of 22 ± 2°C and 55 ± 5% relative humidity on a 12-h light/dark cycle (lights on at 07:00 AM), and with free access to tap water and food (murine chow pellets provided by LABOFEED H, Poland: 22% proteins (with 1.5% of lysine), 5% crude fibre, 4% crude fat, 6.5% crude ash, and 13.4 kcal/g of energy).

Ten days before exposure to alcohol, the animals were transferred to individual cages and remained there throughout the entire experiment. The animals were six weeks old, and weighed 37–38 g (HA line) and 34–35 g (LA line) at the onset of the experiment.

In order to evaluate the effects of alcohol consumption under normal conditions (NC) and CMS, mice of each line were randomly assigned to four groups: two without and two with access to alcohol. One group of each pair was maintained without stressing (NC) throughout the entire 11-week experiment, whereas the other group of each pair was exposed to CMS throughout the second part of the experiment (weeks 6 through 11) (Fig. 1). Each group consisted of 10 mice.

Additionally, 60 mice of the same age, sex and generation were used to evaluate the effect of desipramine (DMI) on behavior in TST test. These mice were maintained in NC and had no access to alcohol.

The experimental protocol was approved by the State Ethics Commission, in conformity with Polish law. All the procedures are commonly used and considered ethically acceptable in all European Union countries and North America. They also conform to the NIH Guide for the Care and Use of Laboratory Animals.

Procedures

Desipramine (DMI) testing

To compare the effect of DMI (tricyclic antidepressant) administration on depression-like behavior in HA and LA mice, 15 mice from each line, housed in NC, were given once daily i.p. (intraperitoneal) injec-

tions of DMI (Sigma Aldrich, St. Louis, MO) at a dose of 10 mg/kg. DMI was dissolved in saline (0.9% NaCl) and sterilized by filtration. The control animals (15 animals from HA and LA line) received i.p. injections of saline. Duration of immobility in TST was measured 30 min after i.p. injection of DMI or saline.

Alcohol preference testing

As in our previous study (Sacharczuk et al. 2008), 20 mice of each line could choose freely between 8% alcohol and tap water from two 25-ml graduated glass bottles. To eliminate possible place preference, the position of the alcohol- and the water-containing bottles was alternated each day.

The 8% alcohol solutions were prepared by diluting 96% alcohol (Chempur®, Poland) with distilled water. Twenty-four-hour intakes of alcohol and water were assessed by weighing the alcohol and water bottles to the nearest 0.01 g every day before changing the bottles. The mice were also weighed at that time. Food was always available ad libitum and the amount eaten was assessed three times per week.

Alcohol intake, in grams of 100% alcohol per kg body weight, was calculated after correction of the consumed alcohol solution for the specific gravity of alcohol. The preference for alcohol was determined as a percent of alcohol solution intake of the total amount of fluids ingested during the two-bottle test.

Chronic mild stress (CMS)

CMS was adapted from the procedures described by Willner and coworkers (1987) for mice and by Moreau and others (1992) for rats. The animals were subjected over 6 weeks to various kinds of stress factors changing in 12-h cycles. Each week of stress regimen consisted of: two periods of food deprivation (8 h), two periods of 45º cage tilt (12 h), one period of soiled cage (200 ml water in sawdust bedding, 12 h), two periods of paired housing (1 h) (in this time bottles with alcohol were removed), two periods of low-intensity stroboscopic illumination (8 h), two periods of overnight illumination, one period of removed bedding (12 h), one period of noise emitted by a radio receiver tuned out of the station (white noise combined with cage tilt, 12 h), one period of restraint in a plastic tube 11.5 cm long and 3 cm in diameter (15 min), and two periods of no stress (12 h). The paired-housing stress consisted of exposing a mouse to another stressed mouse of the same line. Each mouse was in successive turns a resident or an intruder, and was paired alternately with two other mice (intruder or resident) throughout the experiment. Stressors were administered in a pseudo-random manner during both light and dark phases. All mice received the same treatment schedule, with treatments occurring in different orders in different weeks. During CMS, the groups of mice drinking alcohol had full access to alcohol (only during periods of paired housing the bottles with alcohol were removed).

Testing for depressive behavior and nociception

Because differences in general locomotor activity can influence TST results, locomotor activity in open field (OF), including total immobility and mobility duration, velocity and distance moved were evaluated five days before providing access to alcohol.

The behavioral changes caused by CMS and alcohol were assessed with the HP test for nociception, and with the TST for depression-like state. The experiments were conducted on all animals used in concor-

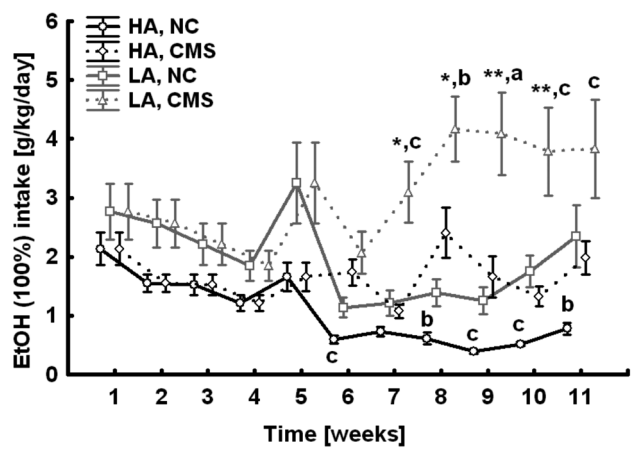

Fig. 2. Ethanol intake of HA (grey lines) and LA (black lines) mice in a two-bottle free-choice drinking of 8% ethanol and water during normal conditions (NC) and during the chronic mild stress conditions (CMS). Values are mean ± SEM; n=10 per group. *P<0.05, **P<0.01 (*post hoc* test: LA-CMS *versus* HA-CMS group); ^{c}P<0.05, ^{b}P<0.01 (*post hoc* test: HA-CMS *versus* HA-NC group and LA-CMS *versus* LA- NC group) (Sacharczuk et al. 2008).

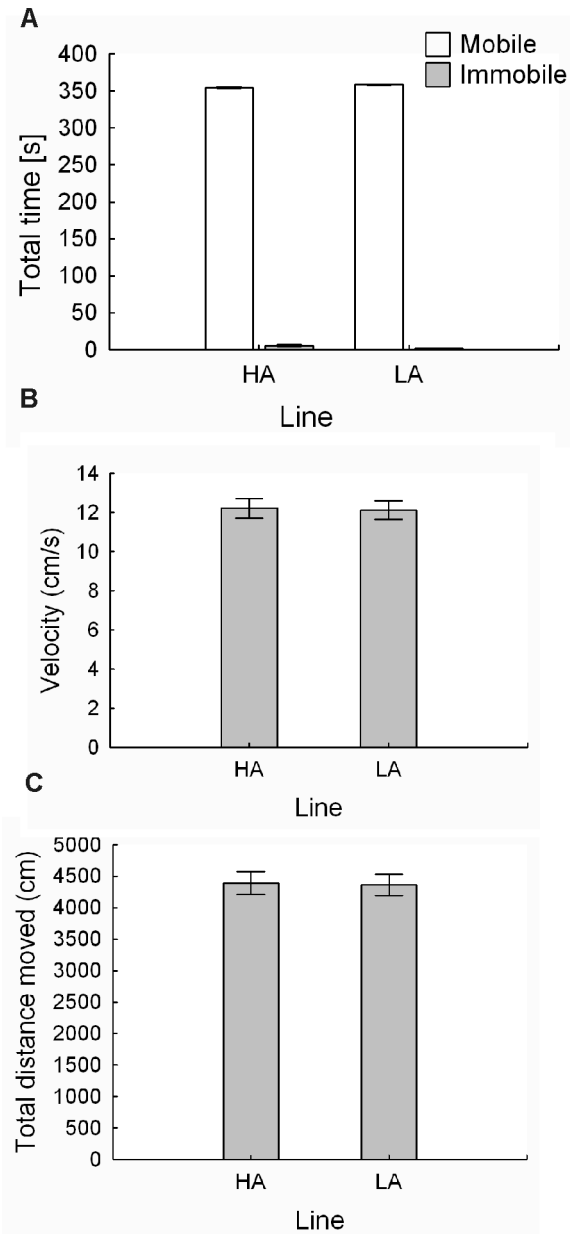

Fig. 3. Locomotor activity in OF including total immobility and mobility duration, mean velocity and total distance moved during a 6 minute experimental session. Each line consisted of 40 mice. (A) Total immobility and mobility duration (s); (B) mean velocity (cm/s); (C) distance moved [cm]

dance with the following schedule: (1) determination of nociception in HP test; and (2) determination of depression behavior in TST. Nociception and TST were conducted between 09:00 AM and 04:00 PM on the day following the last NC or CMS session, in compartments separated from the animal colony room. The tests were spaced with a 6 h interval, during which the animals were separated from their conspecifics in order to prevent social modulation of behavior (Langford et al. 2006). In order to avoid acute alcohol withdrawal during behavioral testing (which typically causes hyperexcitability), as a result of abstinence from voluntary alcohol drinking (Stevenson et al. 2008), alcohol bottles were removed shortly before behavioral testing. The person performing the tests was unaware of the line, conditions and treatment.

Open field test (OF)

OF was used to assess the spontaneous locomotor activity in a novel environment (a box measuring 43 cm × 43 cm × 16 cm). After placing a mouse in the box, locomotor activity, including total immobility and mobility duration, mean velocity and distance moved was videotaped for 6 min and assessed using EthoVision system (Noldus, Wageningen, the Netherlands).

Hot-plate test (HP)

A mouse was placed on a metal plate heated with water thermostatically maintained at 56°C. The pain threshold was reflected by latency of a characteristic hind paw lifting/flinching response, after which the animal was immediately removed from the plate to minimize the discomfort (Casey and Dubner 1989).

Tail suspension test (TST)

TST was performed as suggested by Steru and coauthors (1985). The animals were observed in a 680 (high) × 365 (wide) × 280 (deep)-mm wooden box with the front wall removed. A fabric ribbon (200 × 17 × 1 mm) was attached to a cover. A mouse was suspended from the cover by attaching its tail with an adhesive tape to the ribbon. The adhesive tape was placed 30 mm from the base of the tail. The suspended animal was 120 mm away from the box walls. Total duration of immobility (that is, when the mouse was hanging without moving its paws and with its head pointed down) was scored for 6 minutes using the EthoVision system (Noldus, Wageningen, the Netherlands) as described in detail by Juszczak and colleagues (2006).

Data analysis

The results were analyzed using a three-way analysis of variance (ANOVA), with line, condition (CMS vs. NC) and access to alcohol as experimental factors. Subsequently, a two-way ANOVA was used to analyze the effects of conditions and alcohol within lines. To evaluate the effects of desipramine, a two-way ANOVA was used, considering the mouse lines and treatment (DMI vs. saline) as the main factors. When a significant effect was revealed by ANOVA, a *post hoc* analysis was performed using an all pair-wise Tukey's honestly significant difference (HSD) test. The criterion for significance was set at $P<0.05$.

RESULTS

Open Field Test

Mice were taken from their home cages, immediately placed in OF and observed for 6 min. There was no significant difference between the HA and LA lines in the locomotor activity measured as (1) total immobility and mobility duration, (2) mean velocity, and (3) distance moved (Fig. 3 A–C).

The effect of DMI on depression-like behavior

Two-way ANOVA (mice without access to alcohol and housed in NC) revealed that DMI shortened the immobility duration in TST ($F_{1,60}$=12.1, $P<0.001$) in a line-dependent manner (line × DMI interaction) ($F_{1,60}$=5.68, $P<0.05$). Subsequent *post-hoc* test showed a significant antidepressive effect of DMI in HA mice ($P<0.001$), but not in LA mice (Fig. 4).

The effect of CMS on depression-like behavior and pain sensitivity

CMS in mice with no access to alcohol prolonged significantly the duration of immobility in HA but not in LA mice (Fig. 5). Two-way ANOVA showed that the effects of line ($F_{1,36}$=105) and CMS ($F_{1,36}$=12.8) were highly significant ($P<0.001$). Significant line × CMS interaction ($F_{1,36}$=5.1, $P<0.05$) reflects the differences between the lines in response to CMS. Subsequent *post-hoc* test confirmed that this effect was significant in mice from the HA ($P<0.001$) but not the LA line (Fig. 5).

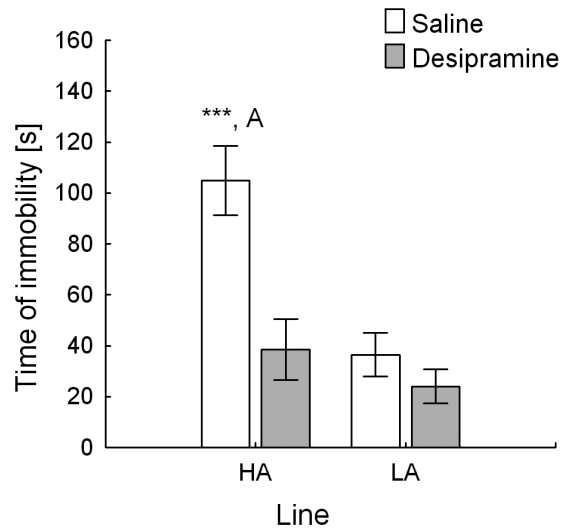

Fig. 4. Mean time of immobility (± SEM) in tail suspension test (TST) performed 30 min after i.p. injection of desipramine hydrochloride (10 mg/kg) or saline (control group). n=15 per group. $^{***}P<0.001$ (*post hoc* test: HA-saline *versus* LA-saline group); $^{A}P<0.001$ (*post hoc* test: HA-saline *versus* HA-desipramine group).

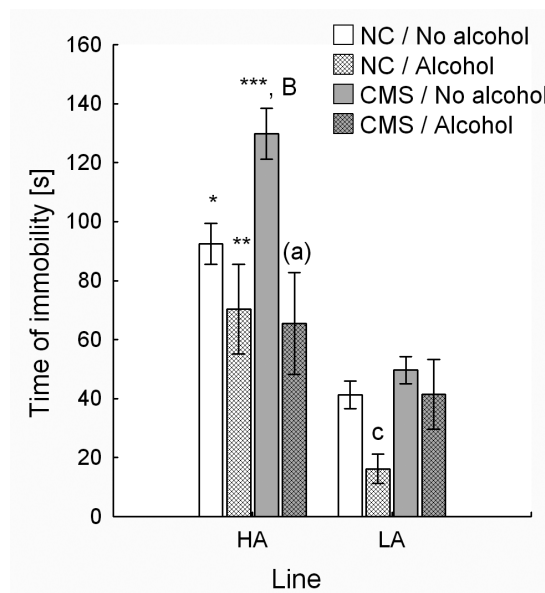

Fig. 5. Mean time of immobility (± SEM) in tail suspension test (TST) in the HA and LA mice after normal conditions (NC) or during the chronic mild stress conditions (CMS) and with access to 8% alcohol or only to water. n=10 per group. $^{*}P<0.05$; $^{**}P<0.01$; $^{***}P<0.001$ (*post hoc* test: subgroups from HA line *versus* subgroups from LA line); $^{B}P<0.01$ (*post hoc* test: HA-CMS/no alcohol *versus* HA-NC/no alcohol group); $^{a}P<0.001$ (*post hoc* test: HA-CMS/alcohol *versus* HA-CMS/no alcohol group).

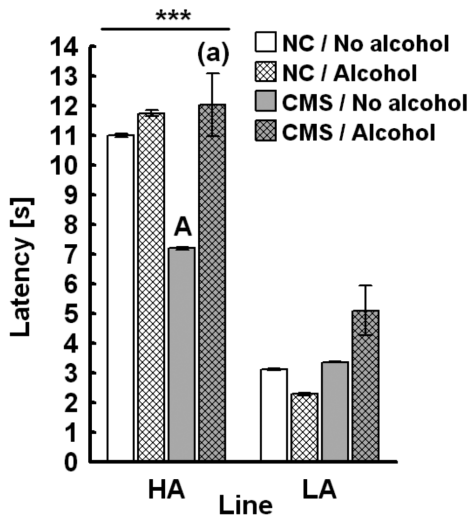

Fig. 6. Mean duration of latency (± SEM) in hot-plate test (HP) in the HA and LA mice after normal conditions (NC) or during the chronic mild stress conditions (CMS) and with access to 8% alcohol or only to water. n=10 per group. $^{***}P$<0.001 (*post hoc* test: subgroups from HA line *versus* subgroups from LA line); ^{A}P<0.001 (*post hoc* test: HA-CMS/no alcohol *versus* HA-NC/no alcohol group); ^{a}P<0.001 (*post hoc* test: HA-CMS/alcohol *versus* HA-CMS/no alcohol group).

CMS increased nociception assessed with the hot plate in HA but not in LA mice (Fig. 6). The effects of line ($F_{1,36}$=21280) and condition ($F_{1,36}$=1944) were highly significant (P<0.001). A significant line × condition interaction ($F_{1,36}$=2539, P<0.001) reflects the differences between the lines in response to CMS. Subsequent *post-hoc* test confirmed that the effect of CMS was significant in mice from the HA (P<0.001) but not the LA line. The results suggest depressive and pronociceptive effects of CMS in HA mice.

The effect of alcohol on depression-like behavior and pain sensitivity

Alcohol decreased the duration of immobility in HA and LA mice housed in normal conditions (Fig. 5). Two-way ANOVA showed that the effects of the line ($F_{1,36}$=29.5, P<0.001) and alcohol ($F_{1,36}$=6.0, P<0.05) were significant. However, line × alcohol interaction was insignificant, suggesting lack of differences between the lines in depression-like behavior in response to alcohol.

Two-way ANOVA showed that despite significant effects of line on basal nociception ($F_{1,36}$=19801), the effects of alcohol and line × alcohol interaction were insignificant, indicating lack of differences in thermal nociception between the lines treated with alcohol (Fig. 6). The results suggest anti-depressive properties of alcohol.

The effect of alcohol × stress × line interaction on depression-like behavior and pain sensitivity

Three-way ANOVA for depression-like behavior showed significant effects of the mouse lines ($F_{1,72}$=51.6, P<0.001), CMS ($F_{1,72}$=5.1, P<0.05), alcohol ($F_{1,72}$=16.9, P<0.001), and an interaction [mouse lines × CMS × alcohol ($F_{1,72}$=4.1, P<0.05)] on the duration of immobility in TST. Analysis of the results from the HP test revealed significant effects of the mouse lines ($F_{1,72}$=428, P<0.001) and alcohol ($F_{1,72}$=22.9, P<0.001) as well as significant interactions: mouse lines × alcohol ($F_{1,72}$=11.7, P<0.001), mouse lines × CMS ($F_{1,72}$=23.4, P<0.001), and alcohol × CMS ($F_{1,72}$=24, P<0.001).

Two-way ANOVA, separate for HA and LA lines, revealed that alcohol shortened the duration of immobility in TST ($F_{1,36}$=12.4, P<0.001) and reduced nociception ($F_{1,36}$=4.1, P<0.05) in the HA but not in the LA mice.

Post-hoc analyses performed for the HA line revealed that alcohol did not affect behavior in animals kept under normal conditions, but significantly attenuated the depressive (P<0.001) and pronociceptive effect of CMS (P<0.01). The results suggest an antidepressive and antinociceptive character of alcohol in HA mice housed in stress conditions.

DISCUSSION

In this study we found that when housed in normal conditions and without access to alcohol HA mice displayed longer basal immobility in the TST and longer basal HP latencies than LA mice. DMI, a prototypic, tricyclic antidepressant, shortened the duration of immobility in TST in HA mice and was ineffective in LA mice. Positive reaction to desipramine is generally accepted as a reliable indicator of a depression-like state in animals. Therefore, it may be postulated that HA mice are in a chronic depression-like state.

Moreover, in HA mice the duration of the TST immobility was prolonged and nociception was enhanced by CMS. CMS, which simulates stressful situations observed in human life, frequently leads to a depression-like state and decreased pain threshold in animals

(Kompagne et al. 2008). Abnormal pain sensitivity during depression is effectively attenuated by antidepressants, especially the tricyclics (Jann and Slade 2007). Similarly to antidepressants, alcohol has been shown to exert analgesic effects (Campbell et al. 2006, 2007).

As it was shown previously (Sacharczuk et al. 2008), there was no difference between the lines in tolerance to alcohol and alcohol metabolism. Moreover, analysis of the intakes of food, alcohol and water in HA and LA mice showed lack of correlations between total food consumption and total alcohol intake. Therefore, it can be accepted that the concentrations of alcohol in blood correspond to alcohol consumption by HA or LA mice. Of course, in addition to direct behavioral and nociceptive response to ethanol, brain changes caused by long-term ethanol consumption could be involved in final behavior.

In HA mice alcohol slightly attenuated basal depression-like behavior and much more the depression-like effect of CMS. Moreover, alcohol decreased nociception, attenuating the pronociceptive effect of CMS. In contrast, LA mice with down-regulated opioid system were found resistant to the depression-like and pronociceptive effect of CMS. The results suggest antidepressive and antinociceptive effects of alcohol in stress conditions in HA but not in LA mice.

Different effects of alcohol observed in HA and LA mice support a hypothesis that selective breeding for high and low stress-induced analgesia has modified the degree of opioid involvement in the mechanisms of depression and endogenous analgesia. However, given that LA mice show no effects of CMS, we cannot infer with certainty whether or not alcohol has any antidepressant or analgesic actions in this line under stress conditions.

A particular finding, which can not be simply explained, is concerned with the inverse relationship between opioid system activity and depression. According to currently prevailing opinion, activation of μ and δ opioid receptors causes a similar antidepressive effect (Mangold et al. 2000). Because HA and LA mice differ in opioid system activity in the rank order of HA > LA, the rank order of their basal immobility in TST should be HA < LA. In the present study we observed an inversed rank: HA > LA. However, Filliol and others (2000) showed that mice lacking μ receptors display decreased depressive and anxiety behaviors, while mice lacking δ opioid receptors show intensification of these behaviors. This finding suggests an opposite influence of these two types of opioid receptors on depression. When compared to the LA line, HA mice display higher activity of three major classes of opiate receptors: μ, δ and κ. However, selection caused a two-fold increase in the activity of μ when compared to δ receptors. LA mice display almost the same activity of μ and δ receptors (Kest et al. 1999). Consequently, differences in the activity of μ and δ receptors seem to be critical in final behavior of HA/LA mice. These results are in accordance with a finding that mice differing in sensitivity to opiate agonists do not differ in the duration of basal immobility during forced swimming test (Amir 1982). However, changes in opioid system function can influence antiimmobility action of antidepressants (Natan et al. 1984, Eschalier et al. 1987).

Moreover, the dynorphin system, stimulation of which leads to dysphoria in humans (Pfeiffer et al. 1986) and animals (Mague et al. 2003, Carlezon et al. 2006), has recently been evaluated as an important component involved in neurobiology of depression-like behavioral phenotypes. On the other hand, the binding of dynorphins to κ receptors, which are overexpressed in HA mice, has been shown to produce aversive states, which may reduce alcohol intake and prevent the development of alcoholism (Lindholm et al. 2001, Saito et al. 2003, Xuei et al. 2006). Therefore, higher depression-like behavior of HA mice linked with lower alcohol consumption might be explained by a higher activity of the κ opioid system in this line. Higher effectiveness of alcohol as an antidepressive and antinociceptive agent in HA mice may be due to higher μ and δ opioid system activity. Blocking these receptors by selective antagonists, CTAP and naltrindole, respectively, attenuates the antinociceptive effect of alcohol (Campbell et al. 2007).

The nature of the differences between the lines in depressive behavior may be, in addition to the opioid component, mediated by several nonopioid neurotransmitter systems. For example, the nonopioid component of SSIA in LA and HA mice was differentially reversed by dizocilpine, a noncompetitive antagonist of NMDA receptors, which can reflect differences in glutaminergic system activity (Mogil et al. 1993). Antidepressant-type effect of the NK3 tachykinin receptor agonist aminosenktide (NH_2-SENK) was also revealed in HA mice. In LA mice, with reduced activity of the opioid system, this effect was not observed (Panocka et al. 2001).

CONCLUSIONS

The present study was aimed at evaluating the effect of interaction between chronic mild stress and ethanol intake in mice genetically selected for high (HA) and low (LA) swim stress-induced analgesia. Previous studies demonstrated that, compared to the LA line, the HA line has an upregulation of opioid receptor system function. Considering the significance of the brain opioid system in the regulation of alcohol addictive behaviors and depression, the HA and LA lines, with congenital differences in opioid functions, may represent populations differing in the predisposition to alcoholism and depression, and appear to be particularly suited for such studies. The correlation between CMS and alcohol drinking was strong enough to suggest that opioid system activity links predispositions to depression and to alcoholism, and determines the effect of alcohol on behavior under stress.

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