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Desipramine blocks alcohol-induced anxiety- and depressive-like behaviors in two rat strains ☆

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ABSTRACT

Epidemiological studies indicate significant co-morbid expression of alcoholism, anxiety, and depression. These symptoms are often under-diagnosed and under-treated and can worsen prognostic and treatment outcome for alcoholism. Nonetheless, a causal relationship between alcoholism and these conditions is yet to be established. In this study we sought to determine the effects of daily alcohol administration on the indices of anxiety and depression in two rat strains, one of which exhibits inherent depressive-like characteristics. Moreover, it was of relevance to examine the effects of a clinically useful antidepressant on alcohol-induced behavioral changes. Wistar–Kyoto (WKY) rats derived from Wistar stock show low levels of locomotor activity in an open field and high levels of immobility in the forced swim test (FST) which is considered a measure of their helplessness and hence are considered a putative animal model of depression. Adult female WKY and Wistar rats were exposed for 3 hrs daily to 95% ethanol vapor to achieve a mean blood alcohol level (BAL) of approximately 150 mg/dL. Controls were exposed to air in similar inhalation chambers. Sixteen to 18 hrs following 7 or 14 days of exposure to alcohol, locomotor activity (LCA) in open field, duration of time spent in the open arm of the elevated plus-maze (EPM), reflective of anxiety-like behavior and immobility in FST were evaluated. Alcohol exposure for 7 or 14 days reduced LCA only in Wistar rats but enhanced FST immobility in both strains at both time points. Only 14 day alcohol exposure reduced EPM open arm time in both WKY and Wistar rats. Daily treatment with desipramine (8 mg/kg) blocked all the changes induced by alcohol in both strains. Thus, subchronic (7 day) exposure to alcohol induces depressive-like characteristics in Wistar rats and exacerbates that of WKY rats. Chronic (14 day) exposure, however, also induces an anxiety-like effect in both strains. The depressive- and anxiety-like behaviors induced by alcohol were blocked by daily treatment with a tricyclic antidepressant. It may be suggested that prophylactic treatment of alcoholics with an antidepressant prior to detoxification may improve treatment outcome for alcoholism.

1. Introduction

Alcoholism has high co-morbid expression with anxiety and depressive disorders (Helzer and Pryzbeck, 1988; Kessler et al., 1997; Schuckit et al., 1997; Hasin and Grant, 2002; Hasin et al., 2007; Davis et al., 2008). It is estimated that the rates of anxiety and depression in alcoholics are 1.5 and 2 times that of general population, respectively (U.S. Department of Health and Human Services, 1993). These co-morbid conditions are manifested more in alcoholic women (50%) than men (30%) (U.S. Department of Health and Human Services, 1993; Kessler et al., 1994; Arolt and Driessen, 1996; Schuckit et al., 1997; Berglund and Ojehagen, 1998; Swendsen et al., 1998; Tondo et al., 1999) and are particularly high during and/or following alcohol withdrawal (Behar et al., 1984; Turnbull and Gomberg, 1988). Anxiety and depression are purported to result in an early and increased alcohol relapse risk (Glenn and Parsons, 1991; De Witte et al., 2003). Whereas the relapse rates for alcoholic patients without co-morbid disorders may be about 40%, these rates jump to about 69% or 77% for alcoholics with anxiety or the combination of anxiety and depressive disorders, respectively (Driessen et al., 2001). Although manifestation of these symptoms in alcoholics may facilitate seeking of treatment for alcoholism, they are general indicators of poorer outcomes (Kendall and Clarkin, 1992; Grothues et al., 2008; Lejoyeux et al., 2008). Hence, treatment of alcoholism may be improved by addition of pharmacological treatments for anxiety and/or depression.

Animal models that can mimic these disorders can aid in providing relevant answers to such contentions. One of the animal models currently used to mimic mood disorders, particularly depressive-like behavior, is Wistar Kyoto (WKY) rats. WKY rats, derived from Wistar stock, show exaggerated immobility in the forced swim test (FST), reflective of their helplessness and are also prone to develop stress-induced anxiety-like characteristics (Soderpalm, 1989; Paré, 1993; Paré and Redei, 1993; Pini et al., 1997). Interestingly, similar to what is seen in

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human population, higher prevalence of these behaviors is manifested in the female compared to male WKY rats (Paré and Redei, 1993).

A lingering question on association of alcoholism with anxiety and/or depression is which condition precedes which? It has been suggested that mood disorders precede alcoholism in women whereas in men alcoholism is followed by these disorders (Kasperowicz-Dabrowiecka and Rybakowski, 2001). Thus, it is believed that initial alcohol intake, particularly in women, may be an attempt at self-medication for symptoms of anxiety and/or depression with the consequence of developing addiction to alcohol. However, high levels of blood alcohol concentrations due to excess drinking in both men and women may adversely affect a variety of neurotransmitter systems that are involved in mood regulation (Draski and Deitrich, 1995). Hence, an alcoholic woman may further exaggerate her symptoms of anxiety and/or depression due to heavy drinking whereas in men such symptoms, if not present prior to high alcohol consumption, would be manifested following such addiction. Alternatively, both alcoholism and affective disorder may develop as the result of a common genetic predisposition or as completely separate illnesses (Merikangas and Gelernter, 1990; Nurnberger and Berrettini, 1998). In any case, animal models can provide some clues to association of alcohol and mood disorders and may suggest effective interventions (Nestler et al., 2002).

The current study was designed to determine the effects of subchronic (7 day) and chronic (14 day) daily alcohol-exposure on measures of anxiety and depression in female WKY and Wistar rats. Specifically, we hypothesized that subchronic or chronic alcohol administration will induce anxiety- and/or depression-like behaviors in Wistar rats and exacerbate the depressive-like characteristics of WKY rats. We further hypothesized that these behaviors can be blocked by pretreatment with a clinically useful antidepressant.

2. Materials and method

2.1. Animals

Age matched adult female WKY and Wistar rats (Charles Rivers, Raleigh, NC) were used throughout the study. Animals were housed in groups of four in standard polypropylene shoebox cages (42×20.5×20 cm) on hardwood chip bedding (alpha-dry) in a room designated for female rats. Throughout the experiment animals had access to food (Harlan Tek Lab) and water ad libitum. The room was maintained at 24–26 °C at 51–66% relative humidity, on a 12-h reversed light/dark cycle (lights on at 1900 hr). All experiments were carried out in accordance with NIH guidelines as approved by the Institutional Animal Care and Use Committee.

To acclimate the subjects to housing conditions, animals arrived one week prior to testing. During this period, they were gentled once daily in order to minimize any stress effects that might result from routine handling. The animals were weighted once a week for the duration of the study. All behavioral testing were carried out in the early portion of dark phase between 09:00 A.M. and 12:00 P.M using a red light as source of illumination. Different groups of rats were used for the time period exposure and the drug studies. A total of 144 rats (72 Wistar and 72 WKY) were used. Each experiment consisted of 4 groups of rats (8 rats/group) plus 2 additional rats of each strain to determine the blood alcohol concentration.

2.2. Vapor ethanol exposure and drug treatment

Inhalation chambers were used to expose the animals to ethanol (La Jolla Alcohol Research Inc., La Jolla, CA). Briefly, 95% ethanol was pumped at regulated rate from 5 gallon reservoir via a peristaltic pump to a 5000 ml Erlenmeyer vacuum flask that was kept on a warming tray (52 °C). The ethanol was then volatilized and mixed with pressurized air. The flow of this mixture was controlled by a pressure gauge as it was delivered to individual chambers. The control group received only air via exactly similar system. The inhalation chamber has the advantage of easily achieving and maintaining the targeted blood alcohol level (BAL) (Kliethermes et al., 2004). Moreover, the variability in the ethanol concentration between similarly controlled chambers is minimal (Lee et al., 2000).

USP 200 proof ethyl alcohol was purchased from VWR Scientific Products (Bridgeport, New Jersey) and was diluted down with distilled water to 95% ethanol v/v. Desipramine (DES) HCl was purchased from Sigma-Aldrich Co. (St. Louis, MO, USA), was dissolved in saline and injected intraperitoneally (i.p.) (8 mg/kg) in volume of 1 ml/kg.

Ethanol-naive female WKY and Wistar rats were randomly placed in either ethanol inhalation or air chambers (4 animals per chamber). Ethanol vapor was administered for 3 h daily either for 7 or 14 days. Preliminary data indicated that 3 h of ethanol vapor exposure (60 ml/h drip rate) was required to achieve target BAL of 150 mg% in these rat strains. Importantly, there was no significant BAL difference between the two strains despite their body weight differences. This BAL is pharmacologically relevant to human intake. Moreover, to minimize problems of condensation of ethanol vapor on the sides of the chambers, the following parameters were used: air pressure ≈5 psi, airflow rate ≈15–20 l/min and ethanol flow rate=60 ml/h.

For the DES study, the exact same alcohol exposure protocol as above was used. But the daily alcohol exposure was followed by i.p. injection of DES. Controls received saline.

2.3. Blood alcohol determination

To determine the blood alcohol concentration at various time points, a separate group of WKY and Wistar rats were exposed to the chambers under identical conditions. Blood was sampled by tail bleed technique every three days immediately after the end of daily ethanol exposure. Briefly, tail blood (0.4 ml) was collected in tubes coated with 0.2 M ethylenediaminetetraacetic acid (EDTA) (Sigma-Aldrich CO., St. Louis, MO) and centrifuged for 5 min at 1500 g at 4 °C. The plasma was extracted and BALs were assayed by injecting 5 µL plasma into GM7 Micro-Stat Analyzer (Analox Instruments Ltd., Lunenburg, MA).

2.4. Behavioral testing

On days 8 and 15, 14–16 h after last ethanol exposure and at least 1 h before behavioral tests, animals were moved from the housing units to the testing room in their home cages. All animals in each group were tested alternately for the three behaviors. Open field locomotor activity test was conducted first in each animal for 10 min. This was followed immediately by 5 min exposure to the elevated plus maze which in turn was immediately followed by 5 min forced swim test.

2.5. Locomotor Activity (LCA) Monitoring

Locomotor activity was measured first for each animal during a 10 min period. An open-field activity monitoring cage (27×27×20.3 cm, Med Associates, Inc., St. Albans, VT) was used to assess activity. Ambulatory counts representing the number of infrared beam interruptions were recorded.

2.6. Elevated Plus-Maze (EPM)

The EPM test is one of the most widely used non-conditioned tests to evaluate anxiety-like behaviors (Pellow et al., 1985; Baldwin et al., 1991; Rassnick et al., 1993). EPM apparatus consists of two opposite open arms 50×10 cm and two opposite arms enclosed by 40 cm high walls and elevated 50 cm from the floor. The arms are connected by a central 10×10 cm square, and thus the maze forms a “plus” shape (File et al., 1999).

Table 1
Changes in body weight of Wistar and WKY rats

Treatment group	Time point	Wistar	WKY
Control	Day 1	270.6±5.83	226.6±3.98***
	Day 7	271.3±4.14	228.8±4.39***
	Day 14	272.5±8.44	236.9±3.49***
Alcohol	Day 1	262.5±4.10	224.4±3.46***
	Day 7	264.4±2.74	225.8±3.96***
	Day 14	271.9±4.48	226.9±3.52***

Mean body weight±S.E.M of Wistar and WKY rats in grams at different time points during the duration of the experiment. ***P<0.001 compared to Wistar. N=8/group.

In this test, each rat is placed in the central square with the head facing the closed arm of the EPM and its behavior is observed for 5 min. Anxiety-like behaviors are defined as the decrease in the total time spent in the open arm (Cruz et al., 1994). Each animal's activity in EPM was recorded using a video camera for subsequent analysis of total time spent in the open arm.

2.7. Forced swim test (FST)

The method of Porsolt et al. (1977) with modification by Detke et al. (1995) was used to assess the immobility of the rats as a measure of their helplessness or depressive-like behavior. Immediately after the EPM test, the rat was placed in a round Pyrex cylinder pool measuring 17 cm in diameter and 60 cm in height for 5 min. The cylinder was filled with 30 cm water (25±1 °C) to ensure that the animal could not touch the bottom of the container with its hind paws or its tail (Lucki, 1997). The animal's FST activity was video recorded for subsequent analysis. The rat was removed after 5 min, dried, and placed in its home cage.

A time sampling scoring technique was used whereby the predominant behavior in each 5-s period of the 300-s test was recorded. Inactivity (immobility) and swimming were distinguished as mutually exclusive behavioral states. Swimming behavior was defined as movement (usually horizontal) throughout the cylinder. Immobility was defined when no additional activity was observed other than that required to keep the rat's head above the water.

2.8. Statistical Analysis

All data were analyzed using Two-way analysis of variance (ANOVA), followed by Tukey's post hoc test when significant main effects were indicated. All analyses were two-tailed and P<0.05 was considered significant.

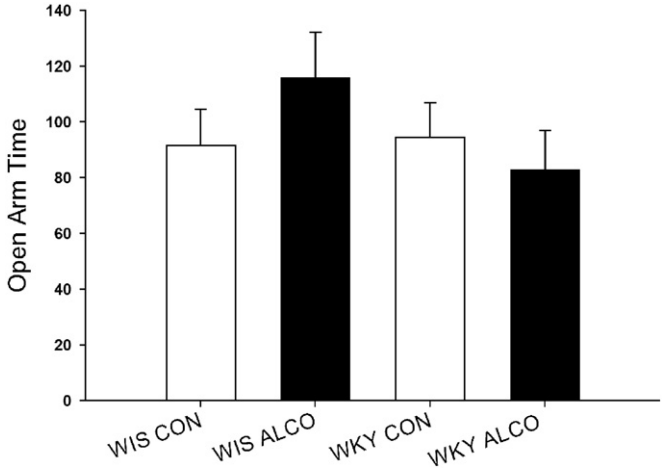

Fig. 2. Effect of 7 days daily alcohol vapor exposure on EPM open arm time of Wistar and WKY rats. Values are mean±SEM. Testing was conducted 14-16 h after the last alcohol exposure. N=8/group.

3. Results

3.1. Body weight

Table 1 depicts weekly body weight changes of the study animals. There were no significant differences between alcohol-treated and control groups of either strain at any of the time points. However, Wistar rats of the same age tend to be heavier than WKY rats. Moreover, there was no effect of DES on the body weights (data not shown).

3.2. Effects of desipramine on locomotor activity, elevated plus-maze and forced swim test following 7 days of alcohol vapor exposure

Fig. 1 illustrates open field LCA of Wistar and WKY rats following 7 days of daily alcohol vapor exposure. At baseline, WKY rats showed reduced LCA compared to Wistar rats $F(1,28)=159$, $p<0.001$. However, 7 day alcohol exposure reduced LCA in Wistar rats only $F(1,28)=12.02$, $P<0.01$.

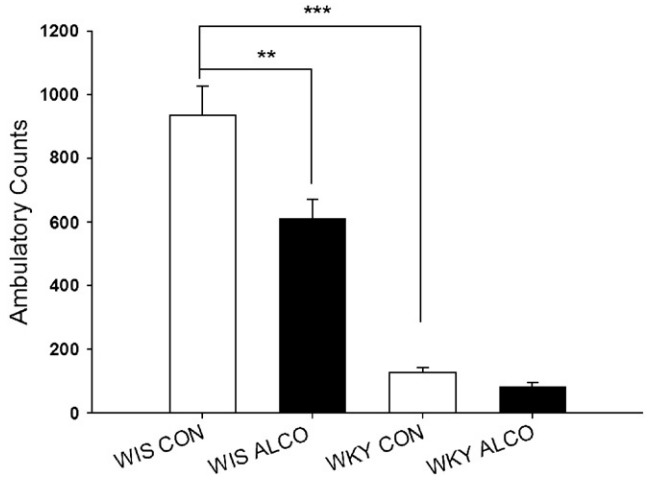

Fig. 1. Effect of 7 days daily alcohol vapor exposure on LCA of Wistar and WKY rats. Values are mean ambulatory counts±SEM. Testing was conducted 14-16 h after the last alcohol exposure. **P<0.01, ***P<0.001. N=8/group.

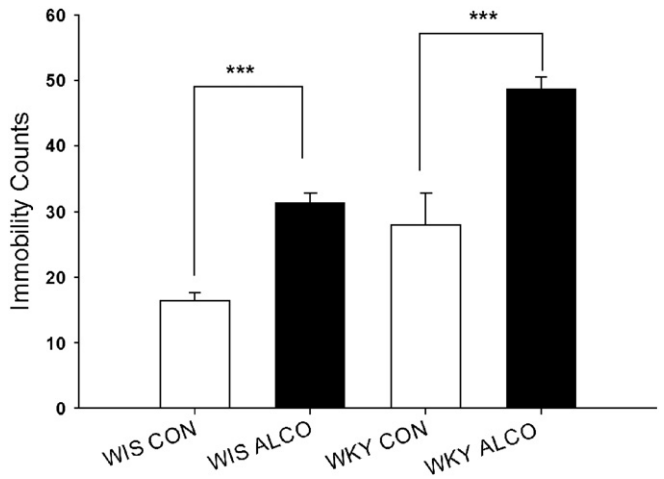

Fig. 3. Effect of 7 days daily alcohol vapor exposure on FST immobility counts of Wistar and WKY rats. Values are mean±SEM. Testing was conducted 14-16 h after the last alcohol exposure. ***P<0.001. N=8/group.

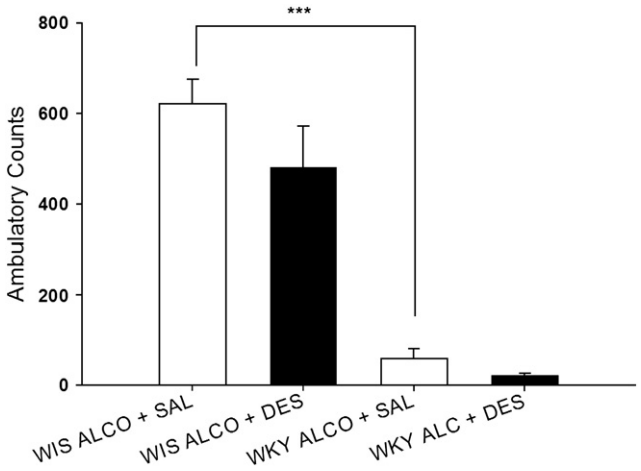

Fig. 4. Effect of 7 days daily DES treatment following daily alcohol vapor exposure on LCA of Wistar and WKY rats. Controls received saline (SAL). Values are mean ± SEM. Testing was conducted 14-16 h after the last alcohol exposure.

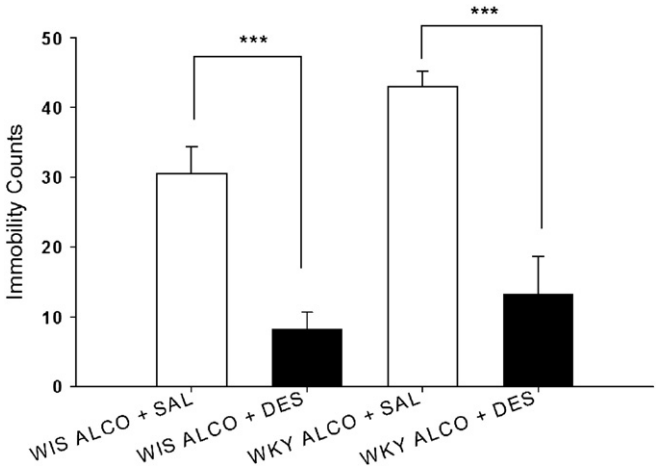

Fig. 6. Effect of 7 day DES treatment following daily alcohol vapor exposure on immobility in the FST of Wistar and WKY rats. Controls received SAL. Values are mean ± SEM. Testing was conducted 14-16 hrs after the last alcohol exposure. ***$P<0.001$. $N=8$/group.

Fig. 2 illustrates the total time spent in the open arm for Wistar and WKY rats following 7 days of daily alcohol vapor exposure. There were no differences between the Wistar or WKY either at baseline $F(1,28)=1.08$, $P=0.31$ or after alcohol exposure $F(1,28)=0.23$, $P=0.63$.

Fig. 3 illustrates the immobility counts in the FST for Wistar and WKY rats following 7 days of daily alcohol vapor exposure. As expected, baseline immobility was higher in WKY rats $F(1,28)=6.8$, $P=0.014$. Seven day alcohol exposure resulted in significant increases in FST immobility in both Wistar and WKY rats $F(1,28)=66.8$, $P<0.001$.

Fig. 4 depicts the effects of 7 days DES treatment on open field LCA of Wistar and WKY rats following daily alcohol vapor exposure. DES treated animals tended to have lower LCA, however, this effect was not statistically significant.

Fig. 5 depicts the effects of 7 days DES treatment on open arm time of Wistar and WKY rats following daily alcohol vapor exposure. No significant effect of DES was noted.

Fig. 6 depicts the effects of 7 days DES treatment on immobility in the FST of Wistar and WKY rats following daily alcohol vapor exposure. DES significantly attenuated the immobility induced by alcohol in both strains $F(1,28)=47.1$, $P<0.001$.

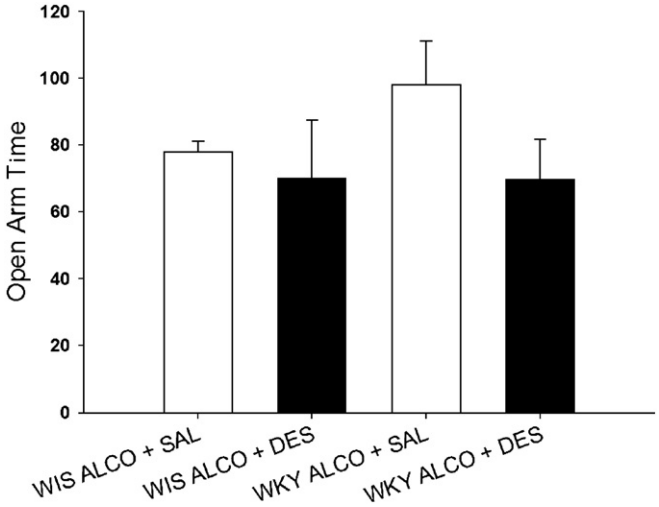

Fig. 5. Effect of 7 day DES treatment following daily alcohol vapor exposure on open arm time in EPM of Wistar and WKY rats. Controls received SAL. Values are mean ± SEM. Testing was conducted 14-16 h after the last alcohol exposure. $N=8$/group.

3.3. Effects of desipramine on locomotor activity, elevated plus-maze and forced swim test following 14 days of alcohol vapor exposure

Fig. 7 illustrates open field LCA of Wistar and WKY rats following 14 days of daily alcohol vapor exposure. Very similar to 7 days result, WKY rats showed reduced LCA at baseline compared to Wistar rats $F(1,28)=61.05$, $P<0.001$. Moreover, 14 days alcohol exposure reduced LCA in Wistar rats only $F(1,28)=9.13$, $P=0.013$.

Fig. 8 illustrates the total time spent in the open arm for Wistar and WKY rats following 14 days of daily alcohol vapor exposure. In this case, alcohol exposure resulted in reduction of time spent in the open arm for both Wistar and WKY rats $F(1,28)=10.1$, $P<0.05$.

Fig. 9 illustrates the immobility counts in the FST for Wistar and WKY rats following 14 days of daily alcohol vapor exposure. Similar to 7 days exposure, there were significant increases in FST immobility counts in both Wistar and WKY rats $F(1,28)=55.8$, $P<0.001$.

Fig. 10 depicts the effects of 14 days DES treatment on open field LCA of Wistar and WKY rats following daily alcohol vapor exposure. Similar to what was observed in 7 day treatment DES did not modify the locomotors effect of alcohol in Wistar rats.

Fig. 11 depicts the effects of 14 days DES treatment on EPM open arm time of Wistar and WKY rats following daily alcohol vapor

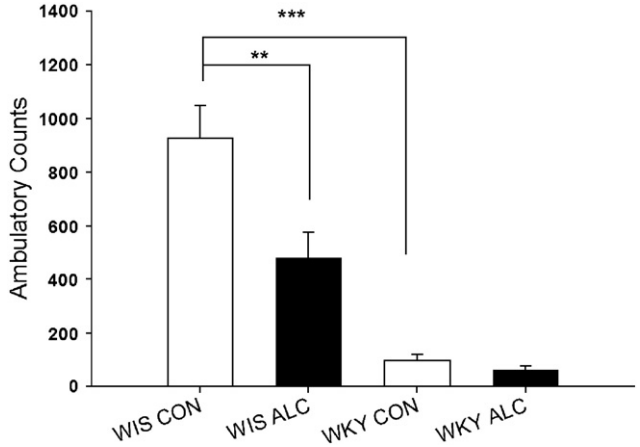

Fig. 7. Effect of 14 days daily alcohol vapor exposure on LCA of Wistar and WKY rats. Values are mean ambulatory counts ± SEM. Testing was conducted 14-16 h after the last alcohol exposure. **$P<0.05$, ***$P<0.001$. $N=8$/group.

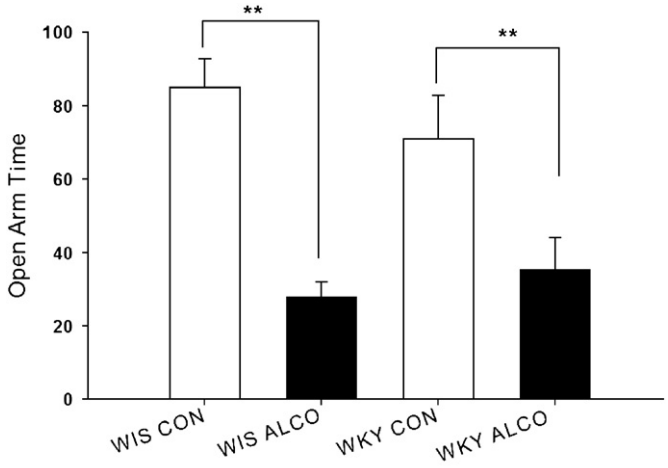

Fig. 8. Effect of 14 days daily alcohol vapor exposure on EPM open arm time of Wistar and WKY rats. Values are mean±SEM. Testing was conducted 14-16 hrs after the last alcohol exposure. $N=8$/group ** $P<0.05$.

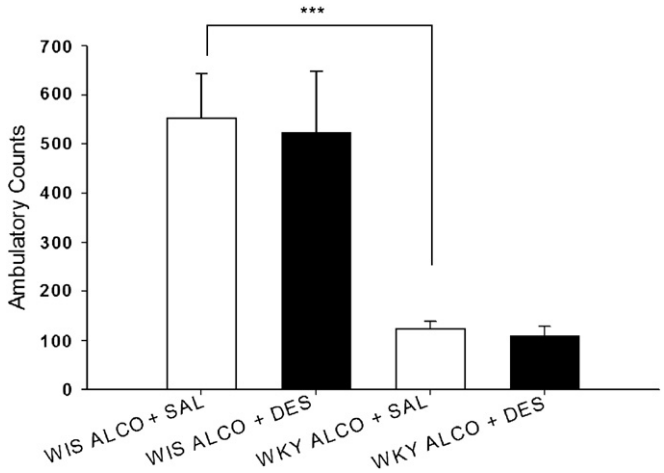

Fig. 10. Effect of 14 day DES treatment following daily alcohol vapor exposure on LCA of WKY and Wistar rats. Controls received SAL. Values are mean±SEM. Testing was conducted 14-16 h after the last alcohol exposure. ***$P<0.001$. $N=8$/group.

exposure. DES blocked the effect of alcohol on open arm time in both strains $F(1,28)=13.86$, $P<0.001$. The time spent in open arm of the EPM following DES was very similar to what was observed in control animals (Fig. 8).

Fig. 12 depicts the effects of 14 days DES treatment on immobility in the FST of Wistar and WKY rats following daily alcohol vapor exposure. Similar to 7 day treatment, DES significantly attenuated the immobility induced by alcohol in both strains $F(1,28)=49.4$, $P<0.001$.

4. Discussion

Behavioral symptoms of alcohol abuse often mimic various psychiatric disorders including anxiety and depression. Thus, co-occurrence of alcoholism with neuropsychological disorders such as anxiety and/or depression, can introduce therapeutic challenges for treatment of alcoholism. This is most readily manifested in terms of relapse prevention as such mood disorders may significantly facilitate relapse to alcohol use (Glenn and Parsons, 1991; Driessen et al., 2001; De Witte et al., 2003; Saatcioglu et al., 2008). The results of current study, using an animal model, suggest that administration of an antidepressant can counteract anxiety- and depressive-like behavior induced by chronic alcohol administration. Specifically our results indicate that daily dosing of selective rat strains with relatively high dose of alcohol can induce depressive-like behavior in otherwise normal rats and exacerbate an already existing such behavior in a genetically susceptible strain. Moreover, prolongation of the same dose regimen also results in anxiety-like behavior in both strains. However, daily treatment with a tricyclic antidepressant was effective in blocking both the depressive- and anxiety-like behaviors induced by alcohol. Thus, incorporation of an antidepressant regimen prior to and during detoxification may be of benefit in at least a subpopulation of alcoholics seeking treatment.

Curiously, in this study treatment with an antidepressant was also effective in blocking anxiety-like effects induced by prolonged administration of alcohol. However, anxiety and depression can co-occur and may represent a continuum of symptoms underlying an overlap in some central circuitries (Carpenter and Hasin, 1999; Drevets, 2000). Although the importance of anxiety and depression in alcohol relapse are well documented (Driessen et al., 2001) it remains of interest to determine the extent to which such pre-existing conditions may lead to alcoholism. Based on observance of higher prevalence of co-morbidity of anxiety and depression with alcoholism in women, it has been suggested that anxiety and depression may precede alcoholism in women, whereas in men alcoholism may precede such conditions (Kasperowicz-Dabrowiecka and Rybakowski, 2001). In fact in a study conducted in males with major affective

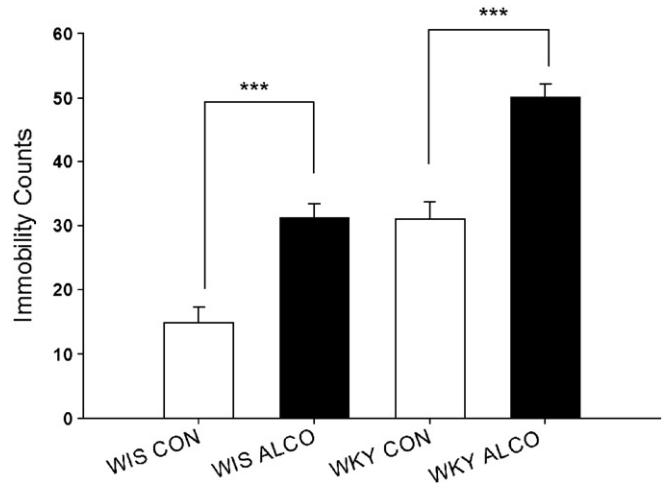

Fig. 9. Effect of 14 days daily alcohol vapor exposure on FST immobility counts of Wistar and WKY rats. Values are mean±SEM. Testing was conducted 14-16 h after the last alcohol exposure. ***$P<0.001$. $N=8$/group.

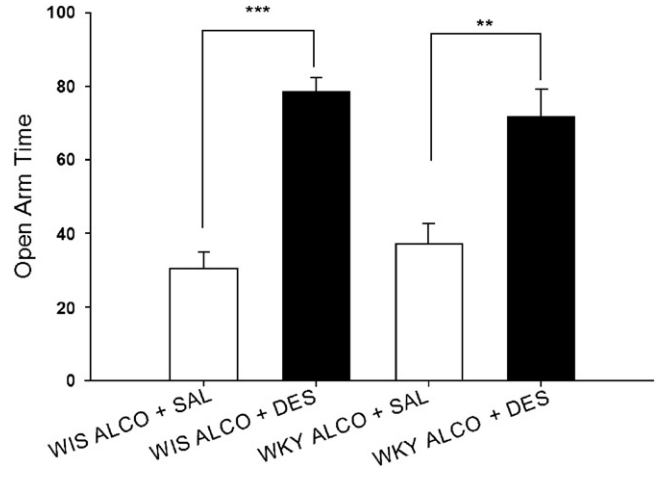

Fig. 11. Effect of 14 day DES treatment following daily alcohol vapor exposure on open arm time in EPM of Wistar and WKY rats. Controls received SAL. Values are mean±SEM. Testing was conducted 14-16 h after the last alcohol exposure. **$P<0.05$, ***$P<0.001$. $N=8$/group.

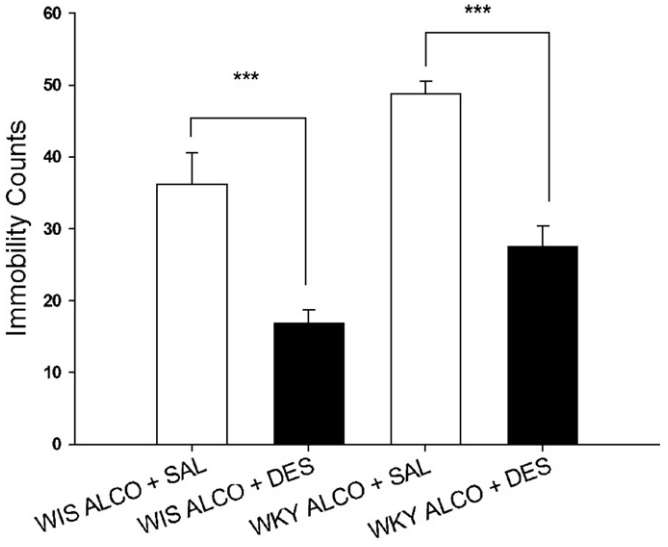

Fig. 12. Effect of 14 day DES treatment following daily alcohol vapor exposure on immobility in the FST of Wistar and WKY rats. Controls received SAL. Values are mean ± SEM. Testing was conducted 14-16 h after the last alcohol exposure. ***$P<0.001$. $N=8$/group.

disorder, the risk for alcoholism was nearly twice that of males without affective disorder. Among females, this risk was raised sevenfold (Nurnberger et al., 2001). Since anxiolytics are primary medications employed in alcohol detoxification regardless of gender, the use of antidepressants may be of added benefit. This contention is further supported by the fact that anxiolytics are effective in dampening the immediate autonomic hyperactivity following alcohol cessation whereas depression may be a lingering mood state that would facilitate later relapse (Carpenter and Hasin, 1999; Koob and Le, 2004; Ritvo and Park, 2007).

Interestingly, in our model, a longer duration of alcohol treatment was required to induce anxiety. If a similar sequence is also manifested in human condition, then addressing the depression component prior to detoxification may facilitate abstinence. In this regard, it is noteworthy that promising results have also been reported with the use of desipramine in the treatment of individuals with co-morbid alcohol dependence and major depression (Mason et al., 1996). Thus, in addition to producing a significant decline in depressive symptomatology, a 6 month course of desipramine was associated with significantly longer abstinence from alcohol (Mason et al., 1996).

Clearly, inherent limitations in extending animal models to human conditions exist. For example in our paradigm, alcohol lowered the locomotor activity in Wistar rats only. Since WKY rats show significant immobility in locomotor activity, they might have already achieved a minimum threshold and hence lack of alcohol effect. However, 7 days of desipramine treatment tended to reduce locomotor activity in both strains albeit non-significantly. On the other hand, 14 day DES treatment had no such effect on LCA suggesting a short duration of DES effect on LCA if any. In addition, WKY rats, as a putative animal model of depression, may not respond to selective serotonin uptake inhibitors (SSRI) such as fluoxetine or paroxetine (Griebel et al., 1994; Lahmame et al., 1997; Lopez-Rubalcava and Lucki, 2000; Tejani-Butt et al., 2003). Thus, other animal models are necessary to explore not only the effectiveness of antidepressants but also possible neurochemical bases of the behavioral changes induced by chronic alcohol use. This need is further supported by studies indicating that patients with co-occurring mental and substance use disorders have a more persistent and severe illness course that are more refractive to treatment than those with only a single disorder (Grant et al., 1996; Burns and Teesson, 2002).

In summary, our results indicate that chronic alcohol exposure can lead to both depressive- and anxiety-like symptoms in two rat strains and that these behavioral effects can be blocked by treatment with a tricyclic antidepressant. Thus, prophylactic treatment of alcoholics with an antidepressant prior to detoxification may improve treatment outcome for at least a subpopulation of such patients.

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