Neuroscience Letters 553 (2013) 196–200

Contents lists available at ScienceDirect

Neuroscience Letters

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

# The role of L-type calcium channels in the development and expression of behavioral sensitization to ethanol

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## HIGHLIGHTS

- Blocking L-type calcium channels decreases the stimulant effects of ethanol.
- Diltiazem and verapamil decrease blood ethanol levels.
- L-type calcium channels do not contribute to sensitization to ethanol.
- Distinct mechanisms mediate sensitization to ethanol and other addictive drugs.

## ARTICLE INFO

*Article history:*
Received 24 June 2013
Received in revised form 4 August 2013
Accepted 5 August 2013

*Keywords:*
Ethanol
Alcohol
Behavioral sensitization
L-type calcium channel blockers
Locomotor activity
Mice

## ABSTRACT

Behavioral sensitization is thought to play a significant role in drug addiction. L-type calcium channels have been implicated in sensitization to stimulant and opiate drugs but it is unclear if these channels also contribute to sensitization to ethanol. The effects of three L-type calcium channel blockers, nifedipine (1–7.5 mg/kg), diltiazem (12.5–50 mg/kg), and verapamil (12.5 and 25 mg/kg), on sensitization to ethanol (2 g/kg) were examined in DBA/2J mice. All three blockers reduced but did not prevent expression of sensitization. Only nifedipine blocked acquisition of sensitization. Nifedipine and verapamil decreased blood ethanol levels. The current findings suggest L-type calcium channels do not play a substantial role in sensitization to ethanol and that the neural mechanisms underlying sensitization to ethanol are distinct from those mediating sensitization to stimulants and opiates.



## 1. Introduction

Persistent neuroadaptive responses that develop following repeated use of addictive drugs are hypothesized to play an important role in addiction. One neuroadaptive response thought to contribute to addiction is behavioral sensitization [16,18]. Sensitization develops to many different addictive drugs [17] and, like addiction, is persistent [7,13]. Moreover, sensitization is linked to increased drug use [11] and relapse [6], although its role in addiction is still unclear [17].

A number of different neurotransmitter systems have been implicated in sensitization to stimulants and opiates [17]. Several of these neurotransmitter systems produce their effects, in part, by stimulating L-type voltage-activated calcium channels, increasing calcium influx and the activity of the transcription factor cAMP response element binding protein (CREB) [10]. Blocking L-type calcium channels prevents acquisition and expression of sensitization to opiates and stimulants [8,9,15,20].

Sensitization is consistently observed following repeated administration of ethanol [5] and some evidence suggests that, like sensitization to stimulants and opiates, L-type calcium channels may play a role in sensitization to ethanol. L-type calcium channel blockers block the stimulant effects of ethanol [1] as well as cross-sensitization between ethanol and nicotine [3]. A mixed L/N calcium channel blocker was reported to prevent both the acquisition and expression of sensitization to ethanol [2]. However, it has not been determined if specific L-type calcium channel blockers prevent sensitization to ethanol.

Five experiments were conducted to examine the ability of L-type calcium channel blockers to prevent the acquisition and expression of sensitization to the locomotor stimulant effects of ethanol. The doses and pretreatment times used for each calcium channel blocker were based on previous studies [1,3,9,19] and pilot experiments from this laboratory.

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http://dx.doi.org/10.1016/j.neulet.2013.08.008

## 2. Materials and methods

### 2.1. Animals

Six-week old male DBA/2J mice (Jackson Laboratory, Bar Harbor, Maine) were used. For additional methodological details see Broadbent et al. [5]. All procedures were approved by the University Committee on the Use and Care of Animals and carried out according to the NIH "Principles of Laboratory Animal Care."

### 2.2. Drugs

Nifedipine, verapamil and diltiazem were purchased from Sigma–Aldrich (St. Louis, MO). All drugs were administered intraperitonally (i.p.) and were dissolved in 0.9% saline except nifedipine, which was administered in a 1% Tween solution. Ethanol (2 g/kg, 20%, v/v) was administered i.p. immediately before trials and tests.

### 2.3. Procedure

Locomotor activity was measured by a computer interfaced with Plexiglas activity cages (28.5 cm × 23 cm × 20.5 cm) each of which had eight photobeams placed at approximately 3 cm intervals 2 cm above the floor (Med Associates, East Fairfield, VT). Activity cages were placed inside sound- and light-attenuating chambers. Experiments consisted of a single 5 min habituation trial immediately before which all animals were injected with 12.5 ml/kg of the vehicle solution, eight 5 min locomotor activity trials, and a test trial. The effects of diltiazem on expression of sensitization were examined in a second test in the diltiazem acquisition study. Two 5 min trials separated the tests. Locomotor activity levels on these trials were similar to those observed before the first test. Trials were conducted at approximately the same time of day on Mondays, Wednesdays, and Fridays (one trial per day).

The effects of drugs on acquisition of sensitization were tested by administering the test drugs before each of the eight trials followed by saline or ethanol. On the test, all mice received a vehicle injection in place of the test drug, and ethanol immediately before the test. Expression of sensitization was assessed by administering saline or ethanol before each trial. On the test, mice received an injection of vehicle or the test drug and an injection of ethanol. The duration of tests was 30 min for all drugs with the exception of the verapamil experiment. A 20 min test was used in this experiment in order to test blood ethanol levels approximately 20 min after injection. For additional methodological details see Broadbent et al. [5].

### 2.4. Data analysis

All data were analyzed using analysis of variance (ANOVA; Systat, SPSS Inc.) followed by Tukey HSD tests when appropriate.

## 3. Results

### 3.1. Effects of nifedipine on expression of sensitization

Mice given ethanol on trials developed sensitization whereas the locomotor activity of saline groups tended to decrease across trials. On the first trial mean (±S.E.M.) locomotor activity levels per minute for the saline groups were 127.8 (±22), 126.2 (±12), and 123.4 (±13), and on the last trial were 90.2 (±10), 92.0 (±9), and 93.0 (±8). In contrast mean activity levels for ethanol groups on the first trial were 171.7 (±20), 189.3 (±14), and 183.4 (±19), and on the last trial were 264.3 (±17), 271.7 (±10), and 290.9 (±21). A three-way ANOVA [Group (saline or ethanol) × Nifedipine dose × Trial] indicated a main effect of Group [$F(1,85) = 245.5$, $P < 0.001$], a main effect of Trial [$F(7,595) = 10.1$, $P < 0.001$], and a Trial × Group interaction [$F(7,595) = 31.1$, $P < 0.001$].

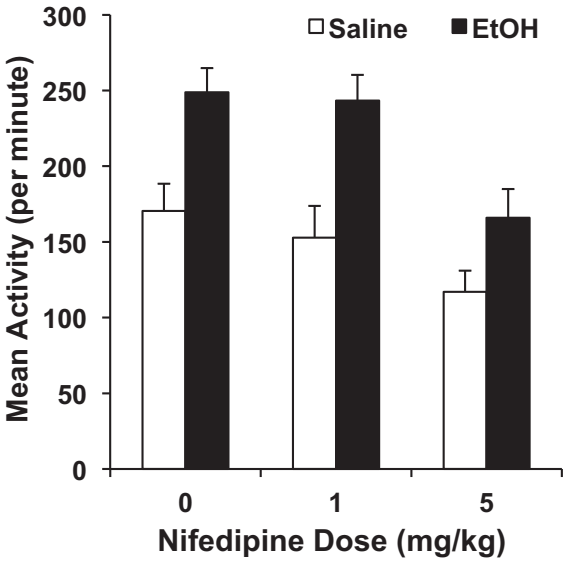


**Fig. 1.** Effects of nifedipine on expression of behavioral sensitization. Bars represent mean locomotor activity per min (+S.E.M.) during the test. Black and open bars represent locomotor activity levels of mice treated with ethanol (EtOH, 2 g/kg i.p.) or saline immediately before the eight trials that preceded the test, respectively. All mice received 2 g/kg of ethanol before the test. In addition, mice received an injection of vehicle or nifedipine i.p. 20 min before the test. $n = 13$–16 mice per group.

On the test the highest dose of nifedipine tended to decrease the magnitude of sensitization however sensitization was still present (Fig. 1). Nifedipine also dose-dependently decreased locomotor activity in the saline groups indicating that it suppressed ethanol-stimulated activity. A three-way ANOVA [Group (saline or ethanol) × Nifedipine dose × Time (10 min blocks during the test)] showed a main effect of Group [$F(1,85) = 25.5$, $P < 0.001$], a main effect of Nifedipine dose [$F(2,85) = 8.4$, $P < .001$], a main effect of Time [$F(2,170) = 84.9$, $P < 0.001$], and a Time × Group interaction [$F(2,170) = 12.9$, $P < 0.001$]. The lack of a Group × Nifedipine dose interaction suggests that sensitization was observed in all ethanol groups and that nifedipine reduced the stimulant response to ethanol in the saline groups.

### 3.2. Effects of nifedipine on acquisition of sensitization

As 5.0 mg/kg of nifedipine decreased expression of sensitization but 1.0 mg/kg was ineffective, doses of 5.0 and 7.5 mg/kg were tested on acquisition of sensitization. Nifedipine suppressed ethanol's stimulant effect on trials and modestly decreased basal locomotor activity in saline groups (Fig. 2). A three-way ANOVA [Group (ethanol or saline) × Nifedipine dose × Trial] revealed a main effect of Group [$F(1,87) = 48.5$, $P < 0.001$], a main effect of Nifedipine dose [$F(2,87) = 19.2$, $P < 0.001$], a Group × Nifedipine dose interaction [$F(2,87) = 6.5$, $P < 0.01$], and a Trial × Group interaction [$F(7,609) = 18.5$, $P < 0.001$]. Follow-up of the Group × Nifedipine dose interaction revealed significant effects of nifedipine in both the saline [$F(2,45) = 3.62$, $P < 0.05$)] and ethanol groups [$F(2,42) = 15.94$, $P < 0.001$)], but a much larger effect in the ethanol groups. Locomotor activity levels of ethanol groups treated with both doses of nifedipine differed significantly from the control group ($P_s < 0.001$) whereas in the saline groups only the activity of the high dose group differed from the control group ($P < 0.05$).

Nifedipine blocked acquisition of sensitization at both doses. Mean (±S.E.M.) locomotor activity levels per minute on the test

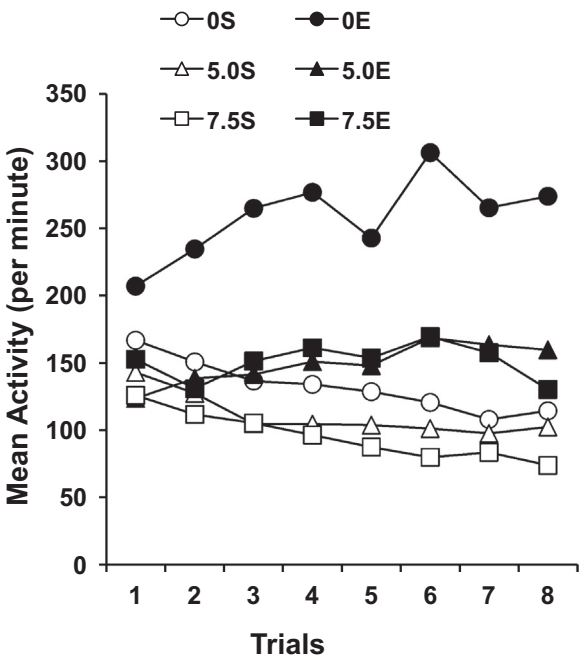


**Fig. 2.** Effects of nifedipine on acquisition of sensitization. Filled and open symbols represent the mean locomotor activity levels per min of mice treated with ethanol (*E*, 2 g/kg i.p.) or saline (S) before the eight 5 min trials that preceded the test, respectively. Mice also received an injection of vehicle (0) or nifedipine i.p. 20 min before trials. $n = 14$–16 mice per group.

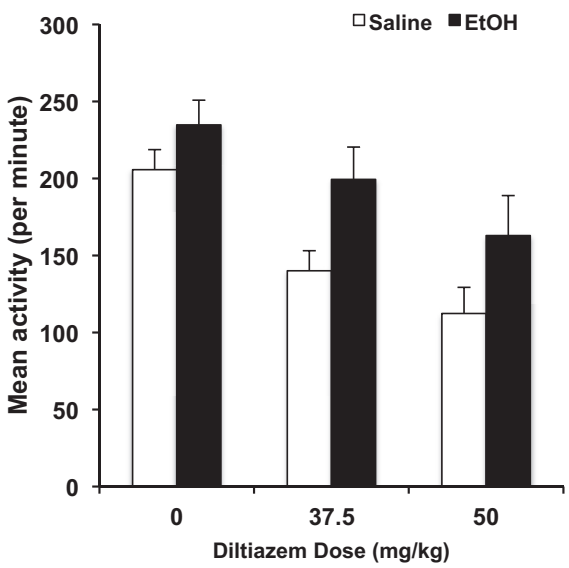


**Fig. 3.** Effects of diltiazem on expression of sensitization. Diltiazem was given i.p. 30 min before the test. $n = 16$ mice per group. For additional details see Fig. 1.

were 169.8 (±13), 199.8 (±18), and 202.0 (±17) for the saline groups given vehicle, the low and the high dose of nifedipine, respectively whereas the mean activity levels were 260.3 (±13), 191.1 (±20), and 197.2 (±20) for the ethanol groups given vehicle, the low dose and the high dose of nifedipine, respectively. A three-way ANOVA [Group (saline or ethanol) × Nifedipine dose × Time (10 min blocks)] revealed a Group × Dose interaction [$F(2,830) = 5.5$, $P < 0.01$], a main effect of Time [$F(2,166) = 34.2$, $P < 0.001$], and a Time × Group interaction [$F(2,166) = 9.3$, $P < 0.001$]. Comparison of groups treated with the same dose of nifedipine with one-way ANOVAs showed that sensitization was only present in the group treated with vehicle plus ethanol on trials [$F(1,28) = 23.4$, $P < 0.001$].

### 3.3. Effects of nifedipine on blood ethanol levels

Blood samples taken from ethanol treated groups immediately after a 5 min trial conducted after the sensitization test showed that nifedipine significantly decreases ethanol levels: mean (±S.E.M.) levels were 168.1 (±8), 139.7 (±9), and 129.0 (±8) mg/dl for the vehicle, 5 mg/kg, and 7.5 mg/kg dose nifedipine groups, respectively. A one-way ANOVA followed by a Tukey test indicated a main effect of Nifedipine dose [$F(2,40) = 6.0$, $P < 0.01$] and a significant difference between the vehicle group and the high dose nifedipine group. The difference in ethanol levels between the vehicle and low dose nifedipine group just missed being significant ($P = 0.053$).

### 3.4. Influence of diltiazem on acquisition of sensitization

Diltiazem administered 30 min before trials did not retard acquisition of sensitization or suppress ethanol-induced locomotor stimulation on trials ($n = 16$ per group). A three-way ANOVA [Group (ethanol or saline) × Diltiazem dose × Trial] revealed a main effect of Group [$F(1,90) = 321.2$, $P < 0.001$], a main effect of Trial [$F(7,630) = 16.0$, $P < 0.001$], a Trial × Group interaction [$F(7,630) = 36.4$, $P < 0.001$], and a weak Trial × Diltiazem dose interaction [$F(14,630) = 2.2$, $P < 0.05$]. The Trial × Group interaction in the absence of a Trial × Group × Diltiazem dose interaction suggests that locomotor activity increased in all ethanol groups across trials.

Sensitization in all ethanol groups was confirmed on the test. Mean (±S.E.M.) locomotor activity levels per minute for the saline, low dose, and high dose diltiazem groups given saline before trials were 202 (±12), 187 (±12), and 184 (±14), respectively. Mean activity levels for the saline, low and high dose diltiazem groups also given ethanol before trials were 245 (±16), 268 (±12), and 244 (±14), respectively. A three-way ANOVA [Group (ethanol or saline) × Diltiazem dose × Time (10 min blocks)] revealed a main effect of Group [$F(1,90) = 26.9$, $P < 0.001$], a main effect of Time [$F(2,180) = 36.9$, $P < 0.001$], and a Time × Group interaction [$F(2,180) = 15.7$, $P < 0.001$].

### 3.5. Influence of diltiazem on expression of sensitization

As 12.5 and 25.0 mg/kg of diltiazem did not block acquisition of sensitization the effects of higher doses of diltiazem (37.5 and 50.0 mg/kg) were tested on expression of sensitization in a second test (Fig. 3). Although diltiazem reduced the stimulant effects of ethanol, expression of sensitization was observed in all ethanol groups. The three-way ANOVA [Group (ethanol or saline) × Diltiazem dose × Time (10 min blocks)] showed a main effect of Group [$F(1,90) = 9.6$, $P < 0.001$], a main effect of Diltiazem dose [$F(2,90) = 10.3$, $P < 0.001$], a main effect of Time [$F(2,180) = 51.1$, $P < .001$], and a Time × Group interaction [$F(2,180) = 23.9$, $P < 0.001$].

### 3.6. Influence of verapamil on acquisition of sensitization

Verapamil (12.5 or 25.0 mg/kg) administered 30 min before trials did not suppress the locomotor stimulant effects of ethanol or basal activity of saline groups. Moreover, all ethanol groups acquired sensitization across trials regardless of treatment with verapamil ($n = 16$ per group) A three-way ANOVA [Group (saline or ethanol) × Verapamil dose × Trials] revealed a main effect of Group [$F(1,90) = 230.8$, $P < 0.001$], a main effect of Trial [$F(7,630) = 14.2$, $P < 0.001$], and a Trial × Group interaction [$F(7,630) = 39.3$, $P < 0.001$].

Acquisition of sensitization was observed in all ethanol groups on the test. Mean (±S.E.M.) locomotor activity levels per min for

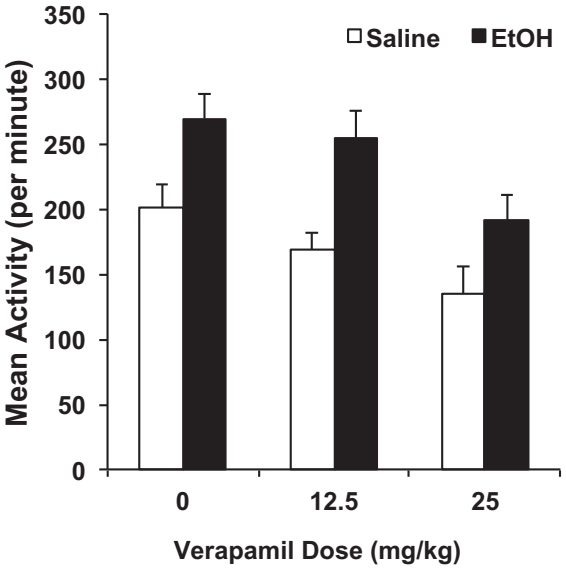


**Fig. 4.** Effects of verapamil on expression of sensitization. Verapamil was given i.p. 30 min before the test. $n = 16$ mice per group. For additional details see Fig. 1.

the saline, low dose, and high dose verapamil groups given saline before trials were 179.5 (±18), 196.9 (±14), and 184.2 (±16), respectively. Mean locomotor activity levels for the saline, low and high dose verapamil groups given ethanol before trials were 248.6 (±18), 235.0 (±13), and 243.2 (±14), respectively. A three-way ANOVA [Group (ethanol or saline) × Verapamil dose × Time (10 min blocks)] revealed a main effect of Group [$F(1,90) = 19.1$, $P < 0.001$], a main effect of Time [$F(2,180) = 70.6$, $P < 0.001$], and a Time × Group interaction [$F(2,180) = 21.7$, $P < 0.001$].

### 3.7. Influence of verapamil on expression of sensitization

Locomotor activity levels of ethanol groups increased across trials whereas activity levels of saline groups decreased across trials. On the first trial mean (±S.E.M.) activity levels per min for the saline groups were 99.0 (±14), 113.5 (±13), and 91.6 (±9), and on the last trial were 83.1 (±13), 82.3 (±13), and 92.0 (±10). Mean locomotor activity levels for ethanol groups on the first trial were 160.0 (±19), 174.7 (±18), and 167.7 (±15), and on the last trial were 282.4 (±18), 282.9 (±18), and 284.9 (±15). A three-way ANOVA [Group (saline or ethanol) × Verapamil dose × Trial] revealed a main effect of Group [$F(1,90) = 181.5$, $P < 0.001$), a main effect of Trial [$F(7,630) = 22.3$, $P < 0.001$) and a Trial × Group interaction [$F(7,630) = 35.1$, $P < 0.001$].

On the test, verapamil reduced the locomotor stimulant effects of ethanol and the sensitized response, especially at the highest dose, but did not completely prevent expression of sensitization (Fig. 4). These observations were confirmed by a three-way ANOVA in which the main effect of Group [$F(1,86) = 31.0$, $P < 0.001$], Verapamil dose [$F(2,86) = 7.1$, $P < 0.005$], and Time [$F(1,86) = 70.8$, $P < 0.001$] were significant. The Time × Group [$F(1,86) = 8.6$, $P < 0.01$], and Time × Verapamil dose interactions [$F(2,86) = 7.8$, $P < 0.01$] were also significant.

### 3.8. Effects of verapamil on blood ethanol levels

Blood samples were taken immediately after the expression test. Decreases in ethanol levels were observed in groups given verapamil. Mean blood ethanol levels for the saline, low dose and high verapamil dose saline groups were 203.5 (±4), 183.0 (±3), and 176.8 (±4) mg/dl, respectively. Mean blood ethanol levels for ethanol groups given saline, the low and high dose of verapamil were 198.1 (±6), 185.8 (±3), and 171.9 (±5), respectively. A two-way ANOVA (Group × Verapamil dose) only revealed a main effect of Verapamil dose [$F(2,86) = 20.5$, $P < 0.001$]. A Tukey test indicated significant differences in blood ethanol levels between the saline group and both verapamil groups ($P_s < 0.001$).

## 4. Discussion

The present experiments were designed to determine if L-type calcium channel blockers affect behavioral sensitization to ethanol. The calcium channel blockers decreased the locomotor stimulant effects of ethanol on acquisition trials or on the sensitization test indicating that behaviorally active doses were tested. These findings support a previous report that, at similar doses to those used in the current experiments, diltiazem and verapamil decrease ethanol's locomotor stimulant effects [1]. It is unclear why verapamil did not reduce ethanol's stimulant effects on acquisition trials. The same doses of verapamil decreased ethanol's stimulant effects on the expression test. Perhaps decreases would have been observed if longer trials had been used.

All three calcium channel blockers decreased but did not eliminate expression of sensitization suggesting that L-type calcium channels do not play a critical role in this neuroadaptive response. Indeed, it is possible that the effects of nifedipine and verapamil on activity levels and expression of sensitization were secondary to changes in blood ethanol levels. Changes in blood ethanol levels may also account for the effects of diltiazem. Although doses of diltiazem up to 25 mg/kg did not affect blood ethanol levels in a previous experiment, the higher doses that produced behavioral effects may alter ethanol levels.

Only nifedipine blocked acquisition of sensitization. The effects of nifedipine may be explained by the diminished locomotor stimulant response to ethanol on acquisition trials although a stimulant response on trials is not necessary for development of sensitization [4]. Alternatively, nifedipine's ability to decrease blood ethanol levels may account for its ability to block acquisition of sensitization. Verapamil and diltiazem did not alter acquisition of sensitization. Although it is tempting to suggest that sensitization developed because the blockers did not suppress ethanol's stimulant effects, evidence indicates that different neural mechanisms mediate ethanol's stimulant effects and sensitization [14]. Hence, the presence of a stimulant response may not ensure acquisition of sensitization.

Cilnidipine, a mixed L/N type calcium channel blocker has been reported to block acquisition and sensitization to ethanol [2]. In light of the current findings, it is probable that the efficacy of cilnidipine is due to blockade of N-type calcium channels. Although the effects of cilnidipine on blood ethanol levels were not assessed, it did not alter the effects of ethanol on rotarod performance indicating blood ethanol levels were not altered. Moreover, NP078585, a mixed N and T-type calcium channel blocker prevented the locomotor stimulant effects of ethanol in mice without affecting blood ethanol levels [12]. Additional studies assessing the effects of N-type calcium channel blockers on sensitization to ethanol may be valuable.

The inability of L-type calcium channel blockers to alter sensitization to ethanol sharply contrasts with their effects on sensitization to other drugs. Nifedipine, nimodipine and verapamil prevent acquisition and expression of sensitization to opiates and stimulants [8,9,15,20]. These differences suggest that distinct neural mechanisms mediate sensitization to ethanol, stimulants, and opiates.

In summary, at behaviorally active doses the L-type calcium channel blockers failed to completely suppress expression of sensitization. Nifedipine was effective in preventing acquisition of

sensitization however it substantially decreased blood ethanol levels, which may account for its effects. These findings underscore the need to examine the effects of test drugs on blood ethanol levels and suggest that important differences may exist in the neural mechanisms mediating sensitization to ethanol and other addictive drugs.

## Acknowledgements

The author would like to thank Ms. Sharon Koonse for her expert technical assistance. This work was partially supported by NIAAA grant AA012090.

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