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Context-specific tolerance to the ataxic effects of alcohol

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Abstract

Tolerance to alcohol and many other drugs can become conditioned to specific contextual cues present at the time of drug administration. Context-specific tolerance occurs to a variety of alcohol's effects, including changes in hormone levels, body temperature and locomotor activity. The present study investigated whether context-specific tolerance can occur to the ataxic effects of alcohol. Baseline levels of motor coordination were assessed using a tilting plane apparatus. During a 7-day tolerance acquisition phase, subjects received an injection of either alcohol (1.5 g/kg ip) or saline (15 ml/kg ip) in a novel testing room and were then placed in the tilting plane apparatus for a period of 20 min. Approximately 5 h after the first injection, subjects received a second injection in the colony room and were then placed in their home cages. One group of subjects, the *paired* group, received alcohol in the testing room and saline in the colony room. An *unpaired* group received saline in the testing room and alcohol in the colony room. A no alcohol *control* group received saline in both environments. Following the tolerance acquisition phase, all subjects were injected with alcohol (1.5 g/kg ip) and tested for ataxia in the tilting plane apparatus. Subjects in the *paired* group were less ataxic than subjects in the *control* group during all four testing blocks following alcohol administration. In contrast, subjects in the *unpaired* group were less ataxic than the *control* subjects only during the 15-min testing block. Relative to baseline scores, the *paired* group exhibited deficits only during the 5- and 10-min testing blocks, while subjects in the *unpaired* and *control* groups exhibited deficits during all four testing blocks. These data strongly suggest that tolerance to the ataxic effects of alcohol can become conditioned to contextual cues present at the time of alcohol administration.

Keywords: Tolerance; Context; Ataxia; Conditioning; Learning

1. Introduction

Tolerance to alcohol and many other drugs can become conditioned to specific contextual cues that are present at the time of drug administration. Through Pavlovian conditioning, environmental cues that are consistently present during drug exposure become associated with the effects of the drug (Siegel, 1987). As a result, the environmental cues come to elicit conditioned compensatory responses that help minimize the anticipated deviations in homeostasis produced by the drug (Siegel and Larson, 1996; for review, see Woods and Ramsay, 2000).

Context-specific tolerance has been observed for a variety of alcohol-induced behavioral and physiological changes. For instance, Duncan et al. (2000) observed a greater degree of tolerance to the effects of alcohol on locomotor activity in an environment that was previously paired with alcohol than in an environment that was previously paired with saline. McCusker and Brown (1990) observed that subjects given alcohol in a familiar context (i.e., a simulated bar) exhibited smaller cognitive and motor impairments than subjects given alcohol in an unusual context (i.e., an office setting). Seeley et al. (1996) reported that tolerance to the corticosterone-elevating effects of alcohol was disrupted when subjects were moved into a novel room prior to alcohol administration. Similarly, there are a number of reports that suggest that tolerance to alcohol-induced hypothermia is disrupted by movement of subjects to a novel environment, or an environment previously paired with saline, prior to drug injection (Le et al., 1979; Melchior, 1988; Tirelli et al., 1992).

Siegel and Larson (1996) recently provided indirect evidence for context-specific conditioned tolerance to the ataxic effects of alcohol. The authors assessed the impact of

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alcohol on motor coordination using a tilting plane apparatus. After tolerance developed to alcohol-induced ataxia, the authors introduced novel stimuli (white noise and a strobe light) into the testing environment. The novel stimuli disrupted tolerance in the alcohol-treated group, suggesting that such tolerance had become conditioned to cues present in the room during the initial treatment period. Similar results occurred when stimuli present in the room during tolerance development were removed prior to testing (Larson and Siegel, 1998).

The present study was designed to obtain further, more direct, evidence that tolerance to the ataxic effects of alcohol can become conditioned to specific contexts. Baseline levels of motor coordination were assessed using a tilting plane apparatus (see Siegel and Larson, 1996). During a 7-day tolerance acquisition phase, subjects received an injection of either alcohol (1.5 g/kg ip) or saline (15 ml/kg ip) in a novel testing room and were then placed in the tilting plane apparatus for a period of 20 min. No measures of motor coordination were taken during the tolerance acquisition phase. Approximately 5 h after the first injection, subjects received a second injection in the colony room and were immediately placed in their home cage. One group of subjects, the *paired* group, received alcohol in the testing room and saline in the colony room. An *unpaired* group received saline in the testing room and alcohol in the colony room. A *control* group received saline in both environments. Following the tolerance acquisition phase, all subjects were injected with alcohol (1.5 g/kg ip) and were then tested in the tilting plane apparatus. If tolerance to the ataxic effects of alcohol became conditioned to cues present at the time of injection, then subjects in the *paired* group should exhibit smaller motor impairments than subjects in the *unpaired* and *control* groups.

2. Methods

2.1. Subjects

Twenty-seven male Long–Evans hooded rats from Charles River were housed individually in plastic cages in an approved animal colony and maintained on a 12:12-h light/dark cycle (lights on at 7:00 a.m.).

2.2. Apparatus

The tilting plane apparatus consisted of a clear Plexiglas box similar to that used by Siegel and Larson (1996). It was 24 cm high, and the floor was 61 cm long and 20 cm wide. A glass floor insert was placed in the apparatus and wiped clean between each tilt. The box was hinged at one end and could be tilted via a wooden arm protruding from the nonhinged end. A yardstick, leaning against the end of the box lifted by the wooden arm, was used to measure the height at which subjects began to slide down the floor of the box.

2.3. Procedures

Five baseline measurements of motor coordination were taken for all subjects on each of 3 days (D1–D3). The subject was placed in the apparatus facing towards the end of the box from which the wooden arm protruded. The wooden arm was then lifted slowly until the subject began to slide down the floor of the apparatus. The height at which the subject began to slide was measured via the attached yardstick and the procedure was repeated. Slip angles were later calculated using the length of the apparatus and the height at which subjects began to slide.

Baseline scores were used to counterbalance assignment of subjects into three matched groups ($n = 9$, each): *paired*, *unpaired* and *control*. Thus, baseline scores for the three groups were nearly identical [$F(2,24) = 0.12$, $P > .90$].

Following baseline testing, the tilting plane apparatus was moved into a novel laboratory room rich with distal cues. During a 7-day tolerance acquisition period (D4–D11), subjects in all groups were given two injections per day. The first injection took place in the room containing the tilting plane apparatus. Immediately following this injection, subjects were placed inside of the apparatus for a period of 20 min. No slip angle measurements were taken during the tolerance acquisition period. Approximately 5 h after the first injection, subjects were given a second injection in the colony room and were immediately placed in their home cages.

The *paired* group was administered alcohol injections (1.5 g/kg ip) in the testing room and saline injections (15 ml/kg ip) in the colony room. The *unpaired* group received saline injections in the testing room and alcohol in the colony room. The *control* group received saline injections in both environments.

Following the tolerance acquisition phase, all subjects were tested under 1.5-g/kg alcohol on 2 days (D12–D13). Five slip angle measurements were taken in quick succession at each of the following four testing points after alcohol administration: 5-, 10-, 15- and 20-min postinjection.

2.4. Statistical analyses

For each subject, an average slip angle score was calculated from the 3 days of baseline testing. Average scores were also calculated from the 2 days of testing under alcohol during each of the four testing blocks (i.e., 5-, 10-, 15- and 20-min postinjection). To assess whether alcohol disrupted motor coordination, a two-way mixed-design ANOVA (Group × Testing block) was performed to compare scores from baseline and the four alcohol testing blocks for the three groups. One-way ANOVA and Student *t* tests were performed to determine sources of significance in the larger analysis.

3. Results

Alcohol reduced slip angles, and the level of ataxia differed significantly across groups [see Fig. 1; two-way (Group × Testing block) ANOVA: main effect of testing block [$F(2,24) = 5.87$, $P < .01$], Group × Testing block interaction [$F(8,96) = 3.62$, $P < .001$]. Group differences were observed during all four testing blocks following alcohol administration [one-way ANOVA: $F(2,24)$, all P's < .02].

Previous experience with alcohol in the testing room reduced the ataxic effects of alcohol. Subjects in the *paired* group were less ataxic than subjects in the *control* group during all four testing blocks following ethanol administration [$t(16)$, all P's < .01]. In contrast, subjects in the *unpaired* group were less ataxic than subjects in the control group only during the third testing block [i.e., 15-min postinjection; $t(16) = 2.35$, $P < .05$]. Performances of subjects in the *paired* and *unpaired* groups did not differ significantly during any of the four testing blocks [$t(16)$, all P's > .05].

Relative to their baseline scores, subjects in the *paired* group exhibited deficits during the 5- and 10-min testing blocks [$t(8) = 3.46$, $P < .01$ and $t(8) = 2.99$, $P < .05$, respectively] but performed at baseline levels during the 15- and 20-min testing blocks [$t(8) = 2.11$, $P > .05$ and $t(8) = 1.62$, $P > .10$, respectively]. In contrast, subjects in both the *unpaired* and *control* groups were impaired relative to their baseline scores during all four testing blocks following alcohol administration [$t(8)$, all P's < .01].

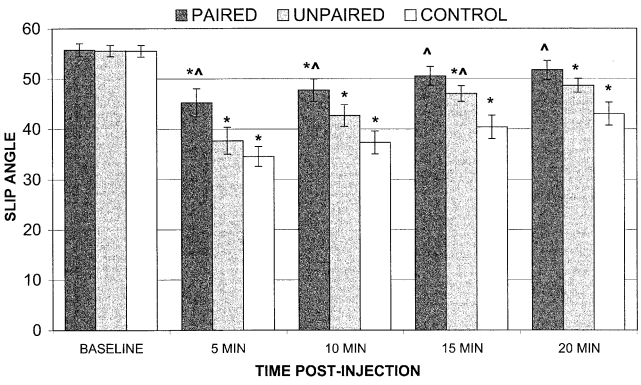

Fig. 1. The effects of 1.5-g/kg alcohol on motor coordination following a 1-week tolerance development phase. Previous experience with alcohol in the testing room diminished the impact of alcohol on performance. Subjects in the *paired* group were less ataxic than subjects in the *control* group during all four testing blocks following alcohol administration, while subjects in the *unpaired* group differed from the *control* group only during the 15-min block. Relative to baseline scores, subjects in the *paired* group exhibited deficits only during the 5- and 10-min blocks, while subjects in the *unpaired* and *control* groups exhibited deficits during all four blocks. * $P < .05$, difference relative to baseline; ^ $P < .05$, difference relative to control group.

4. Discussion

Conditioned context-specific tolerance developed to the ataxic effects of alcohol. Subjects in the *paired* group were less ataxic than subjects in the *control* group during all four testing blocks following alcohol administration. In contrast, subjects in the *unpaired* group were less ataxic that *control* subjects only during the 15-min testing block. Further, relative to baseline scores, the *paired* group exhibited deficits only during the 5- and 10-min testing blocks, while subjects in the *unpaired* and *control* groups exhibited deficits during all four testing blocks. These data strongly suggest that tolerance to the ataxic effects of alcohol can become conditioned to contextual cues present at the time of alcohol administration.

The findings of the present study are in agreement with previous research demonstrating that the repeated pairing of alcohol with contextual cues can lead to tolerance that is maximally expressed when such cues are present. For instance, Le et al. (1979) administered alcohol to subjects in a single environment over many days and recorded core body temperature. While alcohol initially reduced body temperature, tolerance developed to this effect over days. However, such tolerance was disrupted when subjects were moved to a novel environment prior to drug administration. Similarly, Thiele et al. (1998) reported that tolerance developed to alcohol-induced increases in c-Fos levels in the paraventricular nucleus and locus coeruleus when alcohol was repeatedly administered in the same environment. However, this tolerance was partially reversed when subjects were given alcohol in an environment previously paired with saline.

Melchior (1990) reported that context-specific tolerance can actually protect subjects from the lethal effects of alcohol. Mice were given alcohol in the same environment over a period of 4 days. On the fifth day, subjects were given much higher doses of alcohol in either the same environment or a novel environment. The LD_{50} for alcohol was higher for subjects tested in the same, or alcohol paired, environment than in the novel environment. Similar context-specific tolerance has been observed for alcohol's impact on heart rate (Dafters and Anderson, 1982; Staiger and White, 1988; McCaul et al., 1989; McCusker and Brown, 1990), operant responding (Cunningham et al., 1992), skin conductance (McCaul et al., 1989), locomotor activity (Cole et al., 1999; Duncan et al., 2000), circulating hormone levels (Seeley et al., 1996) and cognitive skills (McCusker and Brown, 1990).

The mechanisms underlying the context-specific tolerance observed in the present study are unclear. Research suggests that alcohol produces ataxia in part by disrupting cellular activity in the cerebellum (Dar, 1995). Alcohol alters the firing of cerebellar Purkinje cells (Sinclair et al., 1980; Palmer et al., 1988), and the degree of alteration correlates strongly with the degree of ataxia produced by alcohol (Pearson et al., 1997). Intracerebellar infusion of the

$GABA_A$ inverse agonist, Ro15-4513, partially reverses alcohol-induced ataxia (Dar, 1995) and changes in Purkinje cell firing (Palmer et al., 1988), strongly suggesting GABAergic involvement in the effects of alcohol on motor coordination and cerebellar function. Tolerance begins to develop to alcohol's effects on cerebellar function within minutes of alcohol administration. Pearson et al. (1997) reported that tolerance to alcohol-induced suppression of Purkinje cell firing developed within 5 min of alcohol exposure. Similar acute tolerance has been observed for alcohol's effects of GABA-mediated Cl^- flux in cerebellar microsacs (Allan and Harris, 1987).

Based on the above evidence, it seems possible that context-specific tolerance to alcohol's effects on motor coordination involves the conditioning of mechanisms underlying acute tolerance to cues present during alcohol exposure. During repeated pairings of contextual cues with alcohol-induced disruptions in cerebellar function and motor activity, the organism might learn to predict the ensuing disruptions by the presence of the contextual cues. The organism might then learn to respond to these cues by mobilizing the mechanisms underlying acute neuronal tolerance to protect itself from the anticipated deviations in homeostasis. Such conditioning would minimize alcohol-induced disruptions in homeostasis and, in the event that alcohol is not administered, evoke behavioral changes typically opposite of those normally produced by alcohol (Staiger and White, 1988).

It is important to note that not all conditioned reactions to cues paired with alcohol are compensatory in nature. Evidence suggests that, in some cases, cues reliably paired with alcohol can produce effects in the same direction as those produced by the drug itself. For instance, cues associated with alcohol administration have been shown to increase dopamine levels in the nucleus accumbens, an effect similar to that produced by the drug itself (Philpot and Kirstein, 1998).

In summary, context-specific tolerance developed to the ataxic effects of alcohol. Subjects tested in an environment in which they had previously received alcohol were less ataxic than subjects who had never received alcohol or who had received alcohol in a different context. These findings add to a growing body of evidence that tolerance to many of the effects of alcohol can become conditioned to contextual cues present at the time of alcohol administration.

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