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Volume and Dose Effects of Experimenter-Administered Ethanol Preloads on Ethanol-Seeking and Self-Administration

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Abstract

The present experiment used a behavioral model developed to separate the initial behavior required to obtain access to ethanol (appetitive responding, or lever-presses) from the actual self-administration (consummatory responding, or intake) to test the hypothesis that these responses are under the control of different behavioral/physiological processes, and therefore differentially affected by an ethanol priming dose. In male, Long Evans rats, “preload” volume (0.5 and 2.0 ml) and dose (approximately 10%, 25% and 50% of the total normally consumed in non-treatment sessions translating to 0.1, 0.25 and 0.5 g/kg) of ethanol were varied and administered by the experimenter via oral gavage prior to an operant session. Overall, there were no priming effects, or increases, in ethanol-reinforced responding resulting from the ethanol preloads. The findings showed that the low preload volume produced linear, dose-dependent decreases in both intake and seeking. However, while the high volume also produced a linear dose-dependent decrease in ethanol-seeking, there was a decrease in intake at every dose. That is, ethanol-seeking was insensitive to preload volume, while intake was affected in a dose-dependent manner except at the lowest dose when preload volume did play a role in intake regulation. These findings indicate that “fullness” and pharmacological cues differentially impact the appetitive and consummatory behaviors reinforced by ethanol solutions, with intake being more sensitive to preload volume and seeking being more sensitive to preload pharmacology.

Keywords

appetitive; consummatory; ethanol; seeking; preload; priming

1. INTRODUCTION

Anecdotal and experimental evidence shows that alcohol stimulates appetite in general (Caton et al., 2004; Hetherington et al., 2001; Yeomans et al., 1999), and a first or “priming” drink is thought to increase the likelihood of subsequent drinking. In fact, Jellinek’s (1960) disease model of alcoholism is predicated on this idea that loss of control drinking is primed by the first drink. In 1974, Ludwig and Wikler showed that an ethanol preload dose increased craving in alcoholics. Hodgson et al. (1979) also found that ethanol preloads increased “desire for a drink” and behavioral measures of craving in severe alcoholics, but not in moderate alcoholics. In an early attempt to model alcohol-seeking, Bigelow et al. (1977) found that an ethanol preload increased the amount of time that abstinent alcoholics were willing to ride a stationary bicycle to gain access to more alcohol. These findings have been extended to include social drinkers who demonstrated a dose-dependent increase in desire for alcohol (Kirk & de Wit, 2000; Rose & Duka, 2006), increased alcohol consumption (Hobbs et al., 2005), and an

increased likelihood of choosing alcohol over an alternate reinforcer (Chutuape et al., 1994; de Wit and Chutuape, 1993), following an alcohol prime.

In contrast, animal models generally show that subjects are likely to titrate their alcohol intake in response to a variety of manipulations (Czachowski et al., 2003; Karoly et al., 1978; Meisch & Thompson, 1974; Samson, 1986; Samson et al., 2003a), and therefore self-administered preloads can actually decrease ethanol consumption. For instance, our group (Samson et al., 2002) found that a self-administered alcohol preload in nonselected Long Evans rats decreased subsequent ethanol intake in a manner that was related to pharmacology rather than “fullness” since a water preload of the same volume did not have the same effect. At a relatively high self-administered preload dose (0.44 g/kg consumed in 2 minutes), there was also an attenuation of ethanol-seeking as demonstrated by a failure to complete the response requirement in half of the trials, which also was not observed following the water preload. In the genetically-selected alcohol preferring (P) rat, seeking was also more susceptible than drinking to the effects of a self-administered alcohol preload as measured during single extinction trials showing a long-lasting attenuation of responding that failed to return to baseline over repeated preload tests (Samson et al., 2003b). The effects of experimenter-administered ethanol preloads on subsequent ethanol seeking and consumption have not been investigated. It could be argued that experimenter preload procedures in rats may more closely model human laboratory self-administration procedures since participants are generally given a fixed dose and instructed to consume that dose quickly in a very limited time [e.g., Kirk & DeWit (2000): 0.8g/kg ethanol in 450mls to be consumed in 4 equal portions over 10 min]] unlike the rat self-administration preload models where the subjects controlled the dose and timing of consumption.

In the present study, a behavioral model that procedurally separates seeking from intake was used to distinctly assess these two reinforcer-directed behaviors (e.g., Czachowski & Samson, 1999; Samson et al., 2000). In this paradigm, rats consume pharmacologically relevant amounts of ethanol and the model is sensitive to pharmacological manipulations that specifically affect either the seeking (Czachowski et al., 2001a; Czachowski et al., 2002) or the consumption (Czachowski et al., 2001b) component of the reinforced responding. Moreover, we have recently demonstrated that the seeking response (the extinction session lever-press behavior) in this model is stable over repeated measurements (Samson et al., 2001) and reflects a prior association with the post-ingestive, pharmacological effects of ethanol (Samson et al., 2004). For this experiment, ethanol preload dose and volume were manipulated to assess the differential effects of these characteristics on subsequent appetitive and consummatory responding for ethanol.

2. MATERIALS AND METHODS

2.1 Animals

The subjects were 7 male Long Evans rats obtained from Harlan Sprague-Dawley, Indianapolis, IN. Body weights ranged from 221-245 grams (mean 232 ± 3) at the start of the experiment. Ad libitum access to food and water was maintained except as noted below. The rats were housed individually on a 12 hr light/dark cycle (6:00AM to 6:00PM), and animal care procedures were in accordance with NIH guidelines (Guide for the Care and Use of Laboratory Animals) and approved by the Institutional Animal Care and Use Committee at Brown University.

2.2 Apparatus

Daily sessions were conducted in modular operant chambers (Med-Associates; St. Albans, VT). Each chamber (30cm × 30cm × 24.5cm) was equipped with a houselight, a retractable

lever, and a retractable graduated cylinder tube with rubber stopper and a stainless steel sipper spout with double ball bearings to prevent leakage. The lever was located on the wall opposite to the sipper tube drinking bottle. All chambers were housed in sound attenuated enclosures equipped with exhaust fans that masked external noise. Electrical inputs and outputs of each chamber were controlled using Med-Associates software (Med-Associates, St. Albans, VT).

Ethanol solutions were prepared volume/volume (v/v) in water from 95% (v/v) ethanol. For sucrose/ethanol solutions, the sucrose solution was used as a solute.

2.3 Operant Training and Ethanol Initiation

Upon arrival, subjects were weighed and handled for a minimum of three days. Daily sessions were conducted five days each week, at the same time each day during the lights-on cycle. A modified sucrose-substitution procedure (Samson, 1986) was used to initiate 10% ethanol (10E) as the reinforcer. Subjects were initially trained to press the lever on a fixed-ratio (FR) one schedule that resulted in 15 sec of access to the sipper tube with 10% sucrose in 30-min sessions. Subjects were water-restricted for the initial 2-5 sessions only, after which food and water were available ad lib in the home cage. Over a three-week period, the training/sucrose-fading procedures involved increasing the FR from 1 to 4, and introducing ethanol and increasing the concentration from 2 to 10% (10E) while fading the sucrose out completely. The procedural separation between seeking (lever-pressing) and consumption was then instituted. Following a single response requirement, access to the sipper tube was provided for 20 min. Over four weeks, the response requirement was increased from 4 to 20, and then the response requirement of 20 was maintained for six weeks. To acclimate subjects to the oral gavage procedure, sham gavages (no fluid) were given three times, 2 hours after a session during weeks 5 and 6.

2.4 Gavage Manipulations and Extinction Sessions

All subjects had a single baseline extinction determination. Extinction sessions consisted of 20 min of access to the lever, with no presentation of the sipper tube spout (the 10E was present in sipper to control for scent cues). The gavage testing was then conducted over 7 weeks. All oral gavages were administered 15 min prior to the operant sessions. A sham gavage functioned as a zero dose/zero volume control. The experimental manipulation included two volumes (Low: 0.5ml; High: 2.0ml) and three doses (0.1, 0.25 and 0.5 g/kg). Concentrations, therefore, necessarily varied by animal body weight, and were calculated to balance between a reasonable weight "bin size" (i.e., not a different concentration for every few grams) and whole number concentrations. For example, for the 0.5 ml volume, the 0.25 g/kg ethanol condition used 16 gram weight bins for each whole number concentration (e.g., 434-449: 28%, 450-465: 29%). The three ethanol doses chosen for the experimenter-administered preloads were intended to be approximately 10, 25 and 50% of the total normally consumed in non-treatment sessions translating to 0.1, 0.25 and 0.5 g/kg. This placed the two low doses below those found to be "detectable" using stimulus discrimination procedures, and the high dose in the range shown to be discriminated by rats following oral administration (Hodge et al., 2001; Macenski & Shelton, 2001). For the "fullness" manipulation, the volumes were intended to be so low as to be nearly undetectable (0.5 ml) or noticeable (2.0 ml) but in the range routinely used with this size rat for oral ethanol gavage (Chester et al., 2005; Quartemont et al., 2003).

Operant sessions were conducted five days per week for the duration of the experiment. In any given week, there was a consistent volume/dose gavage (held constant across animals) with an attempt to avoid any order effects of dose (order of volume/dose by week: high/high, low/high, high/low, low/low, high/medium, low/medium). During weeks 1-3 and 5-7 the schedule was: Monday and Thursday - no gavage/reinforced sessions; Tuesday - sham gavage/reinforced session; Wednesday - gavage/reinforced session; Friday - gavage/extinction session. Intake

effects were assessed using data from Tuesdays and Wednesdays. During week 4, no gavages were given and Friday's extinction session followed a sham gavage. Seeking effects were assessed using Week 4 extinction as sham control, and all other Friday extinctions as treatment days.

2.5 Blood Ethanol Concentration (BEC) Determination

BECs were determined after all behavioral testing was complete, in all subjects at 15 minutes after oral gavage for the low and high preload doses at the low and high volumes. Blood samples were collected (100 μ l) from the cut tip of the tail into heparinized capillary tubes while the rats were restrained for a maximum of 2-4 min. Samples were stored sealed on ice during collection, and then immediately centrifuged and a 5 μ l sample of plasma was analyzed using the AM1 Analyser (Analox Instruments, Lunenburg MA). Ethanol concentration is determined with an amperometric oxygen electrode that measures oxygen consumption during the enzymatic oxidation of alcohol to acetaldehyde.

2.6 Data Analyses and Statistics

Total session intakes were determined from the change in fluid volume in the graduated cylinder sipper tube. Ethanol intake (g/kg) was calculated from the intake volume and daily body weight measures. Total lever-presses and licks, as well as a cumulative record of responding and licking were recorded for each session.

Repeated measures analysis of variance (RM ANOVA) was used to assess intake measures over the six sham gavage/reinforced sessions. There was no difference between sessions, so all sham gavage data were collapsed for each subject. Planned comparisons were then made using one-way RM ANOVA within Dose and within Volume for each dependent measure. To determine whether there were interaction effects between Dose and Volume, two-way RM ANOVA was used on the intake and extinction data from the treatment conditions only (the single zero dose/zero volume control was not included as this did not allow for a balanced comparison). Post hoc comparisons were performed using Student-Newman-Keuls method when appropriate. Paired t-tests were used to compare the blood ethanol concentrations between gavage volumes at the low and high doses, as well as intake and extinction before and after sham procedures.

3. RESULTS

3.1 Preload Effects on Seeking Responses

Analysis within volume showed a main effect of treatment on the number of lever press responses (Fig. 1) made during extinction sessions at the low [$F(3,18)=6.3, p<.01$] and high volumes [$F(3,18)=3.4, p<.05$]. In both cases, mean sham responding was greater following sham than the middle and high doses ($p<0.05$). Within each dose, there was a main effect of treatment at the middle [$F(2,12)=7.0, p<0.01$] and high doses [$F(2,12)=7.4, p<0.01$] again with more responding following sham as compared to both volumes. The two-way analysis of both volume and dose showed no effect of either treatment alone and no interaction between volume and dose when examining the six treatment conditions only.

Paired t-test confirmed that the oral gavage procedure alone had no effect on seeking, with average sham extinction of 78.3 (± 13.2) (as shown in Fig. 1) and average baseline extinction prior to any gavage treatments of 92.0 (± 11.4). Analyses within volume and dose confirmed that there were no effects of ethanol preload on the latency to make the first lever-press response.

3.2 Preload Effects on Intake Responses

Analysis within volume showed a main effect of treatment on ethanol intake (Fig. 2) for both low [$F(3,18)=5.7, p<.01$] and high volumes [$F(3,18)=13.3, p<.01$]. Within the low volume, mean intake in the sham condition was significantly higher than in the high dose condition ($p<0.05$). Within the high volume, mean intake in the sham condition was greater than in the low and high dose conditions ($p<0.05$), but did not differ from intake at the middle dose. Analyses within each dose also showed a main effect of treatment at each dose (low [$F(2,12)=15.9, p<0.01$], middle [$F(2,12)=4.0, p<0.05$] and high [$F(2,12)=21.2, p<0.01$] doses). At all doses, mean sham intake was significantly greater than in the high volume conditions ($p<0.05$). Mean sham intake was significantly higher than the low volume condition at the high dose only ($p<0.05$). The two-way analysis of both volume and dose showed an effect of volume alone [$F(1,12)=13.1, p<0.05$] (high volume lower intake than low volume) and dose alone [$F(2,12)=4.1, p<0.05$] (high dose lower intake than the medium dose only) but no interaction between volume and dose when examining the six treatment conditions.

Paired t-test confirmed that the oral gavage procedure alone had no effect on intake, with average sham intake of $0.73 (\pm 0.03)$ (as shown in Fig. 2) and average intake from a representative non-pretreatment session on the same day of the week prior to any gavage habituations or treatments of $0.79 \text{ g/kg} (\pm 0.09)$.

3.3 BEC

Concentration of ethanol necessarily varied at a given dose for the different preload volumes, therefore confirmation of similar BECs would rule this out as a contributing factor in any observed behavioral effects. Mean ($\pm$ SEM) BEC (mg%) for the low (0.1 g/kg) dose preload was $23.9 (\pm 0.4)$ at the Low Volume and $23.1 (\pm 1.3)$ at the High Volume. At the high (0.5 g/kg) ethanol preload dose, it was $53.5 (\pm 6.4)$ at the Low Volume and $49.8 (\pm 5.2)$ at the High Volume. Paired t-test confirmed that there were no differences in BEC at a given volume.

4. DISCUSSION

Ethanol-seeking was dose-dependently attenuated by an experimenter-administered ethanol preload regardless of preload volume, suggesting that regulation of this response was related to the pharmacological effects of ethanol. Importantly, there were no effects of the ethanol preload on latency to press the lever (i.e., seeking attenuation was not due to general motor impairment) and blood ethanol concentrations (BECs) were equivalent between different volumes at the same given dose (i.e., different blood alcohol levels could not have played a role if there were differences in responding at different preload volumes).

Intake regulation, on the other hand, seemed to be affected primarily by volume, or “fullness” versus dose or “pharmacology”, since the high volume preloads decreased intake regardless of dose. In the low volume conditions, there was a tendency to titrate intake by decreasing total consumption to compensate for the gavage dose given. The titration of ethanol intake has been seen previously following a variety of manipulations, including varying the ethanol concentration for self-administration of ethanol in the rat (Czachowski et al., 2003; Samson et al., 2003a) and changing dose/injection or administering intravenous ethanol preloads in monkeys (Karoly et al., 1978). Modest but not robust compensation for ethanol intake has been observed with the use of an open gastric fistula (i.e., “sham drinking” where fluid is redirected from reaching the stomach) in both non-selected (Rowland & Barnett, 1992) and alcohol-preferring P rats (Rowland & Morian, 1994), also providing evidence for a tendency to attempt to titrate but an absence of strict pharmacological regulation of ethanol drinking as seen in this study. In the present experiment, the high volume gavage conditions seemed to provide a satiety signal that decreased subsequent ethanol consumption, even though the 2ml gavage is smaller

than that frequently used in intragastric gavage administration of ethanol in rats of this size (e.g., Chester et al., 2005; Quartemont et al., 2003). Interestingly, the high volume/LOW dose gavage resulted in one of the lowest amounts of subsequent ethanol intake, perhaps because the internal cue produced by this condition was fullness in the absence of any pharmacological effects. As noted above, this finding could not have been due to differences in BEC produced by different preload volumes at the low dose, since BECs were equivalent. The high volume/high dose condition did seem to result in drinking at a level that suggested titration of dose, with the total gavage-plus-intake equaling approximately intake alone on a non-gavage day.

No priming effects were observed following any of the experimenter-administered reinforcer gavages. That is, no increases in ethanol-reinforced behaviors resulted from the ethanol preloads. These findings are consistent with those previously observed using self-administered ethanol preloads in both Long Evans (Samson et al., 2002) and alcohol-preferring (P) rats (Samson et al., 2003b). The attenuation of ethanol-reinforced lever-press responding is also somewhat consistent with previous studies using reinstatement models. In general, both self-administered (Samson & Chappell, 2002) and experimenter administered ethanol preloads (Le et al., 1998) produce very low levels of response reinstatement following extinction as compared to other drugs of abuse (e.g., Chiamulera et al., 1996; de Wit and Stewart, 1981; 1983), and compared to stress-induced relapse-like responding (Le et al., 1998). Therefore it appears that having ethanol on board does not promote subsequent ethanol-seeking behavior in rats in both models.

The preload-induced decreases in seeking and intake are not consistent with the literature in the human population, however. Alcoholics show increased craving and intake following an alcohol prime (Bigelow et al., 1977; Hodgson et al., 1979; Ludwig & Wikler, 1974). It should be noted, though, that the present behavioral paradigm does not address dependence or model alcoholics, but rather addresses alcohol reinforcement in daily, “binge-like”, self-administered doses in nondependent animals. Response reinstatement models also generally do not use alcohol-dependent rats (Samson & Chappell, 2002; Le et al., 1998). On the other hand, studies assessing nondependent humans do suggest that alcohol preloads in the dose range used in rats increase craving and alcohol consumption (Chutuape et al., 1994; de Wit & Chutuape, 1993; Hobbs et al., 2005; Rose & Duka, 2006). More recent work (Kirk & de Wit, 2000) qualified these findings somewhat by showing that only a relatively high preload (0.8 g/kg) increased desire to drink, and this high dose increased choice for alcohol only in a subset of subjects that reported the greatest positive mood effects from ethanol. Importantly, the nondependent subjects in these studies generally have a history of moderate alcohol consumption. For example, Kirk and de Wit (2000) had inclusion criteria that necessitated an average of a minimum of six drinks per week and at least three on one occasion per week. Therefore, it may be that the pharmacological effects of ethanol interact with complex mood and/or expectancy effects to generate the alcohol preload-induced craving seen in the human laboratory studies. These effects are not modeled in the rodent experimental paradigms, which may account for the lack of priming effects of ethanol preloads on seeking and intake behaviors.

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Fig. 1.

Mean ($\pm$ SEM) number of lever-press responses during the 20-min extinction sessions (no ethanol made available) following either the sham gavage or the ethanol preloads (administered 15 min prior to the session) that varied by volume (low volume: lighter bars; high volume: darker bars) and dose as indicated. Asterisks indicate significant difference from sham gavage when analyzed within both volume and dose.

Fig. 2.

Mean ($\pm$ SEM) ethanol intake (g/kg) in reinforced sessions (response requirement of 20) following either the sham gavage or the ethanol preloads (administered 15 min prior to the session) that varied by volume (low volume: lighter bars; high volume: darker bars) and dose as indicated. Asterisks indicate significant difference from sham gavage when analyzed within both volume and dose; plus sign indicates significant difference from sham when analyzed within dose only.