

An analysis of the anxiolytic effects of ethanol on consummatory successive negative contrast*

Un análisis de los efectos ansiolíticos del etanol sobre el contraste negativo sucesivo consumatorio

GISELLE V. KAMENETZKY, ALBA E. MUSTACA,

Instituto de Investigaciones Médicas Lanari (CONICET) Universidad de Buenos Aires, Argentina

MAURICIO R. PAPINI**

Texas Christian University, USA

Abstract

The anxiolytic properties of ethanol (1 g/kg, 15% dose, i.p.) were studied in two experiments with rats involving incentive downshifts from a 32% to a 4% sucrose solution. In Experiment 1, alcohol administration before a downshift from 32% to 4% sucrose prevented the development of consummatory suppression (consummatory successive negative contrast, cSNC). In Experiment 2, ethanol prevented the attenuating effects of partial reinforcement (random sequence of 32% sucrose and nothing) on cSNC, causing a retardation of recovery from contrast. These effects of ethanol on cSNC are analogous to those described for the benzodiazepine anxiolytic chlordiazepoxide, suggesting that at least some of its anxiolytic effects are mediated by the same mechanisms.

Key words: incentive downshift; ethanol; consummatory successive negative contrast; rats.

Resumen

Las propiedades ansiolíticas del etanol (1 g/kg, dosis de 15% intraperitoneal) fueron estudiadas en dos experimentos con ratas que fueron expuestas a una disminución sorpresiva del incentivo, una solución azucarada, del 32% al 4%. En el Experimento 1, la administración del alcohol antes del cambio negativo de 32% a 4% previno el desarrollo de la supresión consumatoria (contraste sucesivo negativo consumatorio, CSNc). En el experimento 2, el etanol previno los efectos atenuantes del reforzamiento parcial (consistente en una secuencia aleatoria de solución azucarada al 32% o agua sin azúcar) sobre el CSNc, causando un retardo en la recuperación del contraste. Estos efectos del etanol sobre el CSNc son análogos a aquellos descritos para la benzodiazepina ansiolítica clordiazepóxido, sugiriendo que al menos sus efectos ansiolíticos están mediados por el mismo mecanismo.

Palabras clave: disminución del incentivo; etanol; contraste sucesivo negativo consumatorio; ratas.

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** Correspondence concerning this paper may be addressed to Alba E. Mustaca, Laboratorio de Psicología Experimental y Aplicada, Instituto de Investigaciones Médicas Lanari, Av. Combatientes de Malvinas 3150, 1426 – Buenos Aires, Argentina (E-mail: mustaca@psi.uba.ar), or to Mauricio Papini, Department of Psychology, Texas Christian University: Box 298920, Fort Worth, TX 76129, USA. E-mail: m.papini@tcu.edu.

Introduction

Consummatory successive negative contrast (cSNC) is induced by a surprising downshift in the magnitude of an appetitive reinforcer. In a typical experiment (see Flaherty, 1996), rats receive training during 15 daily trials, each one allowing animals 5 min of access to a sucrose solution. For the downshifted condition, trial 1-10 are paired with 32% sucrose, whereas trials 11-15 with 4% sucrose; for the unshifted controls, all trials are paired with 4% sucrose. cSNC occurs when the downshifted group exhibits a sharp suppression of consummatory behavior on trial 11, from which it recovers gradually during the following 4 trials until it exhibits a behavior similar to that of the unshifted controls. Evidence indicates that incentive downshift triggers an emotional response that may be referred to as frustration (Amsel, 1992). For example, posttrial 11 injections of corticosterone enhance the cSNC effect (Bentosela, Ruetti, Muzio, Mustaca, & Papini, 2006). Because corticosterone is a well-known marker of emotional stress that enhances aversive memories in fear conditioning situations (McGaugh, 2000), this result is consistent with the hypothesis that incentive downshift triggers a frustrative response. Plasma levels of corticosterone are elevated before and after trial 12 (Flaherty, Becker, & Pohorecky, 1985; Mitchell & Flaherty, 1998), suggesting again that the downshift experience of trial 11 was aversive and that anticipation of incentive downshift in trial 12 triggers a frustrative response. Furthermore, the administration of benzodiazepine anxiolytics (Flaherty & Rowan, 1989; Flaherty, Grigson, & Rowan, 1986; Mustaca, Bentosela, & Papini, 2000) and of some opioid agonists (Rowan & Flaherty, 1987; Wood, Daniel, & Papini, 2005) reduce the size of the cSNC effect. Natural "anxiolytics," such as the opportunity to engage in sexual behavior and ejaculation before being exposed to incentive downshift, also diminished the size of the cSNC effect (Freidin, Kamenetzky, & Mustaca, 2005).

Ethanol also has anxiolytic effects on the cSNC situation. For example, the administration of 0.75 and 1 g/kg of a 15% ethanol solution before trial 12 reduced the magnitude of the cSNC effect

(Becker & Flaherty, 1982, 1983). With higher or lower doses, the anxiolytic effects disappeared. This effect was also not present when ethanol was administered before trial 11, a dissociation also reported for the benzodiazepine anxiolytic chlor-diazepoxide (CDP). The anxiolytic effects of CDP are observed when administered before trial 12, but not before trial 11 (Flaherty & Rowan, 1989; Flaherty et al., 1986). Interestingly, ethanol and CDP have an additive effect on cSNC; thus, marginally effective doses of these two drugs become effective when administered together (Becker & Flaherty, 1983). Furthermore, the reduction of cSNC by ethanol treatment can be reversed by the coadministration of drugs that interfere with the γ -aminobutyric acid (GABA) receptor, including the GABA antagonist picrotoxin (Becker & Anton, 1990), and the partial inverse agonist Ro 15-4513 (Becker & Hale, 1991).

The anxiolytic properties of ethanol are further explored here in two different situations: repeated downshifts (Experiment 1) and partial reinforcement (Experiment 2).

Experiment 1

Although CDP fails to reduce the size of the cSNC effect when administered before the first postshift trial, such an effect can be induced if rats are downshifted more than once. In one experiment involving eight cycles in each of which rats received 3 trials with 32% sucrose and 2 trials with 4% sucrose, CDP effectively reduced cSNC in the first postshift trial after four downshifts and it completely eliminated the effect after five or more downshifts (Flaherty, Clarke, & Coppotelli, 1996). Similar, but somewhat stronger reducing effects of ethanol were observed in free-fed rats (Flaherty, Coppotelli, & Potaki, 1996). Experiment 1 was thus designed to determine whether repeated incentive downshifts would endow ethanol with the ability to reduce cSNC during the first trial. To avoid the potential confounding of ethanol effects with downshift experience beyond that of the first downshifted trial, rats were never exposed to the 4% sucrose solution for more than one trial in a row. Moreover, the ethanol-saline manipulation was im-

plemented as a within-subject factor to increase the sensitivity of the design to detect ethanol effects. Finally, downshifts were implemented early in training so that the effects of ethanol could be related to the emergence of cSNC.

Method

Subjects. The subjects were 14 adults Wistar rats, 4 males and 10 females, all experimentally naïve and bred at the Instituto de Investigaciones Médicas Lanari, Universidad de Buenos Aires. There are evidences that sex differences may not exist in SNC in consummatory behavior (Flaherty, 1996). Besides, ethanol have similar anxiolytic effects in male and females (Wilson et. Al, 2004). Thus, males and females were included in this research.

Ad libitum weights varied between 314-367 g (males) and 202-230 g (females). Animals were maintained in a colony kept under a 12:12 h light:dark cycle (lights on at 06:00 h), and at a constant temperature (23 °C). Animals had free access to water throughout the experiment. Ten days before the start of this experiment, rats were transferred to individual wire-bottom cages and deprived of food to an 85% of their ad lib weight. A constant deprivation level was maintained by posttrial feeding, not less than 20 min after the end of each trial.

Apparatus. Animals received consummatory training in three conditioning boxes (MED Associates, Vermont, USA), each measuring 29.2x24.1x21 cm (LxWxH). The floor was made of aluminum bars measuring 0.4 cm in diameter and spaced apart 1.1 cm (from center to center). On one of the lateral walls there was a 5x5 cm cubicle, 3.5 cm in depth, and located 10 cm above the floor. The sipper tube was inserted into this cubicle from outside of the box, protruding approximately 2 cm inside the cubicle. Rats had to insert the head into this cubicle to reach the sipper tube from which they could drink either a 32% (or 4%) sucrose solution (w/w), prepared by mixing 32 g (or 4 g) of commercial sugar for every 68 g (or 96 g) of tap water. Goal-tracking time (in 0.01 s units) was measured by a computer that registered the cumulative amount of time a photocell located in front of the drinking tube was activated during the trial. Each box was

enclosed in a sound- and light-attenuating cubicle equipped with a source of white noise and diffuse house light.

Procedure. Pairs of rats matched for weight and sex were randomly assigned one of two groups ($n = 7$), depending on the solution delivered during training trials, either 32% or 4% sucrose solution. A day before the start of training, rats were exposed to the sucrose solution during 30 min in their home cages. Each rat received exposure to the concentration that corresponded to the training trials (either 32% or 4% sucrose). This pretraining exposure was aimed at reducing taste neophobia. Training started the next day and lasted 18 daily trials, each involving 5 min of access to the solution starting from the first disruption of the photocell located by the sipper tube. In each trial, the animal was introduced into the conditioning box while the house light was already on. At the end of the trial, after 5 min of access to the sipper tube, the house light was turned off and the animal carried back to its home cage. Starting on trial 4, both groups were exposed to the 4% solution every other day in test trials. All test trials involved a downshift for rats in Group 32-4, but not for rats in Group 4-4. Rats received the training solution, either 32% or 4% sucrose, in the intervening trials. Before all test trials, rats were injected with either 15% ethanol (1 g/kg, i.p.) or with an equal-volume injection of isotonic saline, 10 min before the start of the trial. Four animals in each group started the sequence with ethanol and thereafter alternated with saline every other day; the remaining three rats started with saline and alternated thereafter with ethanol. No injections were administered before training trials. There were a total of 4 ethanol and 4 saline trials for each animal.

The main dependent variable was goal tracking time (0.01 s), defined as the cumulative amount of time per trial during which the photocell located by the sipper tube was activated (maximum: 5 min). Previous research showed consistent and significant positive correlations between goal tracking time and the amount of fluid consumed under the same conditions used in the current experiments (Mustaca, Freidin, & Papini, 2002). Furthermore, goal tracking time has been extensively used in

several labs and has been shown to produce results similar to those of other dependent variables (e.g., Papini, Mustaca, & Bitterman, 1988; Riley & Dunlap, 1979; Wood et al., 2005). Data were subjected to conventional analysis of variance. Fisher's LSD tests were used to assess pairwise effects with the appropriate error term. All statistics were computed with SPSS and with the alpha value set at the 0.05 level.

Results and Discussion

The main results of this experiment are presented in Figure 1. The effects of ethanol vs. saline were assessed in the same subjects. The difference between the downshifted 32-4 group and the unshifted 4-4 control was greater in the 4% trials preceded by a saline injection than in the trials preceded by ethanol administration. Furthermore, in the saline condition and as indicated by the variability around the mean, the differences between the groups was weaker in the first two trials than it was in the last two. Similar performance in the initial two downshift trials across groups probably reflects limited amount of training with the 32% sucrose solution. These results were supported by an analysis of variance including Contrast (32%, 4%), Drug (ethanol, saline), and Trials as factors, with the last two being repeated-measures factors. The reduction of contrast by ethanol administration was detected in terms of a significant trial by drug interaction, $F(3, 30) = 4.43, p < 0.02$. There was also a significant contrast by drug interaction, $F(3, 30) = 3.75, p < 0.05$, that detected higher goal tracking times in Group 32-4 for ethanol trials than for saline trials. There was also a significant trial effect, $F(3, 30) = 4.82, p < 0.008$. The triple interaction fell short of significance, $F(9, 30) = 2.19, p = 0.052$, but the other factors were clearly nonsignificant, $F_s < 1.85, p_s > 0.20$. Individual analyses for the group difference in each trial indicated that Groups 32-4 and 4-4 did not differ significantly in any of the four ethanol trials, $F_s(1, 12) < 3.72, p_s > 0.07$, but while there were no differences for the first two trials in the saline condition, $F_s(1, 12) < 3.17, p_s > 0.10$, the group difference was significant for the last two saline trials, $F_s(1, 12) > 9.60, p_s < 0.01$.

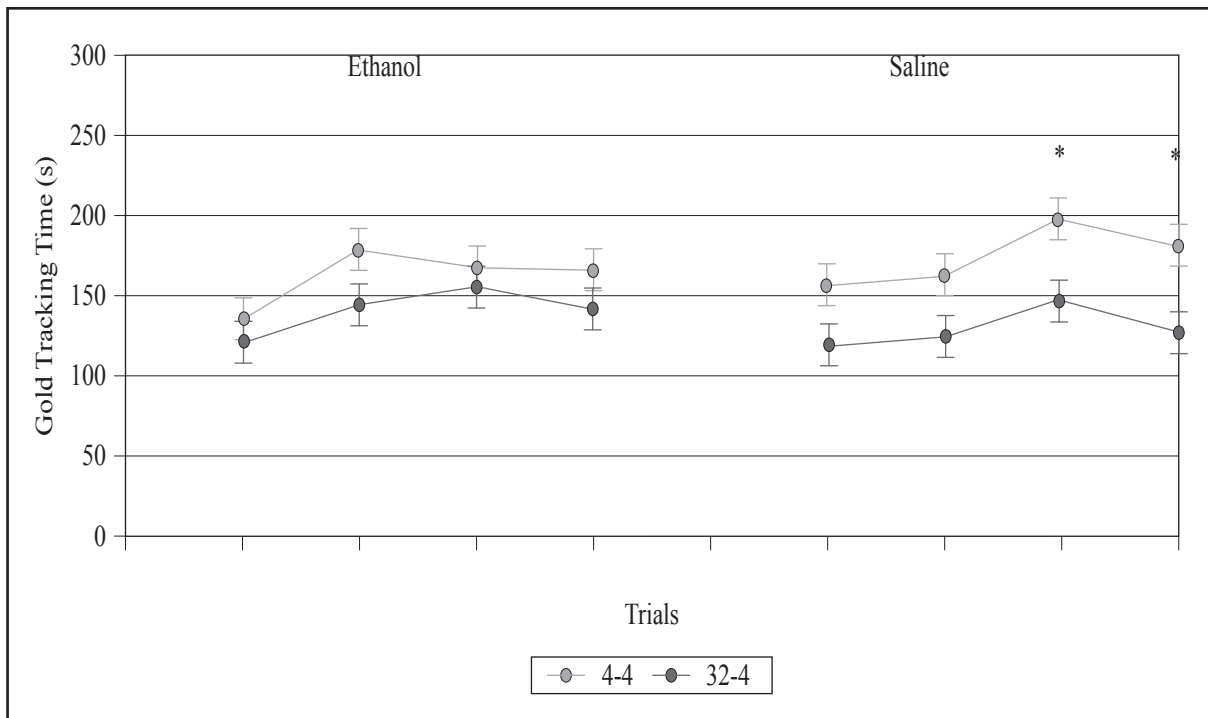
Experiment 2

The random intermixing of trials in which rats have access to the 32% sucrose solution and trials in which rats have access to water attenuates the cSNC effect when rats are finally downshifted to a 4% solution (Pellegrini, Muzio, Mustaca, & Papini, 2004; Wood et al., 2005). This is analogous to the effects of partial reinforcement training on instrumental SNC (e.g., Ison, Glass, & Daly, 1969). Interestingly, treatment with CDP (5 mg/kg) before each N trial during the preshift phase eliminates the reducing effects of partial reinforcement on cSNC (Pellegrini et al., 2004). Experiment 2 was designed to determine whether the administration of ethanol before each N trial of a partial reinforcement preshift phase also eliminates the enhancement of recovery after incentive downshift.

Method

Subjects and Apparatus. The subjects were 30 adult Wistar rats, 12 males and 18 females, all experimentally naïve. The average ad lib weights varied between 208-322 g for males, and between 167-255 g for females. The source, housing, deprivation, and other maintenance conditions were as described in Experiment 1. The same conditioning boxes described previously were used for this experiment.

Procedure. Quadruplets of rats matched for weight and sex were randomly assigned to one of four groups. Rats were exposed to the 32% sucrose solution for 30 min in their home cages a day before the start of training. All the groups received 30 daily trials of training under the same general conditions as those described in the previous experiment, except for the following. For *Group P/E* ($n = 8$), half of trials 1 to 20 were reinforced (i.e., access to the 32% solution), and the rest were nonreinforced (i.e., access to an empty tube). This procedure is called "partial reinforcement" to indicate that the sucrose solution was available on a random half of the trials. The sequence of reinforced (R) and nonreinforced (N) trials was the same for all the rats in both PR groups: RNRNRNRNRNRNRNRNRNRNR. Ten min before each N trial, rats in this group were injected with 15% ethanol (1 g/kg, i.p.). *Group P/S* ($n = 8$) received the same treatment as



Fuente: elaboración propia

Figure 1. Goal tracking times for groups exposed to a 32-4 downshift in the availability of a sucrose solution, or to 4-4 unshifted conditions. The same animals within each concentration group were injected with either 15% ethanol (1 g/kg, i.p.) or an equal volume of isotonic saline. Ethanol and saline trials alternated, with the sequence counterbalance within each group. All the data shown in this figure were collected in trials with access to the 4% solution. Means and SEMs are shown in this figure. Stars denote significant pairwise differences, $p < 0.01$. The present results confirm that the effects of ethanol on cSNC resemble closely the effects of CDP under analogous training conditions. In particular, the present training procedure involving an alternation of 32% and 4% sucrose trials (and thus a single downshifted trial in a row), resulted in the development of a cSNC after about three such downshifts and after a saline injection. In addition, ethanol prevented the emergence of a difference in consummatory performance between the downshifted and unshifted groups, disrupting the cSNC effect during the final two trials. The absence of an ethanol effect on consummatory behavior during the initial two downshifts, when there was also no evidence of cSNC, suggests that the effects of ethanol are specific to a downshift that involves contrast, not just to any downshift.

described for the previous group, except 10 min before each N trial these rats were injected with isotonic saline (equal volume, i.p.). Groups C/E ($n = 7$) and C/S ($n = 7$) were treated identically to the previous two groups, except that each of trials 1 to 20 involved access to the 32% sucrose solution (called “continuous reinforcement” in reference to the availability of the sucrose solution in every trial). Rats in these two groups were injected with either ethanol or saline before the trials that corresponded to the N trials in the partially reinforced groups. In trials 21 to 30, all the rats were downshifted to the

4% solution. No injections were administered during these postshift trials. Other procedural aspects were the same as in Experiment 1.

Results and Discussion

The main results of this experiment are presented in Figure 2. As expected based on previous results (Pellegrini et al., 2004; Wood et al., 2005), N trials resulted in a sharp decline in goal tracking times for the two groups exposed to the partial reinforcement schedule. The decline on N trials was consistently greater for Group P/E than for Group P/S, but there

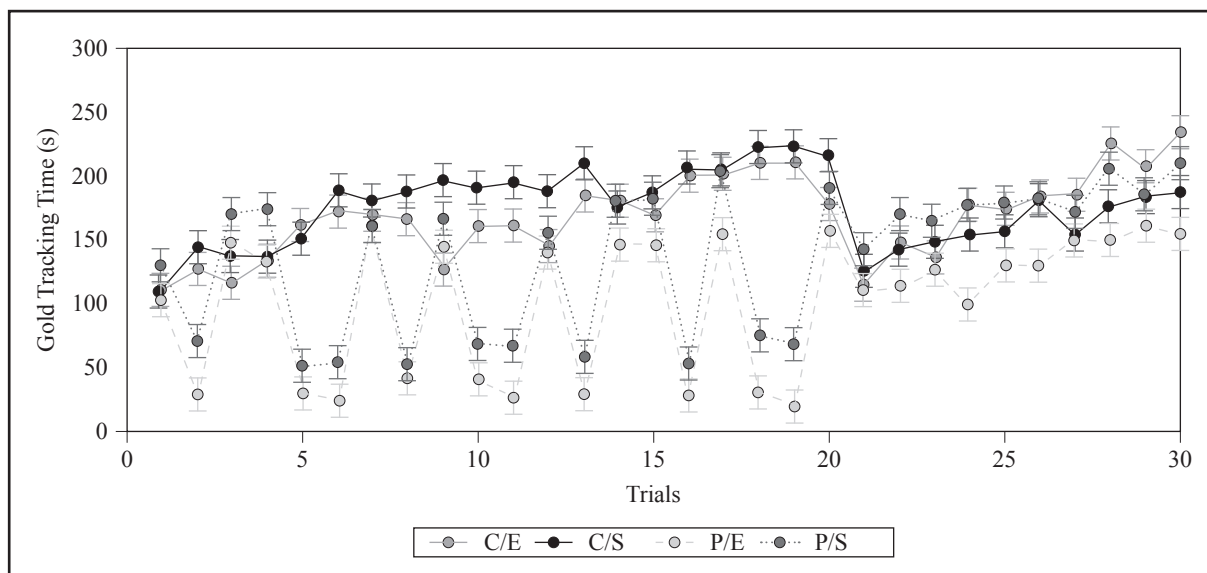
was also a tendency for Group C/E to score below Group C/S. Ethanol, thus, tended to reduce contact with the sipper tube. On postshift trials, however, Group P/E exhibited the slowest recovery of the four, consistently remaining at the bottom of the scores throughout the entire postshift phase.

The statistical analyses provide confirmation for these conclusions. A Schedule (P, C) by Drug (ethanol, saline) by Trial analysis for the 10 R trials of the preshift phase indicated a significant triple interaction, $F(9, 234) = 2.40, p < 0.02$, and a significant schedule by trial interaction, $F(9, 234) = 3.36, p < 0.002$. These interactions capture the generally lower level of consummatory responding in the groups trained under partial reinforcement and also in animals injected with ethanol before N trials. The latter effect was evident despite the fact that this analysis dealt only with R trials. A lower performance for ethanol-injected rats was also indicated by a significant main effect of drug, $F(1, 26) = 5.76, p < 0.03$. There was also a significant increase across trials, $F(9, 234) = 19.24, p < 0.001$,

but other effects failed to reach a significant level, $F_s < 1.35, p_s > 0.20$.

A similar Schedule by Drug by Trial analysis was computed for the 10 N trials. In this case, there was a large and significant difference between the partial and continuous groups, $F(1, 26) = 281.79, p < 0.001$, as is plainly obvious in Figure 2. This difference increased across trials, as shown by a significant drug by trial interaction, $F(9, 234) = 7.69, p < 0.001$. Ethanol also caused a significant reduction in consummatory behavior, $F(1, 26) = 7.60, p < 0.02$, but this effect was not differential across partial and continuous groups, as shown by a nonsignificant schedule by drug interaction, $F < 1$, as well as by negligible effects for the trial by drug and for the schedule by trial by drug interactions, $F_s < 1$.

A Schedule by Drug by Trial analysis was also calculated over the 10 postshift trials, with the following results. The lower performance of Group P/E compared to the rest was captured by a significant schedule by drug interaction, $F(1, 26) = 12.25$,



Fuente: elaboración propia

Figure 2. Goal tracking times for groups receiving either 50% partial reinforcement (access to 32% sucrose randomly intermixed with access to an empty sipper tube) or continuous reinforcement (always access to 32% sucrose). All groups received injections (either ethanol or saline) 10 min before nonreinforced trials in Groups P/E and P/S. Means and SEMs are shown in this figure.

$p < 0.003$. Also significant were the schedule by trial, drug by trial, and schedule by drug by trial interactions, $F_s(9, 234) > 1.95$, $ps < 0.05$, as well as the recovery from incentive downshift, $F(9, 234) = 29.13$, $p < 0.001$. Only the main effects of schedule and of drug failed to achieve significance, $F_s(1, 26) < 2.71$, $ps > 0.11$.

Separate analysis of Groups P/S and C/S for the 10 postshift trials failed to detect an attenuating effect of partial reinforcement on recovery. There was neither a schedule by trial effect, nor a main effect of schedule, $F_s < 2.18$, $ps > 0.16$. Recovery across trials was significant, $F(9, 117) = 9.31$, $p < 0.001$. However, the early consummatory performance of Group P/S was significantly higher than that of Group C/S. Thus, a Schedule by Trial analysis for the initial 5 postshift trials indicated a significant schedule effect, $F(1, 13) = 5.00$, $p < 0.05$, as well as a recovery effect, $F(4, 52) = 4.64$, $p < 0.004$. The schedule by trial interaction was nonsignificant, $F < 1$. Thus, although not strong, there was some evidence that partial reinforcement attenuated the decremental effect of incentive downshift on consummatory behavior. A Schedule by Trial analysis for the 10 postshift trials of the ethanol groups indicated that the scores in these groups diverged significantly across trials, $F(9, 117) = 5.78$, $p < 0.001$. Moreover, Group C/E performed significantly above Group P/E, $F(1, 13) = 10.91$, $p < 0.007$, and the recovery across trials was also significant, $F(9, 117) = 24.34$, $p < 0.001$. These three factors were also significant when only the initial five trials were included in the analysis, $F_s > 6.70$, $ps < 0.02$.

Like CDP in analogous experiments (e.g., Pellegrini et al., 2004), ethanol disrupted the attenuating effects of partial reinforcement on incentive downshift. However, unlike CDP, ethanol caused a more extensive disruption of the recovery process, leading Group P/E (but not Group C/E) to a significantly slower recovery process. The differential effect of ethanol on recovery after partial vs. continuous reinforcement treatment, as indicated by the significant schedule by drug by trial triple interaction pointed out above, indicates that it was not just ethanol administration that affected recovery because Group C/E showed no effect compared to

the saline controls. Thus, it is the joint effects of ethanol and nonreinforcement that led to a retarded recovery during postshift trials.

General Discussion

Ethanol attenuated cSNC during the only downshift trial, but only after several 32-4 downshift episodes and also reversed the attenuating effects of partial reinforcement on cSNC. Both of these effects had been previously demonstrated in the cSNC situation with the benzodiazepine anxiolytic CDP (Flaherty, Clarke, & Coppotelli, 1996; Pellegrini et al., 2004). These results contribute to the view that ethanol's anxiolytic effects are mediated by activation of the GABA receptor complex.

It had previously been established that ethanol attenuated cSNC, having an effect analogous to that of more selective anxiolytics such as CDP (Becker & Flaherty, 1982, 1983). As Flaherty (1996) pointed out, the attenuating effects of ethanol and CDP on cSNC appeared to be mediated by the same mechanism, namely, through their action on the GABA-benzodiazepine receptor complex. In one experiment (Becker & Anton, 1990), the coadministration of ethanol (1 g/kg) and picrotoxin (2 mg/kg), an indirect GABA antagonist, neutralized the attenuating effects of ethanol alone on cSNC (see also Becker & Hale, 1991). GABAergic compounds also affect the ability of ethanol to modulate behavior in situations inducing conflict through the concurrent administration of food and electric shock (Koob et al., 1989; Liljequist & Engel, 1982). For example, rats trained to lever press for food and switched to a situation in which each lever press produces both food and electric shock (i.e., approach-avoidance conflict) show response suppression. Ethanol alleviates suppression in this situation, but isopropyl-bicyclopophosphate, a drug that binds to the picrotoxin site of the GABA receptor complex, reversed the effects of ethanol on punished responding in a dose-dependent manner. Thus, behavioral evidence from situations involving the conditioning of both fear and frustration provide convergent information that at least some of the anxiolytic effects of ethanol may be mediated by its ability to activate the GABA receptor.

An aspect of the present results inconsistent with this general conclusion is the relatively strong effect of ethanol treatment on recovery from incentive downshift observed in Experiment 2. Ethanol administered before nonreinforced preshift trials subsequently impaired recovery from a 32-4 downshift. Because ethanol did not have a similar effect when administered to a group exposed always to the 32% solution during preshift trials, the effect results from a drug-contrast interaction. If the anxiolytic effects of ethanol cancelled out the effects of N trials, thus making the nominal partial reinforcement schedule more like a continuous reinforcement schedule (as it was argued for CDP; Pellegrini et al., 2004), then one could expect a recovery similar to that of Group C/S, but not one that is even slower. The reason is that Group P/E has half the number of R trials than Group C/S and, therefore, its recovery should, if anything, be faster, not slower (see Pellegrini et

al., 2004). The apparent inconsistency between the results of Experiment 2 with ethanol and those reported by Pellegrini et al. (2004) with CDP may simply reflect the use of nonequivalent doses for these two drugs. In the CDP experiment, a 5 mg/kg dose was used, but larger doses have been found to also reduce cSNC, including 8 and 10 mg/kg (see Flaherty, 1996). It is possible that a larger dose of CDP in a partial reinforcement situation like that used in Experiment 2 may retard recovery in a manner similar to that observed in Experiment 2 with ethanol. Vice versa, a lower dose of ethanol may lead to a faster recovery than that observed here. However, and despite previously reviewed evidence on the relationship between ethanol and GABAergic activity, it may be that the effect of ethanol on consummatory behavior modulated by partial reinforcement (as reported in Experiment 2) reflects an anxiolytic-like action not mediated by the GABA receptor complex.

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