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Relationship of Components of an Alcohol Interoceptive Stimulus to Induction of Desire for Alcohol in Social Drinkers

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DUKA, T., A. JACKSON, D. C. SMITH AND D. N. STEPHENS. *Relationship of components of an alcohol interoceptive stimulus to induction of desire for alcohol in social drinkers.* PHARMACOL BIOCHEM BEHAV **64**(2) 301–309, 1999.—The ability of a low (0.2 g/kg) oral dose of ethanol to provide a drug discriminative stimulus was studied in young healthy human volunteers, who were social drinkers. Seventeen of 24 subjects acquired the discrimination following 10 trials in which they received aliquots of ethanol or of placebo drink (tonic water mixed with Tabasco sauce). In generalization studies, in which the dose of ethanol was varied, discrimination performance was dose dependent; doses greater than 0.05 g/kg gave rise to significant ethanol-appropriate responding. Concurrent estimates of the subjective effects of doses administered as discriminative stimuli revealed that two factors—taste and light-headedness—were associated with discrimination; at the training dose, 0.2 g/kg, although both the factors taste and light-headedness were significantly increased, only taste predicted discrimination performance. At lower doses, taste did not contribute to discrimination, but the subjective rating light-headedness correlated significantly with discrimination accuracy. Post hoc analyses of the influence of the amount of alcohol regularly drunk by the volunteers, on discrimination performance suggested light-headedness correlated with discriminative performance only in social drinkers drinking more than 20 units per week. In a second experiment, groups of "high" (mean 40 units per week) and "low" (mean 10 units per week) social drinkers were prospectively identified. Discrimination performance of 0.2 g/kg ethanol in orange juice vs. orange juice vehicle indicated that both groups were able to perform the discrimination following a single training trial, and that generalization curves over the range 0.05–0.2 g/kg were dose dependent, and not different between the groups. At the lowest dose, discrimination performance was predicted by taste, stimulation, and light-headedness in the "high" group, but not in the "low" group. The ability of these ethanol doses to induce feelings of craving for ethanol were assessed in parallel, using the Desire for Alcohol Questionnaire (DAQ). "High" drinkers showed higher desire for ethanol on all factors of the DAQ except the "positive negative reinforcement" factor, and sampling ethanol tended to increase desire in these measures. However, at each dose, the induction of feelings of desire for ethanol showed a negative correlation with discrimination performance. These findings are discussed in the context of the ability of animals and humans to use several components of drug-induced stimuli in the performance of drug discrimination, and the role of such discriminative stimuli in priming of ethanol drinking. © 1999 Elsevier Science Inc.

Ethanol Priming Craving Drug discrimination Subjective ratings

DRUG discrimination is frequently asserted to be an important method for evaluating the abuse and/or dependence potential of drugs, although in reality little attempt has been made to investigate the validity of this notion. Such claims are based on the assumption that the discriminative stimulus provided by abused drugs is inseparable from the mode of action on which their abuse potential is predicated. Thus, inasmuch as the discriminative stimulus of certain opiates is related to their action at μ-receptors, as is their dependence potential, the fact that a drug provides a discriminative stimulus based on activity at μ-receptors is evidence of dependence liability, but no more than other pharmacological actions depending on agonism at μ-receptors may be used to predict such potential. Such correlational approaches do not provide strong evidence that drug stimuli capable of supporting discrimination behavior may contribute to the abuse or dependence liability of drugs. Nor, until very recently, has evidence been available that self-administered drugs are capable of giving rise to discriminative stimuli (44). Nevertheless, although ability to provide a discriminative stimulus cannot be in itself a reliable predictor of abuse liability, it would be surprising to find an abused agent that was not able to provide a discriminative stimulus.

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If the discriminative stimulus properties of drugs are important in determining their abuse liability, then the drug discriminative stimulus might be expected to possess a higher salience in drug abusers or addicted individuals than in nonabusers. Relatively little work appears to have been carried out to investigate the effects of previous experience of drug use on drug discrimination performance. In a fascinating preliminary study, Ator and Griffiths (3) trained two baboons to discriminate between midazolam (0.32 mg/kg, IV) and its vehicle. Following training to stable performance, the effect of parametrically varying the dose of midazolam was tested and dose–response curves established for discrimination performance. The baboons were now trained to an operant response to obtain an intravenous administration of midazolam, subsequently reexposed to the drug-discrimination paradigm, and the dose–response curve of midazolam in supporting the discrimination reestablished. The animals that had had the opportunity to self-administer midazolam now showed a shift of the generalization dose–response curve to the left (more sensitive to the S^D). During a subsequent retraining, the baboons were administered midazolam by the experimenter, according to the same pattern in which they had previously self-administered the drug. Following drug administration under these forced conditions, the dose–response curve in the drug discrimination paradigm was now shifted to the right. Although carried out in only very few animals, this experiment suggests that animals experienced in self-administering drugs may show a facilitation of drug-discrimination, consistent with the animals having learned to attend more closely to the stimulus provided by the midazolam as a result of the drug having acquired motivational significance.

EFFECTS OF DRUG EXPERIENCE ON HUMAN DISCRIMINATIVE PERFORMANCE

In a recent experiment (11) using human subjects, we also found evidence that previous drug experience may have consequences for drug discriminative performance. Studies in humans have the potential advantage over animal studies in that it is possible to relate discriminative performance to the subjective feeling engendered by the drug, and to obtain self-reports that may allow insight into the nature of the drug stimulus. Although it is widely assumed that the interoceptive discriminative stimulus provided by a drug treatment is related to the subjective effect of that treatment, this may not necessarily be the case, because, at least theoretically, stimuli may come to control behavior even when they are not accessible to conscious experience. Attempts in animal studies to relate drug discriminative stimuli to experiential constructs such as anxiety, euphoria, etc., have met with only the most limited success [e.g., (1), and it seems clear that if one is to relate a drug discriminative stimulus to a subjective effect, then these two phenomena need to be studied in parallel in subjects able to provide a subjective report. In the existing literature, the relationship between behavioral discrimination and subjective effects is complex, but at a general level there does appear to be a good correspondence between discriminative and subjective effects, with drugs that are discriminated from each other typically producing different subjective effects, or different doses of the same drug producing different magnitudes of effect (37).

Human Discrimination Training

In our experiments, a low training dose and concentration of ethanol were selected (0.2 g /kg at a maximum concentration of 7%), and discrimination performance assessed using a procedure adapted from Perkins et al. (36). Each subject participated in two phases: phase one (2 days) involved the discrimination training (day 1) and discrimination testing (days 1 and 2). Phase two (day 3) involved the discrimination retraining and generalization testing phase. Subjects were requested to refrain from smoking, ethanol, caffeine, and other foods and drinks containing xanthine derivatives (e.g., coffee, tea, chocolate, cola), and from excessive physical exercise, from waking until the end of each session.

During training trials, subjects were presented with the training ethanol dose (0.2 g/kg, in 200 ml tonic water; Schweppes Ltd, Uxbridge, UK) mixed with Tabasco sauce (McIlhenny Co., Avery Island, CA) or placebo (200 ml tonic water mixed with Tabasco sauce), in random order, separated by 90 min, and told that one drink was drink A and the other, drink B; subjects were instructed to drink one 50-ml portion every 15 s and then to wait for 9 min while contemplating the properties of the drink. No information was provided as to which drinks contained alcohol. The amount and concentration of ethanol administered was decided on the basis of pilot studies that demonstrated that neither taste nor ethanol effects were recognized without training (i.e., on first sampling the drink).

After a further 90 min, the subject returned to the test cubicle and was presented with an uncoded drink, which he/she was asked to drink in 50-ml portions as above; following the contemplation time, he/she was asked to respond as quickly as possible to a computer program inquiring whether the drink was A or B; subjects were informed whether their responses were correct, and rewarded with 50 pence for each correct answer (to be added to their participation payment). Further drinks were given in random order at 90-min intervals, with the restriction that no more than two successive presentations of the ethanol condition occurred. There were five such testing trials with ethanol and five with placebo. Criterion performance was set at 80% correct discrimination. Subjects failing to reach criterion were rejected from the generalization phase of the study.

During generalization testing subjects were presented in random order at intervals of 90 min with five 200-ml drinks containing tonic water mixed with Tabasco and either 0 (placebo), 0.025, 0.05, 0.1, or 0.2 g/kg of ethanol. For two trials preceeding the five generalization testing trials, subjects were reintroduced to the two training drinks and informed of their identity (discrimination retraining). These two trials served to remind subjects of the properties of each drink. Subjects were informed that they would experience different doses of ethanol, but not told how many doses. They were further instructed that they should indicate, through the two-choice behavioral discrimination task, the similarity of each stimulus to the training stimuli A and B. They were given 10 tokens and were asked to distribute them between two boxes, labeled A and B. Subjects were told they would be rewarded with 50 p for each accurate response (percentage of the discriminative dose to the training dose) at the end of the experiment. Ethanol-appropriate responding was defined as the number of tokens distributed on the side relating to the ethanol training dose. Trials were carried out in double-blind format, no feedback regarding the accuracy of each response was provided, and all subjects received the maximum payment of £2.50.

Subjective ratings of mood states and of known ethanol effects were used to identify the subjective cues used for discrimination, and multiple regression analyses of the measurements affected by ethanol on discrimination performance

were used to identify the importance of the rated subjective effects of ethanol for discrimination. In addition, the behavioral history of the subjects with respect to drinking patterns was documented.

Ethanol Discrimination in Social Drinkers

Of the 25 subjects (13 male 12 female) aged between 18 and 41 years (mean 24.3 ± 6.7) who entered the study, 17 (68%; 10 female and 7 male) successfully reached the 80% correct criterion for accurate discrimination between 0 g/kg and 0.2 g/kg ethanol. Average ethanol consumption in these subjects ranged between 3 and 40 units (mean 17.3 ± 10.3) per week; eight subjects were arbitrarily defined as high drinkers (>20 units per week) and nine subjects as low drinkers (<15 units per week). No differences were found between males and females or high and low drinkers in any of the ethanol effects.

Figure 1 shows ethanol-appropriate responding, defined as the number of tokens placed on the same side as the 0.2-g/kg training dose, at the different ethanol doses in the generalization phase of the experiment. Repeated-measure analysis of variance (ANOVA) revealed that token response was significantly affected by dose, $F(4, 64) = 6.14$, $p < 0.001$. Repeated-measure ANOVAs on differences between response under ethanol, and placebo, indicate that taste, $F(3, 48) = 2.92$, $p < 0.05$, alertness, $F(3, 48) = 3.27$, $p < 0.05$, and light-headedness, $F(3, 48) = 2.81$, $p < 0.05$, were significantly affected by dose.

To assess the relative contributions of the factors significantly affected by dose (i.e., self-ratings of taste, alertness, and light-headedness) to ethanol appropriate responding, stepwise multiple regression analyses for each of the four doses were performed. For doses 0.025 g/kg, $r = 0.78$; $F(1, 15) = 24.00$, $p < 0.001$, and 0.05 g/kg, $r = 0.57$, $F(1, 15) = 7.32$, $p < 0.05$, light-headedness was the only predictor of ethanol-appropriate responding, while at the maximum dose, 0.2 g/kg, $r = 0.57$, $F(1, 15) = 7.34$, $p < 0.05$, taste was the only predictor. Correlation coefficient values for each of the factors taste, light-headedness, and alertness are shown in Table 1. Although at the 0.2-g/kg dose, ratings of light-headedness were greater than at the lower doses, individual ratings did not correlate with discrimination performance.

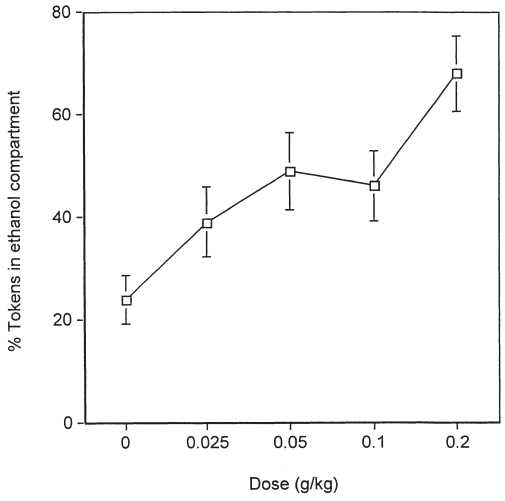

FIG. 1. Ethanol appropriate responding, defined as the number of tokens placed on the same side as the training dose (0.2 g/kg), at diffeent ethanol doses during the generalization test.

Generalization testing with doses of ethanol differing from the training dose, produced dose related increases in ethanol-appropriate responding with the lowest dose that was successfully discriminated from placebo being 0.05 g/kg. The concentration of this dose of ethanol was about 1.5 %, and the amount of ethanol ingested was approximately 3 g for a subject of 70-kg body weight, equivalent to less than half a glass of wine. The results of the step-wise multiple regression analyses indicate that taste, at the highest dose, and light-headedness, at the lower doses, were the most important cues used by subjects to perform the discrimination. This observation is curious, because the highest dose was that used for discrimination training, so that it can be assumed that during acquisition of the discrimination, the subjects had learned to discriminate ethanol on the basis of its taste. Nevertheless, they additionally appear to have learned a sufficient amount about the alternative cue, light-headedness, for this to acquire discriminative stimulus properties. It is worth noting that at the highest dose, light-headedness was rated at its highest, although this factor did not apparently contribute to discrimination performance. It should be remembered that all of the subjects in the present experiment had had previous experience with ethanol, so that it is likely that the association of drinking with light-headedness was already established, and simply needed to be applied to performance of the discrimination. In an informal test of this hypothesis, the data were reanalyzed on the basis of the subjects' reported weekly ethanol consumption. In subjects with "higher" weekly consumption (20–40 units per week), there was a high correlation between reports of light-headedness and discrimination performance (0.025 g/kg: $r = 0.96$; $p < 0.0001$; 0.05 g/kg: $r = 0.71$, $p < 0.05$), but for subjects with "low" reported weekly intakes (3–15 units per week), the relationship was not statistically reliable (0.025 g/kg: $r = 0.65$, $p = 0.06$.; 0.05 g/kg: $r = 0.51$; $p = 0.15$). Taste, on the other hand, appeared equally salient for the two groups.

Thus, it appears that the more experienced drinkers may have employed the light-headedness experience to identify the presence of ethanol. It is nevertheless puzzling that when taste was the predominant cue (i.e., at the highest dose), light-headedness, although present (see Fig. 2b), did not correlate with ethanol-appropriate responding. This may have resulted simply because the high level of light-headedness in most subjects at this dose did not allow a statistical relationship to be revealed, even though light-headedness was being used as a discriminative stimulus.

TABLE 1

PEARSON CORRELATION COEFFICIENT (r) AND p-VALUES FOR ALERTNESS, LIGHT-HEADEDNESS, AND TASTE (DIFFERENCES FROM PLACEBO) AGAINST DISCRIMINATIVE PERFORMANCE AT EACH DOSE

	Ethanol Dose (g/kg)							
	0.025		0.05		0.1		0.2	
Self Ratings of	r	p	r	p	r	p	r	p
Alertness	−0.13	0.63	−0.13	0.61	−.005	0.86	−0.04	0.87
Light headed	0.78	0.00	0.57	0.02	0.47	0.06	0.45	0.07
Taste	0.05	0.84	0.21	0.42	0.14	0.60	0.57	0.02

Alternatively, this finding may suggest that the more salient stimulus, in this case taste, distracts from the importance of other cues experienced by the subjects. On this basis, the cues provided by high and low doses of ethanol may be based on different subjective states, and cues present at high doses may mask cues discernible at lower doses. A related observation was made in the study of Huber et al. (24), who trained subjects to discriminate ethanol through the use of external cues (i.e., knowledge about the amount of ethanol consumed). This group found that not only could subjects discriminate on the basis of these cues, but that, once trained, they could also successfully discriminate in their absence. To account for this Huber et al. (24) argued that, during training, subjects acquire additional internal subjective cues that are not apparent in the presence of more salient cues (i.e., masked by knowledge about the amount consumed). Our data seem to support this view in that light-headedness, as a discriminative cue, was identified only at the lower doses, when the more salient cue, taste, was no longer discriminable.

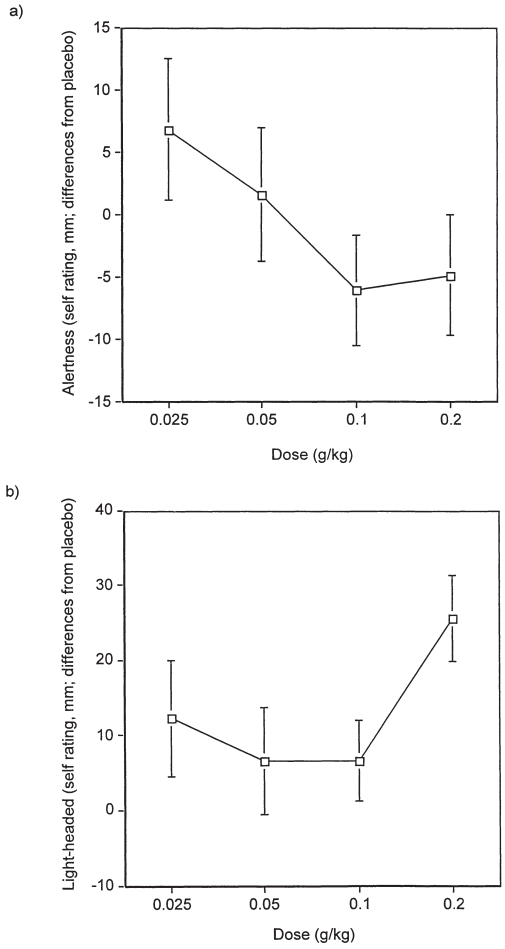

FIG. 2. Effect of ethanol dose on the subjective ratings (a) "Alertness" and (b) "light-headedness." Self ratings were obtained using 100-mm Likert scales (0 = not at all, 100 = very much; 50 = usual state), and the values are expressed as mean differences (SEM) from each individual's placebo response. Repeated-measure ANOVA performed on this measure indicated a significant effect of dose, $F(3, 48) = 2.81$; $p < 0.05$).

These data suggest that the nature of the discriminative process in people is complex. The ethanol discriminative stimulus appears to possess several components—i.e., at least taste, and the experience of light-headedness. Of particular interest is the possibility that although subjects appeared to learn the discrimination on the basis of the taste of the alcoholic drink, they nevertheless acquired knowledge of other features of the drug experience that could subsequently serve as discriminative stimuli. Thus, the more salient cue, taste, acquired during discrimination training, may have masked additional cues in the subjects' subjective experience. These additional interoceptive drug cues became apparent only when subjects were discriminating small doses of ethanol during generalization tests; of the measurements performed in the present study, only light-headedness appeared to be a significant interoceptive cue at these low doses.

Secondly, the ability to use the light-headedness stimulus may have been limited to regular moderate drinkers. Whether this is a practice effect—the regular drinkers having learned to attend to this feature during previous drug taking—or a factor predisposing to higher rates of drinking is not clear. However, in the context of the study of Ator and Griffiths (3), it may be that experienced drug users become sensitive to discriminative stimuli, or to certain components of such stimuli.

CRAVING AND DRUG DISCRIMINATION

In the Duka et al. (11) study, the analysis of the nature of the cue used by experienced and relatively inexperienced drinkers was carried out post hoc, and was based on an arbitrary division of the subject group into heavy and light drinkers. We, therefore, carried out a second study in which groups of high and low drinkers were recruited prospectively, and an attempt was made to relate the discriminative stimulus more directly to issues relevant to drug abuse. In this second experiment, we carried out parallel observations of ethanol's ability to provide a discriminative stimulus, and to induce desire for further ethanol drinking. The ingestion of a small amount of alcohol has been shown to increase subsequent ethanol intake [e.g., (5,8,20,22), a phenomenon known as priming. Although the priming effect has been frequently demonstrated as increases in amount drunk or speed of drinking, there are no equivalent demonstrations that consumption of a small sample of ethanol results in increased desire or urges. Utilizing a recently developed craving questionnaire [Desire for Alcohol Questionaire (DAQ); (29)] we investigated the effect of the same alcohol doses that were discriminated in the previous study (0, 0.05, 0.1, and 0.2 g/kg) in subjects recruited on the basis of high and low drinking patterns on craving for alcohol in social drinkers.

Two groups each of 14 subjects were prospectively recruited from the student population of the University of Sussex. The "high" drinkers consumed more than 32 units per week (mean 42.9 ± 2.7), while the "low" group consumed 18 or fewer units per week (mean 10.5 ± 1.3). Weekly ethanol intakes were estimated from retrospective detailed reports of the subjects of daily intakes of named brands of alcohol. Both groups were similar in age (22.1 ± 1.4 vs. 25.2 ± 1.8), and were matched for gender (each eight males and six females). In contrast to the previous study, the vehicle was orange juice. Discrimination training took the form of one sampling each of 0.2 g/kg ethanol in orange juice, and 90 min later orange juice alone; these drinks were labeled "A" and "B," and the subjects instructed to contemplate the properties of the drinks

and associate them with the appropriate label. Following a further 90 min, they were introduced to generalization testing following the procedure outlined previously. Immediately following each discriminative response, subjects were required to rate the factors taste, light-headedness, alertness, stimulation, relaxed, contentedness, and irritability using Likert scales, as in the previous experiment, and to complete the DAQ (29). The DAQ analyses responses to questions relating to desire to take drug. Factor analysis indicates that the outcomes may be classified under four factors, "positive and negative reinforcement," "strong desires and intentions," "mild desires and intentions," and "control over drinking." Each of these factors was treated as an independent measure.

Discrimination Performance, Subjective Effect, and Desire to Drink in High and Low Social Drinkers

Figure 3 shows that both high and low groups discriminated ethanol from vehicle in a dose-dependent manner, $F(3, 78) = 60.0$, $p < 0.0001$, but that the groups did not differ in their discrimination performance, $F(1, 26) = 0.07$, NS. Alcohol also influenced subjective ratings in a dose-dependent manner [light-headed, $F(2, 52) = 6.9$, $p < 0.01$; taste, $F(2, 52) = 62.6$, $p < 0.0001$; stimulated, $F(2, 52) = 3.8$, $p < 0.05$], but had no significant effects on the ratings alert, contented, irritable, or relaxed. There were no differences between high and low drinkers in any of the subjective rating scales.

These observations generally confirm those in the previous study, though, because, in order to optimize the priming aspect of the experiment we were less rigorous in attempting to mask the taste of ethanol; taste was a more salient stimulus at low doses than in the previous study. Additionally, we demonstrate that in humans, drug discrimination can be performed by individuals with a minimal amount of formal training (a single exposure). In contrast to our previous experiment, we found no effects of the doses of ethanol tested on the rating "alert," but found an effect on "stimulated." Because these two ratings may be considered as closely resembling each other, it cannot be ruled out that the subjects in the two experiments were simply using different criteria to classify these two subjective ratings.

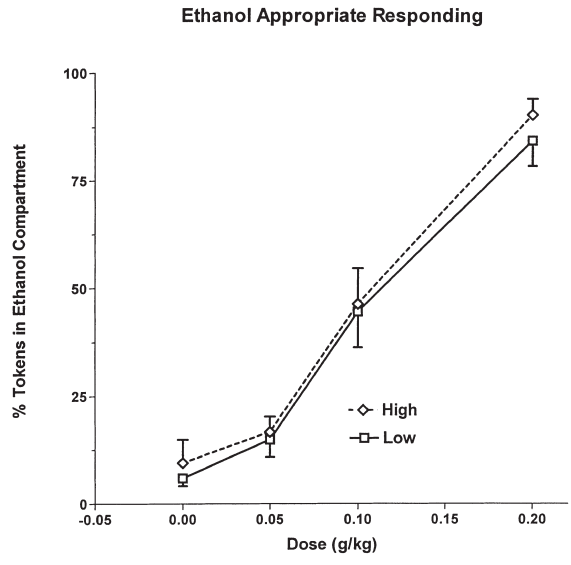

FIG. 3. Ethanol-appropriate responding, defined as the number of tokens placed on the same side as the training dose (0.2 g/kg), at different ethanol doses during the generalization test, in groups of social drinkers with a "high" or "low" weekly ethanol consumption.

The high and low drinkers showed differences in their responses on the DAQ, in the factors "strong desires and intentions" and "mild desires and intentions," and "control over drinking," Fs$(1, 26) > 4.24$, $p < 0.05$; high drinkers had higher ratings. Ingestion of ethanol increased the factor "mild desires and intentions," and decreased the factor "control over drinking" in a dose-dependent manner, at levels approaching significance, $F(3, 78) = 2.52$, and 2.53, respectively, ps $= 0.06$, there were no significant group $\times$ dose interactions. Thus, although the DAQ was sufficiently sensitive to reveal overall differences in motivation for alcohol between groups of social drinkers with high and low weekly levels of consumption, and in this small population to suggest priming effects of consumption of ethanol on desire for further ethanol, there was no evidence that the high and low drinkers responded differently to this effect of ethanol.

We performed stepwise multiple regression analyses between discrimination performance, and those subjective ratings that showed dose-related effects of ethanol (light-headedness, taste, and stimulation). The findings in general supported the conclusions from our first study. Although in this population, at the highest dose, 0.2 g/kg, no single subjective rating predicted discriminative performance in either group, probably because of ceiling performance in discrimination ruling out the possibility of correlations; at the 0.1 g/kg dose, taste was the most reliable predictor for both groups [high, $F(1, 12) = 7.1$, $p < 0.02$; low, $F(1, 12) = 6.1$, $p < 0.03$]. At lower doses, however, the high and low groups differed; while no reliable predictor was found for the discriminative performance in the low drinkers, in the high drinkers group all three subjective ratings predicted discrimination performance, $F(3, 10) = 27.6$, $p < 0.0001$, in the following sequence of reliability: taste ($\beta = 0.76$, $p < 0.0001$), stimulation ($\beta = 0.57$, $p < 0.001$), light-headedness ($\beta = 0.3$, $p < 0.02$). Thus, although these findings differ in detail from our previous experiment, probably because we made little attempt to disguise the taste of ethanol in this experiment, they support our previous findings that social drinkers with high weekly intakes (mean of 42.9 units per week) are more sensitive to the discriminative stimuli provided by very low ethanol intakes than social drinkers with low weekly intakes (mean of 10.2 units per week).

We also explored the relationship between discrimination performance and the ability of ethanol to induce desire for ethanol. At the higher dose (0.2 g/kg), both high and low drinkers showed reliable correlations between discrimination performance and DAQ ratings; whereas, in the case of the high drinkers group, "strong desires and intentions" (r −0.75, $p < 0.002$) and "mild desires and intentions" ($r = -0.57$, $p < 0.03$) factors both correlated with discriminative performance, in the low group "positive and negative reinforcement" ($r = -0.55$, $p < 0.05$) correlated with discrimination performance.

At the lower doses (0.1 and 0.05 g/kg), however, DAQ ratings were correlated with discrimination performance only in high drinkers. In this group, "positive and negative reinforcement" ($r = -0.55$, $p < 0.05$) and "mild desires and intentions" ($r = -0.62$, $p < 0.05$) correlated with discrimination performance at 0.1 g/kg; at the 0.05-g/kg dose, "positive and negative reinforcement," and "strong desires and intentions" correlated with discrimination performance (respectively, $r = -0.64$, $p < 0.05$; $r = -0.84$, $p < 0.0001$). Figure 4 shows the relationship between the factor "mild desire and intentions"

and discrimination performance for both groups at all doses. Note that although both the DAQ rating and discrimination performance increase with dose, within each dose all the significant correlations are negative. That is, within each dose, and group, the ability of individuals to use the ethanol stimulus to perform a discrimination task was inversely related to the ability of that dose in that individual to induce feelings of desire for ethanol. Ethanol's priming effect was thus negatively related to its ability to provide a discriminative stimulus.

Correlations between drug properties are difficult to interpret, but the present findings provide little support for the idea that the ethanol discriminative stimulus plays an important role in enhancing desire for alcohol. On the other hand, it would be premature to conclude that discriminative stimulus properties are not related to the addictive properties of drugs. It may be important that in order for priming, as measured by changes in subjective desire for ethanol, to occur, it is important that subjects have no awareness that they have taken ethanol; an awareness that alcohol had been consumed (as suggested by good discrimination) may even have led to the subjects consciously suppressing their willingness to acknowledge a desire for ethanol. Furthermore, there is some evidence to suggest that measures of consumption may be more sensitive to priming effects in humans, than subjective measures of desire (22), and it is, therefore, important to carry out analogous experiments using amount drunk, rather than subjective craving, as the dependent measure.

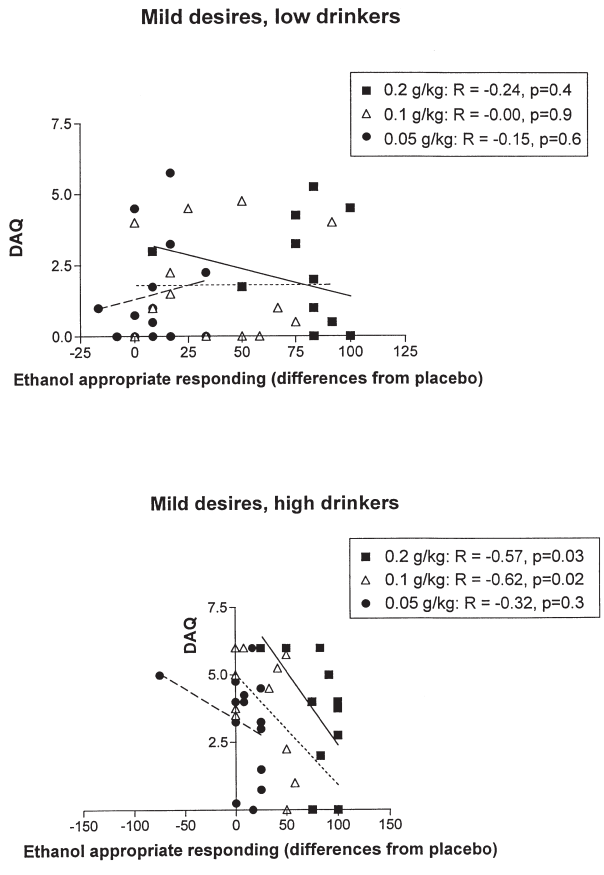

FIG. 4. Correlation between the Desire for Alcohol Questionaire (DAQ) factor "mild desire" and discrimination performance following sampling of three doses of ethanol, in groups of high and low social drinkers.

Our findings from studies of ethanol discrimination in humans thus suggest a number of propositions. First, individual subjects appear to learn about more than one dimension of a drug discriminative stimulus, although they may only utilize a restricted set of dimensions in performing a particular discrimination. Second, individuals who have experienced the internal stimuli provided by a drug in the context of drug self-administration, may utilize a different set of dimensions from individuals who are relatively inexperienced with drugs in performing drug discriminations. Third, the ability of drugs to act as primers, initiating feelings of desire, and perhaps further drug taking, may be independent of the internal stimulus properties of the drugs as revealed by drug discrimination. We are currently testing these hypotheses.

EVIDENCE FOR ABILITY TO USE DIFFERENT COMPONENTS OF COMPLEX CUES IN RATS

To what extent can these propositions derived from human drug discrimination be useful in understanding drug discrimination in animals? From learning theory, one might have anticipated from our first study that the availability of the more salient cue, taste, may have overshadowed learning about the less salient element, light-headedness. However, the conditions under which overshadowing can be demonstrated are not always easy to establish, and within the drug discrimination literature there are now several examples of discriminative cues based on explicit provision of multiple interoceptive stimuli by using drug mixtures [e.g., (47)]. In these experiments, and depending on the precise combination of drugs, the animals appear to acquire information regarding the discriminative stimulus properties of multiple elements. Thus, in the case of discriminative stimuli based on mixtures of nicotine and a benzodiazepine, Stolerman and his colleagues found that either component when given alone was able to maintain the discrimination, although the extent to which each component contributed to the discriminative stimulus depended on a number of factors, including the animal's previous drug experience [e.g., (47); and references therein].

These sorts of ideas can be applied to understanding discrimination of single drug cues, especially in cases where the training drug (e.g., alcohol or benzodiazepines) possesses actions at several receptors, or receptor subtypes. An example comes from drug discriminative stimuli provided by drugs acting at benzodiazepine receptors [e.g., (2)]. Benzodiazepine possess several behavioral pharmacological properties, including anxiolytic, sedative, muscle relaxant, and amnestic properties. Potentially, any state corresponding to these actions might give rise to a discriminative stimulus, and although some have suggested that the discriminative stimulus provided by standard benzodiazepines may depend on their sedative properties [e.g., (6)], it has proven difficult to attribute the stimulus to any particular psychological construct (1). Benzodiazepines act as modulators of $GABA_A$-receptor function, and recently several subtypes of the $GABA_A$ receptor have been identified. Conventional benzodiazepines act at only a subset of the receptors, and more recently developed drugs such as zolpidem and abecarnil act at a further restricted subset of benzodiazepine-sensitive $GABA_A$ receptors (sometimes for convenience characterized as BZ_1 subtypes). In rats, the discriminative stimulus provided by conventional benzodiazepines shows generalization to zolpidem and abecarnil, suggesting that their stimulus properties resemble each

other. However, in rats trained to discriminate abecarnil or zolpidem from vehicle, the discriminative stimulus shows only poor generalization to conventional benzodiazepines such as diazepam (2,39). Because abecarnil and zolpidem possess a subset (but only a subset) of the properties of diazepam, we conceive of this asymmetrical generalization pattern as reflecting an ability of a stimulus provided by diazepam, but not abecarnil, to mask the discriminative stimulus provided by the training drug. This is illustrated in Fig. 5. Although we are not able to identify the respective stimulus components that abecarnil and zolpidem, on the one hand, and benzodiazepines such as midazolam have in common, and those in which they differ, they presumably relate to abecarnil and zolpidem binding to only a subset of the brain's benzodiazepine receptors.

In common with other pharmacological properties of benzodiazepines, the discriminative stimulus properties can be shown to develop tolerance following chronic treatment (38). Lytle et al. (32) showed that the discriminative stimulus provided by the nonselective benzodiazepine, midazolam, generalized to abecarnil, and that decreasing the doses of both drugs resulted in a very similar stimulus generalization decrement (dose–response curve). Following chronic administration of another nonselective benzodiazepine, diazepam, these dose–response curves for both midazolam and abecarnil showed a modest shift to the right, indicating that the tolerance that had developed during chronic treatment had weakened the pharmacological bases of the discriminative stimulus of both agents. Following a period of no drug treatment, to allow tolerance to dissipate, the dose–response curves to midazolam and abecarnil were reestablished and found to closely resemble those obtained during the first phase of the experiment before chronic treatment. In the next phase, the animals were chronically treated with abecarnil, and again, the dose–response curves for midazolam and abecarnil reestablished. The curve for abecarnil was now found to be shifted markedly to the right, indicating tolerance development in those pharmacological properties responsible for abecarnil's discriminative stimulus properties, in rats trained to discriminate midazolam. In contrast, the midazolam dose–response curve showed no indication of tolerance, suggesting that the pharmacological properties responsible for midazolam's discriminative stimulus had not been affected by the chronic abecarnil treatment that had weakened abecarnil's discriminative stimulus.

This complex set of data can be explained in terms of Fig. 5. In the case of chronic benzodiazepine treatment, tolerance can be expected to have developed to all components of the midazolam discriminative stimulus, including those components on which the abecarnil generalization was based; thus, a shift in the dose–response curve was seen for both drugs. Following chronic abecarnil treatment, however, because abecarnil acts at only a subset of midazolam-sensitive receptors, only the interoceptive stimulus components dependent on that subset could have undergone tolerance, leaving the remaining elements unchanged. Consequently, the dose–response curve for abecarnil was shifted appropriately to the right; that the dose–response curve for midazolam was not suggests that the animals were now able to use the unchanged components of the midazolam stimulus complex to perform the discrimination of midazolam from vehicle. In other words, the rats were able to make use of different components of the discriminative stimulus, depending on whether they were discriminating abecarnil or midazolam, even though they had originally been trained using the midazolam stimulus. This would seem to resemble the phenomenon we observed in low-dose ethanol discrimination in human subjects, in which the discrimination at the training dose was performed on the basis of taste, but when, at low doses, taste was not available as a cue, the discrimination was performed on the basis of the alternative component, light-headedness.

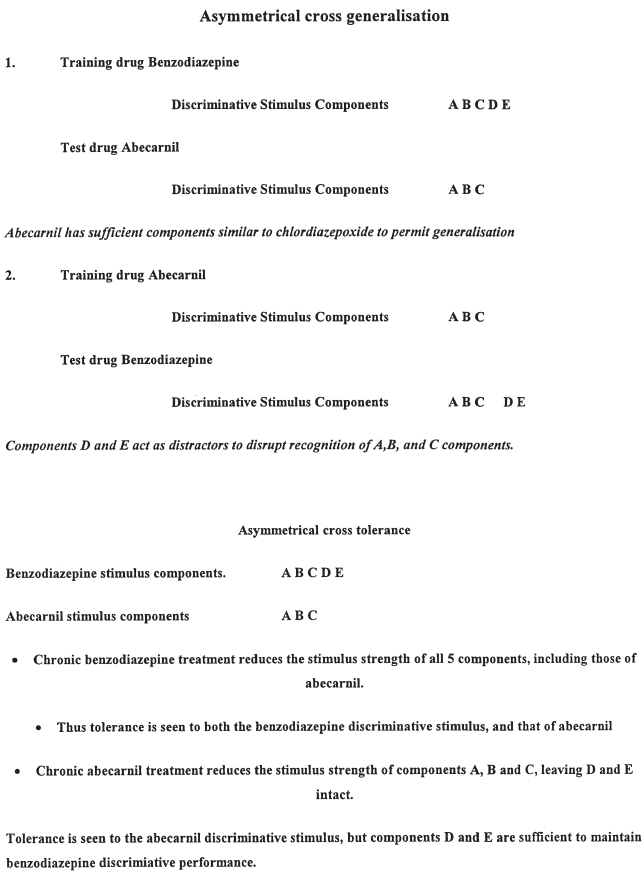

FIG. 5. Explanation of asymmetrical cross tolerance between benzodiazepines and a selective β-carboline agonist at benzodiazepine receptors.

PHARMACOLOGICAL CHARACTERIZATION OF THE ETHANOL DISCRIMINATIVE STIMULUS

The ethanol discriminative stimulus also possesses several components, and may relate to a variety of different subjective effects that could serve as interoceptive cues. Many of these effects appear to depend on variables such as environmental context, dose, time since last administration, previous experiences, and the expectation bias of the subjects (9,13, 14,27). Ethanol possesses a complex pharmacology (28), which includes facilitation of GABAergic transmission through an action at the GABA–benzodiazepine–Cl^-- channel complex (35,49), antagonism of glutamatergic transmission through an action at NMDA glutamatergic receptors (23,31), an action at 5-HT_3 (30), and 5-HT_1 receptors (19), and an interaction with neuronal voltage-gated calcium channels (28,50). In animal studies, the ethanol discriminative stimulus has been demonstrated to involve all these receptors (7,12,16,17,19,21,42,43). Although NMDA antagonists mimic the discriminative stimulus in ethanol-trained rats (4,18,40,43), the extent to which they do this depends on the ethanol dose discriminated (18), while the importance of an action at

$GABA_A$ receptors is independent of the ethanol training dose (7,15). Not all BZ-receptor agonists mimic the ethanol stimulus; agonists that have selectivity for the BZ_1 subpopulation of receptors such as alpidem and zolpidem either do not, or only partially, mimic the stimulus (40,41). Thus, although mechanisms related to $GABA_A$-receptors are involved in the subjective effects of alcohol across a wide range of ethanol doses, they may be restricted to a BZ-receptor subtype.

Consistent with these pharmacological effects, the ethanol discriminative stimulus has been related to sedative effects of ethanol (33). However, the fact that substitution for the ethanol cue by the stimulant MDMA (3,4-methylenedioxymetamphetamine; ecstasy) has been shown, in ethanol-trained (high drinking) rats, and that ethanol-trained (high drinking) rats may be more responsive to the stimulating effects of ethanol (26), may suggest additional behavioral effects of ethanol contributing to its discriminative stimulus properties (34). Indeed, there is some evidence to suggest that ethanol may give rise to both sedative and stimulant cues, the salience of either component depending on the time postadministration at which the discriminative stimulus properties are tested. Shippenberg and Altshuler (45) and Spanagel (46) were able to distinguish between a discriminative stimulus provided by ethanol 6 min following administration from that provided by the same dose at 30 min. In these studies, the ethanol stimulus that was antagonizable by naloxone or another μ-opioid antagonist, cyprodime, occurred at an early time point, 6 min following the administration of alcohol. In contrast, naloxone failed to block the stimulus arising 30 min following administration of alcohol; moreover, discriminative stimuli in two groups of rats trained with alcohol administered either at 6 or at 30 min before testing, did not crossgeneralize (45).

These results suggest that the mechanisms underlying alcohol discriminative stimuli in rats vary across time, with opioids being involved soon after drug administration, rather than later. There are interesting parallels here with findings from opioid–alcohol interaction studies in humans. Swift et al. (48) used a Biphasic Alcohol Effects Scale to measure both stimulant and sedative effects of ethanol in human subjects. The scale revealed higher stimulant ratings during rising blood alcohol concentrations (early after consumption), but higher sedative ratings during falling blood alcohol concentrations (later after consumption). Naltrexone reduced stimulant scores and enhanced sedative ratings, when compared to placebo. Although Doty and DeWit (10) failed to antagonise alcohol-induced positive responses with naltrexone in human subjects, King et al. (25) have recently reported attenuation by naltrexone of alcohol-induced stimulant subjective effects in sons of alcoholics, so that an involvement of μ-opiate receptors in the stimulant component of the ethanol discriminative stimulus may occur in both rats and in humans.

Such findings emphasize the complexity of the alcohol discriminative stimulus, pharmacologically, in its time course, and in relationship to individual differences arising from drug taking history, and possibly, from genetic background. Relating these findings back to our finding of a negative correlation between the discriminative stiumulus properties of alcohol, and its ability to induce desire for drug, it is conceivable that the alcohol cue we were studying is not the cue, which is important in inducing priming. Future studies of the relationship between the alcohol discriminative stimulus and priming may need to use several approaches to manipulating the cue in an attempt to relate other potential alcohol cues to priming.

Although it is difficult at present to relate such pharmacological analyses of various components of the ethanol discriminative stimulus to our work analyzing the subjective and craving correlates of the same administration, this promises to be a fruitful approach for future studies. In such studies, we can anticipate that the use of human subjects will continue to enlighten our understanding of the relationship of drug discriminative stimuli to subjective effects of drugs, and will be useful in understanding whether drug discriminative stimuli play a role in drug abuse. On the other hand, animal studies will continue to be useful in investigating the pharmacological nature of drug cues. Bringing the two areas together represents an unsolved challenge.

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