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Strategies for Understanding the Pharmacological Effects of Ethanol With Drug Discrimination Procedures

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GRANT, K. A. *Strategies for understanding the pharmacological effects of ethanol with drug discrimination procedures.* PHARMACOL BIOCHEM BEHAV **64**(2) 261–267, 1999.—Ethanol appears to produce a stimulus complex, or compound cue, composed of distinct components that are mediated by different receptor systems. In ethanol vs. water discriminations, it appears that ethanol produces a redundant stimulus complex such that separate, receptor-mediated activity can serve as the basis for the discrimination. These discriminations have been termed redundant, because multiple features of the cue could serve as the basis of the discrimination. In ethanol vs. water discriminations, one common feature is the asymmetrical generalizations between components of the ethanol cue and ethanol. There is also evidence for overshadowing of one component by other components of the ethanol stimulus complex. It appears possible to transfer the basis of the ethanol cue from a redundant cue to a conditional cue with specific training procedures. When the discriminative stimulus effects of ethanol are juxtoposed with those of one component of the ethanol complex, as in ethanol vs. water vs. pentobarbital discriminations, the ethanol discrimination shifts to a conditional basis. The ability to antagonize an ethanol discrimination may be dependent upon whether the discrimination is based on redundant component stimuli or conditional presence of all component stimuli. © 1999 Elsevier Science Inc.

Ethanol Drug discrimination Asymmetrical generalizations Overshadowing Antagonism Stimulus complex Conditional discrimination

THE application of electrophysiological, biochemical, and molecular techniques has provided conclusive data that show that ethanol acts as a modulator at particular receptor complexes and selectively alters neurochemical processes in discrete regions of the brain (35). The discriminative stimulus effects of psychoactive drugs are believed to reflect specific receptor-mediated activity (18,39) and receptor subtypes that are implicated in the discriminative stimulus effects of ethanol include the γ-aminobutyric acid $_A$ ($GABA_A$), *N*-methly-D-aspartate (NMDA) glutamate, and 5-$HT_{1B/2C}$ receptors.

$GABA_A$-gated ion channels are one subtype of GABA receptors that confer inhibitory neurotransmission in the brain. $GABA_A$ receptors are structurally complex and, depending on the subunits present, incorporate binding sites for different classes of ligands. For example, there are separate binding sites for GABA agonists and antagonists, benzodiazepines, barbiturates, neurosteroids, and convulsants (53). The benzodiazepine, barbiturate, and neurosteroid sites are generally considered modulatory to channel activity. In general, positive modulators enhance the GABA-activated flow of Cl^-, and result in an increased inhibitory tone in the CNS (e.g, sedation, hypnosis, anesthesia). Negative modulators inhibit the GABA-activated flow of Cl^- and result in a decreased inhibitory tone, which may be manifested in anxiety and seizures. Ethanol appears to act as a positive modulator of $GABA_A$ receptors and to enhance GABA-activated flow of Cl^- (1).

$GABA_A$-positive modulators consistently substitute for ethanol in ethanol vs. water discriminations. Specifically, the barbiturates pentobarbital, phenobarbital and barbital produce ethanol-like discriminative stimulus effects in rats and monkeys (14,26,28,45,46,59,60,65,74,75). The benzodiazepines chlordiazepoxide, diazepam, lorazepam, oxazepam, triazolam, and midazolam produce ethanol-like discriminative stimulus effects in rats, mice, gerbils, and pigeons (26,37,42,45,46,55,58, 59,63,65). In addition, positive modulators at the neurosteroid site such as allotetrahydrodeoxycorticosterone (5α-THDOC), tetrahydrodeoxycorticosterone (5β-THDOC), and allopregnanolone (3α,5α-P), also produce ethanol-like discriminative stimulus effects in rats and monkeys (2,10,13,28). Thus, positive modulation of the $GABA_A$ receptor system appears to be a robust component of the ethanol cue.

The NMDA channel conducts excitatory neurotransmission, primarily though the gating of Na^+ and Ca^{++} ions into the neuron. The primary components of NMDA receptors

are a NMDA recognition site, a strychnine-insensitive glycine site, a polyamine site, and a receptor-coupled cation channel that contains a binding site for dissociative anesthetics (47). Biochemical and electrophysiological data show that ethanol attenuates an NMDA-mediated cation flux (38,48). Shortly after these in vitro findings of ethanol were reported, the NMDA channel antagonists ketamine, phencyclidine (PCP), and dizocilpine were reported to substitute for the discriminative stimulus effects of ethanol in mice and pigeons (15,33). Dizocilpine, phencyclidine, and ketamine also consistently produce ethanol-like discriminative stimulus effects in rats (26,29,36,58,64,65,67). In addition to the channel blockers, some studies have shown the NMDA competitive antagonists CGS 19755 and CPPene completely substitute in an ethanol discrimination (15,29,58). However, other studies show only partial substitution of the competitive antagonists CGS 19755, NPC 17742, and CPPene in rats trained to discriminate ethanol (29,65). Finally, the few studies investigating glycine site antagonists in an ethanol discrimination report no substantial substitution of ACEA-1021 (6,40) or L 701,324 (40). Similar to the glycine site antagonists, the polyamine site antagonists tested to date, eliprodil, arcaine, or speridine, do not produce ethanol-like discriminative stimulus effects (40,58). The composite picture from the various NMDA ligands tested suggest that NMDA channel antagonists produce discriminative stimulus effects most similar to ethanol. Interestingly, detoxified alcoholics report the subjective effects of ketamine are similar to high doses of ethanol (43). Thus, attenuating NMDA channel activity appears to be sufficient to produce discriminative stimulus and subjective effects similar to ethanol.

Data implicating serotonergic receptor systems in mediating the discriminative stimulus effects of ethanol are less comprehensive than those address GABAergic and glutamatergic mechanisms. The first examinations of a serotonergic mediation of an ethanol discrimination used *para*-chlorophenylalamine (PCPA) to deplete brain 5-HT content. Following treatment with PCPA, there was either no effect (73) or a transient decrease (61) in the ability of rats to discriminate ethanol from vehicle. Specific 5-HT agonists and antagonists were not investigated until the 5-$HT_{1B/2C}$ agonist TFMPP was reported to substitute for ethanol (66).

5-HT_{1B} receptors are negatively coupled to cAMP through Gi proteins, and act as presynaptic autoreceptors and heteroreceptors to decrease neurotransmitter release (17). The finding that a metabotropic receptor ligand could produce discriminative stimulus effects similar to ethanol was unusual. Prior to this report, most receptor ligands substituting for ethanol acted at ionotropic receptor systems. Subsequent studies replicated the substitution of TFMPP for 1.0 and 1.5 g/kg ethanol, but not in rats trained to discriminate 2.0 g/kg ethanol (31,34). Due to the possible action of TFMPP at several 5-HT receptor subtypes (17), the mechanism mediating the discriminative stimulus effects of TFMPP that are similar to those of ethanol is difficult to determine. However, a subsequent study found that the 5-HT agonists RU 24969, mCPP, and CGS 12066B each substituted for ethanol, with enhanced efficacy and potency at lower training doses of ethanol (32). Based on the binding selectivity of TFMPP, RU 24969, mCPP, and CGS 12066B, together with their profile of substitution, some of the discriminative stimulus effects of ethanol appear to be mediated through 5-HT_{1B} and/or 5-HT_{2C} receptors [for an extensive discussion, see (32)]. A recent study has replicated substitution of mCPP for the discriminative stimulus effects of ethanol and extended the list of 5-HT_{1B} receptor agonists that substitute to include the selective agonist CP 94,253 (52). Finally, the agonist mCPP produces ethanol-like subjective effects and alcohol craving in recently detoxified alcoholics (9,16,44). Overall, these results with the 5-$HT_{1B/2C}$ agonists suggests that there is a serotonergic component as well as $GABA_A$ and NMDA components to the ethanol cue.

The discrimination studies reviewed above suggest that ethanol is a stimulus complex, composed of distinct components mediated by different receptor systems (19,41). Discriminations that are based upon a complex of cues (or multidimensional cues) have been defined as either "conditional" or "redundant" (49). In a redundant discrimination, presentation of any component of the cue is sufficient for generalization from the stimulus complex; in a conditional discrimination, all the composite stimuli must be present for generalization to occur (41,49). Stolerman and colleagues have studied the discriminative stimulus effects of drug mixtures (e.g., nicotine and midazolam mixtures), and have found that the drug mixtures do not result in conditional discriminations (21,50, 70,71). Instead, the components of the mixture can each produce generalization, suggesting that the discrimination is based on redundant information. Specifically, when drugs from different pharmacological classes are mixed together and then trained as the discriminative stimulus, either drug alone engenders complete substitution for the training mixture. Similar to these drug mixture studies, it appears that ethanol produces a redundant stimulus complex, such that separate receptor-mediated activity can serve as the basis for the discrimination of the ethanol (Fig. 1).

One possible characteristic of a stimulus complex based on redundant relevant stimuli is the occurrence of asymmetrical generalizations between the stimulus complex and the components of the complex. Asymmetrical, or one-way, generalizations are often used as a measure of similarity between two discriminative stimuli (3). If two different training drugs generalize to each other, then they produce discriminative stimulus effects that are essentially interchangeable under the training conditions. However, if one of the training drugs generalizes to the other training drug and the reverse is not the case, then they do not have completely overlapping qualities. As pointed out previously, the similarity in discriminative stimulus effects are believed to reflect similarity in receptor-mediated activity (18,39). Asymmetrical generalizations have been viewed in terms of hierarchical relationships said to reflect the receptor specificity of contrasting drugs (3,4). Thus, asymmetrical generalizations are most likely to occur between two drugs if one drug has a wide spectrum of activity that includes, but is not limited to, the specific receptor-mediated activity of the second drug. These additional aspects of a broad-spectrum drug could serve to mask the common discriminative stimuli. Perceptual masking of discriminative cues have been commonly reported (24,25). Alternatively, the asymmetrical generalizations could be based on receptor efficacy at $GABA_A$ receptors, reflecting the differences between full and partial agonists (56,57).

Asymmetrical generalizations between ethanol and $GABA_A$-positive modulators, NMDA antagonists and 5-HT agonists, appear to be a consistent characteristic of ethanol's discriminative stimulus effects (7). This characteristic was noted in the very early studies of ethanol discrimination where pentobarbital or chlordiazepoxide as the training stimulus inconsistently produced generalization to ethanol [see (8)]. More recently, asymmetrical generalizations have been reported between ethanol and GABA-positive modulators that are barbiturates (20,74) and benzodiazepines (20,37,42,63). Similar to the $GABA_A$-positive modulators, asymmetrical generalizations between ethanol and NMDA antagonists have been consistently reported. When ethanol is the training drug,

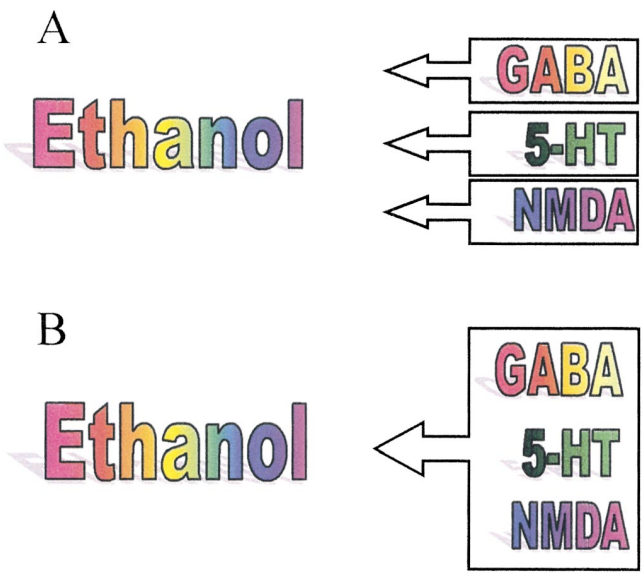

FIG. 1. (A) Representation of an ethanol discrimination based on redundant relevant stimuli. The ethanol cue is a stimulus complex, represented by the spectrum of colors. Each color range represents a different aspect of a receptor basis for the stimulus effects of ethanol. In a redundant discrimination, each component stimuli can substitute for ethanol, independent of the presence of the other relevant stimuli (represented by separate arrows). (B) Representation of an ethanol discrimination based on the conditional presentation of relevant stimuli. As in A, the ethanol cue is a stimulus complex, and the color ranges represent different aspects of ethanol's stimulus effects. In the conditional discrimination, only the cooccurrence of all component stimuli can produce substitution (represented by the box encircling the components of the cue and a single arrow).

dizocilpine, phencyclidine, and ketamine substitute for ethanol. However, ethanol does not substitute for the discriminative stimulus effects of the NMDA channel blockers dizocilpine (15), phencyclidine (5,15,29), or ketamine (36). Asymmetrical generalization has also been reported between ethanol and the competitive NMDA antagonists CGS-19755 (15) and NPC 12626 (5). Finally, ethanol does not substitute for the 5-HT_1 receptor agonist TFMPP (62). Thus, for every major neurotransmitter system identified as mediating ethanol-like discriminative stimulus effects, an asymmetrical pattern of stimulus substitution between ethanol and the receptor ligand is apparent. Examples of asymmetrical generalizations between ethanol and other sedative hypnotics are consistent with the conclusion that ethanol has diverse discriminative stimulus effects in comparison to drugs such as barbiturates (3,7). Taken together, the data suggest that the asymmetrical generalizations with ethanol appear attributable to ethanol serving as a stimulus complex in discrimination paradigms, where the composite stimuli readily provide a redundant basis for the discrimination. Yet the presence of other relevant stimuli of the ethanol complex appears to interfere with substitution for a discrimination based on the discrete stimulus effects of each component.

A discrimination based on redundant information provides the possibility for associative learning to influence the basis of the discrimination. One possibility is overshadowing of one component stimulus over another component stimulus within the stimulus complex. Overshadowing can occur if conditioning to a relatively weak stimulus is always presented in combination with a more intense stimulus (49). There is strong evidence that overshadowing does exist within the context of training drug mixtures (33,41,71). For example, in rats trained to discriminate a mixture of two drugs with pharmacologically distinct mechanisms of action (i.e., midazolam and nicotine) the degree of stimulus control by either drug depends upon the ratio of the two drugs in the training mixture. In a 2:1 dose (mg/kg) mixture of nicotine and midazolam, stimulus control was mostly attributed to midazolam. When the ratio was increased to 3.2:1, both components produced strong discriminative responses. Raising the ratio further to 8:1 shifted the predominant stimulus control to nicotine (21). Similar results have been obtained with mixtures of amphetamine plus pentobarbital and nicotine plus morphine (69).

There is evidence that overshadowing can occur between the component stimuli of ethanol (34). The relative prominence of the $GABA_A$ component and 5-$HT_{1B/2C}$ components appears to be greater at lower training doses of ethanol and diminished with higher ethanol training doses (30–32,34). That is, the potency of pentobarbital and several 5-$HT_{1B/2C}$ agonists to produce substitution is decreased in rats trained to discriminate 2.0 g/kg compared to 1.0 g/kg ethanol. Similar profiles have been found with both between-group designs (30–32) and within-subject designs (34). These results have been interpreted as evidence that at higher training doses of ethanol, other aspects of the ethanol cue overshadow the $GABA_A$ and 5-$HT_{1B/2C}$ actions of ethanol.

Alternatively, a higher training dose could reflect a discrimination based on an overall increase in the intensity of the cue necessary to produce generalization. In this case, all dose–response determinations would be expected to be shifted to the right. Eventually, the discriminative stimulus effects of higher doses will not be assessable because the ability to respond under these high doses will be directly affected. However, this does not appear to be the case with ethanol as a training stimulus. In particular, at higher ethanol training doses the potency of dizocilpine to substitute for ethanol is either enhanced (29) or remains the same (34) compared to lower training doses. Thus, the NMDA antagonist substitution patterns do not support the hypothesis that higher training doses of ethanol represent shifts in a quantitative dimension of the discrimination. The mechanism that underlies the apparent overshadowing of $GABA_A$ and $5HT_{1B/2C}$-mediated stimulus effects at higher training doses of ethanol is unknown. Possible mechanisms might be the introduction of a new receptor-mediated effect of ethanol at high training doses, ethanol's separate activity at receptor systems producing novel interaction effects at higher doses, or differential tolerance to component stimuli, including desensitization of receptors. Whatever the mechanism, it appears that overshadowing is a distinct possibility with ethanol as a training stimulus, and different ethanol training doses could result in differential profiles of receptor activity.

Another approach in characterizing a stimulus complex is to investigate the basis of the discrimination when subjects are trained to discriminate the complex from one of its components. These discriminations have been termed AND (the drug mixture)-OR (either of the component drugs) discriminations (51,68). In striking contrast to AND (drug mixture) vs. vehicle discriminations, AND-OR discriminations show no generalization to the individual drugs that comprise the mixture, essentially converting a "redundant" stimulus complex into a "conditional" one. For example, when a midazolam/nicotine mixture is trained vs. saline, either midazolam or nicotine produce complete substitution. Thus midazolam and nicotine are redundant in relation to one another in producing the midazolam/nicotine discrimination (70). However,

if a midazolam/nicotine mixture is associated with one lever and midazolam alone or nicotine alone are both associated with the other lever, then only midazolam/nicotine mixtures substitute for the midazolam/nicotine cue. The latter discrimination is a conditional discrimination in regard to the midazolam/nicotine cue.

An approach similar to the AND-OR discriminations was recently explored in training a series of ethanol vs. pentobarbital vs. water discriminations or ethanol vs. dizocilpine vs. water discriminations (11–13,22). The primary goal of these discriminations was to isolate the different components of the ethanol cue. The animals were trained to discriminate the effects of ethanol from the stimulus effects of one component of the ethanol stimulus. Pentobarbital served as the ligand representative of ethanol's positive modulatory effects at $GABA_A$ receptors, and dizocilpine served as the ligand representative of ethanol's attenuation of NMDA channel function. In the ethanol–pentobarbital–vehicle discriminations, diazepam, midazolam, and allopregnanolone completely substituted for pentobarbital, and did not substitute for ethanol. These data suggest that the pentobarbital discrimination represented the stimulus effects of $GABA_A$-positive modulation, and that $GABA_A$ modulation was not a basis of the ethanol discrimination (11,12). Likewise, in the dizocilpine–ethanol–water discriminations, phencyclidine and ketamine completely substituted for dizocilpine, and did not substitute for ethanol. These data suggest that the dizocilpine discrimination represented the stimulus effects of NMDA channel blockade, and that the NMDA antagonism was not a basis of the ethanol discrimination (13,22). Thus, the resultant ethanol discriminations in the ethanol vs. "component" vs. water training procedures must have been based on either other redundant relevant stimulus effects of ethanol (Fig. 1A) or, alternatively, the conditional presentation of all ethanol's stimulus effects (Fig. 1B).

The three-choice ethanol discrimination described above differs from Stolerman's use of AND-OR discriminations in that only one component of the stimulus complex is trained against the "mixture" ethanol. Thus, in these "partial OR" discriminations, the other orthogonal components of the ethanol stimulus complex could, presumably, substitute for ethanol. Such is the case when dizocilpine was the contrasting stimulus in the three-choice discriminations with either 1.5 g/kg ethanol (22) or 2.0 g/kg ethanol (13) training dose of ethanol. Specifically, the $GABA_A$-positive modulators continued to produce ethanol substitution, even though NMDA antagonism was apparently removed as a basis for the ethanol discrimination (Table 1). Thus, juxtaposing the discriminative stimulus effects of ethanol with the NMDA antagonist dizocilpine resulted in an ethanol cue that retained the redundant nature of the $GABA_A$- and $5\text{-}HT_1$–mediated components to produce ethanol substitution (13,22). In contrast, following training of the ethanol–pentobarbital–water discriminations, NMDA antagonists and 5-HT agonists produced less ethanol-like effects compared to results from two-choice ethanol–water discriminations (11,12). Indeed, the group data show that complete substitution was found only with the short-chain alcohol isopropanol. The results suggest that using pentobarbital as a contrasting stimulus forced a strategy of conditional discrimination with regard to the ethanol cue in a number of rats (Table 1).

Overton (54) demonstrated that the more similar two stimuli are with respect to their pharmacology, the more specific the basis for the resultant drug–drug discrimination. Thus, a greater degree of overlapping pharmacology between ethanol and pentobarbital, compared to dizocilpine, would be predicted to increase the specificity (conditional nature) of the ethanol cue in an ethanol–pentobarbital–water compared to an ethanol–dizocilpine–water discrimination. One prediction of these outcomes is that training a $GABA_A$ ligand that has a pharmacological profile that is less similar to ethanol compared to pentobarbital, should not force a conditional discrimination as the basis for the ethanol cue. Indeed, it may be possible to determine the relative similarities between ethanol and other receptor ligands by measuring the basis of the ethanol discrimination following three-choice discrimination

TABLE 1

SUMMARY OF THE PERCENTAGE OF RATS SHOWING COMPLETE SUBSTITUTION (>80% ETHANOL-APPROPRIATE RESPONDING AT ANY DOSE OF DRUG TESTED) FOR VARIOUS DRUGS TRAINED IN A SERIES OF ETHANOL DISCRIMINATIONS

			Ethanol vs. Drug vs. Water		
	Ethanol vs. Water		Pentobarbital		Dizocilpine
Test Drug*	1.0 g/kg	2.0 g/kg	1.0 g/kg	2.0 g/kg	2.0 g/kg
Ethanol (IG)	100	100	100	100	100
Pentobarbital (IG)	100	100	0	0	100
Pentobarbital (IP)	100	50			100
Midazolam (IP)	75	75	0	14	100
Diazepam (IP)	100	71	0	29	60
3α,5α-P (IP)	100	75	0	14	100
Dizocilpine (IP)	100	100	67	57	0
PCP (IP)	100	100	50	57	0
RU 24969 (IP)	100	100	50	57	43
CGS 12066B (IP)	100	25	20	14	

Ethanol training dose was eigher 1.0 or 2.0 g/kg (IG). Ethanol was trained in two-choice discriminations vs. water and three-choice discriminations of ethanol vs. pentobarbital (10 mg/kg; IG) vs. water or ethanol vs. dizocilpine (0.17 mg/kg, IG) vs. water.

*Drugs are grouped according to $GABA_A$, NMDA, or 5-HT mechanisms of actions.

training. When juxtaposed with ethanol, receptor activity that represents an integral component of the ethanol cue would be expected to produce a highly specific, conditional basis for the ethanol discrimination, whereas receptor mechanisms that are more independent may be isolated without compromising the ability of remaining receptor mechanisms to produce the ethanol stimulus and preserve a redundant basis for the ethanol discrimination.

The apparent conditional vs. the redundant nature of the ethanol stimulus complex has important implications for investigating antagonism of the stimulus effects of ethanol. If the discrimination of a stimulus complex is based on redundant relevant stimuli, then blocking only a single component of the stimulus complex should be insufficient to attenuate the discrimination. For example, a midazolam/nicotine mixture vs. saline discrimination is not blocked by either the benzodiazepine antagonist flumazenil or the nicotinic antagonist mecamylamine (70). However, combinations of flumazenil and mecamylamine were sufficient to block the discriminative stimulus effects of a midazolam/nicotine mixture (72). These data suggest that in an ethanol vs. water discrimination, pretreatment with antagonists for only one component of ethanol should be insufficient to completely block the discriminative stimulus effects of ethanol. Interestingly, there have been mixed reports concerning the antagonism of ethanol's discriminative stimulus effects by a variety of agents. By far the most positive results are with the $GABA_A$ partial inverse agonist Ro 15-4513. However, even this potential ethanol antagonist has produced inconsistent data [see (27)]. Recently, Ro 15-4513 was examined in three different training doses of ethanol vs. water discriminations (23). In all three training groups, Ro 15-4513 blocked the discriminative stimulus effects of 1.0 to 1.5 g/kg ethanol, but higher doses of ethanol overcame the blockade. The data have several implications. First, given above, if the discriminative stimulus effects of a lower dose of ethanol have a robust $GABA_A$ component, then the functional blockade of $GABA_A$ activity with Ro 15-4513 would be expected to block the discriminative stimulus effects of low ethanol doses. Second, as the dose of ethanol is increased, other receptor mechanisms may provide redundant information to serve as the basis of the discrimination. Alternatively, higher doses of ethanol could overcome the Ro 15-4513 blockade in a competitive manner at $GABA_A$ receptors. Separating these mechanisms may require the use of antagonist mixtures, similar to the approach taken by White and Stolerman (72) with mecamylamine/flumazenil mixtures to block the discriminative stimulus effects of nicotine/midazolam mixtures. For example, mixtures of Ro 15-4513 and NMDA may be required to block the discriminative stimulus effects of higher doses of ethanol (e.g., 2.0 g/kg). If this is the case, then there would be evidence that the discrimination of higher doses of ethanol are based on redundant relevant stimuli that are not as prominent at the lower doses of ethanol.

On the other hand, if the ethanol discrimination is based on the conditional presence of multiple stimuli, then the predicted outcome of antagonist pretreatment is very different. Specifically, if each component is necessary in a conditional stimulus, then antagonism of any component should block the stimulus effects of ethanol. These predictions appear to hold for the case of drug mixtures. When animals are trained to discriminate the mixture nicotine/midazolam from either nicotine or midazolam (an AND-OR discrimination), pretreatment with mecamylamine or flumazenil prior to the mixture results in significant attenuation of the discriminative stimulus effects of the mixture (51). This finding is in marked contrast to the lack of significant attenuation when the same drug mixture is trained against water (an AND discrimination) (70,72). Thus, the effectiveness of antagonists is also dependent upon the conditional or redundant nature of the stimulus complex. In the ethanol vs. pentobarbital vs. water discriminations, it appeared that the discrimination of ethanol was based on the conditional presence of ethanol's component stimuli. The prediction for antagonism of ethanol when trained against pentobarbital is that the ethanol cue would be more sensitive to blockade by either a functional $GABA_A$ antagonist, a functional NMDA agonist, or a $5\text{-}HT_{1B/2C}$ antagonist compared to an ethanol cue trained against water. Thus, rather than requiring a mixture of antagonists to block 2.0 g/kg ethanol, blockade of any of the components comprising the ethanol cue should result in blockade of the ethanol cue itself. These predictions remain to be tested.

In summary, the redundant vs. conditional nature of the stimulus complex produced by ethanol is determined by the requirements of the discrimination. In two-choice ethanol–water discriminations, the basis for ethanol discrimination appears redundant, such that ethanol can generalize to each component stimuli, independent of the presence of the other relevant stimuli. There appears to be unequal contribution of these redundant stimuli to the ethanol complex as a function of dose, such that at higher ethanol doses the $GABA_A$-positive modulatory effects and the $5\text{-}HT_{1A/2C}$ agonist effects are overshadowed. The specificity of the ethanol cue can be increased in three-choice discriminations in which one component of ethanol is discriminated from the ethanol complex. One hypothesis is that the more similar the contrasting stimulus is to ethanol in a three-choice discrimination, the more likely the ethanol discrimination will be based on the conditional presence of all ethanol's stimulus elements. By requiring such a specific basis for ethanol discrimination, a full ethanol-like effect may be produced only by those drugs with pharmacological activity highly similar to the heterogeneous effects of ethanol (e.g., other alcohols). Finally, the efficacy of potential antagonists to block the ethanol cue is dependent upon the discrimination requirements. Antagonists should not be robust in ethanol vs. water discriminations, but may be very effective in three-choice discrimination if the basis of the ethanol discrimination is conditional in nature.

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