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Discriminative Effects of Compound Drug Stimuli: A Focus on Attention

DAVID V. GAUVIN* AND THEODORE J. BAIRD†

**Drug Enforcement Administration, Office of Diversion Control, Drug & Chemical Evaluation Section, Washington, DC 20537, and †Department of Pharmacology, 1301 MSRB III, University of Michigan School of Medicine, 1150 W. Medical Center Drive, Ann Arbor, MI 48109-0632*

GAUVIN, D. V. AND T. J. BAIRD. *Discriminative effects of compound drug stimuli: A focus on attention.* PHARMACOL BIOCHEM BEHAV **64**(2) 229–235, 1999.—Discrimination research has increasingly used compound stimuli emerging from drugs acting through multiple neurotransmitter systems or from injections of drug mixtures that approximate "streetwise" drug-taking behaviors. Accompanying this trend has been an interest in the role of cognitive factors in drug discrimination learning. Accounts of multidimensional drug stimuli have focused mainly on specific neuronal mechanisms, and have largely ignored the contribution of stimulus information to the perception of internal events or to the selection processes, heretofore called attention mechanisms, which may underlie the observer's idiosyncratic response to drug administration. It is argued here that research in drug discrimination may benefit from a more detailed consideration of the processes by which an observer interacts with the emergent stimulus properties of drug administration. Therapeutic intervention initiatives may critically depend on knowing the interactions between the specific attributes of the drug experience that capture the attention of the individual and that may later acquire stimulus control over complex drug-taking behaviors. © 1999 Elsevier Science Inc.

Drug discrimination Compound stimuli Stimulus control Attention Selection processes Morphine Cocaine Ethanol Nicotine

OVER the last 40 years, drug discrimination studies have helped to clarify our thinking about how and what is learned about the effects of drugs. According to Balster (1), most of the uses of psychoactive drugs that behavioral pharmacologists are most interested in involve repeated administration. Therefore, learning theory is of particular importance in explaining how experience with drugs modifies their effects. Although almost 4 decades of drug stimulus control data have accumulated, there is a paucity of data characterizing what specific attribute(s) of drug administration gain stimulus control and whether or not these emergent properties of drugs vary between individuals.

The first principle of Gestalt psychology with regards to the basic attributes of stimuli is that the whole is more than the sum of its parts. Arrays of stimuli have emergent properties that cannot be ascribed to any component stimulus element. Compound or complex stimuli normally involve multiple and related sources of stimulus information, and questions naturally arise about the relative contributions of different features of the stimulus to the perception of the whole (11,12). As with more traditional (exteroceptive) stimuli, subjects in drug discrimination studies are thought to "select" a single element or a subset of available stimulus elements or arrays produced by the training dose of the drug that is used in the discrimination training [cf, (15,36,37)].

Keller and Shoenfeld (41) first proposed that "conceptual behavior" was demonstrated when an animal responded similarly to members of one stimulus class and differently to members of other stimulus classes. Wasserman and Bhatt (57) have defined "stimulus class" as a collection of discriminably different stimuli, each of which is nevertheless more similar to members of that class than it is to members of other classes of stimuli. From this definition it can be inferred that generalization profiles in discrimination tasks represent stimulus similarity and not identity of effects. The drug discrimination literature is replete with evidence that both animals and humans can learn these discriminations and, for the most part, that these discriminations are specific to the pharmacological class of the training drug. However, there has been little focus on what is actually being learned by the subject about the drug as a "stimulus."

Requests for reprints should be addressed to David V. Gauvin, Ph.D., Drug Enforcement Administration, Office of Diversion Control, Drug & Chemical Evaluation Section, Washington, DC 20537.

Early psychologists typically studied and viewed simple stimuli. Within the exteroceptive stimulus literature often the stimulus was a single physical continuum such as wavelength of light, the orientation of a line, or sound frequency or intensity. For interoceptive drug-induced stimuli psychologists typically have used single drugs hypothesized to produce their stimulus arrays from actions on a single receptor system. The rationale for the selection of stimuli seemed clear: it permitted the precise analysis of stimulus control of responding. The use of these single element stimuli has increased our understanding of stimulus control of behavior by both exteroceptive and interoceptive stimuli.

With respect to stimulus control by compound exteroceptive stimuli, it repeatedly has been demonstrated that the specific or particular stimulus dimension that controls the behavioral operant is largely beyond experimental control (10,29,50,58). Which specific aspect of the compound cue (e.g., "form or color" or "light or tone") becomes the "functional" or "effective" stimulus controlling the response can be determined by a number of possible factors. It has even been suggested that the functional or effective stimulus that acquires stimulus control may even be idiosyncratic (10,29,50).

The systematic study of stimulus control, in general, requires the acquisition of a response in the presence of one or more stimuli on the dimension of generalization. Blough and Blough (2) have concluded that good stimulus control requires, by definition, an attentive subject. It is well known from the discrimination studies examining exteroceptive stimulus control that even when the conditions of dimensional acquisition are kept constant, the nature of stimulus control manifested after such training will vary from animal to animal and from group to group. A number of researchers have discovered that animal subjects do not always learn to respond equally to all aspects of stimuli differing along multiple dimensions (4,13,30,39,54–56). For example, in 1961 Reynolds (49) demonstrated that different aspects of a compound stimulus acquired control over responding in different subjects. In the initial experiment, Reynolds trained two pigeons on a successive discrimination in which the S+ was a white triangle on a red background and S− was a white circle on a green background. Once trained, it was discovered that neither pigeon responded to either the green background or to the white circle. That is, the S− acquired control over not responding. However, one bird responded only when the red background was presented, whereas the other pigeon responded only when the white triangle was presented. Only one aspect of the S+ controlled responding, and it did so in an unpredicted manner. Using morphine as a training stimulus in a discrimination task, Gauvin et al. (15) demonstrated conceptually similar results to the Reynolds study described above.

In 1996, Gauvin et al. trained rats to discriminate the presence and absence of a 5.6 mg/kg morphine training stimulus. Once trained, crossgeneralization tests were conducted with the psychoactive ingredients of a number of over-the-counter medications that have proven to produce elements of the subjective experience resulting from morphine injections in humans including, sedation, lethargy, analgesia, and anxiolysis. Although each drug tested failed to produce complete crossgeneralization with the training stimulus, a unique drug mixture was found for each rat that did engender complete (>90%) morphine-appropriate responding. The mixture of simpler elementary drug stimuli appeared to form compound drug mixture stimuli that were subjectively similar enough to the morphine training stimulus to produce patterns of responding similar to those engendered by the 5.6-mg/kg morphine injection. Interestingly, the compound drug mixtures were different for each of the nine rats that finished the study. Typical mixture tests are shown in Fig. 1. Each over-the-counter elementary drug stimulus was tested for crossgeneralization singly and then combined with each other to form a compound stimulus that engendered complete crossgeneralization with the morphine training stimulus. It could be concluded that for each subject in the experiment some subset of simpler stimulus elementary cues (e.g., analgesia, lethargy, relaxation, CNS depression, and so forth), which are shared by a number of other drugs, controlled the response choice measure. The question, then, is, "Do these morphine-related data reflect a unique situation?" The individualized "morphine-like" compound stimulus created through a process of stimulus additivity in the Gauvin et al. (15) study is not the only report demonstrating the creation of over-the-counter compound drug mixtures that produce subjective profiles similar to those produced by controlled drugs of abuse. The creation of a "cocaine-like" stimulus has been accomplished by the mixing of sets of other over-the-counter cold and diet aids containing ephedrine, phenylpropanolamine, and caffeine (20), by the combination of two antihistamines (doxylamine and diphenhydramine) (17), and, more recently, by combinations of commonly used over-the-counter cold medications "dextromethorphan and ephedrine" and "dextromethorphan and diphenhydramine" (25).

Drug-taking behavior never occurs in isolation. Complex or compound situations involving multiple sources of information are ecologically more valid, and seem more informative about behavior in the real world (11,12). Brunswik (3) long ago demonstrated the advantages of studying behavior in situations where the natural covariations between variables was preserved because such situations were more representative of naturalistic conditions. Herrnstein and Loveland (34) were instrumental in shifting to this new perspective. In one study, pigeons were trained to discriminate pictures of people or parts of people from pictures that did not contain people. Subsequent studies focusing on category recognition demonstrated that pigeons can accurately report the presence versus absence of a class of objects (e.g., buildings, trees, fish) in complex visual stimuli (31–33,35). Although these studies have clearly demonstrated a more Gestalt-like orientation in the approach to the study of control by complex or compound stimuli by animals, humans do not simply sort stimuli into object-present and object-absent categories (57). Drug stimuli are most usually not experienced in isolation. The cup of coffee, the cigarettes smoked, the over-the-counter cold or headache tablets administered prior to the illicit drug administration all contribute to the "drug experience." Humans not only classify natural stimuli, but also stimuli that we have ourselves created or experience on an idiosyncratic or personal basis as is the case with self-administered drugs. As earlier reviewed by Terrace (53), differential reinforcement may be considered to be a sufficient condition for some elementary dimension of a complex stimulus to gain control over a particular response. However, we still do not know whether it is a necessary condition. It seems quite probable that, in many situations, innate factors may determine the "effectiveness" or "distinctness" of a particular stimulus element without the benefit of differential reinforcement with respect to that element. In fact, it is quite probable that the stimulus element can itself act to reinforce the situation, for example, when a drug with anxiolytic attributes is taken under a subjective state of anxiety.

For some researchers, this variability in the nature of stimulus control between subjects has been the defining charac-

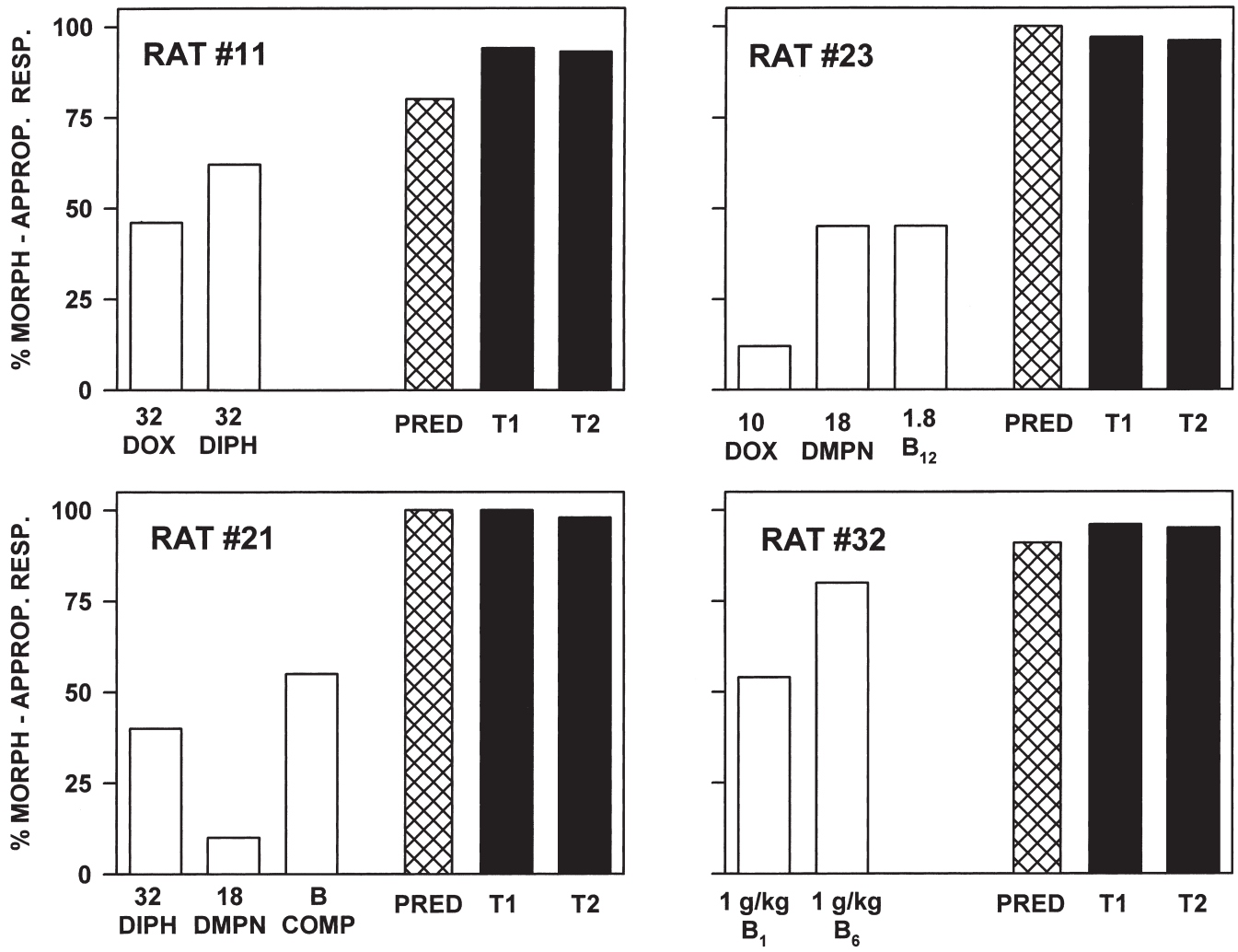

FIG. 1. Individual rat crossgeneralization functions. Single-dose tests were conducted with the active ingredients of a variety of over-the-counter drugs in rats trained to discriminate the presence and absence of 5.6 mg/kg morphine sulfate. The percentage of test session responses emitted on the morphine-appropriate lever are shown for four representative rats to demonstrate the diversity of responding produced by tests with individual drugs (open bars) and their combination (filled bars). The hatched bars represent the predicted results of combining single drug elements based on "simple effect additivity." The filled bars represent the results of two independent test sessions conducted with the combination of each of the single drug doses represented in each panel. See (15) for details. DOX: doxylamine; DIPH: diphenhydramine; DMPN: dextromethorphan; B_1: thiamine, vitamin B_1; B_6: pyridoxine, vitamin B_6; B COMP: B complex (1.8 mg/kg—B_{12} + 180 mg/kg of B_1 and B_6).

teristic of "attention" (53), while others use the term "attention" to refer to a class of experimental operations (37). Here, the term "attention" is defined by Mackintosh (43), and refers to a parameter of stimulus control whose value determines first the amount of change in associative strength of a given stimulus dimension as a consequence of reinforcement and nonreinforcement and, to the extent to which the subject's behavior will be actually controlled by that stimulus dimension(s) rather than by another at any particular moment. The distinguishing characteristics of attention or stimulus-selection models of discrimination learning is that a potential cue, or stimulus element, is viewed as competing with other available elements for the behavioral effects resulting from reinforcement and nonreinforcement. All current selection theories have a commonality in suggesting that the response-eliciting properties of a single stimulus element of a compound cue depends not only on the reinforcement schedule associated with the presence vs. absence of that element, but also on the validity of the other available elements. Considering drug discrimination studies, the most obvious controlling mechanism directing which specific attribute will gain stimulus control or guide the behavioral choice of the subject would be the specific dose selected for the training drug stimulus.

Colpaert (9) and Gauvin and Young (26) have previously demonstrated that the training dose selected for discrimination training is a critical factor in regulating the qualitative specificity of the resulting generalization profiles. The degree of specificity of the stimulus control acquired by the training cue appears to be governed by the magnitude or intensity of the dose selected for training. Although Colpaert (9) and Gauvin and Young (26) used single drug stimuli, the effect of training dose selection in compound drug discrimination tasks

has been demonstrated by Gauvin and Holloway (23). Rats were trained to discriminate the presence and absence of an ethanol-nicotine combination. The specific doses used for the compound cue were based on previous data, and were selected to reduce the probability of behavioral toxicity and to create a compound stimulus whose individual elements would equally contribute to the saliency of the resulting compound drug cue. The initial training dose of 0.5 g/kg ethanol was selected to be combined with 0.5 mg/kg nicotine. Once the training criteria for stimulus control was achieved, generalization tests were conducted with both ethanol and nicotine administered singly. It was discovered that the 0.5 mg/kg nicotine portion of the compound cue controlled the choice selection to the compound drug mixture-appropriate lever (i.e., overshadowing). The 0.5 mg/kg ethanol dose element minimally controlled the response choice measure, and only engendered approximately 10% mixture-appropriate responding. In an attempt to redirect the attention of the subjects to the ethanol element of the compound cue, additional training was instituted with a higher dose of 1.0 g/kg ethanol in combination with a lower dose of 0.3 mg/kg nicotine. After 1 month of additional training new generalization tests were conducted. Both nicotine and ethanol training elements engendered approximately 50% mixture-appropriate responding, suggesting equivalent stimulus saliency between the two elementary stimuli of the compound cue. In response to an upward shift of the ethanol training dose and the downward shift in the nicotine training dose, the subjects appeared to equivalently shift their attention to both elements of the training drug mixture.

Most stimulus-selection theories have acknowledged the importance of irrelevant or incidental stimuli in determining discrimination performance. In a series of position papers Restle (46–48) attempted to show how a variety of discrimination phenomena may be accounted for in terms of the differential significance of incidental cues. As discussed above, Gauvin et al. (7,15,20,24,25) have shown that combinations of drug elements which, on the surface and when tested singly, may appear to be quite benign and produce limited crossgeneralization with the training drug, appear to summate in a simple additive fashion to engender a response pattern similar to that induced by the training dose of the training drug. Within a clinical population of drug abusers, it has been suggested that the need to coadminister drugs is determined by the need for a specific subjective state change at any given time (40). There are numerous reports demonstrating the growth in polydrug abuse over the last 2 decades. If the coadministration of drugs is motivated by an individual's need for the addition of incidental stimuli, and if this stimulus additivity is an important ingredient in the production of a particular phenomenon leading to continued drug usage, then it should be possible to demonstrate an idiosyncratic response to drug administration in clinical populations as well.

Chait (5–7) and Chait, Uhlenhuth, and Johanson (8) have investigated the individual differences in the subjective effects produced by the single administration of psychomotor stimulants including ephedrine, amphetamine, and methylphenidate. In these studies a number of factors appeared to contribute to the between- and within-subject responses to drug administration, including gender, baseline mood measures, personality characteristics, and drug history. As detailed in Gauvin et al. (15), one of the clearest examples of the idiosyncratic response to drugs of abuse within a clinical population has been given by Kumor et al. (42). These authors used multidimensional scaling techniques to distinguish between three distinct opiates—morphine, cyclazocine, and ketocyclazocine—in a population of polydrug abusers. Goodness-of-fit measures for the four distinct dimensions that best characterized the subjective effects of the three distinct opioids varied across individual participants. For three of the participants all four dimensions were important to classify the training drugs; for one participant only one dimension (Dimension 1) was important, and another dimension (Dimension 3) was irrelevant to classify the drugs; and for another participant that same third dimension accounted for the largest portion of the participant's judgment, and the fourth dimension was totally irrelevant. None of the 14 stimulus objects utilized by the multidimensional scaling technique was responsive to the quantitative dimensionality or dose relatedness of the information. Kumor et al. (42) concluded that the dimensional ordering of morphine resulted from the large number of symptoms produced rather than any particular subjective effect of morphine, such as euphoria.

The issue of "what is being attended to" during drug administration is extremely relevant in the study of drugs as stimuli, to the role these stimuli may play in a drug's abuse liability, and to the intervention initiatives taken to reduce the intake of drugs of abuse in the general population. During the initial drug experiences subjects come to identify certain elements of their internal milieu and learn the language or parlance for those subjective experiences. The labeling of these unique internal events occur without ever knowing if their own subjective changes are identical to those around them. The physiological and psychological changes labeled with the terms "buzzed" or "rush" or "coasting" are subjective, because there is no objective reality to their assessment. Once the terms are learned, the exact nature of the drug experience becomes somewhat universal, yet the subjective experience remains unique and idiosyncratic. Over repeated drug exposures the subjective drug experiences may change, but the adjective check list of terms used to identify their experiences may not. When these subjects are brought into the lab and attempts are made to characterize or objectively measure the individual's response to controlled drug administration the individual variability is identified.

McMillan, Sun, and Hardwick (44) have conducted sequential drug discrimination training procedures in pigeons. They demonstrated that drug stimuli can continue to exert stimulus control over behavior for extended periods, and that the pigeons could maintain multiple drugs as cues for the same response, even when these drugs were from different pharmacological classes. Analogously, humans may learn about many drug experiences and maintain the same verbal response (i.e., buzzed, high, rush, etc.) to describe all of them.

The McMillan study used a number of drugs from divergent pharmacological classes and clearly demonstrated that subjects can attend to diverse arrays of stimuli through extradimensional training. The long series of training and retraining appeared to direct the attention of the experimental subjects to be overinclusive, resulting in a more global set of arrays controlling the behavioral operant. If attentional mechanisms are involved in drug stimulus control, we would predict that these results could not be replicated if sequential techniques were used with intradimensional training. There are some basic tenets of perception, one of which is that it is impossible to experience polar opposites in subjective experiences; we cannot subjectively experience hot and cold, we cannot simultaneously attend to figure and background in figure–ground relationships; and we cannot experience anxiety and anxiolysis at the same time.

We have recently completed a study examining the sequential training of the acute or intoxicating effects of ethanol and ethanol-induced hangover on the premise that these two pharmacological states represent bipolar ends of the anxiety-relaxation continuum [cf, (14,16,18,19,21,22,27)]. We predicted that our results would differ from the McMillan study with extradimensional stimulus training. The McMillan studies demonstrated that, through sequential training, *d*-amphetamine, morphine, pentobarbital, and diazepam would maintain similar response choice profiles. Our prediction was that subjects would not demonstrate similar response crossgeneralization profiles between ethanol's intoxicating effects and its hangover effects. The basic premise of subjective experience is that subjects cannot maintain the same response associated with the perceived feelings of "relaxation" with the subjective experience of "anxiety." We predicted that through sequential training, the crossgeneralization profiles would shift from the anxiolytic-like acute effects of ethanol to an anxiogenic-like profile engendered by ethanol hangover.

Fourteen male Sprague–Dawley rats were trained to discriminate the presence and absence of 1.25 g/kg ethanol (15 min ptmt.) in a 15-min two-choice food-reinforced procedure [for more detailed training procedures, see (18,27)]. Once rats met training criteria demonstrating stimulus control (>90% accuracy for four consecutive sessions), they were tested in individual sessions with various doses of ethanol, chlordiazepoxide, and pentylenetetrazole. Figure 2 shows the crossgeneralization profiles from this initial training. Ethanol and chlordiazepoxide, drugs with an anxiolytic profile, engendered a dose-dependent increase in the percentage of total session responses emitted on the ethanol-appropriate lever. Pentylenetetrazole, and anxiogenic agent, failed to generalize with the ethanol training stimulus. At the completion of these tests rats were retrained to press the same ethanol-appropriate lever during periods of acute ethanol withdrawal or "hangover." Experimental hangover was induced by injecting each rat with 4 g/kg ethanol 18 h before the training session [see (18) for details]. Volume control saline injections were administered on saline training days. The first training session with the new "hangover" stimulus produced a majority of responses emitted on the saline- or default-appropriate lever. Over successive training sessions subjects shifted their choice lever-press responding over to the new "hangover"-appropriate lever. Once rats demonstrated stimulus control by the hangover cue the crossgeneralization profiles were redetermined (Fig. 3). Tests with the previous training stimulus (1.25 g/kg ethanol, 15 min ptmt.) failed to engender any "hangover"-appropriate responding (the point labeled E-TD1 on ethanol abscissa). After the second sequence of training, chlordiazepoxide engendered only saline- or default-appropriate responding up to a test dose of 32 mg/kg. But more importantly, pentylenetetrazole now engendered a dose-related increase in the percentage of session responses emitted on the "hangover"-appropriate lever. The data are congruent with the hypothesis that the sequential training of ethanol and hangover stimuli shifted the attention of the experimental subjects from the relaxation or anxiolysis end of the affective continuum down to the polar opposite, anxiety, end of the dimension. We suggest that these data demonstrate that intradimensional training may be one historical factor regulating the subjective state changes occurring over repeated drug administration.

According to the traditional views of stimulus control (45,52), the elemental features of complex stimulus events

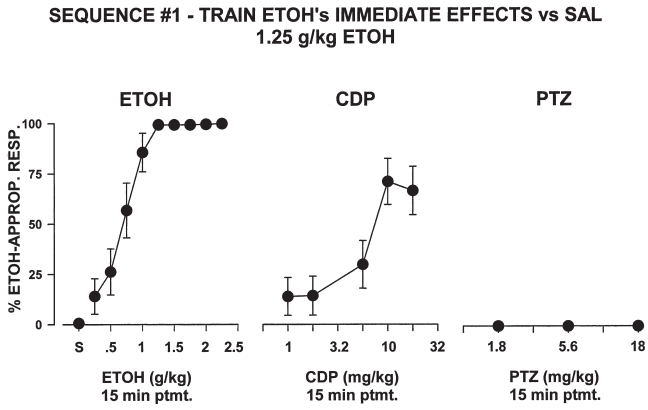

FIG. 2. Stimulus generalization functions from training sequence #1—the group mean percentage of total test session responses emitted on the ethanol-appropriate lever are plotted as a function of the test dose administered 15 min prior to the test session. The training drug, ethanol, demonstrated a dose-dependent increase in the percentage of responses emitted on the ethanol-appropriate lever (left panel). Chlordiazepoxide (CDP) partially generalized with the 1.25 g/kg ethanol training cue (center panel). Pentylenetetrazole (PTZ) doses engendered exclusive responding on the saline- or default-appropriate lever (right panel). Each point represents the mean of 14 rats. The point above the "S" on the ethanol abscissa shows the results of the saline test session.

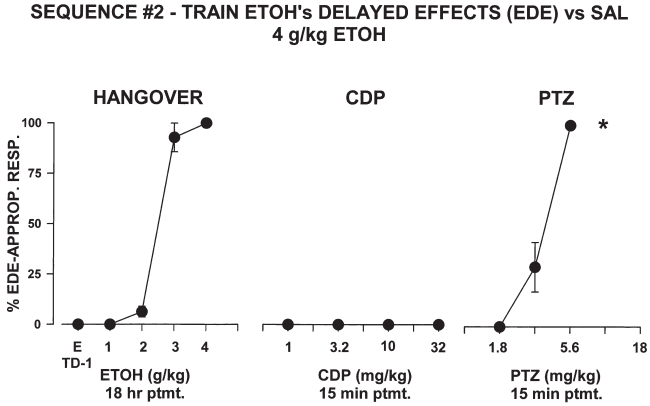

FIG. 3. Stimulus generalization functions from training sequence #2—the group mean percentage of total test session responses emitted on the "ethanol-delayed effect" (EDE)-appropriate lever are plotted as a function of the test dose. High-dose pretreatments of the training drug, ethanol, administered 18 h prior to the test session demonstrated a dose-dependent experimentally induced hangover that produced increases in the percentage of responses emitted on the EDE-appropriate lever (left panel). Chlordiazepoxide (CDP) failed to produce any crossgeneralization with ethanol hangover training cue (center panel). Most interestingly, the second sequence in the training resulted in full crossgeneralization with the anxiogenic drug, pentylenetetrazole (right panel). Each point represents the mean of 14 rats. The point above the "E—TD1" on the ethanol abscissa shows the results of the test conducted with the 1.25 g/kg ethanol training dose used in the first sequence of training. The acute or immediate effects of ethanol failed to generalize with the new hangover stimulus. The * on the PTZ generalization function indicates a test dose that induced clonic seizures during the pretreatment interval; therefore, rats were not tested in the discrimination task.

compete for limited associative strength so that control by one element or stimulus dimension is gained at the expense of others (11,12,38). Which specific stimulus dimension or set of dimensions captures the attention of the individual subject becomes a critical question when developing intervention strategies. If drug-seeking or drug-taking behaviors come under the control of interoceptive states, and if these internal states are idiosyncratic in nature, then what is the likelihood of developing a single therapeutic "magic bullet" which is 1) functional, 2) demonstrates patient compliance, and 3) equivalently blocks the internal cues produced by a given drug in all drug takers? The current database suggests a minimal probability of success.

Because drugs of abuse represent a complex multidimensional stimulus event, we question whether a single receptor system adequately addresses the initiating events in the cascade of drug-seeking and drug-taking behaviors. As first proposed by Fetterman (11) for exteroceptive stimuli, we believe the concept of the drug stimulus needs to be liberalized. Animals have evolved to cue into predictive variations in patterns of stimuli (28,51); what may appear to be a highly complex pattern within the tradition that holds that a stimulus is something discrete and momentary may be simple from the observer's point of view. A stimulus may consist of a pattern of change or the relations between features. Current reductionist approaches to stimulus control should be supplemented by psychophysical analyses that relate behavior to higher order stimulus events. Many ecologically relevant stimulus events involve multiple sources of stimulus information that often are not completely redundant predictors of positive reinforcement. Approaches to the experimental analysis of drug stimulus control that emphasize cue competition should be complemented by those that consider the ways in which nonredundant and incidental stimuli, that compose compound stimulus events, influence drug-taking behaviors.

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This article was presented at the fifth international meeting on drug discrimination held in Beerse, Belgium, August 30 through September 1, 1998, cosponsored by the European Behavioural Pharmacology Society and the Society for Stimulus Properties of Drugs. Since this talk was presented, two demonstrative illustrations of some basic concepts that I discussed have been published. The concept of "emergent properties" has most recently been applied to neural networks of biological pathways by Bhalla, U. S.; Iyenger, R.: Emergent properties of networks of biological signaling pathways. Science 283:381–387; 1999. Similar neural networks may underly the basic phenomena discussed in this article. The differential contribution of multiple systems on the behavioral effects of drugs has also been illuminated in reports by Gainetdinov, R. R.; Wetsel, W. C.; Jones, S. R.; Levin, E. D.; Jaber, M.; Caron, M. G.: Role of serotonin in the paradoxical calming effects of psychostimulants on hyperactivity. Science 283:397–401; 1999; and by Ledent, C.; Valverde, O.; Cossu, G.; Petitet, F.; Aubert, J.-F.; Beslot, F.; Böhme, G. A.; Imperato, A.; Pedrazzini, T.; Roques, B. P.; Vassart, G.; Fratta, W.; Parmentier, M.: Unresponsiveness to cannabinoids and reduced addictive effects of opiates in CB_1 receptor knockout mice. Science 283:401–404; 1999.

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