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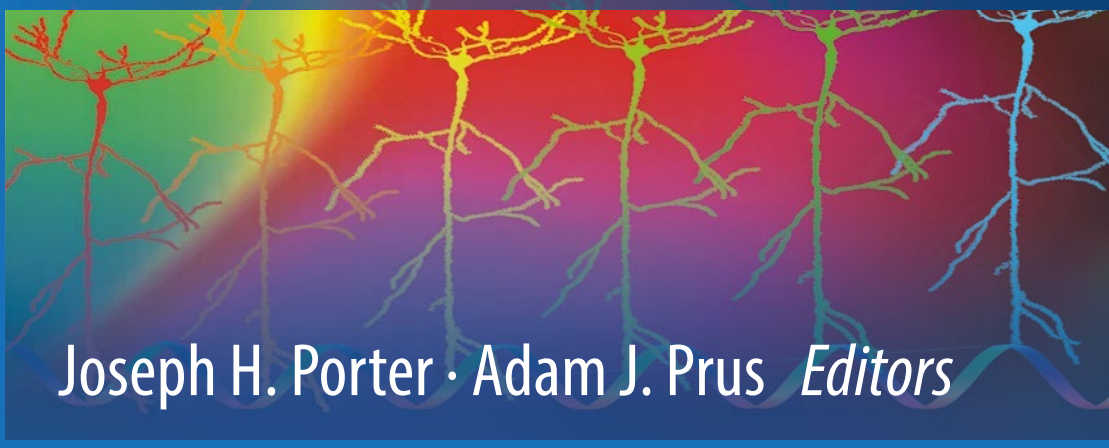

Joseph H. Porter · Adam J. Prus *Editors*

The Behavioral Neuroscience of Drug Discrimination

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The Behavioral Neuroscience of Drug Discrimination

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Preface

The year 2018 marks the 40th anniversary of the founding of the Society for the Stimulus Properties of Drugs (SSPD). The events that led to the founding of SSPD with its first official meeting on June 3, 1978, in Baltimore, MD, USA, have been described by the society's first three presidents Donald A. Overton, John A. Rosecrans, and Herbert Barry III in a special issue on drug discrimination published in *Pharmacology Biochemistry and Behavior* (Overton et al. 1999). Even prior to that first meeting of SSPD in 1978, books were beginning to appear about this new, exciting area of research that allowed behavioral pharmacologists to measure the "subjective effects" of drugs and, perhaps even more importantly, to demonstrate that the discriminative stimulus properties were related to specific pharmacological activity at the receptors of brain neurotransmitters in the central nervous system. There have been at least six different books written specially about drug discrimination and the discriminative stimulus properties of drugs (Colpaert and Balster 1988; Colpaert and Rosecrans 1978; Colpaert and Slangen 1982; Glennon and Young 2011; Ho et al. 1978; Thompson and Pickens 1971), and there also have been several special issues of journals that focused on drug discrimination studies published over the years [*Drug Development Research*, Vol. 16, 1989; *NIDA Research Monograph* 116 (DHHS pub. # ADM 92-1878), 1991; *Behavioural Pharmacology*, Vol. 2, 1991; *Pharmacology Biochemistry and Behavior*, Vol. 64 (2), 1999; *Psychopharmacology*, Vol., 2009]. Thus, there is a rich history of researchers in this field periodically coming together to present an update on the most current information about the discriminative stimulus properties of drugs. This book continues this tradition and is published as part of the *Current Topics in Behavioral Neurosciences (CTBN)* series published by Springer and is titled *The Behavioural Neuroscience of Drug Discrimination*. The goal of this volume is to provide up-to-date summaries on a number of diverse topics that encompass the current research literature for the stimulus properties of drugs.

As with any writing project like this, there are many people to thank. First and foremost, we would like to thank Bart Ellenbroek who first approached me (JHP) several years ago to see if I would be interested in editing a book on drug

discrimination. I of course said yes and then didn't think anything else about it until Bart contacted me some time later and said the project had been approved. I immediately asked Adam Prus to join me as a co-editor as he was a logical choice for a co-editor, plus I knew that this project would require a tremendous amount of time—recruiting potential authors for the various chapters and, of course, the actual editing of each chapter as they were completed. As with any writing project of this scope, there were many delays along the way and the editors and staff at Springer (K. Adeitia, Alameluh Damodharan, Susanne Dathe, Wilma McHugh, Sujitha Shiney, and Nayak SulataKumari) have displayed an amazing level of patience dealing with a large group of authors (including the co-editors!) who failed to meet deadlines much too often. Finally though, we have a finished project with 14 chapters that cover a wide diversity of topics in the field of drug discrimination. We want to thank all the contributors to each chapter as this book would not have been possible without them. Also, there are several individuals (Scott Bowen, Herbert Covington, and Richard Young) who graciously gave of their time to help out with the review process for one or more chapters. Their input was extremely valuable and helped to improve the quality and clarity of the individual chapters and of course the entire book itself. At the end of the chapter "Drug Discrimination: Historical Origins, Important Concepts, and Principles," we discuss the individual chapters and authors, and in the chapter "A Prospective Evaluation of Drug Discrimination in Pharmacology," Ellen Walker helps to put all of these diverse chapter topics into perspective.

Finally, as we noted in the first paragraph, completion of this book marks the 40th anniversary of the founding Society for the Stimulus Properties of Drugs, but it is also a bit bittersweet, as it also marks the end of this society. As often happens with small research societies, they have a natural life span—the birth of the society, the growth and development of that research field into adulthood, the maturing of that field into old age, and of course the natural ending of its existence. While we are a bit sad about this, we realize that drug discrimination has become an extremely valuable behavioral assay in the field of behavioral pharmacology and that it is utilized in many research labs around the world. It still remains the best (and perhaps the only) approach for studying the subjective effects of drugs that possess psychostimulant properties. For that reason, we are confident that drug discrimination will remain an extremely valuable research assay, with no demise in sight!

Richmond, VA, USA — Joseph H. Porter
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Contents

Drug Discrimination: Historical Origins, Important Concepts, and Principles

Joseph H. Porter, Adam J. Prus, and Donald A. Overton

Abstract Research on the stimulus properties of drugs began with studies on state dependent learning during the first half of the twentieth century. From that research, an entirely new approach evolved called drug discrimination. Animals (including humans) could discriminate the presence or absence of a drug; once learned, the drug could serve as a discriminative stimulus, signaling the availability or nonavailability of reinforcement. Early drug discrimination research involved the use of a T-maze task, which evolved in the 1970s into a two-lever operant drug discrimination task that is still used today. A number of important concepts and principles of drug discrimination are discussed. (1) The discriminative stimulus properties of drugs are believed in large part to reflect the subjective effects of drugs. While it has been impossible to directly measure subjective effects in nonhuman animals, drug discrimination studies in human subjects have generally supported the belief that discriminative stimulus properties of drugs in nonhuman animals correlate highly with subjective effects of drugs in humans. In addition to the ability of the drug discrimination procedure to measure the subjective effects of drugs, it has a number of other strengths that help make it a valuable preclinical assay. (2) Drug discrimination can be used for classification of drugs based on shared discriminative stimulus properties. (3) The phenomena of tolerance and cross-tolerance can be studied with drug discrimination. (4) Discriminative stimulus properties of drugs typically have been found to be stereospecific, if a drug is comprised of enantiomers. (5) Discriminative stimulus properties of drugs reflect specific CNS activity at neurotransmitter receptors. (6) Both human and nonhuman subjects display individual differences in their sensitivity to discriminative stimuli and drugs. (7) The drug discrimination procedure has been used extensively as a preclinical assay in drug development. This

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chapter is the first in the volume The Behavioural Neuroscience of Drug Discrimination, which includes chapters concerning the discriminative stimulus properties of various classes of psychoactive drugs as well as sections on the applications and approaches for using this procedure.

Keywords Cross-tolerance · Discriminative stimulus · Drug development · Drug discrimination · Individual differences · State dependent learning · Stereospecific · Stimulus properties · Subjective effects · Tolerance

Contents

1 Introduction

Drug discrimination is a paradigm in which an organism learns to discriminate the pharmacological effects of a drug from the absence of drug or from the noticeably different pharmacologically effects produced by other drugs. The procedure as established today primarily relies on operant responding procedures (however, see Riley et al. 2016, this volume) and has been used in a wide variety of species, most commonly including rats, mice, and pigeons, and also in nonhuman primates and humans. Operant drug discrimination procedures require extensive training in order for an organism to accurately learn to identify the effects produced by a drug (or a combination of drugs) and the dose of that drug. The drug is referred to as a *training drug*. An appeal of this procedure is that discriminative stimulus properties of a drug can consist of those identified as *subjective*, rather than *objective*, and that the drug is a stimulus (see Catania 1971). As Catania (1971) emphasizes, discriminative control by a drug represents a *behavioral* relationship between environmental events (a drug in this case) and responses. Also, it is not necessary to understand the underlying receptor mechanisms responsible for this stimulus control, in order to understand the relationship between the interoceptive event and the response. Regardless, drug discrimination has been used extensively to study recreational and abused

substances in order to identify underlying pharmacological actions and mechanisms responsible for their subjective effects. Drug discrimination also has been utilized for studying therapeutic psychoactive drugs, such as antidepressants, anxiolytics, and antipsychotics. For a number of years, the drug discrimination paradigm has been used in both academia and industry to help elucidate the pharmacological basis of psychoactive substances. This volume, titled "*The Behavioural Neuroscience of Drug Discrimination*" as part of the *Current Topics in Behavioral Neurosciences* (CTBN) series provides reviews of the current literature for a number of either specific drugs or categories of drugs. This introductory chapter provides an overview of the historical origins of the drug discrimination procedure and discusses some important concepts and principles regarding the drug discrimination procedure.

The individual chapters in this book review the current state of the art regarding the discriminative stimulus effects of the primary classes of psychoactive drugs. The chapters highlight seminal and key findings in these areas sufficient to cover general scope of knowledge from these fields and focus on the utility of these procedures for CNS pharmacology research. Whenever possible, chapters connect the stimulus properties of drugs to mediating neuropharmacological actions (i.e., effects on specific receptor mechanisms). Moreover, the chapters in this book all document how the discriminative stimulus effects shown in animals translate to humans. Finally, by featuring leading experts in their respective areas, the chapters update and provide insight into future avenues of study with the drug discrimination paradigm.

2 Historical Origins

2.1 State Dependent Learning

As a number of excellent reviews have been written documenting the early history and concepts of the control of behavior by drugs as stimuli (e.g., Overton 1971, 1982, 1991; Schuster and Balster 1977), we will only briefly describe the historical antecedents to drug discrimination before focusing primarily on the transition from the T-maze drug discrimination developed by Overton (see Overton 1991), to the currently used operant drug discrimination procedure.

The first report of *dissociated* learning produced by drugs, later called *state dependent learning*, was by Combe (1835) who published a report of a delivery man who left a package at an incorrect address while drunk and then could not remember where he had left it until he was again intoxicated. The idea that memories might be linked to a drug state was later popularized in Wilkie Collins' classic novel "The Moonstone" (1868), which cited Combe's report as proof of the possibility. In both of these sources, the amnesic effect was apparently asymmetrical in that memories formed while drugged were unavailable without drug; however, memories formed while sober would generalize into the drug state. Later at the end of the nineteenth century, Théodule-Armand Ribot, a famous French psychologist,

developed a theory for memory retrieval in which interoceptive stimulus cues played an important role (Ribot 1882, 1891). His model predicted symmetrical amnesias with retrieval impairments after either normal to abnormal or abnormal to normal changes in body physiology. Ribot presented no new data and his theory apparently was an integral part of the intense interest in dissociation that existed in Europe throughout the last half of the nineteenth century.

The next real data about drug state dependent learning was not published until 1937 when Girden and Culler (1937) reported impaired retrieval of conditioned leg flexion responses in dogs after drug (D) to no drug (N) transitions. The effects of N to D transitions were not tested. These findings made their way into contemporary textbooks (Morgan and Stellar 1950, p 449) but seem not to have been very well integrated into the neuroscience of the time and led to only one replication attempt Gardner and McCullough (1962). It would be hard to argue that the scattered reports just described were part of a program of research about drug effects on memory retrieval. Instead, it appears that they were put in the "scientific curiosities" category and received little attention. However, the beginnings of the drug discrimination procedure can be traced back to this early work on state dependent learning conducted during the 19th and the first half of the twentieth century (Overton 1991).

2.2 Drug Discrimination

A major advancement in understanding state dependent learning came from the theories of Neal Miller, a widely respected psychologist, who argued that drug effects should act as memory retrieval cues and that laboratory experiments using a 2 × 2 design could show these effects (Grossman and Miller 1961; Miller 1957; Miller and Barry 1960). Incidentally, the 2 × 2 design employs four groups of subjects that are trained and later tested for retrieval using the drug conditions N–N, N–D, D–N, and D–D. Studies by one of the present authors (Overton 1961, 1964, 1966) also played an important role during this transition period, as it obtained convincing results and was widely read and cited. It used escape training in a T-maze drug discrimination paradigm and showed that the frank dissociative amnesias produced by high dosages were replaced by gradually acquired discriminative control at lower dosages – hence linking state dependent learning and drug discrimination phenomena.

As a better understanding of the ability of drugs to serve as stimuli (in a manner analogous to sensory stimuli) was obtained, the state dependent learning procedure evolved to produce a drug discrimination procedure. This allowed researchers to demonstrate for the first time that animals could reliably distinguish a drug state from a nondrug state and that the effects of drugs could be established as discriminative stimuli. The first drug discrimination study actually had been conducted several years earlier by Conger (1951) who used an approach/avoidance task in which rats were trained to approach when "inebriated" and to avoid when "sober," or vice versa. Thus, Conger was able to demonstrate that ethanol exerted discriminative

control over the behavior of the rats and, like other stimuli, drugs could set the occasion for responding – i.e., drugs could serve as *discriminative stimuli*. Overton (1961, 1964) further refined the drug discrimination procedure, introducing the two-choice T-maze (escape from shock), which was a symmetrical procedure in that the discriminative cue properties of the drug and nondrug conditions were demonstrated by a response selection rather than by response occurrence. Another early study reported that rats could discriminate the typical antipsychotic drug chlorpromazine from saline (Stewart 1962). Using a three-compartment test chamber (somewhat similar to a T-maze), rats were successfully trained to discriminate 4.0 mg/kg (i.p.) chlorpromazine from saline in a shock-avoidance task, and tests showed that several phenothiazines fully substituted for chlorpromazine, while the tricyclic antidepressant imipramine did not. A definitive review of this early research was published by Overton (1968). Over the next 20 years, a large number of drug discrimination studies were conducted with the T-maze procedure (see Overton 1982), but a major change in the drug discrimination procedure took place in the 1970s with the introduction of an operant task requiring rats to press response levers instead of running in a T-maze.

2.3 Two-Lever Operant Drug Discrimination

In 1968, Harris and Balster trained three rats on a two-lever multiple fixed ratio 50/differential-reinforcement-of-low rate 20 s (MULT FR 50 DRL 20 s) to discriminate DL-amphetamine from saline. After completion of discrimination testing, the rats were tested under extinction conditions in the presence of the drug cue and nondrug cue (saline). All three rats successfully acquired the amphetamine discrimination and responded primarily on the condition-appropriate lever. Harris and Balster concluded that the internal state (i.e., subjective effects of drug or no drug) of the animal controlled this responding, and that "*a more complete understanding of drug behavior interactions can be achieved by considering the* ***stimulus properties of drugs*** [emphasis added] *in addition to their traditionally emphasized pharmacological effects.*" This last statement really was both insightful and predictive as the use of the drug discrimination paradigm exploded over the next 30–40 years and became one of the most important assays for understanding the behavioral effects of drugs in vivo (see McMahon 2015). Following the Harris and Balster (1968) publication, there were a number of studies that employed this new two-lever operant drug discrimination approach, but it took several years before the procedures became more standardized. Also, as noted by Overton (1991), it soon became that two-lever operant drug discrimination procedures were more sensitive to drug stimulus effects at doses much lower than those needed in the T-maze studies and many other behavioral tests (see Kubena and Barry 1969a, b) – clearly, an advantage.

In 1971, Harris and Balster subsequently published a chapter exploring multiple two-lever drug discrimination procedures (they also tested single-lever multiple

schedules which we will not address) (Harris and Balster 1971). While they only tested a few rats under each schedule condition, they generally obtained comparable results for each drug tested in four different multiple schedules (MULT CRF CRF, MULT DRL DRL, MULT FR FR, and MULT FR EXT; CRF = continuous reinforcement, DRL = differential reinforcement of low rate 20 s, FR = fixed ratio 50, and EXT = extinction). One obvious advantage of the FR operant schedule was that it engendered higher response rates, which could be advantageous when testing was conducted under extinction conditions.

Kubena and Barry (1969a, b) subsequently demonstrated that the two-lever drug discrimination procedure could be used not only to train rats to discriminate subjective drug effects but also that novel drugs could be tested to determine if they shared discriminative stimulus properties with the training drug. Kubena and Berry (1969b) trained rats to discriminate either alcohol (1,200 mg/kg) or atropine sulfate (10 mg/kg) from saline in a two-lever drug discrimination procedure using a variable interval (VI) 1 min food reinforcement schedule. In the alcohol-trained rats, they found that pentobarbital, chlordiazepoxide, and chloral hydrate shared discriminative stimulus properties with alcohol producing almost complete alcohol-appropriate lever responding at the higher tested doses (i.e., full substitution). In the atropine-trained rats, scopolamine produced full substitution for atropine producing 100% atropine-appropriate lever responding at a dose of 1.0 mg/kg. This study demonstrated several useful properties of the two-lever operant drug discrimination. First, similar to Overton (1961) this study demonstrated that *the discriminative stimulus properties of drugs are mediated primarily by their central nervous system effects* as atropine's discriminative cue did not generalize to atropine methyl bromide, which does not cross the blood–brain barrier (i.e., it only has peripheral nervous system effects). Second, *the ED_{50} values for the dose–effect curves in the operant drug discrimination procedure were much lower than those seen in studies that used the T-maze drug discrimination procedure*. This suggested that the operant two-lever procedure was more sensitive to the behavioral effects of drugs than the T-maze procedure. Third, having response requirements for both drug- and saline-appropriate responding that are equivalent and physically adjacent is an advantage, as this makes it easier to measure the non-discriminative stimulus properties of a drug (e.g., decreasing response rates because of sedative effects).

A series of studies by Colpaert in the 1970s played a major role in helping to demonstrate the value of the two-lever operant drug discrimination procedure and to standardize the two-lever operant drug discrimination procedure. For example, Colpaert and Niemegeers (1975) trained rats to discriminate the narcotic (opioid) fentanyl (0.04 mg/kg, s.c.) from vehicle in a two-lever drug discrimination procedure using a fixed ratio (FR) food reinforcement schedule in which a food pellet was delivered after every tenth response on the condition-appropriate lever (responses on the incorrect lever had no consequence). Then, they did substitution tests with four opioids (dextromoramide, phenoperidine, piritramide, and morphine) and found that the fentanyl cue fully generalized to each of these drugs. In contrast, the neuroleptic haloperidol did not generate fentanyl-appropriate responding. Thus, this study was able to demonstrate that the "narcotic" cue produced by fentanyl generalized to other

opioids, but not to a drug from another behavioral classification (i.e., the neuroleptic haloperidol) – this showed that the discriminative stimulus properties of a drug appeared to be specific to drugs in a single pharmacological category. This study also was important as it helped to make the use of FR schedules the standard approach in two-lever operant studies. Colpaert et al. emphasized that response rates could reveal drug-induced stimulatory or inhibitory effects, while the animal's lever selection indicated difference in the drug-induced stimulus. In a subsequent study, Colpaert et al. (1975) were able to further confirm the specificity of the "narcotic" cue in 0.04 mg/kg fentanyl-trained rats and demonstrated dose-dependent generalization curves for five narcotic drugs: dextromoramide, fentanyl (the training drug), fentatienil (Sufenta® is a synthetic opioid analgesic that is more potent than its parent drug, fentanyl), morphine, and piritramide, which fully substituted for the fentanyl cue and significant reductions in responding at the highest dose tested for each drug. In contrast, the nonnarcotic drugs amphetamine, atropine, caffeine, cocaine, chlordiazepoxide, chlorpromazine, desipramine, dexetimide, haloperidol, imipramine, isopropamide, LSD, mescaline, nicotine, pentobarbital, and spiperone did not engender fentanyl-appropriate responding.

An important paper by Shannon and Holtzman in 1976 helped to lay the groundwork for establishing many of the standard approaches for studying drug effects in the two-lever operant procedure and also demonstrated the utility of the two-lever drug discrimination procedure for understanding the pharmacology underlying the discriminative stimulus properties of a drug. They trained male rats to discriminate 3.0 mg/kg morphine (s.c.) from saline in a shock-avoidance procedure (thus, the rats were not food deprived) and between 50% and 60% of the rats acquired the discrimination with greater than 90% accuracy in 6–8 weeks of training. In this study, they demonstrated a number of important features about the discriminative stimulus properties of morphine: (1) Morphine's discriminative cue was *time-dependent* with full generalization being observed within 30 min after injection and lever choice returning to the saline lever by 3.5 h after injection, (2) morphine's discriminative stimulus was *dose dependent* as they found that 0.1 mg/kg produced saline-appropriate responding while 3.0 (training dose) and 10 mg/kg produced greater than 90% morphine-lever responding (a 100-fold range), (3) morphine's discriminative cue was *pharmacologically specific* as the narcotic antagonist naloxone tested with morphine produced a rightward shift in morphine's generalization curve, (4) morphine's discriminative cue was *stereoselective* as inactive isomers of morphine and levorphanol (thebaine and dextrorphan, respectively) did not produce morphine-appropriate responding, and (5) finally, they demonstrated *cross-tolerance* to morphine's discriminative cue with methadone and the lack of cross-tolerance to pentobarbital.

Thus, by the mid-1970s the drug discrimination procedure was being used by increasing numbers of behavioral pharmacologists. As described by Overton, Rosecrans, and Barry, this increased interest in the drug discrimination paradigm led to the creation of the Society for the Stimulus Properties of Drugs (SSPD) in 1978 with the first official meeting being held that year in Baltimore, Maryland in conjunction with the CPDD (College on Problems of Drug Dependence) meeting (Overton et al.

1999). SSPD continued to hold yearly meetings until its last official meeting in 2012 in New Orleans, Louisiana. There were an increasing number of studies utilizing the drug discrimination procedure that grew exponentially through the late 1980s and peaked in 1998 with a little over 200 publications that year, followed by a subsequent decline (Bolin et al. 2016a, this volume; McMahon 2015; Stolerman et al. 1989).

There have been a few theories regarding explanation for the recent decline in the number of drug discrimination studies. One explanation is offered by McMahon (2015). Much of the drug discrimination literature has focused on drugs of abuse and many studies have used the drug discrimination assay to help determine abuse liability of new compounds. The drug self-administration paradigm appears to be replacing its use to a certain extent. As McMahon describes, self-administration certainly has greater face validity than drug discrimination with regard to drug-taking behavior in that the animals have to "work" in order to obtain the drug. Furthermore, there has been a downsizing of preclinical neuropharmacological research by many pharmaceutical companies in recent years. This has further contributed to a decline in this line of research. Despite this, drug discrimination remains a valuable tool for preclinical behavioral research.

3 Important Concepts and Principles of the Drug Discrimination Paradigm

We will not try to provide a detailed methodology for how to conduct drug discrimination studies, as there are several excellent articles/book chapters, which have been written and provided comprehensive details of training and testing methods for both human (Bolin et al. 2016b) and nonhuman (Solinas et al. 2006; Young 2009; Glennon and Young 2011a) drug discrimination studies. Rather, this section focuses on a number of important concepts and principles inherent to the drug discrimination paradigm that make it such a valuable preclinical assay for studying in vivo behavioral effects of drugs and relating those effects to specific pharmacological mechanisms.

3.1 A Method to Measure Subjective Effects

One of the most important questions to ask about drug discrimination is *what does it measure*? One commonly held assumption has been that the "*discriminative stimulus effects of drugs may be based entirely or in part upon their* ***subjective effects*** [emphasis added]" (Balster 1988). Balster further argues that understanding the underlying neural (pharmacological) mechanisms of these discriminative stimulus effects should aid in the understanding of the neural mechanisms of subjective

experiences and mood states in humans. While there are procedures for assessing and quantifying verbal reports of drugs' subjective effects in humans, verbal reports obviously cannot be obtained from nonhuman animals. This is where the drug discrimination procedure has proven to be so valuable as it allows us "*to ask*" animals "how they perceive (*feel*)" the subjective effects of drug administration. Drug discrimination is the only procedure known to the current authors to allow this unique insight into the subjective effects of drugs in animals. For example, Schuster and Johanson (1988) provided a nice review of the relationship between discriminative stimulus properties and subjective effects of drugs in both human and nonhuman studies. In experienced drug users, the subjective effects of psychotropic drugs have been assessed to help evaluate their abuse potential by comparing these effects to the subjective effects produced by known drugs of abuse. Human drug discrimination studies (e.g., Chait et al. 1985, 1986; see Bolin et al. 2016a, this volume) have helped to demonstrate that the discriminative stimulus effects of drugs correlate highly with subjective effects as assessed by verbal reports. Although Preston and Bigelow (1991) caution that "*there is a relationship* [between subjective and discriminative drug effects in human subjects]*, though not a simple one, and that the nature of the relationship is likely to be influenced by the procedural details of specific drug discrimination training and testing paradigms*." Schuster and Johanson (1988) conclude that it is very reasonable to assume that these two processes are similar in nonhuman animals. This is what makes the drug discrimination procedure so valuable for studying the subjective effects of both known and novel drugs.

Colpaert argues that since the morphine discriminative cue is due to its central narcotic action (i.e., CNS effects as opposed to peripheral effects), drug discrimination provides "*an original means by which to investigate subjectively experienced drug effects*" (Colpaert and Niemegeers 1975; see also Colpaert et al. 1975). Colpaert extended this idea to state "*that the discriminative stimulus properties of drugs, as assessed by this animal method* [i.e. drug discrimination], *may be relevant to subjectively experienced drug effects in humans*" (Colpaert et al. 1976). Other researchers in this newly emerging field of discrimination shared this viewpoint. Hirschhorn and Rosecrans (1976) stated that "*The observation that certain drugs can serve as discriminative stimuli for laboratory animals . . . demonstrates that animals can distinguish the effects of these drugs from the non-drug condition and suggests a possible method by which* ***subjective drug effects*** [emphasis added] *can be studied in animals*." Shannon and Holtzman (1976) argued that the results of their two-lever morphine discrimination study with rats "*suggest that the component of action of morphine that enables it to function as a discriminative stimulus in the rat is analogous to the component of action of morphine responsible for producing subjective effects in man*." Thus, although definitive proofs may still be elusive, there has been widespread agreement that the drug discrimination procedure provides a unique opportunity to measure the *subjective effects* of drugs by studying their discriminative stimulus properties.

3.2 Classification of Drugs

In addition to the ability of the drug discrimination procedure to measure the subjective effects of drugs, it has a number of other strengths that help make it such a valuable preclinical assay. One of these is that drug discrimination can be used to create a *classification of drugs based on shared discriminative stimulus properties*. Herbert Barry, III was one of the first to stress the utility of the drug discrimination procedure for classification of drugs according to their discriminable effects (Barry 1974). Reviewing findings from the drug discrimination literature that included both T-maze and early operant procedures, Barry summarized that the study of the discriminative stimulus properties of a large number of drugs has identified several categories including: (1) central sedatives (e.g., barbiturates and minor tranquilizers like chlordiazepoxide), (2) central anticholinergics (specifically antimuscarinic drugs), (3) nicotine, (4) marihuana (Δ^9-THC), and (5) hallucinogens (e.g., mescaline and LSD). Not surprisingly, much of the focus in the drug discrimination field has been on drugs of abuse as it was hoped that the drug discrimination paradigm would provide a unique insight into subjective effects of drugs that could relate to the abuse potential of drugs in humans. While this has been realized to a great extent, Barry stressed in his early paper the need to develop uniform procedures in the drug discrimination field. As described above (Sect. 2), the introduction of the two-lever operant drug discrimination procedure (primarily with FR schedules of reinforcement) answered this need for the most part, although as Barry (1974) pointed out there is a "*special need for the development of techniques for more rapid training of drug discrimination in rats and other laboratory animals*." This objective still has not been realized with operant drug discrimination procedures; although, a more rapid approach has been developed utilizing the "*conditioned taste aversion discrimination procedure*" (see Riley et al. 2016, this volume).

Classification of drugs with the drug discrimination procedure has been a major use of this procedure over the years. In the 1970s, as discussed above in Sect. 2, Colpaert and Niemegeers (1975) and Colpaert et al. (1975) utilized drug discrimination to identify the specificity of the stimulus properties of narcotic drugs (fentanyl was the training drug); however, the drug discrimination procedure can also be used to classify drugs for other behavioral classifications. For example, Porter et al. (2000) trained rats to discriminate a low dose of the atypical antipsychotic clozapine (1.25 mg/kg, i.p.). As shown in Table 1, all but two of the atypical antipsychotic drugs tested fully substituted for clozapine (i.e., they generated >80% clozapine-appropriate responding) and one of those produced partial substitution (>60% and <80% clozapine-appropriate responding). In contrast, none of the four typical antipsychotics fully substituted for clozapine, although thioridazine did produce partial substitution. These studies demonstrate the usefulness of the drug discrimination procedure for assigning drugs to different categories.

Table 1 Results of generalization testing in rats trained to discriminate a low dose (1.25 mg/kg) of the atypical antipsychotic clozapine form vehicle (adapted from results in Porter et al. 2000)

Test drug	Maximum percentage of clozapine-lever responding	Level of substitution[a]
Atypical antipsychotics		
Clozapine (training drug)	96.7% at 5.0 mg/kg	Full
Olanzapine	90.3% at 1.0 mg/kg	Full
Sertindole	99.8% at 5.0 mg/kg	Full
Risperidone	87.1% at 0.5 mg/kg	Full
Quetiapine	66.4% at 10.0 mg/kg	Partial
Remoxipride[b]	23.1% at 4.0 mg/kg	No
Typical antipsychotics		
Chlorpromazine	27.9% at 1.0 mg/kg	No
Fluphenazine	29.5% at 0.25 mg/kg	No
Thioridazine	74.3% at 5.0 mg/kg	Partial

[a]Level of substitution: Full = >80% drug lever responding (DRL); Partial = >60–<80% DLR; No = <60% DLR

[b]Although remoxipride is typically classified as an atypical antipsychotic, it is sometimes considered to be a typical antipsychotic (see Nadal 2001); lack of full or partial substitution for clozapine supports this conclusion

3.3 Tolerance and Cross-Tolerance

The phenomenon of *tolerance* to effects of drugs after repeated (chronic) administration has been common knowledge for a long time. As defined on the National Institute on Drug Abuse (NIDA) website (https://www.drugabuse.gov/publications/teaching-packets/neurobiology-drug-addiction/section-iii-action-heroin-morphine/6-definition-tolerance), "*When drugs such as heroin are used repeatedly over time, tolerance may develop. Tolerance occurs when the person no longer responds to the drug in the way that person initially responded. Stated another way, it takes a higher dose of the drug to achieve the same level of response achieved initially. For example, in the case of heroin or morphine, tolerance develops rapidly to the analgesic effects of the drug*." They also point out that tolerance is not the same thing as addiction, although addiction may occur to drugs that produce tolerance.

The drug discrimination procedure requires repeated administration of drugs over long periods of time (usually months of training and testing), yet the discriminative stimulus properties of drugs typically remain very stable and no evidence of tolerance or sensitivity is usually seen. For example, Colpaert et al. (1976) trained rats to discriminate 0.04 mg/kg fentanyl (i.p.) from saline and then over a period of 17 weeks fentanyl or morphine generalization curves were obtained. During each week, the rats received either two or three doses of fentanyl and/or saline (five injections each week) as part of the training regimen. The ED_{50} values for these generalization curves did not change over the 4-month period. However, the same rats used in the drug discrimination experiments did develop a marked tolerance to

the analgesic effects of fentanyl and morphine. Based on these results, the authors concluded that tolerance did not develop to the discriminative stimulus properties of narcotic analgesics.

However, under the right testing conditions, it is possible to demonstrate tolerance to drugs in the drug discrimination paradigm. Young (1991) has provided an excellent review of the conditions required to demonstrate tolerance in the drug discrimination procedure. After establishing morphine (3.2 mg/kg) as a discriminative stimulus in rats, training and testing are suspended and then the subjects were treated daily with various doses of morphine for approximately 2 weeks (varied across the studies she reviewed). Tolerance to morphine was dose dependent as low doses (3.2 or 10 mg/kg) produced little or no tolerance (i.e., the generalization curve did not change from baseline); however, the generalization curve displayed increasingly greater rightward shifts (increased tolerance) as the morphine dose was increased (maximum of 17.8 mg/kg, 2×/day). This tolerance disappeared after 3–5 days of suspending morphine treatments. Other studies she reviewed found that tolerance increased as a function of the length of morphine treatment (up to 2 weeks) and that *cross-tolerance to methadone also was evident*. (Cross-tolerance occurs when tolerance to a drug's effects produces tolerance to another drug's effects. These drugs typically belong to the same classification group and often affect the same receptor mechanisms.)

While most of the studies examining the phenomena of tolerance and cross-tolerance to the discriminative stimulus properties of drugs have focused on drugs of abuse, a series of studies also have shown tolerance and cross-tolerance with antipsychotic drugs in several drug discrimination studies. Goudie et al. (2007a) first established clozapine (5.0 mg/kg, i.p.) as a training drug in rats and determined a dose–effect curve (DEC1). Then, training and testing were suspended for 10 days and then a second DEC2 was determined. Finally, a third DEC3 was determined after a 10-day "wash-out" period during which no drug was administered and testing and training were suspended. Results revealed a significant rightward shift after the 10 days of repeated clozapine dosing (5.0 mg/kg, 2×/day) – i.e., *tolerance* to clozapine's discriminative cue was obtained. Following the 10 days of no drug treatment, the tolerance to clozapine's cue was lost and DEC3 was similar to DEC1. Using the same procedures, *cross-tolerance* was obtained with cyproheptadine (an anti-allergy/appetite stimulant), which has a binding profile very similar to clozapine. A second study by Goudie et al. (2007b) reported similar findings (cross-tolerance) with the atypical antipsychotic olanzapine and the compound JL13 (a clozapine congener). Goudie et al. concluded that the tolerance between these compounds provides a further demonstration of shared mechanisms of action. Wiebelhaus et al. (2011) used a similar procedure and demonstrated that repeated dosing with N-desmethylclozapine (major active metabolite of clozapine) and N-desmethylolanzapine (major active metabolite of olanzapine) produced cross-tolerance to clozapine (2.5 mg/kg, s.c.) in C57BL/6 mice. Cross-tolerance between these two metabolites and the atypical antipsychotic clozapine was interpreted as evidence that the discriminative stimulus properties of all three compounds shared common underlying pharmacological mechanisms.

It should be noted that Colpaert (1995) has argued that studies reporting tolerance to the discriminative stimulus of opiate drugs have in fact *not* demonstrated tolerance, although we feel that the articles discussed above (and others not cited in this review) have demonstrated tolerance. It should be noted, however, that it does appear to require specific testing conditions in order to demonstrate tolerance to the discriminative stimulus properties of drugs. While it is beyond the scope of this chapter to explore these issues thoroughly, the interested reader is encouraged to read Colpaert's (1995) review article.

3.4 Stereospecificity of Discriminative Stimulus Effects

Another important aspect of drug effects that is often not addressed in drug discrimination studies is the *stereospecificity* of the training drug. Glennon and Young (2011b) devoted an entire chapter to this topic and provided many examples of this. As they discuss, many drugs are composed of enantiomers (isomers) in a 50–50 composition, and, unless otherwise stated in a study, it should be assumed that the racemic (+) form of the drug is being used. As Glennon and Young state, "*Structural isomers are chemical entities with identical empirical formulas that differ in the nature or sequence of their atoms*." Importantly, these isomers can differ in terms of their pharmacological effects or to the extent that they are responsible for the discriminative stimulus properties of the racemic drug (see Glennon and Young 2011b for full discussion on this topic). An example of this is shown in Fig. 2. Donahue et al. (2014) trained mice to discriminate the (*S*)-isomer (10 mg/kg, s.c.) of the atypical antipsychotic drug amisulpride from vehicle. In substitution tests with *rac*-amisulpride and the (*R*)-isomer, they found that rac-amisulpride was about 3 times less potent than (*S*)-amisulpride and that (R)-amisulpride was about 10 times less potent than (*S*)-amisulpride in producing (S)-amisulpride-like responding. Figure 1 shows significant rightward shifts in the dose–response curves for *rac*-amisulpride and (*R*)-amisulpride relative to (*S*)-amisulpride. This demonstrated that the discriminative stimulus effects of amisulpride are *stereoselective* and that the (*S*)-isomer contributes more to the stimulus properties of *rac*-amisulpride than does the (*R*)-isomer (see Donahue et al. 2017 for additional confirmation of this finding). Interestingly, the potency relationships between (*S*)-, (*R*)-, and *rac*-amisulpride suggested that the stimulus effects of amisulpride could be mediated, at least in part, by activity at dopamine receptors as these potency relationships were somewhat similar to those reported in binding studies. These studies found that (*S*)-amisulpride is approximately 2 times and 20–50 times more potent than *rac*-amisulpride and (*R*)-amisulpride, respectively, with regard to binding affinity to dopamine $D_{2/3}$ receptors (Castelli et al. 2001; Marchese et al. 2002a, b). Thus, stereochemistry of a drug can be an important aspect of understanding the discriminative stimulus properties of a drug. The isomers of a drug may both contribute to the discriminative stimulus properties of the drug with one isomer being more potent than the other (i.e., stereoselectivity), or one of the isomers may have similar properties to the parent drug and contribute to its discriminative stimulus, while

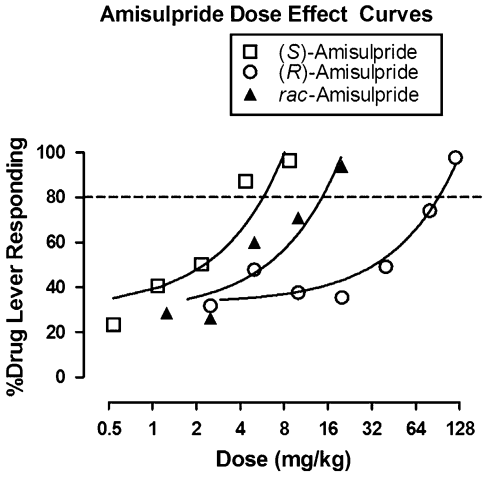


Fig. 1 This figure presents a direct comparison of the dose–response curves of %drug lever responding (DLR) for rac-amisulpride and its (S)- and (R)-enantiomers with regression lines. Doses for (S)-amisulpride were adjusted to the base form for direct comparison (ED50¼ 1.57 mg/kg [95% C.I.¼1.14–2.15 mg/kg]). From Donahue et al. (2014) – reproduced with permission

the other does not (i.e., stereospecificity) (for more complete discussion of this, see Chapter 4 in Glennon and Young 2011b).

3.5 *Receptor Mechanisms and Discriminative Stimulus Effects*

In 1988, an entire book was devoted to *transduction mechanisms of drug stimuli* (Colpaert and Balster 1988). A major theme of this book was that discriminative stimulus properties of drugs reflect specific CNS effects at *neurotransmitter receptors*. As Balster (1988) states "*If discriminative effects are related to subjective effects, then it seems reasonable to hope that studies of the neural mechanisms for these effects may lead us toward an understanding of the neural mechanisms of some of the subjective experiences and mood states that are the basis of our perception of drug effects*." Balster concludes with "*Studies of discriminative stimulus properties of drugs and their mechanisms of transduction can provide us important insights into basic brain-behavior relationships*." An early example of this was a study by Rosecrans and Glennon (1979) in which they used drug cues to study psychoactive mechanisms by comparison to other drugs (i.e., substitution tests) and by determining if the drug cue could be antagonized (i.e., blocked) with specific receptor antagonists. For example, in morphine-trained rats they demonstrated that methadone was equally potent in producing a similar dose-dependent generalization curve;

whereas, meperidine was significantly less potent as indicated by a rightward shift in the generalization curve. In antagonism studies, they found that the discriminative stimulus of LSD could be antagonized in a dose-dependent manner (i.e., greater antagonism with increasing doses) by the serotonin antagonist (BC105). Perhaps more interestingly, they presented findings comparing serotonin binding affinities (data presented as pA2 values from rat fundus assays) in a series of tryptamine analogs to the ability of these compounds to substitute for 5-OMeDMT (1.5 mg/kg training dose). As shown in Fig. 2 from that study, there was a strong correlation between the pA2 values and the equivalent dose at which each compound substituted for 5-OMeDMT, which is a hallucinogen with strong affinity for serotonin 5-HT2 and 5-HT1A receptors. These data clearly demonstrated that the discriminative stimulus properties of 5-OMeDMT were related to its binding affinity to serotonin receptors. In a study in which two separate groups of Sprague-Dawley rats were trained to discriminate either the atypical antipsychotic clozapine (5.0 mg/kg, i.p.) or the muscarinic antagonist scopolamine (0.5 mg/kg, i.p.) from vehicle, it was found that complete *cross-generalization* occurred between clozapine and scopolamine, indicating a shared underlying mechanism for their respective discriminative stimuli. In addition, only drugs that display high binding affinities for muscarinic cholinergic

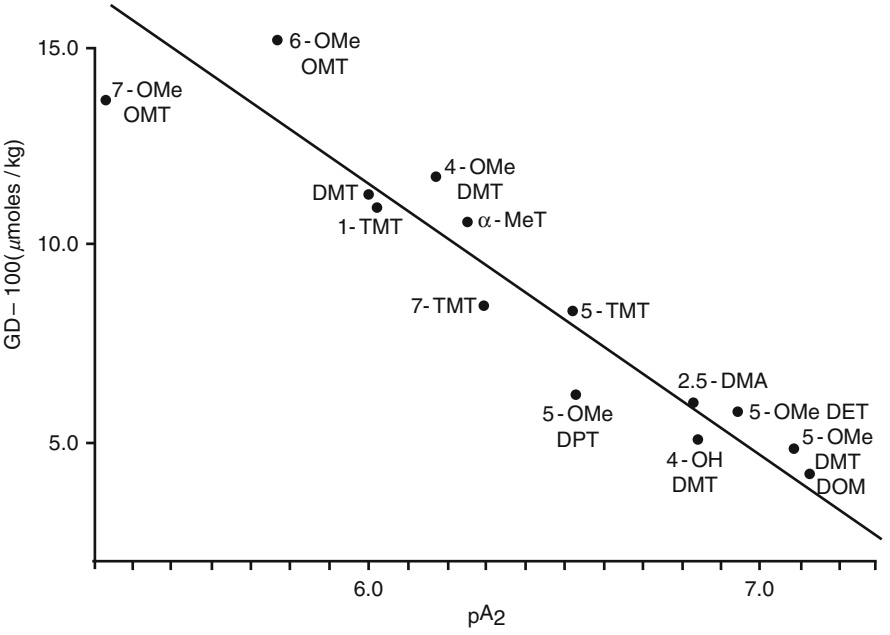


Fig. 2 This figure presents the correlation between the discriminative stimulus (DS) properties and pA2 values of a series of tryptamine and phenylisopropylamine analogs. The GD-100 value represents the equivalent dose at which each compound generalized with the training dose of 5-OMeDMT (1.5 mg/kg) when it was used as the DS. Each drug was administered at various doses 15 min prior to being placed in the operant chamber for a 15-min test session. From Rosecrans and Glennon (1979) – reproduced with permission

receptors substituted for these two training drugs. Based on these results, the authors concluded that antagonism of muscarinic receptors (especially M_1) plays an important role in the discriminative stimulus properties of clozapine in rats (Kelley and Porter 1997). In contrast, in C57BL/6 mice, clozapine's discriminative cue appears to be mediated by antagonism of serotonergic 5-HT_2 receptors and α_1 adrenoreceptors (Philibin et al. 2005, 2009). Thus, it is often possible to ascertain the underlying receptor mechanisms that mediate the discriminative stimulus properties of a drug. However, as these studies show, these mechanisms may differ across species. Therefore, some caution must be exercised when making inferences across different species, including humans.

3.6 *Individual Differences Between Subjects*

An important, but understudied topic in drug discrimination research concerns *individual differences* between subjects in their sensitivity to the discriminative stimulus properties of drugs. These differences are often reflected in the number of training sessions required for individual subjects to meet the discrimination criterion – i.e., some subjects will acquire the discrimination in fewer training sessions than other subjects. The first operant study to systematically explore the importance of the speed of acquisition of the discrimination was by Martin Schechter in 1983. Twelve male Sprague-Dawley rats were trained to discriminate 0.16 mg/kg apomorphine from saline with responding reinforced according to an FR 10 reinforcement schedule. Half of the rats acquired the discrimination in a mean of 22.5 sessions (*early learners*) and the other half in a mean of 44.2 sessions (*late learners*) (significantly different, $p < 0.001$). When apomorphine generalization curves were established, the early learners had an $ED_{50} = 0.01$ mg/kg; whereas, the late learners had an $ED_{50} = 0.07$ mg/kg, which represented a 3.9-fold rightward shift in the generalization curve (the dose–response curves were parallel). Thus, the early learning group was more sensitive to apomorphine's discriminative stimulus than was the late learning group. While it has been well established that higher training doses result in higher ED_{50} values for the dose–response curves (see review by Stolerman et al. 2011), Schechter's (1983) study was the first to demonstrate that sensitivity to the training drug's discriminative cue also could affect the ED_{50}.

A second study by O'Neal et al. (1988) examined how the rate of acquisition of Δ^9-THC (delta-9-tetrahydrocannabinol) discrimination reflected sensitivity to Δ^9-THC's discriminative stimulus. Male Sprague-Dawley rats were trained to discriminate 3.0 mg/kg Δ^9-THC from saline in a two-lever operant discrimination task (FR 10) and after acquisition of the Δ^9-THC discriminative cue, the rats were divided into two groups using a median split – slow learners and fast learners. For the slow learners, the mean number of sessions to criterion (STC) = 50.0; for the fast learners, the STC = 27.3 (significantly different, $p < 0.001$). Similar to results found in the Schechter's (1983) study, the slow learners displayed a rightward shift in the Δ^9-THC generalization curve with an $ED_{50} = 1.63$ mg/kg; whereas, the ED_{50} for the fast

learners = 0.77 mg/kg. Thus, the fast learners displayed a greater sensitivity to Δ^9-THC, replicating the greater sensitivity to apomorphine shown by the fast learners in the Schechter's (1983) study. We have not been able to find additional studies that have examined the relationship between speed of acquisition and the subsequent sensitivity of individual subjects to a drug's discriminative cue. Nonetheless, both of these studies suggest that reporting the number of sessions required to reach the training criteria should be information routinely provided in publications.

Bevins et al. (1997) reported that individual differences in rats in the sensitivity to amphetamine in several behavioral assays (novelty-induced activity, novelty-induced place preference, novel-object interaction, and amphetamine-induced activity) were related to differences in amphetamine discrimination. For example, rats more sensitive to the activating effects of amphetamine were also more sensitive to amphetamine in the drug discrimination assay. Individual differences in *human subjects* also have been shown in nicotine drug discrimination studies. Perkins (2011) summarizes some of the factors that contribute to individual differences in human nicotine drug discrimination studies. For example, these studies find that women, generally, are less sensitive to nicotine's discriminative stimulus properties as reflected in more difficulty in acquiring the cue or showed flattened generalization curves. Individual differences in animal studies with nicotine drug discrimination also have been shown that may be related to genetic differences (e.g., Quarta et al. 2009). Finally, Morgan and Picker (1996) reported three- to tenfold differences in the lowest doses of several opiates that would substitute for morphine in rats trained to discriminate morphine (3.0 mg/kg) from vehicle in a two-lever drug discrimination study. Individual differences were also observed in the antinociceptive effects of these opiates in a hot water tail-withdrawal procedure. These authors concluded that these individual differences between subjects are probably determined in large part by the relative efficacy of these drugs at the *mu* opioid receptor.

Finally, it is also possible that differential sensitivity among subjects to the discriminative stimulus properties of drugs may reflect the fact that different subjects may "tune" into different components of a cue. It has been well established that "compound" discriminative stimuli can be demonstrated with drug mixtures as the cue (see review by Stolerman et al. 1999). However, it is also possible for a single drug to have a *compound* discriminative cue. For example, in rats trained to discriminate ethanol from water, asymmetrical generalization of ethanol to gamma-Aminobutyric acid (GABA) enhancers (e.g., chlordiazepoxide), to N-methyl-D-aspartate (NMDA) antagonists (e.g., dizocilpine [MK-801]), and to serotonin (5-HT) agonists (e.g., trifluoromethylphenylpiperazine) was found. Stolerman et al. (1999) concluded from these studies that their finding supported the concepts of ethanol having a compound stimulus (see also Grant 1999), since ethanol generalized to drugs of more than one pharmacological classification. It certainly seems reasonable to assume that subjects might attend to one or more components of a drug's pharmacological actions, which make up its compound cue and might explain individual differences in acquisition to a drug's discriminative cue.

3.7 Drug Development

As a preclinical behavioral assay, drug discrimination has proven to be a useful tool. For example, clozapine is an atypical antipsychotic drug that is considered to be the "gold standard," prototypical of the second generation of antipsychotic drugs and it remains the standard by which other atypical antipsychotic drugs are compared (Hippius 1991; Porter and Prus 2009). When the antipsychotic olanzapine was being developed by Eli Lilly and Company, Moore et al. (1992) published an article on the behavioral pharmacology of olanzapine. One of the behavioral assays employed in that study was two-lever drug discrimination in which clozapine 5.0 mg/kg, i.p. was trained as a discriminative stimulus. Olanzapine fully substituted for clozapine's cue, indicating that olanzapine's discriminative stimulus properties were similar to those of clozapine. Based on these results, and results from a number of other behavioral assays used in this study, the authors concluded that olanzapine would have the profile of an atypical antipsychotic drug (like clozapine). Olanzapine was later approved by the FDA in 1996 for treatment of schizophrenia.

Drug discrimination has been frequently used by pharmaceutical companies (e.g., Millan et al. 1999) and in academia (e.g., Burgdorf et al. 2013) to help characterize the behavioral pharmacology of novel compounds and by government agencies like the Drug Enforcement Agency (DEA) to aid in scheduling the abuse liability of drugs (see Ator and Griffiths 2003; Balster and Bigelow 2003). In addition to the atypical antipsychotic drug olanzapine (see above), another good example is the atypical antipsychotic risperidone. Colpaert (2003) has written an excellent review of the discovery process for risperidone and how important the study of subjective effects in laboratory animals was to this process. He concluded that "*the pathway to risperidone chiefly cut across the field of in vivo pharmacology, and in particular behavioral pharmacology, underscoring the unique contribution of the field to drug discovery*." In 2002, the In Vivo Pharmacology Training Group published a commentary on "*The rise and fall of in vivo pharmacology*." In this article, they stated "*Pharmacology is, by definition, the study of the mechanism of action of drugs, and requires a knowledge and understanding of responses to drugs induced both in vitro and in vivo. Such analysis of drug action is needed to transform molecular or cellular discoveries into clinical practice and, equally, to identify the molecular questions that arise from clinical observations. These studies are essential because responses observed in vitro can be magnified, diminished or totally different in the more complex integrated system. . . .. . .This article . . .. . . outlines why in vivo work is vital for the analysis of drug action and for the discovery and development of new therapeutic agents*." (In Vivo Pharmacology Training Group 2002). We concur with these conclusions and recognize the utility and value of preclinical behavioral assays in the drug development process. Behavioral (in vivo) assays (like drug discrimination) are just as important as in vitro assays for this process and the two approaches go hand-in-hand in the discovery and development of new therapeutic drugs.

4 Summary and Overview of This Volume

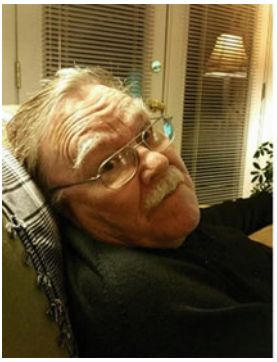
The current chapter (Chapter 1 in Part 1, this volume) provided a brief overview of the historical origins of the drug discrimination procedure and described how its beginnings can be traced to state dependent learning, and then how it transitioned from the first drug discrimination studies in a T-maze task in the 1960s to a two-lever operant procedure in the 1970s. Then, we discussed how the discriminative stimulus properties of drugs are believed in large part to reflect the subjective effects of drugs and that drug discrimination studies in human subjects have generally supported the belief that discriminative stimulus properties of drugs in nonhuman animals correlate highly with subjective effects of drugs in humans. Finally, we discussed a number of other concepts and principles that help make drug discrimination a valuable preclinical assay.

The chapters in Part 2 of this volume review the current state of the art regarding the discriminative stimulus effects of the primary classes of psychoactive drugs. In Chapter 2, William Fantegrossi provides an overview of early drug discrimination work on psychostimulant drugs but also includes coverage of recent findings on the discriminative stimulus effects of bath salts. Chapter 3 provides a thorough summary about the discriminative stimulus effects of nicotine and recognizes the influential work of John Rosecrans, who is posthumous co-author of this chapter with Richard Young. The discriminative stimulus effects of ethanol are addressed extensively by Kathleen Grant's group in Chapter 4, and the chapter pays particular attention to the stimulus effects of ethanol across different species, including humans. Of particular relevance for interpreting the subjective effects of ethanol from these studies, this chapter points out the qualitatively different stimulus properties of low versus higher training doses of ethanol. In Chapter 5, Keith Shelton takes us through studies designed to evaluate the subjective effects of inhalants and devotes some emphasis to the unique methodological challenges involved in this work. In Chapter 6, Tsutomu Suzuki, with Tomohisa Mori, reviews an extensive literature on the discriminative stimulus effects of hallucinogens and dissociative anesthetic drugs, e.g., ketamine, and gives a glimpse of future directions in drug discrimination research as he associates intracellular signaling processes to the mediation of certain stimulus effects. In Chapter 7, two of the leading experts on the behavioral pharmacology of cannabinoids, Jenny Wiley and Aron Lichtman, contribute to a review on the discriminative stimulus effects of cannabinoids, which includes stimulus effects of endocannabinoids as well as synthetic cannabinoid compounds. Eduardo Butelman and Mary Jeanne Kreek, in Chapter 8, gave an up-to-date account on drug discrimination for opioid compounds and provided novel thoughts on future directions in this area. Chapter 9 is the first of two chapters that focused on the discriminative stimulus effects of drugs for mental illness. Chapter 9, written by the co-editors of this volume, along with the assistance of Kevin Webster, reviews studies evaluating the stimulus effects of antipsychotic drugs, with an emphasis on

the utility of this procedure for identifying effective antipsychotic drugs for schizophrenia. The chapter also connects reported subjective effects of antipsychotic drugs in human patients to certain receptors known to mediate stimulus effects of antipsychotics in animals. Chapter 10, also co-authored by the editors of this volume, uses the same approach to evaluate the discriminative stimulus effects of antidepressants and anxiolytics.

Part 3 of this volume, called "Approaches to Drug Discrimination," provides a variety of perspectives on ways to understand the drug discrimination procedures along with some of its applications. In Chapter 11, Steve Negus and Matthew Banks discuss analyzing drug discrimination data using pharmacokinetic–pharmacodynamic analyses. In Chapter 12, Craig Rush reviews drug discrimination studies conducted in humans and some of the methodological advantages and challenges. In Chapter 13, Anthony Riley and others from his group demonstrate how the stimulus properties of drugs can be studied using conditioned taste aversion procedures. In this volume's final chapter (Chapter 14), Ellen Walker provides commentary on the chapters in this volume and discusses new directions for the use of drug discrimination in pharmacology research. Overall, this volume on the drug discrimination provides an insightful evaluation of a wide array of critical topics in this field written by leading experts on this procedure. The editors of this volume are grateful to all of the authors who have made this a notable addition to the literature in behavioral neuroscience.

Finally, we would like to dedicate this volume to the memory of two pioneer researchers in the field of drug discrimination. Dr. John A. Rosecrans and Dr. Torbjörn U.C. Järbe were two of the early scientists in drug discrimination research who did so much to help shape this newly emerging area of research back in the 1970s and whose influence continued into this century. Their legacy and influence in this field lives on and will be remembered always. We will miss both of them.



John A. Rosecrans
(1935–2015)

Torbjörn U.C. Järbe
(1946–2017)