A Prospective Evaluation of Drug Discrimination in Pharmacology

Ellen A. Walker

Abstract As investigators, we use many methodologies to answer both practical and theoretical questions in our field. Occasionally, we must stop and collect the latest findings or trends and then look forward to where our ideas, findings, and hypotheses may take us. Similar to volumes that were published in previous years on drug discrimination (Glennon and Young, Drug discrimination applications to medicinal chemistry and drug studies. Wiley, Hoboken, 2011; Ho et al., Drug discrimination and state dependent learning. Academic Press, New York, 1978), this collection in Current Topics in Behavioral Neurosciences serves as a current analysis of the continued value of the drug discrimination procedure to the fields of pharmacology, neuroscience, and psychology and as a stepping stone to where drug discrimination methodology can be applied next, in both a practical and theoretical sense. This final chapter represents one investigator's perspective on the utility and possibilities for a methodology that she fell in love with over 30 years ago.

Keywords Abuse liability testing · Complex cues · Drug discrimination · Interoceptive states · Receptor theory

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For several decades, drug discrimination has been used as a tool to understand the pharmacology of different drug classes or has been involved in the discovery of new drug targets or receptors (Porter et al. 2018). This trend continues today. In a practical sense, drug discrimination is an excellent procedure to understand the

E. A. Walker (✉)
Department of Pharmaceutical Sciences, Temple University School of Pharmacy, Philadelphia, PA, USA
e-mail: ellen.walker@temple.edu

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underlying pharmacology, mechanisms, and functional outcomes for drug-receptor interactions. Bar none, the pharmacological selectivity, orderly adherence to biological principles, and sensitivity to antagonism made drug discrimination a key tool in neuropharmacology. As stated by the late Francis Colpaert "... the DD [*drug discrimination*] paradigm offers an exquisitely specific, selective, and sensitive approach to the in vivo analysis of drug-receptor interactions ..." (Colpaert 2011).

1 Drug Discrimination as a Tool to Define Receptor Pharmacology

In the current volume, a number of excellent chapters have reviewed the history and our current understanding of drug-receptor interactions as defined by drug discrimination methodology for a range of drug classes in various species, including humans. For example, Mori and Suzuki (2016) nicely outlined the necessity for 5-HT_2 receptor activation as the critical component with a clear role for 5-HT_{1A} modulatory function for the discriminative stimulus effects of hallucinogens such as MDMA and LSD. Furthermore, through drug discrimination, investigators were able to differentiate the contributions of 5-HT to the effects of MDMA and distinguish substitution patterns for different psychostimulants such as *N,N*-DMT, 5-MeO-DMT, and methamphetamine. These patterns could then be compared and contrasted to cocaine and opioid discriminative stimuli (Mori and Suzuki 2016). In the opioid field, the high selectivity of opioid drug discrimination is readily demonstrated as only MOP, KOP, or DOP receptor ligands substitute for morphine, U50,488, SNC80, and BW373U86 discriminative stimuli and only receptor selective antagonists such as CTAP, nor-BNI, or naltrindole will block these cues, respectively (Butelman and Kreek 2016). More recently, drug discrimination has been extended to the selectivity of NOP or nociceptin receptor ligands. For example, when the NOP receptor agonist Ro 64-6198 was trained as a discriminative stimulus in rats, morphine, U50,488, and SNC80 failed to substitute for Ro 64-6198 and Ro 64-6198 failed to substitute for morphine in rats trained to discriminate morphine suggesting this NOP receptor agonist is selective for NOP and no other opioid receptors (Recker and Higgins 2004). Finally, a classic collection of studies on drug discrimination in receptor classification was reviewed by Rosecrans and Young (2017). In these studies, investigators demonstrated that the (−)-nicotine discriminative stimulus was blocked by antagonists such as mecamylamine and DHβE (dihydro-β-erythroidine), which demonstrated the roles of α4β2 nicotinic acetylcholine receptors in the brain and for underlying the discriminative stimulus effects of (−)-nicotine.

An additional requirement in the classification of drug-receptor interactions and the understanding of pharmacological action is the demonstration of stereoselectivity, sensitivity to time course, and pharmacokinetics to substitution patterns. For example, the stereoselectivity or time course for opioids (Butelman and Kreek 2016) and

stimulants (Berquist and Fantegrossi 2017; Rosecrans and Young 2017) has long played an important role in determining patterns of stimulus substitution and discriminability for different training drugs. Interestingly, Negus and Banks (2016) actually use the relationship of pharmacokinetics (PK) to pharmacodynamics (PD) to analyze the variable relationship over time for the discriminative stimulus effects of cocaine and various metabolites which influences conclusions of drug action. This interesting PK/PD relationship allows a unique perspective of potential species differences in the discriminative stimulus effects of drugs.

Taken as a whole, the studies reviewed in this volume are just a fraction of the literature demonstrating the high receptor selectivity, stereoselectivity, and susceptibility to competitive antagonism for drugs trained as discriminative stimuli, the classic receptor pharmacology principles required to define a drug class. In the future, drug discrimination will still be needed to characterize new ligands, new enantiomers, and novel antagonists especially those agents with likely CNS activity. Although radioligand binding assays or functional GPCR assays are clearly the first steps to screen new compounds, a functional assay in a whole animal, such as drug discrimination, will always be needed to validate the results of more molecular characterizations.

2 Drug Discrimination as a Tool to Reveal Complex Cues and Pharmacological Actions

The early characterization of fentanyl as a discriminative stimulus and the corresponding receptor neuropharmacology of this direct acting opioid agonist (Colpaert 2011) led to using training drugs with more indirect or unique mechanisms of action as discriminative stimuli. Indeed, drug discrimination studies were key in distinguishing potential underlying neural mechanisms. For example, drug discrimination studies differentiated the stimulus effects of PCP (phencyclidine) and MK-801 (dizocilpine) as noncompetitive NMDA antagonists as opposed to direct acting NMDA (*N*-methyl-D-aspartate) receptor antagonists revealing a complex or compound cue involving the regulation of dopaminergic and serotoninergic systems with sigma1 receptor function likely involved (Mori and Suzuki 2016). Psychostimulants, such as cocaine, amphetamine, and more recently synthetic cathinones that possess a mix of transporter inhibition, release, or reverse transporters have been trained as discriminative stimulus and reviewed in this volume (Berquist and Fantegrossi 2017). Drug discrimination techniques can be very useful for studying and classifying opioids with complex pharmacology at multiple receptors, as these can vary significantly across species due to likely different receptor proportions or signaling across species (e.g., Zhu et al. 1997). Drug discrimination techniques have been critical for understanding the role of endogenous cannabinoids and their various metabolic activities and for the pharmacological effects of phytocannabinoids and the synthetic cannabinoid agents (Wiley et al. 2016). For example,

the complexity that can be revealed by training metabolic enzyme inhibitors as a discriminative stimuli to tap into endocannabinoid function was recently demonstrated by training SA-57, a dual fatty acid amide hydrolase (FAAH) and monoacylglycerol lipase101 (MAGL) inhibitor and by training selective MAGL inhibitor MJN110. Using the patterns of substitution for other dual FAAH/MAGL, MAGL, or FAAH inhibitors to substitute for MJN110 as well as cannabinoid agonists, these authors suggest that the MJN110 discriminative stimulus through selective MAGL inhibition is mediated through 2-AG-mediated stimulation of CB1 receptors. Furthermore, under normal endogenous conditions, MAGL may reduce endocannabinoid-mediated overstimulation of the CB1 receptor, thereby preventing induction of a cannabimimetic subjective state (Owens et al. 2017). This example and others reviewed in this volume highlight the manner in which investigators can use drug discrimination techniques to enhance our understanding of the roles of endogenous regulators of drug action.

There are numerous examples highlighted in the current volume that reveal certain drugs can have compound pharmacological cues and drug discrimination methodology has been used to dissect the relative contributions of each component. For example, cocaine, scopolamine, and D_1 and D_2 agonists substitute for the bupropion discriminative stimulus, and these effects were either fully or partially blocked by DA receptor antagonists (Prus and Porter 2016). Similarly, the discriminative stimulus effects of competitive and noncompetitive NMDA receptor antagonists tap into dopaminergic and serotonergic systems as well as sigma-1 receptor actions suggesting that training these agents can result in a compound cue (Mori and Suzuki 2016). Inhalants as a class of discriminative stimuli also fall into the category of interacting with multiple receptor systems such as $GABA_A$-positive modulators and NMDA, for example, depending on the particular inhalant trained as the discriminative stimulus (Shelton 2016). Using drug discrimination to characterize the inhalants allows an investigator to meaningfully group these substance inhalants together despite being such a heterogeneous pharmacological group. The most studied complex discriminative stimulus is ethanol in which GABA (*gamma*-aminobutyric acid) and glutamate ionotropic receptors and serotonergic mechanisms all contribute to the discriminative stimulus effects especially dependent on training dose (Allen et al. 2017). Indeed, there have been clever control experiments designed to separate exteroceptive vs. interoceptive cue components such as route of administration studies to eliminate odor as providing a key role in the discriminative stimulus effects of toluene as reviewed by Shelton (2016).

Interestingly, drug discrimination procedures can be modified to further separate out complex cues for drugs with overlapping pharmacological mechanisms by training dose-dose or three-choice discriminations. For example, Berquist and Fantegrossi (2017) nicely review the usefulness of three-choice discriminations, especially for analyzing the effects of enantiomers in the substitution patterns of MDMA (3,4-methylenedioxymethamphetamine, commonly known as ecstasy). Three-choice discriminations for MDMA, saline, and d-amphetamine reveal a likely serotoninergic-dopaminergic continuum for the underlying neuropharmacological mechanisms of MDMA (Harper et al. 2011; Goodwin and Baker 2000) based on

substitution patterns of different psychostimulants and doses. Three-choice discriminations can also be established with high and low doses of drugs to parcel out the role of efficacy in discriminative stimulus effects (e.g., Jones et al. 1999; Vanecek and Young 1995). Leveraging different mouse strains to further triangulate on components of a complex discriminative stimulus such as clozapine has been a fruitful strategy (Porter et al. 2017) essentially similar to varying a training dose. Narrowing the conditions under which generalization will occur with each new cue or dose that can be trained is a sophisticated strategy to dissect out pharmacological mechanisms under particular contingencies and may explain individual subject substitution patterns.

The observation that individuals can attend to one component of a complex cue more than others has precedence in the literature. In a classic experiment, Reynolds (1961) demonstrated that when two individual pigeons were trained to respond in the presence of a white triangle on a red key and tested with either the triangle or red background alone, one pigeon exclusively attended to the triangle while the other the red background. Drugs with multiple pharmacological components could certainly serve similar functions in individual subjects so that in a group of subjects, some could attend more to one component of the complex stimulus or the other or perhaps even only the Gestalt of the multiple components together. Possibly, component pharmacology or cues could be a contributing factor to some of the inter-subject variability obtained in drug discrimination experiments and one of the reasons examining a pattern of substitution and antagonism in individual subjects is an important part of data analysis in this field. Indeed, this notion has been well-studied by researchers investigating mixtures of drugs (e.g., Stolerman et al. 1999).

3 Drug Discrimination to Study Internal States

Whereas the use of drug discrimination to understand contributions of complex underlying pharmacological mechanisms to drug effects has been invaluable to researchers, one may argue that the ability of discrimination methodologies to tap into the various interoceptive effects of drug stimuli that control behavior makes it a unique procedure without parallel. As described in the first chapter of this volume, drug discrimination grew out of the interest in the effects of drugs on memory retrieval and state-dependent learning (Porter et al. 2018). Two examples of "states" produced by drugs, or the withdrawal of drugs, are worth mentioning because these examples reveal what is especially novel about the results from drug discrimination studies. Rosecrans and Young (2017) reviewed a study in which rats were trained to discriminate pentylenetetrazol from saline and suggested that the basis for the discrimination was pentylenetetrazol-induced anxiety (Harris et al. 1986). When the pentylenetetrazol-trained rats were administered high doses of nicotine for a 3-week period and then were withdrawn from nicotine dosing, the rats responded partially on the pentylenetetrazol-appropriate lever 24 h after the cessation of dosing. These investigators suggested that rats in nicotine withdrawal may be experiencing

"anxiety" as measured by their pentylenetetrazol generalization response. The possibility that pentylenetetrazol as a discriminative stimulus may represent a state akin to anxiety in animals was followed up with additional pharmacological characterization (Jung et al. 2002), and ethologically relevant drug discrimination experiments demonstrating an interoceptive state associated with species-specific defense reactions in rats produced by exposure to cat predators were similar to the discriminative stimulus cues produced by pentylenetetrazol (Gauvin and Holloway 1991).

Other withdrawal states have been modelled in drug discrimination, including those from repeated agonist administration followed up by later discrimination training sessions with antagonists. Excellent examples include experiments where opioid withdrawal substitutes for the discriminative stimulus effects of naltrexone (e.g., Becker et al. 2008) or partial agonist nalbuphine (Walker et al. 2004) and THC withdrawal substitutes for the discriminative stimulus effects of cannabinoid antagonist rimonabant (e.g., Stewart and McMahon 2010). Peptides and drugs with potential anorexic effects have been tested in rats trained to discriminate between 22- and 2-h food deprivations, a methodology of studying the internal state of "hunger" (Jewett et al. 2006, 2009).

Antagonists in general can be difficult to train as discriminative stimuli although there is a long history of training and testing antipsychotic agents (Prus and Porter 2016; Porter 2011) and noncompetitive NMDA antagonists (Balster 1991; Koek 1999). Often many of these antagonists reveal complex, compound cues which may or may not be reversed by agonist administration and the cue may depend on the species studied (Porter 2011). For some drug classes, modifications of procedures are employed such as maintaining the subjects dependent on an agonist as described above. The maintenance of a subject on chronic agonist treatment induces a certain change in homeostasis or an increase in endogenous tone that can be disrupted with antagonists or drug withdrawal. Another modification of the drug discrimination assay to train antagonists such as phencyclidine, diprenorphine, naloxone, naltrexone, and rimonabant as discriminative stimuli without chronic agonist treatment is the conditioned taste aversion methodology reviewed by Riley et al. (2016). One possibility for the establishment of antagonists as discriminative stimuli to control behavior has been suggested to be the disruption of an endogenous tone by the antagonist. In drug-naïve subjects, one might simply suspect basal endogenous tone would be the same after the injection of a given dose of antagonist irrespective of the training procedure. Yet, antagonists can easily serve as discriminative stimuli to control taste aversion learning at lower doses than previously attempted using operant-based training techniques, and these antagonist doses can be trained much more quickly using conditioned taste aversion. These studies demonstrate that the discriminative stimulus properties of a drug are not inviolate properties of the pharmacology but more so intimately tied to the training conditions and predictive consequences of that discriminative stimulus.

In humans, investigators are able to compare subjective effect questionnaires to the results obtained from drug discrimination assays allowing for an assessment of whether drug discrimination is a model of subjective effects. Overall, there is a relatively good correspondence between the discriminative stimulus and subjective

effects in humans across the different pharmacological classes; however, there are some interesting exceptions. Bolin et al. (2016) provide an interesting discussion regarding the face validity and some potential limitations of drug discrimination procedures in humans for studying the abuse potential of drugs (see also McMahon 2015). For example, drug discrimination in humans is relatively insensitive to circulating blood levels of drug such that the time course of the discriminative stimulus effects, or the proportion of responses to the drug-appropriate option, does not always follow the measured blood levels (Kelly et al. 1997). Although we believe that humans are able to articulate the stimuli that may be controlling their behavior, this is probably an overstatement. For example, in humans responding to receive i.m. injections of morphine, much lower doses of morphine were self-administered as compared to those doses that occasioned positive reports of subjective drug effects (Lamb et al. 1991). The notion that to be a discriminative stimulus, a drug must produce something akin to a subjective effect leaves out some discriminative stimuli that likely do not possess strong subjective effects. For example, MAO inhibitors such as iproniazid, nialamide, phenelzine, and tranylcypromine can be discriminated using a T-maze procedure (Overton 1982), and Ca++ channel blockers can be discriminative stimuli in traditional operant procedures (Schechter 1995) when these agents are not likely to have what would be considered strong subjective effects. Finally, the observation that antidepressants can be trained in rats and mice that are not depressed suggests that the underlying pharmacology of these agents interacts with underlying basal states to support a salient enough stimulus to control behavior (Prus and Porter 2016) and reveal how the drug discrimination procedure is an exceedingly sensitive methodology.

4 In Praise of Drug Discrimination

As outlined in the many chapters of this volume, there are few experimental models we have available today that are as pharmacologically selective, sensitive, and such an objective measure an interoceptive state in an organism. As Berquist and Fantegrossi (2017) state in the current volume, “Nevertheless, the drug discrimination assay, in its most basic form, reveals pharmacological effects that occur within the central nervous system in species that display little to no verbal communication. We consider this an achievement in scientific research in general, and we submit that the drug discrimination approach is among the most useful in vivo analyses available to behavioral pharmacology.” Drug discrimination is essentially unchallenged as a method to characterize drug stimuli and resulting behavior. Even with the advanced technologies available today, the ability to study pharmacologically and disease-relevant doses with such specificity in a preclinical experiment is readily available using drug discrimination. Drug discrimination will likely continue to contribute to our understanding of drug-receptor interactions and basic pharmacological characterization in combination with other technologies such as imaging, optogenetics, gene delivery strategies, RNA interference technology, and

designer receptors exclusively activated by designer drugs (DREADD)-based chemogenetic tools. All of these more recent technologies provide exquisite detail on molecular and cellular signaling and brain circuitry; however, to deliver a representation of either drug stimuli or internal states of physiology, a particular cue will have to be specifically trained in an experimental animal. For any question that requires a functional output and a precise, selective pharmacological result, drug discrimination will always be the answer. The only limitation is our creativity.

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