DRUG DISCRIMINATION

APPLICATIONS TO MEDICINAL CHEMISTRY AND DRUG STUDIES

EDITED BY

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WILEY

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PREFACE

This book is intended for the medicinal chemist and/or neuroscientist interested in investigations of neurochemical mechanisms that underlie the discriminative stimulus, or subjective, properties of drugs. Such studies in our laboratories have been focused on the idea that the effects of psychoactive agents are best expressed both in qualitative and quantitative terms. Our aim is to show that this approach has usefulness in the advancement of basic science, and is of practical value in the study of ethical pharmaceuticals and in the evaluation of drugs of abuse. For example, in certain instances, the stimulus potencies of drugs have been related to their human potencies. Furthermore, drug discrimination studies with animals have a human counterpart: drug discrimination studies with human subjects. The publication should serve as a ready reference for many investigators. They can refer to the book for details of the various methodologies commonly employed, available information applicable to numerous drugs and drug classes, discussions of how drug discrimination studies are designed and interpreted, and the limitations of the paradigm; most chapters are replete with actual data and illustrations.

During the past four decades, remarkable advances have been made in the study of drugs as discriminative stimuli. These will be described. In a number of ways, this book attempts to bridge the gap between earlier and newer topics in drug discrimination. The older and well-developed topics are related to newly developing areas. Our view is that the discriminative stimulus effects of drugs are a rapidly changing and expanding area of science. In no sense, however, can this book be regarded as some final description of the discriminative stimulus properties of drugs; rather, it must be viewed as a momentary state-of-the-science overview. The book provides historical background, presents a snapshot of where we are today (with opposing and controversial viewpoints where applicable), and includes some insight to where the field is headed. Indeed, the field evolves still. Thus, the book is a record of work done in this field, and provides results obtained not only by us but also by other investigators. The interested reader should find the book a good introduction to the background and procedures of drugs as discriminative stimuli, a useful introduction to the wealth of information that can be obtained from the paradigm, as well as being informative on the relatively complex processes of structure–activity relationships and mechanisms of drug action. Medicinal chemists need not be as fully versed in drug discrimination techniques as behaviorists to appreciate the utility of the drug discrimination paradigm

any more than behaviorists need be fully versed in topics fully understood by medicinal chemists—such as stereochemistry and drug design. Nevertheless, this book attempts to bridge these rather disparate but, in our opinion, complementary endeavors so that investigators on both extremes have a common vocabulary—so those designing and synthesizing novel chemical entities appreciate how their compounds can be evaluated, and so that those conducting the evaluations know what is behind the design and synthesis of the compounds they are examining. Chemists might find certain of the topics described herein to be rather trivial or mundane; behaviorists might find certain other chapters likewise. But, our intent is to bridge the gap between the various disciplines. What is common-knowledge to one might be a revelation to the other.

Studies on the subjective effects of drugs are of interest not only because they open up the possibility to gain new and accurate knowledge of the effects of many useful and experimental drugs, but also because they open up new vistas of how certain factors (e.g., dose and nature of training drug, presession injection intervals, route of administration, specific techniques, and animal species) can influence the qualitative and quantitative effects of drugs. The editors have attempted to organize the material in each chapter so that it is not described in isolation from other chapters; each chapter reflects, to some degree, the principles and/or concepts described in earlier chapters and, on occasion, is in anticipation of what will be described as issues in later chapters. Throughout the book, there are summaries of past research in the field as well as speculations or predictions of the future.

Inevitably, a book composed of chapters by multiple authors, with different styles and viewpoints, may vary in the interpretation of particular research findings; but no attempt has been made by the editors to impose conformity of viewpoint. The editors hope that differences in methodology or occasional inconsistencies in the interpretation of data will serve as a stimulus (no pun intended) for further research. Although the editors and invited authors may differ in their approaches to particular questions, or in their research techniques or orientation, all are dedicated to an objective and experimental evaluation of the discriminative stimulus properties of drugs.

In organizing the contents of this book, the editors decided early on that an attempt to provide exhaustive reviews of the stimulus properties of well-known drugs or of major drug classes was not our general goal; unfortunately, then, we were unable to invite many great practitioners of drug discrimination to contribute chapters (but perhaps in a future book?). Clearly, an attempt to explore these areas *in extenso* would have led to a multi-volume enterprise. Thus, the content of the book is restricted to subject areas generally not available elsewhere in a compact integrated form. The editors discuss basic principles of drug discrimination and the application of medicinal chemistry to drug discrimination studies in the first seven chapters. These chapters not only serve to highlight issues (and, sometimes, controversies) in drug discrimination but also might be helpful in other procedures and areas of behavioral pharmacology, medicinal chemistry, psychology, biology, physiology, and psychiatry. Thus, Part I (Chapters 1–7) describes the drug discrimination paradigm, the various methods and techniques employed, practical considerations, and examples of the general application of the method to investigate problems of interest. Chapters 1–3 should be of interest to those medicinal chemists not well versed in behavioral studies, whereas Chapters 4–7

might be particularly useful to those neuroscientists with limited training in stereochemistry, drug design, and drug development. Part II (Chapters 8–16) consists of invited chapters from investigators who have published extensively in the field of drug discrimination. They were invited to address specific topics or techniques that are of interest in drug evaluation and drug development. The editors are deeply indebted to these contributors. Their diligence and patience are warmly acknowledged as we arrived at a final publishable form of the book. On several occasions in Part II, material is referred to or included in order to point out its (as yet) incompletely realized promise as a field of study. It is hoped that others may continue to follow these promising studies.

From the editors' point of view, many contributions (scientific and otherwise) for Chapters 1–7 came from our students, technicians, postdoctoral fellows, and colleagues whose questions sometimes forced us to re-examine issues that we thought we had already understood, and whose research projects provided intellectual stimulation and (most of the time) fun. At this point, spanning more than 65 years of combined work by the editors, there are too many individuals to name—you know who you are (and many are cited in references that are provided)—who have helped us in clarifying some of the issues and provided the data that appear in Chapters 1–7. Last, but certainly not least, we both wish to acknowledge the aid of several individuals whose assistance was of great value to us: Jonathan Rose of Wiley Publishing, Dr. Malgorzata Dukat (experienced and published both in medicinal chemistry and behavioral studies) for her constructive comments on selected chapters, and Ms. Jennifer Degarmo, who was involved in the early phases of organizing the book, contacting authors, performing administrative tasks, and advising the editors. Finally, the editors acknowledge that their basic outlook of drugs as discriminative stimuli is, in many ways, a reflection of their numerous conversations with, and insights and suggestions from, Dr. John A. Rosecrans—a pioneer in this field, to whom we are greatly indebted. Our sense of gratitude is too great to be expressed simply.

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PART I

Part I is a detailed description of the drug discrimination paradigm, various methods and techniques employed, practical considerations, and examples of the general application of such methods to investigate problems of interest. Chapter 1 provides background/overview perspectives and specific commentary on the likelihood that a relationship may (or may not) exist between drugs as discriminative stimuli and drug abuse. Chapter 2 concentrates on specific methodological variables pertinent to studies of drug discrimination: 1) apparatus used, 2) subjects employed, and 3) a basic but relatively concise review of vocabulary for operant conditioning procedures. The beginning of Chapter 3 presents an impressive, but partial, list of drugs that have served as discriminative stimuli and then explores numerous issues, schemes, and tactics that confront investigators. Chapter 4 stresses the impact of chemical isomers when employed as training drugs and/or test agents. Chapter 5 illustrates how data obtained from drug discrimination studies are summarized and coherent structure–activity relationships (SAR) formulated. Chapter 6 provides examples of the mechanisms of action that are linked to the stimulus properties of certain drugs such as classical hallucinogens, amphetamine-related stimulants, designer drugs (e.g., MDMA, PMMA, α-ethyltryptamine), and therapeutic (e.g., antianxiety) agents. Finally, Part I closes with Chapter 7, which provides an overview of the relationships between drug discrimination studies and the development of agents as novel therapeutic entities or pharmacological tools.

Drug Discrimination: Applications to Medicinal Chemistry and Drug Studies, First Edition.
Edited by Richard A. Glennon, Richard Young.

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AN INTRODUCTION TO DRUG DISCRIMINATION

A. GENERAL SCOPE AND INTRODUCTORY COMMENTS

Subjects (animals, including nonhuman and human primates) are considered able to *distinguish* or *discriminate* between two (or more) distinct stimuli if they can be trained to respond in a different manner when each stimulus is presented. The greater the difference between two stimuli, the more likely subjects are able to distinguish or discriminate between them. *Differentiation of* discriminable stimuli *is the basis for the drug discrimination method*. Discriminative stimulus control of behavior, a concept closely linked to operant conditioning, is a behavioral technique whereby a particular behavior (i.e., a particular response) is reinforced—at least during training. The drug

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discrimination procedure—basically, a "*drug detection*" paradigm—uses a pharmacologically active agent as the discriminative stimulus. The technique has broad applicability both to the study of *animal behavior* and *investigations of drug action*. A closely related procedure, drug self-administration, utilizes relatively similar conditions to examine drugs as *reinforcers* (e.g., see Chapter 11 in Part II. by Negus and Banks). Whereas many investigators, particularly experimental psychologists, might utilize a drug as a "*discriminative stimulus*" or "*interoceptive cue*" (or, simply, "*cue*") to investigate animal behavior (i.e., the drug is held constant to investigate behavior), others, particularly pharmacologists and medicinal chemists, use the behavior to assess the actions of drugs (i.e., the behavioral component is held relatively constant to evaluate drug effects). The former approach has been addressed in psychology texts. With respect to the latter, there is no comprehensive text that describes the methods and approaches employed to study drug action. Those investigators trained in drug discrimination techniques ordinarily acquire their knowledge by serving as graduate students or postdoctoral fellows in laboratories where the technique is employed. Yet those trained in drug design are rarely schooled in drug discrimination. The purpose of this book is to bridge the gap and to focus on the drug discrimination procedure as it applies to the study of pharmacologically active substances. Here, emphasis is placed on the pharmacological and medicinal chemistry aspects of drug discrimination studies, including the role of stereochemistry, in examining structure–activity relationships and mechanisms of drug action, rather than on the use of the technique to investigate animal behavior.

Whereas the drug discrimination procedure is chiefly employed by those with training in psychology or pharmacology, those trained in drug design and drug development (e.g., medicinal chemists) typically have only a rudimentary grasp—at best—of the procedure. The drug discrimination paradigm, although somewhat labor intensive (and, hence, not particularly practical or suitable for the rapid screening of large series of agents), is of enormous applicability to the understanding of drug action. The present narrative will address the practical aspects of drug discrimination such as: What procedures can be used? How do the various procedures differ? How are drug discrimination studies conducted? What types of data can be obtained? How are data interpreted? Of what value are drug discrimination data? When are drug discrimination studies not applicable? And, what are the limitations of the drug discrimination procedure? One hopes that individuals involved in drug design and development who are not currently familiar with the drug discrimination technique will learn to appreciate the exquisite nature and power of this procedure and will become skilled at asking the types of questions that can be answered by those conducting drug discrimination studies. Whereas medicinal chemists should come to learn the types of information that drug discrimination studies can offer, pharmacologists might come to realize how medicinal chemists can apply the types of information that the paradigm routinely provides. As such, knowledge of more than one of the aforementioned disciplines should lead to a higher regard for the usefulness of the procedure. Indeed, a greater appreciation of the multidisciplinary perspectives of these disciplines may usher the contribution of even more intriguing scientific inquiries in the future. In addition, portions of this text will be of a very practical nature and will describe how such studies are conducted, their advan-

tages over certain other types of pharmacological evaluations, and their acknowledged limitations. Thus, this book is aimed at graduate students and both academic and industrial scientists, including pharmacologists, psychologists, psychiatrists, biologists, biochemists, chemists, medicinal chemists, and other investigators whose interests involve the design, development, and/or action of agents that act (primarily) at the level of the central nervous system.

The book is divided into two parts. Part I (Chapters 1–7) describes the drug discrimination paradigm, the various methods and techniques employed, and practical considerations, as well as examples of the general application of the methods utilized to investigate problems of interest. Part II (Chapters 8–16) consists of invited chapters from investigators who have published extensively in this area. They address specific topics or techniques that are of interest in drug evaluation and development.

As evidenced over the years, the drug discrimination paradigm is a robust and reliable technique that produces very reproducible results across laboratories. Many examples used in Part I of this book to illustrate the applicability of the drug discrimination paradigm to investigations of drug action are from studies conducted over the past 30+ years in our laboratories. The discussions are meant to be illustrative rather than comprehensive. That is, this volume is not intended to be a comprehensive review of the drug discrimination literature, or even a review of a specific drug or drug class. Indeed, many thousands of drug discrimination (i.e., stimulus generalization and antagonism) studies have been reported. What is presented in Part I is meant to serve as examples of the types of studies that can be conducted.

The chemical structures of some of the training drugs that have been employed in our laboratories, and that form the basis for a large part of the discussions in Part I, are shown in Figure 1-1. One reason for the focus on work from our laboratories is that our studies maintained relatively consistent methodologies and techniques and, consequently, have minimized the role of procedural or methodological differences. In general, there is excellent agreement between drug discrimination results from different laboratories regardless of animal species, schedule of reinforcement, and other factors. However, different training doses, pre-session injection intervals (PSIIs), animals (species or strain), routes of administration, schedules of reinforcement, and other factors can sometimes make it difficult to compare results between laboratories. For example, we have demonstrated that results of stimulus antagonism studies using 5-methoxy-*N*,*N*-dimethyltryptamine (5-OMe DMT; see Figure 1-1 for chemical structure), a relatively short-acting serotonergic-mediated hallucinogenic agent, as training drug differ dramatically depending upon the training dose employed [1]. That is, a 1.5 mg/kg training dose of 5-OMe DMT produces a discriminative stimulus that is quite different from that produced by a 3.0 mg/kg training dose, even when all other factors were held constant. This represents only a 2-fold change in training dose. Had these studies been conducted in two different laboratories, with one laboratory using the lower training dose and the other laboratory using the higher training dose, the results would have appeared inconsistent and in relative conflict with one another. Furthermore, had there been any methodological differences between the two laboratories, these differences might have been thought responsible for the inconsistencies observed. Likewise, Appel and co-workers [2] noted differences in stimulus generalization

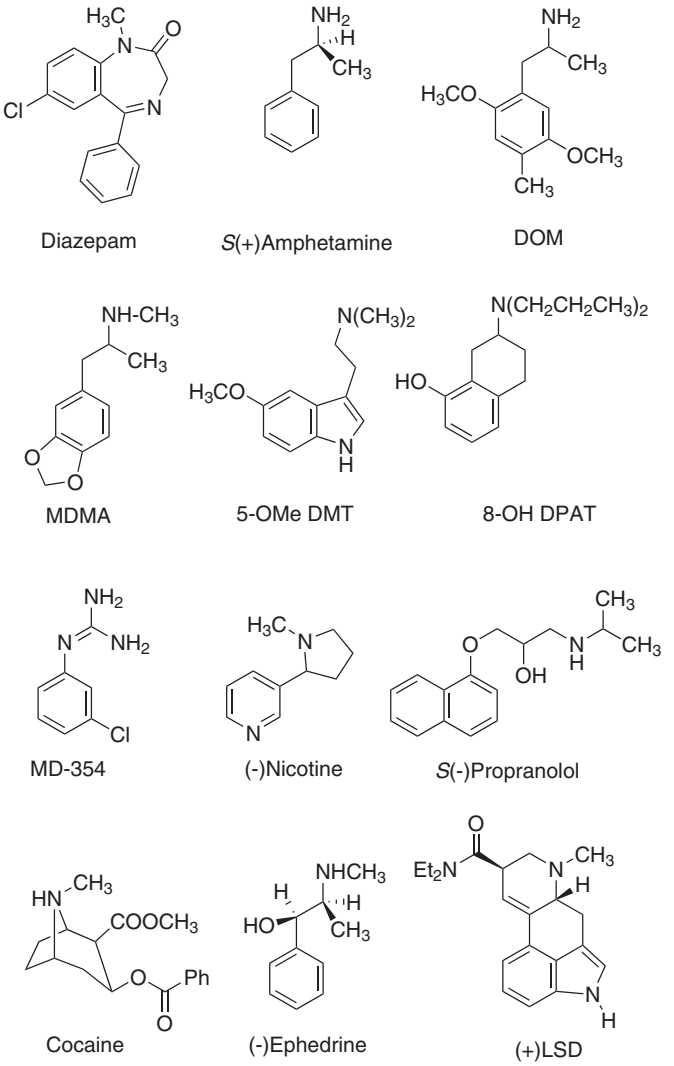

Figure 1-1. Chemical structures of some representative examples of agents that have been used as training drugs in our laboratories: diazepam, S(+)amphetamine, 1-(2,5-dimethoxy-4-methyl)phenyl-2-aminopropane (DOM), N-methyl-1-(3,4-methylenedioxyphenyl)-2-aminopropane (MDMA), 5-methoxy-N,N-dimethyltryptamine (5-OMe DMT), 8-hydroxy-2-(N,N-di-n-propylamino)tetralin, 3-chlorophenylguanidine (MD-354), (–)nicotine, S(–) propranolol, cocaine, (–)ephedrine, and (+)lysergic acid diethylamide.

(including stimulus generalization studies with 5-OMe DMT) and antagonism results employing (+)lysergic acid diethylamide (LSD) training doses of 0.02, 0.08, and 0.32 mg/kg. For further discussion of this issue see Chapter 3.

As a final note: much of the data from our laboratories was previously published in tabular rather than graphic form. These tabular data were used to prepare new graphical depictions for the present work. In a few instances, where data might have been previously presented in graphical form, graphs were replotted to abstract certain data from a published figure or to combine data published earlier in several different plots.

B. BACKGROUND AND UTILITY OF THE DRUG DISCRIMINATION PARADIGM

Humans have ingested and experienced the effects of psychoactive agents throughout history. In fact, the use of drugs can be traced through anthropological and archaeological evidence that dates back at least 5,000 to 10,000 years; for example, ancient Sumerians of 4000 B.C. referred to the poppy as the "joy plant" [e.g., 3]. "Psychoactive" drugs refer to chemical agents that exert an action upon the central nervous system (CNS), alter brain activity, and, consequently, produce a temporary change in an individual's mood, feeling, perception, and/or behavior. Such agents might be used for their religious or spiritual effects ("*entheogens*"), prescribed as therapeutic medications (e.g., opioids, anxiolytic agents, antidepressants, and antipsychotics), and/or are used (or abused) as recreational drugs (e.g., hallucinogens, stimulants, and related designer drugs). In each case, the subjective effects produced by such agents are generally not readily accessible to independent verification by an observer. However, methods were developed over 50 years ago whereby human subjects administered such drugs could self-rate their experiences on questionnaires [4]. Today, various subjective scales and behavioral inventories of the effects of drugs are often used and have become important tools for basic and clinical neuroscience research. For example, frequently used questionnaires include 1) scales of global drug effects, that rate the "overall strength," "liking," "good" or "bad" effects of an agent [e.g., see 5]; 2) the Addiction Research Center Inventory (ARCI) [6–8] that contains subscales of physical, emotional, subjective, and potential for abuse effects of a test agent in relation to those of standard drugs and/or drug groupings such as the Mar Scale (i.e., effects of marijuana as reference), Morphine-Benzedrine Group (MBG; index of euphoria), Pentobarbital-Chlorpromazine Group (PCAG; index of apathetic sedation), and Lysergic Acid Diethylamide Group (LSDG; index of dysphoria or somatic discomfort); 3) a Profile of Mood States (POMS) [9–11] that estimates the degree of similarity of a test agent to standard drugs (e.g., stimulants, sedatives, or anxiolytics) and identifies effects that might be aversive (e.g., tension-anxiety, depression-dejection, anger-hostility, fatigue, or confusion-bewilderment); and 4) the Drug-Class Questionnaire, which asks subjects to compare the effect(s) of a test drug to that of a list of drugs/drug classes [12, 13]. Generally, subjects furnish information about themselves through self-inventories and profiles are created of the perceptible effects and pharmacologic properties (e.g., potency and time course) of a drug; in practice, the effects of test agents are often compared to those of

known reference drugs. Scales and questionnaires are convenient because they do not usually require the services of a group of raters or interviewers. Their potential disadvantage might be that individuals do not completely comprehend the effect of the drug or their drug "experience" and, therefore, might not always give a report that is completely thorough or amenable to appropriate quantitative analysis, or open to definitive interpretation. Lastly, a newly synthesized agent is precluded, for obvious ethical and pragmatic reasons, from initial assessment in humans to determine whether its pharmacological action is similar to that of a known psychoactive agent. In such instances, animal protocols offer an alternative approach to characterize the pharmacological actions, mechanism of action, and safety of an agent. Common goals of such studies are to offer a possible mechanism of action and prediction of the pharmacological effects (and side effects) of an agent in humans.

The use of nonhuman animal subjects can be justified in such experiments on the basis of at least three criteria in that they 1) allow relatively precise control of extraneous variables; 2) are presumed to be simpler organisms that allow the study of drug action at a relatively elementary level but yet can form the foundation for deriving more complex aspects of drug action that are presumably reflected in human subjects; and 3) may be used to study the influence of certain drug effects that may (or could) not be studied with human subjects. As such, nonhuman animals could, and in some cases, be "more suitable" subjects for studying certain drugs than would humans. The rodent, for example, is not so "encumbered" with past experiences of drug effects and symbolic language-factors that might, perhaps, render the human subject as being "too complex" in certain evaluations of novel chemical entities.

The drug discrimination paradigm is an assay of, and relates to, the subjective effects of drugs in nonhuman or human animals. In a typical operant experiment, there are four basic components: 1) the subject and their "motivational condition," which increases the effectiveness of an event as reinforcement (e.g., an animal is often subjected to food restriction, which makes the presentation of food more effective as reinforcement); 2) the administration of a drug dose that exerts an effect on the subject, or its vehicle, and precedes a response by the subject; 3) an appropriate (or correct) response; and 4) presentation of reinforcement. *These elements may be termed the basic components of an operant analysis of drugs as discriminative stimuli:*

SUBJECT → DOSE of TRAINING DRUG (or VEHICLE) → RESPONSE → REINFORCEMENT

The drug or non-drug (i.e., vehicle) condition that leads to, or results in, a behavioral event (i.e., a particular response) and is followed by the presentation of reinforcement is called the *discriminative stimulus*. In laboratory subjects, discriminative control of behavior by (usually, but see Chapter 3) two treatments is established through the use of reinforcement (often referred to as *reward*). The treatments are used as antecedent "help" or "aid" events to control appropriate behavioral responses that are followed by reinforcement. Subjects are usually trained to distinguish the effects of a dose of drug (i.e., a dose of training drug) *versus* non-drug or vehicle (i.e., usually saline, a