Behavioral Pharmacology

Second Edition

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Preface to the Second Edition

Since the publication of the first edition there have been rapid advances in the field, especially in understanding of basic neuropharmacology. Thus, a new family of possible chemical transmitters in brain—the neuropeptides—has been discovered, and rapid advances in neurochemical studies of brain receptors for drugs and transmitters have been made. These topics have been incorporated into the second edition, with special attention being given to the opioid peptides with regard to both their analgesic and their reinforcing properties. The second section of the book, dealing with the actions of particular groups of drugs on behavior, has been completely restructured, so that drug effects on different facets of behavior are now treated in a series of separate chapters. Wherever possible, some discussion of the practical application of this research to the use of psychoactive drugs in man has been included. The second edition proved to be a far larger undertaking than at first envisaged, but we hope it represents a substantial improvement on the coverage and structure of the original text.

Cambridge
August 1980

S.D.I.
L.L.I.

Preface to the First Edition

Neuropharmacology is concerned with the study of the effects of drugs on nervous tissue; psychopharmacology is concerned with the study of the effects of drugs on behavior. The discovery, in recent years, of highly effective drugs for treating various categories of mental illness in man has stimulated research in both areas and encouraged closer ties between them. In several instances, these drugs are now known to have specific neuropharmacological actions, and this has provided an added impetus to efforts to define the effects of such drugs on normal animal behavior precisely and to devise animal model behavior systems for discovering and assessing modifications of these clinically valuable drugs.

In this book we describe the achievements of psychopharmacology in providing behavioral methods for assaying drug action, and we give a brief resumé of the subject matter of neuropharmacology. The major classes of psychoactive drugs are described from both of these points of view. In the final section, examples are described where the marriage of neuro- and psychopharmacology is throwing new light on some old clinical problems.

Cambridge
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S.D.I.
L.L.I.

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I. Principles of Behavioral Pharmacology

1. The Analysis of Behavior

There are many ways of studying behavior, and opinions differ as to which are the most useful assays for assessing pharmacological effects. In this chapter we will confess ourselves immediately to be advocates of the descriptive behaviorism originally expounded by B. F. Skinner. This approach is grounded in the belief that by selecting a clearly defined element of behavior and objectively describing its occurrence under a variety of conditions, a predictive explanation of behavior emerges. This approach avoids any subjective and anthropomorphic interpretations of animal behavior. Many have found such an approach to behavior unacceptable. As we shall see later, for example, if one is interested in the effects of drugs on memory processes, performance levels of free-operant responses are not relevant measures of the behavior. Other critics view lever pressing in the rat or key pecking in the pigeon both as unnatural behaviors and as artificially selected elements of a much more complex behavior pattern. The relevance of studies of animal behavior to an understanding of human behavior, whether normal or abnormal, appears to reinforce the conviction that we should be concerned with "whole" behavior patterns rather than their individual elements. As Dews (1958) remarked, "why is it, that when somebody learns how to study a single nerve cell or a single renal tubule or to isolate a single enzyme everyone (rightly) says 'Bravo'; but when attempts are made to isolate functional units of behaviour for study many people say 'Ah, but you are neglecting all other concurrent behaviour and therefore your results are meaningless.'"

We hope to show, however, that the methods devised by Skinner have played a historic role in the development of psychopharmacology and have served it well (Dews, 1978). This is not to say that there is no room for other behavioral methods in the analysis of drug action. In Chapters 1 and 3 the variables that determine patterns of responding are described, and in Section II (Chapters 4–10) we go on to show how the major classes of psychoactive drugs can be identified by the manner in which they modify the control these variables have over behavior. A more detailed discussion of some of the behavioral issues and further definition of terms may be found in Blackman (1974), Rachlin (1970), and Reynolds (1968).

NORMAL BEHAVIOR

Classical and operant conditioning

In this chapter we will review some of the principles and techniques used in the experimental analysis of animal behavior. Under natural conditions, an animal is observed to make two kinds of behavioral responses, ELICITED and EMITTED. Elicited responses are those that can be induced reliably by a specific stimulus and under normal conditions only by that stimulus or one very similar to it. Such responses are reflexive; for example, withdrawal of a limb to a painful stimulus, pricking of the ear to sound, contraction of the pupil to light, and salivation to food. Elicited responses are precisely determined by the properties of the eliciting stimulus (its frequency of presentation, duration, and intensity) and are objectively quantified by their latency of onset, their amplitude, and the intensity of eliciting stimulus required to induce them. Emitted responses, by contrast, are not induced by any identifiable stimulus. Rats, for example, placed in an activity box run about. The amount of running characteristically decreases gradually with time, and many variables, such as time of day, degree of deprivation, estrous state in the female, temperature, and experience with the box, influence the characteristics of this habituation. Yet in such conditions, eliciting stimuli are not readily identified, and the behavior cannot therefore be controlled. If one is interested in using baselines of spontaneously emitted behavior for evaluating drug actions, one must resort to the observational methods of the ethologist, recording all the elements of behavior, as far as they can be defined, and their sequence. The studies of Chance and Silverman (1964) on rat social behavior provide an example of this method.

In certain natural patterns of behavior the relationship between emitted and elicited responses is complex. In many animals, for example, courtship and mating involve predominantly emitted behavior initially. Gradually, however, elicited behaviors under precise stimulus control emerge in sequence, and, finally, copulation, a reflexive action controlled primarily by the autonomic nervous system, occurs.

Elicited and emitted responses may be modified by conditioning. There are two kinds of conditioning—CLASSICAL (respondent or type 1) and OPERANT (instrumental or type 2)—and it is generally accepted that elicited responses are most easily conditioned classically and emitted responses operantly. Classical conditioning was originally described by Pavlov and is a process of stimulus substitution achieved by stimulus contiguity. A given response (the unconditioned response, UR) is elicited by a certain stimulus (unconditioned stimulus, US). A neutral stimulus (conditioned stimulus, CS) that would not normally elicit the response (UR) is presented at the same time as the natural elicitor (US), and, after the response to the paired stimuli has occurred, the previously neutral stimulus (CS) will now elicit that response (CR). If, for example, the sound of a bell (CS) is paired with the presentation of food (US), salivation (UR) can be elicited eventually by the bell alone (CR). It has been suggested that the UR and CR, although superficially similar, actually differ basically; for example, the chemical composition of saliva is different when it is naturally elicited than when it is conditioned to occur.

Classically conditioned responses have clearly defined properties, which distinguish them from operantly conditioned responses (Kimble, 1961). Stimulus parameters of the CS such as its intensity and duration are crucial, and the way in which the US and CS stimuli are paired, the interval between conditioning trials, and the regularity of the pairing also influence the CR. For example, short weak stimuli, which do not reliably occur together, constitute less than ideal conditions for classical conditioning. Even if strongly established, conditioned responses may quickly disappear (EXTINGUISH), once the stimulus contiguity is broken. When stimulus pairing is irregular, and conditioning accordingly weaker, extinction is even more rapid.

Operant conditioning, by contrast, is not concerned with modifying the eliciting conditions for behavior but with the processes by which the consequences of present behavior determine future behavior. If a response is followed by a pleasant or an unpleasant consequence, the probability of that response occurring again is changed. A pleasant consequence is called REINFORCEMENT and an unpleasant one PUNISHMENT. The former increases the probability of responding and the latter decreases it.

The basic concepts of operant conditioning were developed by the American school of behavior theory initiated by Thorndike. The original experiments were largely concerned with the learning of such complex tasks as mazes for rats or puzzle boxes for cats. The properties of operant conditioning, however, were most clearly defined by B. F. Skinner. In contrast to other theorists, who studied complex learned responses, Skinner believed that the principles of operant conditioning could be demonstrated most clearly when a simple response was studied. The lever press of a rat or the key peck of a pigeon served well for this purpose, and an automated apparatus for recording such behavior was developed, the so-called Skinner box. When placed in a small chamber with a lever on one wall, the rat emits a whole variety of responses, none of which is obviously elicited by stimuli in the environment. The lever is electrically connected so that when it is pressed a food reward drops into the cup below. Often the rat manipulates the lever by chance, and the process of reinforcement begins to operate. To speed this up, "free" reinforcements are given in the food well to encourage the rat to emit most of its behavior in the vicinity of the lever. Following "shaping" with reinforcement, further bar presses are likely to occur.

The development of apparatus for automating reinforcement delivery and recording responses has played a large role in advancing experimental analyses of operant conditioning. Electromagnetic or solid-state switching circuits are used to control the stimuli in the testing chamber, the schedule of reinforcement, and the delivery of reinforcement when appropriate responses have been made. The responses to the lever, the key or other device are counted, and, if required, their rate distribution over time can be plotted on cumulative recorders. This is a pen and paper recording method; the paper moves over a drum at a given speed, and each response moves the recording pen one step across the paper. The pen resets after crossing the paper. The rate and pattern of responding can be seen immediately: with high, regular rates of responding, the pen crosses the paper within a short time, whereas, with slow rates, the slope of the response line is proportionately less steep (Fig. 1–1). There are two major approaches to quantifying operantly conditioned responses and both are valuable in behavioral pharmacology. First, there is the FREE OPERANT method derived directly from Skinner's work, in which the main dependent variable is the *rate* of performing a specific act, such as key pecking in the pigeon. Rates of responding are sensitive indices of motivation, emotion, and drug-induced changes. Coupled with the use of schedules of reinforcement which influence rate of responding over time, free-operant methodology has much to

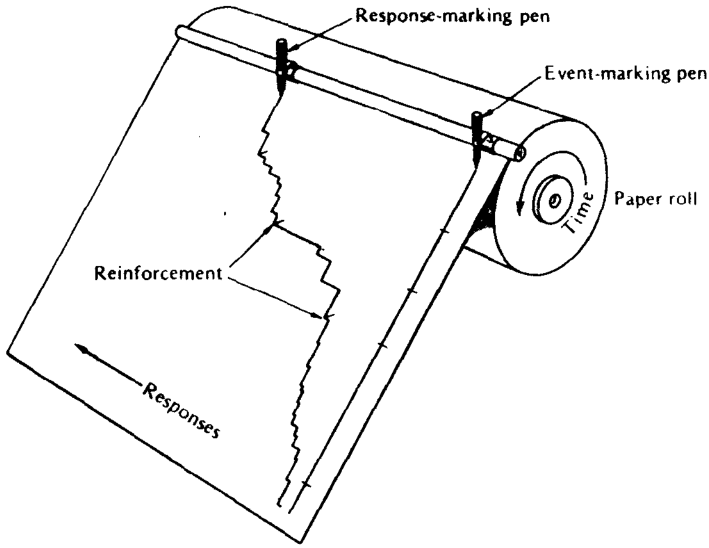

Fig. 1–1 A schematic drawing of the cumulative recorder. The paper unrolls under the two pens with time. Each occurrence of the response moves the response-marking pen up one unit toward the top of the paper. Reinforcement is indicated by a hatch-mark on the cumulative record. Additional events during an experimental session can be indicated along the horizontal line at the bottom (or top) of the record by the event-marking pen. (Reproduced from Reynolds, 1968.)

offer quantitative behavioral pharmacology. However, some drug effects are not readily reflected in changes in the rate or pattern of responding. Within this category fall changes in sensory thresholds, discrimination, and memory processes. Here it is sufficient to present a stimulus and to determine the *probability* and *accuracy* of the response to that stimulus. Failure to detect the stimulus, discriminate it from others, or to retain the information results in loss of performance. The physical characteristics of the stimulus or the period of time for which it has to be retained can be varied to assess the limits of threshold, discriminability, and memory. DISCRETE TRIAL PROCEDURES serve these purposes (Heise, 1975). In these procedures a single response to a stimulus is all that is required for reinforcement. Performance is measured in terms of probability; in other words the proportion of times the subject identifies the stimulus and makes the required response. Such methods are widely used in human experimental psychology, and sophisticated methods of analyzing response probabilities are available. Signal detection theory allows one to differentiate changes in sensitivity from response bias (Appel and Dykstra, 1977) and offers a powerful new analytic tool to behavioral pharmacology. Some of these procedures are mentioned in Section II (Chapters 4–10) in relation to particular drug groups.

Evaluation of classical and operant conditioning procedures

Although much has been made of the distinction between classical and operant conditioning, recent experimental evidence brings this emphasis into question (Mackintosh, 1974; 1978). Classical conditioning involves the relationship between a stimulus and a reinforcer, whereas operant conditioning is defined in terms of the relationship between a response and a reinforcer. There is no doubt that *procedurally* the two are different. The distinction becomes blurred, however, when conditioning situations are examined more closely. It is clear that stimulus–reinforcer (S–Re) relations can be modified during operant conditioning and similarly that response–reinforcer (R–Re) relations can be modified during classical conditioning. If a pigeon learns to press an illuminated key for food, the assumption is that the probability of the key press response increases because it is followed by reinforcement. Equally possible in such a situation, however, is that illumination of one key is reliably associated with the delivery of food. It is possible, therefore, that the emergence of key pecking is controlled by stimulus–reinforcer concurrence rather than by, or in addition to, the response–reinforcer contingency. To cite the opposite case, one may consider classical conditioning of leg withdrawal to shock. The dog reliably withdraws its leg to a conditioned stimulus, having been exposed to the CS paired with shock to the foot. However, it is possible that in addition to control by a stimulus–response contingency, behavior is also modified by the operant conditioning (response–reinforcer) contingency. When the dog withdraws its leg, the shock to the paw becomes less painful, that is, the leg withdrawal response is negatively reinforced and this response–reinforcement contingency may well contribute to the maintenance of behavior.

Another difference between the two procedures concerns the widely held belief that visceral responses controlled by the autonomic nervous system are *always* elicited rather than emitted and that only emitted behavior is controlled by the so-called voluntary motor nervous system. Considering the nature of the two conditioning procedures, it was reasoned that involuntary responses were modified by classical conditioning and voluntary re-