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Behavioural Techniques

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THE expanding importance of CNS pharmacology has led to the use of behavioural techniques borrowed directly from modern behavioural sciences. It is clear that the study of CNS functions—and the study of the effects of drugs thereon—requires an analysis of the complex interactions between the intact organism and its environment which we call *behaviour*. To do so is simply to include in biological investigations a level of analysis that is no less necessary than the physiological or biochemical level, though the most refined methods and concepts of behavioural sciences are at the present time far less sophisticated than those of physiology or biochemistry.

Behaviour, being the complex functioning of a whole and mainly intact organism, may be changed by altering any part of it. Behavioural modifications induced by drugs are therefore not necessarily evidence of a direct pharmacological action on the CNS. They may result from many peripheral effects: peripheral muscle relaxation will interfere with the performance of a motor response, dry mouth after the administration of peripheral anticholinergics will indirectly alter food-reinforced behaviour, local anaesthetics will change escape or avoidance responses maintained by nociceptive stimulation, and so on. Such possibilities should be excluded before interpreting behavioural changes as being the direct consequence of the central action of a drug.

Behavioural methods resorted to in experimental pharmacology generally use animal subjects*; they could be applied to human subjects but they are not, for practical reasons. Some of these reasons are similar to those dictating the widespread use of animals in pharmacological research, others are specific to the study of behaviour. This, of course, raises a special problem as to the extrapolation of results to the field of human therapeutics: we know too little concerning the nature and origin of behavioural disturbances in humans to legitimate analogical arguments drawn from animal research. Any claim to produce equivalents of human neuroses or psychoses in infra-human organisms is scientifically naive. Though they were often used to this end in the early stages of psychopharmacology, behavioural methods do not help, at the present state of our knowledge, in predicting the therapeutic value of psychotropic drugs (except for strictly correlational predictions). They must be taken as tools—thus completing the array of modern

* Pharmacological research on humans sometimes resorts to psychometric testing and the like; the context of such research is similar to clinical investigations and these methods have little relevance for the experimental pharmacologist. They will receive no attention here.

techniques described in this book—which are useful in classifying drugs, in comparing and analysing pharmacological effects, and, when systematically combined with biochemical and neurophysiological analysis, in exploring the underlying mechanisms of drug action.

Available methods differ in several respects and should be selected by the experimenter according to the specific aims and conditions of his investigation. They differ as to the level of complexity of the behaviour considered, the degree of refinement in experimental control, the possibilities of quantification, the amount of pharmacological studies already done and with which new data can be compared, the time required to obtain reliable results, the kind of theoretical and technical training necessary for correct application, and so on.

For our purposes, we will consider two main categories of behavioural techniques:

(1) general motor activity and complex reflex tests;

(2) conditioning techniques.

14.1. GENERAL MOTOR ACTIVITY AND COMPLEX REFLEX TESTS

When an animal is allowed to move freely in a given environment, he will do so as a consequence of a number of factors, although we cannot identify them as precisely as we might describe the stimulus responsible for a scratch reflex. General or spontaneous motor activity may be studied in an environment that is not familiar to the subject. It is then called *exploratory behaviour*. A classical example is the open-field test, in which the movements and simple emotional manifestations of a rat in a circular space are observed and counted. One must be aware of the fact that an unfamiliar environment may induce reactions for which the term *exploration* is inappropriate. For example, depending upon the characteristics of the species, illumination or noise level may have aversive properties resulting in escape responses and the like. Drug effects will, of course, vary as a function of such factors. It is therefore necessary to analyse them systematically.

When an animal is allowed to move freely in a familiar environment repeatedly and/or for long uninterrupted periods of time, *actometers* are used to provide automatic recording of motor activity. A number of devices are available, as adapted for various species, primarily rats, mice, dogs, guinea-pigs, fishes, etc.* Very common in pharmacological studies are the classical *activity wheel*, which rotates on its axis when the subject walks on it, the *jiggle-cage* mounted on springs or bearings so that slight movements of the subject cause the cage to oscillate and close a circuit, the photo-cell network arranged on the walls of an experimental space, etc.

* Continuous records of spontaneous activity are common in the study of circadian rhythms. Therefore, the experimenter will find in this field the best solution to his technical problems.

The effects of drugs on motility and on gross reaction to stimuli can be tested in more specific situations, such as the rotating rod for mice, the traction test, the chimney test, the natatory-exhaustion test, the climbing-pole test, etc. It must be noted that an action of psychopharmacological agents on these tests is generally obtained with subtoxic doses responsible for deep muscle relaxation or serious impairment of motor coordination. These, like the preceding techniques, are described in all recent handbooks on screening methods in pharmacology [18] (see also [11] and [8]).

Supposedly unlearned aggressive reactions to members of the same or another species are also often used. Some strains of rats exhibit an aggressive killing behaviour towards mice [9]. Interspecific or intraspecific aggression can be induced by putting the animals in isolation, by delivering electric shocks, or by producing cerebral lesions. The same drug does not affect equally the various types of aggressive behaviour, some of which are highly resistant to psychotropic agents. None of these tests is to be taken as predictive of the anti-aggressive properties of drugs in human patients.

All these techniques generally take little time and allow for large group studies. Automatic recording is most often feasible and, if not, observers devoid of scientific background can be trained easily. Results are ready for statistical treatment and do not require refined interpretation in behavioural terms. For these reasons, they are traditionally included in screening procedures. However, they provide little information as to the interactions between drugs and crucial variables in the analysis of behaviour. These parameters are evaluated by the second class of techniques now to be described.

14.2. CONDITIONING TECHNIQUES

Following a convenient classification, we can distinguish two experimental procedures in conditioning: the Pavlovian (respondent, classical or type I) and the operant (or type II).

The Pavlovian procedure, as exemplified by the conditioned salivation experiments in dogs, is familiar to physiologists and will not be described here (see [12] and [7]). It offers the psychopharmacologist a wide variety of tests supported by elaborate psychophysiological concepts and a growing knowledge of neurophysiological correlates. Though a number of variables may be controlled automatically with modern equipment, the presence of the experimenter throughout the experiment is generally required. In most cases, the response to be conditioned (generally autonomic: salivation, gastric secretion, heart rate, vasomotor reaction, etc.) is recorded by means of the usual physiological instrumentation. The presentation of unconditioned and conditioned stimuli also requires physiological techniques (fistulae, catheters and the like) when applied to internal organs. For these technical reasons, animals of a certain size, such as dogs, monkeys or sheep, are generally preferred.

Though it is the favoured technique in Soviet psychopharmacological laboratories, Pavlovian conditioning has not been extensively used in this field by western workers. It is clear, however, that several important aspects of the

Pavlovian approach—especially the study of the interdependence between the higher nervous system and the internal organs, as analysed in interoceptive conditioning research [1, 2]—should be given serious attention not only by psychopharmacologists but by pharmacologists in general if they wish to understand the mode of action of drugs in the intact organism.

In the operant conditioning experiment, as initially developed by Skinner [16], a subject emits a response—any defined motor action, e.g. pressing a lever—which is reinforced by food. This consequence, or reinforcement, increases the probability that the response will again be emitted in the same situation. Note that there is no physiological pre-established connection between the reinforcer and the selected response, as is the case between the unconditioned stimulus and the unconditioned response of the Pavlovian experiment. This very simple paradigm reflects a very basic principle of behaviour. The relation between response and reinforcement may be complicated *ad infinitum*, for instance by increasing the number of responses required for one reinforcement, by introducing temporal conditions, by making the effectiveness of responses contingent upon the presence of some external discriminative stimuli, etc. Modalities of relations between response and reinforcement are described as *schedules of reinforcement* [5]. The behaviour may be placed under the control of positive reinforcers, such as food, drink, rewarding electrical brain stimulation, or under aversive control, in which the subject escapes or avoids anticipatively an aversive stimulus (electric shock, excessive heat or noise, etc.) by emitting the specified response. As a general rule, operant behaviour will be kept strong if it is followed by the presentation of a positive reinforcing stimulus or by the withdrawal of a negative reinforcing stimulus; conversely, it will be extinguished if the positive reinforcer is no longer delivered, or if the behaviour is punished by an aversive stimulation. Conflict situations can be broken down into these basic components.

Though other dimensions of behaviour may be considered, results are generally expressed in terms of the *rate* of the response. Control of the experimental variables and recording of the data are fully automated: they are actually far too complex to be performed by a human operator, whose permanent presence is no longer required. This is an evident advantage in the study of chronic treatment with drugs. Long-term studies of individual animals are feasible. Specific contingencies of reinforcement produce specific patterns of behaviour which are reproducible over a wide range of species, thus allowing for significant interspecific comparisons (the most popular species in the field are rats, cats, pigeons and monkeys).

For these and other reasons, operant conditioning techniques are currently the most widely used in experimental psychopharmacology (if we except screening procedures), at least in western laboratories. They provide a highly valuable and sensitive tool for assessing the general properties of drugs at the behavioural level: dose-effect relationship, type of action, duration of action, effect of prolonged treatment, drug combinations, etc. (see [15]).

The differential analysis of the effects of drugs on behaviour controlled by various schedules of reinforcement has drawn attention to the importance, in characterizing drug action, of specifying the type of behaviour being considered and the environmental variables that control it. From the results of such an experimental analysis, it is evident that general terms—largely inherited from mentalistic psychology—such as *anxiety*, *aggressivity*, *emotionality*, *activity*, *memory* and the like do

not help in describing or explaining behaviour and its modifications by drugs. The concept of *drug behaviour interaction* is central in operant conditioning psychopharmacology. It is elegantly illustrated in experiments using *multiple schedules*, in which the behaviour of the animal is controlled, in alternating periods, by two (or more) different sets of contingencies: for instance, during 10 min, the animal must avoid an electric shock by pressing a lever at a sustained rate, and during another 10 min every 20th response will be rewarded by food. A given drug may show different effects on the two types of behaviour, as exhibited in the same animal in a given experimental session. It must be emphasized that every aspect of drug effects as measured at the behavioural level, be it dose-effect curve, general direction of action, duration of action, tolerance, potentiation or antagonism by other compounds, depends to some extent upon the type of behaviour being studied.

Because they are frequently misinterpreted, the so-called *experimental neuroses* are worth a final comment. First described in Pavlovian laboratories, these consist of disruptions of conditioning induced by well-defined experimental conditions such as the interference of a strong fear-producing stimulus, or the presentation of a discrimination task beyond the present capacities of the animal, or, in an operant situation, by punishing the subject while he is performing a response rewarded by food. These situations are interesting in the study of emotional correlates of approach-avoidance conflicts and of the intricacies of positive and negative motivational systems. But they are not simplified models of human neuroses and should not be simplistically taken as such in psychopharmacological research. Actually, drug studies show that they are not better indicators of any given psychotropic property than other behavioural tests.

The reader will find simple methodological information on operant conditioning in Reynolds [13] and Richelle [14] and numerous examples of applications as well as theoretical discussions on behavioural pharmacology [3, 4, 6, 8, 17].

In addition to the two main categories of behavioural techniques, it is fair to mention a slightly different approach to the analysis of behaviour, i.e. the ethological observational method. This approach emphasizes the analysis of the structures of behaviour as they can be observed in the natural conditions of life of the species. It resorts essentially to observational methods, since any experimental manœuvre, unless carefully designed to leave the natural environment untouched, is considered artificial and hence likely to destroy the very object under investigation. Attempts were recently made to apply such methods to psychopharmacological research (Chance, in [8]). Whatever the theoretical interest of this approach, it is too early to evaluate its ultimate relevance to the field of pharmacology as compared with the methods described above, which have undoubtedly the advantage of providing refined experimental control and which are equally appropriate in a wide range of uses of behavioural analysis, be it for its own sake or in close connection with biochemical or neurophysiological investigations.

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