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Factors Controlling Drug Reinforced Behavior

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MEISCH, R. A. *Factors controlling drug reinforced behavior.* PHARMACOL BIOCHEM BEHAV 27(2) 367–371, 1987.—An overview is provided of factors controlling drug reinforced behavior. Drug reinforced behavior is defined, and control procedures for rigorously identifying such behavior are discussed. Factors affecting drug reinforced behavior include the drug itself, animal species, route of administration, current circumstance variables, subject's experimental history, and response consequences. Current circumstance variables concern conditions present during opportunities for drug self-administration and include such factors as stimulus control, food deprivation, drug-access conditions, and brain lesions. Response consequence variables include reinforcement schedule, punishment, drug dose, and competing reinforcers. Drug reinforced behavior is a member of a more general class of behavior, namely operant behavior. Over the last 25 years there has been a rapid increase in understanding drug reinforcement, and this pattern of expanding knowledge suggests that the high rate of progress will continue.

Drug reinforcement Drug self-administration Drug addiction Animal models Operant behavior

A critical point in studies of drug seeking behavior was the demonstration by James Weeks in 1962 that rats would repeatedly press a lever when lever presses resulted in intravenous morphine injections [32]. This was a clear demonstration of drug seeking behavior. This experiment by Weeks was also important from a technical standpoint for Weeks showed that it was possible to have a catheter chronically placed in the vein of a freely moving animal. Such an arrangement permitted the immediate delivery of a drug injection following an operant response, and thus a rapid acquisition of drug reinforced behavior was possible.

EXPERIMENTAL ARRANGEMENT

The drug self-administration procedure described by Weeks is a type of experimental preparation that is similar in principle to other types of experimental preparations used to study drug effects [28]. It differs from other preparations mainly in that the dependent variables measured are behavioral variables. This preparation has been used to analyze the factors that control drug reinforced behavior. Many different factors have been studied, and the purpose of this paper is to give an overview of these factors. Some of the most commonly studied factors are the particular drug employed, the drug dose, and the schedule of reinforcement. Other features that have been varied include the route of administration and the species of animal. Before considering these factors, it is important to define what drug reinforced behavior is and how to distinguish it from other behaviors.

DRUG REINFORCED BEHAVIOR

Drug reinforced behavior is behavior controlled by delivery of a drug that is serving as a reinforcer. Most studies have been concerned with drugs functioning as positive reinforcers, although a few have dealt with drugs acting as negative reinforcers [9]. A positive reinforcer is defined as an event whose presentation, contingent upon a response, increases the future probability of that response. Occasionally investigators confuse drug self-administration with drug reinforcement. One can obtain drug self-administration by having an animal drink a drug that is dissolved in a sweet tasting vehicle. Or one might get drug self-administration when a drug causes a large increase in activity such that there are frequent nonspecific presses on a lever that produce drug injections. In these two examples intake of the drug is due to factors other than drug reinforcement. Studies of drug reinforced behavior are a subset of drug self-administration studies. The critical feature of drug reinforced behavior shows that its occurrence is based on the response contingent presentation of the drug and is not due to any other factor.

A number of control procedures are necessary to rigorously demonstrate that a self-administered drug is actually serving as a reinforcer. One of these procedures is the use of a second lever or "dummy" lever to show that the self-administered drug does not produce a nonspecific increase in lever pressing. When a drug functions as a reinforcer, only presses on the "active" lever increase. A related manipulation is a lever reversal where presses on the formerly active lever have no effect whereas presses on the formerly inactive lever lead to drug injections [26]. If the drug is serving as a reinforcer, responding will shift to the formerly inactive lever. In other words if a drug is serving as a reinforcer, response rates should change in an orderly manner when active and inactive levers are reversed. A second procedure

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is to give drug infusions noncontingently in approximately the same pattern that the animal would have self-administered the drug [26]. If the drug is acting as a reinforcer, the rate of lever pressing should decline when infusions are given noncontingently.

A third procedure that is particularly critical is to compare rates of responding when lever presses deliver the vehicle. This test should be conducted under the same conditions as when lever presses produce infusions of the drug in the vehicle solution. Obviously the drug should maintain higher response rates than the vehicle. Sometimes this is not easy to demonstrate. If, for example, animals have a history of cocaine reinforced responding, high rates of lever pressing may persist for extended periods when saline infusions are the only consequence of lever pressing [16]. Lack of a difference between vehicle and vehicle plus drug is less likely to be seen if large response requirements, such as large fixed-ratio values, are used [14,16]. A related control procedure is to have the vehicle solution concurrently available with the drug solution such that lever presses can result in either drug or vehicle injections [21]. This use of two solutions is technically more difficult than the use of a single drug or vehicle solution, but may be more sensitive to drug reinforcement effects.

There are two other procedures that can yield strong supporting data for drug reinforcement effects. One is to demonstrate that contingent drug injections will reinforce behavior under intermittent reinforcement schedules. A second is to demonstrate orderly dose response relations.

DRUGS

Many factors control drug reinforced behavior, and one of these is the drug itself. In general drugs that function as reinforcers for humans also function as reinforcers for other animals, and drugs that do not act as reinforcers for humans do not act as reinforcers for other animals [10,19]. For example, nicotine can serve as a reinforcer as can drugs from four pharmacological classes: the psychomotor stimulants, the opioids, the dissociative anesthetics, and the general CNS depressants including ethanol, the barbiturates, the benzodiazepines, the gaseous anesthetics, and some solvents.

Within drug classes such as the psychomotor stimulants a number of drugs have been systematically studied and compared [11]. One conclusion from such studies is that not all drugs are equally effective as reinforcers.

SPECIES

Drugs serve as reinforcers for a wide range of mammalian species including mice, rats, cats, dogs, squirrel monkeys, rhesus monkeys, and baboons. A major gap in the literature is the lack of studies in which different strains of a single species have been compared in terms of drug self-administration. Although most animals tested will self-administer drugs such as cocaine, there are differences between animals in amount of self-administration behavior. Some of these differences may be due to genetic factors [25]. In some studies humans have been used as subjects [13]. However, more studies with humans would be desirable for a number of reasons, and one of these is to correlate findings with humans with those of other species.

ROUTE OF ADMINISTRATION

A number of routes of administration have been utilized. Drugs can serve as reinforcers when injected intravenously, intragastrically, intramuscularly, intracerebrally, and when taken orally or by inhalation. Although drugs are effective when administered by various routes, systematic comparisons among routes have not been conducted.

CURRENT CIRCUMSTANCES

Current circumstance variables are conditions present at the time of testing and include such factors as stimulus control, food deprivation, drug access conditions, and brain lesions. These factors differ from response consequences and experimental history which are covered in subsequent sections.

Stimulus Control

Stimuli present at the time of drug injection can also control drug reinforced behavior. These stimuli include both external stimuli paired with drug injection and internal stimuli such as the effects produced by the reinforcing drug. By noncontingently injecting a drug such as cocaine one can temporarily restore responding that has decreased due to extinction [4]. These rate increases are not the result of nonspecific activation of behavior since rate of responding is selectively increased only on the lever that has produced injections in the past.

Food Deprivation

A new variable that has only recently been studied is food deprivation. Food deprivation causes large increases in intake of reinforcing drugs [3]. Drugs appear to be more effective as reinforcers when animals are food deprived. Why this is the case is not known. However, the increased drug intake is not secondary to increased activity or increased intake of the vehicle.

Drug Access Conditions

Drugs can be available for injection for 24 hours, day after day, or they can be available for only a few hours each day. The periods of drug availability are often termed drug access conditions, and these conditions can have a major impact on the pattern and consequences of drug intake [36]. For example, when psychomotor stimulants such as cocaine and d-amphetamine are available under 24-hour conditions, patterns of intake are highly variable, and toxic effects occur [20]. There is substantial day-to-day variability in the number of infusions taken. Bouts of drug taking that may last several days are followed by periods of no responding. This variability in intake occurs with animals from several species, such as rats, dogs, and cats. In contrast, when access is limited to several hours per day regular patterns of intake are observed. A general finding is that drugs can serve as very effective reinforcers under limited access conditions. This had been a particularly important discovery since it demonstrates that strong drug seeking behavior can occur when physical dependence is minimal or absent.

Brain Lesions

Selective lesions have been made in the brains of rats to evaluate which of the catecholaminergic pathways are involved in cocaine reinforced behavior. The lesions were made using 6-hydroxydopamine. Lesions in areas with noradrenergergic neurons had no effect on responding.

However, lesions in an area with dopaminergic neurons, the nucleus accumbens, resulted in a significant decrease in cocaine self-administration [27].

Drug Effects on Drug Reinforced Behavior

A frequently studied variable is the effect of one drug on the self-administration of another drug. The rationales for such studies have been diverse. One major objective has been to use drugs as tools to analyze mechanisms of action. This type of research can be illustrated by recent work at the University of Chicago and at Louisana State University. The results further implicate dopamine as the critical neurotransmitter mediating the reinforcing effects of cocaine. With rhesus monkeys a number of agonists at the dopamine D_2 receptor (apomorphine, piribedil, propylbutyldopamine, and bromocriptine) serve as reinforcers whereas an agonist at the D_1 receptor (SKF 38393) failed to maintain behavior [34]. Additionally, lever pressing reinforced by cocaine or piribedil was increased by intermediate doses of pimozide, a D_2 antagonist, but not by SCH 23390, a D_1 antagonist [33]. This is further evidence that the D_2 receptor is involved.

In another series of studies [5] a procedure was used whereby rats were able to self inject nanoliter volumes of drug solution directly into specific brain regions such as the medial prefrontal cortex. Sulpiride, a D_2 antagonist, attenuated cocaine self-administration whereas a D_1 antagonist (SCH 23390) did not [7]. Direct attenuation was also not observed with the muscarinic antagonist atropine or with the beta adrenergic antagonist propranolol. A primary mode of cocaine action at the presynaptic dopaminergic terminal was demonstrated by the elimination of cocaine reinforced responding that followed lesions made with 6-hyroxydopamine [6]. Responding could be restored by substituting dopamine for the cocaine. Dopamine self-administration was also attenuated by sulpiride. Thus, findings from these two research groups point to dopamine as the critical neurotransmitter underlying cocaine reinforcement.

SUBJECT'S EXPERIMENTAL HISTORY

Experimental history refers to manipulations that were made at some distant point in time. The evaluation of such factors often involves group designs, and thus not many studies have been conducted. In one experiment cocaine was established as a reinforcer for one group of rhesus monkeys, and codeine was established as a reinforcer for another group. When the monkeys were later tested with opiates and opioids the monkeys with the codeine history took more injections and showed less variability than the monkeys originally trained with cocaine [15]. Thus, past training with a particular drug affected subsequent performance maintained by a second drug.

RESPONSE CONSEQUENCES

A major category of factors that control drug reinforced behavior consists of response consequence variables. This class includes such important factors as the drug dose and the schedule of reinforcement. The defining feature of this class of variables is that they are the events whose occurrence is contingent upon responding.

Reinforcement Schedule

The schedule of reinforcement has been one of the most commonly studied factors. The schedule specifies the contingency between responses and the delivery of the reinforcer. The drugs most commonly studied under intermittent schedules are the psychomotor stimulants. In the initial studies with these drugs, rates of responding were much lower than those seen with other reinforcers such as food. This raised the possibility that there were fundamental differences between behavior reinforced by drugs and behavior reinforced by other reinforcers such as food. However, subsequent studies demonstrated that if appropriate doses were used, under certain conditions drugs could maintain high rates of responding over extended periods of time, and thus, the responding was similar to that seen in studies of food reinforced lever pressing [8].

Cocaine injections can maintain behavior under more complex schedules such as second order schedules. Under second order schedules, responding under one schedule, termed the "secondary schedule," leads to the presentation of a stimulus that is intermittently paired with drug delivery. This response sequence is treated as a unitary response that must be emitted to meet the contingency specified by the primary schedule. For example, under a second order fixed-interval schedule with fixed-ratio components, each completion of an FR component results in a signal such as a light flash, and the first FR component completed after the FI has elapsed produces the signal and delivery of the reinforcer. Under second order schedules, high rates of responding can be maintained over extended periods of time, even when drug injections occur infrequently. These findings have been interpreted as demonstrating the importance of both schedule factors and stimulus factors in controlling drug reinforced behavior [22].

With animals drug reinforced behavior has also been studied under conditions where two doses of a drug or two drugs are made available in either a choice situation or according to concurrent schedules. In general higher doses are preferred to lower doses [21]. Although cocaine is preferred to certain other drugs such as diethylpropion, cocaine is not always preferred. For example, in choice tests methylphenidate and d,l-cathinone appear equally effective [21,35].

An unanticipated outcome occurs when responding under a VI schedule results in cocaine infusions and responding under a concurrently operating FI schedule results in time out or escape from the schedule of cocaine reinforcement. Monkeys develop high rates of responding on the FI schedule even though it leads to significant decreases in the frequency of cocaine injections [29]. This is not a unique finding with cocaine since similar behavior can occur with food reinforcement [31]. These findings have been interpreted as emphasizing our limited understanding of drug reinforced behavior [30].

Dose

A fundamental variable that affects the frequency of drug injections is the drug dose. An inverted U-shaped relationship between dose and injection frequency is a common finding. Often the total amount of drug injected per session increases somewhat with increases in drug dose. In a recent review of animal drug self-administration studies Young and Herling [36] noted an important general finding of studies with cocaine: there appears to be a direct relation between schedule value and the dose of cocaine required to maintain maximal response rates. For example, with fixed-interval schedules as the interval is increased, progressively higher doses are needed to maintain maximal response rates. Their

conclusion is based on a summary of findings from a number of studies. This finding is not limited to cocaine for studies with pentobarbital demonstrate that as schedule value is increased, progressively larger amounts of pentobarbital are required to maintain behavior [23,24].

Punishment

The effects of punishing drug reinforced responding with electric shock have been the focus of several studies. Responding reinforced with cocaine was suppressed by shock delivery, and the degree of suppression was directly related to the intensity of the shock [12]. When intermediate shock intensities were used, adaptation to the shock occurred across sessions [2]. The effects of electric shock punishment have also been analyzed with a choice paradigm where one of two choices produced shock in addition to drug delivery. When equal doses of cocaine were used, monkeys preferred the absence of shock. However, as the dose of cocaine was increased on the shocked side, monkeys chose the combination of shock plus the higher dose [17,18].

Competing Reinforcers

One way to decrease the frequency of drug taking is to give an organism a mutually exclusive choice between drug and another reinforcer. For example, rhesus monkeys were given a mutually exclusive choice between cocaine and food. The monkeys almost exclusively chose cocaine [1].

SUMMARY

In summary, the variables that control the taking of drugs are the same variables that control operant behavior maintained by more conventional reinforcers such as food. Thus, the taking of drugs is a particular instance of operant behavior. Over the past 25 years there has been a progressive expansion in our understanding of drug reinforced behavior. The sophistication of the experimental preparation has increased. Routes of administration other than the intravenous route are now commonly used. An enlarging number of controlling variables have been identified and interactions among variables are being analyzed. Comparable findings have been obtained across a number of species, and the parallels with human abuse of drugs are many and support the validity of the infrahuman experimental preparation. This increase in knowledge will continue, and it will be linked to progress in pharmacology and in the experimental analysis of behavior.

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