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DRUG SELF-ADMINISTRATION BY LABORATORY ANIMALS: CONTROL BY SCHEDULES OF REINFORCEMENT[1]

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Roger D. Spealman and Steven R. Goldberg
Harvard Medical School, Boston, Massachusetts 02115 and New England Regional Primate Research Center, Southborough, Massachusetts 01772

INTRODUCTION

A common factor underlying all concepts of drug dependence is the persistent maintenance of behavior that leads to drug self-administration (1, 2). Early studies of drug self-administration by laboratory animals involved morphine and employed subjects that were made physiologically (physically) dependent by repeated injections prior to the initiation of self-administration behavior (3–9). This emphasis on physiological dependence strengthened the belief that drugs were self-administered by laboratory animals chiefly because their administration terminated or postponed the characteristic withdrawal syndrome induced by drug abstinence. While physiological dependence may profoundly influence drug self-administration behavior, it is not necessary for the maintenance of that behavior. With psychomotor stimulant drugs, for example, no clear signs of withdrawal occur after chronic administration is terminated, yet these drugs are persistently self-administered by laboratory animals (10–16). Even with drugs such as narcotic analgesics, barbiturates, and ethanol that can induce physiological dependence, the initiation of drug self-administration by drug-naive animals must result from other factors (17). Moreover, many experiments have shown that self-administration can be maintained by these drugs in the absence of any demonstrable physiological dependence when access to drug is limited to short periods of time each day and when small doses of drug are used (18–28). Considerations such as these have prompted the investigation of behavioral factors underlying drug dependence.

[1]This work is dedicated to the memory of Dr. Maurice H. Seevers, a distinguished pharmacologist whose pioneering research will long influence the study of drug dependence.

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Drugs As Reinforcers

When an environmental event occurs as a consequence of a particular response, the rate of occurrence of that response may increase and this increased rate of responding may then be maintained on subsequent occasions. In such cases, the response is defined as an operant; the consequent event is defined as a reinforcer; and the increased rate and subsequent maintenance of responding is defined as the process of reinforcement. Events as diverse as the presentation of food or water, the electrical stimulation of the brain, the termination of a stimulus associated with electric shock, and the delivery of electric shock can act similarly in reinforcing operant behavior under suitable conditions (29, 30). The injection of various drugs also can be included among the events that can serve as reinforcers. For example, the injection of cocaine following a lever-pressing response by a rat or monkey can increase the rate of lever pressing and can maintain this increased rate on subsequent occasions. Under these conditions the injection of cocaine is defined as a reinforcer. The advantage of considering drugs as reinforcers is not that this explains why drugs are self-administered but rather that it makes it possible to analyze drugs functionally in the same way as other events that can maintain behavior. This view provides a systematic empirical framework within which drug self-administration studies can be integrated and evaluated.

Schedules of Reinforcement

In many experiments on drug self-administration, each response by an individual subject results in the injection of a drug. Although experiments of this type have demonstrated that drugs from several pharmacological classes can act as reinforcers (17), they represent only an initial step in the analysis of drugs as reinforcers. Many of the most interesting and important characteristics of operant behavior are revealed only when reinforcers are scheduled intermittently (31, 32). Schedules of reinforcement are simply those rules that govern the sequential and temporal relations between responses and reinforcers. A formal classification of schedules is often made on the basis of whether the reinforcer follows a given number of responses (ratio schedules) or follows a response after a given period of time has elapsed (interval schedules). Several comprehensive accounts of behavior under schedules of reinforcement have been published (31, 33–36). Each class of schedule engenders characteristic rates and temporal patterns of responding that are reproducible across a wide range of species, response topographies, and consequent events. These characteristic schedule-controlled performances provide a meaningful way to compare the effectiveness of drugs and other events as reinforcers.

Generalized Effects of Drugs

Drugs that can act as reinforcers can also have other effects on schedule-controlled behavior. For example, intermediate doses of certain drugs increase responding maintained by a variety of events, whereas higher doses decrease responding (37–39). For understanding performances maintained under schedules of drug self-administration, it is important to realize that responding can be influenced not only

by the reinforcing effects of drugs but also by the rate-increasing or rate-decreasing effects of these same drugs. These latter effects of drugs are referred to as generalized effects in the present review.

When a drug is administered frequently, the rate of responding may be determined in large part by the generalized effects of cumulative drug intake. For example, when every tenth response by a rhesus monkey produces an intravenous injection of morphine, only low rates of responding are maintained at any dose (23, 24). Yet such low rates of responding are not inevitable. Morphine can maintain very high rates of responding under schedules in which injections occur far less frequently (40–42). Only by studying responding under a wide range of schedules can the optimal and limiting conditions of drug self-administration be evaluated comprehensively.

General Methods

Drugs can be self-administered by various routes: by intravenous, intramuscular, intraperitoneal, or intracerebral injection; by inhalation; and by mouth. Since only the intravenous route has been studied extensively with a variety of reinforcement schedules, most consideration is given to this route in this review. Several aspects are common to most studies of intravenous self-administration. A chronic venous catheter is implanted, often by way of a jugular vein. The subject is usually fitted with a jacket or harness to protect the catheter and is often restrained during study. Drugs then can be delivered rapidly through the catheter by an injection pump operated by automatic programming equipment. Additional programming equipment performs scheduling and recording functions. To reduce unwanted external influences, experiments are usually conducted in sound- and light-attenuating isolation chambers. Details of specific methods and techniques have been described for rats (43, 44), rhesus monkeys (17, 45, 46), squirrel monkeys (47–49), dogs (50), and cats (51, 52).

RATIO SCHEDULES OF DRUG SELF-ADMINISTRATION

Under ratio schedules of drug self-administration, the drug is injected when the animal completes a required number of responses. The response requirement may be constant (fixed-ratio schedules), may increase systematically (progressive-ratio schedules), or may vary irregularly from injection to injection (variable-ratio schedule). Only fixed-ratio and progressive-ratio schedules of drug injection have been studied in detail.

An important feature of ratio schedules is the direct relation between rate of responding and frequency of drug injection. Even with short-acting drugs, successive doses may cumulate rapidly while responding is sustained. Because of this, the rate of responding may be limited by the cumulative rate-decreasing effects of the drug on behavior. Indeed, the average rate of responding under ratio schedules of drug injection is often inversely related to the dose per injection over a wide range of doses (7, 9, 19–24, 26–28, 47, 53–75).

Fixed-Ratio Schedules

The most commonly studied ratio schedule is the fixed-ratio schedule. At moderate response requirements (10 to 50 responses per reinforcement), behavior maintained under fixed-ratio schedules is characterized by a brief pause in responding at the beginning of the fixed ratio followed by an abrupt transition to a high steady rate of responding that ends with reinforcement. This characteristic pattern occurs reliably when responding is maintained by a variety of events in a variety of species (31, 33–36, 76–78). Average rates of fixed-ratio responding maintained by such diverse events as the presentation of food, the electrical stimulation of the brain, and the termination of a stimulus associated with electric shock approach and often exceed one response per second (76–78).

Responding by laboratory animals has been maintained under fixed-ratio schedules by intravenous injections of drugs from several pharmacological classes, including psychomotor stimulants (17, 19–21, 23, 24, 26, 47, 52, 54–56, 58, 59, 63–69, 71, 71a, 72, 79–87), narcotic analgesics (7, 9, 17, 21, 23, 24, 26, 27, 50, 53, 57, 58, 60, 61, 70, 70a, 79, 80, 88–96), narcotic antagonists (23, 27, 60, 92), sedatives and hypnotics (17, 20–22, 25, 28, 81a, 97–101), and dissociative anesthetics (62, 75). In many studies, rates and patterns of responding maintained under fixed-ratio schedules of drug injection differed from fixed-ratio performances maintained by other events. In some cases where each response produced an injection, rates of responding were very low (usually less than 0.01 responses per second). In other cases where more than one response was required to produce an injection, pauses in responding at the beginning of the fixed ratios were often long (several minutes or more) and often followed by irregular responding at rates lower than those maintained under comparable schedules by other events. In one study (23), for example, responding by rhesus monkeys was maintained under a 10-response fixed-ratio schedule by injections of several drugs, including morphine (0.01 to 500 μg/kg per injection) and cocaine (50 μg/kg per injection). The maximal rate of responding maintained by morphine (at 25 μg/kg per injection) was about 0.05 responses per second; that maintained by cocaine was about 0.12 responses per second. These low rates of responding probably resulted from the generalized rate-decreasing effects of the self-administered drugs which cumulated over the course of each 3-hr experimental session; rates of responding generally declined as the session progressed at these doses. Moreover, cumulation of the rate-decreasing effects of the drugs appears to have been directly related to their durations of action. The short-acting psychomotor stimulant, cocaine, maintained higher rates of responding than the longer-acting opiate. A similar relation has been observed in a study comparing rates of responding maintained under a one-response fixed-ratio schedule by injections of several barbiturates that have different durations of action (28).

Some recent experiments have been concerned with improving the schedule control of drug-maintained responding by limiting the cumulative rate-decreasing effects of the drug on behavior. These cumulative effects can be limited by restricting the number of injections per experimental session and by determining the lowest dose per injection that maintains maximal rates of responding. In one such study

(26), rhesus monkeys produced injections of cocaine (1 to 300 μg/kg per injection) or codeine (1 to 1000 μg/kg per injection) under a 30-response fixed-ratio schedule in which total drug intake was limited to 48 injections per session. The maximal rate of responding maintained by cocaine (at 3 μg/kg per injection) approached one response per second—a rate similar to that maintained under comparable schedules by other events. The maximal rate of responding maintained by the relatively long-acting codeine (at 30 μg/kg per injection) was less than one third that maintained by cocaine.

Cumulative effects of drug injections can be reduced further by interposing periods of time between successive fixed ratios during which a distinctive stimulus is present and drug is unavailable (timeouts). Because drug injections never occur during timeouts, responding usually falls abruptly to low levels at these times. In addition to limiting the frequency of drug injection, the arrangement of timeouts between successive opportunities to produce drug can be useful for dissociating generalized activity-enhancing effects of a drug from its effects in maintaining schedule-controlled behavior. Such generalized effects would be expected to result in increased responding during timeouts.

Responding by squirrel monkeys has been studied under fixed-ratio schedules requiring 10, 30, or 50 responses to produce injections of cocaine (6 to 400 μg/kg per injection) or *d*-amphetamine (1.5 to 25 μg/kg per injection) (47). The total session time was limited to 100 minutes and a 1-min timeout followed each injection. Rates of responding above one response per second were maintained by cocaine (12 to 100 μg/kg per injection) or by *d*-amphetamine (6 μg/kg per injection). Responding by rhesus monkeys also has been studied under a 30-response fixed-ratio schedule of cocaine injection (10 or 30 μg/kg per injection) in which the number of injections was limited to 50 per session and a 1-min timeout followed each injection (69). Again, rates of responding that approached or exceeded one response per second were maintained by each dose of cocaine. Similar high rates of responding by rhesus monkeys have been obtained under 20-response fixed-ratio schedules of codeine, morphine, or methadone injection (100 μg/kg per injection) when the number of injections was limited to 35 per session and a 1-min timeout followed each injection (79), and under a 30-response fixed-ratio schedule of methohexital injection (200 μg/kg per injection) when sessions ended after 100 min and a 4-min timeout followed each injection (101). Thus, performances characteristic of fixed-ratio schedules were maintained by injections of drugs from several pharmacological classes when suitable doses per injection were used and when the frequency of injection was restricted. Moreover, doses of these drugs that maintained characteristic fixed-ratio performances had little tendency to increase responding during timeouts, indicating that the high rates of responding maintained under the fixed-ratio schedules were the result of the reinforcing effects of drug injection and not the result of a generalized increase in activity produced by the drugs.

Comparison of Drug-Maintained and Food-Maintained Responding

Fixed-ratio performances maintained by cocaine or *d*-amphetamine injection have been compared directly with performances maintained by food presentation in a

series of experiments with squirrel monkeys (47). During 100-min experimental sessions, every tenth or thirtieth response produced either drug injection or food presentation followed by a 1-min timeout. Average rates of responding first increased and then decreased as the dose of cocaine (6 to 400 μg/kg) or *d*-amphetamine (1.5 to 25 μg/kg) per injection increased or as the amount of food (0 to 2000 mg) per presentation increased. At intermediate doses of cocaine or *d*-amphetamine and at the lower amounts of food, rates of responding exceeded one response per second. Decreasing the dose of cocaine or *d*-amphetamine per injection or discontinuing food presentation resulted in irregular responding at reduced rates. Increasing the dose of cocaine or *d*-amphetamine per injection or the amount of food per presentation resulted in responding that occurred at high rates at the beginning of the session but that declined over the course of the session. Although high doses of cocaine or *d*-amphetamine and large amounts of food had similar effects, one should not assume that the decline in responding under these conditions necessarily reflects a common process (e.g. satiation). It is likely that the cumulative intake of a drug would disrupt behavior maintained by other events (for example, electric shock) more than would the cumulative intake of food. Nonetheless, these findings show that drug injections can serve as effectively as other events in maintaining characteristic fixed-ratio performances when scheduled in similar ways.

That similar characteristic performances can be maintained by drugs and other events has particular relevance to studies comparing the effects of presession drug treatments on schedule-controlled behavior maintained by those events (102–104). Such comparisons are most meaningful under conditions where each event maintains comparable rates and patterns of responding.

Progressive-Ratio Schedules

Under progressive-ratio schedules, the number of responses required for reinforcement increases systematically, usually until responding falls below some criterion level. The response requirement at which this occurs is called the breakpoint. Orderly increases in breakpoint have been obtained by increasing the level of food deprivation or the concentration or volume of liquid food under progressive-ratio schedules of food presentation (105, 106) and by increasing the intensity or duration of stimulation under progressive-ratio schedules of electrical stimulation of the brain (107, 108). For this reason, the breakpoint under progressive-ratio schedules has been offered as an index of the reinforcing effectiveness of the consequent event (105, 106).

Responding by laboratory animals has been maintained under progressive-ratio schedules by intravenous injections of a variety of drugs, including psychomotor stimulants (64, 109–113), sedatives and hypnotics (110, 112, 114), and narcotic analgesics (64, 111). In one study (113), baboons responded under progressive-ratio schedules of cocaine, diethylpropion, chlorphentermine, or fenfluramine injection. A 3-hr timeout followed each injection and sessions were conducted 24 hr per day. Initially, 160 responses were required for drug injection. Thereafter, the response requirement was increased each day in steps of 160 or 1200 responses per injection until no more than one ratio was completed within 24 hr. Under these conditions, cocaine (0.1 to 0.4 mg/kg per injection) maintained the highest breakpoint, followed

in order by diethylpropion (1.0 to 3.0 mg/kg per injection) and chlorphentermine (1.0 to 5.6 mg/kg per injection). Fenfluramine did not maintain a criterion level of responding at any dose tested. Progressive-ratio schedules appear to provide a promising method for evaluating the effectiveness of drugs in maintaining responding under conditions that require large amounts of behavior. The sensitivity of progressive-ratio schedules for estimating the degree to which drugs differ in their effectiveness in maintaining responding under other conditions awaits direct comparison.

INTERVAL SCHEDULES OF DRUG SELF-ADMINISTRATION

Under interval schedules of drug self-administration, the first response occurring after a specified interval of time has elapsed produces the injection of drug. The interval between the availability of successive drug injections may be constant (fixed-interval schedules) or may vary from injection to injection around a given mean value with specified range (variable-interval schedules). Since interinjection intervals are specified in advance, the frequency of injection under interval schedules is relatively independent of the rate of responding over a wide range of response rates. This feature affords the experimenter more direct control over the maximal frequency of drug injection than is possible under ratio schedules. Nonetheless, if the intervals between drug injections are short or if timeouts do not follow injections, successive doses of the drug still may cumulate and responding may be influenced by generalized rate-increasing and rate-decreasing effects of drugs.

Variable-Interval Schedules

Under variable-interval schedules, behavior maintained by a variety of events is characterized by relatively constant responding at moderate rates (31, 33–36, 78, 115–118). Although variable-interval schedules of drug injection have not been studied extensively, responding has been maintained under these schedules by intravenous injections of morphine (19, 118a), codeine (119), cocaine (12, 120), and ethanol (119). Responding usually occurred at relatively constant rates between successive injections, but rates of responding often declined during the experimental session. In one study (119), for example, rhesus monkeys responded under 2-min variable-interval schedules of codeine (0.003 to 1.0 mg/kg per injection) or ethanol injection (32 to 560 mg/kg per injection); timeouts did not follow injections. Doses of codeine above 0.01 mg/kg per injection or of ethanol above 100 mg/kg per injection maintained moderate to high rates of responding at the beginning of the 1-hr session, but responding usually declined and, in some cases, ceased by the end of the session. It is likely that generalized rate-decreasing effects of cumulative drug intake were, in large part, responsible for the progressive decline in responding over the course of the session.

Fixed-Interval Schedules

In contrast to the relatively constant responding under variable-interval schedules, performance under fixed-interval schedules is characterized by a pause at the beginning of the interval followed by a period during which responding accelerates to a

rate that is then maintained until the end of the interval. Under most conditions, only about one quarter of the total responses in each fixed interval is emitted during the first 50–70% of the interval (quarter life). This characteristic pattern occurs when responding is maintained by a variety of events, in a variety of species, and over a wide range of fixed-interval values (31, 33–36, 77, 115, 116, 121–127). Moreover, responding under fixed-interval schedules is highly sensitive to both rate-increasing and rate-decreasing effects of presession drug treatments (37–39). It is surprising, therefore, that fixed-interval schedules have received relatively little attention in drug self-administration studies.

Although responding can be maintained under fixed-interval schedules by injections of morphine (8) and methohexital (101) or by presentations of ethanol solutions (128, 129), only fixed-interval schedules of intravenous cocaine injection have been studied in detail (12, 69, 87, 120, 130, 131). In one study (69), rhesus and squirrel monkeys responded under a 5-min fixed-interval schedule of cocaine injection (12 to 300 μg/kg per injection); a 60- or 100-second timeout followed each injection and sessions ended after the tenth injection. Optimal rates (0.6 to 0.7 responses per second) and patterns of responding (quarter-life values between 50 and 70% of the interval) were maintained at doses of 30 μg/kg per injection (rhesus monkey) or 50 μg/kg per injection (squirrel monkeys). Although cocaine tends to disrupt responding maintained under fixed-interval schedules by other events (127, 132–134), characteristic fixed-interval patterns of responding occurred when cocaine was self-administered at these doses. Apparently, cocaine injections can maintain responding under fixed-interval schedules at doses lower than those that alter characteristic response patterns. At doses above those that maintained optimal performances, however, responding became irregular and less characteristic of that maintained under fixed-interval schedules. At these higher doses of cocaine, it is likely that rates and patterns of responding were influenced by the generalized effects of the drug.

Comparison of Fixed-Interval and Fixed-Ratio Responding

Characteristic responding can be maintained under fixed-interval schedules of drug injection by doses that disrupt performances under fixed-ratio schedules (69, 87). Responding by rhesus and squirrel monkeys has been studied under a multiple fixed-interval and fixed-ratio schedule of cocaine injection (69). In the presence of one stimulus, responding was maintained under a 5-min fixed-interval schedule; in the presence of a second stimulus, responding was maintained under a 10-response (rhesus monkeys) or 30-response (squirrel monkeys) fixed-ratio schedule. The alternating fixed-interval and fixed-ratio components of the multiple schedule were separated by 60- or 100-sec timeouts. As the dose of cocaine was increased from 6 to 100 μg/kg per injection (squirrel monkeys) or from 30 to 600 μg/kg per injection (rhesus monkeys), characteristic rates and patterns of responding were usually maintained over a wider range of doses in the fixed-interval component than in the fixed-ratio component. At doses of cocaine above 100 or 300 μg/kg per injection, rates of responding were actually lower in the fixed-ratio component than in the fixed-interval component. Although other factors may be involved, these results

suggest that the marked decreases in fixed-ratio responding at higher doses of cocaine reflect the greater sensitivity of fixed-ratio responding to the generalized rate-decreasing effects of high doses of cocaine (132–134).

Comparison of Drug-Maintained and Food-Maintained Responding

The effects of cumulative drug intake on behavior have been assessed by comparing performances maintained under fixed-interval schedules of cocaine injection or food presentation within a multiple schedule (130). In the presence of one stimulus, responding by rhesus monkeys was maintained under a 9-min fixed-interval schedule of cocaine injection; in the presence of a second stimulus, responding was maintained under an identical schedule of food presentation. A 15-min timeout followed each injection of cocaine or presentation of food. At doses of cocaine between 25 and 200 μg/kg per injection, characteristic patterns of fixed-interval responding were maintained in each component of the multiple schedule. At higher doses of cocaine (400 or 800 μg/kg per injection), however, patterns of responding were disrupted in each component and responding often occurred during timeouts. Rates of responding in the cocaine component generally increased as the dose of cocaine increased while rates of responding in the food component either remained unchanged or decreased at the highest doses. These initial findings suggest that increases in responding in the cocaine component did not necessarily result from the generalized rate-increasing effects of cocaine on behavior. However, the failure to observe increased responding in the food component at some doses of cocaine is surprising since intermediate doses of this drug reliably increase responding under fixed-interval schedules of food presentation (127, 132–134). The extent to which the generalized rate-increasing and rate-decreasing effects of drugs can influence rates and patterns of responding under fixed-interval schedules of drug injection is not clear at present.

Although characteristic performances can be maintained under fixed-interval schedules of drug injection, further studies are needed to establish the conditions under which different drugs can maintain responding over a wide range of fixed-interval parameters. Fixed-interval schedules may be particularly useful for future studies of drug self-administration because the results can be evaluated within the context of the large body of information currently available about the behavioral effects of drugs on fixed-interval performances maintained by other events.

SECOND-ORDER SCHEDULES OF DRUG SELF-ADMINISTRATION

Ratio and interval schedules of drug injection can be used as units to form more complex second-order schedules (135). Under second-order schedules, the behavioral requirement specified by one schedule is treated as a unit of responding that is itself reinforced according to a second schedule (136, 137). Fixed-interval schedules of drug injection with fixed-ratio units have been studied most extensively. Under this type of second-order schedule, the completion of each fixed-ratio unit produces a brief visual stimulus, and the first fixed-ratio completed after a specified

interval of time has elapsed produces both the brief stimulus and injection of a drug. Responding by rhesus and squirrel monkeys has been maintained under fixed-interval schedules with fixed-ratio units by intravenous and intramuscular injections of cocaine (47, 87, 101, 135, 138–140) or morphine (40–42, 140), and by intravenous injection of methohexital (101).

In one study (139), squirrel monkeys responded under a second-order schedule in which the completion of every 30-response fixed-ratio unit produced a 2-sec light; the first fixed-ratio unit completed after 5 min elapsed produced the 2-sec light and an injection of cocaine. A 1-min timeout followed each injection, and experimental sessions ended after the fifteenth injection. Repeated sequences of rapid responding occurred throughout each experimental session at doses of 100 or 200 μg/kg per injection. Rates and patterns of responding within the fixed-ratio units were characteristic of those maintained under fixed-ratio schedules. Because presentations of the brief visual stimulus maintained characteristic fixed-ratio performances throughout most of the 5-min fixed interval, average rates of responding under the second-order schedule (up to two to three responses per second) were much higher than those maintained by comparable doses of cocaine under a simple 5-min fixed-interval schedule (69, 87). Similar enhancement of responding has also been observed in a rhesus monkey when a 10-min fixed-interval schedule of cocaine injection (30 μg/kg per injection) was changed to a second-order schedule with 3- or 10-response fixed-ratio units (101). The role of brief-stimulus presentations in maintaining high rates of responding under second-order schedules is discussed later.

Comparison of Drug-Maintained and Food-Maintained Responding

Differences between performances maintained by drug injection and food presentation have been reported under second-order schedules. Recent evidence suggests that intravenous cocaine injections generally maintain higher rates of responding than do food presentations under comparable second-order schedules (133, 139, 141), although this phenomenon is not always observed (47). In one study (141), the completion of each 5-min fixed-interval unit produced a 2-sec light and the completion of the tenth fixed-interval unit produced the light and either injection of cocaine or presentation of food for different groups of squirrel monkeys. A 100-sec timeout followed each cocaine injection or food presentation, and sessions ended after the third injection or food presentation. Patterns of responding characteristic of fixed-interval schedules were maintained by presentations of the brief visual stimulus at doses of cocaine between 30 and 300 μg/kg per injection and amounts of food between 0.75 and 7.5 g per presentation. Average rates of responding maintained by these doses of cocaine were higher than those maintained by any amount of food studied. The reasons for these apparent differences in rates of responding maintained under second-order schedules of cocaine injection or food presentation are not clear at present. Perhaps the differences reflect an enhancement of the effectiveness of the brief stimuli in maintaining responding that depends on the presence of the drug (142, 143). Alternatively, these differences may simply reflect the generalized rate-increasing effects of cocaine on schedule-controlled behavior (127, 132–134).

Under second-order schedules, long and orderly sequences of behavior can be maintained at times when generalized rate-increasing or rate-decreasing effects of the drug are minimal or absent. In squirrel and rhesus monkeys, for example, responding has been maintained under 30-response fixed-ratio units of 1-hr fixed-interval schedules by intravenous injections of cocaine (87,101) or morphine (40–42). Drug injections occurred only at the end of the 1-hr fixed interval and at least 23 hr elapsed before the start of the next interval. Preliminary data indicate that rates of responding maintained under this extended second-order schedule by intravenous injection of morphine are similar to those maintained under a comparable schedule of food presentation (41). Further investigations are needed to determine the range of conditions under which comparably high rates of responding can be maintained under second-order schedules by drug injections and other events.

Comparison of Responding With and Without Brief Stimulus Presentations

Under second-order schedules, brief stimuli associated with injections of drug come to control rates and patterns of responding characteristic of fixed-interval or fixed-ratio schedules. The strong control of responding by the brief stimuli becomes most apparent when the brief stimuli are omitted. When squirrel monkeys were studied under a second-order schedule in which a 2-sec light was presented at completion of each 5-min fixed interval and every tenth completion of the fixed interval produced both the light and injection of cocaine, characteristic patterns of responding developed and were maintained within the fixed-interval units (141). Omission of the brief visual stimulus at the completion of the first nine fixed-interval units decreased average rates of responding and eliminated the recurring patterns of responding (quarter-life values within the fixed-interval units decreased to about 25%). When saline was substituted for cocaine and the brief stimulus was omitted and then presented again during successive sessions, the control of rates and patterns of responding by the brief stimulus was particularly striking. During sessions in which neither the brief stimulus nor cocaine was presented, rates of responding had decreased to low levels and quarter-life values were near 25%. When responding again produced the brief stimulus, rates and patterns of responding characteristic of fixed-interval schedules returned for as many as six consecutive sessions despite the continued absence of cocaine injections.

In another study (41), responding by rhesus and squirrel monkeys was maintained by injections of morphine under a fixed-interval schedule with fixed-ratio units. Completion of each 30-response fixed-ratio unit produced a 2-sec light and the first fixed-ratio unit completed after 1 hr elapsed produced the light and an intravenous injection of a high dose of morphine (1.0 to 6.0 mg/kg). Average rates of responding as high as one response per second and characteristic patterns of responding were maintained within the fixed-ratio units under this schedule. Again, omission of the brief stimulus decreased average rates of responding and disrupted the fixed-ratio patterns of responding.

Although the development and maintenance of behavior under the second-order schedules used in these two series of experiments depended ultimately upon the

injection of cocaine or morphine, responding often could be modified as rapidly by omitting the brief stimuli as by omitting cocaine or morphine. Such findings indicate that second-order schedules will be particularly useful for future studies of the ways in which stimuli associated with drugs can come to control the persistent maintenance of long sequences of behavior leading to drug administration.

CHOICE PROCEDURES AND CONCURRENT SCHEDULES OF DRUG SELF-ADMINISTRATION

An important determinant of the control of behavior by its consequences is the magnitude of the event that maintains responding. Since high doses of drugs that can act as reinforcers also can decrease rates of responding, the effectiveness of these doses in maintaining schedule-controlled performances may be masked by their generalized effects on behavior. Two closely related procedures have been used in an attempt to control the influence of generalized effects of drugs when comparisons are made of responding maintained by different drugs or by different doses of a particular drug. Both procedures employ alternative responses maintained by different consequences. Under the first procedure, often called a choice or preference procedure, the occurrence of either alternative response results in the initiation of one of two mutually exclusive schedules of reinforcement. Under the second procedure, formally termed a concurrent schedule, each alternative response is maintained by one of two schedules of reinforcement that operate simultaneously.

Although absolute rates of responding are usually measured under these procedures, the primary dependent variable is the relative frequency of occurrence of the alternative responses. A potential advantage of choice procedures and concurrent schedules is suggested by behavioral studies indicating that changes in the relative frequency of the alternative responses are often more closely related to changes in the parameters of reinforcement (for example, amount of food per presentation) than are absolute rates of responding under simple ratio and interval schedules (144–148). A second potential advantage of these procedures is that the relative frequency of alternative responses may be less influenced by the generalized effects of high doses of drugs on behavior than are absolute rates of responding.

Choice Procedures

Choice procedures have been used to study drugs from such pharmacological classes as psychomotor stimulants (66, 72, 149–153), sedatives and hypnotics (46), and narcotic analgesics (114, 154). Comparisons have been made between drug and saline or between different doses of the same drug. In one series of experiments (66, 72, 149, 150), responding by rhesus monkeys was maintained first under a multiple schedule. In the presence of a visual stimulus above one of two levers, every fifth response on the appropriate lever produced an intravenous injection of cocaine; in the presence of a second stimulus above one of the levers, every fifth response produced an injection of either saline or a different dose of cocaine. Each component of the multiple schedule lasted until five injections were delivered and each was followed by a 30-min timeout. Then, during choice trials, the stimuli associated with each component were presented simultaneously, one above each lever. Five re-

sponses were again required to produce an injection, and the first response on either lever terminated the stimulus and schedule associated with the other lever. A 15-min timeout followed each trial.

When various doses of cocaine (0.05 to 1.5 mg/kg per injection) were compared with saline, responding occurred almost exclusively on the lever associated with cocaine injection. When two different doses of cocaine were compared and each was 0.5 mg/kg per injection or less, responding on the lever associated with the higher dose occurred during more than 90% of the trials. When doses of cocaine higher than 0.5 mg/kg per injection were compared, however, responding usually occurred on one lever, but not necessarily on the lever associated with the higher dose of cocaine. This perseverative responding suggests that the relative frequency of responding was influenced by generalized behavioral effects of these high doses of cocaine. Comparisons of different doses of methylphenidate (0.075 to 0.7 mg/kg per injection) or of diethylpropion (0.5 and 1.0 mg/kg per injection) also showed that, when responding occurred systematically, it was usually maintained on the lever associated with the higher of the two doses. These results are similar to those obtained when different amounts of food (146) or different intensities of electrical stimulation of the brain (155) were compared under choice procedures. In each case, responding was maintained almost exclusively by the schedule associated with the larger magnitude of the reinforcer.

Choice procedures have also been used to compare different drugs from the same pharmacological class (66, 72, 150) or drugs from different pharmacological classes (151). Under the trial procedure described above, cocaine (0.1 and 0.5 mg/kg per injection) was compared with either methylphenidate (0.075 to 0.7 mg/kg per injection) or diethylpropion (0.5 and 1.0 mg/kg per injection) (66, 72, 150). When cocaine and methylphenidate were compared at these doses, reponding usually occurred on the lever associated with the higher dose regardless of drug. These results are striking because, under the multiple schedule, the maximal rate of responding maintained by cocaine injection was usually twice that maintained by methylphenidate injection. When cocaine and diethylpropion were compared, responding usually occurred on the lever associated with cocaine injection regardless of dose, although responding sometimes occurred equally on each lever.

Whether or not choice procedures result in relative measures of responding that are common to a wide variety of conditions is unclear at present. For example, the drug that is self-administered during one trial might have generalized effects which persist and influence the outcome of subsequent choice trials. The persistence of generalized effects may be particularly troublesome when drugs from different pharmacological classes or drugs having different durations of action are compared. It is possible, however, to minimize or eliminate the generalized effects of drugs and drug combinations on behavior by scheduling choice trials during interposed test sessions in which neither drug is injected. Preliminary data under this procedure (151) are consistent with findings that the higher relative frequency of responding is maintained by the larger dose of cocaine. A major limitation of this procedure is that responding would be expected to cease eventually during test sessions since responding never produces drug injections when both of the alternative responses are made available.

Concurrent Schedules

Concurrent schedules have also been used to compare responding maintained by different doses of drugs. Under concurrent schedules, responding is maintained by two or more simultaneously operating schedules, each associated with a different response. Under a two-lever concurrent schedule, for example, responding on one lever may be maintained under one schedule of reinforcement (often a variable-interval schedule), while responding on another lever is maintained under a second schedule (for example, an identical variable-interval schedule that arranges a different magnitude of the reinforcer). Like choice procedures, concurrent schedules have been used to compare responding maintained by different magnitudes of food presentation (144) or electrical stimulation of the brain (156, 157). A potential advantage of concurrent schedules over choice procedures is that the relative frequency of responding is often graded according to the difference in the magnitude of the reinforcer arranged under the two concurrently operating schedules (144, 145, 147, 148). Thus, a quantitative, rather than qualitative, relation between the magnitude of the reinforcer and its effectiveness in maintaining responding is sometimes inferred. This relation is usually expressed as the matching of relative frequency of responding to relative magnitude of the reinforcer associated with the concurrent schedules (145, 147, 148).

Responding by rhesus monkeys has been studied under concurrent schedules of intravenous cocaine injection in which responding on each lever produced injections according to a 1-min variable-interval schedule (158). Each injection was followed by a 5-min timeout during which neither schedule operated. At all other times, the two variable-interval schedules operated independently so that the availability of an injection under one schedule had no effect on the operation of the second schedule. Responding on one lever produced a constant dose of cocaine (either 0.05 or 0.1 mg/kg per injection), while responding on the other lever produced one of several comparison doses of cocaine (0.013 to 0.8 mg/kg per injection). The relative frequency of responding on the lever associated with the higher dose of cocaine always exceeded that associated with the lower dose, confirming the results obtained under choice procedures. In some cases, the relative frequency of responding was graded according to the difference between the constant and comparison doses. In other cases, responding occurred almost exclusively on the lever associated with the higher dose. In these latter cases, the lower dose was rarely, if ever, self-administered. In all cases, however, the relative frequency of responding approximately matched the relative drug intake. These results indicate a difficulty in interpreting concurrent performances in terms of relative response and relative reinforcement measures. When responding occurs exclusively on one lever, perfect matching between relative response and relative reinforcement measures is necessarily obtained and little can be inferred about the possibility of a quantitative relation between dose and reinforcing effectiveness (159).

Concurrent schedules can be arranged to preclude exclusive responding on one lever by requiring that a reinforcer made available under one schedule be produced by responding under that schedule before a reinforcer can be made available under

the second schedule (160). Responding maintained by different doses of cocaine have been compared under this nonindependent concurrent schedule (161, 162). As under the comparable independent concurrent schedule, the relative frequency of responding on the lever associated with the higher dose of cocaine always exceeded that associated with the lower dose. Unlike the independent concurrent schedule, however, the nonindependent schedule eliminated exclusive responding on one lever and resulted in a graded relation between relative frequency of responding and relative drug intake over the lower portion of the comparison dose range (below 0.1 or 0.2 mg/kg per injection). At higher comparison doses, the relative frequency of responding was insensitive to further increases in the comparison dose. Thus, deviations from perfect matching of relative response to relative reinforcement measures often occurred at high comparison doses. These deviations would be expected even if saline were compared with cocaine; the nonindependent concurrent schedule required that responding be maintained on both levers if the drug was to be injected. It would be premature to conclude that doses of cocaine above 0.1 or 0.2 mg/kg per injection do not differ in their ability to maintain responding.

The results obtained under both concurrent schedules and choice procedures show that over a moderate range, higher doses of cocaine can be more effective in maintaining responding than lower doses. Under each type of schedule, however, relative measures of responding appear to have been influenced by generalized effects of cocaine when high doses were compared. Whether or not very high doses can be more effective in maintaining responding than more moderate doses remains to be determined.

HISTORICAL AND CONTEXTUAL DETERMINANTS OF DRUG SELF-ADMINISTRATION BEHAVIOR

Although the schedule of drug self-administration can be a fundamental determinant of the effectiveness of a drug in maintaining responding, the schedule should not be considered in isolation from the historical and current environmental context in which it is imbedded. The effectiveness of a particular dose of a drug in initiating and maintaining responding can be profoundly influenced by the subject's previous experience with drugs and by the conditions under which injections of the drug are scheduled to occur.

History

A subject's experience with a particular drug may influence responding that is subsequently maintained by scheduled injections of that drug. For example, a low dose of cocaine (12 μg/kg per injection) that was initially ineffective in maintaining responding by a squirrel monkey under a 30-response fixed-ratio schedule later maintained characteristic rates and patterns of responding under a 30- or 50-response fixed-ratio schedule after a six-week period of exposure to response-produced cocaine injections (47). Similarly, responding maintained by maximally effective doses of a drug may be influenced by a history of exposure to that drug. In one study (26), responding by rhesus monkeys was maintained by injections of

cocaine under a 30-response fixed-ratio schedule. As the dose of cocaine was increased, rates of responding first increased and then decreased; maximal rates were maintained at 3 or 10 μg/kg per injection of cocaine. During redeterminations at the 3 and 10 μg/kg doses, rates of responding were much higher than they had been originally. Similar results have been reported when responding by rhesus monkeys was maintained under a 2-min variable-interval schedule by injections of ethanol (119). Thus, subjects with an extensive history of drug-maintained responding may respond at higher rates and at lower doses of drug than subjects with a more limited history of drug-maintained responding. There is some evidence that both a history of drug injections given independently of responding and a history of responding maintained by events other than drug injection can contribute to such effects (163).

A history of responding maintained by injections of one drug may also influence responding that is subsequently maintained by injections of another drug. In one study (21), responding by rhesus monkeys was maintained under a 10-response fixed-ratio schedule by injections of either cocaine, pentobarbital, or codeine. Later, responding was maintained by injections of *d*-amphetamine. Under the fixed-ratio schedule of *d*-amphetamine injection, responding occurred at higher rates, was more regularly patterned, and was maintained over a wider range of doses in monkeys with a history of cocaine-maintained responding than in monkeys with a history of pentobarbital- or codeine-maintained responding. In another study (23), rhesus monkeys with a history of codeine-maintained responding responded at higher rates under fixed-ratio schedules of morphine, codeine, pentazocine, propiram, or dextropropoxyphene injection than did rhesus monkeys with a history of cocaine-maintained responding. A history of responding maintained by injections of one drug may even play a critical role in determining whether or not a second drug will be self-administered. One study (164) has reported that responding could be maintained by injections of Δ^9-tetrahydrocannabinol in rhesus monkeys with a history of phencyclidine self-administration but not in rhesus monkeys without this history.

Context

Whether or not a particular drug will be effective in initiating and maintaining self-administration behavior also can depend on the prevailing environmental context in which the drug is made available. Various intermittent schedules of food presentation have been shown to induce excessive drinking of water (polydipsia) in laboratory animals (165–169). In the original demonstration of this effect (165), rats exposed to an intermittent schedule of food presentation drank about one half their body weights in water (several times their normal 24-hr intake) in a little over 3 hr. Subsequently, it was shown that laboratory animals would drink large volumes of an ethanol solution when food was presented intermittently during experimental sessions (169–190). In one such study (178), rats were exposed to a schedule in which a pellet of food was delivered every 2 min during a 1-hr session. Sessions were separated by 3 hr. At first, water was concurrently available. After the rats became polydipsic, a solution of ethanol and water was substituted in place of water. When

the concentration of the ethanol solution was 5% (volume/volume), most rats drank between 11 and 15 g of ethanol per kg of body weight per day. The rats became physiologically dependent on ethanol; when the ethanol solution was removed, noise produced by shaking keys resulted in tonic-clonic seizures. Control rats that had unlimited access to 5% ethanol but were not exposed to the intermittent schedule of food delivery consumed very little ethanol and did not become physiologically dependent. Several experiments also have shown that once ethanol drinking is induced, it may continue to occur even when the intermittent schedule of food presentation is removed (173–175, 182, 184). Moreover, lever-pressing responses then can be maintained by the presentation of ethanol under fixed-ratio and fixed-interval schedules (128, 182, 189, 191). Schedule-induced polydipsia can, therefore, be used to establish ethanol as a reinforcer. Schedule-induced polydipsia also has been shown to engender drinking of solutions of barbiturates (192, 193) and narcotic analgesics (194, 195). Thus, drinking of drug solutions that are not consumed readily can be induced by suitably arranging the environmental context.

Drugs can even have opposite effects that depend on the conditions of their administration. In rhesus monkeys that were physiologically dependent on morphine, for example, responding was maintained by the termination of a visual stimulus associated with periodic 50 μg/kg injections of the narcotic antagonists, pentazocine or propiram, but in nondependent monkeys response-produced injections of the same dose of pentazocine or propiram maintained responding (60). There is also evidence that injections of nalorphine or naloxone can maintain behavior that leads both to their presentation and to their termination. In one study (196), responding by rhesus monkeys that were physiologically dependent on morphine was maintained when each response produced a 100 μg/kg injection of morphine 24 hr a day. When injections of either saline or nalorphine (2 to 200 μg/kg) were substituted for morphine during 7.5-hr sessions once every two or three days, higher rates of responding were maintained by nalorphine than by morphine or saline, even though response-produced injections of nalorphine induced signs of severe withdrawal. However, when the conditions were changed so that responding terminated a visual stimulus associated with periodic 5 μg/kg injections of nalorphine under a fixed-ratio schedule, characteristic rates and patterns of responding were maintained. In another study (197), morphine-dependent rhesus monkeys responded under a schedule in which every thirtieth response terminated and/or postponed 2 μg/kg injections of naloxone that were scheduled to occur every 30 sec in the presence of a distinctive visual stimulus. Characteristic fixed-ratio performances were maintained under this schedule. Then the schedule was changed so that the completion of every 30-response fixed-ratio produced a brief 1.5-sec visual stimulus; the completion of every fifth or tenth fixed-ratio unit produced the brief stimulus and a 2 μg/kg injection of naloxone. Under this second-order schedule, rates of responding between 1.5 and 3.65 responses per second were maintained by response-produced injections of naloxone for as many as 15 consecutive sessions. Although responding declined eventually under the second-order schedule of naloxone injection, these results suggest that under suitable conditions naloxone, as well as nalorphine, can maintain responding both when responses produce injections of the drug and when responses terminate or postpone drug injections.

Disparate effects also have been reported for *d*-amphetamine and apomorphine. Responding by rats was maintained when each response produced an intravenous injection of *d*-amphetamine (0.25 mg/kg) or apomorphine (0.5 mg/kg) (198). However, when rats received an intravenous injection of *d*-amphetamine (1.0 mg/kg) or apomorphine (0.5 mg/kg) after drinking a saccharin solution, they subsequently drank much less of the solution than did control rats that received an intravenous injection of saline after drinking saccharin, an effect called conditioned taste aversion (199, 200).

Disparate effects of the same event are not restricted to drug injections. Under a wide variety of conditions, responding can be maintained by termination or postponement of electric shock (77, 201–203). By controlling the subject's ongoing behavior and previous experience with electric shock, however, it is possible to develop schedule-controlled performances that are maintained by presentations of electric shock (29, 30). Responding also can be maintained by either presentation or postponement of the same intensity and frequency of electrical stimulation of the brain (204). Similarly, responding can be maintained when it terminates a visual stimulus associated with food presentation (205, 206). These findings emphasize the importance of environmental factors other than the intrinsic properties of different events, including injections of drugs, in determining how those events control behavior.

SUMMARY

In most early studies of drug self-administration each response by an individual subject produced an injection of drug. Although these experiments demonstrated that drugs can act as reinforcers, the level of responding maintained by drug injections was surprisingly low. With only these facts, one might have assumed incorrectly that drug injections were relatively ineffective reinforcers. In recent years, research on schedules of drug self-administration has provided useful data on the dynamic properties of drugs as reinforcers. Under ratio and interval schedules of drug self-administration, rates and temporal patterns of responding characteristic of those maintained by a variety of other events have been developed and maintained by injections of drugs from several pharmacological classes. Moreover, characteristic performances can be maintained under more complex multiple, second-order and concurrent schedules. The effectiveness of a drug in maintaining responding depends critically on the precise scheduling conditions under which the drug is self-administered.

Since drugs that can act as reinforcers also have other effects on schedule-controlled behavior, the level of responding maintained by drug injections can reflect these actions. For understanding performances maintained under schedules of drug self-administration it is useful to be able to dissociate the reinforcing effects of drugs from their other effects on behavior. Several studies have attempted to minimize or eliminate generalized behavioral effects of drugs either by interposing timeouts between successive periods in which the schedule of drug injection is in effect or by limiting the maximal number of injections, in some cases to one injection per session.

Under these conditions, the control of behavior by schedules of drug self-administration has been improved. Other studies have attempted to reduce the influence of generalized effects of drugs by using derived quantitative measures of responding (e.g. relative frequency of responding) rather than absolute rates of responding. It has been assumed that relative response measures are less influenced by the generalized effects of drugs on behavior than are absolute response measures. At present, there is little evidence either to support or refute this assumption. There is a clear need for further assessment of the reinforcing effects of drugs relative to their other behavioral effects.

It is often assumed that drugs have intrinsic properties that determine how effectively they will function as reinforcers in drug self-administration studies. The assumption often is made explicit when different drugs (or different doses of a particular drug) are compared directly under concurrent schedules or choice procedures because a rank order of reinforcing effectiveness is usually inferred from relative measures of responding. The assumption often is made implicit when different drugs are compared under other schedules. Yet many studies have shown that rates and patterns of responding can be influenced markedly by the schedule of drug injection and by the historical and prevailing context in which the schedule occurs. Preoccupation with inherent properties of drugs may hamper studies of behavioral factors that determine the effectiveness of drugs as reinforcers. It may be more profitable to compare drugs on the basis of the range of conditions under which they can inititate and maintain self-administration behavior. Such comparisons will likely provide relevant data about unique properties of drugs as events that control behavior.

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