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REVIEW

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Toward a mathematical description of dose-effect functions for self-administered drugs in laboratory animal models

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Abstract *Rationale:* The interpretation of dose-effect functions for self-administered drugs remains elusive. Since, for self-administered drugs, the amount of drug in an animal depends on its behavior, a mathematical theory of drug self-administration must include terms relevant to receptor theory, as well as a description of how an organism's behavior affects the amount of drug in the animal over time. *Objective:* A theory was constructed in which the ability of a dose to maintain responding was described in terms of receptor theory and the function relating rate of responding to amount of drug self-administered. The main predictions of the theory were that: 1) there should be no ascending limb for drugs self-administered under ratio schedules, 2) running rate of response should not change as a function of dose and, 3) pause duration should be an exponential function of dose. *Results:* Low doses of cocaine were either self-administered at high rates, or not at all. Run rates, though somewhat variable, did not change as an orderly function of dose. Pause duration could be well described by an exponential function. *Conclusions:* The theory provides an acceptable, though no doubt preliminary, description of drug self-administration.

Keywords Response-rate dose-effect function · Receptor theory · Feedback function · Reinforcement

Introduction

In their review of the literature on progressive-ratio schedules of drug self-administration, Stafford et al. (1998) wrote: "We conceive of reinforcing efficacy as a malleable aspect of a dose/drug that is determined by interactions between the dose/drug's pharmacological effects, the prevailing environmental circumstances [emphasis ours, G.S. and T.M.], the concurrent presence or absence of other drugs, and the organism's behavioral and pharmacological history, rather than as a fixed physical property inherent in each dose/drug." The position expressed in this paper is essentially consistent with this view, and the paper will focus on the interaction of two of the above domains. It will focus on a drug's pharmacological effects and how these interact with the prevailing environmental circumstances, namely the schedule of reinforcement under which responding is maintained. The paper is theoretical; no attempt is made to survey the literature, although some data will be offered in support of it. The goal is to elucidate a mathematical theory of drug self-administration that utilizes concepts that are relevant to a variety of circumstances. This paper will deal mostly with a circumscribed aspect of this total description; the response-rate dose-effect functions for self-administered drugs under a few different schedules. In accounting for response-rate dose-effect functions from a theoretical perspective, this paper uses elements of the mathematics of receptor pharmacology, as well as mathematical descriptions of schedules of reinforcement. Part I deals briefly with the mathematics underlying receptor pharmacology, while Part II details the ways in which these events are contextually determined by the schedule.

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Part I

Classical treatment of dose-effect curves in pharmacology

The evolution of the quantitative treatment of dose-effect curves in pharmacology can generally be traced to the evolution of receptor theories of drug action. Although the term receptor was actually coined in the early 1900s by Paul Ehrlich (1909), it was not until the late 1930s that a mathematical treatment relating drug concentration to quantitative effects in biological systems emerged (Clark 1937). This treatment, referred to as occupation

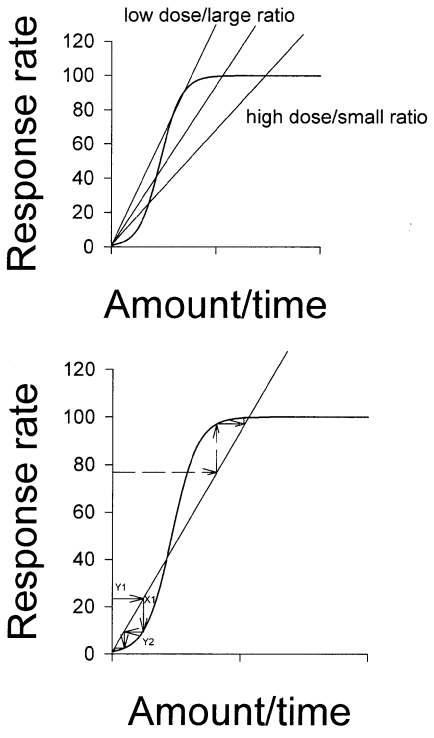

Fig. 1 Three feedback functions for different ratio schedules at a constant dose, or different doses at constant ratio, and the PRF (*top panel*) and the qualitative dynamics of their interaction (*bottom panel*). If responding is below the "middle intersection point", the system will be driven to the steady-state at the origin. If it is above this point, the system will be driven to the steady-state at the asymptote. The "middle intersection point" is an unstable steady-state, and the system would usually not occupy this state

theory, used the Langmuir adsorption isotherm (describing the adsorption of molecules to the surface of charcoal) as a model to describe receptor binding of drug molecules. This model predicts that percent receptor occupancy follows a hyperbolic relationship with respect to drug concentration. In other words, the binding of drug to receptor increases proportionally with increasing drug concentration, to a point, and then plateaus at saturating concentrations. The more commonly used relationship (Kenakin 1997) is the sigmoidal (S-shaped) function (see Fig. 1, top panel) that describes receptor occupancy as a function of the logarithm of drug concentration. Although numerous modifications of occupancy theory have evolved as well as entirely different treatments of receptor theory, all of these theories basically center around drug receptor interactions following Langmuirian kinetics and hence a sigmoidal log(dose)-effect relationship (see Kenakin 1997 for a more extensive discussion and historical perspective). These theories were developed using isolated tissue preparations in which the investigator possessed a greater degree of control over drug concentrations at or near the receptor as well as a well-defined, measurable response. These conditions obviously exist to a much lesser degree in whole animal studies, but nevertheless, the modeling of dose-effect data from whole animal studies in which behavioral variables comprise the dependent measure have proven to be successful using sigmoidal log(dose)-effect functions.

Drug self-administration differs from other areas of behavioral pharmacology in that the amount of drug available to interact with receptors is partially under the control of the organism. This fact is of immense importance to the theory presented here.

Part II

The pharmacological reinforcement function

In the description of pharmacological events, and the resulting S-shaped dose-effect function presented in Part I, the effect of a drug was attributed to events that depended on the amount of drug administered. When we simply inject an organism with a drug, the amount (weight of the drug alone or drug weight/weight of the organism) administered is an adequate description. In circumstances in which an organism is self-administering a drug, we may meaningfully plot some dependent variable as a function of dose, but in order to begin to understand the phenomenon in a dynamic "system" sense, we must consider the fact that the behavior of the organism determines the amount of drug that can at any time enter into the kind of pharmacodynamic events described in Part I. Toward this end, the "standard pharmacological function" may be re-plotted in a space with the x-axis being amount of drug/time. The y-axis of the space to be considered is response rate (specifically, it is the "run rate" – the rate of response after the animal starts responding). The pharmacological function in this space will be referred to as the pharmacological reinforcement function (PRF).

Feedback functions: ratio schedules

In addition to the standard S-shaped pharmacology function, a preliminary description of the qualitative behavior of the system requires another type of function. The function in question is the so-called feedback function (FF; Baum 1973) which gives rate of reinforcement as a function of rate of response for a given schedule of reinforcement. The notion of the feedback function was intended to supplant the framework utilized by Ferster and Skinner (1957) in their explanation of various phenomena in the field of schedules of reinforcement. To a large extent, Baum's (1973) notions followed directly from Herrnstein's (1970) "matching law," which portrayed the allocation of responding on two concurrently available manipulanda as a function of the relative rates of reinforcement obtained on those alternatives. This analysis, thus, made no mention of the conditions prevailing at the moment of reinforcement upon which Ferster and Skinner's (1957) analysis relied heavily. Instead, rate of response was seen largely as a function of rate of rein-

forcement. Baum's (1973) analysis explicitly incorporated the dependency between response and reinforcer, and he argued that important aspects of responding under different schedules of reinforcement could be understood in terms of the feedback function that they arrange.

The feedback functions utilized here differ slightly from those offered by Baum (1973) in that the function expresses the relation between rate of response and amount of drug per unit time rather than between rate of response and rate of reinforcement. Thus, the characteristics of the feedback function will depend not only on the type of schedule and schedule parameter, but also on dose. That is, for a ratio schedule (i.e., schedule in which the rate of reinforcement depends only on the rate of responding) the FF is r=p/F, where r=rate of reinforcement, p=rate of lever-pressing, and F=the number of responses required per reinforcer. This function is a line that intersects the origin and whose slope is 1/F. In the case of drug self-administration, the FF is given by r=pd/F, where d is the dose. For this linear function, the slope is d/F. Thus, doubling the dose is equal to halving the ratio requirement in terms of the function generated.

A qualitative analysis of the system

The top panel of Fig. 1 shows the PRF and the FFs for three different parameters of a ratio schedule, or for three different doses under a single ratio schedule. Under steady-state conditions, both of the relevant functions must be simultaneously satisfied, the PRF by assumption, and the FF by definition of the particular schedule by which infusions are arranged, along with the dose. The sigmoidal function is simply the standard form that is in widespread use in pharmacology. Its parameters are arbitrary, since it is simply for illustrative purposes. From the top panel of Fig. 1, it is apparent that for ratio schedules (within a particular range of parameters) there are only three possible places in the space in which the equations can be simultaneously satisfied, the origin, the asymptote and a point somewhere between them. Although the treatment does not specify changes in these variables over an infinitesimal amount of time (e.g., it is not a differential-equation treatment), some qualitative aspects of the system can now be described.

The bottom panel of Fig. 1 shows how one might expect the system to behave given different initial rates of response. Consider the point labeled Y1. If the initial rate of response is Y1, the amount of drug/time will correspond, given this specific FF, to X1, and X1 will, in turn, correspond to a level of response rate, Y2, given by the PRF. If this process is continued, it becomes apparent that the system must eventually be attracted to the steady-state that lies at the origin. On the other hand, if rate of response is initially high, the system will be attracted to the steady-state that lies at the asymptote (dotted line). The remaining point in the space is a steady-state in the mathematical sense, but it is a state that would be unstable; any deviation in rate of response would drive the system in one direction or another.

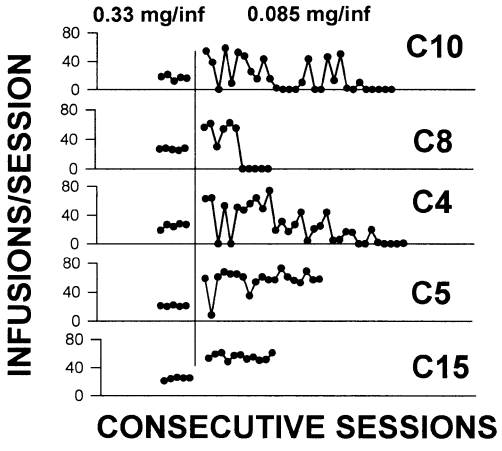

Fig. 2 Number of infusions per session for five rats. Shown is responding for the last five sessions under 0.33 mg/infusion of cocaine and subsequently all of the sessions during which 0.085 mg/infusion was available

The above description suggests something about the ascending limb of individual-subject response-rate dose-effect functions for drugs self-administered under ratio schedules – namely that there should not be much of one. That is, there should typically be no steady-state response rates observed that are intermediate to those observed when saline is available, and those observed at, or very near, the peak of the empirical dose-effect function. Notice that, in the top panel of Fig. 1, the FF for the low dose/large ratio condition could produce a steady-state slightly below the level of the asymptote, and such steady-states would constitute the extent of the ascending limb. It is important to remember that this applies only to individual-subject functions; averaging the data across subjects would be expected to produce an ascending limb. It is possible, even given the system as described, for responding to be "maintained" at low doses for an extended period of time, and for the average to be intermediate to levels observed when saline is available and levels observed when the dose that maintains peak levels is available. It is not clear, however, that such states are steady-states. In this laboratory, efforts to maintain responding at 0.085 mg/infusion of cocaine under an FR10 schedule illustrate this point. Figure 2 shows data from five Fischer 344 rats following the change from 0.33 to 0.085 mg/infusion of cocaine as well as the five sessions preceding the change. These rats had experience with saline extinction as well. For two of the five subjects, responding was maintained under this dose, and for one subject responding quickly fell to saline levels. For the two remaining subjects, however, rate of response fluctuated wildly for many sessions before finally falling to levels comparable to those maintained by saline. For these two subjects, the experimental phase could have been terminated after a number of sessions (but before responding ceased) and data from the last several sessions averaged. For these two

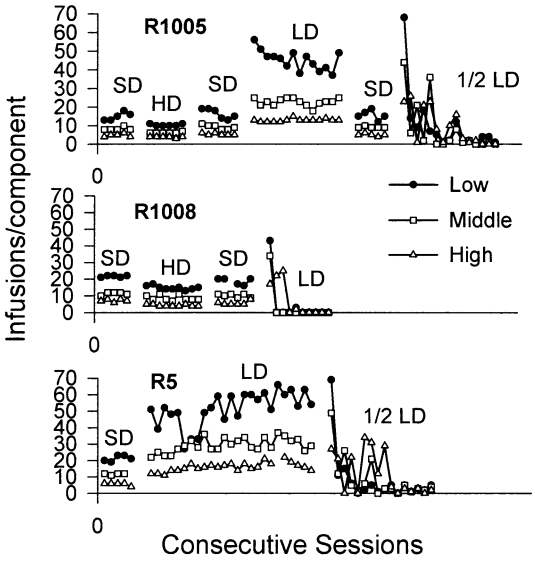

Fig. 3 Number of infusions per component under different ascending series of doses. The abbreviations *SD*, *HD*, and *LD* stand for "standard doses," "high doses," and "low doses." The term *1/2 LD* indicates a series of doses equal to 1/2 the LD series. The different series are: *SD* 0.17, 0.33, and 0.67 mg/infusion. *HD* 0.25, 0.5, and 1.0 mg/infusion. *LD* 0.0425, 0.085, and 0.17 mg/infusion

Table 1 History of exposure to different doses

R1005	R1008	R5
0.17, 0.33, 0.67 mg/infusion (SD*)	SD	SD
0.25, 0.5, 1.0 mg/infusion (HD**)	HD	LD
SD	SD	1/2 LD
0.0425, 0.085, 0.17 mg/infusion (LD***)	LD	
SD		
0.02125, 0.0425, 0.085 mg/infusion (1/2 LD)		

*Standard dose
**high dose
***low dose

subjects there might, depending on which sessions' data were averaged together, appear to be an ascending limb, but the points would clearly not represent a steady state.

Figure 3 shows data from three subjects collected under a wider variety of doses. In this procedure, three doses were available per session in ascending order of magnitude. Each dose was available for 1 h and a 10-min blackout separated components. Two responses were required per infusion (FR2). The dose was manipulated, within each series of three doses, by changing infusion durations, which were always 3.08, 6.16, and 12.2 s. The different series of doses were accomplished by adjusting the drug concentration. Each subject was trained in sessions consisting of 0.17, 0.33, and 0.67 mg/infusion ("standard doses;" SD) and subsequently exposed to saline extinction. Table 1 lists the doses to which each subject was exposed following this history.

Despite the wide range of doses evaluated, only a descending function could be obtained. For rats R1005 and R5, responding was maintained under the low (LD), standard (SD), and high dose (HD) series. For rat R1008, responding could not be maintained under the LD series, and the 1/2 LD series was not made available.

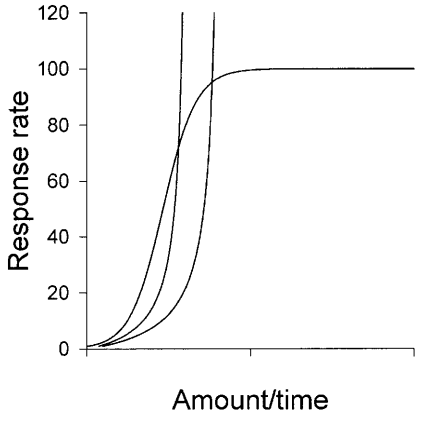

Fig. 4 Two interval-schedule feedback functions and a PRF

It might be argued that some aspects of the data are inconsistent with the theory; specifically, some doses maintained responding when they were part of one series, but not when they were part of another. Such "overlapping" doses differ in two respects: temporal location in the session and infusion duration (e.g., 0.17 mg/infusion occurs in the first component of the SD series and is delivered over 3.08 s, whereas it occurs at the end of the LD series and is infused over 12.32 s). The fact that, for example, 0.0425 and 0.085 mg/infusion maintain responding under the LD series, but not the 1/2 LD series, could be viewed as inconsistent with the theory because it does not contain terms that explicitly deal with infusion duration. Infusion duration could, however, be incorporated, and its importance is suggested by the general direction of the theory. That is, the fact that a dose infused over a long duration does not maintain responding, although the same dose infused over a short duration does, is consistent with the premise that amount of drug/time is crucial. Strategies for incorporating this variable, as well as post-infusion timeouts, into the theory is discussed briefly below (see Other variables: infusion duration and post-infusion timeout).

It is not clear that the failure of some doses to maintain responding was solely a matter of infusion duration. As was mentioned, "overlapping doses" differ in terms of their location in the session as well as infusion duration. A dose of 0.17 mg/infusion in the LD series is preceded by 0.0425 and 0.085 mg/infusion, and this may have something to do with the failure of infusions to maintain responding. This possibility is discussed briefly below (see Further predictions: "local" history effects).

Feedback functions: interval schedules

Behavior maintained under interval schedules of drug infusion would be expected to be different in some ways from that maintained under ratio schedules. Figure 4

shows the PRF and FFs for different interval schedules, or different doses under the same interval schedule. The function for interval schedules is usually given (Baum 1973) as r=1/(I+0.5/p), where I=the interval schedule parameter. For drug self-administration, where amount per unit time is the critical measure, the FF is r=d/(I+0.5/p). In contrast to the system where ratio schedules are arranged, the points of intersection shown in Fig. 4 are always stable steady-states. Under these conditions, it would be much more likely that one would observe steady-states that are intermediate to those observed when saline is available, and those at the peak of the dose-effect function.

Dose-effect functions: overall rate of response and the descending limb

The theory, as described so far, predicts that the response-rate (run rate) dose-effect functions for interval, but not ratio, schedules should increase as a function of dose, but then level off at the asymptote of the PRF. It suggests that under ratio schedules, rate of responding (run rate) should be the same at every dose that maintains responding. Such a discussion is, however, incomplete. What is missing is a discussion of drug effects that produce decrements in overall rate of response (i.e., rate of response that is calculated by dividing total responses by time in the session).

Over a wide range of doses on the descending limb, pause duration increases as a function of dose and inter-infusion intervals tend to be quite consistent for cocaine (Pickens and Thompson 1968) and heroin (Koob et al. 1984; Hemby et al. 1995). These infusion-induced pauses are thus a major determinant of overall rate of response. This fact plays a large role in the developing theory presented here, with the PRF and pause function (PF) determining the overall rates observed.

The pause-time function

In the model proposed here, the time spent pausing does not enter into the feedback portion of the theory shown in the bottom panel of Fig. 1. According to the theory, the feedback operates only during the time that responding is occurring post-pause. This position, though not necessarily predicated upon it, is consistent with the view that organisms “titrate” levels of cocaine or extracellular levels of neurotransmitters (Pettit and Justice 1989). The notion is especially consonant with the view of Tsibulsky and Norman (1999), who argue that infusion of cocaine results in a period of satiation, whose duration depends on the dose, as well as pharmacokinetics and pharmacodynamics. However, no specific explanation of the pause need be given here, and it may just as easily be considered to be due to general disruptive effects. Indeed, this latter view may be more reasonable, as there is evidence that response-independent IV administration of cocaine produces pauses in food-maintained

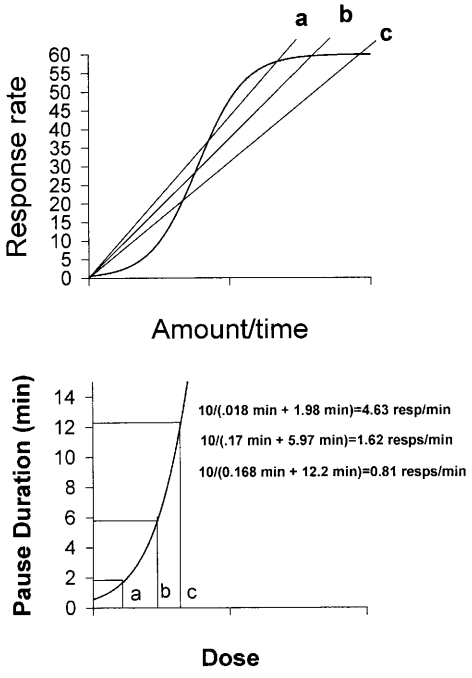

Fig. 5 Three ratio feedback functions associated with different doses intersect the PRF (*top panel*), and the function relating pause duration to dose (*bottom panel*). This pause time is then added to the denominator of the rate calculation resulting in a descending function if one plots overall response rate as a function of dose

responding that are of the same duration as the pauses seen under cocaine self-administration of the same doses (Pickens and Thompson 1968).

Figure 5 illustrates the operation of the model adopted here. The top panel shows three different doses (a, b, and c) at a constant ratio value plotted in the space with the PRF. Assuming the doses are sufficiently large, the system will be attracted to the steady-states that lay on the asymptote. The values that correspond to these steady-states are run rates. The bottom panel shows the pause-time dose-effect function (pause function; PF). This function would not be expected to have an asymptote. It is difficult to imagine any drug in which, say, doubling a large dose would not result in substantially longer post-infusion pauses – this state of affairs would presumably hold up to the point of lethal doses. The overall rate of response for the system would be given by adding the pause time to the denominator of the rate calculation for run rates that would follow from the top panel. The calculations contained in the bottom panel illustrate this process for an FR10 schedule. For dose a, a run rate equal to approximately 56 responses/min would result in ratios being completed in approximately 0.18 min once responding starts. The pause duration given by the PF is approximately 1.98 min. Thus, the overall rate of response maintained by this dose would be 10/(0.18+1.98 min)=4.63 responses/min.

The top two panels of Fig. 6 show pause data for the two rats for which responding was evaluated under the

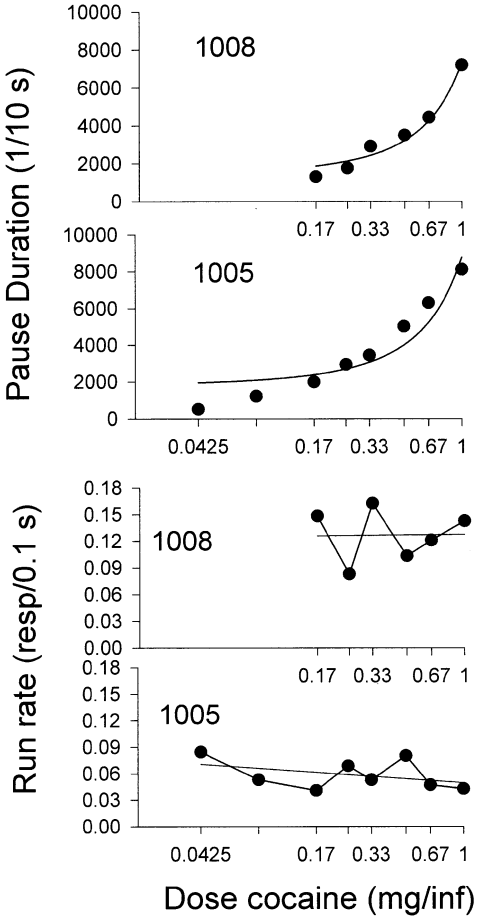

Fig. 6 Pause duration (*top two panels*) and run rate (*bottom two panels*) as a function of dose of self-administered cocaine. Shown are data from two of the subjects whose data are shown in Fig. 3. The fitted functions in the top panel are two-parameter exponential functions of the form, $y=ae^{bx}$

high dose series, as well as the standard dose. Fit to these data are two parameter exponential functions of the form, $y=ae^{bx}$. For rat 1008, more than 96% of the variance is accounted for, while for rat 1005, 88% is accounted for. Although this is a respectable amount of variance accounted for, it is possible that the use of a three-parameter exponential function is justifiable. The three-parameter function is of the form $y=y_0+ae^{bx}$. The only function of the third parameter is, thus, to adjust the y-intercept. This third parameter may be justifiable in that pause duration would become meaningless at low doses that do not maintain much responding and, indeed, becomes undefined where responding ceases.

In the treatment given above, discussion proceeded as if each infusion produced a long pause. The model espoused here, however, does not depend on this being the case. The PF may be treated as expressing the average pause. This is an important caveat since all drugs may not produce the great regularity in interinfusion intervals that, for example, cocaine does. Balster and Schuster (1979), for example, reported that amphetamine self-administration produced bursts of ratio completion separated by long pauses, and other self-administered drugs may show a similar pattern.

The complete system: ratio schedules

The model advanced so far is consistent with the basic features of cocaine self-administration. The most controversial aspect of the model will certainly be the prediction that there is not an ascending limb for single-subject response-rate dose-effect functions. This statement should hold with respect to doses made available on a phase basis (the dose is available every session for long enough to obtain a steady-state), on a within-session basis, and on a substitution basis (the dose is made available for single sessions but behavior is usually maintained by a different dose) as long as a dose is examined enough times to ascertain whether or not responding would be maintained. It would not be expected to hold true where doses are made available for set periods of time with, for example, the last 5 days constituting a datum point on the dose-effect function.

As was stated earlier, it has become clear that, for rats self-administering cocaine on small fixed-ratio schedules, there is no way to maintain rates of response intermediate to those maintained by saline and the maximum of the dose-effect function. Whether or not this holds up with respect to other species, at large ratios, or with other drugs needs to be examined. It is doubtful that this matter can be settled simply by looking at the existing literature, though this endeavor is obviously instructive. In evaluating the claims made here, extreme caution must be exercised in judging the stability of the data.

Another claim likely to be controversial involves the narrow range of run rates predicted by the theory under ratio schedules. Data concerning run rates are difficult to find. Goldberg (1973) reported that run rate was an inverse function of dose under FR schedules of cocaine and *d*-amphetamine. In this laboratory, run rates maintained by cocaine (see Fig. 6, bottom two panels, below), heroin, or cocaine/heroin combinations under small FR schedules typically show little or no variation as a function of dose but larger ratios may be more susceptible to disruption.

The bottom two panels of Fig. 6 show run-rate data from the two subjects whose pause data are presented in the top two panels. Although there is a rather wide range of variability displayed in these data, there is little or no orderly trend as a function of dose. For rat 1008, a regression fit to the data is horizontal and accounts for almost no variance. For rat 1005, there is a downward trend present but it is difficult to place much importance on this trend and the regression line accounts for little more than 17% of the variance. That is, as the theory predicts, run rate does not appear to change as a function of dose. It is important to note that the data from these subjects were not selected from a pool of data. When some of the reviewers of the original manuscript requested some data be included (other than that shown in

Fig. 2), four subjects that were self-administering cocaine were exposed to different series of doses, as described earlier, as they finished up other experiments. Data from three of those subjects appear in Fig. 3 (the jugular catheter came out of the fourth). For the third subject, R5, pause times and run rates were not collected.

For the present time, run rates will be treated as suggested by the theory and the data presented in Fig. 6, but accommodating changes in run rates as a function of dose, under other conditions, should not be an insurmountable problem, and some mention of strategies for this should be made. If run rates change systematically at all as a function of dose under ratio schedules, it is likely that they decrease as dose increases. The first thing to be decided if this turns out to be the case is whether or not the "spirit of the theory" is violated. That is, the temporal patterning of behavior may closely adhere to the theory as described but a single response may occur "early" on higher doses with little or no further responding until the preponderance of the responding occurs at steady rate. Further, it has been suggested (Drake Morgan, personal communication) that some monkeys respond during the stimulus complex initiated when infusions begin, and that a response or two may occur immediately after the stimulus complex ends. Responding, in this case as well, would then resume at the end of the "real pause," occurring at the steady rate depicted in the theory. If run rates show a "real decrease", however, then this will have to be dealt with. A preliminary suggestion would be that the PRF becomes a function that is the difference of two functions, one that describes "unaffected run rates" (i.e., run rates that would accrue if drugs did not have direct effects) and a second s-shaped function that describes the amount of disruption produced by the drug. The value of this function would be low at small and moderate doses, but would begin to rise at higher doses. The function would be subtracted from the "unaffected rates" function and the PRF would become an S-shaped function in which the portion that was the asymptote turns downward slightly.

The complete system: interval schedules

Interval schedules have already been discussed with respect to the ascending limb but the discussion requires some modification. Because the feedback is assumed to operate exclusive of the pause duration, the feedback functions must be modified. That is, the functional interval value is the interval parameter minus the pause generated by the dose. Interval schedules with parameter values less than the duration of the pause generated by the dose being self-administered are equivalent to FR1 schedules. With larger schedule parameter values, the interval properties of the schedule begin to predominate.

As was mentioned earlier, the response-rate dose-effect functions for interval schedules should be truly bitonic in the sense of possessing an ascending limb in which response rates are chronically maintained that are intermediate to those maintained by saline and those maintained by the dose representing the maximum.

The possibility and usefulness of fitting functions

It seems likely that there are data that can be fit with the functions suggested here. Any data characterized by run rates that do not change much as a function of dose, but where the overall rate is a monotonic decreasing function of dose, are capable of being so described. Given the number of parameters defining the two pharmacological functions, though, this should be of little comfort. A different state of affairs exists, though, if functions fit to ratio-schedule data make successful predictions concerning interval-schedule data and vice versa. Here the reader should keep in mind this caveat concerning the precision claimed here. The goal of the paper is to put forth a model sufficiently simple to be explored but complex enough to account for major features of behavior maintained under different schedules across a range of schedule parameters and doses.

It is important to acknowledge, at this point, a potential problem with the model. Given the way that "run rate" is defined (i.e., the rate of response calculated over the period of time beginning with the first response after the previous reinforcer and the occurrence of the reinforcer) run rates may only approach zero. Run rate may become extremely low but, as soon as it falls so low that no reinforcers occur during the measurement period, run rate becomes undefined. Thus, fitting a sigmoidal function to run-rate data plotted as a function of amount per time is not possible if run rates decline to this point.

Relevant experiments

The best course of action in approaching this problem would be to resume gathering data from individual subjects across a wide range of doses, schedules, and schedule parameters. Perhaps the first thing that should be done is to examine the predictions relevant to the ascending limb. Experiments relevant to this issue would involve simply attempting to maintain responding intermediate to those maintained by vehicle and those maintained by doses supporting near maximal response rates. In the context of the data presented in Fig. 2, dose could have been manipulated in even smaller increments; for those subjects in whom responding was maintained at 0.085 mg/infusion of cocaine the dose could have been reduced and for those for whom 0.085 mg/infusion did not maintain responding the dose could have been slightly increased after responding was re-established under 0.33 mg/infusion. After rigorously attempting to maintain intermediate rates, the schedule maintaining responding could be switched to an interval schedule and some of the same doses made available. In experiments like this, great caution must be exercised in evaluating

the long term stability of responding under small doses. The theory could be seen as being supported if intermediate rates of response (rates of response intermediate to those maintained by saline and those maintained at the peak of the function) could not be chronically maintained under ratio schedules but could be maintained under interval schedules.

A second type of experiment would involve an evaluation of the symmetry of dose and schedule parameter that characterizes the simple model presented here (i.e., halving the dose is equivalent to doubling the schedule parameter). This aspect of the model is almost sure to be of somewhat limited generality; it is too easy to imagine circumstances in which this is sure to fail. If responding were maintained under a moderately large FR schedule by a large dose, it is likely that the dose could be cut in half and responding would still be maintained – doubling the ratio value, however, would almost certainly result in the cessation of responding. If the ratio value were pushed to near its maximum under a large dose, however, both decreasing the dose and increasing the ratio would be expected to cause responding to cease. This symmetry relationship should be evaluated under interval schedules as well as ratio schedules. A more sophisticated model than the one presented here would have to be constructed to accommodate the differences between manipulating schedule parameter and dose when the amount of drug/time is held constant. The finding that such manipulations are not symmetrical as suggested in the current model does not mean that the fundamental features of the model should be abandoned. There is no easy way to make the decision as to whether or not the model is worth changing and elaborating. Modifying theories post-hoc can produce a theory that "explains" much but predicts little. On the other hand, it would be a mistake to reject a theory prematurely because it fails to account for what are, relatively speaking, empirical nuances.

A third tactic might be to first explore a range of interval schedules under a single dose. Such a manipulation guarantees that a large range of possible x-axis (amount of drug/time) values are explored, whereas responding maintained under ratio schedules tends to result in a narrow range of intake rates. The result of such a manipulation should be a clear picture of the PRF. Once in possession of this function, one should be able to roughly predict the minimal dose that could support responding under a given ratio schedule. This experiment has the added advantage that subjects first exposed to the interval schedules would already have a large history with intermittent reinforcement.

Further predictions: "local" history effects

The model as presented here, suggests that responding maintained under ratio schedules might show hysteresis (i.e., the steady-state maintained depends on the local history of manipulations). Such effects would be observable when dose is manipulated over a wide range "in different directions" (ascending versus descending). Doses that will maintain responding under circumstances in which behavior was previously well maintained may not do so if imposed when behavior is not well maintained. The reason for this is related to the reason that there is no ascending limb under ratio schedules; if low run rates are prevailing responding must somehow rise high enough that the system might be "captured" by the attractor on the asymptote. If high response rates are prevailing they might not fall low enough to be "captured" by the attractor at the origin.

Some of the data presented in Fig. 3 appear consistent with this notion. The failure of doses, that maintained responding in the context of higher doses, to maintain responding in the context of lower doses can be interpreted, in part, by reference to the rates produced by the lower doses.

The PRF and progressive-ratio schedules

Progressive-ratio schedules of drug self-administration raise interesting and difficult issues; one heretofore unacknowledged difficulty with the theory is that it really does not have much to say about whether or not possible non-zero steady-states will be observed at low doses (or large ratios) under ratio schedules. That is, just because a non-zero steady-state is possible under a particular ratio schedule and dose does not mean that that steady-state will be observed. The theory does, however, suggest that the possibility of the maintenance of behavior would grow increasingly tenuous at low doses or large ratios. Obviously, if the FF relevant to a dose/schedule parameter does not intersect the PRF at all (except at the origin), responding cannot be maintained. If the FF intersects the PRF at only two points (i.e., the second, non-origin, point is the tangent) responding would, similarly, be unlikely. Only where the function describing a dose/ratio combination intersects the PRF in three places would one expect that responding might be maintained at the upper, non-zero state. But one would expect responding to be very fragile; as dose becomes small (or the ratio becomes large), the point that rate of responding must surpass (the "middle intersection point") becomes higher and higher. If rate of response falls below this point, it is likely that responding will rapidly decline and never recover. PR schedules, whether arranged as a within-session or across-session increase in ratio value, are of considerable importance to the approach suggested here. Indeed, exploring PR schedules is the kind of experiment that one might do to examine the notions put forth here. It is the symmetrical analog (in the sense that symmetry is meant above) to gradually lowering the dose within or across sessions. A valuable experiment would be to compare, within individual subjects, the effects of progressive-ratio schedules with the effects of what might be called regressive-dose schedules (the ratio stays the same but dose declines within or across sessions).

Other variables: infusion duration and post-infusion timeout

Both infusion duration (Balster and Schuster 1973; but see Caine et al. 2000) and duration of post-infusion timeout (Winger 1993) are variables that are known sometimes to affect self-administration dose-effect functions. Both of these variables are scheduling variables which constrain the amount of drug/time that can be self-administered but they are outside the scope of feedback functions; parts of the session in which reinforcement cannot be obtained, and which are correlated with distinctive stimuli (i.e., timeouts), are not generally included in feedback functions, and there does not seem to be any precedent for describing variables comparable to infusion duration (since feedback functions are traditionally descriptive of the relation between rate of response and rate of reinforcement). One way to describe the effect of these variables within the framework presented here is to consider that they shift the PRF to the right. Thus, much of the description of the system is the same as it would be if there was no post-infusion timeout or extended infusion duration.

The effects of neuropharmacological manipulations

The functions depicted in the theory would be, presumably, altered by a variety of manipulations. A description of the way the functions are altered would, thus, be a characterization of the effects of those manipulations. A manipulation could change one or both functions, even shifting or altering them in opposite directions. Consider, for example, the effects of 6-hydroxydopamine lesions of the nucleus accumbens, and the effects of systemically administered dopaminergic antagonists, on responding maintained under fixed- and progressive-ratio schedules of cocaine self-administration. The former results in reductions in the overall rate of response maintained under FR schedules, while the latter produces increases. Both manipulations, however, decrease breakpoint under PR schedules. It has been suggested that the effects upon FR-maintained responding are not interpretable in terms of the modification of the reinforcing effects of cocaine (Arnold and Roberts 1997) and this is partly true – the effects are not interpretable solely in terms of modification of the reinforcing effects of cocaine. But the effects are interpretable in terms of the relatively simple model proposed here. The commonality of effect upon breakpoint suggests that both manipulations either shift the PRF to the right, downward, or decrease the slope of the fast-rising portion of the PRF. The divergence of effect of these manipulations upon FR-maintained responding, on the other hand, suggests that each affects the PF differently; the DA antagonists shift it to the right, and the lesion either does not effect, or shifts the PF to the left.

Future directions

The possibility that other functions would have to be incorporated into the theory has already been mentioned. In addition to a separate function describing the effects of drugs on run rates, it is possible that even a fourth function might have to be incorporated. This function would be one that describes the direct stimulating effects of some self-administered drugs. It is possible that under some schedules of drug infusion response rate is increased by the direct effects of the drug. Spealman and Kelleher (1979), for example, found that response-independent infusions of cocaine altered monkeys' responding that was maintained under FI300 s schedules of electric shock (response-produced shock). The function relating overall response rate to dose was an inverted U-shaped function that closely resembled the response-rate dose-effect functions for these same monkeys when cocaine was self-administered in another component. As Bergman and Katz (1998) point out:

"It seems reasonable that the direct effects of cocaine comparably influenced responding in both cocaine and shock components of the multiple schedule and, therefore, that both increases and decreases in response rates of cocaine self-administration behavior could be ascribed to the direct rate-altering effects of the accumulated self-administered dosages of cocaine." We do not hold a view quite as strong as that of Bergman and Katz (1998) but there is little reason to believe that the direct rate-increasing effects of drugs would never be manifested in drug self-administration. These rate-increasing effects would be expected to occur only under certain circumstances, unlike the PRF and PF that are postulated to exist, in some sense, independent of the schedule. This would seem to add a further complication as the function describing these rate-increasing effects changes as a function of the schedule. Perhaps a model that dispenses with separate pause and rate functions could be workable; the PRF could be thought of as operating as suggested here, but the overall rate calculation would be produced by a single transformation of this function that would reflect the rate-dependent effects of certain drugs.

The likely proliferation of functions and the resulting complexity should not be regarded as a shortcoming of the approach. The approach taken here does not create the complexity inherent in drug self-administration, it simply attempts to describe it in a fashion more rigorous than ordinary-language descriptions. Further, the approach represents a step that eventually must be taken in the analysis of drug self-administration and, indeed, in the study of schedule-control in general.

An ultimate goal of this kind of approach would be a moment-to-moment description of responding maintained by drugs. Such an endeavor involves specifying a system of differential equations. It is difficult to say at present what such a system might look like. It is clear that the system would have to incorporate pharmacokinetics as well as pharmacodynamics. A step in this direction is the system put forth by Tsibulsky and Norman (1999) de-

scribing cocaine self-administration. According to this model, the probability of self-administration of cocaine is low, if cocaine levels in the body are above a certain value, but the probability approaches one when levels drop below this "satiety threshold." The factors that determine the length of inter-infusion intervals are dose, and cocaine's half-life. Some treatment similar to this would have to be incorporated but this is by no means a complete solution. What is not clear is how to produce a system of equations relevant to schedule-controlled behavior and how this treatment might combine with something like Tsibulsky and Norman's (1999) approach.

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