8 How Drugs Affect Cells and Reinforcement Affects Behavior: Formal Analogies

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INTRODUCTION

In operant psychology there has been a trend toward quantitative analysis. In the first years of this discipline (e.g., Skinner, 1938), research reports were typically organized around a graphic representation of the experimental results. These graphs, called *cumulative recorder tracings*, showed a moment-to-moment account of the reinforced response: When the subject, such as a rat, pressed a lever, a pen was stepped along a continuously moving roll of paper. Thus, a train of responses would show up as a smooth line, and the faster the rate of responding, the steeper the slope of the line. Recent operant research papers, however, rarely include cumulative recorder tracings (see Skinner, 1976, for a eulogy). Now it is more likely for such papers to be based on a mathematical model of the experimental conditions. The models are derived from theories, for example, the assumption that subjects in operant experiments maximize some dimension of reinforcement (e.g., Rachlin, 1980), and the goal of the research is to fit the model, and thereby test the theory. In effect, vignettes, in which the subject's behavior was played back just as it occurred, (e.g., Ferster & Skinner, 1957), have been replaced by calculations and goodness-of-fit tests.

The most influential quantitative theory in operant psychology is the matching law. Herrnstein (1970) introduced this theory, and he initially demonstrated that it described the relationship between response rate and reinforcement rate in a study in which the subjects were pigeons and the reinforcer was grain. Since this introduction, the matching law has been shown to describe the results for different species, including humans (e.g., Bradshaw, Szabadi, & Bevan, 1978a), and for different procedures, including those that use nonconsummatory reinforcers, for

example, brain stimulation (Hamilton, Stellar, & Hart, 1985) and money (Bradshaw et al., 1978a). The matching law has also been applied in research areas other than operant. One such extension recently occurred in psychopharmacology. Researchers used the matching law to analyze the effects of drugs on behavior (Bradshaw, Ruddle, & Szabadi, 1981; Hamilton, Stellar, & Hart, 1985; Heyman & Coons, 1981). This chapter discusses these studies; its goal is to show that the matching law can be used to solve a long-standing problem in psychopharmacology research.

Attempts to identify the biochemical substrates of reinforcement have produced controversy (see review by Wise, 1982). One position is that dopamine, a neurotransmitter found in the brain and other tissue, is an important biochemical link in the physiological changes that accompany the strengthening of a response by a rewarding stimulus. Important evidence for this view is that drugs that block dopamine receptors, for example, neuroleptics, produce a pattern of responding that resembles the effects of removing the reinforcer maintaining the response ("behavioral extinction"). For example, following a dose of pimozide (Wise, Spindler, de Wit, & Gerber, 1978), response rates were at or near baseline levels at the start of the session, but, as the session wore on, response rate gradually declined, approaching zero. Control conditions indicated that this pattern of findings could not be explained by fatigue or satiation, so the investigators concluded that the reinforcer sustaining the response had lost its efficacy. Other considerations, however, indicate that the extinction pattern is ambiguous.

There is a positive feedback loop between responding and reinforcement in those procedures in which neuroleptics produced a gradual decline in response rate. Each response produces a reinforcer. Consequently, a motor deficit, however small, will necessarily reduce reinforcement rate relative to baseline. The decrease in reinforcement rate will, in turn, further weaken response rate, so that in time response and reinforcement rates will drive each other ever lower. Thus, because of the feedback loop, a motor deficit could lead to a gradual decline in response rate. Data support this interpretation. For example, neuroleptics do not produce response extinction when the procedure uncouples changes in reinforcement rate from changes in response rate, as in interval schedule experiments (Fibiger, Carter, & Phillips, 1976).

The problem is that rate of responding depends on a host of factors (e.g., reinforcement rate, motor capacity, the response requirement, stimulus conditions, deprivation, etc.). Consequently, researchers who use response rate to index reinforcement processes require criteria for distinguishing between the many possible competing interpretations.

Some of the ambiguities inherent in response rate measures can be removed with the matching law analysis. The customary notation is

$$B = \frac{kR}{R + R_e} \tag{1}$$

where B represents response rate, R represents reinforcement rate and k and R_e are fitted parameters, obtained from the data. Figure 8.1 shows a graph of Equation 1, along with the curve-fitting definitions of k and R_e.

On the x-axis is reinforcement rate and on the y-axis is response rate. The parameter k is counted in response-rate units, typically responses per minute, and it is equal to the response-rate asymptote. For example, according to Equation 1, response rate approaches k as reinforcement rate increases. The parameter R_e is counted in reinforcement rate units, typically reinforcers per hour, and it is equal to the rate of reinforcement that maintains a one-half asymptotic rate (k/2). For example, according to Equation 1 response rate is equal to k/2 when the reinforcement rate is set to R_e.

Figure 8.2 shows the patterns of response-rate changes that accompany changes in k and R_e. The first panel shows that proportional shifts in response rate correspond to a shift in k. Because k is the upper limit on response rates, a change in k implies that the topography of the response and/or the capacity to respond changed. Consequently, it is reasonable to use k to measure motor performance.

The second panel in Fig. 8.2 shows that an inverse relationship between response-rate change and reinforcement rate corresponds to a change in R_e. Because R_e specifies how much reinforcement is needed to maintain a one-half asymptotic response rate, it is reasonable to use R_e to measure the efficacy of the reinforcer. For example, if reward "A" produced a higher proportion of

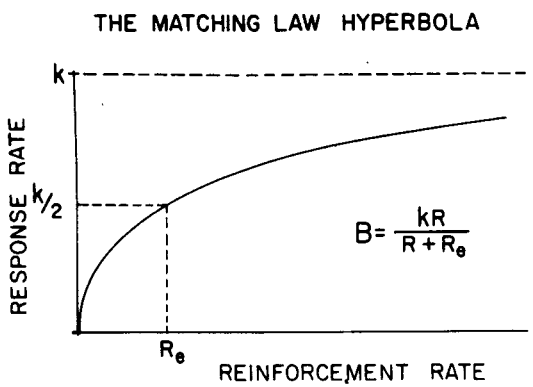

FIG. 8.1. The matching law hyperbola. The line intersecting the y-axis marks the asymptotic response rate and is equal in magnitude to k. The line intersecting the x-axis marks the rate of reinforcement that maintains a one-half asymptotic response rate and is equal in magnitude to R_e.

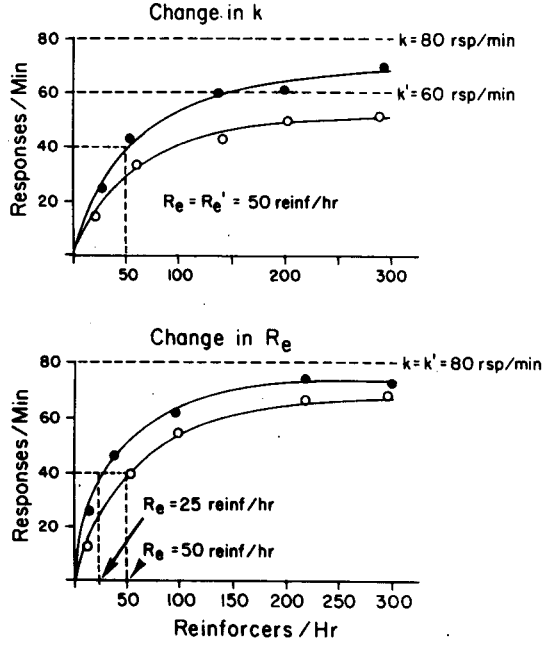

FIG. 8.2. Response-rate patterns for changes in k and R_e. The two data sets in the top panel, filled and unfilled points, produced equal values of R_e but different values of k. In contrast, the data sets in the bottom panel produced equal values for k but different values for R_e.

asymptotic responding than reward "B," and there are equal amounts of "A" and "B," then "A" is by definition more reinforcing.

The curve-fitting definitions of k and R_e provide a rationale for empirical interpretations. However, other logical accounts have been given and these lead to different interpretations of the parameters (see, e.g., Killeen, 1981; McDowell & Kessel, 1979). Therefore, we must turn to other sources to decide how to interpret the parameters k and R_e. The remainder of this chapter is concerned with this task. In a subsequent section is a derivation of Equation 1. The derivation is based on analogies between receptor-binding studies and reinforced-behavior experiments. The results lead to the conclusion that k measures response topography and the R_e measures the efficacy of the reinforcer. Experimental manipulations that affect k and R_e are also briefly reviewed. The empirical results support the derivation. Last, Equation 1 is used to evaluate the behavioral effects of three widely studied drugs: pimozide, chlorpromazine, and amphetamine. These three drugs affect the availability of dopamine at postsynaptic receptors. The results from these experiments indicated that dopamine is a substrate for both reinforcement processes and motor performance.

HOW DRUGS AFFECT CELLS: QUANTITATIVE ASPECTS

By the late nineteenth century, scientists had uncovered the basic features of the structure and function of living cells. One offshoot of the modern conceptualization of cells was the hypothesis that drug effects were mediated at the cellular level (Parascandola, 1982). Although the evidence was indirect—there was no technology for measuring drug–cell interactions—a theory emerged that has since been found to be essentially correct. It was supposed that (a) drug molecules formed a temporary reversible bond with specialized areas of the cell membrane; (b) the temporary drug-membrane complex altered the functioning of the cell; and (c) this cellular change initiated a chain of events that terminated in a physiological response, for example, an increase in muscle tension. The specialized area of cell membrane was referred to as a "receptor."

The theory that drug effects were mediated at the cellular level was accompanied by parametric studies of multicellular physiological units. For example, researchers would apply a small amount of drug, such as acetylcholine, to a strip of striated muscle and measure the strength of the resulting contractions. These results could often be described by mathematical curves in which drug dose ran along the x-axis and strength of response along the y-axis. The orderly quantitative results called for an explanation.

In 1933, A. J. Clark outlined a hypothesis based on the then-hypothetical receptor. Clark assumed that the receptor was in one of two states: occupied or unoccupied by drug molecules. For a given dose of drug, the number of occupied receptors remained stable. Because it was thought that the drug molecules formed a temporary bond with the receptor, stability implied that the rate at which the drug molecules attached to the cell must equal the rate at which they separated from the cell. These binding rates necessarily determined the number of occupied receptors, but there was no way of measuring them. Consequently, Clark assumed the simple case that binding rate was proportional to the amount of available drug and the number of available receptors. The resulting equation for rate of binding was:

$$B = k_1[\mathrm{R}][\mathrm{L}] \tag{2a}$$

where B is rate of binding, [R] is the number of unoccupied receptors, [L] is the amount of available drug, (referred to as "ligand"), and k_1 is the rate constant. Similarly, the rate of drug-receptor dissociation was:

$$D = k_2[\mathrm{RL}] \tag{2b}$$

where D is rate of dissociation, [RL] is the number of occupied receptor sites, and k_2 is the dissociation constant.

Clark believed that the next step—the pathway from receptor-drug complex to physiological response—was likely rather complex. However, for some sim-

pler systems, he had reason to suppose that the strength of the physiological response was proportional to the number of bound receptors. Appendix A shows how this assumption along with Equations 2a and 2b combine to establish a quantitative relationship between drug dose and physiological response. In words, the result is that the strength of a receptor-mediated-drug response is a hyperbolic function of the amount of drug:

$$P = \frac{SR_{tot}[L]}{[L] + k_2/k_1} \tag{3}$$

where P represents the level of the physiological response, R_{tot} represents the total number of receptors, [L] represents the amount of drug, S represents characteristics of the pathway linking the receptor-drug complex to a physiological response, and k_2 and k_1 are the dissociation and binding constants.

Figure 8.3 shows an application of Equation 3 adapted from Clark's text. Clark's assumptions and logic lead to the following interpretations. The asymptotic intensity of the muscle contraction is determined by the number of available

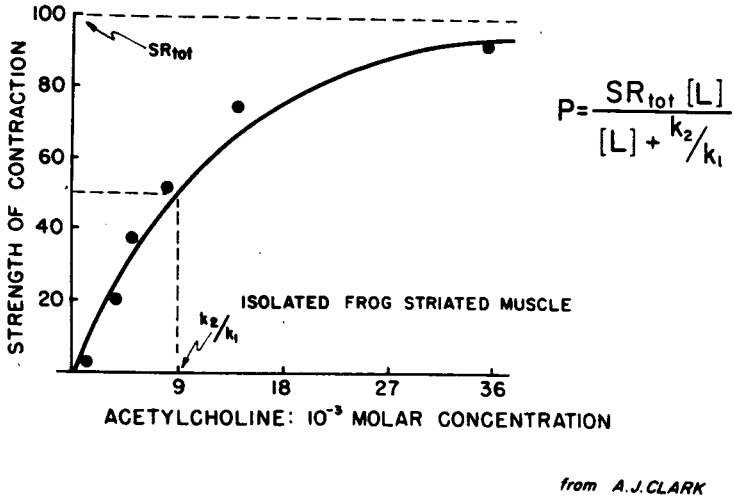

FIG. 8.3. The effects of acetylcholine on isolated sections of striated muscle fibers (from Clark, 1933). The shape of the relationship between muscle contraction and drug dose is representative of the results from a large number of studies. The asymptote is equal in magnitude to SR_{tot}, and according to Clark's derivation it reflects the total number of receptors and steps leading from receptor to response. The line intersecting the x-axis is equal in magnitude to the amount of drug necessary for a one-half asymptotic response. According to Clark's derivation this term is determined by the binding and dissociation rates.

receptors. For example, the same drug and the same species of receptor could yield different responses if the total number of receptors was changed, as in some diseases. Second, the amount of drug necessary for a given subasymptotic level of responding depends on the binding and dissociation rates. For example, holding number of receptors and amount of drug constant, the physiological response will decrease if the dissociation constant is increased, as can occur with temperature changes.

Clark's derivation gave the drug-dose response curves physical interpretations. These interpretations established, and remain, the basic conceptual framework for understanding how cells mediate drug effects. For example, drugs are classified by their affinity for a particular area of brain tissue, and tissue is classified by its receptor populations. One practical consequence of this perspective is that the constants of Equation 3 provide rational criteria for designing therapies for the many disorders that affect receptors. Figures 8.4 and 8.5 show examples of research based on the physical interpretations that followed from Clark's (1933) derivation.

The results shown in Fig. 8.4 are from an experiment in which slices of normal and diseased brains were tagged with a radioactive label (Reisine, Fields, Bird, Spokes, & Yamamura, 1978). The graph shows that the asymptotic binding levels for the normal and diseased brains differed, whereas the values of k_2/k_1 were about the same. According to Clark's theory, this means that the disease, Huntington's Chorea, decreased the number of dopaminergic receptors in the brain. Independent evidence based on staining and anatomical methods confirmed this prediction (Reisine et al., 1978).

Figure 8.5 shows that temperature affects the amount of drug necessary to fill one-half of the available receptors (Speth, Wastek, & Yamamura, 1979). According to Clark's theory, temperature changed this parameter by changing the

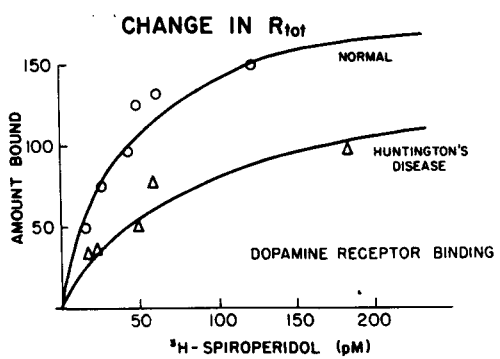

FIG. 8.4. Huntington's disease decreases the asymptote of the function relating number of bound receptors to amount of drug. According to Clark's derivation, this means that the disease reduced the number of receptors.

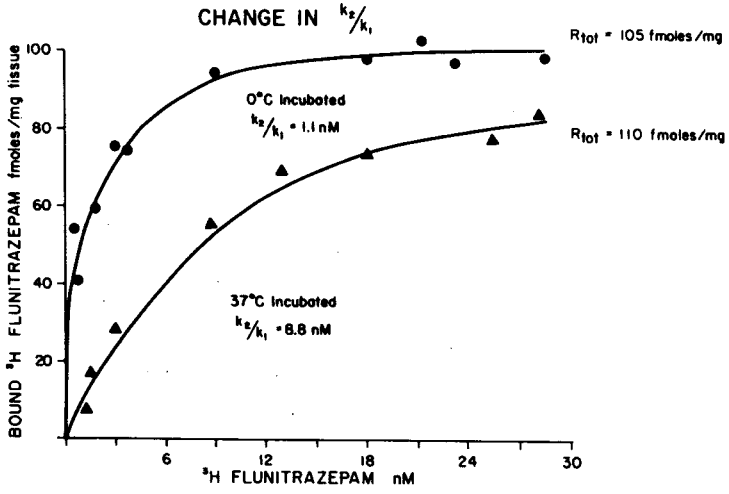

FIG. 8.5. Temperature affects the amount of drug necessary for a one-half asymptotic-binding rate. According to Clark's derivation this means that temperature affected the binding and/or dissociation rates.

binding and/or dissociation rates. Direct measurement of the association and dissociation rates showed that both increased, but that the dissociation rate increased more (Speth, Waster, & Yamamura, 1979).

THE MATCHING LAW AND ELEMENTARY FEATURES OF REINFORCED BEHAVIOR

The matching law is identical in form to Clark's model for drug-receptor interactions; both are rectangular hyperbolas. However, the matching law was introduced on empirical grounds. Herrnstein showed that the equation approximated the relationship between peck rate and reinforcement rate in an experiment with pigeons (1970); he did not derive the model from elementary principles. However, as shown next, elementary aspects of operant behavior, when represented mathematically, yield the hyperbolic relationship first observed in pigeons pecking for grain.

In operant experiments, the subject, by definition, engages in two nonoverlapping activities and switches from time to time between the two. One activity is participation in the experimental task, for example, pressing a lever; the second activity is participation in "other" behavior, such as investigating the corners of the chamber, chewing on the houselights, resting, and so forth. Many researchers have drawn attention to this fundamental dichotomy (e.g., Mazur &

Hylsop, 1982; Nevin & Baum, 1980; Pear & Rector, 1979; Zeiler & Blakely, 1983). Their descriptions agree on the following points:

1. The amount of time spent in reinforced activity is a monotonic function of reinforcement rate.
2. During the reinforced activity, response units, either discrete unitary acts such as key pecks, or more complex multicomponent acts such as sequences of pauses and responses (Zeiler & Blakely, 1983), are emitted at a constant rate, referred to as "response tempo" (Nevin & Baum, 1980).
3. Tempo is independent of reinforcement rate.
4. Consequently, changes in overall response rate are due to changes in the amount of time devoted to the reinforced activity. Note that response rate is the total number of responses divided by the time during which the response can occur, whereas response tempo is the total number of responses divided by the amount of time devoted to the reinforced activity.

This two-state characterization of operant behavior is conveniently summarized by the expression:

$$\frac{B}{T_s} = \frac{M(TR)}{T_s}, \tag{4}$$

where B represents the total number of response units, M represents the tempo of the reinforced activity (the rate as measured while it is occurring, M = B/(TR)), (TR) represents the amount of time the subject spends at the reinforced activity, and T_s represents the total amount of time during which the response can occur, for example, session time less the time taken up in consuming the reinforcer.

Equation 4 summarizes some of the elementary features of operant behavior. If the logic of Clark's derivation is combined with these features, the matching law hyperbola (Equation 1) emerges, as follows.

1. Assume that the rate at which the subject switches from alternative activity into reinforced activity is proportional to (a) the rate of reinforcement and (b) the amount of time spent at alternative activity. That is:

$$\frac{S_1}{T_s} = \frac{v_1 R(T_s - (TR))}{T_s}. \tag{5}$$

where S_1 is the total number of switches to the reinforced activity, T_s is the duration of the experimental session (less time for consuming the reinforcer), R is total number of reinforcements, (TR) is the amount of time spent at the reinforced activity, and v_1 is the switching constant.

2. Assume that the rate of switching to alternative activities is proportional to the amount of time spent in reinforced activity:

$$\frac{S_2}{T_s} = \frac{v_2(TR)}{T_s}, \tag{6},$$

where S_2 is the total number of switches into alternative activity (S_1 and S_2 differ by no more than one 1 because there are only two possible states), and v_2 is the rate constant. Next, we need to ensure that the nominal quantities approximate the effective quantities.

3. The amount of reinforcement that the subject consumes is negligible in relation to the amount that it can consume, which is to say that deprivation conditions remain approximately constant throughout the session.
4. Changes in the reinforcer produces monotonic changes in response rate. For example, a more complex analysis is needed for many brain-stimulation reward experiments, because increasing the stimulation parameters can turn a purely positive reinforcer into a mixture of positive and aversive stimulation (e.g., Neeley & Stellar, 1983).
5. The moment-to-moment probability of the response unit is constant. For example, in variable-interval (Blough & Blough, 1968; Mazur, 1983) and variable-ratio (Mazur & Hylsop, 1982) schedules, the probability of the response unit is either approximately constant or varies unsystematically as a function of time.

Equations 4, 5, and 6 can be combined so as to yield a hyperbolic relationship between response rate and reinforcement rate. First, if there is a stable response rate, then Equation 4 implies that the amount of time devoted to reinforced activity is in equilibrium with the amount of time devoted to alternative activities. Second, if the amount of time spent at the reinforced activity and the amount of time spent at alternative activities are stable, then the rates of switching from one state to the other must be equal. Equations 5 and 6 describe the switching rates, so that a stable response rate implies:

$$v_1R(T_s - (TR)) = v_2(TR) \tag{7}$$

It is now a simple matter to find the relationship between the amount of time spent at reinforced activity, the dependent variable, and reinforcement rate, the independent variable. Merely rearrange Equation 7 as follows:

$$(TR) = \frac{T_sR}{R + v_2/v_1} \tag{8}$$

Equation 8 says that the amount of time spent at reinforced activity (TR) is a hyperbolic function of reinforcement rate (R). To find the relationship between

response rate and reinforcement rate, substitute for time at reinforced activity according to Equation 4:

$$\frac{B}{T_s} = \frac{MR}{R + v_2/v_1} \tag{9}$$

Equation 9 specifies the same relationship between response rate and reinforcement rate as does Herrnstein's matching law (Equation 1). Herrnstein (1970) arrived at his result empirically; Equation 1 fit the data. However, Equation 9 was formulated on the basis of elementary features of operant behavior and logic. The theoretical approach has the advantage of implying behavioral interpretations for the parameters.

In Equation 9 the ratio v_2/v_1 is equal in magnitude to the rate of reinforcement that maintains a one-half asymptotic response rate and is, thus, equal to R_e of the matching law (Equation 1). The derivation, therefore, supplies the meaning that R_e is a function of switching rates. The term in the numerator, v_2, is equal to the conditional rate of switching from reinforced activity into alternative activity ($v_2 = S_2/(TR)$), and v_1, in the denominator, is a function of the rate of switching in the opposite direction ($v_1 = S_1/(T_s - (TR))R$). Accordingly, the ratio v_2/v_1 scales the tendency of the subject to switch away from the reinforced activity, with lower values indicating a weaker tendency. This interpretation suggests that v_2/v_1 should change with treatments that alter the saliency of the reinforcer. Results from a number of experiments support this suggestion. In at least nine studies, the experimental manipulation altered the magnitude of v_2/v_1 without altering M. In each of these studies, the experimenter either changed deprivation conditions (Bradshaw, Szabadi, Ruddle, & Pears, 1983; Conrad & Sidman, 1956; Heyman & Monaghan, 1987; Logan, 1960; and see de Villiers & Herrnstein, 1976) or some aspect of the reinforcer (Bradshaw, Szabadi, & Bevan, 1978a; Guttman, 1954; Hamilton, Stellar, & Hart, 1985; Kraeling, 1961; Woods & Holland, 1964). For example, in an experiment with rats, substituting sucrose for glucose decreased v_2/v_1 by about 35% without systematically changing M (Guttman, 1954). Following the tradition in pharmacology, the notation v_2/v_1 will be simplified to a single term, K_r. Accordingly, Equation 9 becomes:

$$\frac{B}{T_s} = \frac{MR}{R + K_r} \tag{10}$$

In Equation 10, M is equal in magnitude to the asymptotic response rate and is, thus, also equal to k of the matching law (Equation 1). The derivation supplies the meaning that the response-rate asymptote is a function of response tempo. If this is correct, then the response rate asymptote should vary with manipulations that alter the temporal characteristics of the reinforced response. The literature shows the following results. In four studies (Bradshaw, Szabadi, & Ruddle, 1983; Hamilton, Stellar, & Hart, 1985; Heyman & Monaghan, 1987; McSweeney, 1978) the experimental manipulation led to systematic changes in

M that were not accompanied by changes in K_r. In each of these studies the experimenter changed the physical characteristics of the manipulandum that defined the reinforced response. For example, in an experiment with pigeons, McSweeney (1978) found that replacing a response key (that the pigeons pecked) with a treadle (that the pigeons kicked) decreased M by about 67%, but produced no systematic changes in K_r.

In addition to studies in which the experimental manipulation changes just one or the other parameter, there are experiments in which the manipulation changed both M and K_r. These studies are featured in comments in the final section of this chapter. The next section describes the effects of drugs on M and K_r.

DRUG-INDUCED CHANGES IN REINFORCED BEHAVIOR: A MATCHING LAW ANALYSIS

Drugs that are used in the treatment of schizophrenia, called neuroleptics, decrease reinforced responding in laboratory animals. For example, chlorpromazine, the first widely used antipsychotic, reduces or eliminates behavior maintained by food, water, and brain-stimulation reward in pigeons, rats, monkeys, and other laboratory animals (Wise, 1982). Neuroleptics also share a common pharmacological property: They block dopamine receptors. This biochemical trait may be linked to the changes in response rate. For example, drugs that enhance the availability of dopamine, such as amphetamine, increase response rates, whereas lesions in dopamine-rich areas of the brain decrease response rate (Wise, 1982).

The first experiment examines the effects of two neuroleptics, chlorpromazine and pimozide, on M and K_r. The second experiment examines the effects of amphetamine on these two parameters.

The experiments were conducted in a standard operant conditioning chamber. There was a lever for responses, an opening in the chamber wall that provided access to a water dipper, and a tone source and light that signaled the reinforcement contingencies (details of the apparatus are in Heyman & Seiden, 1985). The subjects, 8 rats in the chlorpromazine study and 7 in the pimozide study, were approximately 2.5 months old at the start of the experiments, were housed two to a cage, and were put on a water-deprivation regime in which they received a ration of 25 ml of water once per day plus the amount earned in experimental sessions (about 90 to 100 0.025-ml portions of water).

The experimental design was quite simple. Baseline (nondrug) estimates of M and K_r were compared to drug-session estimates of M and K_r. Rats served as subjects, 7 or 8 to a study. They were deprived of water for the 23 hours just preceding the session, and the reinforcer was a small portion of water. Each session consisted of five 7-minute reinforcement periods, with each period providing a different reinforcement rate, according to a variable-interval schedule. The different reinforcement rates, which ranged from about 20 to 700 an

hour, engendered a wide range of response rates. Drug injections occurred twice a week. Each subject received three doses, and each dose was repeated three times. Details of the apparatus, procedure, and statistical methods are in earlier reports (Heyman, Kinzie, & Seiden, 1986; Heyman & Seiden, 1985).

Figure 8.6 shows the group median response rates. Both chlorpromazine and pimozide produced dose-dependent decreases in responding. If these results are compared with those displayed in Fig. 8.2, it can be seen that the lowest dose of each drug produced a pattern of response-rate decreases that are similar to those that accompany an increase in the rate of reinforcement necessary for a one-half asymptotic response rate. According to the derivation of the matching law this means that low doses of pimozide and chlorpromazine decreased reinforcement efficacy. At the higher doses the pattern of response-rate changes reflects changes in both the reinforcement and motor parameters. For example, the response-rate asymptotes appear to have been reduced, and the curves seem flatter.

In Fig. 8.7 the median response rates are displayed so that the slope of the

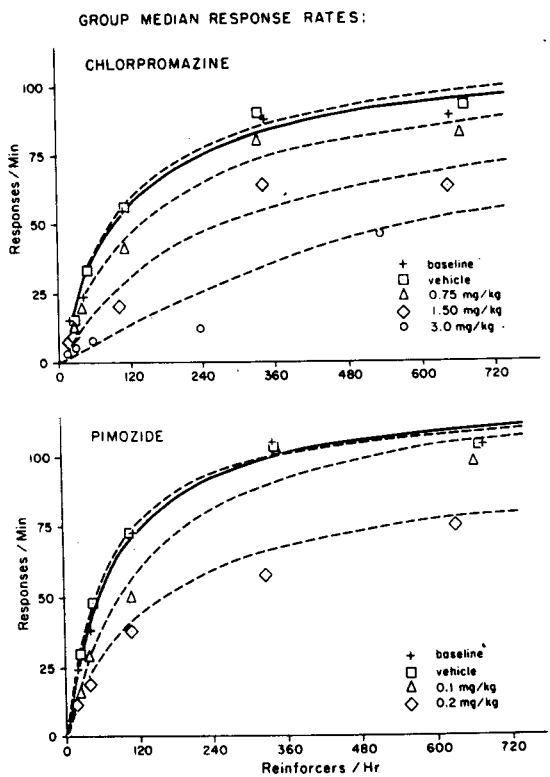

FIG. 8.6. The effect of chlorpromazine and pimozide on response rate.

fitted line corresponds to a transformation of K_r. This transformation ($-K_r^{-1}$) is convenient, because in this form changes in slope directly represent changes in reinforcement efficacy, and the intersection of the fitted line with the x-axis is equal to the response-tempo parameter (M). This type of graph, called a *Scatchard plot* (Scatchard, 1949) is widely used in biochemical studies, but has only just recently been introduced to behavioral research (Heyman, Kinzie, & Seiden, 1986). The change in slope show that the lowest dose of each drug decreased reinforcement efficacy without affecting response tempo, whereas the change in the x-axis intersection shows that the higher doses decreased response tempo (as well as produced further decreases in reinforcement efficacy).

Figures 8.8 and 8.9 show session-by-session results for two representative

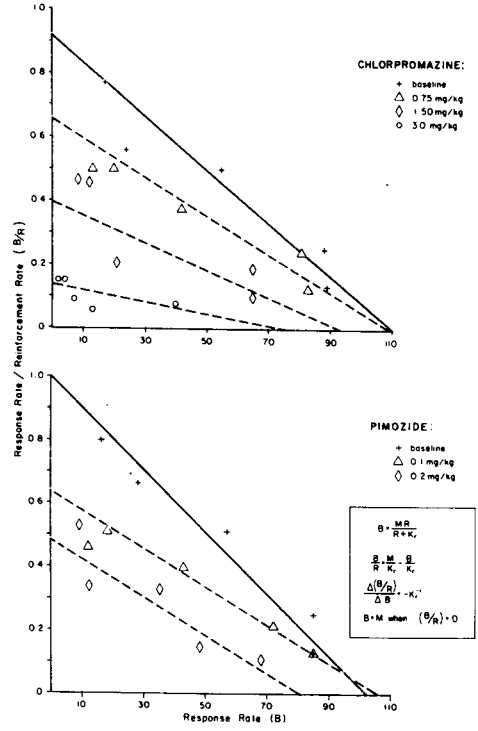

FIG. 8.7. A Scatchard plot analysis of the effects of chlorpromazine and pimozide on the relationship between response rate and reinforcement rate. The x-axis corresponds to response rate, and the x-axis coordinate of the fitted line at $y = 0.0$ is equal to M (the response-rate asymptote). The y-axis corresponds to the ratio of response rate to reinforcement rate, and the slope of the fitted straight line is equal to $-Kr^{-1}$. Therefore, a change in slope is a change in the rate of reinforcement that produced a one-half asymptotic response rate.

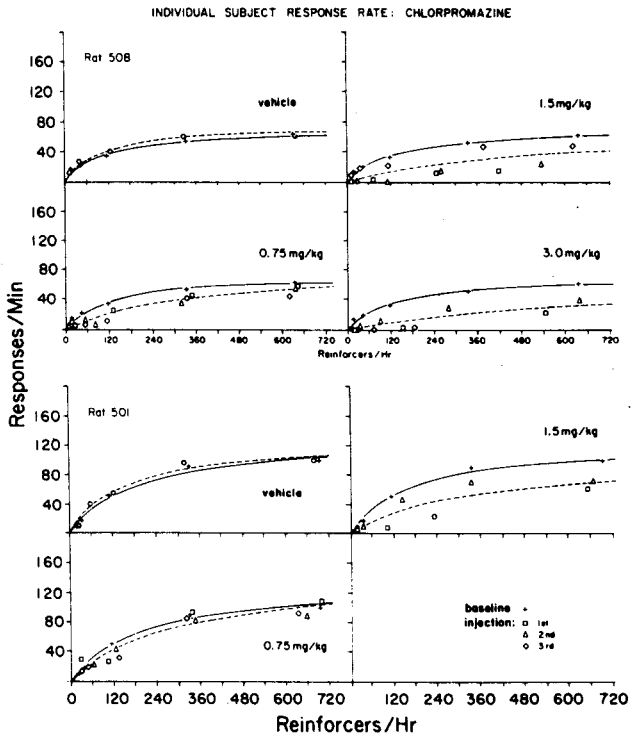

FIG. 8.8. The effect of chlorpromazine on response rate for two representative subjects. In the panels showing drug effects, the different symbols distinguish the three sessions that each dose was given. The crosses show the median response rate for the 18 baseline sessions, and the open squares show the median response rates for the 5 or 6 vehicle session. There are no results in the panel for the 3.0 mg/kg dose for Rat 501, because this dose eliminated responding in this subject.

subjects from each group. There is no evidence of order effects, but there were individual differences in sensitivity to drug. For example, the lowest chlorpromazine dose consistently decreased response rate in Rat 508, but not in Rat 501 (also compare Rat 17 with Rat 21 in the pimozide group).

The second study examined the effects of amphetamine on response rate. Amphetamine produces a variety of pharmacological and behavioral changes, and some are just the opposite of those produced by chlorpromazine and pimozide. For example, amphetamine increases the availability of dopamine at postsynaptic receptors; it attenuates neuroleptic-induced catelepsy; and at low doses it increases reinforced responding. According to some researchers, an important component of amphetamine's behavioral effects is a change in response topography, for example, the duration of the response (Lyon & Robbins,

1975). However, there is also evidence that amphetamine enhances the efficacy of the reinforcer maintaining the response. For example, in brain-stimulation experiments, amphetamine decreases the level of current necessary to maintain responding (Zarevics & Setler, 1979). The experimental procedure for the amphetamine study was the same as in the chlorpromazine and pimozide experiments.

Figure 8.10 shows the changes in average response rate as a function of drug dose. At doses between 0.25 and 1.0 mg/kg, amphetamine increased response rates, and the relative magnitude of the increases was inversely related to reinforcement rate. For example, the 0.50 mg/kg dose increased response rate by 86% in the lowest reinforcement-rate component and by 15% in the highest reinforcement-rate component. The 2.0 mg/kg dose produced a much different pattern of response-rate change. In each of the three lowest reinforcement-rate components, response rate decreased, whereas in the highest reinforcement-rate component response rate increased. The 3.0 mg/kg dose had variable effects. Two subjects stopped lever pressing, two pressed at lower rates in each schedule, and four pressed at lower rates in all but the richest schedule. Because the

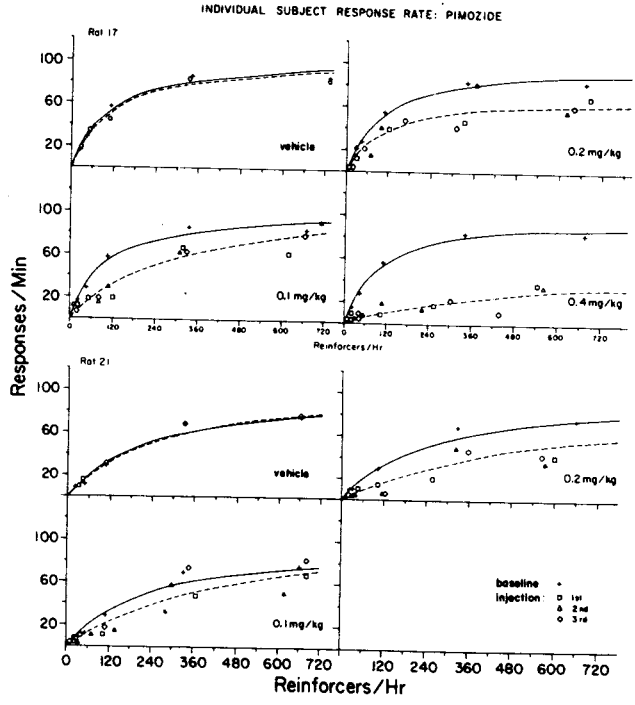

FIG. 8.9. The effect of pimozide on response rate for two representative subjects. The format is the same as in Fig. 8.8.

between-subject variability was so large at this dose, the corresponding symbols in Fig. 8.10 represent medians rather than averages.

Figure 8.11 shows a Scatchard plot analysis of the average response rates. The lowest dose of amphetamine increased the slope of the fitted line without sizably altering the x-axis intersection. This is just the opposite of what the lowest dose of pimozide and chlorpromazine did. According to the definitions supplied by the derivation of the matching law, the increase in slope (change in k_r) means that amphetamine increased reinforcement efficacy without affecting motor performance. The 0.50 and 1.0 mg/kg doses were not as selective. They increased the slope and the x-axis intersection. In contrast, the two highest doses tested, 2.0 and 3.0 mg/kg, had antagonistic effects on the parameters of the Scatchard plot: The slope decreased but the magnitude of the x-axis intersection increased. According to the derivation, this means that reinforcement efficacy decreased, but response tempo increased. The lower panel of Fig. 8.10 shows the pattern of response rate changes that corresponds to these parameter changes. Response rates at the lower reinforcement rates decreased, whereas response rate at the highest reinforcement rate stayed about the same or increased.

Figure 8.12 shows the average response rates for a respresentative subject in the amphetamine study. As with chlorpromazine and pimozide, there were individual differences in drug sensitivity, but a similar overall pattern of behavioral change. Lower doses increased response rate at the lower reinforcement rates, and higher doses were more likely to increase response rates supported by higher reinforcement rates. (Occasionally, high doses produced small changes in response rate because of the nonmonotonic relationship between drug dose and

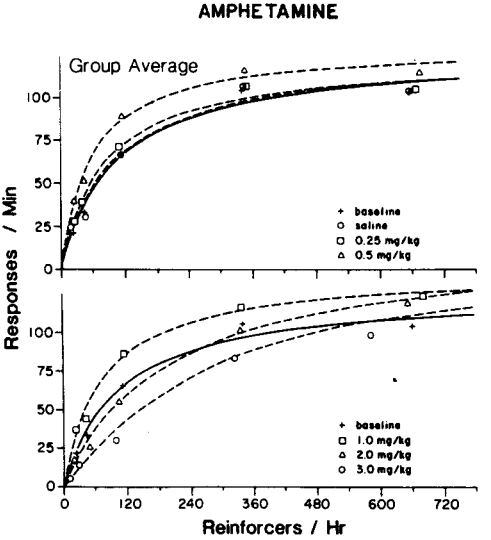

FIG. 8.10. The effect of amphetamine on response rate.

shifts in the response-rate asymptote and because of the counteracting effects of an increase in response-rate asymptote and a decrease in reinforcement efficacy.)

A number of previous studies suggested that neuroleptics decreased the reinforcing efficacy of normally rewarding stimuli (e.g., Wise et al., 1978), whereas other studies supported the view that the response-rate decreases were due to motor deficits (e.g., Ettenberg, Koob, & Bloom, 1981). Similarly, there were experiments that supported the hypothesis that amphetamines enhanced reinforcers (e.g., Zarevics & Setler, 1979), and there are those that suggested that amphetamines changed the physical dimensions of the response (e.g., Lyon & Robbins, 1975). The matching law provides criteria for choosing between the different interpretations. In the present studies, low doses of amphetamine and the two neuroleptics affected only the rate of reinforcement necessary for a one-half asymptotic response rate. Higher doses affected both the response asymptote and the reinforcement requirement. According to the derivation and the empirical results reviewed above, these parameter shifts imply that the response-rate changes following low drug doses were due entirely to a change in reinforcement

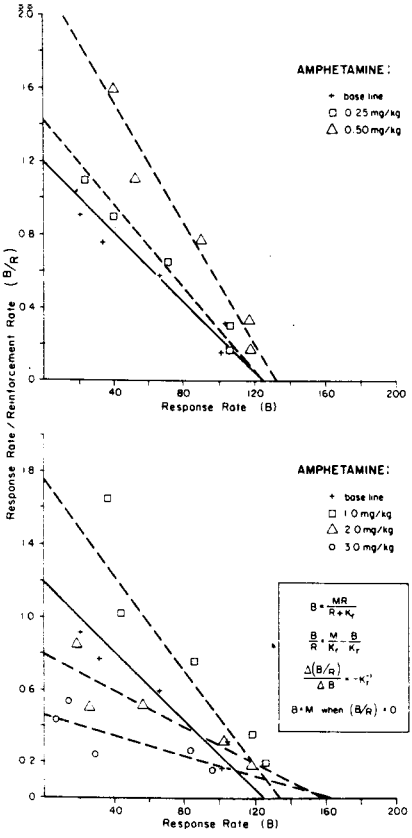

FIG. 8.11. A Scatchard plot analysis of the effect of amphetamine on the relationship between response rate and reinforcement rate. The format is the same as in Fig. 8.7.

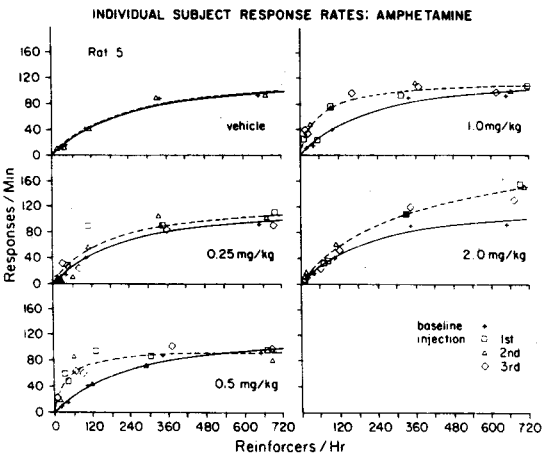

FIG. 8.12. The effect of amphetamine on response rate in a representative subject. Data points show the average response rate. There are no drug results for the 3.0 mg/kg dose, because this dose eliminated responding in this subject.

efficacy, whereas high-dose response-rate changes were due to motor and reward factors.

SUMMARY AND DISCUSSION

The derivation of the matching law presented in this chapter is based on analogies between how biochemical molecules affect cells and how reinforcement affects behavior. The two basis associations are:

1. Just as the strength of the physiological response reflects a balance between occupied and unoccupied receptors, the rate of the reinforced response reflects a balance between time spent in reinforced activity and time spent in alternative activity; and
2. Just as a stable number of bound receptors implies that the binding rate equals the dissociation rate, a stable response rate implies that the rate of switching into reinforced activity equals the rate of switching into alternative activity. These analogies produced the results that response rate is a hyperbolic function of its reinforcement rate and that the two parameters of the hyperbola measured two independent components of response rate: response topography and reinforcement efficacy.

Herrnstein (1974) suggested similar interpretations of the parameters of Equa-