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# THEORETICAL REVIEW

# Rate-Dependent Effects of Drugs: A Review of the Literature[1]

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SANGER, D. J. AND D. E. BLACKMAN. *Rate-dependent effects of drugs: a review of the literature.* PHARMAC. BIOCHEM. BEHAV. 4(1) 73–83, 1976. – It has been claimed that the effects of amphetamines on schedule-controlled behavior depend to a large extent on the rate of responding in control conditions. A review of the literature shows that there is considerable support for this hypothesis if the behavior is not suppressed by aversive procedures, is not under the control of powerful external stimuli or is not occurring very infrequently. The extension of a rate-dependency hypothesis to the effects of other drugs has less empirical support, however. It is argued that many of the procedures used for studying rate-dependent drug effects do not provide critical tests of the hypothesis. If it is to be shown unequivocally that it is rate of operant responding which determines the behavioral effects of drugs, procedures are needed in which other variables such as reinforcement frequency are more adequately controlled.

Drugs Rate-dependence Schedule-control Operant behavior

OPERANT behavior is defined as behavior which is maintained by its consequences. By manipulating the relationship between responses and their consequences, i.e., the schedule of reinforcement, it has been found that a variety of patterns of behavior can be generated and maintained in experimental subjects [34]. Since these patterns are predictable from a knowledge of the reinforcement schedule and can be maintained over relatively long periods of time they provide behavioral baselines eminently suitable for use in the study of psychoactive drugs. More practical advantages offered by operant behavior are that procedures can be easily automated and have been found appropriate for a number of species of experimental animals [105].

One of the most important findings which has emerged from research in this area is that schedules of reinforcement are fundamental determinants of the effects of drugs. Sidman has argued that "Drug effects depend not only on an animal's physiological state and the dose of the drug, but also on the environmental contingencies maintaining its behavior at any given time" [93]. It now seems that in fact the different patterns of behavior which are maintained by the schedules of reinforcement give rise to this differential sensitivity to drugs [54]. This research is of considerable importance since attempts are often made to relate the actions of psychoactive drugs to intervening variables such as cognitive or emotional processes. For example, drugs are often classified in general terms (e.g., as stimulants, depressants, anxiolytics etc.) and their effects have been related to such processes as motivation (e.g., [78]) or inhibition (e.g., [12]). The importance of the research described here, however, lies in the demonstration that the behavioral actions of drugs are frequently predictable simply from a knowledge of the patterns of behavior themselves.

Dews provided one of the first demonstrations of the importance of the schedule of reinforcement as a determinant of drug effects. In the first of his experiments pigeons obtained food either with every 50th peck (a fixed-ratio 50 schedule) or with the first peck after 15 min had elapsed from the previous presentation of food (a fixed-interval 15 min schedule) [21]. These two schedules generated characteristic patterns of responding [34] which are quite different. Dose-response curves were obtained for the effects of pentobarbital on these patterns of behavior, and these curves were found to differ between the two schedules. Not only did the magnitude of the effect of any particular dose depend upon the schedule but even the direction of the behavioral change produced by certain doses, i.e., whether responding was increased or decreased, differed between the two schedules. Thus, the effects of pentobarbital were clearly schedule-dependent. However, it was not clear from this experiment which specific aspects of the performances generated by the two schedules were important in determining the differential drug action.

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## ORIGINAL FORMULATION OF THE RATE-DEPENDENCY HYPOTHESIS

Dews subsequently investigated the effects of several drugs on patterns of operant behavior maintained in pigeons by a number of different schedules of reinforcement [22, 23, 24]. The results of these experiments were important as further demonstrations of the significance of schedules in determining the behavioral effects of drugs. For example, in one of these studies [24] ratio and interval schedules were again used; a fixed-ratio 50 and a variable-interval 1 min (i.e., a peck produced food every minute on the average) generated high rates of pecking (over 60 responses/min) while a fixed-interval 15 min and a modified fixed-ratio 900 were used to generate much lower overall rates. After administration of several doses of methamphetamine (0.0625–1.7 mg) the low response rates were substantially increased by lower doses which had little effect on the high response rates. The higher doses decreased response rates maintained by all four schedules.

On the basis of these and other results Dews suggested for the first time that an important determinant of the effects of amphetamines was the control rate of responding generated by any given schedule [25]. Thus he argued: "... the effects of amphetamines seem to be determined largely (though, of course, not exclusively) by the frequency of occurrence of the response ..." In describing this relationship between response rate and the action of amphetamines Dews may be said to have provided the first exposition of what we shall refer to as the rate-dependency hypothesis which maintains that the effects of amphetamines on operant behavior are inversely related to the response rate under control conditions. Thus, low rates of responding may be considerably increased by doses of these drugs which have little effect on, or may even decrease, higher rates. This hypothesis is a case of the Law of Initial Values which stresses the importance of such relationships in many areas of biology [120]. More recently, rate-dependency has become more widely used both as a descriptive and sometimes as an explanatory principle in behavioral pharmacology in general [54].

## RATE-DEPENDENT EFFECTS OF AMPHETAMINES

### *Comparisons Between Response Rates Maintained by Different Schedules*

As described above, Dews [24] originally studied the effects of methamphetamine on responding maintained by four different schedules of reinforcement and found that low response rates generated by some schedules were increased by doses which had very little effect on higher response rates generated by other schedules. Generally consistent results have been obtained in many other experiments which are reviewed in this section.

It is possible to differentially reinforce low rates of responding (2–10 responses/min) by means of a schedule (DRL) in which reinforcement is obtained only by a response which occurs at least a specified time after the preceding response. The response rates of rats maintained by such a schedule are markedly increased by d- or dl-amphetamine [52, 92, 93] and d-amphetamine has been shown to have similar effects in pigeons [41] and humans [27]. On the other hand high response rates maintained by fixed-ratio or variable-interval schedules (up to 200 responses/min) are generally decreased by similar doses of amphetamines: again such effects have been observed in several species including rats [8, 46, 48, 63, 84, 86, 108] and pigeons [18, 41, 47]. Intermediate response rates can be maintained by fixed-interval schedules with relatively short interval values. Although low doses of amphetamines frequently increase such rates [5, 20, 48, 63, 86] this effect is generally considerably smaller than that observed when responding is maintained by differential reinforcement of low rate schedules.

In general, the experiments referred to above have made use of food or water as reinforcers. Similar drug effects have been observed in experiments which have used other reinforcers. Relatively low response rates can be maintained by schedules in which every response is followed by a reinforcer and amphetamines have been found to facilitate such responding when the reinforcement is the delivery of heat [115], light onset [36,44] or electrical stimulation of the brain [28,95], or when responding avoids the delivery of electric shocks [50, 93, 99]. It is also possible under some conditions to maintain the behavior of monkeys by schedules of shock presentation [55,100], and again the effects of amphetamines on this behavior appear to depend upon the response rate [65, 66, 67].

The results described so far in this section are clearly consistent with the hypothesis that the effects of amphetamines are inversely related to the rate of responding in control conditions. However, such comparisons between different experiments cannot be considered to be tests of the hypothesis because so many other variables differ in these different experimental situations [117]. For instance, differences in species or strain of subjects or procedural differences may give rise to differential drug effects. There are a number of procedures which have been used, however, to minimise the importance of such variables.

One such procedure is to maintain animals on a specified schedule of reinforcement and then to select animals which happen to emit high or low response rates. Ray and Bivens [86] selected two rats with relatively high response rates (approximately 150 responses/min) on a fixed-ratio schedule and two rats with relatively low rates (approximately 50 responses/min). When the effects of a range of doses of dl-amphetamine were compared it was found that the response rates of the low rate responders were increased by a dose (0.25 mg/kg) which had little effect on the response rates of the two animals selected for high rates. Higher doses (1, 3 mg/kg) had greater depressant effects on the high-rate responders than on the low-rate responders. Although these results are clearly consistent with the response-rate hypothesis, the effects of the same drug on rats selected for high (approximately 30 responses/min) or low (approximately 17 responses/min) response rates on a variable-interval schedule were not. In this case the high rates were decreased to a smaller extent than the lower rates by certain drug doses (5, 7 mg/kg).

Other experiments in which rats have been selected as high-rate or low-rate responders have also obtained variable results. While some researchers [48,121] have obtained results consistent with the rate-dependency hypothesis, Weissman [119] did not find a significant correlation between the stimulant action of a dose of d-amphetamine and the baseline response rate of rats on a shock avoidance schedule.

A second and probably more satisfactory technique for relating drug effects to control response rate within an experiment is to maintain animals on multiple schedules of

reinforcement which involve different response rates during different components. Such procedures have been widely used in behavioral pharmacology and in particular a number of investigators have studied the effects of drugs on behavior maintained by multiple fixed-ratio fixed-interval schedules with pigeons [3, 83, 88], rats [14] and primates [9, 17, 53].

When such schedules are used with pigeons it has been shown on several occasions that administration of amphetamines produces an increase in the rate of pecking on the fixed-interval component at doses which either do not affect or which slightly depress responding on the fixed-ratio component [69, 70, 71, 88, 94]. Since pecking rates during interval components are generally much lower than those during the ratio components, this result is entirely consistent with the rate-dependency hypothesis. For instance, McMillan [69, 70, 71] studied the effects of several drugs, including d-amphetamine, on the behavior of pigeons maintained by multiple fixed-interval fixed-ratio schedules. When the interval value was 5 min and the number of responses required to complete the ratio was 30, overall response rates during these two components were approximately 33 responses/min and 120 responses/min, respectively. While the lower fixed-interval response rates were increased by all the doses of d-amphetamine used (0.3–10 mg/kg), fixed-ratio response rates were affected little by the drug except at the highest dose when they were reduced by approximately 50 percent. When the parameters of both the fixed-interval and the fixed-ratio components were changed, the effects of d-amphetamine were still dependent upon response rate. When the fixed-interval size was decreased to 1 min the higher overall response rates generated became considerably less sensitive to the stimulant actions of the drug and more sensitive to the depressant actions. An opposite effect occurred when fixed-ratio response rates were decreased by increasing the ratio size first to 150 and then to 250.

*Detailed Analysis of Performance Maintained by Fixed-interval Schedules*

As indicated above, multiple schedules of reinforcement are very useful for demonstrating rate-dependent drug effects but they are limited in that they can provide only a relatively small number of different response rates. It is possible, however, to obtain a range of different response rates against which the effects of a drug can be assessed by a detailed analysis of performance maintained by fixed-interval schedules since performance maintained by such schedules is characterised by a gradually increasing response rate during each interval [34]. This procedure has recently found favor as a method for investigating rate-dependent drug effects.

Smith [94] studied the effects of d-amphetamine on the responding of pigeons maintained by a multiple schedule of which fixed-interval formed one component. The effects of the drug were analysed in terms of the response rates during the first and last 1 min periods of the 5 min intervals. The very low rates during the initial 1 min periods were substantially increased by doses of d-amphetamine which, however, decreased the much higher response rates during the 1 minute periods which terminated each interval. Response rates maintained by the other component, which was a fixed-ratio 33, were also decreased by the drug.

Similar results were obtained by McMillan [69, 70, 71]. In these experiments the intervals were divided into 10 segments and the effects of d-amphetamine assessed in terms of the mean response rates during each of these segments. Again, low response rates during early segments were increased by doses of d-amphetamine which had a much smaller effect on the higher response rates during later segments.

Similar drug effects have been observed in primates also responding on fixed-interval schedules. Kelleher and Morse [53] trained monkeys on such a schedule either to obtain food or to escape from stimuli which were occasionally paired with electric shocks. The fixed-interval schedule formed one component of a multiple schedule, of which the other component was a fixed-ratio schedule. When d-amphetamine was administered, it was found that its effects did not depend on the nature of the reinforcer which maintained behavior, i.e., food or escape from the conditioned aversive stimulus. In both cases, however, there were differences between the effect of the drug on responding during the fixed-interval component and its effect on fixed-ratio behavior. As in other experiments reviewed in the preceding section, low doses of the drug were found to increase the overall fixed-interval response rates while exerting little effect on the higher overall fixed-ratio response rates. In a later paper [54] the effects of the drug at one dosage (0.3 mg/kg) on responding during the fixed-interval components were analysed further by dividing the intervals into 10 successive 1 min segments. The percentage of control response rate produced by this dose of d-amphetamine was then plotted on a log scale against the average rate of responding during each of these segments. The resulting function closely approximated a straight line of negative slope, indicating that the changes in response rate on the fixed-interval schedule produced by the drug were directly related to the control rate of responding. Thus, the lower response rates observed in the earlier segments of the fixed-interval showed the greatest percentage increase. The higher rates observed in later segments showed a smaller percentage change. The highest response rates were decreased after administration of the drug, and thus the line relating the log of the percentage of control response rate to the log of the baseline rate passed to points below 100 percent on the former scale. The depression of overall fixed-ratio response rates produced by the same dose was also found to be represented by points which lay close to the extrapolation of the line plotted for fixed-interval behavior, thereby further supporting the view that response rate per se acts as a determinant of the drug effects despite the formal differences between the schedules.

In some conditions it is possible to maintain the behavior of monkeys by schedules of shock presentation [55,100]. McKearney [65] has used a fixed-interval schedule of shock presentation to investigate the effects of d-amphetamine on the behavior of monkeys. The results were again analysed in terms of the response rates during successive minutes of the fixed-intervals. The schedule maintained typical fixed-interval performance consisting of a pause after each shock followed by an accelerating response rate up to the next shock. As with fixed-interval schedules involving food presentation, d-amphetamine increased the low response rates during early segments of the intervals while having a much smaller effect on higher response rates during later segments. With a dose of 0.3 mg/kg of d-amphetamine there was a linear relationship

between the logs of control response rates and the logs of percentage of control rates. This relationship was similar to that described by Kelleher and Morse [54]. More recently, McKearney [67] compared the effects of a number of drugs on the responding of squirrel monkeys under fixed-interval schedules of either food or shock presentation. The drug effects were again analysed in terms of average response rate in successive segments of the fixed-interval periods and the effects of d-amphetamine were found to be similar on both schedules.

Analyses of the effects of amphetamine on responding during successive segments of fixed-intervals have also been used in experiments with rats [30, 31, 48]. Evans [30] studied the effects of methamphetamine with a number of procedures including a fixed-interval schedule of food reinforcement. The intervals were divided into quarters and when the log of the percentage of control response rate produced by the drug was plotted against the log of the control rate a straight line was again obtained. It is worth noting that in this experiment two of the doses of methamphetamine to which this analysis was applied (0.8, 1.6 mg/kg) produced a reduction in overall response rate rather than an increase as is the case in most of the experiments using pigeons or monkeys as subjects.

In a later experiment Evans, *et al.* [31] applied similar analyses to the fixed-interval responding of rats during either the light or the dark periods of their diurnal cycle. Similarly shaped relationships between control response rates and the effects of methamphetamine were obtained during both the dark and the light periods although the points did not fit on the same line. However, lower overall response rates during the light period were less sensitive to the stimulant action of a low dose of the drug than the higher rates during the dark. As the authors point out, this aspect of their results is certainly not consistent with a simple rate-dependency hypothesis. An analysis of the fixed-interval responding of rats has also been used to demonstrate rate dependent effects of a dose (1.8 mg/kg) of a different isomer of amphetamine (d-amphetamine) [48].

## EXCEPTIONS TO RATE-DEPENDENT EFFECTS OF AMPHETAMINES

This section reviews a number of apparent exceptions to the hypothesis that the behavioral effects of amphetamines may be predicted simply from the control rate of operant responding. Evidence for these constraints on the generality of the hypothesis is consistently to be found in three areas of research discussed below, and this section ends with a brief discussion of some less consistent anomalies.

### *Responding under Strong Stimulus Control*

One situation in which the effects of amphetamines do not seem to be solely determined by baseline response rate involves procedures in which responding is powerfully controlled by external stimuli. It appears that behavior which is under such strong stimulus control is relatively insensitive to disruption by a number of drugs. Laties and Weiss [57] maintained pigeons on a multiple fixed-interval 5 min schedule of food reinforcement. In one component 5 different stimuli were presented to the birds during the 5 successive minutes of each interval; this procedure was referred to as an added clock. When d-amphetamine was administered to the birds it was found to interfere with the pattern of responding during the component with no clock. However, responding during the component with the added clock was disrupted to a much smaller extent.

The results of this study were somewhat ambiguous, however, since the clock and no-clock conditions differed both in the extent to which behavior was under stimulus control and also in the overall response rates. Laties [56] followed up this research by using a procedure in which, in order to obtain reinforcement, pigeons were required to switch to a second key after having completed a certain number of responses on the first key. In one condition a change in the color of the key light signalled the completion of the ratio requirement on that key. In a second condition no such stimulus was presented. Because of the ratio requirement on the first key, overall response rates remained the same in both conditions but nevertheless responding under stimulus control was disrupted to a much smaller extent by a number of drugs, including d-amphetamine, scopolamine and chlorpromazine.

Carey and Kritkausky [11] have also been able to demonstrate that the actions of d-amphetamine are dependent upon the extent to which behavior is under external stimulus control. In this experiment a dose of the drug (1 mg/kg) increased the low response rates of rats maintained on a differential reinforcement of low rate schedule but if the availability of reinforcement was signalled this rate-increasing effect did not occur.

More recently Leander and McMillan [59] have investigated interactions between the rate-dependent actions of drugs and stimulus control. Pigeons pecked a key for food on either multiple or mixed fixed-interval fixed-ratio schedules. On the multiple schedule different key lights signalled which of the two schedule components was in operation whereas a single light was presented throughout the mixed schedule. When fixed interval responding was analysed during successive segments of the intervals it was found that the effects of d-amphetamine were rate-dependent in both the multiple and mixed conditions. There were, however, some differences between the drug effects during the two conditions suggesting that the rate-dependent actions of amphetamines can be modulated not only by the dose of drug but also by the extent to which responding is under external stimulus control.

### *Responding Suppressed during Stimuli Associated with Electric Shocks*

It is possible to maintain operant responding at low rates by presenting stimuli during which responses lead to electric shocks (punishment procedures [2]) or which end with non-contingent electric shocks (conditioned suppression procedures [29]). If the effects of amphetamines were rate-dependent in these situations, it would be expected that responding maintained at low rates would be facilitated by drug administration. However, although there have been some demonstrations of such effects in punishment [77] and conditioned suppression [10] procedures, most of the published research has obtained very different results.

Brady [6] reported that the relatively low rates of responding during a stimulus which preceded an unavoidable shock were decreased further after the administration of dl-amphetamine at doses which increased the higher rate of responding in the absence of the stimulus. There have

also been several reports that responding maintained at low rates because of a punishment procedure may be either unaffected or further suppressed by amphetamines [16, 40, 45, 49, 81].

These results appear to lead to the conclusion that the effects of amphetamines on suppressed responding do not depend simply upon the control response rate [54]. However, it seems that in some circumstances the rate-dependency hypothesis can be applied to the effects of amphetamines on punished responding. McMillan and his colleagues [35,72] studied the effects of punishment in pigeons maintained on either multiple fixed-interval fixed-interval or fixed-interval fixed-ratio schedules. Superimposed on either one or both components was a punishment procedure in which every response was punished by an electric shock. This considerably reduced overall response rates but nevertheless the typical pattern of responding during the fixed-interval components was maintained. The effects of a number of drugs were assessed by dividing the intervals into segments. Although there was little evidence that d-amphetamine increased the overall rates of responding during punishment components, the effects of this drug on responding within the intervals often appeared to be rate-dependent as the very low response rates at the beginning of the intervals tended to be increased. The results of these experiments appear to be variable but the authors concluded nevertheless that control response rate is an important determinant of the effects of d-amphetamine on punished behavior.

*Responding Maintained at Very Low Rates*

The effects of amphetamines also appear not to be consistently rate-dependent in the case of very low overall response rates. Such effects occur with rates of responding which are lower than those normally maintained by schedules which differentially reinforce low rates. Verhave [109], for example, studied the effects of methamphetamine on the unreinforced lever pressing of rats. The drug did not consistently increase response rates above the very low control response rates. Similarly Dews [22] reported that methamphetamine did not increase the infrequent responding of pigeons during a stimulus which signalled an extinction component of a multiple schedule. A number of other experiments, however, have shown that low response rates during stimuli associated with extinction may be facilitated by amphetamines [14, 77, 118]. Kelleher and Morse [54] have pointed out that these differences may be related to differences in procedure.

When fixed-intervals are segmented to give a range of different response rates, as described in a previous section, responding during the first segment after reinforcement is typically at a very low rate. Again these rates are not always increased to the extent which would be predicted on the basis of a simple rate-dependence function. McMillan [69] observed such an effect after administration of d-amphetamine and suggested that a certain minimum tendency to respond was necessary before the rate-dependent effects of the drug become apparent.

*Other Anomalies*

In discussing the evidence for rate-dependent effects of amphetamines (previous section) some anomalous results have been mentioned when these have arisen from experiments whose results are generally supportive of the rate-dependency hypothesis. There have been several other experiments which have reported results not entirely consistent with the rate-dependency hypothesis.

Although operant responding maintained by schedules which differentially reinforce low response rates is generally substantially increased by administration of amphetamines, it appears that pigeons are much less sensitive than rats to this rate-increasing effect. Hearst and Vane [47] were unable to demonstrate a consistent stimulant action of d-amphetamine (0.25–8.0 mg/kg) with pigeons responding on such a schedule. McMillan and Campbell [73] also reported that d-amphetamine (0.3–3.0 mg/kg) did not generally increase the response rates of pigeons maintained by a similar schedule. There have also been failures to obtain an amphetamine induced facilitation of low response rates in humans [97,116]. Thus, species differences appear to be important.

Glick and Muller [42] reported that very low doses of d-amphetamine (below 0.5 mg/kg) increased the already high response rates (up to 100 responses/min) of rats maintained by a fixed-ratio 30 schedule. However, these researchers measured the drug effects only on the overall response rate and it is possible, therefore, that the stimulant action may have been related to a decrease in the duration of the pauses after reinforcement which are typically observed on fixed-ratio schedules [34], with the response rate itself being unaffected. As yet it appears that this facilitation of fixed-ratio responding has not been replicated.

## RATE-DEPENDENT EFFECTS OF OTHER DRUGS

As was pointed out earlier, the rate-dependency hypothesis was formulated specifically in the context of the effects of amphetamines on operant behavior [25]. Nevertheless, since the original formulation of the hypothesis several researchers have claimed that the effects of a variety of other drugs on schedule controlled behavior also depend critically on control response rate.

*Barbiturates and Minor Tranquilizers*

Although barbiturates have depressant effects at higher doses, they have also been shown to exert rate increasing effects on behavior maintained by several schedules of reinforcement. These include schedules which differentially reinforce low response rates [52, 101, 102]. However, it appears that high response rates generated by schedules such as fixed-ratios are even more sensitive to this facilitatory effect than are lower rates [21, 88, 111].

This is clearly inconsistent with the view that low response rates are more sensitive to the facilitatory effects of barbiturates than are higher rates but it appears, nevertheless, that the effects of barbiturates on responding maintained by fixed-interval schedules can be described as rate dependent. Dews [26] used a fixed-interval 500 sec schedule to control the key pecking of pigeons. A light was presented during alternate 50 sec periods of each interval. Since the first presentation of the light was always during the first 50 sec of each interval, and it was therefore never present when reinforcement was obtained, response rates in the presence of the light were in general lower than those in its absence. Following the administration of several doses of amobarbital response rates were found to be increased. Division of the intervals into 50 sec segments showed that

low rates were increased to a greater extent than high rates, regardless of whether the light was present or absent.

More recently McKearney [64] has described the results of a similar experiment. Pigeons pecked a key to obtain food on a fixed-interval 10 min schedule, and intermittent changes in either key light or house light illumination were used to vary response rates within individual intervals. The effect of amobarbital in general was to increase overall response rates in a way which was dependent upon the control response rate during particular segments of the intervals. However, unlike the results obtained by Dews [26], the drug effect during periods of stimulus presentation did not in general fit the same function as the effect during no-stimulus periods. The low response rates during the stimuli tended to be increased to a smaller extent than the rates during the periods without stimuli. The effects were also dependent upon whether key light or house light changes were used and the brightness of the stimuli. McKearney concluded that the effects of amobarbital were dependent upon both control response rate and the extent to which responding was under external stimulus control.

Unlike the amphetamines, barbiturates have been found reliably to increase low response rates produced by punishment or conditioned suppression procedures [16, 40, 58, 72, 82]. It has been suggested [72,82] that this effect may simply be due to a general tendency for barbiturates to increase low response rates. However, in an experiment designed to investigate this possibility McMillan [72] found that although pentobarbital increased low rates of both punished and unpunished responding, the extent of the increase depended on both the control response rate and whether or not punishment was involved.

The benzodiazepines are another class of psychoactive drugs with the property of increasing suppressed response rates [15, 16, 39, 43, 58, 60, 62, 76, 77, 96, 110, 122, 123]. Again the possibility has been raised [122] that this effect does not represent a specific action on responding suppressed by stimuli associated with shock, but is rather an example of a general tendency for these drugs to increase low response rates. Wuttke and Kelleher [122] showed that the effects of three benzodiazepines (chlordiazepoxide, diazepam and nitrazepam) on the fixed-interval responding of pigeons were dependent upon control response rates, and that data from experiments involving either punished or unpunished responding fitted the same function. Other researchers, however, have not obtained results so consistent with the rate-dependency hypothesis [15, 72, 76, 77, 89].

Miczek [76] has provided an elegant demonstration that the effects of chlordiazepoxide and diazepam cannot be explained simply in terms of a general tendency to enhance low response rates. Rats were trained to press a lever for food on a variable-interval schedule. With some animals responding was suppressed during a stimulus which preceded an electric foot shock, while in others suppression was produced by a stimulus which preceded the free delivery of sweetened milk. The minor tranquilizers were found to attenuate the suppression produced by the pre-shock stimulus but did not affect the low response rates during the stimulus preceding free milk in a similar way. This result, then, suggests that the effects of benzodiazepines are not critically dependent on the baseline response rate. It is also worth pointing out in this context that although responding maintained at relatively low rates by a schedule of food reinforcement has been shown to be facilitated by chlordiazepoxide [87,90], much higher response rates have also been shown to be increased in some circumstances [89, 112, 113].

*Other psychoactive drugs*

The actions of several drugs which, like the amphetamines, are often described as stimulants have also been considered in terms of the rate-dependency hypothesis. Nicotine has been found to facilitate responding maintained at relatively low rates on differential reinforcement of low rate schedules [79, 80, 85] at doses which have little effect on higher response rates maintained by ratio schedules [19,79]. Stitzer, Morrison and Domino [98] studied the effects of nicotine on the responding of rats maintained by a fixed-interval schedule of water reinforcement. The effects of the drug were analysed in terms of response rates during segments of the fixed-intervals and while increases in response rate were rare even in early parts of the intervals when control rates were low the depressant action of the drug was more pronounced on the higher response rates towards the ends of the intervals.

The effects of cocaine on responding maintained by a fixed-interval schedule also appear to be rate-dependent [94] but this does not seem to be the case with caffeine. McMillan [70] studied the effects of several doses of caffeine on the behavior of pigeons maintained by a multiple fixed-interval fixed-ratio schedule. A low dose (3 mg/kg) slightly increased the response rates maintained by the fixed-interval schedule while a higher dose (30 mg/kg) decreased these rates. However, response rates maintained by the fixed-ratio component were not affected by any of the doses studied.

The effects of chlorpromazine on the overall response rates of pigeons, rats and monkeys are almost entirely depressant regardless of the schedule of reinforcement maintaining the behavior [4, 13, 86, 99, 118]. However, there is some evidence that this general effect of chlorpromazine is also rate-dependent. Several experimenters have studied the actions of chlorpromazine on responding maintained by fixed-interval schedules. When the intervals have been divided into a number of segments and control response rate during these segments plotted against percentage of control rate after drug administration, sloping regression lines have been obtained indicating that the drug effects are rate-dependent [59, 61, 67].

The rate-dependency hypothesis has also been applied to the behavioral actions of morphine. Thompson and his co-workers [106] investigated the effects of this drug on the operant behavior of rats maintained by several ratio or interval schedules. The major effect of morphine was to decrease overall response rates, but the extent of this action depended on control response rates. Thus, in general, higher response rates were depressed more by the drug although at certain low doses a small facilitation of the high fixed-ratio response rates was observed. Responding maintained by multiple fixed-interval fixed-ratio schedules is also affected by morphine in a rate-dependent manner since small doses have been shown to increase the response rates of pigeons on the fixed-interval component while having no effect on responding maintained by the fixed-ratio component [74,75]. McKearney [67], however, did not find that morphine increased fixed-interval response rates of monkeys when intervals terminated with food although such a facilitatory effect was observed when the intervals terminated with shock presentation.

Other psychoactive drugs whose effects have been described as rate dependent include LSD, THC and scopola-

mine. LSD has been shown to facilitate responding maintained by differential reinforcement of low rate [1] and fixed-interval [107] schedules and less consistently to facilitate responding maintained by variable-interval schedules [1, 38, 51]. Responding maintained by fixed-ratio schedules, however, is generally depressed by LSD [37]. THC has also been found to decrease fixed-ratio response rates at doses which increase lower rates maintained by other schedules [32,33] and the actions of scopolamine on fixed-interval responding have also been shown to be rate-dependent [68].

### ASSESSMENT OF THE RATE-DEPENDENCY HYPOTHESIS

It seems clear from the literature reviewed above that research from two distinguishable types of experiment has been claimed to provide evidence for the rate-dependency hypothesis. The first consists of studies in which overall effects of drugs on responding maintained by different schedules are compared. For example, amphetamines have frequently been shown to increase low overall response rates controlled by fixed-interval, differential reinforcement of low rate or high fixed-ratio schedules while the higher rates controlled by low or moderate fixed-ratio schedules are typically unaffected or depressed by similar doses. The overall response rate, however, is far from being the only factor which distinguishes the behavior maintained by these different schedules. It also differs in factors such as frequency and duration of pauses, temporal patterning of responses, the occurrence of irrelevant patterns of behavior and the density of reinforcement.

Recently Thompson and Corr [104] described an experiment in which pigeons pecked a key at different rates although reinforcement frequency was kept constant. Four pigeons were first trained to peck on a variable-interval 1 min schedule. Two were then shifted to a multiple variable-interval 1 min variable-time 1 min, (with variable-time schedules reinforcers are delivered at varying intervals independently of the animals' behavior). The other two pigeons were exposed to a multiple schedule with two similar variable-interval 1 min components in one of which reinforcement availability was signalled by the switching off of the houselight. In both these procedures responding on the conventional variable-interval components was maintained at relatively high rates while the variable-time and the signalled variable-interval components both maintained very low response rates. When d-amphetamine was administered variable-interval response rates were increased by low doses and decreased by higher doses but the very low rates maintained by the other schedule components were not increased by any dose. This result is certainly inconsistent with a simple rate-dependency hypothesis but the authors concluded that responding during the signalled variable-interval component was unaffected by the drug because the behavior was under very strong stimulus control (see EXCEPTIONS, first section). The very low response rates during the variable-time schedule, on the other hand, were said not to be increased because the necessary minimum tendency to respond was not present (see EXCEPTIONS, third section).

Another recent experiment [89] in which response rate was varied but reinforcement frequency held constant was more successful in demonstrating rate-dependent effects of d-amphetamine. In this experiment three rats were exposed to a variable-interval schedule of food reinforcement and three other rats were exposed to a similar variable-interval schedule but with the added constraint that reinforcement could follow only a response which occurred at least 5 sec after the preceding response. This pacing requirement had the effect of maintaining much lower response rates than the unpaced variable-interval schedule although reinforcement frequencies were similar in the two conditions. Administration of d-amphetamine (0.25–2.0 mg/kg) produced a dose-related increase in the low, paced variable-interval response rates and a dose-related decrease in the higher unpaced variable-interval rates.

The second technique which has been used to look at rate-dependent drug effects, and with considerable apparent success, has been to analyse the effects of drugs on patterns of responding maintained by fixed-interval schedules of reinforcement. Thus different average response rates are associated with different segments of the fixed-intervals and this allows the effects of a drug on behavior to be assessed in terms of the rate-dependency hypothesis. However, a gradual acceleration in response rate throughout individual fixed-intervals is not necessarily characteristic of the behavior maintained by such a schedule. For example, Schneider [91] reported that his pigeons paused for varying periods after reinforcement and then showed relatively abrupt transitions to a sustained constant rate of responding until the next reinforcer. In such cases averaging the number of responses made in successive segments of a fixed-interval may produce an average curve which does not represent the behavior during any given fixed-interval merely because of the variability in postreinforcement pauses.

Branch and Gollub [7] have recently reported an experiment which shows the importance of these considerations in the context of the rate-dependency hypothesis. Pigeons were maintained on fixed-interval schedules, the interval durations of which were 40, 100 or 300 sec. These intervals were divided into 10 segments, in the usual way, and when the mean number of responses in each segment was computed the resulting plot suggested a gradually accelerating response rate during the intervals. When the effects of d-amphetamine were investigated by comparing the log of the response rate during each segment after drug administration with the logs of the corresponding control rates the typical straight line functions were obtained, suggesting once more that the drug effect was rate-dependent. However, when the control data were analysed in more detail it became clear that the measures of mean response rates during successive segments of the intervals did not give an accurate picture of the pattern of responding within any given interval, for the pigeons in this experiment responded at fairly constant rates after postreinforcement pauses of varying length. As Branch and Gollub point out, their results raise serious questions about the appropriateness of segmenting fixed-interval schedules in the study of rate-dependent drug effects. More specifically it is possible that the effects of a drug which consistently reduced the duration of pauses during fixed-interval responding would appear rate-dependent in terms of the mean response rates during segments of the intervals. In this context it is appropriate to point out that Weiss and Gott [114] have shown that postreinforcement pauses during responding maintained by a fixed-ratio schedule are sensitive to the effects of a number of drugs.

Another point worth noting is that in discussions of the rate-dependent effects of the amphetamine the different isomers are often treated as if they were almost inter-

changeable. Thus experiments involving d-, dl- and methamphetamine have been described in earlier sections of this review and, while the effects of these drugs generally seem to be very similar, relatively few studies have actually made direct comparisons of these effects. Owen [84] studied the actions of a number of isomers on the responding of rats maintained by a fixed-ratio schedule and found that the effects of the different isomers were similar. More recently, however, Tilson and Sparber [108] have described certain differences between the actions of d- and l-amphetamine on responding maintained by a fixed-interval schedule. This result is interesting since there is evidence that these two isomers have different physiological actions (e.g. [103]). It would seem desirable, however, for more experiments to be carried out which compared the action of different amphetamines in the context of the rate-dependency hypothesis.

## GENERAL CONCLUSIONS

It may be concluded that there is now a relatively large body of information which is consistent with Dews' [25] original hypothesis that the behavioral actions of the amphetamines depend upon the baseline response rate. Many of these results, however, are amenable to alternative explanations, and it also appears that there are a number of behavioral situations to which this hypothesis does not readily apply. In the case of drugs other than amphetamines there is considerably less direct evidence in favor of the rate-dependency hypothesis and caution should therefore perhaps be exercised in asserting that the effects of drugs are generally dependent upon the control rate of responding.

At present two approaches to the evaluation of the rate-dependency hypothesis might be useful. The first of these requires procedures which will make it possible to vary response rates in individuals or groups of subjects while controlling more adequately such factors as reinforcement frequency and degree of stimulus control, thereby making it possible to measure the effects of response rate per se. A second approach might be to design experiments which assess in more detail the importance of variables other than simple response rate, such as the degree of stimulus control, the nature of the reinforcers maintaining the behavior, or the nature of the response chosen for study. Certainly the rate-dependency hypothesis of drug action demands the most rigorous and least ambiguous experimental tests, emphasising as it does the importance of behavioral characteristics in determining the effects of drugs independently of their traditional classifications.

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