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A Critique of Fixed and Progressive Ratio Schedules Used to Examine the Neural Substrates of Drug Reinforcement

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ARNOLD, J. M. AND D. C. S. ROBERTS. *A critique of fixed and progressive ratio schedules used to examine the neural substrates of drug reinforcement.* PHARMACOL BIOCHEM BEHAV **57**(3) 441–447, 1997.—This paper is a critique of fixed and progressive ratio schedules used to examine the neural substrates of cocaine reinforcement. The discussion focuses on problems encountered while examining the effects of neurotoxic lesions and pharmacological pretreatments on cocaine reinforcement. We review the theoretical and interpretational problems associated with the use of the fixed ratio (FR) schedules that have been used in the majority of studies, and we conclude that rate of drug intake cannot directly address the issue of increased or decreased reinforcer efficacy. The progressive ratio (PR) schedule offers some advantages over FR schedules, although it is now clear that the same implementation cannot be applied across all drug classes. It is likely that the motivation to self-administer psychostimulant vs. opiate drugs is qualitatively different. We conclude that there is no single schedule that can quantify all aspects of drug reinforcement and that behavioral paradigms will need to be adapted according to the particular question under study. © 1997 Elsevier Science Inc.

Cocaine Self-administration Schedules of reinforcement Progressive ratio schedule

THE study of drug addiction is a multidimensional and multidisciplinary field of experimentation that relies heavily on the use of animal models. Techniques have been developed that allow animals to self-administer various compounds, typically by oral or intravenous routes. Animal models of drug self-administration have been used to address a range of research interests, which include: (a) the abuse liability of specific compounds, (b) patterns of drug intake, (c) the effect of response contingencies on drug intake, and d) the neural substrates of reinforcement (2,6,7,13–15,17,24–27,30,36,38,46,47,63).

No single model is appropriate for all research questions. Drug self-administration procedures must be adapted to the particular aspect of drug use under study. Just as any biological assay must be tuned and optimized, behavioral paradigms must also be adjusted to generate meaningful data. In the present review we will discuss some of the various procedures that have been employed to investigate the neural bases of drug reinforcement, and we will emphasize problems and pitfalls that are associated with each. An historical perspective will be used. We shall illustrate the evolution of new techniques and the theoretical reasons for their development by tracing studies that have explored the synaptic substrates of cocaine reinforcement.

Both subhuman primates and rats have been used to examine the effects of pretreatment with various neurotransmitter agonists and antagonists on cocaine self-administration. Such experiments have helped to establish the importance of the monoamines, particularly dopamine (DA), in cocaine reinforcement (1,6,7,25,29,35,36,45,50,54,58,59,61,64). Other studies designed to explore anatomical questions through the use of neurotoxic lesions or intracerebral injections of other drugs have almost exclusively used rats as subjects (4,11,16,30,33,34, 41,48,55–57,62). The paradigms and procedures used in these self-administration studies with rats will be the focus of this brief review.

The great majority of self-administration studies with rats, until recently, have used simple fixed ratio (FR) schedules of reinforcement. The FR 1 schedule is useful for exploring patterns of rate of drug intake and can be used effectively for preliminary screening of drugs with abuse liability. We will argue, however, that the use of simple FR schedules is inappropriate in studies attempting to assess changes in the reinforcing effects of cocaine and other drugs. We will show that rate of drug self-administration may be insensitive to changes in reinforcement efficacy and, even if changes are observed, there is little or no theoretical basis for interpreting these changes.

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There are several theoretical problems associated with the interpretation of FR data. One fundamental issue relates to imprecise ideas about what is being examined. For some studies, one critical assumption appears to be that the reinforcing "efficacy" of a drug can be measured and that inferences can then be made about the underlying neural process. In self-administration studies, the behavior most often examined is lever responding, and this is obviously borrowed from the techniques and procedures used by the operant school; however, it must be recognized that the questions being asked and the theoretical issues being explored are quite contrary to the behaviorist tradition. The techniques and procedures employed by the operant school were designed to explore how behavior changed when the contingencies between stimulus and response were altered; the procedures were not designed to estimate reinforcer magnitude. The operant tradition defines a reinforcing stimulus by virtue of its ability to increase the probability of particular responses. However, the operant school would not use this definition to quantitate a reinforcer. The quantity of a reinforcer would be an independent variable measured in number of food pellets or milligrams of drug. The question of whether a particular stimulus was more reinforcing than another was not of interest. Reinforcement "refers neither to a theory of nor an explantion for behavior. It is, instead, a name for a particular relationship between behavioral and environmental events" (8). The idea of quantitating a reinforcer lies outside of this school of thought. In fact, the idea of investigating the neural substrates of any of the behavioral processes was discouraged. Obviously, the neuroscience requirement for assessing the magnitude of a reinforcing effect is fundamentally at odds with the idea of "reinforcement as a relationship." Traditional operant theory is not easily invoked to quantify the reinforcing efficacy of any particular drug. Nonetheless, operant techniques have been borrowed to explore the neural bases of drug reinforcement, usually without explicit statements or definitions of the phenomenon being studied.

It is also important to note that operant theory has little to say about FR 1 responding. To a behaviorist, response rate is a robust and reliable measure. However, response rate in the operant context refers to "local rates" of responding on much leaner schedules. Local rates occur during the interval between reinforcements, and they may take on the characteristic patterns associated with interval or ratio schedules. There are no "local rates" of responding on an FR 1 schedule. This is why operant theory has little to offer by way of explanation for changes of interinfusion intervals in self-administration studies. FR 1 responding is equivalent to the rate of "consumption," and therefore we will refrain from using the term "rate of responding" in the context of an FR schedule and instead use the term "rate of drug intake."

Although there is no theoretically derived method to account for changes in rate of drug intake, there have been explanations offered (10,12,66,67). The most plausible and widely accepted interpretation was offered by Yokel and Wise (68,69). They reasoned that because animals compensate for decreases in the unit injection dosage by increasing their rate of drug intake, then increases seen following various drug pretreatments must reflect a similar compensatory response. It is now widely accepted that increases in rate of drug intake, e.g., following systemic injections of DA antagonists, reflect a decreased reinforcing efficacy and, conversely, decreases in rate reflect an increase in reinforcing efficacy.

Despite the fact that the suggestion of Yokel and Wise appears to account for a wide range of data involving dopaminergic drugs (68,69), there have been a variety of data that are difficult to explain. The problem associated with interpreting rate of drug intake is clearly illustrated by an experiment in which the connection between the mesolimbic DA system and cocaine reinforcement was first established [(56); see Fig. 1]. Bilateral infusion of the neurotoxin 6-OHDA into the nucleus accumbens depleted DA levels and disrupted cocaine self-administration; partial depletion of accumbens DA produced a partial disruption in the rate of cocaine intake. If DA levels were not depleted by greater than 80%, cocaine self-administration returned, initially at a slow rate, and reached baseline levels. Similar results were also seen after 6-OHDA lesions in the ventral tegmental area and bilateral kainic acid lesions in the nucleus accumbens (55,70). Within the context of these experiments, a decrease in rate of lever responding, seen during the recovery period, was interpreted as a decrease in the reinforcing efficacy of cocaine.

This conclusion is opposite to the traditional interpretation (see above) that a slower rate of drug intake reflects an increase in the reinforcing efficacy of a drug. According to the Yokel and Wise (68,69) view it might have been expected that rats would show an increase in drug intake after 6-OHDA lesion of the accumbens in order to compensate for the reduced reinforcing effect, but this did not happen. This phenomenon has been addressed in detail elsewhere; nevertheless, the problem of interpretation is obvious (62). How can both an increase and a decrease in rate of drug intake be used to draw the same conclusion? The dilemma is unmistakable: rate is an ambiguous measure of reinforcing efficacy.

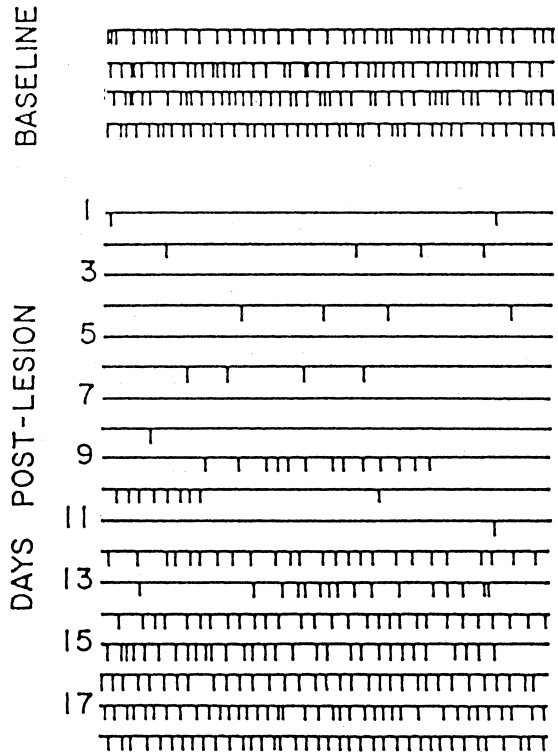

FIG. 1. Event record of cocaine self-administration from a rat after 6-OHDA infusion into the nucleus accumbens. Each line represents one daily 3-h session. Vertical lines indicate the time of a cocaine injection (1.5 mg/kg/injection). The record shows a gradual recovery of rate of cocaine intake following the lesion. [From Roberts et al. (56).]

On occasion, rate of drug intake is also insensitive to changes in reinforcing efficacy. The first indication that this may be the case was also found in the initial studies involving 6-OHDA lesions of the accumbens. To demonstrate that the rats that had stopped self-administering cocaine were in fact capable of responding and that their cannulas were patent, apomorphine was made available on an FR 1 schedule (53). The idea was that, because cocaine is an indirect agonist, the reinforcing effects would be abolished by removal of the presynaptic terminal. However, the reinforcing effects of the direct DA agonist should remain because the postsynaptic receptors would persist or become supersensitive. It was shown that the rate of apomorphine self-administration continued at prelesion rates in the same animals that failed to self-administer cocaine. While it was predicted the rats would continue to self-administer apomorphine, some change in rate was expected. If the DA receptors in the nucleus accumbens were responsible for apomorphine reinforcement, and these receptors became supersensitive, then some change in drug intake should be observed. This was not the case.

To establish whether the reinforcing efficacy of apomorphine had changed or not, we turned to the rate-independent measure offered by the progressive ratio (PR) schedule. This schedule was developed by Hodos and Valenstein to examine the reinforcing efficacy of sweetened milk solutions (21) and had been adapted to study intracranial self-stimulation in rats and drug self-administration in primates (3,5,19,20,22,23). Under this schedule, the response requirements to earn a drug injection escalate after the delivery of each reinforcement. For example, the first injection is delivered after a single lever response. The response requirements for each subsequent injection augment according to a series such as the following exponential function: 2,4,6,9,12,15,20,25,27,32,40,50,62,77,95, etc. The final ratio attained is designated the break point, which is defined as the final ratio of responses successfully completed. The break point under the PR schedule presumably reflects the motivation of the animal to self-administer a drug (9,13, 21,23,28,39,49,52,59,60).

When the effect of 6-OHDA lesions of the nucleus accumbens on apomorphine self-administration was reexamined using the PR schedule, it was found that its reinforcing efficacy had in fact changed with a time course that reflected the development of DA receptor supersensitivity (48). The dose of apomorphine tested was at the lower end of the self-administration curve (0.1 mg/kg). Results showed that prior to the 6-OHDA lesion, apomorphine self-administration had very low break points and an irregular pattern of intake. On average, rats failed to respond to ratios of more than 12 or 15. After the 6-OHDA lesion, animals that had substantial DA depletions showed a dramatic increase in their break point, reaching final ratios of 83–96 during each test session. As in the previous study, the rate of apomorphine self-administration on an FR 1 schedule was not changed by a 6-OHDA lesion. These data clearly show that the motivation to self-administer apomorphine was dramatically altered, yet the rate of drug intake on an FR 1 schedule failed to reflect that fact.

The PR schedule has been adapted to effectively study the reinforcing properties of psychomotor stimulants and opiates (13,24,29,30,32,34,35,38,48,49,51,52,60). The PR schedule has since been used in a number of cocaine self-administration studies, and similar dissociations between rate of drug intake and break point have been observed (30,48,52–54). The PR schedule has a number of features that make it particularly suited to the study of pharmacological pretreatments. Rats will quickly learn to self-administer cocaine under the PR schedule and display regular and controlled responding after only a few test sessions (13). The break point is dose dependent and allows for shifts in the dose–response curve to be studied. During the early part of a test session when the response ratios are relatively small, cocaine infusions are regularly spaced with consistent postreinforcement pauses. Eventually, the response requirements exceed the reinforcing efficacy of the drug and responding ceases (see Fig. 2), allowing the break point to be established during a single test session.

A number of examples will serve to illustrate the disparity between the results of PR and FR schedules of reinforcement. For some manipulations, the relationship between break point and rate of drug intake appears to be well correlated. Both are dose dependent and both are sensitive to the effects of systemic treatment with DA antagonists (25,29,36,38,45,58,61). However, when other treatments are examined, such as intracerebral injections or hormonal effects (52,54), the rate of drug in-

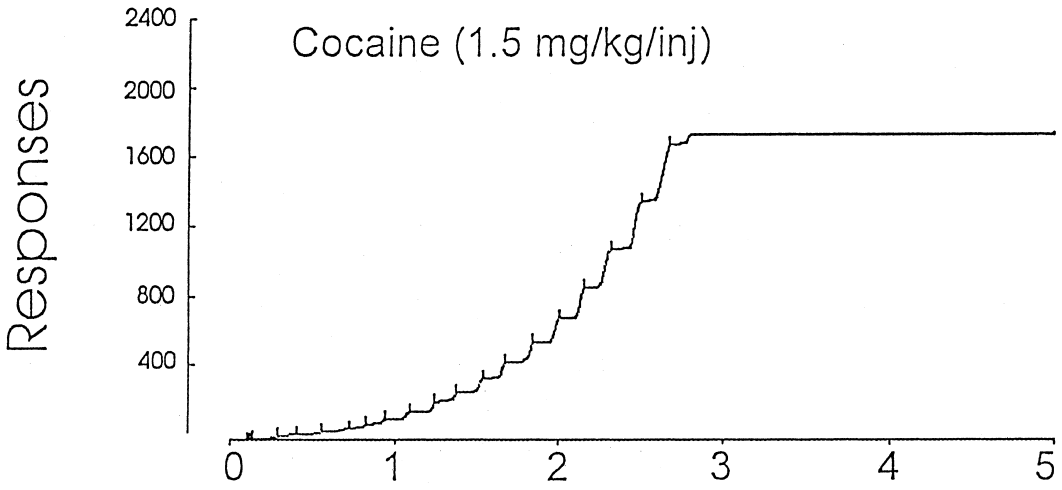

FIG. 2. Cumulative record illustrating the pattern of responding on a PR schedule reinforced by IV cocaine at the unit dose of 1.5 mg/kg/injection of cocaine. Vertical increments indicate lever responses during a 5-h test session. Vertical inflections mark each drug infusion.

take and the break point seem to be uncorrelated. For example, the estrous cycle was found to have no effect on rate of drug intake on the FR 1 schedule, but break points on the PR schedule were found to be dramatically increased during the day of estrus compared with other days within the cycle (52).

Another striking difference between rate of drug intake and break point is seen following serotonergic manipulations. To assess the possible role of 5-HT in cocaine self-administration, forebrain serotonin levels have been depleted through the use of the neurotoxin 5,7-dihydroxytryptamine (5,7-DHT). Although depletion of forebrain 5-HT was found to have no effect on the rate of cocaine intake, large increases in break point were observed on the PR schedule. In general, depletion of 5-HT appears to potentiate cocaine reinforcement, and facilitation of 5-HT function appears to diminish cocaine's reinforcing efficacy. Pretreatment with either L-tryptophan or fluoxetine, a 5-HT precursor and a reuptake inhibitor, respectively, was found to reduce break points for cocaine reinforcement (35,43). Fluoxetine and L-tryptophan decrease psychostimulant intake on an FR schedule (7,40,65). Again, the interpretation of these FR 1 data is ambiguous because they might be interpreted as either an increase or a decrease in reinforcing efficacy, although the conclusion to be drawn from the PR data is clear.

Cocaine has been extensively characterized under the PR schedule using both agonists and antagonists (25,29,36–38, 42,45,48,58,61,64). The ascending limb of the dose–response curve is observed across unit injection doses from 0.18 to 1.5 mg/kg/injection. The curve is sensitive to various dopaminergic (13,25,29,36,38,42,45,50,58,64) and nondopaminergic (6,7, 35,43) pretreatments. In general, typical DA agonists increase and typical DA antagonists reduce break points across the dose–response function (45,54,59,61), although there are exceptions to this rule (64).

The PR schedule is not without limitations [for review, see (44)]. Possibly the most problematic is that only a single data point is provided from an entire session. Unlike rate measures that yield a stream of data that can be useful in determining the time course of a particular drug pretreatment, the PR schedule yields only a single measure. It should also be noted that the time point when the break point is established varies with dose. The low break point values associated with small unit injection doses of cocaine are established relatively early in the session, while higher break points are established later. When investigating the effect of drug pretreatments, therefore, care must be taken to ensure that the break point is reached within an appropriate time frame.

In summary, cocaine self-administration reinforced on a PR schedule is dose dependent and exquisitely sensitive to a number of manipulations. This paradigm appears to be ideal for studying the reinforcing effects of a number of compounds. Indeed, a variety of other stimulant compounds generate dose–response functions that presumably reflect their abuse potential (18).

Surprisingly, opiate self-adminstration is not well maintained on the PR schedule described above. Rats will not respond to high break points for heroin despite the fact that they show a great deal of interest in the lever at the start of a self-administration session. If test sessions begin with a low response requirement, rats will respond to very modest break points. Furthermore, we have been unable to establish a dose–response relationship for heroin self-administration using this type of PR schedule. It appears that once an animal has received its first few injections of heroin, the motivation to respond for further injections dissipates (51). It is possible that the longer duration of action for heroin might account for this fundamentally different pattern of responding, but this is unlikely. Amphetamine, which has a much longer half-life

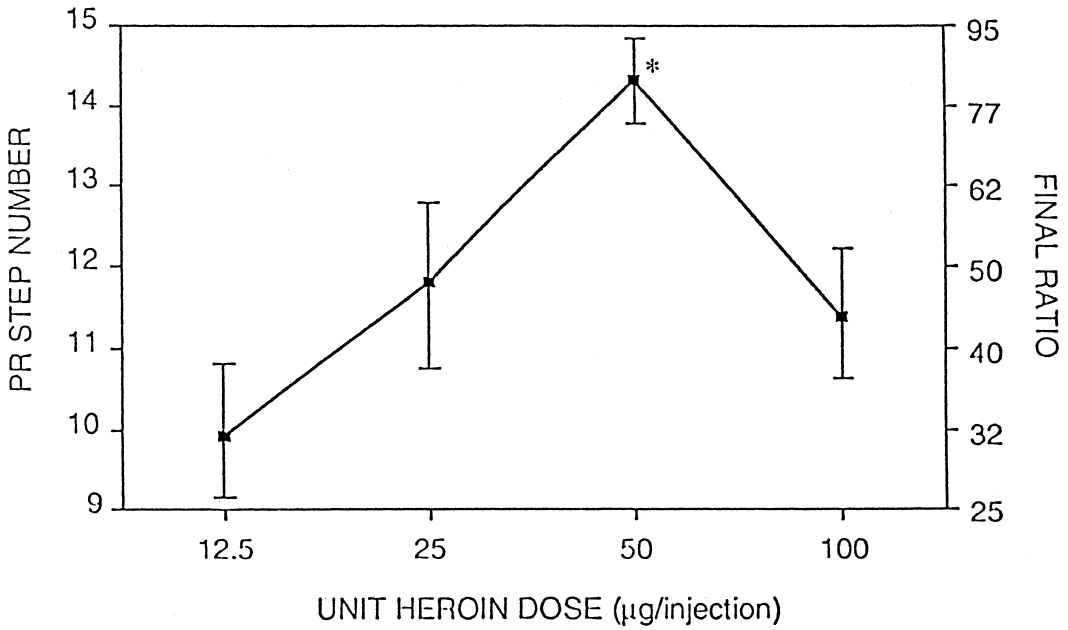

FIG. 3. Effect of changes in heroin dose on self-administration behavior under the modified PR schedule. Points represent mean final ratios (n = 5). The PR step number is indicated on the left axis, and the actual ratio value is shown on the right axis. The asterisk represents a statistically significant difference between the 50- and 12.5-µg/injection doses. [From Roberts and Bennett (51).]

than heroin, produces a pattern of self-administration behavior on the PR schedule that is essentially identical to that for cocaine. The only difference is that with amphetamine animals may respond for upwards of 18 h before a break point is reached, whereas a similar break point will normally be established with cocaine within 4 h (44). Something other than the duration of action must account for the difference between heroin and cocaine.

Our working hypothesis has been that animals self-administering heroin are highly motivated to self-administer the first injection of the day but are less motivated for each subsequent injection. The PR series developed for cocaine self-administration (beginning with one and escalating exponentially with each subsequent drug injection) was clearly ineffective for evaluating the initial motivation to seek opiates.

A PR schedule better suited for characterizing the motivation to self-administer opioids has been developed (51). Under this schedule, the response requirements begin at 1 and escalate through the PR steps outlined earlier. On following test days, the first response requirement is set 2 PR steps below the final ratio completed on the previous day. This modified PR schedule proved to be well suited for the study of heroin self-administration behavior. This new schedule produced break points that were sensitive to manipulations of the unit dose of heroin and to opiate receptor blockade. On average, the peak mean break point occurred at 50 μg/injection and was decreased by daily pretreatment with the opioid antagonist naltrexone [(51); see Fig. 3].

These data suggest that there are fundamental and qualitative differences between psychostimulant and opiate self-administration, and they also serve to illustrate that no single schedule can capture what appear to be fundamental differences between distinct classes of drugs. Rather, several schedules of reinforcement may be required to characterize the multidimensional properties of drugs. Drug self-administration studies have been essential to our current understanding of the neurobiology of addiction. A major problem has been that the standard FR 1 model of drug self-administration propagates the notion that self-administration is a simple behavior and ignores the fluctuations that occur before and during a self-adminstration session. It will be important to continue to develop new paradigms [e.g., (17,31,32)] that will help define the complex nature of the addictive process.

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