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Effects of Reinforcer Limitations on Fixed-Ratio Responding During Repeated Administration of Chlorpromazine

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SMITH, J. B. *Effects of reinforcer limitations on fixed-ratio responding during repeated administration of chlorpromazine.* PHARMACOL BIOCHEM BEHAV 45(3) 565-569, 1993.—Key-pecking was maintained under a 30-response fixed-ratio schedule of food presentation and pigeons received 30 mg/kg/day chlorpromazine immediately prior to experimental sessions. After responding stabilized during chronic drug and animals were receiving all available reinforcers, the time available for receiving reinforcers was systematically varied. When that time was decreased, animals initially received fewer reinforcers but responding subsequently increased to an extent that animals once more received all available reinforcers. When that time was again increased, responding once again decreased but only to an extent that animals continued receiving all available reinforcers. During subsequent reversals of the time for reinforcer availability, responding increased or decreased to an extent always resulting in the maximum number of reinforcers. When drug was discontinued, responding returned to predrug levels. These results demonstrate that effects of chronically administered chlorpromazine were influenced by both drug activity at its site of action and by the behavioral process of reinforcement.

Chlorpromazine Reinforcement Tolerance Fixed-ratio responding Pigeon

THERE is a long-standing appreciation that dynamic and orderly relations can develop between ongoing behavior and features of its preceding, present, and following environmental circumstances (24,28). The importance of such relations between behavior and its environment has been studied for the initial learning of specific behaviors and for transitions of ongoing behavior from present to new conditions. For example, Pavlovian conditioning of the salivary reflex can be dramatically influenced by environmental circumstances as minor as a half-second difference in the temporal separation between a conditioned and unconditioned stimulus (33), and such conditioning hardly occurs at all if the unconditioned stimulus precedes the conditioned stimulus by as little as even a third of a second [cf. (16, p. 156f)]. The initial development of operant behavior is equally affected by training conditions, when, for example, development of stimulus discrimination can vary markedly for animals trained under conditions permitting errors than for animals trained under conditions not permitting errors (34,35).

There is a similar appreciation that transitions of behavior to newly changed environmental circumstances do not always result in the same changes in behavior for all individuals, but that these transitions are instead heavily influenced by previous experiences. For example, Morse and Kelleher summarized different effects of electric stimulation for animals with different operant histories (22) and Pavlov described how skin cauterization, which initially elicited a strong unconditioned defensive response, could be altered by experience to function as a "neutral" conditioned stimulus for the appetitive secretory reflex (24, lecture II). In each of these instances of operant and reflexive behavior, it was experience of the individual, and not properties of the environment alone, that influenced transitions to new behavior [cf. (22)].

Similar kinds of considerations apply for understanding that acutely administered drugs do not have the same effect from individual to individual or for the same individual from one instance to another. Rather, effects of an acutely administered drug can variously depend at least upon differences among individuals with respect to their previously reinforced behavior (1,4,19,20,36), their currently reinforced behavior (6,15), and behavior that is reinforced in other currently available conditions (3,19).

In a similar way, the behavioral effects of chronically administered drugs are not invariant for a given drug or drug dose—or particular behavior—but are influenced by a combination of circumstances surrounding drug administration and ongoing behavior. For a variety of drugs, for example, tolerance either may or may not manifest for initial effects of a drug on behavior maintained by food delivery (9,26) for behavior maintained by postponement of electric stimuli (32),

for the reinforcing effects of self-administered drugs (11,13, 14), for the discriminative effects of drugs (37), or for the effective palliative dose of morphine for cancer pain (12,21, 27). In each of these instances, concepts referring to such behavioral processes as reinforcement history and current reinforcement contingencies are as useful as concepts referring to pharmacological processes for understanding why chronically administered drug sometimes does, and sometimes does not, result in diminished effects.

Some experiments, for example, have studied influences of the initial "behavioral costliness" of a drug's effect on its subsequent chronic effects and reported that tolerance develops much more rapidly for drug-produced increases in operant spaced responding than for drug-produced increases in operant fixed-interval responding (5,7,25,26). Such results have been interpreted in terms to suggest that the reduced frequency of food reinforcers following drug-related changes in spaced responding was a change in the reinforcement *process* that subsequently resulted in behavioral compensation to once again produce a higher frequency of reinforcers. However, in those previous experiments, changes in behavior were studied from the beginning of chronic drug administration so that the initial drug-related decrease in reinforcer delivery, as well as any subsequent adjustments in behavior, coincided with both pharmacodynamic changes in drug action, as well perhaps with changes in behavioral processes other than "response cost," such as discriminable novel effects of the drug. Consequently, it is not easy in those experiments to separate a direct influence of reinforcer frequency from other influences occurring during early exposure to drugs. However, if decreased food frequency can be a major influence on the effects of chronically administered drugs, then its effects should be observed not only during *early* exposure to a drug, but also during prolonged chronic exposure as well when most initial effects of drug action per se have reached equilibrium. The present experiment studied this possibility by varying the time limits to obtain available reinforcers for fixed-ratio responding of pigeons after behavior was stable during chronically administered chlorpromazine (CPZ). When animals had comparatively long times to obtain all available reinforcers, behavior recovered to a lesser extent during chronic CPZ than when animals had a much shorter time for obtaining the reinforcers. In addition, animals remained responsive to altered conditions during several reversals of reinforcer availability.

METHOD

Subjects and Apparatus

Three adult, male White Carneaux pigeons (P-1505, P-1507, and P-1527) were maintained at approximately 80% of free-feeding body weights. Actual weights during experiments were 400–450 g, and water and grit were always available in individual home cages. All had previously responded under fixed-interval and fixed-ratio schedules of food presentation and had received acute administration of a variety of drugs, including CPZ. Experiments were conducted with individual pigeons placed in an experimental chamber containing a standard response key (G6315, Ralph Gerbrands Co., Arlington, MA) mounted on a wall. The key was transilluminated by a red or a blue light and could be operated with a minimum force of about 0.15 N. Access to mixed grain was provided through an opening located beneath the response key. Programming and recording equipment were located in an adjacent room.

Procedure

Key-pecking was maintained under a chained schedule in which the first response after 2 h in the presence of a red key light (FI 2 h) changed the key color to blue and began a 15-min period during which 10-s access to mixed grain was available under a 30-response fixed-ratio schedule of food delivery (Chain FI 2 h, FR 30). Experimental sessions ended after the 10th consecutive food presentation or, in the absence of responding, after 2 h and 15 min. Except for weekends, animals did not receive any food outside the experimental chamber. Adequate feeding in experimental sessions precluded supplemental feeding and helped ensure the importance to subjects of within-session responding. Such limited access to reinforcers is sometimes described as a "closed economy" and has been shown to influence performance in circumstances when "response cost" is a relevant consideration.

The 2-h fixed-interval schedule was used because it provided large samples of behavior spread over considerable "real time" in the absence of explicit external stimuli; the 30-response fixed-ratio schedule was used because it provided a marked contrast in the pattern of maintained behavior; and the chain schedule was used because it provided a measure of "vigilance" appropriate for some of the suspected effects of CPZ on control by external and external stimuli (17,18). Fixed-interval responding is not shown or discussed in the present report, however, because the primary focus was changes in fixed-ratio responding associated with the time available for receiving food reinforcers.

After responding was stable, animals received three to five determinations of twice-weekly (acute) injections of CPZ HCl (1–30 mg/kg, Sigma Chemical Co., St. Louis, MO). The drug was dissolved in 0.9% sodium chloride solution and injected IM (1 ml/kg). For determination of acute effects, animals received CPZ approximately 2 h before experimental sessions on Tuesdays and Fridays. Vehicle was occasionally injected 2 h before sessions on Thursdays, and control responding consisted of the average rate for seven sessions after vehicle injection.

After determining the effects of well-spaced injections of CPZ, animals received 30 mg/kg/day for 30 sessions (42 days counting weekends). Fifteen minutes were allowed for obtaining reinforcers during these sessions, and injections continued to be made approximately 2 h before experimental sessions on Monday-Friday. Injections were made at 12 noon on Saturdays and Sundays. Then, on the 31st session, the time limitation for reinforcers was decreased to 5 min, and animals continued to receive 30 mg/kg/day CPZ for 12 sessions (16 days). The time limitation for reinforcers was subsequently changed back to 15 min for 12 sessions (16 days), and then to 5 min for a final 5 sessions (7 days). Altogether, animals received 30 mg/kg/day CPZ for 59 sessions (81 days) before cessation of drug administration.

RESULTS

Control responding under the chain schedule was similar for all three animals and was like that reported in Smith (31). Responding under the FI schedule occurred at 0.21 ± 0.07 responses/s and was positively accelerated throughout the interval. As mentioned previously, however, fixed-interval responding is not shown or discussed in the present article.

Behavior under the fixed-ratio schedule occurred at higher rates and was characterized by alterations between periods of no responding, typically just after each food delivery, and periods of sustained responding. This behavior was measured two ways. "Overall rate" of responding was calculated by di-

viding all fixed-ratio responses by the total time available for earning all 10 reinforcers. This measure included the time spent pausing after food delivery and is depicted as open circles in Figs. 1 and 2. The second measure, "rate after pause," was calculated by dividing all fixed-ratio responses by a time beginning with the first response after each food delivery and ending at the next food delivery. This measure of behavior reflects rate during sustained sequences of responses excluding pausing after each food delivery and is depicted by squares in Fig. 1. During control conditions, "overall responding" for the three subjects was between 1–2.5 responses/s (Figs. 1 and 2A, unconnected circles), rate after pause was approximately 3 responses/s (Fig. 1, unconnected squares), and animals obtained all 10 available FR 30 reinforcers in 2–2.5 of the 15 min that were available.

Chlorpromazine produced a dose-related decrease in FR response rate and a dose-related increase in the time taken to obtain reinforcers, and animals received only one to two reinforcers after 30 mg/kg (indicated by numbers above the symbols in Fig. 1). However, decreased responding during the fixed-ratio component resulted primarily from increased pausing after reinforcers and not from decreased rates during sequences of sustained responding. After 30 mg/kg chlorpromazine, for example, rate after pause continued to occur at approximately 2.0 responses/s even when overall rate was decreased to approximately 0.20–0.40 responses/s (Fig. 1).

When 30 mg/kg chlorpromazine was given daily, responding was initially decreased and animals did not receive all available reinforcers (Fig. 2B, solid points below the broken line during sessions 10–15). Some tolerance developed to these rate decreases within a week, however, and animals began to receive all 10 reinforcers in 10–15 min (Fig. 2A, open points above the broken line). There was no further diminution in the effects of 30 mg/kg chlorpromazine for up to 30 daily injections when the time allowed for obtaining reinforcers was 15 min. Local rates of responding (not shown) remained approximately 2.0 responses/s (cf. Fig. 1), long pausing did not diminish, and with occasional exceptions (Fig. 2A, solid points after session 15) animals continued to receive all available reinforcers. Then, when the time allowed for obtaining the 10 reinforcers was shortened to 5 min, food frequency was decreased during the first few sessions only (Fig. 2C, solid points below the broken line during sessions 40–45) and then animals once again obtained all 10 reinforcers under the new time allowance (Fig. 2C, open points above the broken line). In subsequent reversals, overall response rates decreased within 2 weeks when 15 min was again allowed for obtaining reinforcers (Fig. 2D) and then increased rapidly when only 5 min was allowed (Fig. 2E). When chlorpromazine was discontinued, overall response rates returned to predrug control levels within 2 weeks (Fig. 2F).

DISCUSSION

The phrase "drug tolerance" usually refers to a condition of decreased responsiveness to the pharmacological effects of a drug resulting from prior exposure to that drug or to a related drug. If the effects of a drug diminish even though its bioavailability remains the same, then that tolerance is described as "functional" and not "dispositional." When the dependent measure of a drug's effects is gross behavior, a further distinction has often been made between tolerance to the behavioral effects of a drug, on the one hand, and behavioral tolerance, on the other, as subtypes of functional tolerance. "Tolerance to the behavioral effects of a drug" is considered to have both behavioral and nonbehavioral influences, and "behavioral tolerance" most often seems to refer to instances in which behavioral factors themselves are primary influences on the time course and extent of tolerance development.

In studying behavioral effects of repeatedly administered

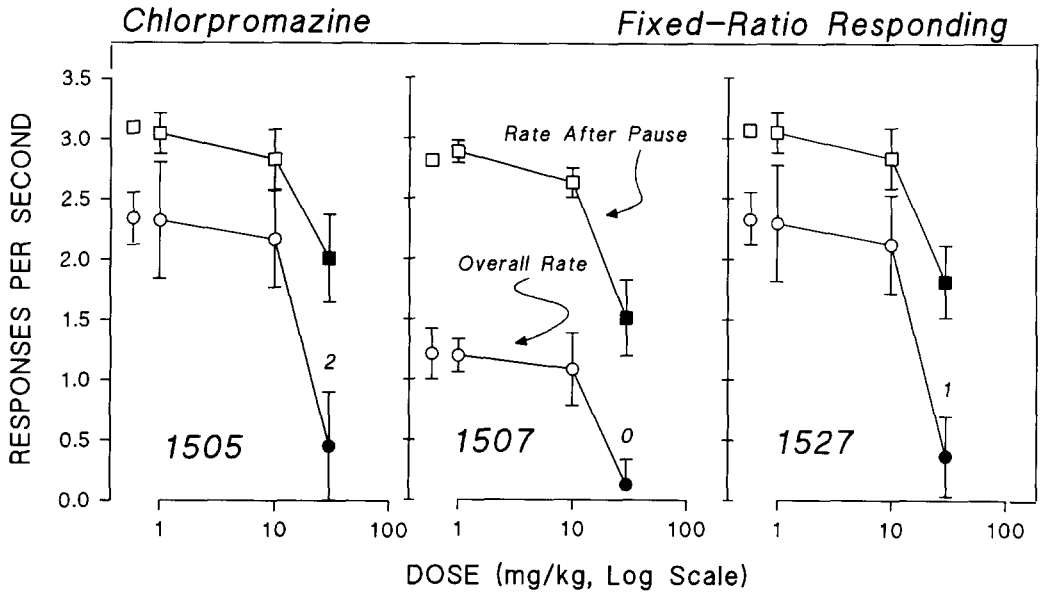

FIG. 1. Effects of chlorpromazine (±1 SD) for rate of overall fixed-ratio responding (circles) and for all response sequences beginning after postfood pauses (squares). Solid points are for sessions when responding did not result in delivery of all available food in the 15-min period, and the numbers adjacent to them represent the number of food deliveries in those sessions. Unconnected points are for seven saline-control sessions, and each connected point represents the mean of three to five determinations.

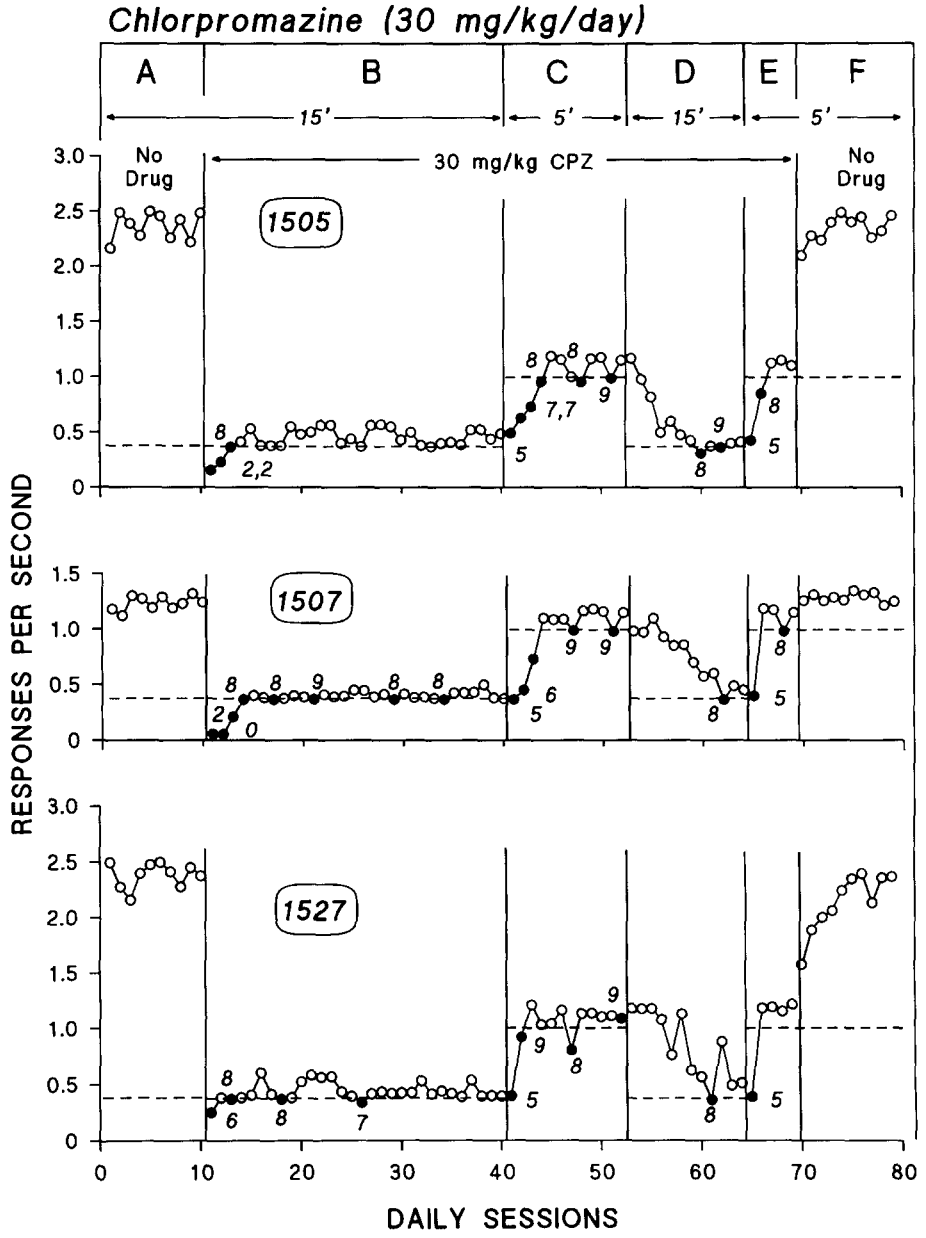

FIG. 2. Effects of repeated daily 30 mg/kg chlorpromazine on responding of each animal (upper, middle, lower) under each experimental condition. (A) Responding under control conditions when there were 15 min to receive reinforcers, and the broken line indicates the minimum overall response rate required for receiving all 10 available reinforcers. (B) Responding during drug when there were 15 min to receive reinforcers. Open points are for sessions when all available reinforcers were delivered and solid points are for sessions when fewer than the maximum numbers of reinforcers were presented (the numbers show the number of reinforcers delivered). (C)Sessions when there were 5 min to receive reinforcers, and the symbols are the same as in (A) and (B). (D) Sessions when the time limitation was changed back to 15 min. (E) Sessions after another reversal of time limitation. (F) Sessions when the drug was discontinued and the time limitation remained 5 min.

drugs, there was once an implicit tendency to consider "behavioral tolerance" as a process somehow standing apart from "real" tolerance. This practice is presently less frequent, however, after so many observations that behavioral processes can systematically influence the effects of chronically administered drugs, and it is currently considered that the drug molecule, its pharmacological receptors, and an individual's previous and ongoing behavior are all active coparticipants in the character and extent of the tolerance process (2,10). Moreover, because changes in the behavioral effects of drugs generally occur in a natural social environment, and not in isolated tissues or receptors, characteristics of behavior and its envi-

ronmental control are more fully appreciated for trying to understand those behavioral effects.

Specific conditions favoring the comparative influence by a particular behavioral process on manifestation of tolerance remain unclear, however, and so it is not evident why reinforcer frequency, for instance, is sometimes overridingly important (8,26,29) and sometimes not so important (23,30). It remains evident, however, that reinforcement processes can routinely influence the initial development of tolerance, and results of the present experiment reemphasize that steady-state behavior in the presence of chronic drug can remain sensitive to its consequences, and that the tolerance process itself continues to be influenced by ongoing behavior.

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