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BRIEF COMMUNICATION

Effects of Fixed-Ratio Requirement on Observed Tolerance to Decreased Responding by Clonidine

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SMITH, J. B. *Effects of fixed-ratio requirement on observed tolerance to decreased responding by clonidine.* PHARMACOL BIOCHEM BEHAV 36(4) 993–995, 1990.—Responding of rats was maintained under either a 10- or a 40-response fixed-ratio schedule, and "local" rates of responding were 0.29–0.37 responses per sec for both schedules. Clonidine decreased responding for both schedules in a similar and dose-dependent manner, and the largest dose tested (0.3 mg/kg) completely suppressed behavior. When 0.1 mg/kg was administered immediately prior to 30 daily experimental sessions, FR10 responding recovered to control levels within 15 sessions, whereas FR40 responding recovered only to approximately 60% of control level at asymptote. These results continue to identify boundary conditions for the influence of reinforcer loss on tolerance development, and they emphasize the overriding influence of behavioral processes on observed tolerance to the behavioral effects of drugs.

Clonidine Tolerance Fixed-ratio responding

THERE is an increasing awareness of behavioral influences on tolerance development from both associative effects of the pairing of drug-produced and environmental stimuli (7,8) and from the effects of response consequences that occur in the presence of those paired stimuli (1, 6, 13–15). However, there remains considerable variation for these influences among different drugs, experimental conditions, and perhaps species. For example, tolerance develops more completely to decreased responding by chronic clonidine when behavior is maintained by food or water presentation (5) than when it is maintained by avoidance or titration of electric stimuli (10,11), in spite of a continued increase in shock intensity or frequency under the latter conditions. In addition, tolerance develops more slowly, and perhaps less completely, for fixed-ratio than for fixed-interval responding of pigeons that is decreased by morphine (9), and complete tolerance may not develop at all for response rate decreases under relatively large fixed-ratio schedules for cocaine (3), physostigmine (2), or the cannabinoid *l*-nantradol (12). The purpose of the present experiment was to continue studying the influence of schedule parameter on tolerance development, and responding in two groups of rats was maintained under either FR10 or FR40 during daily administration of 0.1 mg/kg clonidine.

METHOD

Subjects and Apparatus

Ten experimentally naive male Charles River CD albino rats (F344) were maintained at approximately 300 g body weight. The apparatus has been previously described (13).

Procedure

Nose-key pressing was maintained under a 10-response (n = 5) and a 40-response (n = 5) fixed ratio (FR) schedule of food presentation (0.045 g Noyes pellets) and animals received once weekly IP administration of clonidine hydrochloride immediately prior to 45-min sessions (0.01–0.1 mg/kg; courtesy of Boehringer-Ingelheim). Clonidine has a rapid onset of action and its administration immediately prior to experimental sessions permitted observation of initial behavioral effects. Subsequently, all animals received 0.1 mg/kg clonidine immediately prior to 30 daily sessions. Drug effects are reported as responses per second excluding the latency to first response after each food delivery in order to observe effects on comparable performance under both schedules (see below).

RESULTS AND DISCUSSION

Behavior under both fixed-ratio schedules was characterized by a pause just after food delivery, followed by a comparatively high sustained rate of responding until the next food delivery. Because of different average durations of postfood pause times for the two schedules, overall stable response rate under control conditions was 0.73–0.81 responses per sec under FR10 and 0.48–0.59 responses per sec under FR40. Response rate was more nearly the same after subtracting postfood pause times, and this "localized

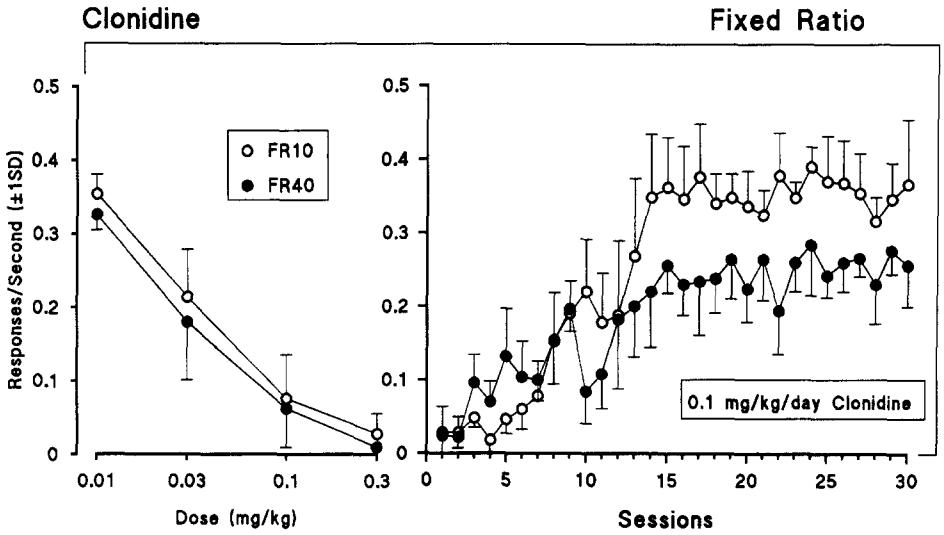

FIG. 1. Effects of acute (left) and repeated daily (right) administration of 0.1 mg/kg clonidine on "local" rate of key pressing (responses per second ± 1 SD) of rats under FR10 (n = 5; open points) and FR40 (n = 5; closed points) schedules of food delivery.

run-rate" was used for comparison of baseline and effects of clonidine (0.29–0.37 responses per sec total range for both schedules).

Saline had no systematic effect on responding under either schedule, and acute administration of clonidine systematically decreased responding for both schedules in a similar and dose-dependent manner (Fig. 1, left). When 0.1 mg/kg clonidine was repeatedly administered prior to daily sessions, responding recovered to a fuller extent for behavior under the FR10 than under the FR40 schedule. FR40 responding remained disrupted and appeared to asymptote at a significantly lower rate from Session 15 onward [Fig. 1, right; $t(30) = 13.579$].

The present results for the FR10 schedule are consistent with a previous experiment reporting tolerance development to rate decreases of clonidine on responding of rats under an FR20 schedule (4), but there are no previous reports of partial tolerance for decreased responding by clonidine for larger FR schedules. The present findings are also consistent with previous experiments reporting the influence of FR requirement on tolerance to behavioral effects of cocaine (3), physostigmine (2), and the cannabinoid *l*-nantradol (12).

The present findings are notable for at least two reasons. First, they continue to help identify boundary conditions for the influence of reinforcer loss (or "response cost") on tolerance development. In the previously mentioned experiment with the cannabinoid *l*-nantradol, pigeons responding under FR300 continued to lose available food for nearly 2 months without any tolerance (12), and in the present experiment, food continued to be lost for one month with incomplete tolerance for rats responding under FR40. Thus, the singular loss of reinforcers is insufficient for engendering complete tolerance under fixed-ratio schedules, and consideration of additional influences like "work requirement" may become useful.

It is important to recognize, of course, that the present data do not indicate whether responding maintained under the FR40 schedule would have returned to predrug rate if clonidine had been discontinued, and so a part of the continued suppression of this responding might have resulted from an altered baseline rather than continued clonidine. However, the very influence of food-related schedule parameters on interpretation of tolerance development emphasizes the notable importance of behavioral processes in helping to understand tolerance to the behavioral effects of drugs. Even though tolerance is not invariant for all circumstances of reinforcement loss, tolerance nevertheless remains strongly influenced by important schedule parameters determining the frequency of reinforcers.

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