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BRIEF COMMUNICATION

Haloperidol Produces Within-Session Increments in Operant Response Duration in Rats

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LIAO, R. M. AND S. C. FOWLER. *Haloperidol produces within-session increments in operant response duration in rats.* PHARMACOL BIOCHEM BEHAV **36**(1) 199–201, 1990.—On the basis of previously reported observations that haloperidol induces within-session decrements in operant response rate in rats, it was suspected that other measures of operant behavior may also display within-session changes after treatement with this neuroleptic. Accordingly, haloperidol (0.02, 0.04, 0.08, 0.16 mg/kg) was administered to six rats trained on a fixed-ratio 20 schedule of liquid food reinforcement, and response duration was recorded as a measure of drug effects independent of response rate. Significant within-session decrements in response rate and *increments* in response duration were observed as responding ensued. At the 0.08 mg/kg dose, 300% increases in response duration were seen during the last third of the responses made in a session. The progressive slowing of individual motor acts were interpreted as neuroleptic-induced Parkinsonism in the rat, and within-session decrements in response rate were likewise seen as a manifestation of the same pharmacological effects that increased response duration.

Neuroleptics Haloperidol Response duration Within-session decrements Parkinsonism Rats

HALOPERIDOL, a relatively selective dopamine (DA) D2 receptor blocker, has received considerable attention for its antipsychotic efficacy as well as induction of unwanted side-effects (e.g., parkinsonian-like syndrome). Wise (16) has presented evidence consistent with the hypothesis that the disruptions of behavior produced by DA antagonists, such as haloperidol, are due to effects on reward mechanisms. However, this proposed "anhedonia" effect is probably not the only action of neuroleptic drugs as indicated by substantial evidence implicating dopaminergic basal ganglia pathways in motor control (2) and other functions (1,12). Numerous studies support the contention that relatively low doses of neuroleptics engender motor deficits in laboratory animals [e.g., (3, 5, 6, 12, 15)] and that deficits in response initiation and maintenance resemble Parkinson's disease symptoms in important ways [e.g., (6,9)]. In addition to slowing the execution of individual operant responses [i.e., a lengthening of response duration (4, 6–8)], haloperidol occasions within-session decrements in operant rate and increments in latency to respond (14). Such within-session decrements in performance have been likened to the rapid fatiguing seen in Parkinson's patients (9,15). We report here that not only does haloperidol produce a within-session decrement in response rate, but it also produces a lengthening of response duration that accompanies the rate decline, and dramatic within-session increases in response duration occur before the haloperidol-treated animals cease responding.

METHOD

Subjects

Six male Sprague-Dawley rats, averaging from 300–350 g in

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weight, were maintained on a diet of restricted food intake that allowed access to food pellets for 1 hr approximately 30 min after daily sessions. Water was continuously available in the individual home cages. Experimental sessions were administered in the early afternoon during the light portion of the light-dark cycle in the vivarium (lights on 0800–2200).

Apparatus

Four conventional operant chambers were used for the present study. Each chamber measured 23 cm long, 20 cm wide, and 19 cm high, and had aluminum panels in the front and back, while the remaining sides and top were clear Plexiglas. Stainless steel rods running parallel to the front of chamber served as a grid floor. Illumination was provided by a 24-volt GE 1819 light bulb 4 cm from the chamber top on the left panel. The top of the manipulandum (Gerbrands Co., Rat Lever G6312) was 8 cm above the grid floor and positioned in the center of the front panel. The lever extended 1.5 cm into the chamber and was calibrated for a 20 g force requirement. Mounted on the lower left corner of the front panel was a cylindrical recession permitting access to a solenoid-operated dipper with a volume of 0.05 ml. The operant chamber was enclosed within a ventilated, sound-attenuating cabinet. Programming of contingencies and recording of data were accomplished with a laboratory computer (Corona PC) and associated peripherals. The data recording system measured response duration (the amount of time the manipulandum was held in the switch-closed position for each operant response) to the nearest 1/32 sec (0.03125 sec).

Procedure

Food-deprived rats learned to press the lever for the reinforcer, which was Borden's sweetened condensed milk diluted with an equal amount of distilled water. Lever pressing was acquired by the rats without experimenter intervention by simply exposing the rats, on two separate days, to two 30-min sessions while a continuous reinforcement contingency was in force. Single sessions of continuous reinforcement, fixed-ratio 5 (FR5), and FR10 schedules were conducted before rats responded on a FR20 schedule. Each daily session was 30 min in duration. Following twenty sessions of FR20 responding, the effects of haloperidol (0.02, 0.04, 0.08 and 0.16 mg/kg) were evaluated. Dosing was counterbalanced across order of administration. Vehicle was given in the session prior to a drug injection session which was followed by an intervening no-injection FR20 session (i.e., drug injections were separated by 72 hr). Haloperidol (McNeil) was prepared in a vehicle solution of warm lactic acid (0.002 M) and injected intraperitoneally 45 min before a session started. Each injection was administered in a constant volume of 1 ml/kg.

RESULTS

Figure 1 illustrates the dose effects of haloperidol on response rate and response duration. Haloperidol significantly decreased response rate, $F(4,20) = 15.793$, $p<0.001$, in a dose-related fashion. Visual inspection of cumulative records (not shown) indicated that at all doses all rats responded at the beginning of the session. These cumulative records also showed that animals ceased responding before session's end as dose increased; for the four doses of haloperidol, in succession, the number of rats that stopped responding before the 30-min session was completed was 1, 1, 3, and 6. Response duration was significantly *increased* by haloperidol: $F(4,20) = 6.203$, $p<0.01$. For both variables, Newman-Keuls post hoc comparison tests indicated that the significant dose effects began at the 0.08 mg/kg dose. A within-session analysis for the response rate variable expressed by the number of responses for

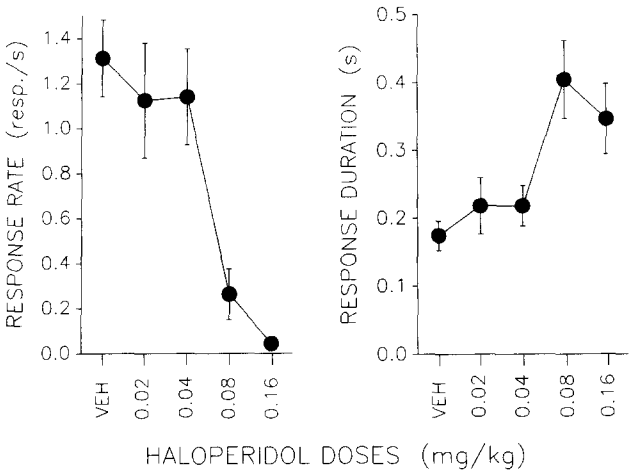

FIG. 1. Haloperidol dose-effect functions for response rate and response duration based on six rats lever pressing on a fixed-ratio 20 schedule of sweetened milk reinforcement. Brackets represent ± 1 standard error of the mean (SEM).

each successive 10-min interval revealed that haloperidol produced a significant within-session decline in responding: $F(2,10) = 15.542$, $p<0.01$.

To the extent that the duration-incrementing effect of haloperidol is similar to a Parkinson's disease symptoms (rapid tiring accompanied by progressive slowing) one would expect that the within-session changes in behavior would be more dependent on the amount of behavior emitted as compared to the mere passage of time within the session. Accordingly, instead of conducting the within-session analysis on the basis of 10-min intervals, the within-session analysis of the duration variable was based on successive one thirds of total responses made in the session (see Fig. 2). In this way the analysis emphasized the possible contribution of the rat's preceding behavior to its subsequent within-session decline in performance. In addition, such an analysis strategy permitted the estimation of mean duration even for rats

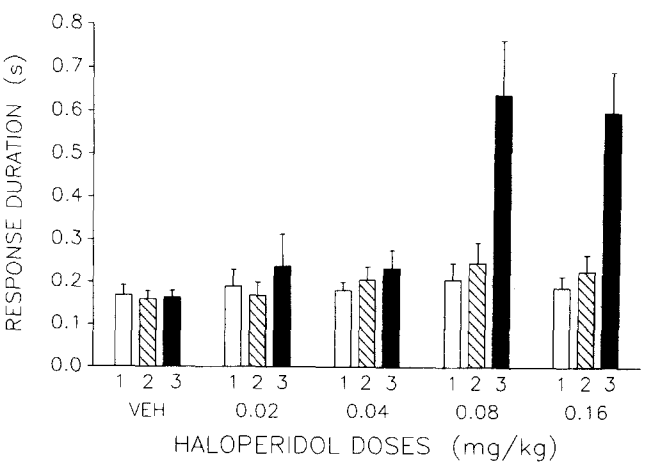

FIG. 2. Joint effects of dose of haloperidol and successive thirds of responding on response duration. Thirds of responding (indicated by the numerals located below each bar) were based on the number of responses each rat emitted instead of the passage of time in the operant session. Brackets denote ± 1 SEM.

that made only a few responses before stopping altogether. Readers familiar with the older conditioning and learning literature will recognize the averaging-by-thirds procedure as "vincentizing" (10). These vincentized duration data were entered into a two-factor repeated measures analysis of variance (three within-session thirds by five doses), and it indicated that haloperidol produced a significant dose effect, $F(4,20) = 10.478$, $p<0.001$, as well as a within-session increment effect, $F(2,10) = 21.472$, $p<0.001$. A significant interaction was also detected: $F(8,40) = 5.609$, $p<0.001$. As shown in Fig. 2, the significant interaction was the result of the absence of within-session change under the vehicle condition with tendencies for small within-session changes at the two lower doses and quite large effects for the last third of responding at the two higher doses.

DISCUSSION

As expected, haloperidol produced significant response suppression of the behavior maintained by a FR20 schedule of liquid food reinforcement. That haloperidol increased response duration suggests that motoric deficits [in the temporal domain, as opposed to the force domain of response execution (7)] may be involved in the rate decrements occasioned by this drug. That is, slowing of individual responses contributes to a decline in overall rate, just as nonresponding does, because longer duration responses mean fewer responses per unit time. Furthermore, the increase in duration that occurred as the responding progressed within a session indicates that the motoric deficit grows as a function of the amount of behavior emitted. It will be recalled that the cumulative records showed that at the two highest doses rats ceased responding before the session ended, and they stopped at different times as well. Thus, the within-session lengthening of response duration was not a simple function of time within the session. Moreover, the dose effect functions in Fig. 1 for both response rate and response duration exhibit an almost step-wise change between 0.04 and 0.08 mg/kg; inspection of the cumulative records and quantitative analyses of other data (9) suggest that this discontinuity in the dose effect curves is the result of some rats' ceasing responding before the session's end. This overall pattern of haloperidol-induced behavioral change (i.e., progressive slowing of individual responses, lengthening of time between responses, and finally abrupt cessation of responding—"on-off" pattern) is Parkinson-like. These observations are consistent with previous reports on the effects of haloperidol on a variety of different behaviors (5, 9, 14, 15). Moreover, on the theoretical side, the relatively rapid within-session decline in behavior has been attributed to depletion of presynaptic DA pools associated with response emission in the face of both postsynaptic DA receptor blockade and neuorleptic-induced increases in DA release (9,15).

In light of existing pharmacokinetic data (11), the observed within-session changes in response rate and duration are *not* likely to be a reflection of increasing levels of drug in the brain during the 30-min observation period. Published data (11) indicate that peak plasma levels of haloperidol are reached within 30 min of IP injection; moreover, maximal effects of haloperidol on conditioned active avoidance are reached between 30 min and 1 hr after IP injection, with the 30-min interval yielding an effect that is 90% of maximal. Thus, according to the pharmacokinetic data, the levels of haloperidol in plasma and brain were either steady or decreasing during the 30-min operant sessions used herein.

Regardless of the theoretical view taken, when computed in terms of successive thirds of responding, the within-session changes in duration produced by haloperidol are quantitatively impressive. For example, at the 0.08 and 0.16 mg/kg doses the last third of responding had durations about 300% higher than the first third of responding (see Fig. 2). This is all the more noteworthy because response duration is a direct measure of the execution of individual motor acts in contrast to response rate which is derived from both responding and nonresponding. Thus, response duration can be seen as an important measurement for complementing response rate in the analysis of neuroleptics' behavioral effects.

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