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An Update of Fowler and Das:[1] Anticholinergic Reversal of Haloperidol-Induced, Within-Session Decrements in Rats' Lapping Behavior

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DAS, S. AND S. C. FOWLER. *An update of Fowler and Das: Anticholinergic reversal of haloperidol-induced, within-session decrements in rats' lapping behavior.* PHARMACOL BIOCHEM BEHAV **53**(4) 853-855, 1996. – Dopamine receptor-blocking neuroleptics produce progressive decrements in response output during behavioral test sessions. If these response decrements reflect Parkinson-like motor effects of neuroleptic treatment, then within-session decrements should be ameliorated by concurrent anticholinergic treatment. To investigate this question, new within-session data analyses were performed on previously published data that addressed haloperidol-scopolamine influences across the entire session (Fowler and Das, 1994). The peak force and duration of individual licks were recorded for 36 rats along with the number of licks emitted in each daily 2-min session. The effects on this behavior of vehicle and three doses of haloperidol (0.06, 0.12, and 0.24 mg/kg, IP, 45 min before sessions) were evaluated alone and in combination with vehicle and two doses of scopolamine HCl (0.1 and 0.2 mg/kg, SC, 60 min before sessions). Despite the brief sessions, haloperidol produced pronounced within-session decrements, and pretreatment with scopolamine reversed the haloperidol-induced within-session decrements in lick emission. Scopolamine by itself produced within-session increments in all three measures of lapping behavior. The results support the idea that within-session decrements in licking behavior are Parkinson-like and diminish confidence in hedonic interpretations of neuroleptic-induced within-session decrements.

Haloperidol Scopolamine Response decrements Licking Lapping Tongue pseudo-Parkinsonism Peak force Rats

NEUROLEPTICS have been reported to produce within-session decrements in tasks involving both learned (1,3,5,9,11) and unlearned behavior (9) in rats. Early in a behavioral session, neuroleptic treatment may have only weak effects or no effects on instrumental responding, but as the session progresses responding becomes less frequent or ceases entirely (3,11). Experiments have shown that within-session decrements do not depend on the type of reinforcer used, as such decrements have been observed for behaviors maintained by electric shock (11), food (3,10,11), sucrose solutions (5), water (12), or intracranial electrical stimulation of the brain (1).

The present study reports a within-session analysis of data from a previously published paper (4) in which it was reported that the muscarinic anticholinergic scopolamine ameliorated the reduction in rats' licking occasioned by haloperidol treatment. Within-session analyses were not undertaken in that study because it was assumed that the 2-min sessions of behavioral observation were too brief to make such an analysis worthwhile, given the computational effort required for such analyses. However, this assumption was in error as the current results amply demonstrate (i.e., large within-session decrements are robust even in very brief sessions). Moreover, to our

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knowledge, this is the first report showing that haloperidol-induced, within-session decrements in motor responding are reversed by concomitant antimuscarinic drug treatment.

METHODS

Subjects, Apparatus, and Procedure

Because the data were taken from a previously reported experiment (4), methodologic details can be obtained from the cited paper. Briefly, 36 thirsty rats were trained to lick water from the surface of a force-sensing disk (7). The peak force and duration of individual licks were recorded along with the number of licks emitted in each daily 2-min session. The effects of vehicle and three doses of haloperidol (0.06, 0.12, and 0.24 mg/kg, IP, 45 min before sessions) were evaluated alone and in combination with vehicle and two doses of scopolamine HCl (0.1 and 0.2 mg/kg, SC, 60 min before sessions).

Quantitative Analysis

Within-session decrements were examined for the three dependent variables: lick peak force, lick duration, and number of licks emitted. Data were divided into first and second 1-min halves for each variable, and the within-session change in behavior was expressed as a change score by subtracting the first half from the second. This procedure (Fig. 1) resulted in within-session decrements having a negative algebraic sign and within-session increments having a positive sign for each rat. Two-way repeated-measures analyses of variance (ANOVA; four levels of haloperidol by three levels of scopolamine) were applied to the change data to assess treatment effects. Selected planned contrasts, trend tests, or simple-effects ANOVAs were performed as needed to address hypotheses about specific subsets of the data. Occasionally, the degrees of freedom were less than expected for 36 subjects, because some subjects did not respond at all or did not respond during the second half of the session. When no licking occurred for an observation interval, number of licks was assigned the value of zero, and peak force and duration were treated as missing data.

In the previously published paper, data on lick rhythm, as quantified by Fourier analysis, were reported (4). The Fourier techniques could not be applied to the within-session analyses because too few sufficiently long bursts of responding occurred in the second half of the session to permit estimation of the power spectrum and the computation of the dominant rhythm.

RESULTS

Number of Licks

The effects of scopolamine HCl alone, haloperidol alone, and these two drugs in combination on within-session changes in number of licks are shown in Fig. 1A. In the two-way ANOVA, the haloperidol dose effect, scopolamine dose effect, and their interaction were all significant [$F(3, 90) = 7.685$, $p < 0.001$; $F(2, 60) = 53.067$, $p < 0.001$; and $F(6, 180) = 3.346$, $p = 0.004$, respectively]. A linear trend test confined to the haloperidol-only data indicated a significant dose-related, within-session decrement [$F(1, 35) = 37.942$, $p < 0.001$]. In contrast, a linear trend test on the data for scopolamine only confirmed a significant, dose-related within-session increment in responding. As shown in Fig. 1A, concomitant treatment with haloperidol and scopolamine

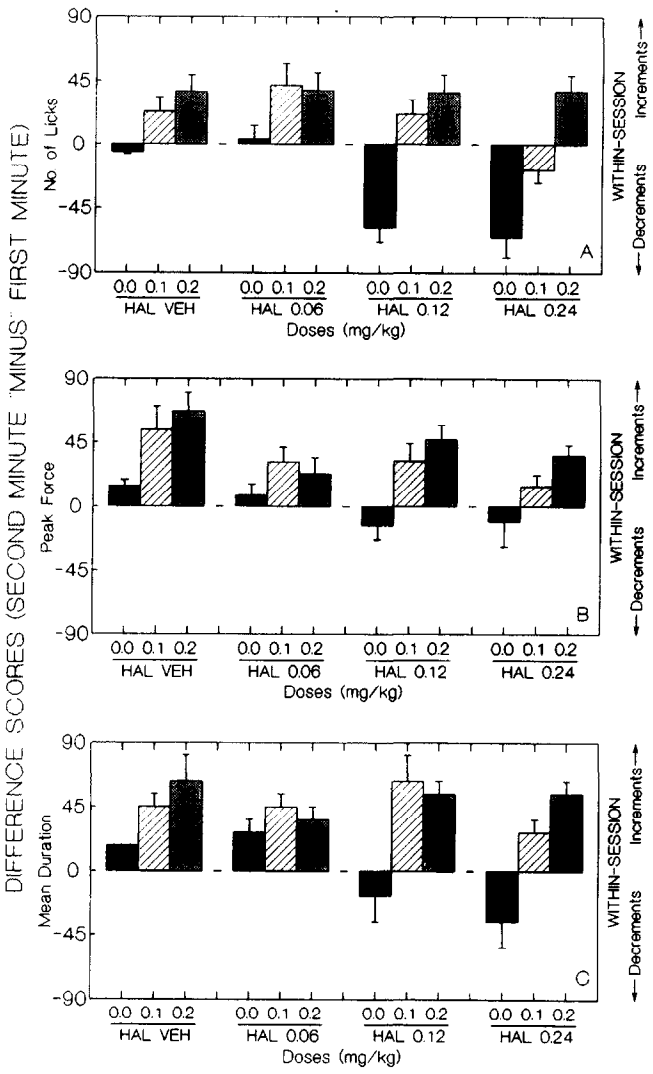

FIG. 1. Effects of haloperidol alone and in combination with scopolamine HCl on changes in lick response output during a 2-min session of rats lapping water from a force-sensing disk. Negative values on each ordinate indicate within-session decrements, and positive values designate within-session increments in lapping behavior. Filled bars give the effects of haloperidol alone. The cross-hatched bars symbolize the effects of scopolamine 0.1 mg/kg administered 15 min before the dose of haloperidol specified by the abscissa labels, and stippled bars indicate the effects of scopolamine 0.2 mg/kg. Dose effects of scopolamine only are given by the leftmost triplet of bars in each panel. Panels A, B, and C are for number of licks, lick peak force, and lick duration, respectively.

transformed the haloperidol decrement into a within-session increment. These effects were quantitatively large. For example, with the 0.24-mg/kg dose of haloperidol in the first half of the session, the mean number of licks was 124.3, but in the second half of the session the average number of licks had dropped to 58.1. When scopolamine 0.2 mg/kg was given 15 min before haloperidol 0.24 mg/kg, these mean values were 186.7 and 224.7 licks for the first and second halves, respectively.

Peak Force

The two-way ANOVA applied to the peak force change data indicated a significant haloperidol dose effect [$F(3, 45) = 4.383$, $p = 0.009$] and a significant scopolamine dose effect [$F(2, 30) = 6.455$, $p = 0.005$]. The interaction was not significant, $F(6, 90) = 0.216$, $p > 0.010$]. The ANOVA supports the graphic view provided in Fig. 1B: Scopolamine generally produced a within-session increment in peak force, whereas haloperidol by itself had little effect on within-session changes in force. The significant main effect for haloperidol in the two-way ANOVA arose from haloperidol's moderation of the magnitude of scopolamine within-session increases in peak force.

Duration

For the lick duration measure, the scopolamine dose effect was significant [$F(2, 30) = 10.188$, $p < 0.001$], but neither the haloperidol dose effect [$F(3, 45) = 1.848$, $p > 0.010$] nor the interaction effect [$F(6, 90) = 1.695$, $p > 0.010$] reached conventional levels of statistical significance. Nevertheless, the graphic trends in Fig. 1C are very similar to those in the other two panels of Fig. 1. It should be recalled that for both the peak force and duration measures, approximately half of the subjects were not included in the repeated-measures ANOVA, because nonresponding in the second half of one or more of the haloperidol-only sessions resulted in missing data. Therefore, for the peak force and duration measures of within-session changes, the ANOVA's probably yielded an underestimate of the drug effects.

Haloperidol-Effects in the 1st Min

For the 1st min of responding, haloperidol produced significant dose-dependent, monotonic decreases in each of the three measures of behavior. ANOVA statistics for dose effects on number of licks, peak force, and duration of licks were $F(3, 105) = 44.066$, $p < 0.001$; $F(3, 102) = 17.201$, $p < 0.001$; and $F(3, 102) = 11.135$, $p < 0.001$, respectively.

DISCUSSION

The data show that even for relatively brief, 2-min samples of intense motor behavior, the neuroleptic haloperidol produced within-session decrements in behavioral output. This finding is in agreement with several other reports on the within-session, behavior-decrementing effects of the classical neuroleptics in somewhat longer task sessions [e.g., (1,3,5,9–12)]. It is important to note that the within-session decrements produced by haloperidol were in addition to dose-related decreases in number of licks, peak force, and duration of licks observed during the 1st min of responding. Thus, the within-session analyses show progressive impairment correlated with the emission of behavior. The fact that the antimuscarinic scopolamine reversed haloperidol-induced, within-session decrements suggests that the within-session decrement is related to haloperidol's Parkinson-like effects (3,4,6). Neuroleptic-induced Parkinsonism in human patients is ameliorated by anticholinergic medication [e.g., (13)], and the symptoms of idiopathic Parkinson's disease are likewise reduced by antimuscarinics [e.g., (8)]. Moreover, progressive response deficits during relatively brief test sessions have been reported for Parkinson's disease patients (2,14). Abrupt cessation of responding by neuroleptic-treated rats (current data, 3) may also be related the on–off phenomenon so often reported for Parkinson's patients [e.g., (8)]. Together, these considerations favor an explanation of neuroleptic-induced within-session decrements as disruptions of motor functions rather than as alterations of motivational processes (15). When administered alone, scopolamine produced significant within-session increments in peak force, duration, and number of licks after initial modest disruptions of these measures of licking behavior (4). We have no straightforward explanation for these results at present, but further analyses of within-session changes in behavior with other anticholinergics and other drug classes appear to be warranted.

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