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Effects of D_1 and D_2 Dopamine Antagonists on Behavior of Polydipsic Rats

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TODD, K. G., C. H. M. BECK AND M. T. MARTIN-IVERSON. *Effects of D_1 and D_2 dopamine antagonists on behavior of polydipsic rats.* PHARMACOL BIOCHEM BEHAV **42**(3) 381-388, 1992—The behavioral and neurochemical effects of SCH3390 (SCH), a dopamine (DA) D_1 antagonist, and haloperidol (HAL), a DA D_2 receptor antagonist, on schedule-induced polydipsia (SIP) were examined. Once animals were made polydipsic, a vehicle or one of three doses of SCH or HAL were administered to seven groups of rats in a series of three five-session blocks in a drug condition, no-drug condition, drug condition design. Detailed behavioral measures and brain regional levels of monoamine neurotransmitters and their major acidic metabolites were analyzed. The volume of water consumed and the percent of time spent drinking was reduced dose dependently by both SCH and HAL. As drinking decreased, the time spent chewing increased for both drugs. The total amount of time animals engaged in all oral behaviors was not changed, suggesting that chewing was substituted for drinking. Neurochemical analysis revealed that HAL increased striatal DA significantly. The polydipsic paradigm may be an advantageous model for examining neuroleptics due to SIP's sensitivity to extrapyramidal side effects.

Schedule-induced polydipsia Drinking Chewing Dopamine SCH23390 Haloperidol Rat Extrapyramidal side effects

FOOD-deprived rats exposed to several sessions of intermittent delivery of food pellets drink voluminous amounts of water (8). Schedule-induced polydipsia (SIP) occurs even though animals are not experiencing any known type of fluid deficit or homeostatic imbalance (9,10).

Dopamine (DA) systems have been implicated in the development of SIP. Specifically, repeated injections of (+)-amphetamine, an indirect DA agonist, facilitated the development of SIP (19), pimozide-, spiperone-, and haloperidol- (DA D_2 antagonists) attenuated SIP (15,24), and lesions of DA-containing terminals in the nucleus accumbens blocked the development and expression of SIP (25,37). Chronic schizophrenia, a condition thought to involve DA system pathology, is often accompanied by polydipsia (34).

DA receptor ligands are also known for their effects on chewing movements (5,7,14,17,20,22,27,28). When ingestion is involved in the drug-induced response, the texture of the food is important. Thus, the DA D_2 receptor agonist (+)-4-propyl-9-hydroxynaphthoxazine (PHNO) induces increased consumption of solid food but not of a liquid diet (18). This may provide another link with polydipsia because the development and expression of polydipsia depends on the texture of the food delivered intermittently. Coarse food elicits polydipsia, whereas powdered food does not (3,21).

These findings raise the possibility that when a DA D_2 antagonist suppresses the drinking of a polydipsic animal drinking decreases as chewing movements increase. If chewing does substitute for drinking, then alternative interpretations for the effect involving reduced hedonic tone (13,30), reduced eating (18,29), and increased sedation (31) would seem less plausible.

Accordingly, the purpose of the present study was to investigate the effects of selective D_1 and D_2 DA antagonists on various types of oral behavior, including drinking, chewing movements, biting objects, and licking, and on neurochemical changes in polydipsic rats. A dose-response analysis was carried out examining the effects of D_1 (SCH23390) and D_2 (haloperidol) receptor antagonists on behaviors elicited by the SIP paradigm. A D_1 and a D_2 antagonist were compared to determine whether these two subtypes of the DA receptor are differentially involved in the maintenance of SIP. In addition, D_1 and D_2 receptor antagonists have been reported to have differential effects on oral behavior (26), although both types of antagonists produce sedation (5) and reduce PHNO-induced feeding (18). Therefore, the two types of DA receptor antagonists might provide a means of dissociating oral behavior effects from sedation or feeding effects. The drugs were administered in five-session blocks in an on-off-on design to

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test for possible differential initiation, withdrawal, and reinitiation effects of the drugs on behavior. In addition, at the end of the experiment the levels of biogenic amines and their major acid metabolites were measured in brain regions containing DA terminals. It was anticipated that relative increases in DA and its metabolites would be found in the striatum. We now report that both DA antagonists reduced drinking and increased nonregulatory chewing movements. Only haloperidol increased DA activity in the striatum.

METHOD

Animals

Fifty-six male Sprague-Dawley rats (University of Alberta, Ellerslie) were housed individually in animal quarters on a 12L:12D cycle with ambient temperature maintained at 22°C. Animals weighed 250–300 g at the start of the project and were given free access to food for 1 week prior to training. Water was freely available throughout the experiment.

Apparatus

Animals were tested in chambers measuring 20 × 23 × 23 cm with Plexiglas walls and ceiling and a metal tray floor. Forty-five-mg pellets were passed from an automatic pellet dispenser to food trays located on a side wall. Water spouts attached to graduated burettes protruding into the chambers 6 cm above the food trays allowed for the measurement of water intake to the nearest 0.1 ml. Training and testing were carried out under low ambient light achieved by covering overhead fluorescent lights with red Mylar film.

Drug Treatments

SCH23390 (Research Biochemicals, Natick, MA) and haloperidol (McNeil, purchased from the University Hospital Pharmacy, Edmonton, Alberta, Canada) were dissolved in distilled water, aliquoted, and kept frozen until immediately before use in volumes of 10μg/ml and 1 mg/ml, respectively. Injections of SCH23390 (SCH) were delivered SC in the haunch 30 min prior to testing. Haloperidol (HAL) was delivered IP 60 min prior to testing. Doses and time intervals of injections were derived from the literature (7,14,17,22).

Procedure

Subjects were handled daily, and their attained weights were recorded as preexperimental weight. Rats were then food deprived and maintained for the duration of the experiment at 80% of their preexperimental weight.

Animals were habituated to the testing room and chambers and made polydipsic through 14 training sessions of 50-min duration. Food pellets were delivered during the sessions on a fixed-time schedule with intervals of 60 s between food deliveries.

Subjects were matched for amount of water consumed at predrug baseline (sessions 13 and 14) and randomly assigned to one of seven treatments with $n = 8$: controls (distilled water, 1 ml/mg); SCH 5, 10, or 20 μg/kg; HAL 0.05, 0.20, or 0.80 mg/kg. Animals were injected and tested behaviorally in squads of seven rats each, with an animal from each drug/dose treatment in each squad. Following training session 14, the experimental sessions consisted of five sessions of drug [*Condition 1* (C1)], five sessions of *no-drug* (ND), and finally five more sessions of drug treatment [*Condition 2* (C2)]. During ND, all animals were injected with distilled water. Videotaped recordings were made of training session 14 (predrug baseline) and of the fifth sessions of C1, ND, and C2. Immediately after the arrival of the last pellet of the last session of C2, animals were removed from the test chamber and killed by decapitation. Brains were removed and the striatum, nucleus accumbens, olfactory tubercule, and prefrontal cortex dissected out on ice. The four brain regions were then stored at −80°C for later biochemical analysis. These brain regions were chosen as they represent primary DA terminal fields of the nigrostriatal, mesolimbic, and mesocortical DA systems. The striatum was expected to show the maximal effect due to its reported involvement in oral behaviors (16,23).

Session videotapes were coded for the following behavioral categories: *drink*, drinking from the water spout; *chew*, any jaw movements observed after ingestion of the pellet and when the mouth is not in contact with the substrate; *bite*, biting the water spout, food tray, or chamber; *rear*, elevation of forepaws from the floor; *lick*, licking of food tray, floor, or walls; *groom*, licking, washing, or scratching of itself; *locomote*, movement of all four limbs from one quadrant of the chamber to another; *immobile*, absence of movement; and *sniff*, investigative movements indicated by nose or head movements that are not accounted for by the other behaviors. An oral composite measure was obtained by combining the measures drink, chew, bite, lick, and groom. Each videotaped session was divided into four 5-min time blocks with interblock intervals of 10 min. For each behavior, percent of total session time spent engaged in the behavior and the frequency of the behavior was recorded. Interobserver and interest reliability measures were obtained for each of the behavioral categories and agreement levels of over 80% were reached for selected sessions.

For each behavior, repeated-measures analysis of variance (ANOVA) was applied to the data with dose as the between- and conditions as the within-subject factors. Heterogeneity of covariance was corrected for with the Greenhouse-Geisser corrections factor and Newman-Keuls analysis was used to assess dose group differences within conditions.

Regional concentrations of noradrenaline (NA), DA, 3,4-dihydroxyphenylacetic acid (DOPAC), homovanillic acid (HVA), 5-hydroxytryptamine (5-HT), and 5-hydroxyindolacetic acid (5-HIAA) were measured using high-pressure liquid chromatography (HPLC) with electrochemical detection (1). Tissues from rats from each experimental group were included in each HPLC run to control for possible incidental variations in HPLC. For each brain region, one-way ANOVA was made of dose effects on neurochemical concentrations, followed by Neuman-Keuls posthoc comparisons of dose differences.

RESULTS

The dose × condition interaction from ANOVA of volume of water consumed was $F(5.0, 47.1) = 7.07$, $p < 0.001$ for SCH and $F(4.2, 39.3) = 61.47$, $p < 0.001$ for HAL. Within both C1 and C2, Newman-Keuls tests showed that the mid- and high-dose groups of both drugs drank significantly less than the vehicle control group (Fig. 1). With SCH treatment, the high-dose group also consumed significantly less water than the low-dose group during both C1 and C2. Following HAL treatment, the high-dose group drank significantly less than the low-dose group in C1 whereas both mid and high drank less than the low group in C2. In the ND condition, the drug holiday between C1 and C2, the volume drunk by experimental animals did not differ from that drunk by the controls. ANOVA of within-condition changes in volume drunk across sessions was not significant so the drug-induced changes in fluid intake occurred quite abruptly.

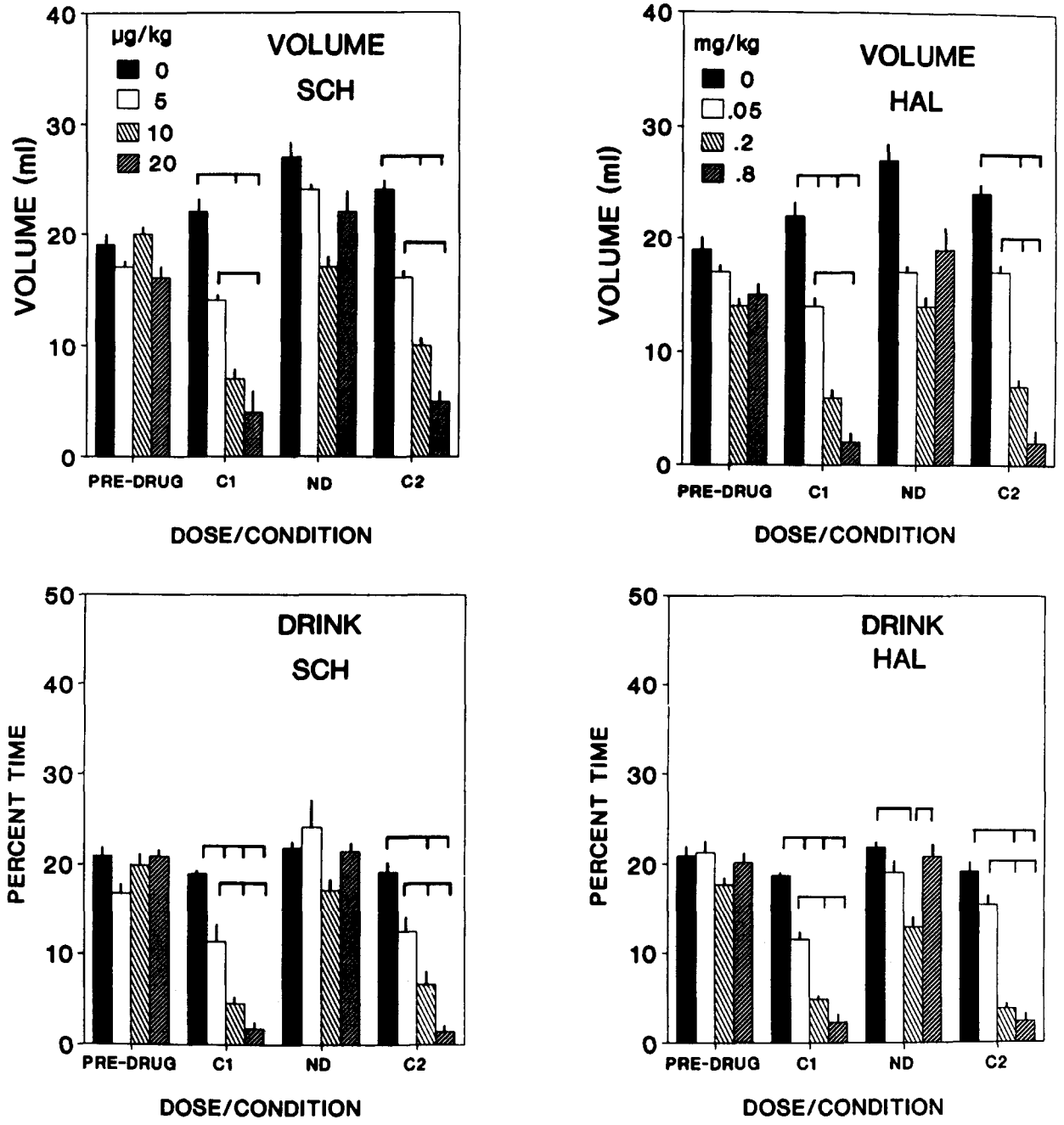

FIG. 1. Mean volume of water consumed and mean percent time per session spent in drink over predrug condition, C1 (first drug condition), ND (no-drug condition), and C2 (second drug condition), for vehicle group and three dose groups for each of SCH23390 (SCH) or haloperidol (HAL) (n = 8). Brackets denote significant differences between dose groups within a condition (Newman-Keuls, $p < 0.05$). Spikes on bars are SEMs.

The percent time engaged in drink behavior supported the findings on the volume consumed. ANOVA produced dose × condition interaction effects of $F(5.3, 49.8) = 8.54$, $p < 0.001$ for SCH and $F(4.6, 42.9) = 14.56$, $p < 0.001$ for HAL. Newman-Keuls comparisons of dose groups within conditions showed that both SCH and HAL dose dependently decreased the amount of time spent drinking during C1 and C2 (Fig. 1). Between C1 and C2, during the no-drug condition, all rats resumed spending normal amounts of time drinking.

ANOVA performed on the percent of time engaged in chew produced dose × condition interactions of $F(3.8, 35.8) = 32.27$, $p < 0.001$ for SCH and $F(3.2, 29.9) = 4.91$, $p < 0.01$ for HAL. Both drugs increased the amount of time animals engaged in chewing in C1 and C2 (Fig. 2). For SCH, this was due to increased chew in all three experimental doses, while for HAL the high-dose group was the only group to increase chewing above within-condition control levels. In the no-drug condition, chew was reduced to control levels for both drugs.

The proportion of interfood intervals in which animals en-

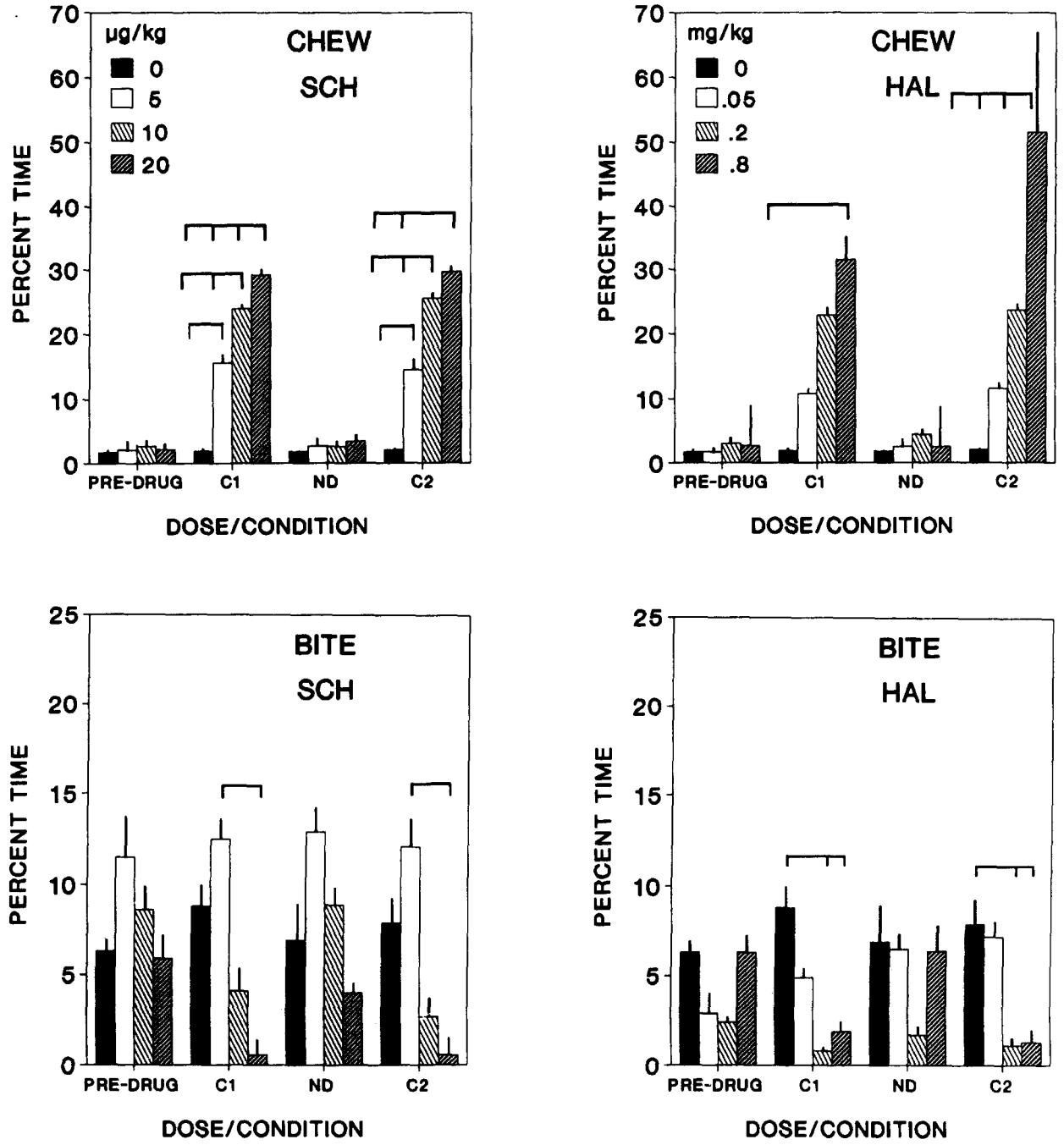

FIG. 2. Mean percent time per session spent in chew and bite during four conditions for vehicle control group and for each of three doses of SCH23390 (SCH) or haloperidol (HAL) (n = 8). Details as in Fig. 1.

gaged in at least one instance of chew did not change significantly as a function of dose or condition for either drug (data not presented).

The percent of time animals engaged in bite produced a dose × condition interaction $F(3.9, 36.4) = 2.71$, $p < 0.05$ for SCH and $F(4.2, 39.3) = 4.25$, $p < 0.01$ for HAL treatment. Pairwise comparisons showed that the high dose of both drugs significantly decreased biting in both C1 and C2 as compared to within-condition vehicle controls (Fig. 2). With HAL treatment, this was also true of the mid-dose animals. In the no-drug condition, the time spent biting did not differ from controls.

The dose × conditions interactions, as well as the main effects for dose and condition, for the behaviors lick and groom were not significant for either drug. Data from the oral composite category obtained by combining the instances of drink, chew, bite, lick, and groom revealed no significant dose × condition interaction (data not presented). Nor were

the dose or condition main effects significant for the oral composite.

ANOVA of time spent in both rear and locomote revealed dose × condition interaction effects for HAL but not SCH, respectively for rear F was not significant with SCH and $F(5.6, 52.5) = 3.1$, $p < 0.05$ with HAL; and for locomote F was nonsignificant with SCH and $F(5.4, 49.9) = 4.77$, $p < 0.01$ with HAL. Within-condition comparisons were significant only for haloperidol (Fig. 3). The drug × condition interactions of time spent immobile were $F(4.8, 44.8) = 4.62$, $p < 0.01$ for SCH and $F(4.6, 42.8) = 9.00$, $p < 0.001$ for HAL. These effects were due to the heightened immobility of the high-dose groups for both drugs (Fig. 3).

ANOVA within brain regions of the relative concentrations of brain neurotransmitters and their metabolites produced significant findings only for the striatum. Mean control levels of

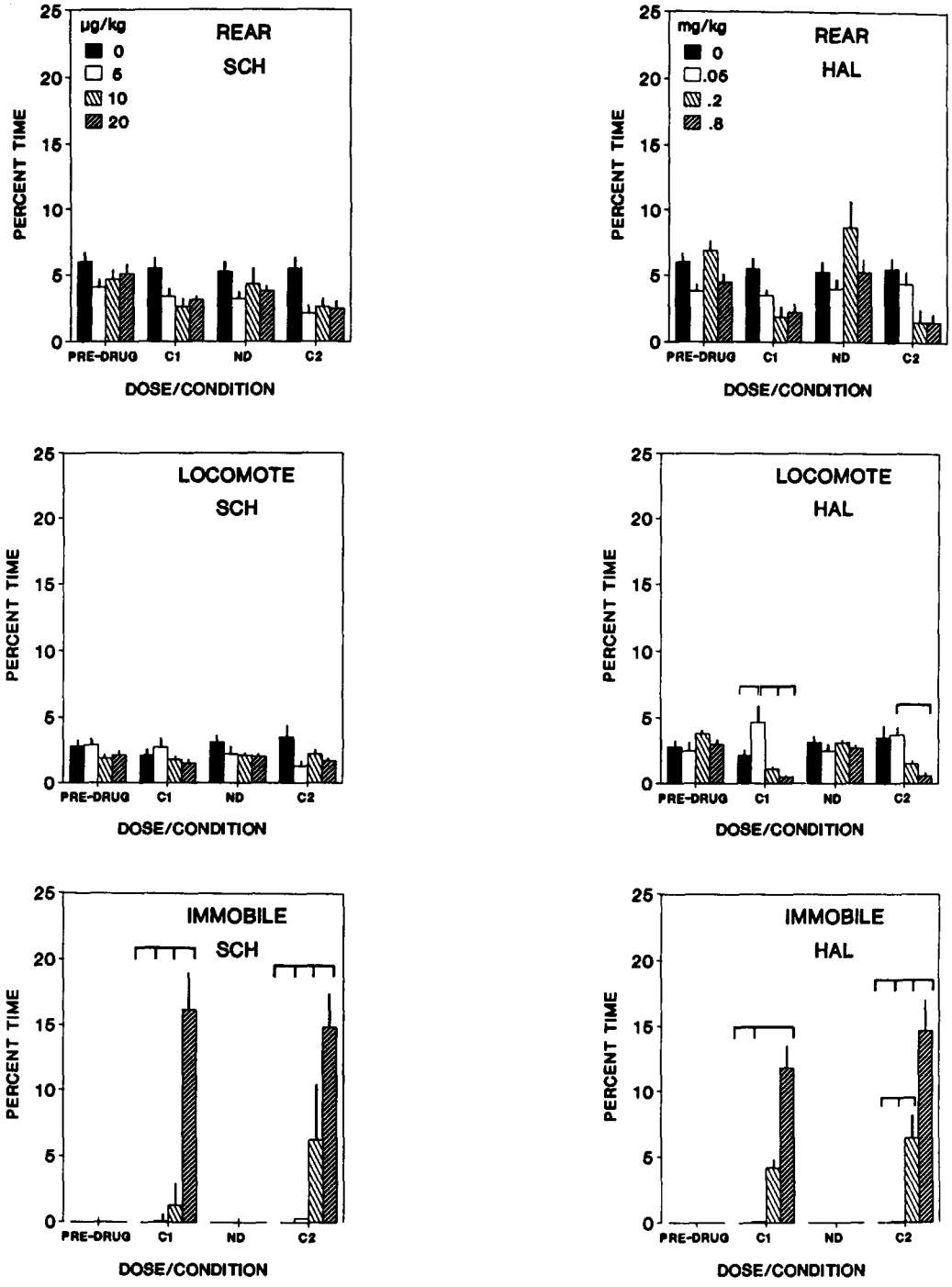

FIG. 3. Mean percent time per session spent in rear, locomote, and immobile during four conditions for vehicle control group and for each of three doses of SCH23390 (SCH) or haloperidol (HAL) ($n = 8$). Details as in Fig. 1.

TABLE 1
MEAN (SEM) IN ng/g FOR LEVELS OF
NEUROTRANSMITTERS AND METABOLITES OF INTEREST IN POLYDIPSIC RATS

	Striatum	Nucleus Accumbens	Olfactory Tubercule	Prefrontal Cortex
NA	516.3 (105)	1031.0 (162)	376.4 (74)	237.6 (64)
DA	3509.1 (380)	4728.3 (451)	1905.1 (257)	129.8 (309)
DOPAC	549.6 (118)	418.2 (130)	351.4 (61)	359.0 (73)
HVA	889.7 (131)	1904.3 (269)	534.4 (111)	246.2 (59)
5-HT	244.1 (86)	297.5 (156)	175.2 (102)	55.7 (92)
5-HIAA	635.8 (69)	1335.0 (168)	671.2 (96)	1366.4 (122)

NA, DA, DOPAC, HVA, 5-HT, and 5-HIAA for the regions are shown in Table 1. Dose main effects of HAL and DA and HVA levels were observed with $F(3, 28) = 4.59$, $p < 0.01$ and $F(3, 28) = 12.47$, $p < 0.001$, respectively, while no effects were found following SCH treatment. Pairwise comparisons showed that HAL low and high doses significantly increased DA levels in the striatum as compared to control (Fig. 4). SCH had no effect on any neurotransmitter or metabolite analyzed in any of the other brain regions, while HAL treatment also resulted in increased HVA in the olfactory tubercule and decreased 5-HT levels in the nucleus accumbens (data not shown).

DISCUSSION

The results confirm previous reports that drinking in SIP rats is dose dependently suppressed by the DA D_2 antagonist haloperidol (15,24). This study is the first to extend the effect of SCH23390, a dopamine D_1 antagonist. Other behaviors that also decreased included bite for both drugs and rear and locomote, primarily for haloperidol.

Our finding of increased chewing movements following haloperidol treatment has frequently been demonstrated for this and other DA D_2 antagonists in nonpolydipsic animals (6,7,17,27,32). Surprisingly, SCH23390 also dose dependently increased chewing. Previous work (26) indicated that vacuous chewing (repetitive jaw movements) is increased by D_1 *agonists* and/or D_2 antagonists, and that this behavior is blocked by coadministration of SCH23390. At the highest dose of both drugs, immobility increased as might have been expected (31).

A principal contribution of the present study is to show how these drug effects are integrated behaviorally. First, reduced fluid intake may have been the result of reduced appetite for food (29). However, the decrease in drinking was not related to decreased consumption of food pellets. This is important because polydipsic animals do not drink if the food pellet is not presented in a specific interval (3). Second, drinking returned to normal levels when drug treatment was suspended and was immediately suppressed when treatment recommenced. This suggests that some short onset, acute effect of the drug was interrupting drinking. Third, the drug-induced increase in immobility would be expected to affect rearing and locomotion more severely than oral behavior (31). Yet, rearing and locomotion were barely affected under haloperidol and not at all under SCH23390. Heavy sedation effects could have decreased drinking by decreasing eating, but this has already been ruled out. In sum, it is unlikely that drinking decreased as a result of loss of appetite, perduring drug effects, or sedation effects.

Rather, it is apparent that drinking and biting declined as chewing increased. Remarkably, the overall level of oral activity remained constant not only across doses but across conditions as well for both SCH23390 and haloperidol. The implication is that the drugs repartitioned the variance allocated to oral subsystems, biasing oral expression toward movements that did not require contact with the substrate. By contrast, apomorphine, a dopamine agonist, biases the animal to make oral movements in contact with the substrate (2,33). In the present study, it is as if the polydipsic rat had a temporal requirement for a high (2–10 × normal) constant oral output per session. As such, the system output is modifiable in topography but not in total duration. In this respect, the drug effect on polydipsic drinking is identical to the effect of powdered food (3). Both substitute drinking and biting for an equal duration of another oral behavior.

The temporal constancy of output of the oral system suggests that a common neural mechanism is in control. The striatum, especially its anteroventral portion, is a likely site (16,23). In the present study, the only significant neurochemical effects of HAL were increases in DA and HVA levels in the striatum. Acute injections of HAL decreased DA levels, yet increased concentrations of DA metabolites in striatal and mesolimbic terminal fields (11). On the other hand, repeated injections of HAL decreased HAL-induced metabolism of DA, likely because of development of depolarization blockade (11). This latter phenomenon is consistent with the present findings of apparent tolerance to the effects of HAL or DA metabolism. However, the degree of tolerance is greater than that previously reported (11). The possibility that haloperidol's effects on DA turnover are different in polydipsic animals compared to normals cannot presently be ruled out.

SCH23390 had no significant effect on monoamine or monoamine metabolites in keeping with the literature (5), suggesting that D_1 antagonists have no effect on DA autoreceptors. This indicates that the D_1 receptor is not involved in the autoregulation of DA neurons, as is the case with D_2 receptors. Since D_1 and D_2 agonists have similar effects on oral behaviors but different effects on DA metabolism, it is clear that the behavioral effects of these drugs are due to actions postsynaptic to the DA neurons. Further, striatal DA levels for control polydipsic rats seen in the present study were approximately two thirds that found in non-food-deprived control rats previously observed in our laboratory, while HVA levels were comparatively increased. Striatal DA levels have also been reported in food-deprived rats to be as high as 9540.0 ng/g (4); these findings suggest SIP may be associated with an increased turnover of DA in the striatum. The greater than usual degree of apparent tolerance to HAL in the poly-

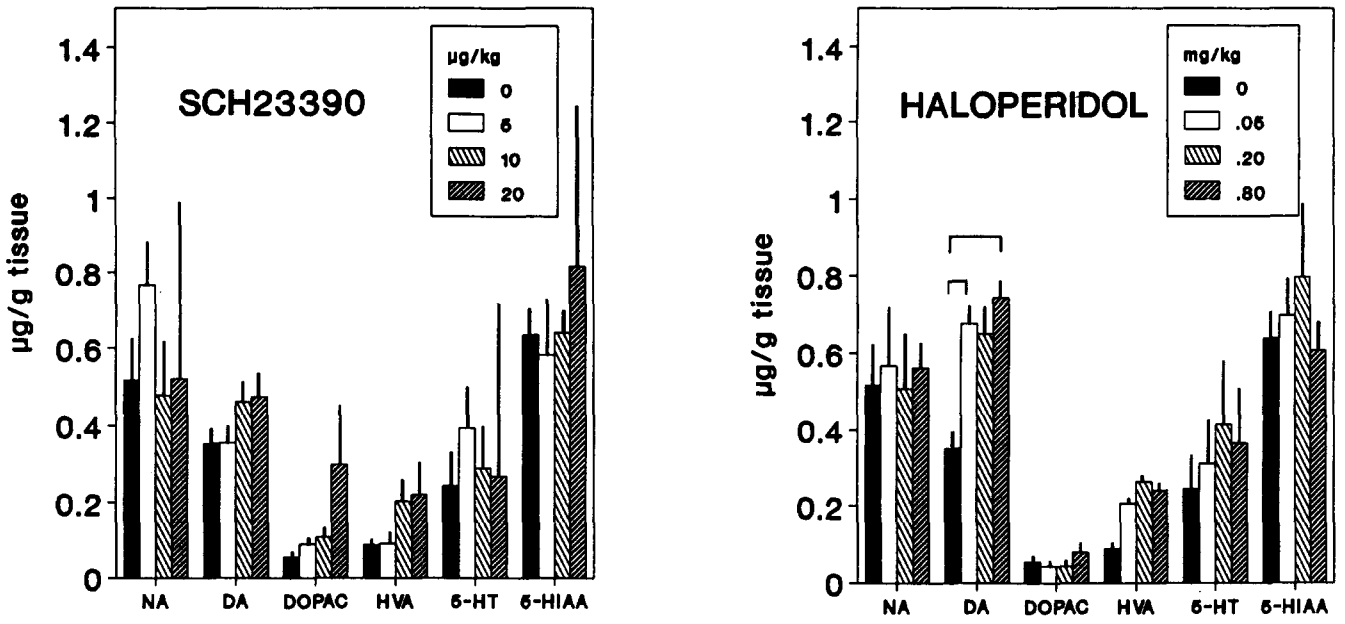

FIG. 4. Mean (µg/g of tissue) striatal concentrations of biogenic amines and their acid metabolites in different groups following treatment with vehicle or three doses of each of SCH or HAL. Ordinate scale for DA, DOPAC, and HVA is 0.1. Brackets denote significant difference of group mean from vehicle control group mean (Newman-Keuls, $p < 0.05$). NA, noradrenaline; DA, dopamine; DOPAC, 3,4-dihydroxyphenylacetic acid; HVA, homovanillic acid; 5-HT, 5-hydroxytryptamine; 5-HIAA, 5-hydroxyindoleacetic acid.

dipsic rats may reflect an increase in basal DA metabolism during polydipsia.

The chewing induced by both drugs may reflect a dystonic movement pattern rather than the dyskinetic pattern typically seen after chronic neuroleptic treatment in humans (27,35). Specifically, chewing in the present study was elicited acutely and did not persist after withdrawal of drug, which is consistent with dystonia (36). Dyskinesias following chronic neuroleptic treatment typically show a late onset with teeth grinding that persists after drug withdrawal (27). A D_1 antagonist (SCH39166) is currently undergoing clinical trials for the treatment of schizophrenia and it is hoped that this drug will have less extrapyramidal side effects (EPS) than do typical antipsychotics, as is the case with clozapine, a neuroleptic with a relatively high affinity for D_1 receptors. However, if chewing in rats with SIP is relevant to EPS, then the present data indicate that D_1 antagonists may have a propensity to induce EPS similar to that of D_2 antagonists. Such a conclusion is supported by oral dystonias induced by SCH23390 in primates withdrawn from 2-year HAL treatment (22) and by a review of preclinical effects of SCH23390 (12). If SCH39166 is found to produce EPS, then the effect of drugs on nonregulatory chewing in the SIP paradigm is likely to be extremely sensitive to the EPS potential of neuroleptics.

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