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Behavioral and Neurochemical Effects of Dopamine D1 and D2 Antagonists on Schedule-Induced Polydipsia

by

Kathryn Grace Todd 

A Thesis

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in Partial Fulfillment of the Requirements for the

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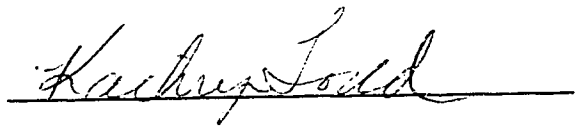

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The undersigned certify that they have read, and recommend to the Faculty of Graduate Studies and Research, for acceptance, a thesis entitled Behavioral and Neurochemical Effects of Dopamine D1 and D2 Antagonists on Schedule-Induced Polydipsia in rats, submitted by Kathryn Grace Todd in partial fulfilment of the requirements for the degree of Master of Science.

Dr. Charles Beck (Supervisor)

Dr. Dallas Treit

Dr. Mathew Martin-Iverson

Date June 19/91

DEDICATION

This thesis is dedicated to my Grandmother, Jean Henning, my mother, Dallas Henning and my sister, Madelyn Todd, whose love and encouragement were unsurpassed and greatly appreciated.

Abstract

The behavioral and neurochemical effects of dopamine D1 and D2 receptor antagonists on schedule-induced polydipsia were examined. Three doses of SCH23390 (D1) and haloperidol (D2) were administered once the animals were made polydipsic. Polydipsic controls were run concurrently with the drug animals. Behavioral analysis and levels of monoamine neurotransmitters and their major acidic metabolites were reported. All drug doses for both drugs attenuated the amount of water consumed in a session. This drinking was restored following drug withdrawal. During drug treatment the percent of time animals were engaged in chewing movements was significantly increased for both drugs. Further behavioral analysis showed the amount of time animals engaged in all oral behaviors was not changed, suggesting that chewing was substituted for drinking. Neurochemical data revealed that polydipsic animals had decreased levels of dopamine in the striatum. Both drugs increased striatal DA levels, haloperidol significantly. The results are interpreted within the context of a sensitization model of schedule-induced polydipsia.

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List of Abbreviations

HAL	Haloperidol
SCH	SCH23390
NA	Noradrenaline
DA	Dopamine
DOPAC	3,4-Dihydroxyphenylacetic acid
HVA	Homovanillic acid
5-HT	5-Hydroxytryptamine
5-HIAA	5-Hydroxyindoleacetic acid
HPLC	High pressure liquid chromatography

I. Introduction

The phenomenon of excessive drinking by hungry rats was first reported by Falk in 1961. He noted that food deprived rats consumed excessive amounts of water while bar pressing for food on a variable-interval schedule. The rats drank almost half of their body weight in water, an amount that exceeded that produced by water deprivation, heat stress or osmotic loading. This behavior then, because of the dependence on a schedule of food delivery and resultant escessive consumption liquid, was coined "schedule-induced polydipsia" (SIP).

A variety of factors affecting the behavior have since been delineated. These factors include the level of food deprivation whereby the amount consumed increased with level of food deprivation (Falk, 1969); the amount of time between food delivery, where increased interfood interval increased drinking until the interval reached 120 seconds at which point drinking was decreased (Flory, 1971); and the amount of food delivered, where larger amounts of food delivered at a single time resulted in less drinking (Yoburn and Flory, 1977). Keeping these conditions in mind, SIP may be reliably elicited with a 45 mg pellet delivered on a fixed-time schedule of 60 sec to rats food deprived to 80% of their free feeding weight. Under these conditions, rats may be seen to gradually increase the amount of water consumed in a

session until a maximum (asymptotic) level is reached, typically in about 14 days (Flory, 1971). The behavior is unique in that is enduring, will extinguish immediately upon cessation of scheduled food delivery and yet will immediately resume if the schedule is reapplied (Falk, 1969). The elicitation of this behavior may also be seen in a variety of species including rats, monkeys (Schuster & Woods, 1966) and humans (Kachanoff, Leveille, McClelland & Wayner, 1973).

Many explanations have been proposed to account for the development of SIP. Included in these are theories that SIP serves an adaptive role in stress reduction. More specifically, Falk (1969) proposed a motivational theory for the development of SIP in that food-deprived rats under scheduled food delivery were motivated to drink because their desire to eat was thwarted by the intermittency of food arrival. That is, the animals displaced their eating behavior with drinking behavior. This motivational theory of SIP is a specific example of Timberlake and Allison's adaptive model of performance (1974). This model suggests that a schedule may indicate the sequence and variability of behavior. These behavioral constraints then conflict with normal behavior. The conflict is then resolved by the performance of an instrumental behavior. Within the SIP model, this theory would predict that the resolution of the conflict for food is resolved by excessive drinking.

Another theory which may characterize SIP is Premack's probability-differential hypothesis (1959) in which he suggested that for any two responses, the more likely response (higher probability) will reinforce the less likely one (lower probability). In the SIP paradigm, the more probable response - eating the delivered pellet may reinforce the less probable response - drinking. However, this theory is somewhat difficult to employ as an explanation for SIP as drinking does not fit the descriptor of low probability response. The SIP paradigm results in relatively few behaviors being expressed other than drinking and eating which are both high probablity responses.

Beck, Huh, Mumby & Fundytus (1989) proposed a form of behavioral sensitization to account for SIP. This theory suggested that animals in a heightened state of arousal due to food deprivation were sensitized to drinking by repeated presentation of food pellets. This sensitization took time to develop, and immediate cessation of the sensitized behavior occured upon withdrawal of the eliciting stimulus. The sensitization theory is attractive in that it accounted for the gradual development of SIP and its immediate reduction upon discontinuance of food delivery.

A number of studies have looked at pharmocological effects on drinking behavior. Cholinergic antagonists were found to decrease drinking somewhat (Singer & Kelly, 1972). Amphetamine treatment was found to decrease drinking (Segal

& Oden, 1968) but also to have no effect on oral type behaviors in a paradigm unrelated to SIP (Levy & Ellison 1987). Diazepam, a benzodiazepine receptor agonist, was found to decrease SIP, however these effects were confounded by a depression in overall activity levels (Mittleman, Jones and Robbins, 1988). To date, pharmacological manipulations have yet to posit a putative neural substate for SIP.

Lesion studies have shown that central dopaminergic systems may be involved in SIP behavior, but they have yet to be clearly elucidated. Specifically, lesions of dopaminergic terminals within the nucleus accumbens were found to block the development of SIP (Robbins & Koob, 1980). More recently, the dopaminergic system has been implicated in a generic category of oral movements in which dopamine D1, D2 and non specific D1/D2 agonists have been found to variously increase, decrease or have no effect on oral behaviors (Clark & White, 1987). However, through all the inconsistencies, oral grooming and abnormal perioral movements habe been reported to be more commonly elicited with dopamine D1 agonists (Clark & White, 1987).

The implication of dopaminergic mechanisms in SIP leads to further hypotheses regarding the mechanisms of this phenomenon. Wise and his colleagues (1982) proposed an "anhedonia" hypothesis of neuroleptic action that suggested neuroleptics (primarily D2 antagonists) reduced the pleasurable (hedonic) value of rewards. Within the SIP

paradigm, the assumption would be that drinking is rewarding and thus increased. Dopamine D2 antagonists then would lead to a decrease in this behavior by reducing its rewarding properties. The anhedonia hypothesis has recently fallen into disfavor due to a lack of internal logic and empirical evidence (Martin-Iverson, Fibiger & Wilkie, 1988). Specifically, it has been shown that that neuroleptics such as haloperidol (D2 antagonist) affect motoric rather than motivational processes (Martin-Iverson, Fibiger & Wilkie, 1988), and that they do not block stimulus control of behaviors (Beninger, 1982). It is unlikely then that the anhedonia hypothesis is relevant to SIP.

A more relevant issue with regard to dopamine functioning and SIP is that involving the effects of stress. A reduction in behavioral responsiveness to environmental stimuli has been observed with decreased functioning of dopamine neurons in diseases such as Parkinsonism (Hornykiewicz, 1979) and in animals lesioned with the dopamine neurotoxin 6-hydroxydopamine (Ungerstedt, 1971). These impairments were suggested to be deficits in activation of responsiveness and not primarily motor or sensory in nature as they could be reversed by adding a stressful or activating stimuli. Further, physiological and psychological stressors have been shown to increase activity of substantia nigra dopamine neurons (Monnet & Lichtensteiger, 1981), release dopamine from terminals in

both cortical and limbic areas (Thierry, Tassin, Blanc & Glowinski, 1976) and in the striatum (Curzon, Hutson & Knott, 1979).

These findings of increased dopamine release may be significant in that dopamine neurons may be involved in two processes; one in mediating the behavioral effects of primary incentive stimuli and the other in general behavioral arousal (Beninger, 1982). In the SIP paradigm, stress may be induced by food deprivation and the food delivery schedule resulting in increased dopamine release in the substantia nigra, cortex, or striatum. The net result may be increased responsiveness to relevant environmental stimuli such as the availability of water, leading to increased drinking behavior. Beninger (1982) stated that neuroleptics would always produce a dose-dependent decrease in operant behavior whether it was conditioned or unconditioned. Within the SIP paradigm this hypothesis would predict that dopamine antagonists would lead to a dose-dependent decrease in drinking by decreasing the animals level of responsiveness to the activating stimuli of food delivery.

The purpose of the present experiment was to more clearly elucidate the role of the dopamine system in SIP. As dopaminergic systems in the striatum, limbic system and cortex have been implicated in motivation (Beninger, 1982) motoric and sensory functioning (Hornykiewicz, 1979) and

stress (Curzon Hutson & Knott, 1979) it was felt a pharmacological manipulation of the system would aid in the definition of neural substrates of SIP. Specifically, the possibility of a receptor sub-type mediation was of particular interest.

Dopamine D1 agonists, acting primarily postsynaptically, have been found to elicit oral type behaviors such as oral grooming and chewing; D2 receptors, located both pre and postsynaptically, have been found to mediate locomotor behaviors such as sniffing and rearing (Clark & White, 1987). Therefore, it was hypothesized that SIP being an oral behavior would be more likely to be elicited and possibly sensitized through D1 rather than D2 receptor activation. Specifically, the gradual development of SIP would result in a gradual sensitization of the D1 receptor leading to increased oral behavior to environmentally relevant stimuli - the water spout.

As polydipsic rats reach an asymptote water intake within 15 days of training in the SIP paradigm (Falk, 1971), it was felt that ceiling effects were likely to occur with an agonist manipulation (ie. it would be impossible for the animals to increase drinking over asymptotic levels), therefore an antagonist manipulation was employed. Dopamine D1 and D2 antagonists have been reported to reduce locomotor activity, rearing, and produce yawning in moderate doses (Clark & White, 1987). Dopamine D2 antagonists have been

reported to induce dyskinetic oral movements after chronic treatment and dystonic movements after acute treatment (Rosengarten, Schweitzer & Friedhoff, 1983). This may reflect an activation of D1 over D2 receptors after D2 blockade.

For the purpose of the present study, two dopamine antagonists, SCH23390 (D1) and haloperidol (D2) were chosen based on their common useage in the literature (Clark & White, 1987). A range of three relatively low doses was chosen to minimize general sedating effects. The hypothesis for the study was that the dopamine D1 antagonist SCH23390 would selectively decrease drinking compared to the D2 antagonist haloperidol. An additional hypothesis was that the drug effect would be abolished upon withdrawal of the drug. The dependent variables considered were volume of water consumed, behavioral expression and levels of biogenic amines and their acid metabolites. An A-B-A experimental design was employed to test these parameters, with drug, no drug and drug conditions.

II. Methods

A. Animals:

Subjects were 56 male Sprague-Dawley rats (University of Alberta, Ellerslie) approximately seven weeks old. Animals weighed between 250 and 300 g at the start of the project and were allowed to free feed for one week. One week after their arrival, the animals were reduced to 80% of their initial free feeding weight by adjusting their daily ration of Purina Rodent Chow. Water was available ad libitum. The animals were housed individually in animal quarters on a 12 hour dark-light cycle.

B. Apparatus:

The test apparatus included seven identical chambers measuring 20 cm x 23 cm x 23 cm with plexiglass walls and ceiling and a metal tray floor. Forty-five-mg pellets were passed from an automatic pellet dispensers via rubber tubing to food trays located 6 cm above the floor on a side wall. The automatic dispensers were wired through an electronic relay system attached to a digital timer thus allowing for the simultaneous food arrival in all chambers. Water spouts protruded into each chamber 6 cm above the food trays. The spouts were attached to graduated burettes allowing 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.

C. Procedures:

Subjects were handled daily, allowed ad lib access to food for one week after their arrival and their attained weights recorded as pre-experimental weight. Animals were then food deprived to 80% of their pre-experimental weight and maintained at this weight throughout the study with premeasured daily rations of Purina rat chow. Once the experimental weight had been attained, animals were habituated to the test room and chambers for four sessions. Subjects were made polydipsic (drinking at least four times their baseline level) through 14 training sessions of 50 min duration. Food pellets were delivered during the session on a fixed-time 60-s (FT 60-s) schedule. SIP developed gradually over 12 days with the animals increasing their water consumption each session. A maximum volume was typically reached by training session 10 or 11. Asymptotic levels were considered to be reached when animals drank within a five-ml range for three consecutive days. The animals were videotaped on training session 14 and pre-drug baseline drinking volumes were obtained by averaging training sessions 13 and 14.

Subjects were quasi-randomly assigned to one of seven groups each with an n of eight. Animals were matched for amount of water consumed at pre-drug baseline. Groups consisted of SCH23390 (SCH) 5, 10, 20 ug/kg SC; Haloperidol (HAL) 0.05, 0.20, 0.80 mg/kg IP; and a distilled water (dH20) control group. Distilled water was used as the drug vehicle.

For the experimental sessions, subjects were injected 30 min (SCH & dH20, SC) and 60 min (HAL & dh20, IP) prior to placement in the test chamber. Sessions lasted 50 min under an FT 60-s schedule of pellet delivery. Animals were immediately removed fron the test chamber after the arrival of the 51st pellet. Fifteen sessions of testing were divided into three blocks of 5 sessions drug, 5 sessions drug holiday (no-drug) and 5 sessions drug.

During the drug holiday, animals were injected with distilled water. Videotaping for behavioral coding took place on sessions 5, 10 and 15. Immediately after arrival of the last pellet on session 15, animals were removed from the test chamber, killed by instant decapitation and their brains removed, dissected on ice and stored at -80°C until biochemical analysis.

Behavioral Data:

Session videotapes were coded for the following 10 behavioral categories: chew (any jaw motion during the

session), bite (biting on the water spout, food tray or chamber), drink (drinking from water spout), lick (licking without water uptake from food tray, floor or walls), rear (elevation of forepaws from the floor and erect posture on back legs), sniff (investigative movements indicated by nose or head movements and which not accounted for by the other behaviors), locomote (movement of all four limbs from one space to another), groom (licking, washing or scratching of the body), immobile (absence of body movement) and forepaw (rapid forepaw movement directed at the feeder tray). An oral composite measure was obtained by combining the measures chew, bite, drink, lick and groom. Each videotaped session was divided into four five-min time blocks with a period of ten min between each block during which no observations were made. Generalization of five time blocks to the entire session (50-min) was made on the basis that analysis of behaviors from a whole session were not statistical different from blocked sessions. For each behavior, percent of total time spent in the behavior was calculated. Because of the low incidence of forepaw, this behavior was not included in the study. Interobserver and intertest reliability measures were obtained for each of the behavioral categories. Agreement levels of over 80% were obtained for randomly selected sessions.

For each behavior, repeated measures analysis of variance was applied to the data with dose as the between

and session time blocks and week blocks as the within subject factors. Heterogeneity of covariance was corrected for with the Geisser-Greenhouse corrections factor and Newman-Keuls analysis performed on group differences when the ANOVA indicated a significant effect.

Total session water intake was also collected for each subject on each of the 15 sessions. Repeated measures analysis of variance was applied to the data with doses as the between and week blocks as the within factors (blocks were collapsed over sessions, as there were no significant differences across sessions). The Geisser-Greenhouse correction factor was applied and significant findings were further analyzed with the Newman-Keuls test.

Neurochemical Data:

Immediately after decapitation, four brain regions were dissected out: striatum, nucleus accumbens, olfactory tubercule, and prefrontal cortex.

The prefrontal cortex was obtained by placing the brain on its ventral surface. A straight slice was made through the dorsal cortical surface just anterior to the genu of the corpus callosum. Portions of the olfactory bulb that adhered to the ventral surface of this block were removed.

The brain was then turned and placed on the dorsal surface and the olfactory tubercles pinched off the brain with micro-dissection forceps.

The accumbens nuclei were approached by employing the anterior commissure as a guide. A 1 mm block of tissue lateral to the septal area and around the anterior commissure was pinched out.

To obtain the striatum, the brain was placed on the ventral surface, the corpus callosum severed and the dorsal cortex unfolded. Using the lateral ventricles as a guide, each striatum was pinched off with microdissection forceps. The tissue samples were stored at -80°C until time of analysis.

Regional concentrations of noradrenaline (NA), dopamine (DA), 3,4-dihydroxyphenylacetic acid (DOPAC), homovanillic acid (HVA), 5-hydroxytryptamine (5-HT), and 5-hydroxyindoleacetic acid (5-HIAA) were measured using high pressure liquid chromatography (HPLC) with electrochemical detection. Samples were homogenized in 0.1 M perchloric acid containing 0.05 mmol ascorbic acid and 10 mg% EDTA. Samples were then centrifuged to remove the protein precipitate and a 15-μl aliquot was placed in the high pressure liquid chromatographer for analysis. HPLC determinations were performed employing a Waters (Milford, MA, U.S.A.) WISP 710B sample injector system, a model 510 pump and a Bioanalytical Systems (BAS, West Lafayette, IN, U.S.A.) Model LC-4B amperometric detector. The integrator used to measure peaks was a Hewlett-Packard model 3392A. The pertinent compounds were oxidized at a glassy carbon electrode set against an

Ag/AgCl reference electrode set at 0.75 V. The rate of flow for the mobile phase was 1 ml/min through an Econosphere-C18 column (4.6mm x250mm; 5 μm particle size, Applied Science Labs, Avondale, PA, U.S.A.) which was coupled to a precolumn composed of the same stationary phase as the analytical column.

The mobile phase consisted of $NaH_2PO_4.H_2O$ (55mM), sodium octyl sulfate (.85 mM), EDTA (0.37mM) and acetonitrile (9%). The mobile phase was filtered through a type HA filter (0.45 um, Millipore) before being degassed and adjusted to a pH of 3.0 with phosphoric acid. Tissue sample levels of the neurotransmitter amines and their acid metabolites were determined by the peak height ratios of the analytes to the internal standard in each sample. Linear regression based on the peak height ratios and the height ratios of known amounts of authentic analyte to a fixed amount of the internal standard resulted in a standard curve. A standard curve consisting of varying concentrations of authentic standards was included in each assay run. Brain amine levels detected by HPLC may vary between laboratories depending on light, temperature and tissue storage (Jakubovic, Fu & Fibiger, 1987). The present investigation conformed to standards reported by other investigators in our laboratory (Baker and Greenshaw, 1989).

Statistical analysis were carried out for each region employing univariate analysis of variance for neurochemical by dose followed by Neuman-Keuls test for post-hoc comparisons.

III. Results

A. Behavioral Data

Volume

All animals were considered polydipsic by the pre-drug session (training sessions 13 and 14) as the volume of water consumed was at least four times greater than during initial baseline (training session 1) which ranged individually from less than 1.0 to 6.5 ml.

As there were no significant differences in volume drunk between sessions within conditions, the data were collapsed into 5-session blocks, one representing each of the four conditions: pre-drug, drug, no-drug, drug. Figure 1 shows the mean volume of water consumed by each dose group for both HAL and SCH over the four conditions.

There were no significant differences in the drinking of the vehicle control groups over the conditions.

SCH The four dose by four condition ANOVA on volume of water consumed revealed that in animals treated with SCH23390, there were dose F $(3,28)=8.77$, and condition F $(1.7,47.1)=76.3$, main effects and a dose by condition interaction F $(5,47.1)=7.07$, (all $p<0.01$). Table 1 provides a summary of significant F values for this and all other behaviors. Newman-Keuls multiple comparisons showed that the mid and high groups drank significantly less than the control group and the high group less than the low within

both drug conditions. The amount of water consumed by these animals decreased during the drug conditions and was restored during the drug holiday relative to pre-drug. The low group drank significantly more during the drug holiday than during pre-drug (all $p<0.05$).

HAL Statistical analysis of volume of water consumed by haloperidol treated animals revealed significant main effects for dose F $(3,28)=12.18$, and condition F $(1.4,39.3)=53.0$, and a dose by condition interaction F $(4.2, 39.3)=61.47$, $p<0.01$. Multiple comparisons showed that within both drug conditions, HAL low, mid and high groups drank significantly less than vehicle control animals during the first drug condition and mid and high during the second drug condition. Additionally, during the first drug session, only HAL high dose groups consumed significantly less water than HAL low dose groups, whereas in the second drug session, both mid and high dose groups drank less than HAL low. The HAL mid and high dose groups also drank significantly less during the drug treatment than they did during the pre-drug condition (all $p<0.05$). The volumes consumed during the drug holiday were not significantly different from pre-drug baseline for all groups.

In summary, animals treated with mid and high doses of SCH drank significantly less than controls during the drug conditions and less than they did during the pre-drug baseline not compared condition. Animals treated with the

low dose of SCH drank significantly more during the drug holiday whereas, mid and low dose groups did not differ from pre-drug baseline. Similarily, the volume of water consumed by HAL treated animals was decreased in a dose related manner during the drug conditions, with HAL mid and HAL high groups drinking significantly less than controls.

Drink

Figure 2 illustrates the percent of session time spent engaged in drink behavior for SCH and HAL.

SCH A four condition by four dose ANOVA resulted in dose F (3,28)=14.88, and condition F (1.8,49.8)=64.94, main effects and a dose by condition interaction F (5.3,49.8)=8.54, $p<0.01$. Multiple comparisons within conditions showed that all dose groups spent significantly less time drinking than controls during the first drug condition. In the second drug condition only the mid and high dose groups were decreased significantly from controls. There was a significant decrease in the amount of time spent drinking between the low dose group compared to both the mid and high dose groups for both drug conditions. Within the drug conditions, the percent of time spent drinking was found to decrease in a dose-related manner. The low SCH group spent significantly more time drinking during the drug holiday than they did during the pre-drug session (all $p<0.05$). The low and mid dose groups did not differ

significantly from pre-drug baseline in the no-drug condition.

HAL The four condition by four dose ANOVA showed dose $F(3,28)=12.44$, and condition $F(2.4,68.2)=105.7$ main effects and a dose by condition interaction $F(7.3,68.2)=14.56$, $p<0.01$. Multiple comparisons showed that similar to SCH, HAL produced a significant decrease in the percent of time spent drinking by animals in all dose groups during the drug conditions relative to pre-drug. Within the first drug condition, animals in all three drug dose groups spent significantly less time drinking than controls, whereas in the second drug condition only the mid and high dose groups were decreased compared to controls. During both drug conditions the mid and high dose groups spent significantly less time drinking than the low dose group. During the no-drug condition, significantly less time was spent drinking by the HAL mid animals than the control or HAL high animals. The difference between the amount of time the HAL mid animals spent drinking during the pre-drug condition and during the no-drug condition was significant, suggesting they did not recover to original levels (all $p<0.05$).

To summarize, both SCH and HAL produced decreases in the amount of time spent engaged in drinking during the two drug conditions. All three doses for both drugs were significantly different from controls during the first drug condition and for only the mid and high during the second

drug condition. Within each drug dose, the percent of time spent drinking was decreased significantly during the drug conditions compared to the pre-drug baseline. Animals treated with the low dose SCH spent a significantly greater amount of time drinking during the drug holiday than they did during the pre-drug session.

Chew

Figure 3 shows the results of a four dose by four condition repeated measures ANOVA on the percent of time spent on the behavior chew for SCH and HAL.

SCH Statistical analysis revealed a dose F (3,28)=33.2 and condition F (1.3,35.8)=215.6 main effect. A dose by condition interaction F (3.8,35.8)=32.2 was also seen ($p<0.01$). Multiple comparisons within conditions showed that increasing drug dose resulted in a significant increase in the percent of time spent chewing in the drug conditions but not in the no-drug condition. The comparisons within dose groups also indicated that animals treated with SCH during the drug conditions spent significantly more time engaged in chewing than they did during the pre-drug condition (all $p<0.05$).

HAL Similiar to the SCH findings, HAL treatment led to an increase in the percent of session time spent chewing. Dose and condition main effects F (3,28)=7.83 and F (1.1,29.9)=14.59 respectively, $p<0.01$ and a dose by

condition interaction F (3.2,29.9)=3.9, $p<0.05$ were revealed through statistical analysis. Multiple comparisons indicated that within the first drug condition, the only significant differences were between the HAL high and the control group. During the second drug condition, HAL high induced sigificantly more chewing than either HAL mid or HAL low although the latter two doses did not differ significantly from controls. Moreover, although an increasing trend was seen with all drug doses, only HAL high resulted in significantly increased chewing behavior during the drug condition compared to the pre-drug condition (all $p<0.05$).

In summary, both drugs tended to increase the percent of time spent engaged in chewing during a drug session, however significant graded dose-response relationship was only seen with SCH. Haloperidol treatment differed from pre-drug controls only in the high dose condition. All doses of SCH led to increased chewing during the drug conditions as compared to the pre-drug condition, whereas with HAL treatment, only the HAL high condition differed significantly from the pre-drug condition. Correlational analysis of all drug doses during the second drug condition of both SCH and HAL drinking with chewing resulted in Pearson coefficients of $r=-.92$ and $-.83$ respectively ($p<.05$).

Bite

Figure 4 shows the results of a four dose by four condition repeated measures ANOVA for bite behavior of subjects in both drug groups.

SCH For the percent of time spent engaged in biting, there was a dose F (3,28)=5.5, $p<0.01$ main effect. An F (9,84)=2.1, $p<0.05$ for the dose by condition interaction was seen. Multiple comparisons showed that within drug conditions, SCH high significantly decreased the amount of time spent biting compared to the low dose group. The SCH high significantly decreased biting behavior in the drug condition compared to the pre-drug condition ($p<0.05$).

HAL Statistical analysis revealed a dose main effect for biting behavior $F(3,28)=5.7$ and a dose by condition interaction $F(6.2,57.9)=4.25$, $p<0.01$. Multiple comparisons showed that within drug conditions, HAL mid and high significantly decreased biting compared to controls. The HAL high group was found to significantly decrease the amount of time spent biting within a drug session compared to pre-drug sessions (all $p<0.05$).

In summary, the main finding for biting behavior indicated that the high dose condition of both drugs significantly decreased biting within both drug conditions. For SCH, the high drug dose significantly decreased biting compared to the low drug dose. Under haloperidol treatment,

both HAL mid and high animals spent significantly less time biting during drug sessions than did control animals.

Groom

Figure 5 shows the results of a four dose by four condition repeated ANOVA for the percent of time engaged in grooming behavior for SCH and HAL.

SCH There were no significant differences across doses F (3,28)=0.39, conditions F (1.3,37.7)=1.5, nor a dose by condition interaction F (4,37.7)=0.8.

HAL With HAL treatment, statistical analysis showed only a condition main effect F (1.8,50.7)=11.5. Doses F (3,28)=0.9 and dose by condition interactions F (5.4,500.7)=1.1 effects were non-significant.

Lick

Figure 6 shows the results of the four dose by four condition repeated measures ANOVA for the percent of time spent licking for both drug groups.

SCH There were no significant main effects for doses or conditions, nor was there dose by condition interaction; F dose(3,28)=0.6, F conditions(1.5,41.8)=0.98 and F dose X condition(4.5,41.8)=.45 respectively.

HAL As with SCH treatment, HAL treatment resulted in no significant effects on licking behavior. F

dose(3,28)=0.5, F conditions(1.7,48.6)=2.9 and F dose X conditions(5.2,48.6)=1.7.

Oral Composite

Figure 7 shows the results of a four dose by four condition repeated measures ANOVA for the oral composite. This measure included drink, chew, bite, groom and lick.

SCH There were no significant differences found with drug doses within condition conditions, between condition conditions or in a dose by condition interaction: F dose(3,28)=1.5; F conditions(2,57))=2.4, and F dose X conditions(6.1,57)=0.80.

HAL As with the SCH treatment, there were no significant effects of HAL treatment on the oral composite: F dose(3,28)=2.3; F conditions(2.7,74.4)=2.5 and F dose X conditions(8,74.4)=1.9.

Figure 8 represents the trial effects within the 50-min sessions for both SCH and HAL treated rats across the four conditions.

SCH A time block main effect and dose by time block interaction were seen with F (2.0,80.4)= 20.7, and F (8.6,80.4)= 2.12 respectively, $p<0.01$. Multiple comparisons showed that there was significantly more time spent engaged in oral behaviors for the SCH low dose in time block 2 as compared with time block 1. The time spent in oral behavior for the SCH mid group in time blocks 3 and 4 was

significantly increased over time 1. The SCH high group spent more time engaged in oral behavior in time blocks 3 and 4 as compared to time block 1 (all $p<0.01$).

HAL A significant time block main effect was also seen HAL treatment $F(2.4,67.3)=12.3$, $p<0.01$.

In summary, there tends to be a general trend for increasing the percent of time spent engaged in oral behaviors for SCH treated rats as a session progresses.

Rear

Figure 9 represents the results of a four dose by four condition repeated measures ANOVA for the percent of time engaged in the behavior rear for both SCH and HAL.

SCH Statistical analysis revealed dose F $(3,28)=3.9$, condition F $(2.5,69.4)=3.9$, $p<0.05$ main effects but a dose by condition interaction F $(7.4,69.4)=0.49$ was not significant. Subsequent multiple comparisons showed no significant differences.

HAL A condition main effect F $(1.9,52.5)=7.4$, $p<0.01$ and a dose by condition interaction F $(5.6,52.5)= 3.1$, $p<0.05$ were seen. There was no significant dose main effect F $(3,28)=1.4$. Multiple comparisons revealed that the HAL mid group spent significantly less time rearing in both drug conditions than they did in the no-drug condition ($p<0.05$).

Figure 10 shows the time block main effect analysis for

the amount of time spent rearing within a 50-min session across the four conditions.

SCH Time block main effect and a time by dose interaction were found to be significant with F (2.5,68.8)=19.9, $p<0.05$ and F (7.4,68.8)=2.09 $p<0.05$, respectively. Subsequent multiple comparisons showed that for all drug doses, time blocks 2, 3 and 4 were significantly decreased for rearing compared to time block 1 (all $p<0.05$).

HAL A time block main effect was also seen with HAL treatment, $F(2.5,71.0)=7.9$, $p<0.01$.

In summary, there seems to be a general trend for rearing behavior to decrease as session time progresses for SCH treated rats.

Locomote

Figure 11 shows the results of the four dose by four condition repeated measures ANOVA for both drugs in percent of session time spent engaged in the behavior locomote.

SCH There were no significant differences found between doses or conditions in time spent locomoting; F (3,28)=2.7, and F (2.5,7.9)=0.4. A dose by condition interaction was also found to be non-significant F (7.6,7.6)=1.2.

HAL Significant dose F (3,28)=4.75, $p<0.01$, condition F (1.8,49.9)=3.7, $p<0.05$ and dose by condition F

(5.4,49.9)=4.77, $p<0.01$ effects were seen. Within session comparisons showed that during the first drug condition, the HAL mid and high groups spent significantly less time locomoting than the low dose group. During the second drug condition, only the HAL high group was significantly depressed in locomotor activity as compared to the HAL low group (all $p<0.05$). Multiple comparisons showed that the HAL mid and high groups spent significantly less time locomoting during the first drug condition than they did during the pre-drug condition. Similiar depression of locomotion during the second drug condition was seen in the high dose group.

To summarize, SCH treatment resulted in no significant effects on locomotion. Haloperidol treatment resulted in both dose and condition effects. Specifically, locomotion was significantly decreased during the first drug condition for both the mid and high doses of HAL and for the high dose group only during the second drug condition compared to the low dose group animals.

Immobile

Figure 12 shows the ANOVA results for the percent of time animals treated with SCH and HAL were rendered immobile.

SCH Statistical analysis resulted in significant dose F (3,28)=6.31, and condition F (1.6,45.0)=7.6, main effects and a dose by condition interaction F(4.8,45)=4.6, all

$p<0.01$. Multiple comparisons within the first and second drug conditions showed that animals treated with SCH high spent significantly more time immobile than control, low or mid dose animals. Additionally, the SCH high animals were significantly more immobile during the drug treatment condition than they were during the pre-drug condition (all $p<0.05$).

HAL As with SCH treatment, HAL treatment resulted in significant dose F (3,28)=12.4, condition F (1.5,42.8)=20.1 main effects and a significant dose by condition interaction F (4.6,42.8)=9.0, all $p<0.01$. The percent of time the HAL high group was immobile was significantly increased over the control, low and mid groups during both the first and second drug conditions. Between conditions, the HAL high group was significantly more immobile during both drug conditions than during the pre-drug session.

To summarize, the high doses of both SCH and HAL significantly increased the amount of time the animals were immobile during the drug conditions. The mid dose of HAL had the same effect during the second drug session.

Sniff

Figure 13 represents the percent of time the animals were not engaged in any of the aforementioned behaviors, but were engaged in an investigative type sniffing behavior involving nose or head movements. There were no significant findings for either drug for this behavior.

Table 1.

F values for ANOVA of significant behavioral data.

Behavior		Effect	df	F
Volume of water consumed	SCH	D	3,28	8.77**
		C	1.7,47.1	76.3 **
		DxC	5,47.1	7.07**
	HAL	D	3,28	12.18**
		C	1.4,39.3	53.0 **
		DxC	4.2,39.3	61.47**
Drink	SCH	D	3,28	14.88**
		C	1.8,49.8	64.94**
		DxC	5.3,49.8	8.54**
	HAL	D	3,28	12.44**
		C	2.4,68.2	105.7 **
		DxC	7.3,68.2	14.56**
Chew	SCH	D	3,28	33.2 **
		C	1.3,35.8	215.6 **
		DxC	3.8,35.8	32.2 **
	HAL	D	3,28	7.83**
		C	1.1,29.9	14.59**
		DxC	3.2,29.9	3.9 **
Bit	SCH	D	3,28	5.5 **
		DxC	9,84	2.1 *
	HAL	D	3,28	5.7 **
		DxC	6.2,57.9	4.25**
Groom	SCH	Non sig.		
	HAL	C	1.8,50.7	11.5 *
Lick	SCH	Non sig.		
	HAL	Non sig.		
Oral Comp.	SCH	Non sig.		
	HAL	Non sig.		
Oral Comp. Time block	SCH	T	2.0,80.4	20.7 **
		DxT	8.6,80.4	2.12**
	HAL	T	2.4,67.3	12.3 **
Rear	SCH	D	3,28	3.9 *
		C	2.5,69.4	3.9 *
	HAL	D	1.9,52.5	7.4 **
		DxC	5.6,52.5	3.1 *
Rear Time Block	SCH	T	2.5,68.8	19.9 *
		DxT	7.4,68.8	2.09*
	HAL	T	2.5,71.0	7.9 **

D=Dose; C=Condition; T=Time; *=p<0.05; **=p<0.01.

Table 1 continued

Behavior		Effect	df	F
Locomote	SCH	Non sig.		
	HAL	D	3,28	4.7 **
		C	1.8,49.9	3.7 *
		DxC	5.4,49.9	4.77**
Immobile	SCH	D	3,28	6.31**
		C	1.6,45.0	7.6 **
		DxC	4.8,45.0	4.6 **
	HAL	D	3,28	12.4 **
		C	1.5,42.8	20.1 **
		DxC	4.6,42.8	9.0 **

D=Dose; C=Condition; T=Time; *=p<0.05; **=p<0.01.

Table 2.

Control levels for neurotransmitters and metabolites of interest. Levels are expressed in ng/g mean (SE).

	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)

B. Neurochemical Data

Figures 14, 15, 16 and 17 represent the results of the HPLC analysis for the striatum, nucleus accumbens, olfactory tubercule and prefrontal cortex. Table 2 shows the mean control levels for the transmitters and metabolites of interest. For all regions and each neurotransmitter a one-way ANOVA of four doses was applied to the data. Post-hoc comparisons were made with Newman-Keuls multiple comparisons on significant findings.

Figure 14 Striatum

SCH There were no main effects of SCH on any neurotransmitter or metabolite analyzed within the striatum.

HAL A significant dose main effect of HAL on dopamine levels was observed with F (28,3)=4.49, $p<0.01$. Multiple comparisons showed that HAL low and high doses significantly increased dopamine levels over control levels. Similarily, there was a main effect of HAL on HVA levels F (28,3)=12.47, $p<0.01$.

Figure 15 Nucleus Accumbens

SCH There were no main effects of SCH on any of the neurotransmitters of metabolites analyzed for this brain region.

HAL A main effect of F (28,3)=3.86, $p<0.05$ for HAL treatment on 5-HT in the nucleus accumbens was observed.

Multiple comparisons showed that HAL high significantly decreased DA levels over controls ($p<0.05$).

Figure 16 Olfactory Tubercule

SCH For SCH treated animals, there were no significant differences between the drug animals and control animals for any of the neurotransmitters or their metabolites.

HAL With HAL treatment, analysis showed a main effect of HAL on HVA levels in this region; $F(27,3)=3.46$, $p<0.05$. Comparison analysis revealed the HAL high group contained significantly higher levels of HVA than the HAL low group.

Figure 17 Prefrontal Cortex

Within this region, no significant differences for either SCH or HAL between controls and drug doses were found for any of the neurotransmitters or their metabolites.

In summary, SCH treatment did not result in an increase of the amines NA, DA, 5-HT or the metabolites DOPAC, HVA or 5-HIAA. HAL treatment did significantly increase levels of DA in the striatum for the low and high dose groups. HAL also resulted in an increase in dopamine metabolite HVA in the striatum and olfactory tubercule while decreasing 5-HT levels in the nucleus accumbens.

IV. Discussion

The major findings of the present study suggest that both SCH23390 and haloperidol (D1 and D2 antagonists respectively) decreased drinking and increased chewing behavior in polydipsic rats. In this investigation polydipsia was verified by all rats consuming at least four times their pre-experimental sessional volume of water (Falk, 1969). Control animals maintained asymptotic volumes of water consumed over the entire experimental procedure, deviating at the most by five ml. This observation was corroborated by the fact that the control animals maintained the same percent of session time engaged in drinking behavior. Moreover, all behaviors engaged in by the control animals were held at a steady state throughout the experimental period.

SCH23390 resulted in a dose dependent decrease in the amount of water consumed and the percent of time spent drinking. Conversely, SCH resulted in a dose dependent increase in the percent of time engaged in chewing behavior.

Haloperidol also decreased the volume of water consumed and amount of time drinking in a dose-related manner. Unlike SCH however, only the HAL high dose significantly increased the percent of time spent engaged in chewing movements during the drug conditions.

These were somewhat controversial findings in that both SCH and HAL have been found to decrease oral movements in non polydipsic rats. Specifically, SCH has been found to block spontaneous oral movements (Levin, See & South, 1989), decrease fluphenazine induced oral movements (Stoessl, Dourish & Iversen, 1989) and to have no effect at very low doses (1ug) on apomorphine induced jaw movements in the dorsal striatum (Koshikawa, Tomiyama, Omiya, deBeltran & Kobayashi, 1990), and globus pallius, but to suppress nucleus accumbens apomorphine induced jaw movements (Koshikawa, Koshikawa, Tomiyama, deBeltran, Kamimura & Kobayashi, 1990). Moreover, it is typically D1 agonists such as SKF38393 that have been found to induce abnormal chewing movements rather than antagonists (Johansson, Levin, Gunne & Ellisen, 1987; Molloy & Waddington, 1989; Rosengarten, Schweitzer & Friedhoff, 1983). These results were consistent however as SKF38393 alone was reported to have no effects on oral movements but when coupled with quinpirole (D2 agonist) did induce oral movements (Arnt, Bogeso, Hyttel & Meier, 1988). A similar effect was reported by Ellison, Johansson, Levin, See and Gunne (1988), who found that SKF38393 increased oral movements and chewing in rats chronically treated with haloperidol.

Haloperidol treatment has been reported to both increase chewing movements (Ellison et al., 1988; Ellison, See, Levin & Kinney, 1987; Rupniak, Jenner & Marsden, 1986),

and decrease chewing movements in non polydipsic rats (Rupniak, Tye & Iversen, 1990).

In polydipsic rats, the present findings suggest that the animals are substituting one oral behavior for another as their overall oral composite did not change significantly. Within the sensitization model, polydipsic animals are sensitized to drink with repeated presentation of a food pellet (Beck et al., 1989). The neuroanatomical correlate to this behavioral sensitization may lie in the decreased striatal dopamine levels for polydipsic rats found in the current investigation as compared to non polydipsic food deprived rats. That is, our control rats showed 3509.0 ng of dopamine per gram of striatal tissue which is decreased compared to reported non polydipsic food deprived levels of 9540.0 ng/g tissue (Chance, Foley-Nelson, Nelson & Fischer, 1987). SIP then may cause a supersensitivity or up-regulation of receptor number due to decreased dopamine content in the striatum. Further, the sensitized receptor may then result in a behavioral sensitivity to drinking.

With administration of both SCH and HAL, dopamine levels within the striatum were increased over control levels - significantly with HAL treatment. This result is likely due to a feed-back mechanism activated by the blockade of post synaptic (SCH) and pre synaptic (HAL) receptors. That is, subsequent to blockade of the D2 autoreceptor by HAL, there is an increase in firing rate of

the cell which in turn causes an increase in synthesis and release of dopamine (Cooper, Bloom & Roth, 1986). It has been shown that HAL treatment often results in abnormal chewing movements particularly at high doses of .5 mg/kg or more (Ellison et al., 1988). These abnormal oral movements have been termed dyskinetic movements and are commonly seen following longterm neuroleptic treatment (Rosengarten et al., 1983). Therefore, the instigation of chewing at the HAL high dose in the present study, is not surprising. The elicitation of chewing by SCH, however, is more puzzling. The current finding however, is not an isolated incident. Gerlach, Casey & Kistrup (1986) found that SCH23390 produced dystonic and dyskinetic oral movements in monkeys withdrawn from long-term haloperidol treatment. The mechanisms involved in the elicitation in SIP rats, remains speculative at best.

Creese & Chen (1985) found an increased number of D1 binding sites in the striatum subsequent to chronic SCH23390 treatment. This increase may be due to receptor blockade and the fact that SCH does not result in signifiant increases in the release of DA (Clark & White, 1987). In the present study, the lack of significantly elevated DA levels following SCH treatment is consistent with this suggestion. In the pre-drug sessions of the present study, SIP may induce changes in the dopaminergic system similar to a D1/D2 mixed agonist such as decrease in dopamine levels, and

resultant increase in receptor cell number or sensitization of receptor cells (Baker & Greenshaw, 1989). Subsequent administration of SCH23390, which has been found to increase the number of D1 receptors (Creese & Chen, 1985; Proceddu, Ongini & Biggio, 1985) may lead to a system that is "primed" for any receptor binding which may occur. This primed system then, may lead to a preferential D1/D2 receptor interaction which has previously been shown to increase oral chewing movements (Clark & White, 1987). Further, SCH23390 has been shown to increase cell firing rates - a response similiar to other neuroleptics such as haloperidol (Onali, Olianas & Gessa, 1984) which may also result in increased activation on the primed system, resulting in chewing movements.

Support for this interpretation may be found in that stereotyped behavior induced by mixed agonist apomorphine (including chewing) was potentiated by repeated administration of SCH23390 (Gandolfi, Roncada, Dall'Olio & Montanaro, 1988). The authors suggested that the potentiated effects were due to a supersensitive D1 receptor. Further support may be found in the present study, as a dose dependent effect of SCH was seen in chewing thereby possibly reflecting increased receptor sensitivity in a dose related manner. Conversely, haloperidol increased chewing in an all-or-none fashion. That is, only at the high dose did haloperidol induce chewing significantly more than controls. At the higher dose, haloperidol may not be specific to D2

receptors, but may also affect D1 receptors, (Seeman & Grigoriais, 1987) possibly implicating the D1 receptor.

To summarize, the increased chewing seen with SCH treatment in the present study may be the result of a doubly sensitized D1 receptor system. The first sensitization occurred due to the SIP paradigm itself which elicits responses similiar to those induced by non specific D1/D2 receptor agonists (Miller, Wickens & Beninger, 1990). (This suggestion was further enhanced by non-systematic observations of head and neck stereotypic-like behaviors in a number of polydipsic rats in the pre and no-drug conditions. The second receptor sensitivity results from the up-regulation of D1 receptor number following SCH23390 treatment (Creese & Chen, 1985). The net result is an increased effect of any dopamine binding on D1 receptors. The likelihood of this occurring, is increased after SCH treatment as although not significant, there were increased striatal dopamine levels compared to controls after SCH mid and high treatments. Therefore, although the original hypothesis of a specific D1 mediated decrease in drinking following SCH treatment and not D2 was not found, the D1 receptor remains highly implicated in oral behaviors.

There seemed to be a specificity for chewing following both SCH and HAL treatment, as drinking and biting were significantly decreased for both drugs, and grooming with HAL. This finding is suggestive of chewing being a dystonic

movement elicited with drug treatment. Dystonia was a more probable explanation for the movement than dyskinesia, as the behavior was found to occur acutely, consisted of purposeless chewing movements and did not persist after withdrawal of drug (Waddington & Molloy, 1987). The dyskinesias found with chronic neuroleptic treatment have been found to have late onset and teeth grinding which persist after drug withdrawl (Rupniak, Jenner & Marsden, 1986).

The oral composite data indicated there were no significant changes in net oral behavior with either SCH or HAL treatment. This follows, considering that chewing behavior replaced drinking with drug treatment. Similarily, licking behavior was not significantly altered with drug treatment and this may reflect a maintainence of oral sensitization for a secondary behavior over no-drug SIP and drug treatment. The lack of change in these motor behaviors also argues against a generalized suppression of behavior. that is, if the drug treated animals were merely sedated or their responsiveness decreased, all categories of behavior would show a reduction in percent time with the exception of immobility which would be increased.

Rearing and locomoting were found to decrease significantly with HAL treatment. This finding may reflect a preference for orality at the non sedating low dose and perhaps a sedating effect at the higher doses (Salamone,

1987). The non significant findings for locomotion and rearing under SCH treatment may also be due to floor effect. That is, animals tended to locomote and rear when initially placed in the test chamber and began to center their activity around the food tray as the session progressed. These suggestions are supported by the rear and oral composite percent time across time blocks within sessions data which indicated a decrease in rearing and an increase in oral behaviors as sessions progressed. Additionally, as the test chamber is somewhat restrictive, locomotor activity was typically very low and any further decrease may not be significant - as in the case of SCH treated animals.

The percent time spent immobilized, was consistent with previous findings that higher doses of SCH and HAL induce catalepsy in rats (Clark & White, 1987). From the current findings, animals under high dose conditions of both drugs still spent a considerable amount of time engaged in chewing when not immobile which may be a result of the aforementioned D1 supersensitivity.

The biochemical data support somewhat the supersensitivity model of SIP. Specifically, HPLC analysis showed decreased striatal dopamine levels in control polydipsic rats which were subsequently increased with drug treatment. This increase is accompanied by elevated DOPAC and HVA levels by HAL treatment which is consistent with previous reports (Cooper, Bloom & Roth, 1986). This affect was also seen in

the nucleus accumbens and olfactory tubercule with HAL treatment in the but not in the prefrontal cortex. These findings suggest a regional differentiation of SIP with the behavior mediated primarily by the striatum and nucleus accumbens.

The 5HT and 5HIAA levels also bear discussion. In the nucleus accumbens and prefrontal cortex, for both control and drug treated animals low 5HT and high 5HIAA levels were seen. It was unlikely that SCH or HAL were binding with high affinity to the 5HT receptor, as drug levels did not differ from control levels. It was more likely that 5HT levels were lowered in animals that were food deprived due to decreased availability of dietary tryptophan (Cooper, Bloom & Roth, 1986). Moreover, it has been shown that subsequent to starvation and semi-starvation 5HT turnover rates were significantly increased resulting in substantially increased levels of metabolite 5HIAA (Knott & Curzon, 1972; Schweiger, Brooks, Tuschl & Pirke, 1989).

The present findings parallel these reports in that polydipsic rats were food deprived thus restricting their tryptophan availability. Similarily the increased 5HIAA levels may reflect increased turnover, however as previously reported this conclusion must be regarded with caution as 5HIAA levels may not accurately reflect 5HT activity (Schweiger, Brooks, Tuschl & Pirke, 1989). Prefrontal and accumbens tissue show the increased 5HIAA and decreased 5HT

levels were likely due to the the dorsal raphe projection to the anterior telencephalon in the rat. As 5HT neurons typically form discrete clusters (Cooper, Bloom and Roth, 1986), perhaps clusters in those regions were included in the tissue dissected.The underlying mechanisms for these effects have yet to be resolved.

In conclusion, the current findings support the sensitization model for SIP and do not support a motor impairment or decreased responsiveness model. Additionally, the data suggest that the SIP behavioral paradigm may be an advantageous method of assessing the efficacy of neuroleptic treatment. This methodological approach is extremely sensitive to extrapyramidal effects of dopamine antagonists, such as non-purposeful chewing that other paradigms are not.

There remains however a plethora of research necessary to more clearly elucidate the effects of dopaminergic agents on SIP. For example, more systematic investigations on the potential of SIP to induce stereotypic behavior are required. Additionally, the effects of D1 and D2 agonists on SIP may more clearly explain the D1/D2 receptor role in oral behaviors. Further, as no neurotransmitter operates in isolation, the possible roles of GABAergic and acetylcholinergic agents in SIP would enhance the understanding of the behavior. Finally, studies of the effects of SIP alone and coupled with dopamine agonists and antagonists on dopamine receptor binding, are urgently

required to resolve the controversies centered around dopaminergic agents and the functionality of dopamine receptor activity.

V. Figures

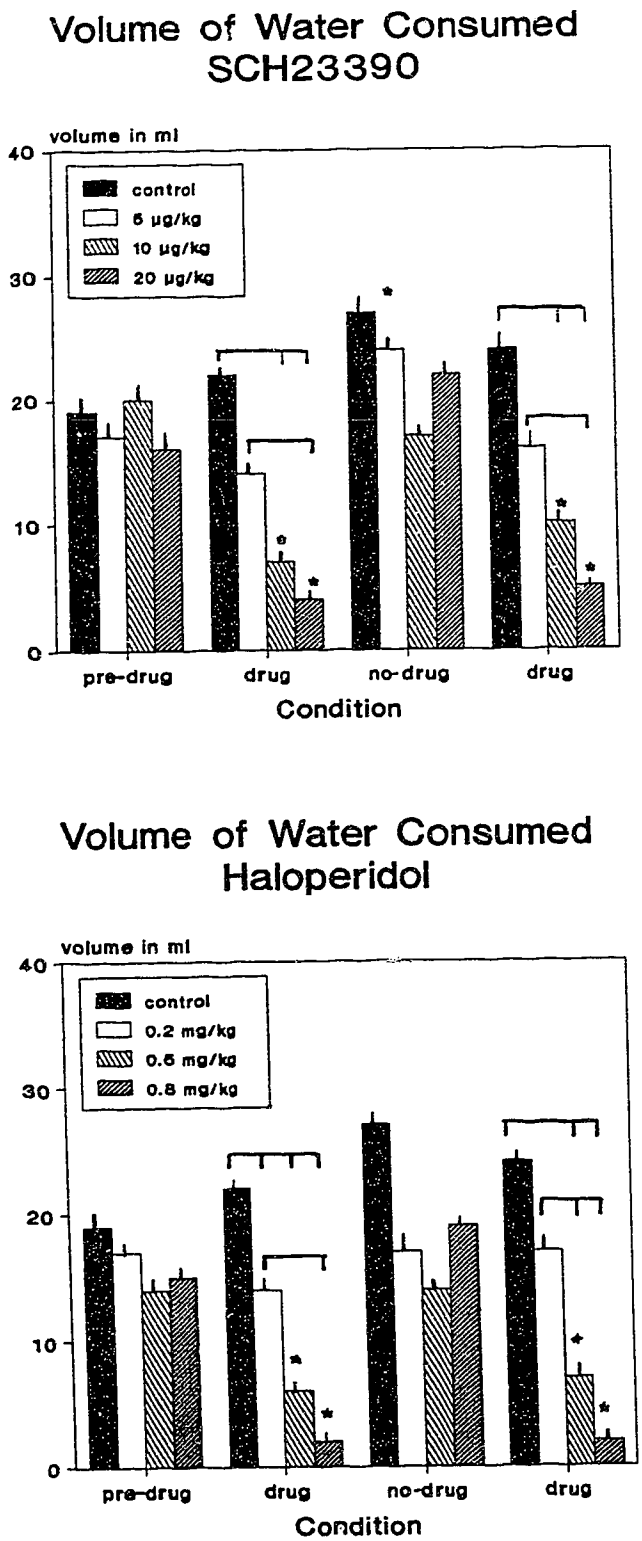


Figure 1. Group means (+SE) for volume of water consumed in ml. Brackets denote significant differences within a condition, dots denote significant differences within a group between conditions relative to predrug ($p<0.05$, Newman-Keuls).

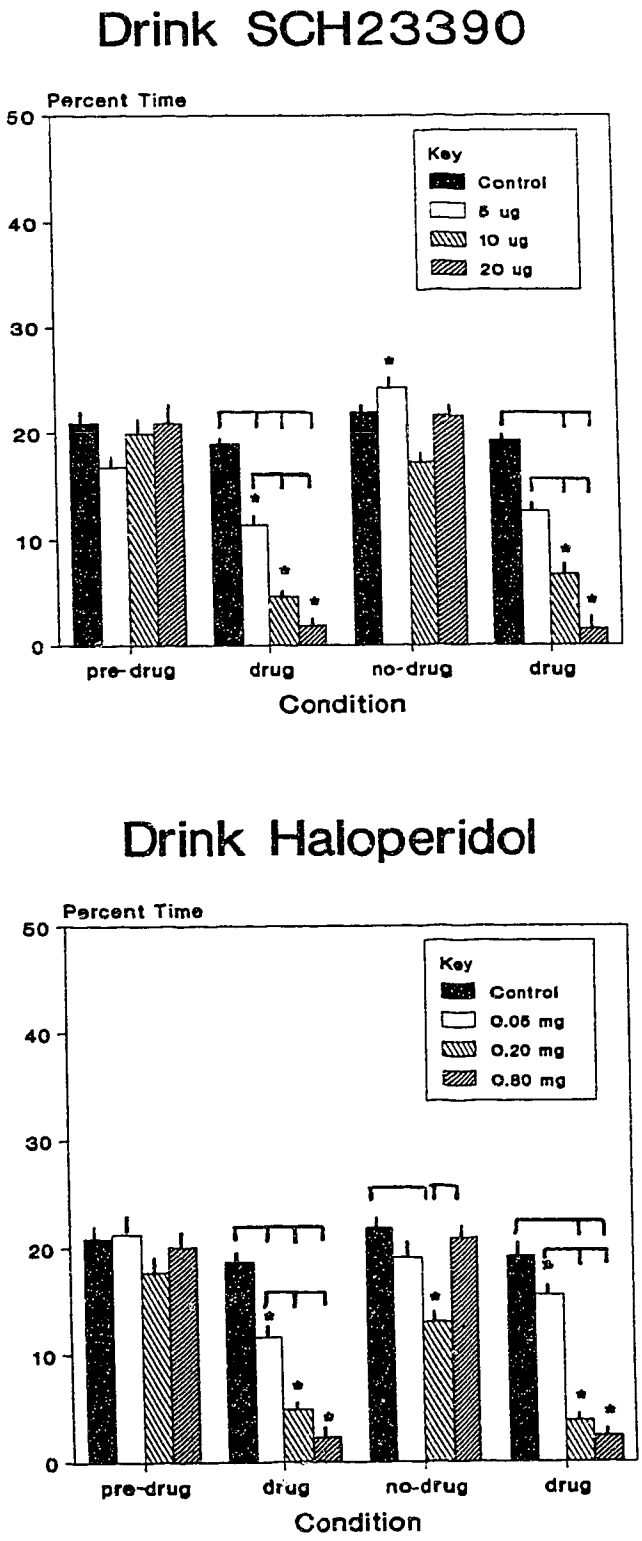
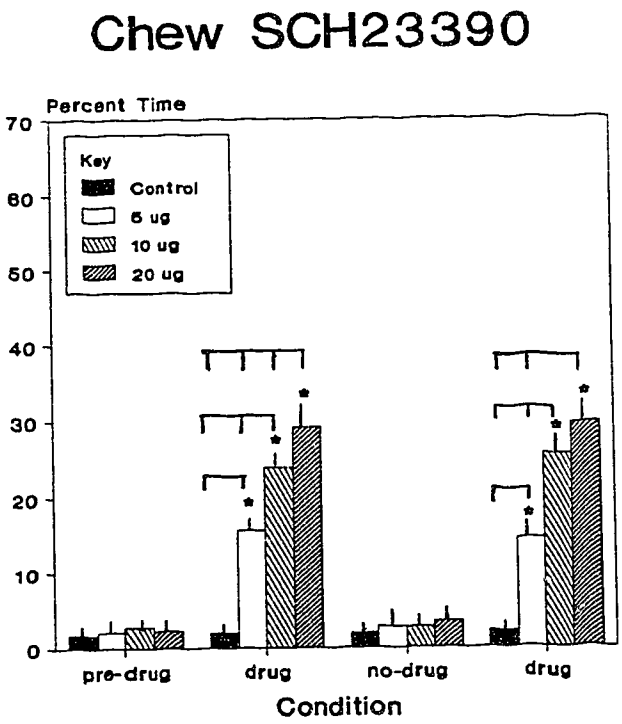


Figure 2. Mean (+SE) percent of total session time engaged in drink. Brackets denote significant differences within a condition, dots denote significant differences within a group between conditions relative to pre-drug ($p<0.05$, Newman-Keuls).



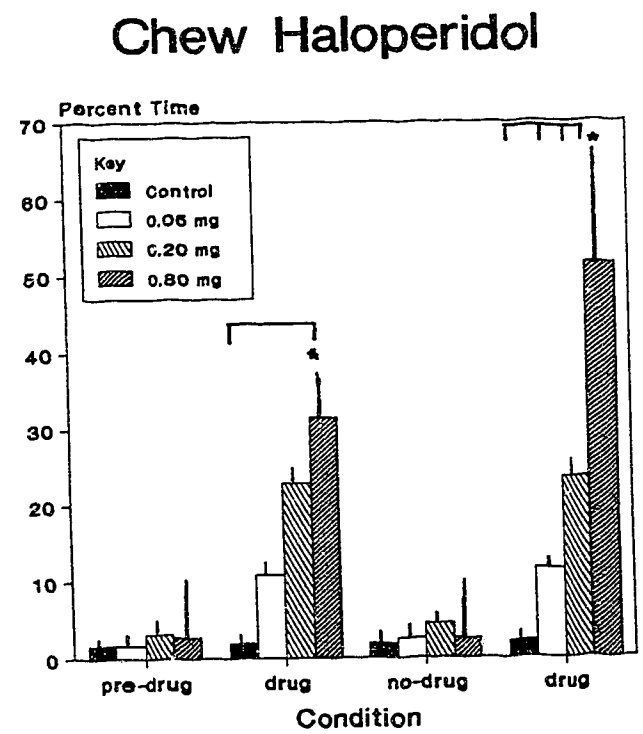
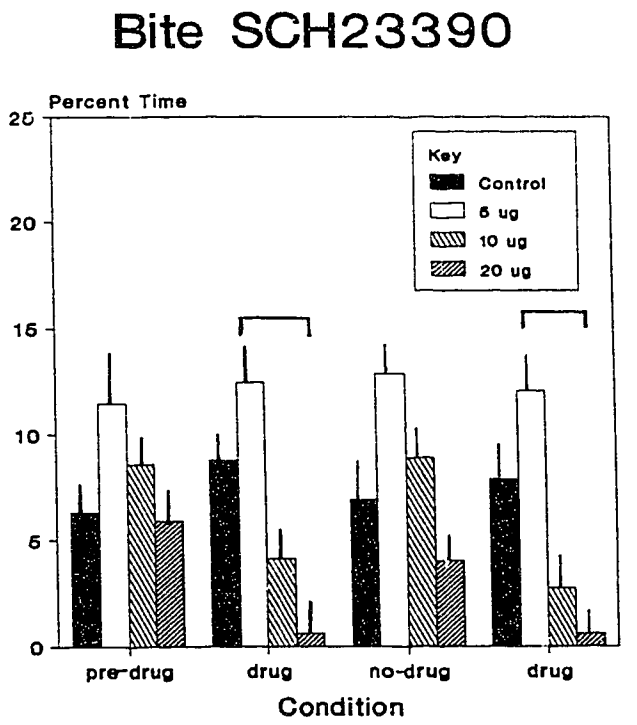


Figure 3. Mean (+SE) percent of total session time engaged in chew. Brackets denote significant differences within a condition, dots denote significant differences within a group between conditions relative to pre-drug ($p<0.05$ Newman-Keuls).



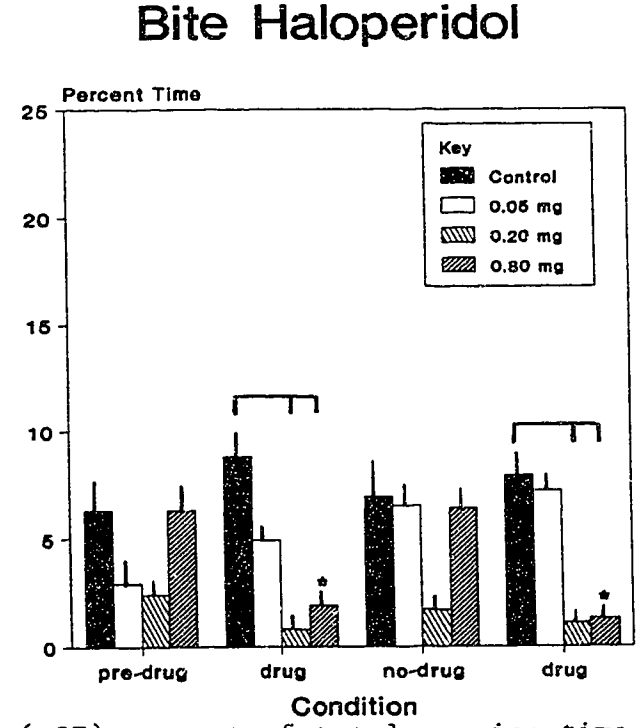
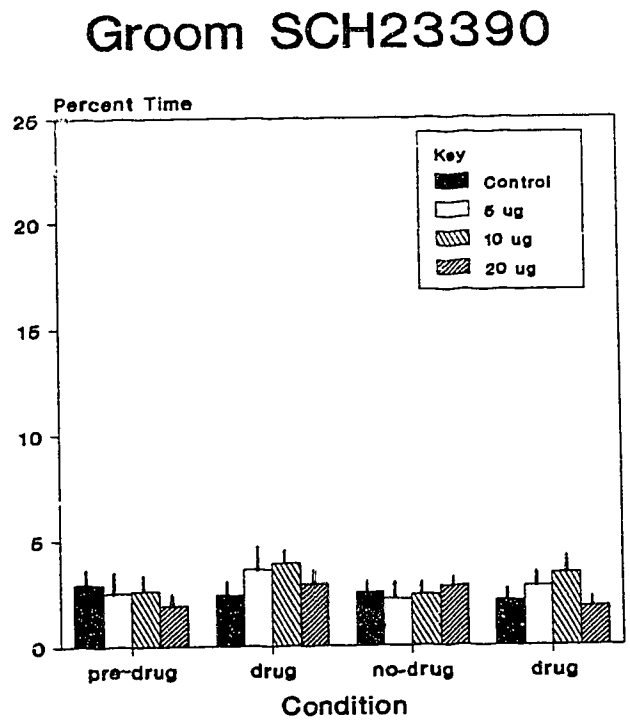


Figure 4. Mean (+SE) percent of total session time engaged in bite. Brackets denote significant differences within a condition, dots denote significant differences within a group between conditions relative to pre-drug ($p<0.05$, Newman-Keuls).



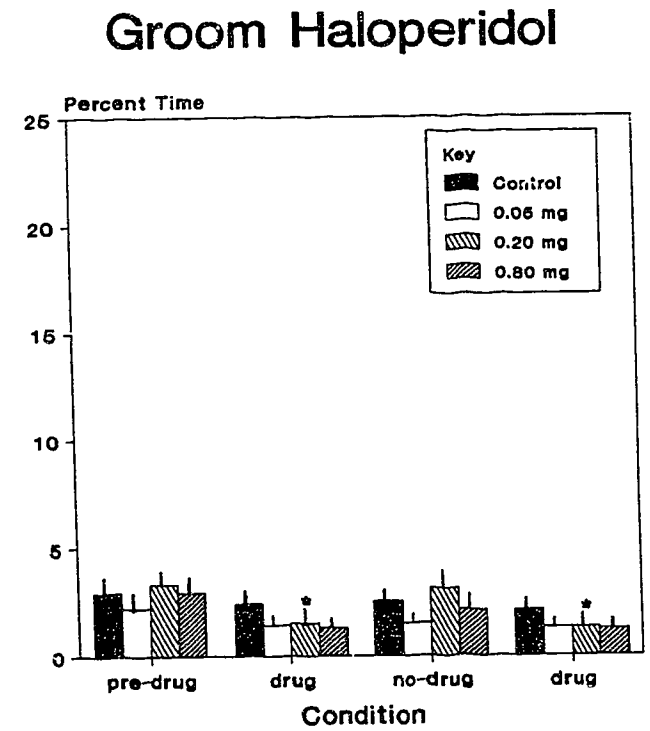
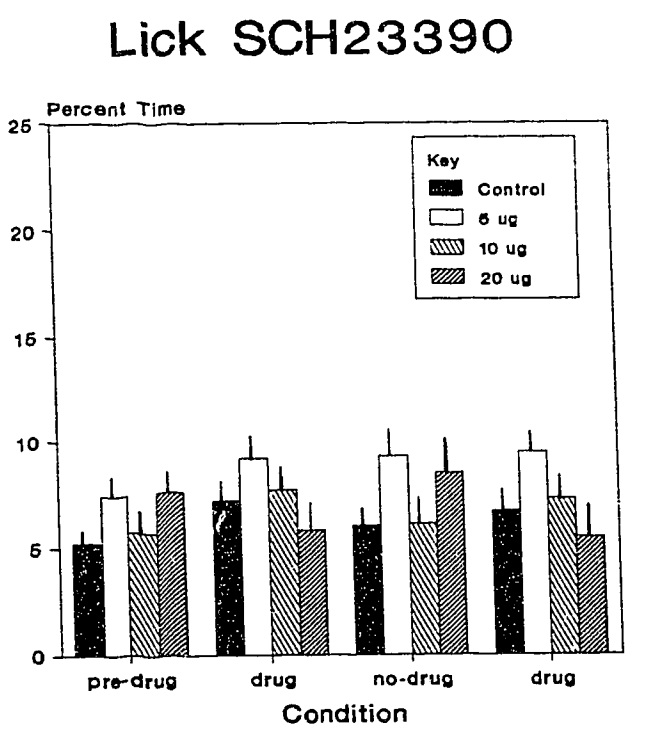


Figure 5. Mean (+SE) percent of total session time engaged in groom. Dots denote significant differences within a group between conditions relative to pre-drug ($p<0.05$, Newman-Keuls).



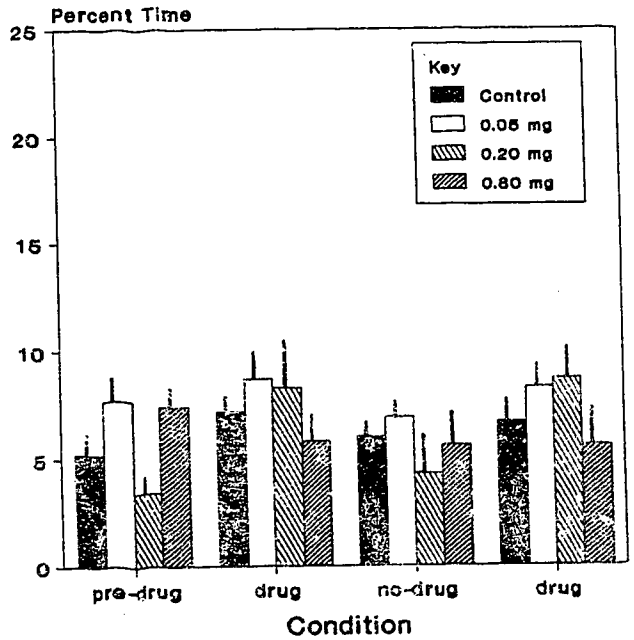
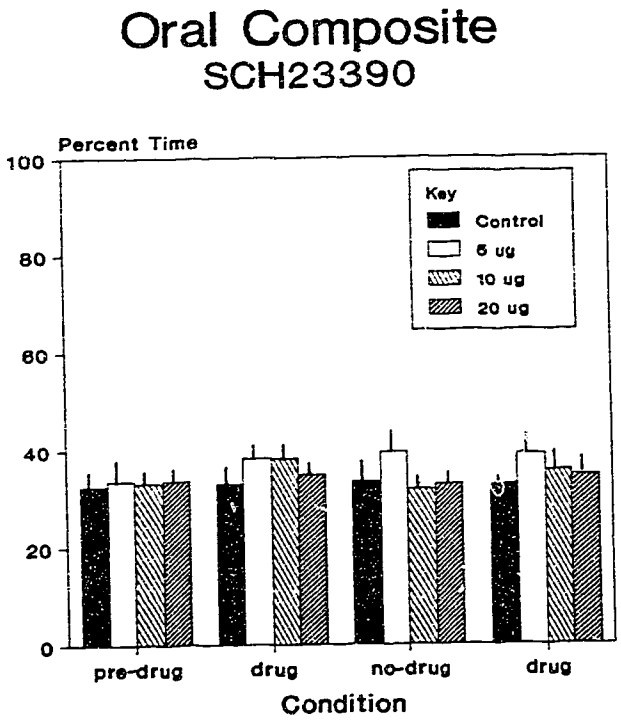


Figure 6. Mean (+SE) percent of total session time engaged in lick.



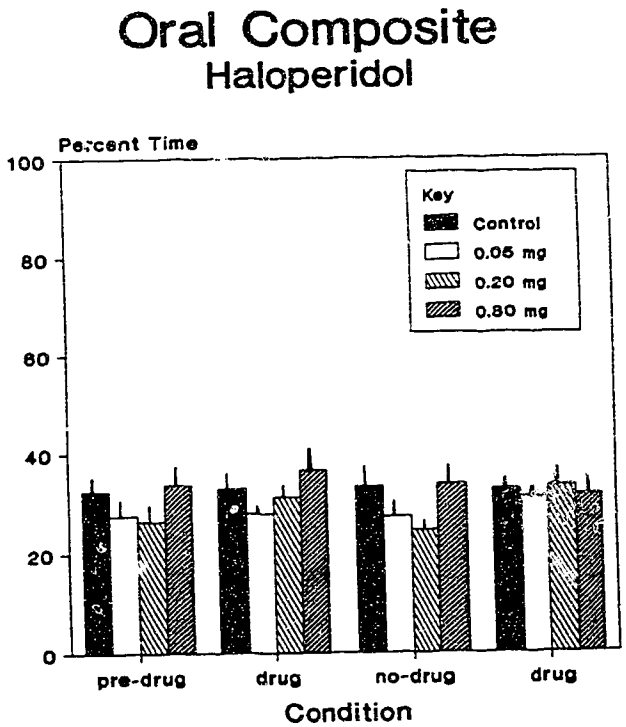
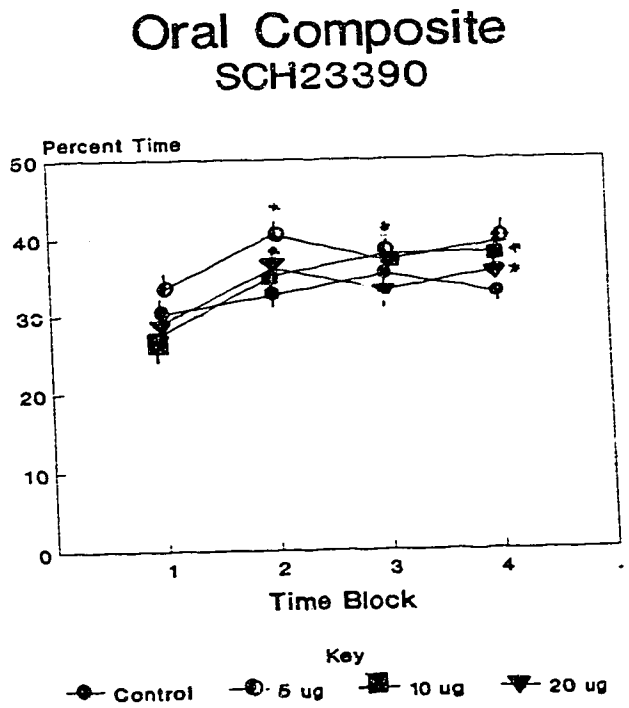


Figure 7. Mean (+SE) of total session time engaged in oral behaviors: drink, chew, bite, groom and lick.



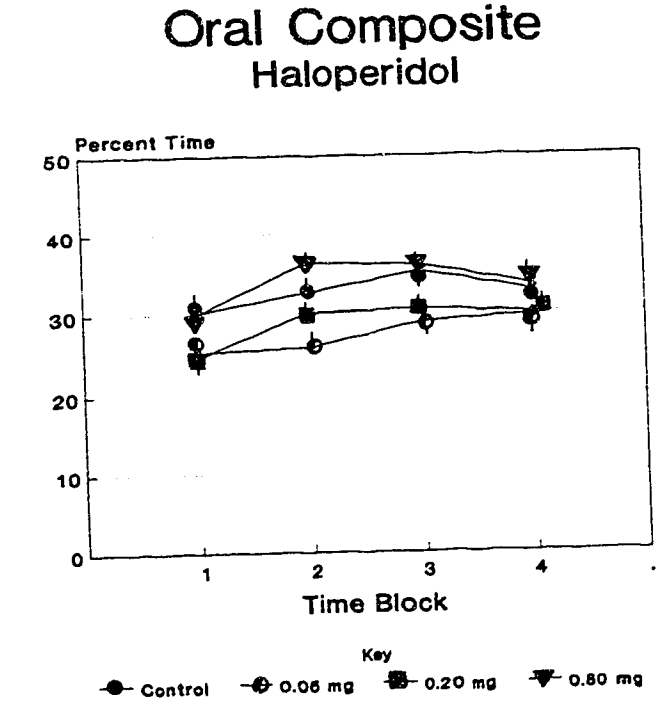


Figure 8. Mean(+SE) percent of total session time engaged in oral behavior within 5 min time blocks within a 50-min session. Dots denote significant differences from Time 1 across all conditions; $p<0.05$, Newman-Keuls.

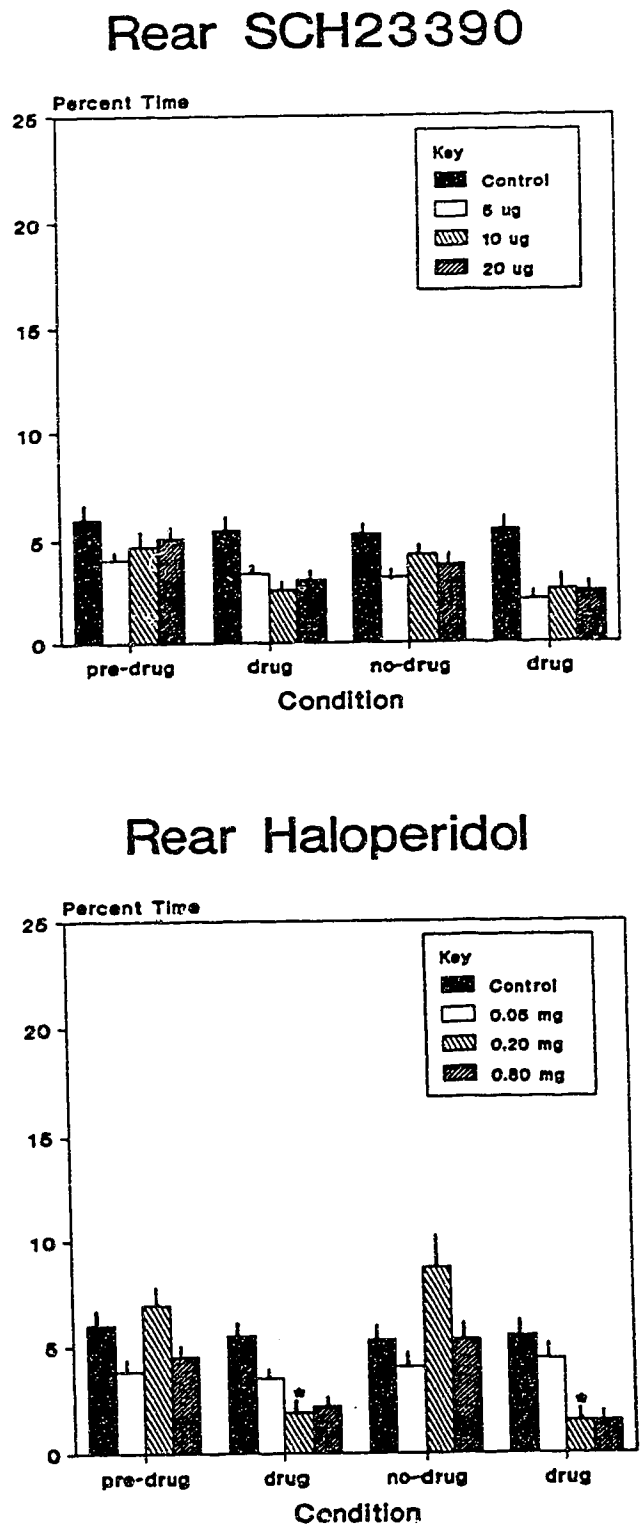
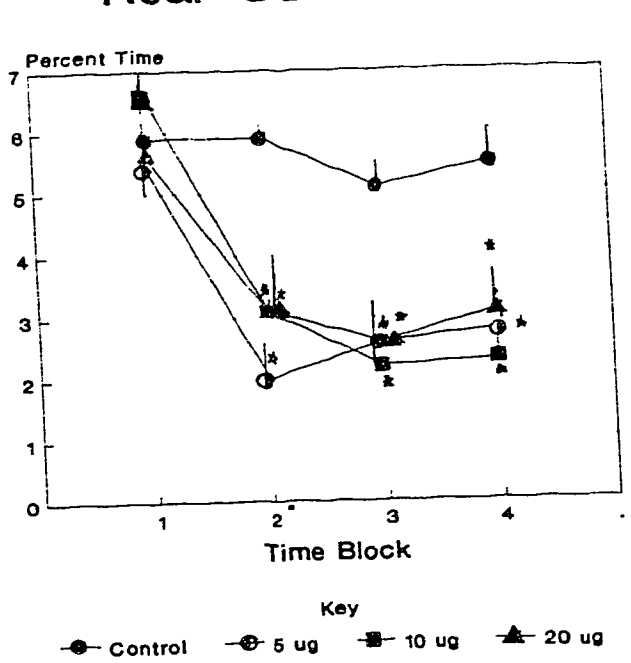


Figure 9. Mean (+SE) percent of total session time engaged in rear. Dots denote significant differences within a group between conditions relative to pre-drug ($p<0.05$, Newman-Keuls).



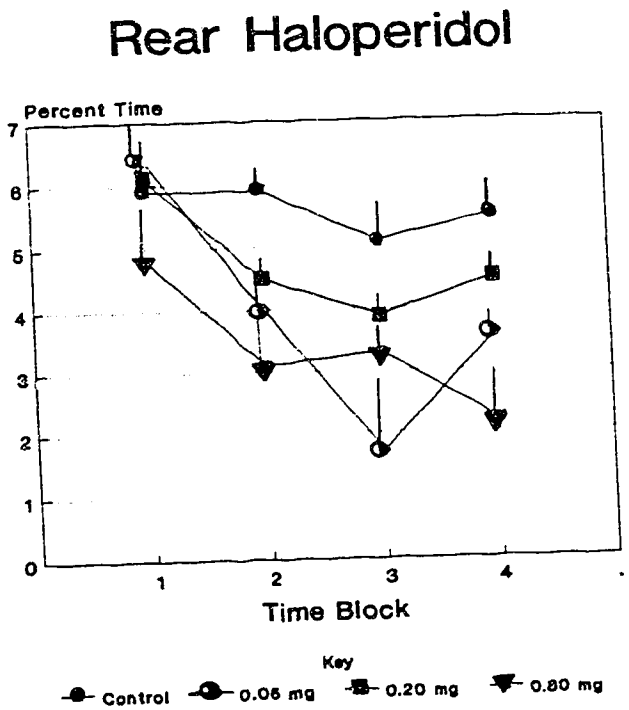


Figure 10. Mean (+SE) percent of total session time rear within 5-min time blocks within a 50-min session. Dots denote significant within drug group differences from Time 1 ($p<0.05$, Newman-Keuls).

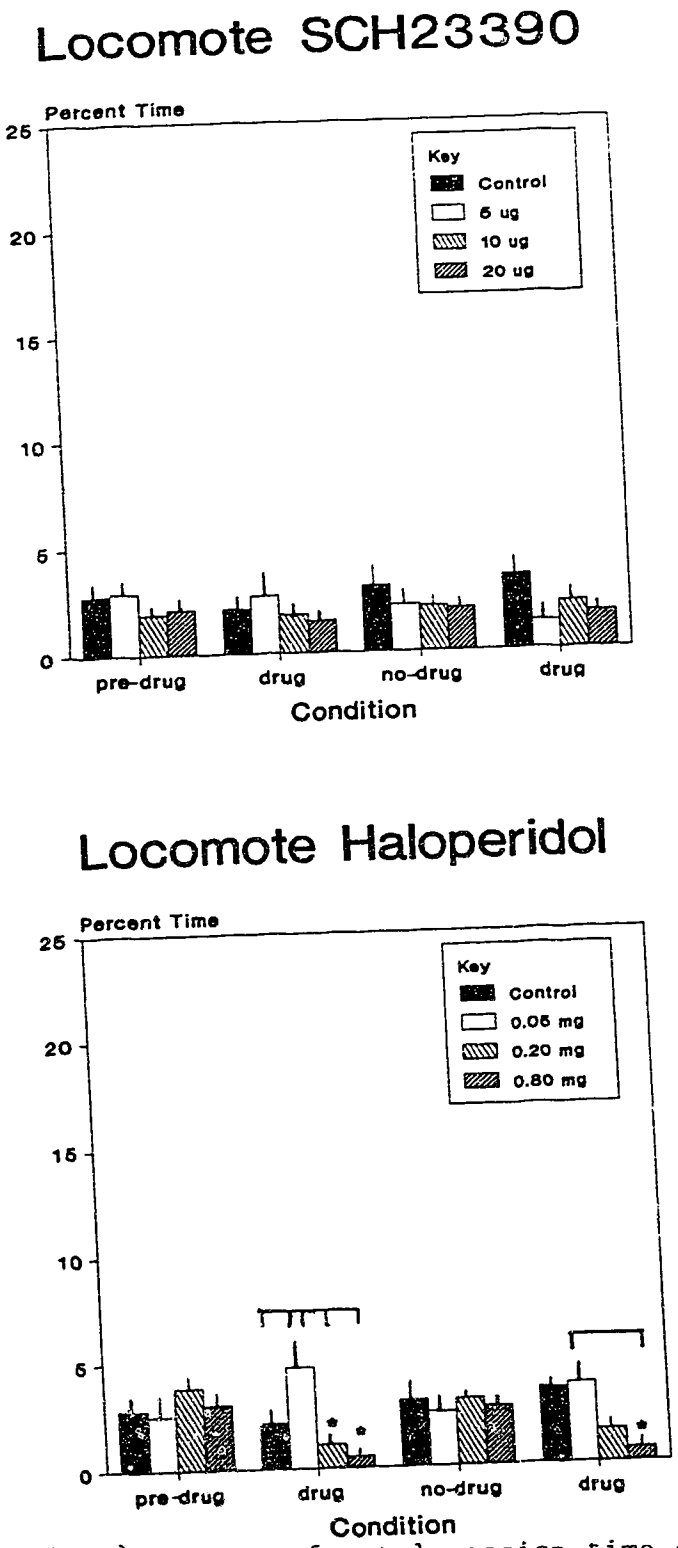
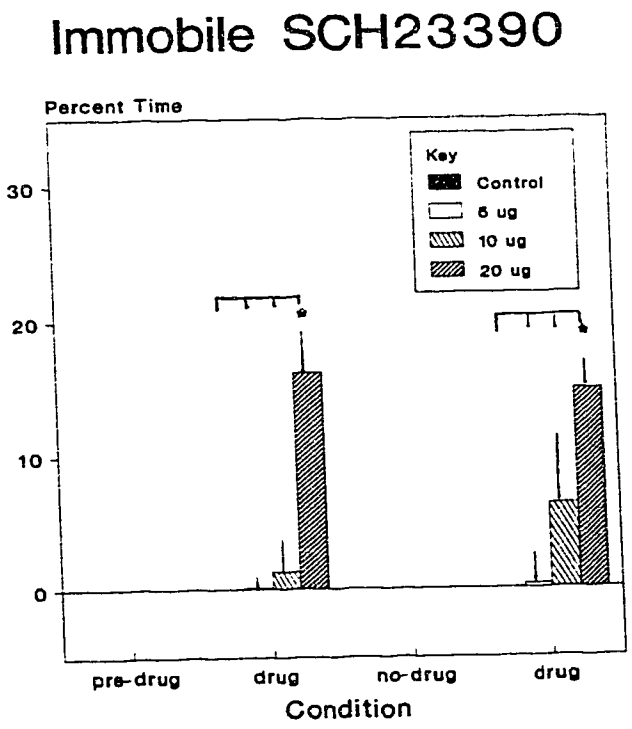


Figure 11. Mean (+SE) percent of total session time engaged in locomote. Brackets denote significant differences within a condition, dots denote significant differences within a group between conditions relative to pre-drug ($p<0.05$, Newman-Keuls).



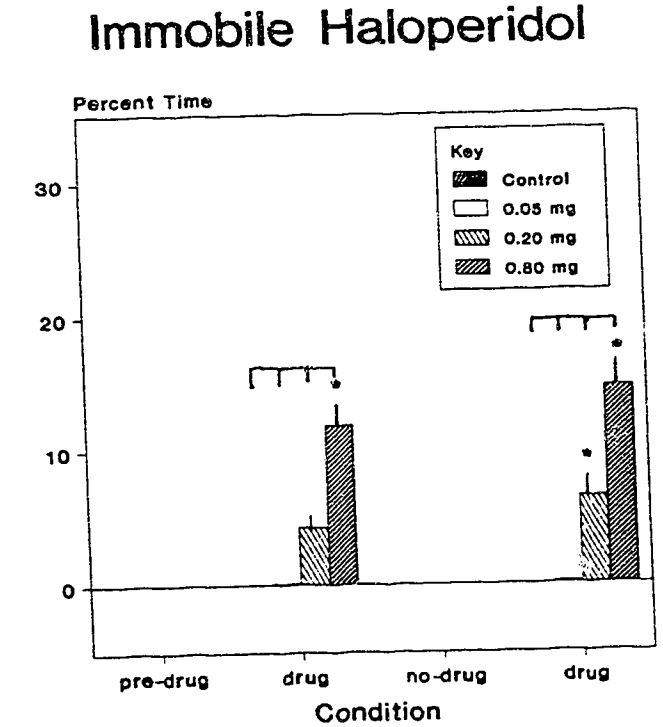


Figure 12. Mean (+SE) percent of total session time animals were immobile. Brackets denote significant differences within a condition, dots denote significant differences within a group between conditions relative to pre-drug ($p<0.05$ Newman-Keuls).

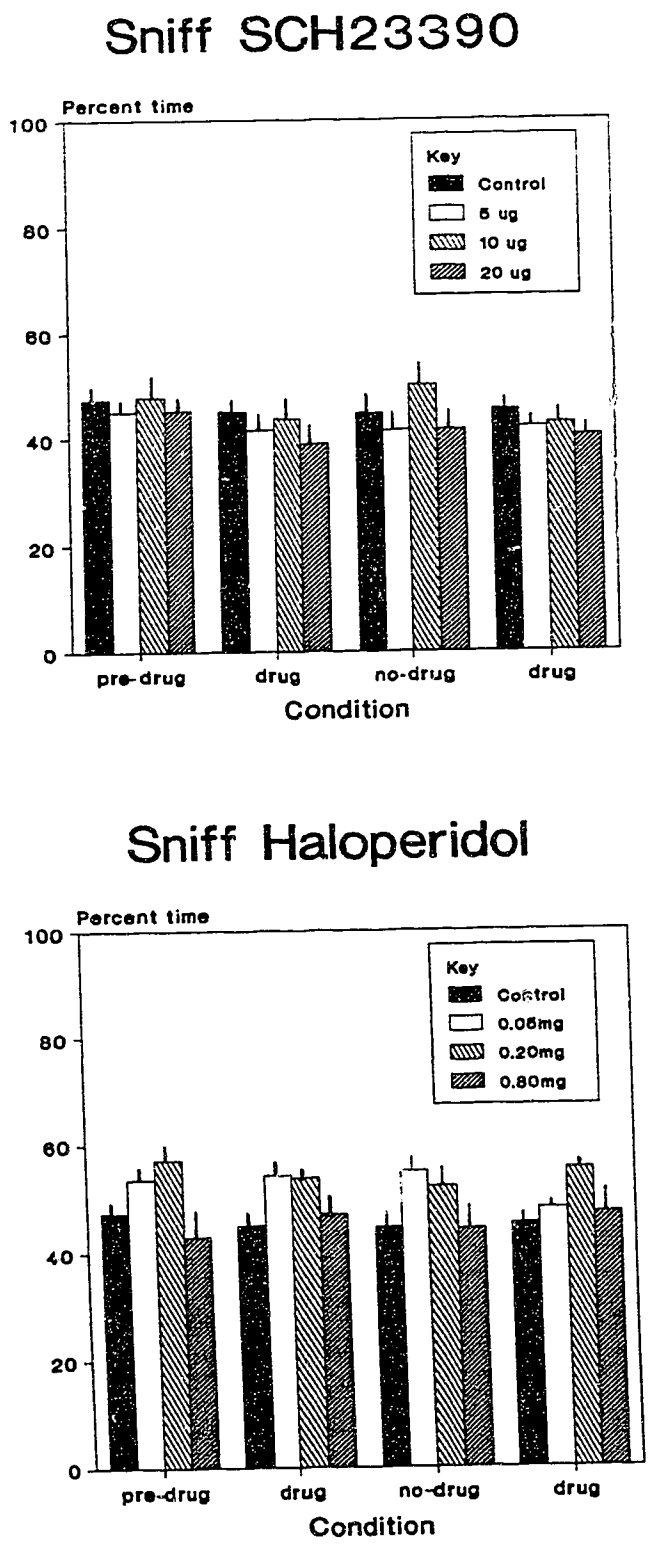
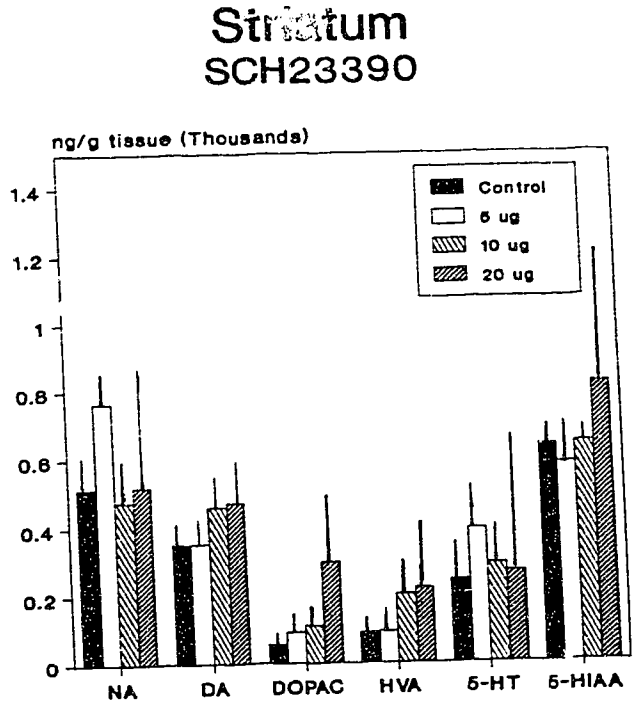


Figure 13. Mean (+SE) percent of total session time engaged in sniff.



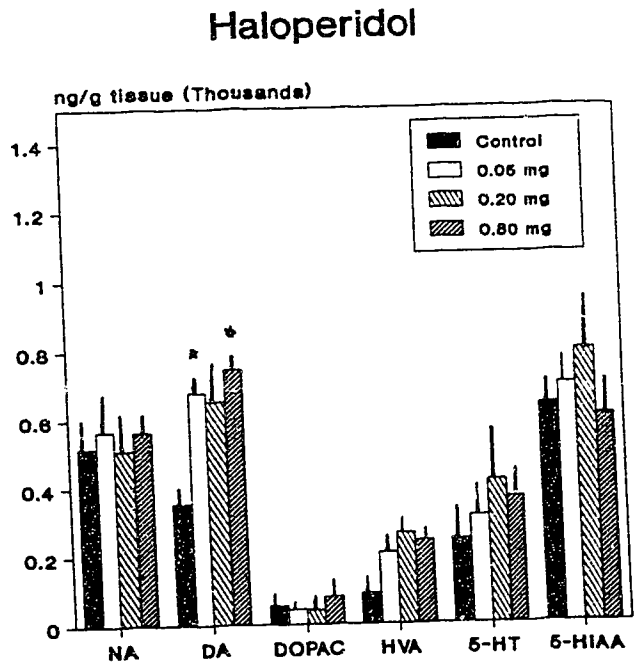


Figure 14. Control and drug levels of NA, DA, DOPAC, HVA, 5-HT and 5-HIAA in the striatum. Values expressed as mean (+SE) ng/g tissue. Scale for DA, DOPAC and HVA is 0.1. Dots denote significant differences from control ($p<0.05$, Newman-Keuls).

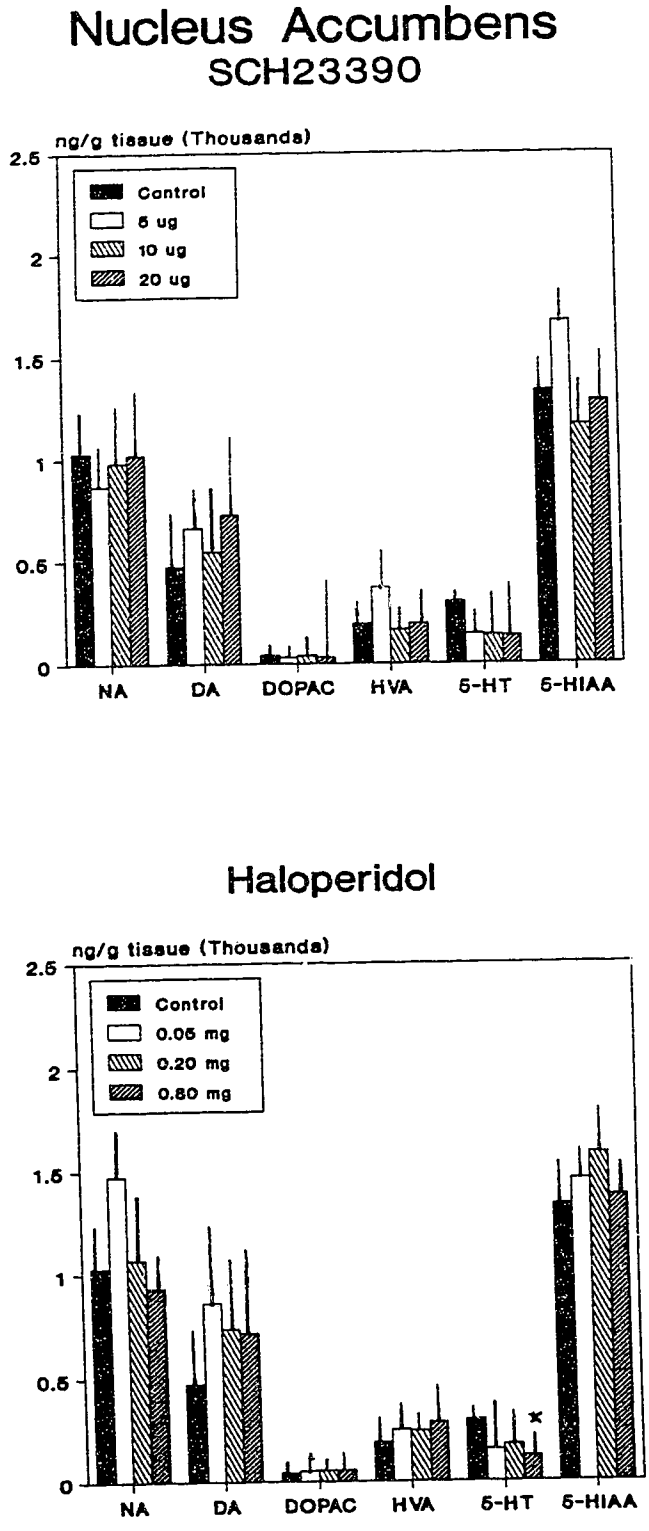
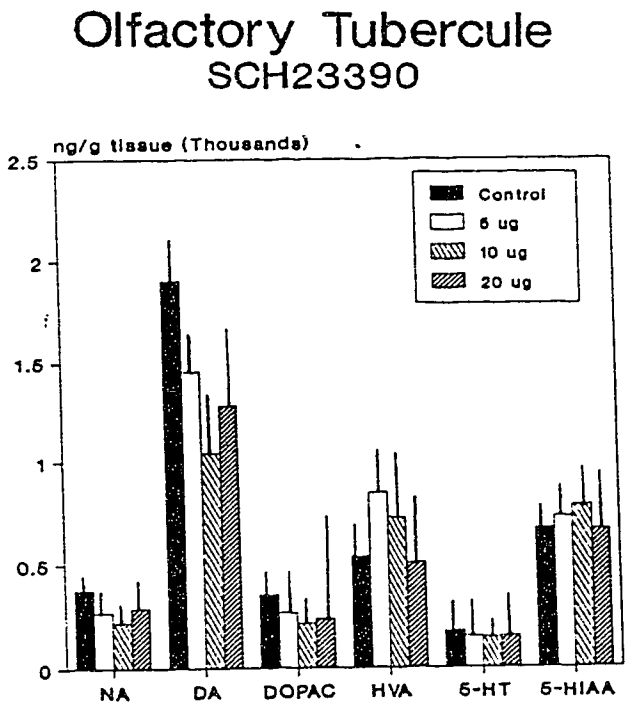


Figure 15. Control and drug levels of NA, DA, DOPAC, HVA, 5-HT, and 5-HIAA in the nucleus accumbens. Values expressed as mean (+SE) ng/g tissue. Scale for DA, DOPAC and HVA is 0.1. Dot denotes significant differences from control ($p<0.05$, Newman Keuls).



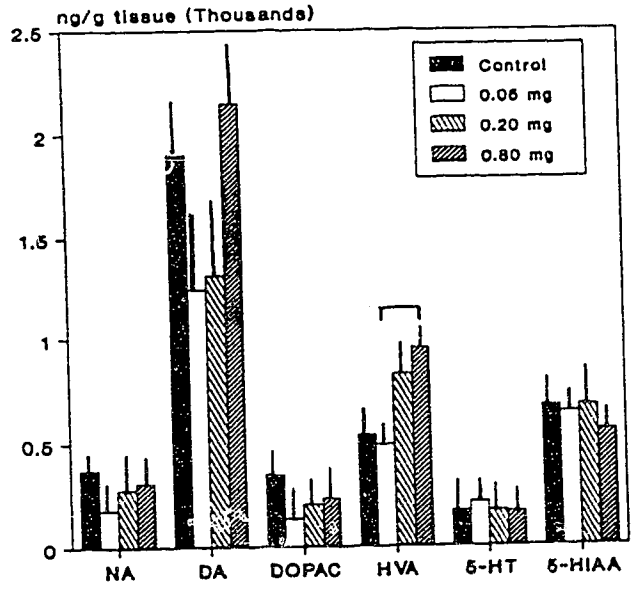


Figure 16. Control and drug levels of NA, DA, DOPAC, 5-HT and 5-HIAA in the olfactory tubercule. Values expressed as mean (+SE) ng/g tissue. Bracket denote significant difference within a drug group ($p<0.05$, Newman-Keuls).

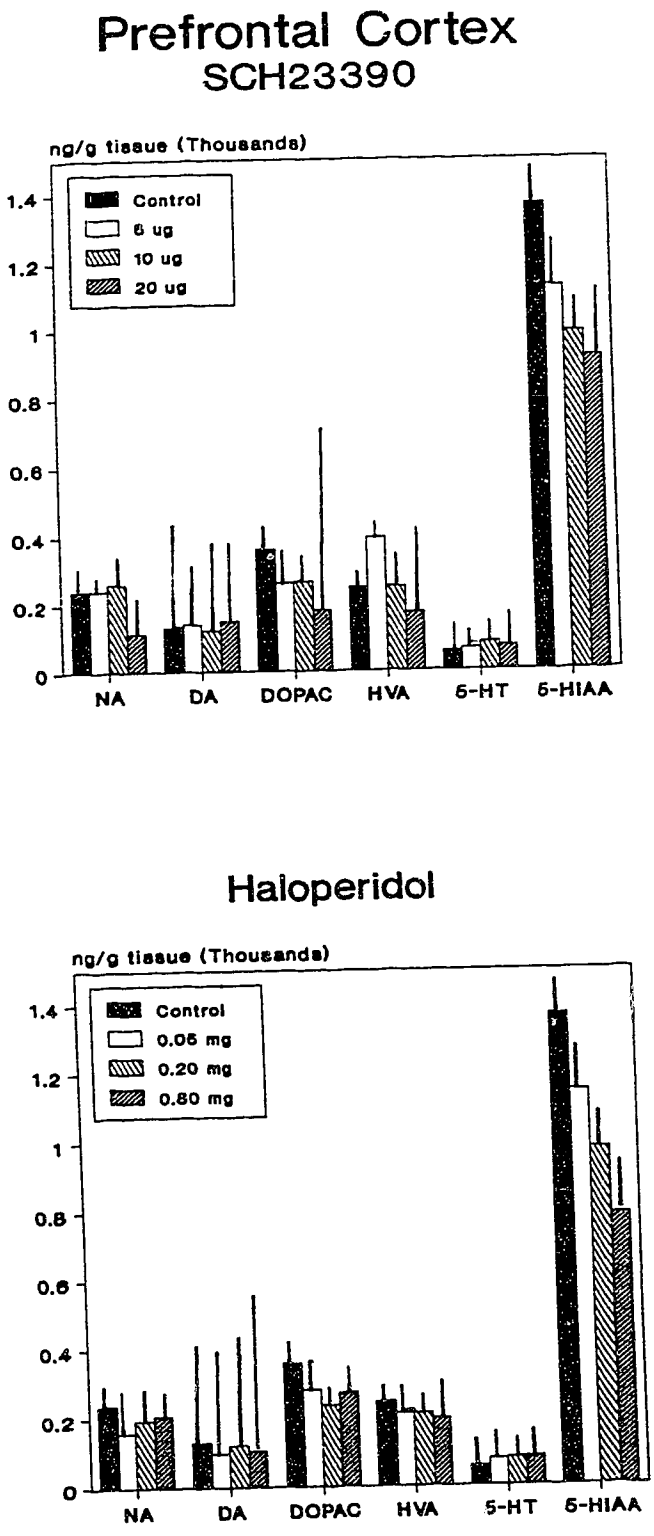


Figure 17. Control and drug levels of NA, DA, DOPAC, HVA, 5-HT and 5-HIAA in the prefrontal cortex. Values are expressed as mean (+SE) ng/g tissue.

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