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ATYPICAL ANTIPSYCHOTICS PRODUCE WITHIN-SESSION DECREMENTS ON SELF-STIMULATION OF THE RAT MEDIAL PREFRONTAL CORTEX

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TABLE OF CONTENTS

1. ABSTRACT

It has been described that "typical" antipsychotic drugs (APDs) induce characteristic within-session response decrements in operant behaviors, including intracranial self-stimulation (ICSS). By contrast, recent reports have shown that in food operant behavior, clozapine and a number of "atypical" APDs do not give rise to within-session effects. However, to elucidate whether or not this is a common property of atypical APDs, their effects on other operant models need to be studied. To address this question we investigated the temporal pattern of ICSS responding, after systemic administration of five atypical APDs and the typical antipsychotic, haloperidol. Rats were trained to lever press for electrical stimulation at the medial prefrontal cortex (mPFC), and response rates were recorded during each 3-min period of the 15-min session. Significant within-session response decrements on mPFC ICSS were observed with haloperidol, risperidone, sertindole and olanzapine but not with clozapine or ziprasidone. The magnitude of within-session decline produced by the APDs tested was positively correlated with their affinity for dopamine D_2 receptors. The results show for the first time that atypical APDs are capable to induce within-session decrements on ICSS behavior, and suggest that this particular temporal pattern of responding is not exclusively characteristic of typical APDs. The results are also consistent with the hypothesis that the ability of APDs to induce greater within-session effects may be related, in part, to potent D_2 antagonism.

2. INTRODUCTION

The new generation of antipsychotic drugs (APDs) is commonly classified as "atypical" primarily because at therapeutic doses they have lower incidence of motor side effects, relative to classical or "typical" medications (1-3). Preclinical investigations have used operant behavioral procedures extensively for identifying and categorizing differences in the acute effects of antipsychotic drugs *in vivo*, which could ultimately provide a theoretical framework for interpreting their different clinical profiles. A distinction has been made on the basis that typical APDs produce an attenuation of instrumental responding, which becomes gradually more marked during the course of the experimental session. This behavioral phenomenon has been shown in different operant behaviors and leads to characteristic within-session response decrements patterns. Early experiments by Fouriezos and co-workers first described an extinction-like decrement pattern in responding when investigating the effects of pimozide and d-butaclamol on intracranial self-stimulation (ICSS) of the hypothalamus (4,5). Within-session response decrements on lever-pressing for hypothalamic and ventral tegmental area ICSS were later reported for other typical APDs such as haloperidol, metoclopramide (6) and raclopride (7). Numerous investigations carried out in operant motivated behaviors, other than ICSS, have also demonstrated the within-session effect of neuroleptics or typical APDs (7-13). Although at present there is no unanimous conclusion (14-16), the particular temporal pattern exhibited by neuroleptics has been interpreted mainly from two points of view, namely as a motivational/incentive deficit (6,11,17) or an impairment of motor function due to dopaminergic blockade (18,19).

Interestingly, two more recent studies have found that a substantial number of atypical APDs do not give rise to within-session response decrements. Thus, clozapine, thioridazine, sulpiride, amisulpiride, risperidone, sertindole, olanzapine and quetiapine, in food-reinforced behavior, produced a stable inhibition of operant responding through the duration of short test sessions, that contrasted with the incremental inhibitory effect of haloperidol (20,21). These effects on standard operant responding (lever pressing for food reward) offer the possibility of differentiating between classical and novel APDs. However, there are two major objections to this interpretation. First unlike classical APDs atypical APDs represent a heterogeneous group of compounds with widely varying pharmacological and clinical profiles (1-3,22) and second, the lack of within-session effects has not been systematically tested in operant behaviors other than responding for food (20,21). Accordingly, it is necessary to asses the effects of atypical APDs in other motivated behaviors before a common temporal pattern for this group of drugs can be defined. The objective of the present experiment was to investigate precisely whether atypical APDs produce within-session response decrements on ICSS obtained at the rat medial prefrontal cortex (mPFC). For this purpose, we examined the temporal pattern of ICSS responding produced by acute administration of haloperidol, the paradigm of typical antipsychotic action, and the atypical APDs clozapine, risperidone, olanzapine, sertindole and ziprasidone. It is interesting to study the effects of APDs on mPFC ICSS because, in contrast to operant behaviors reinforced by food, medial forebrain bundle or ventral tegmental area ICSS, the reward value of mPFC ICSS does not depend critically on mesolimbic dopaminergic function (23-25). This aspect may help to distinguish mesolimbic-mediated blunting of incentive motivation versus nigrostriatal-mediated performance deficits induced by these drugs.

3. MATERIALS AND METHODS

3.1. Animals

Adult male Wistar rats weighing 250-300 g at the time of surgery were housed individually and maintained on a 12/12 h light/dark cycle (8:00-20:00 h) and under constant temperature (22 ºC), with free access to food (diet A04, Panlab, Spain) and water. Experiments were carried out in accordance with the European Union regulations for biological experimentation on animals.

3.2. Surgery and training procedure

Under equithesin anesthesia (2 ml/kg i.p.), two monopolar stimulating electrodes were implanted bilaterally in the mPFC. Electrodes were made from 250 μm stainless-steel insect pins, insulated to within 0.5 mm of the tip. Using the level skull position, stereotaxic coordinates from bregma were: A= +2.7 mm, L=±0.8 mm and 2.8 mm beneath the dura (26). The implant was anchored to the skull with jeweler's screws. One week after surgery, rats were trained to lever-press for mPFC ICSS on a continuous reinforcement schedule. The stimulus consisted of 300 ms train of 0.5 ms square monophasic cathodal pulses delivered at a frecuency of 100 Hz. Daily 30-min sessions were conducted during the following 4-7 days until acquisition was completed. After rate-intensity curves were performed (27), current intensity was individually adjusted for each animal electrode so as to obtain maximal responding without motor side effects (30-40 lever-presses/min) and ranged between 100 and 400 μA. To counterbalance any possible brain asymmetries, the right mPFC electrode was selected for electrical stimulation in half of the animals, and the left side in the remainder. Then ICSS response rate was recorded daily during 15-min sessions. Approximately 10-15 sessions were required to obtain a stable baseline (less than 10% change in overall ICSS rate during 3 consecutive days).

3.3. Drugs

Haloperidol and risperidone (Janssen Pharmaceutica, Beerse, Belgium); sertindole (Lündbeck, Copenhagen, Denmark); ziprasidone hydrochloride (Pfizer, Groton CT, USA) and olanzapine (Lilly, Indianapolis IN, USA) were kindly provided by the above for research purposes. Clozapine was purchased from Biomol (Plymouth Meeting PA, USA). Drugs were dissolved in 0.01 M tartaric acid except for olanzapine (0.1 M tartaric ac.), ziprasidone (0.01 M tartaric ac.+propylene glycol, 1:1, v/v) and sertindole (0.05 N HCl). Solutions were freshly prepared each day before the experiment. On the test day, animals received intraperitonial injections of drug or vehicle in a volume of 2 ml/kg 30 min before ICSS testing except for haloperidol, ziprasidone (60 min) and sertindole

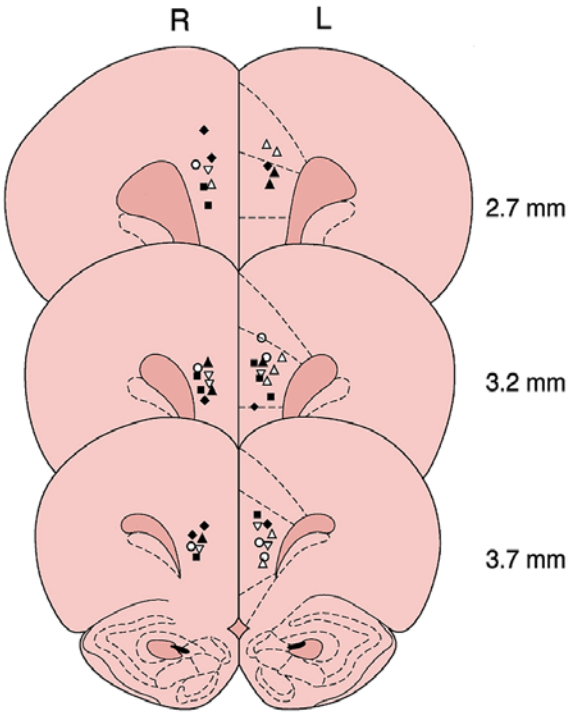

Figure 1. Reconstruction of electrode tip placements, on the right (R) and left (L) mPFC, for all animals included in this Experiment. The coronal sections histological plates were taken from the atlas of Paxinos and Watson (26). Numbers to the right indicate millimeters from bregma. The different symbols indicate group affiliation: (✱) haloperidol; (4) risperidone; (6) olanzapine; (!) ziprasidone; (э) sertindole; (7) clozapine.

(75 min). Three doses for each drug were used: haloperidol (0.05, 0.1, 0.2 mg/kg), clozapine (2.5, 5, 10 mg/kg), risperidone (0.1, 0.15, 0.2 mg/kg), sertindole (2.5, 5, 10 mg/kg), olanzapine (0.25, 0.5, 1 mg/kg) and ziprasidone (0.55, 0.75, 1.5 mg/kg; expressed as salt). Testing time and dose range were selected based on pilot studies and those reported in the literature (20,21). Following a given drug treatment, the dosages that attenuated overall ICSS responding in 5-min by less than 10% or more than 90% from pre-drug baseline were avoided.

3.4. Experimental protocol

The animals were subjected to drug experiments after a minimum of 5 days of stable ICSS responding was established. Rats were assigned to one of six antipsychotic drug groups: haloperidol (n=7), clozapine (n=7), risperidone (n=6), sertindole (n=8), olanzapine (n=8) and ziprasidone (n=9). Each rat was injected with all three doses of a drug and the corresponding vehicle, given in a randomized order. ICSS rate was recorded during five successive 3-min periods of the 15-min session. At least 4 days separated each drug/vehicle injection, during which ICSS was monitored to check for recovery from drug effects. ICSS rate was maintained at a stable level throughout the experiments and no significant differences were found among pre-injection days (repeated measures ANOVAs performed on pre-injection baseline data). As a representative example, ICSS response rate (mean±S.E.M.) on the first and the last pre-injection day of the sertindole group were: 644.7±50.8 and 633.4±54.7 presses/15 min, respectively. For each drug group, control consisted of the average data obtained from baseline sessions on pre-injection days.

3.5. Data analysis

Data were analyzed using ICSS response rate calculated as percentage of the pre-injection control. All results are given as mean±S.E.M. Drug effects on the overall ICSS responding in 15-min were assessed using two-way, repeated measures ANOVA followed by the Dunnett's post-hoc test to compare the effects of each drug with its vehicle. ED_{50} values (effective drug dose in reducing overall ICSS responding to 50% of control) were estimated for the linear portion of the dose response curves using least-squares linear regression analysis. Temporal patterns of responding from separate drugs were analyzed as five 3-min periods of the 15-min session using two-way repeated measures ANOVA, with the time period as repeated measure. When significant dose-by-time interaction or time effect was detected, comparisons between the first 3-min period and the following periods in the session were performed using Dunnett's test. Linear regression was fitted to the dose-effect over time for each rat, 95% confidence intervals were computed for these slopes by drug. One-way ANOVA was performed to assess differences among slopes obtained from a single rat and averaged by drug dose followed by Bonferroni's post-hoc test for individual comparisons.

3.6. Histology

At the end of the experiments, rats were given an overdose of equithesin and perfused transcardially with physiological saline followed by 10% buffered formalin. The brains were removed, stored in fixative and later sliced on a microtome in 40 μm thick sections, that were subsequently stained with cresyl violet for histological verification of electrode tip placements with the aid of the atlas of Paxinos and Watson (26).

4. RESULTS

After histological examination, most electrodes were placed in deep layers of the prelimbic area of the mPFC on the coronal sections of the Paxinos and Watson's rat atlas (26), ranging +3.7-+2.7 mm from bregma (figure 1).

Systemic administration of the six APDs studied produced dose-dependent inhibition on lever pressing in the 15-min session. The analysis of variance showed highly significant effect of dose [$F_{(3,117)}$=108, p<0.0001] on ICSS responding. Compared with the corresponding vehicle, significant reductions in overall ICSS were found with the three doses of haloperidol and the two highest doses of the atypical APDs (figure 2). All APDs tested at the low, medium and high doses, produced equivalent reductions in ICSS and the ANOVA showed no significant interaction between dose and drug treatment [$F_{(15,117)}$=0.78, p=0.70].

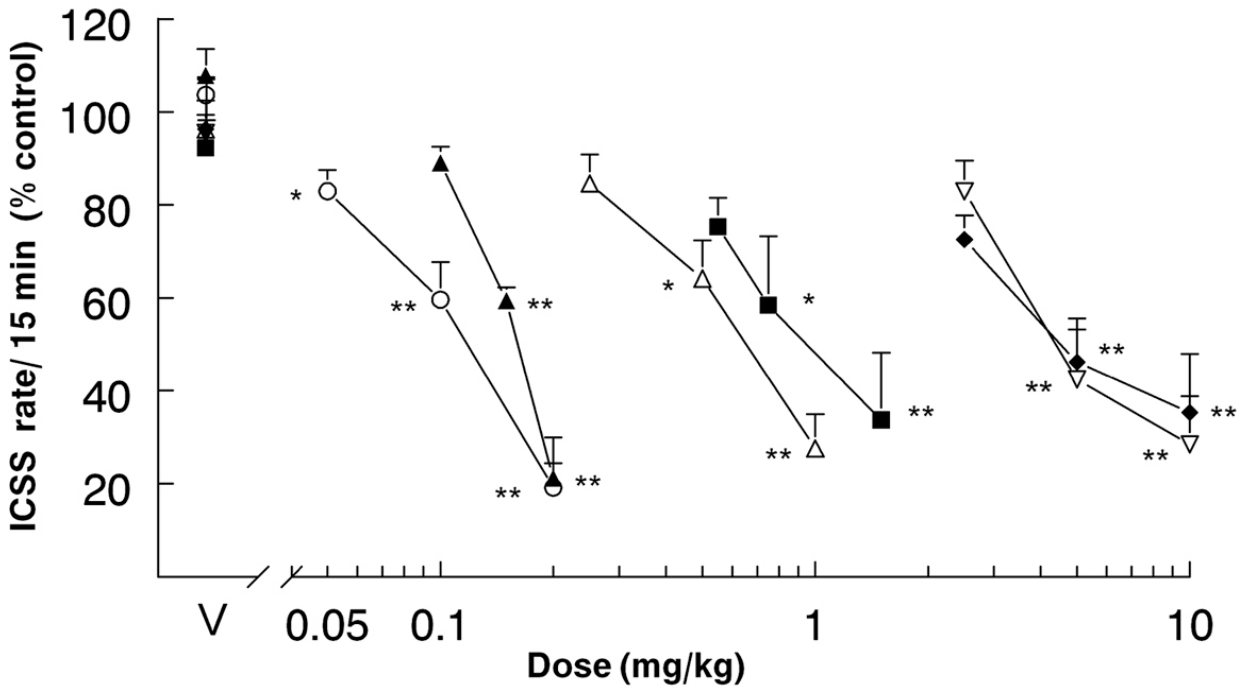

Figure 2. Acute effects of (⁕) haloperidol (0.05, 0.1, 0.2 mg/kg) and the atypical antipsychotics (**4**) risperidone (0.1, 0.15, 0.2 mg/kg); (**6**) olanzapine (0.25, 0.5, 1 mg/kg); (!) ziprasidone (0.55, 0.75, 1.5 mg/kg; (**ɜ**) sertindole (2.5, 5, 10 mg/kg) and (**7**) clozapine (2.5, 5, 10 mg/kg) on ICSS obtained at the mPFC. Each point represents the mean (±S.E.M.) response rate during the 15-min session, expressed as percentage of the pre-injection control. V=vehicle. *p<0.05; **p<0.01 *vs* vehicle (two-way, repeated measures ANOVA followed by Dunnett's test).

APDs reduced overall bar pressing at low doses by 20.3± 2.8% (mean±S.E.M.) of control, whereas medium and high doses produced 46.32±3.8% and 74.1±3.9% reductions, respectively. ED_{50} values in mg/kg for the dose-response curves presented in figure 2 were: haloperidol 0.12; risperidone 0.16; olanzapine 0.77; ziprasidone 1.40; sertindole 3.61 and clozapine 6.67.

The effects of APDs on the temporal pattern of ICSS responding can be seen in figure 3, taking observations at successive 3-min periods of the 15-min session. The typical APD haloperidol, showed highly significant effect of dose [$F_{(3,18)}$=48.79, p<0.0001], time period [$F_{(4,24)}$=12.25, p<0.0001] and dose-by-time interaction [$F_{(12,72)}$=8.58, p<0.0001], indicating dose-related ICSS inhibition and that a sharp early-to-late responding differential was present in certain doses. Significant within-session declines were produced by haloperidol at the two highest doses (0.1 and 0.2 mg/kg), when ICSS obtained in the first period (0-3 min) was compared to that in the following periods of the session. Thus, at the end of the session (fifth period: 13-15 min) haloperidol 0.1 and 0.2 mg/kg produced significant 42% and 88% reductions on ICSS, respectively (figure 3A).

By contrast, clozapine and ziprasidone did not give rise to within-session response decrements at any dose, although both atypical APDs reduced ICSS responding. Statistical analysis showed a significant effect of dose for clozapine [$F_{(3,18)}$=34.63, p<0.0001] and ziprasidone [$F_{(3,24)}$=9.82, p<0.0001]. However, clozapine failed to reach significance for time and dose-by-time interaction indicating that the reduced responding at the three doses remained virtually constant throughout the session. In the case of ziprasidone, the interaction dose-by-time reached significance [$F_{(12,96)}$=1.87, p<0.05], but the time factor did not. Post-hoc analysis showed that the lower dose of ziprasidone (0.55 mg/kg) significantly increase responding by 2nd-4th time periods (6-12 min), whereas the higher dose (1.5 mg/kg) showed a tendency to decline during the course of the session (figure 3C).

As with clozapine and ziprasidone, the rest of atypical APDs studied also showed highly significant effects of dose (sertindole [$F_{(3,21)}$=11.55, p<0.0001], olanzapine [$F_{(3,21)}$=18.22, p<0.0001] and risperidone [$F_{(3,15)}$=36.41, p<0.0001]). However, they produced within-session decrements to different degrees. Thus, significant effects of time and dose-by-time interaction were found for sertindole [$F_{(4,28)}$=5.4, p<0.002; $F_{(12,84)}$=6.1, p<0.0001], olanzapine [$F_{(4,28)}$=3.28, p<0.03; $F_{(12,84)}$=2.34, p< 0.01] and risperidone [$F_{(4,20)}$=3.42, p<0.03; $F_{(12,60)}$=2.19, p<0.02], indicating enhanced early-to-late responding differential as dose increases. As shown in figure 3A,B, within-session effects reached significance at the two highest doses of sertindole tested (5 and 10 mg/kg) and at the highest dose of olanzapine (1 mg/kg) and risperidone (0.2 mg/kg). When ICSS responding obtained in the first 3-min period was compared to that during the last period of the session (13-15 min), the two highest doses of sertindole reduced ICSS

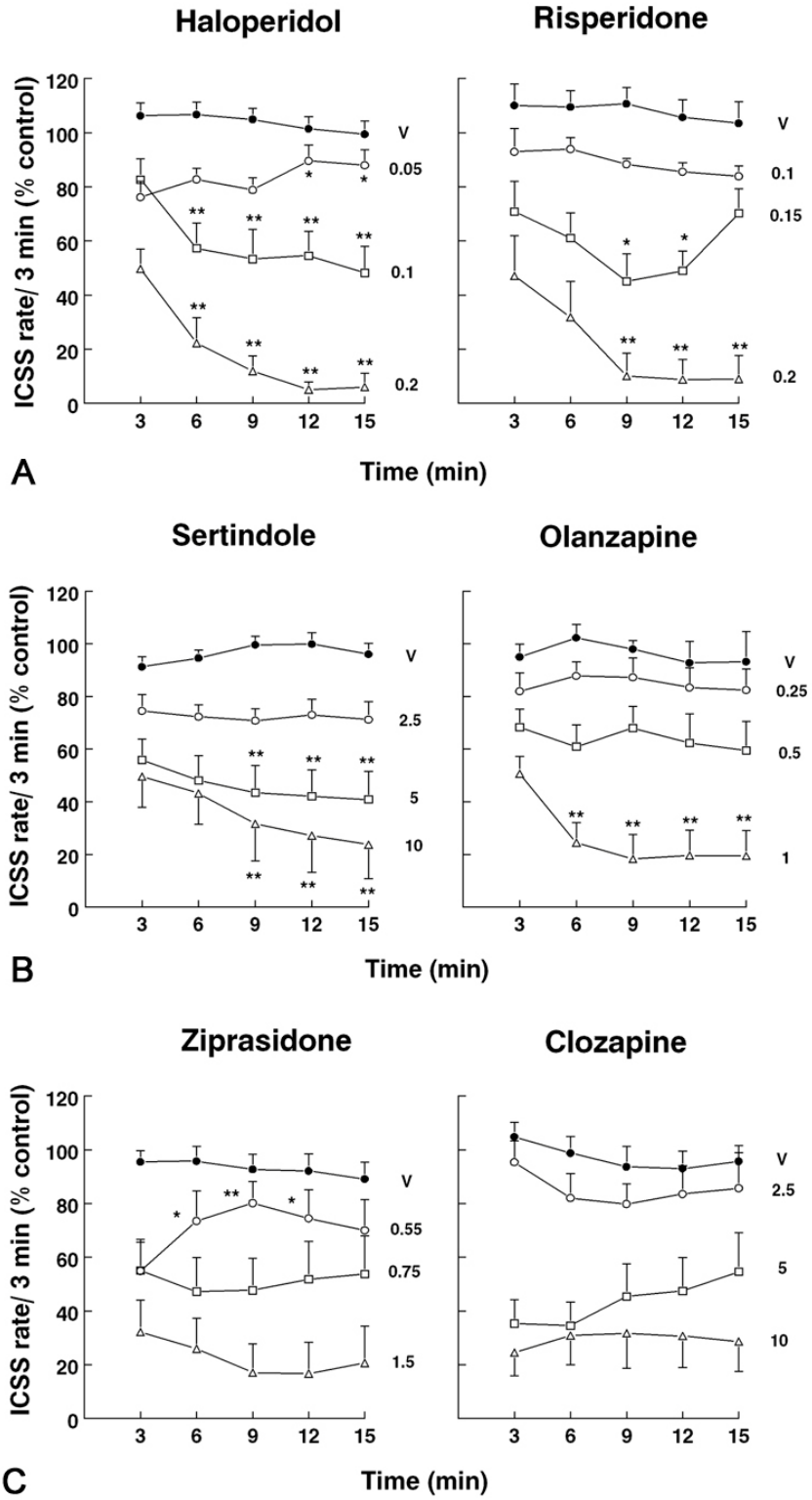

Figure 3. Effects of: A) haloperidol, risperidone, B) sertindole, olanzapine, and C) ziprasidone, clozapine on the within-session patterns of ICSS. Each point represents the mean (±S.E.M.) response rate obtained during each successive period of 3-min in the session, expressed as percentage of control. Numbers in the lateral of individual graphs represent doses in mg/kg. V= vehicle. **p*<0.05; ***p*<0.01 *vs* first 3-min period (0-3 min): (repeated measures ANOVA followed by Dunnett's test).

Table 1. Linear regression analysis of the effects produced over time by APDs on mPFC self-stimulation: *b*: estimated slope with 95% confidence intervals. *p*: significance level

Drug	Dose (mg/kg)	b	95% Confidence interval	*p*
Haloperidol	0.05	+1.01	+0.13 — +1.89	<0.05
	0.1	-2.39 [1]	-4.11 — -0.66	<0.02
	0.2	-3.48 [2]	-4.68 — -2.27	<0.001
Risperidone	0.1	-0.88	-2.54 — +0.78	
	0.15	-0.43	-2.87 — +2.01	
	0.2	-3.31 [1]	-6.28 — -0.33	<0.05
Sertindole	2.5	-0.19	-1.17 — +0.77	
	5	-1.20	-2.24 — -0.16	<0.05
	10	-2.26	-3.71 — -0.81	<0.02
Olanzapine	0.25	-0.11	-1.51 — +1.28	
	0.5	-0.54	-2.34 — +1.25	
	1	-2.24	-4.12 — -0.37	<0.05
Ziprasidone	0.55	+1.04	-1.04 — +3.12	
	0.75	+0.07	-3.21 — +3.35	
	1.5	-1.07	-3.23 — +1.08	
Clozapine	2.5	-0.12	-4.11 — +3.87	
	5	+1.88	-0.31 — +4.08	
	10	+0.45	-1.05 — +1.97	

[1] $p<0.05$; [2] $p<0.02$ *vs* clozapine (one-way ANOVA-Bonferroni).

by 27% and 52%, respectively. The highest dose of olanzapine decreased responding by 62%, whereas in the case of risperidone the reduction was 81%.

The consistency and magnitude of within-session decrements produced on ICSS by the APDs were also revealed by linear regression analysis. ICSS decline over time expressed by significant ($p<0.05$) negative slopes, confirm results obtained in previous analyses. As shown in table 1, the typical APD haloperidol at the highest dose induced the maximum degree of ICSS inhibition through the session (b=-3.48, $p<0.001$). Gradual smaller negative slopes were found at the highest doses of risperidone (b=-3.31, $p<0.05$), sertindole (b=-2.26, $p<0.02$) and olanzapine (b=-2.24, $p<0.05$); while ziprasidone and clozapine produced no significant changes over time. The post-hoc tests showed significant differences in the linear trend across the session (slope) between clozapine and haloperidol at the two highest doses, and between clozapine and risperidone at their respective highest doses.

5. DISCUSSION

The results of this study show that the atypical APDs risperidone, sertindole and olanzapine produce within-session response decrements in ICSS obtained at the mPFC, indicating that this temporal pattern is not an exclusive characteristic of neuroleptics as it could also be derived from previous reports by Sanger and Perrault (20) and Varvel et al. (21) on food-reinforced behavior. In the first study (20) since significant within-session decrements from the eight atypical APDs tested were found only with remoxipride, the authors concluded that *"...most atypical antipsychotics agents do not give rise to haloperidol-like within-session response decrements"*. However, in figures 3 and 4 a tendency for responding to decline over the session is indicated, with the atypical APDs amisulpride, risperidone and sertindole at the highest doses used, although not significant so. In the second study (21) the lack of within-session decrements of atypical APDs is unfortunately mentioned only in the text, and the data are not shown. Thus, as far as the findings of Sanger and Perrault are concerned, differences with our study regarding the atypical APDs risperidone and sertindole are based mainly on the degree of within-session decrements, probably due to the procedural differences between the two studies. To elucidate this question, further investigation is needed.

In addition, our study shows that ziprasidone, for which within-session decrements have not yet been studied, failed to induce significant within-session effects, although a tendency for the highest dose was found. On the other hand, confirming previous findings on food-reinforced operant behavior (8,20,21), we found that haloperidol gave rise to within-session decreases in lever pressing for mPFC ICSS, whereas clozapine did not, despite equivalent dose-related decreases produced by both compounds on ICSS. The differential effects of atypical APDs on mPFC ICSS are in accordance with the notion that these drugs form a heterogeneous group of compounds differing in pharmacological, behavioral and clinical properties (1,2,22).

Although at present the mechanisms underlying within-session decrements are unknown, dopamine antagonism seems to be associated with this temporal pattern of responding. Thus, drugs that characteristically induce within-session declines in operant behaviors such as pimozide and d-butaclamol (5), metoclopramide (6), *cis*-flupentixol (11,12) or haloperidol and remoxipride (6,20,21), are potent and/or selective dopamine D_2 receptor antagonists. In fact, the neuroleptic pimozide, which is a relatively selective D_2 antagonist, induces within-session response decrements in mPFC ICSS (data not shown) at moderate doses (0.2-0.4 mg/kg), similar to the non-selective dopamine receptor antagonist haloperidol. With regard to the dopamine antagonism of APDs, it has been hypothesized that clozapine and the novel atypical drugs differ from haloperidol and other neuroleptics in having lower affinities due to a faster dissociation rate constant (k_{off}) than dopamine, at the dopamine D_2 receptor (28). Thus, transient and low occupancy of D_2 receptors, characteristic of novel APDs, has been proposed as the

main factor responsible of their atypical antipsychotic action, cortico/limbic selectivity and less pronounced motor side effects (28-31). The APDs included in our study can be ordered, according to Seeman (31), from low to high affinity for the D_2 receptor (K_i, nM) as follows: clozapine (63), olanzapine (5.1), ziprasidone (2.7), sertindole (2.3), risperidone (1.1) and haloperidol (0.55). It is worth noting that clozapine, which presents by far the lowest affinity and fastest k_{off} (1.386 min^{-1}) (28), produced no within-session decrements. On the other hand, haloperidol, with the highest affinity and slowest k_{off} (0.017 min^{-1}), showed the maximum within-session decrements, whereas the rest of the atypical APDs tested with relative high affinities and slow dissociation (28) showed intermediate effects on mPFC ICSS. In this respect, the different affinity/lability in their binding to the D_2 receptor could be interpreted as being responsible for the differential effects of these atypical compounds on mPFC ICSS. In fact, for the six APDs included in our study a significant correlation (Spearman's, r=0.8 $p<0.004$) was found between D_2 receptor affinities (31) and the intensity of within-session effects at the two highest doses (table 1, estimated slope).

Furthermore, it has been reported that single doses of haloperidol (0.1-0.2 mg/kg), a dosage which induces decrement patterns in mPFC ICSS, occupy 88%-90% of rat striatal D_2 receptors *in vivo*, whereas 10 mg/kg of clozapine, the highest dose used in our study, hardly achieves 40% occupancy (32,33). Interestingly, doses of risperidone (0.2 mg/kg), olanzapine (1 mg/kg) and sertindole (5, 10 mg/kg) that produced within-session decrements on mPFC ICSS, also occupy D_2 receptors (50%-70%) in high proportions (32-34). With reference to ziprasidone, it has been shown that, notwithstanding its high affinity for D_2 receptors, at doses as high as 5-10 mg/kg unexpectedly it does not give rise to appreciable levels (<50%) of D_2 occupancy (34,35). Thus, low occupancy of D_2 receptors might be one factor causing the lack of within-session effects found with ziprasidone and clozapine and would explain why ziprasidone behaves like clozapine in our operant model, despite the fact that their temporal patterns are not identical because the former exhibited a trend towards decline in the 1.5 mg/kg dose.

In addition to antagonism at the D_2 receptor, the five atypical APDs tested in the present study have in common high to moderate affinity for serotonin 5-HT_2 receptors (35). However, 5-HT_2 receptor antagonism is unlikely to be involved in the temporal pattern of mPFC ICSS exhibited by the drugs tested, either the presence or absence of within-session decrements. Thus, at the dosage used in our study risperidone, which shows 150-fold higher affinity and 10-fold higher occupation at 5-HT_{2A} receptors than haloperidol (35), induces comparable within-session decrements in mPFC ICSS. On the other hand, ziprasidone, which has similar affinity and 5-HT_{2A} receptor occupation to risperidone (35), produces no within-session effects. Furthermore and in contrasts to D_2 receptors, intensity of within session effects (estimated slope) did not correlate with $5HT_{2A}$ affinity or $5HT_{2A}/D_2$ affinity ratio (31,35). This interpretation agrees with previous evidence showing that in food operant responding, ritanserin, a selective $5HT_{2A/2C}$ antagonist, does not affect the production of within-session decrements by haloperidol (20).

Rate-dependent measures of ICSS, like the schedule used in our study to detect antipsychotic-induced response decrement patterns, are believed to be especially sensitive to the nigrostriatal related motor performance effects of dopamine antagonists (36). This, together with the fact that the reward value of mPFC ICSS is relatively independent of the mesolimbic dopaminergic system (23,24), suggest that within-session decrements observed with haloperidol and the atypical APDs risperidone, olanzapine and sertindole might be related to their ability to interact with the striatal dopaminergic mechanisms of motor control. However, although subtle motor disturbances (18,19) could account for the intra-session effects obtained in the present study, recent evidence suggest that haloperidol-induced response decrements are dissociated from its cataleptogenic effect (13) and catalepsy in rats is produced by haloperidol, risperidone and olanzapine, only at doses producing a striatal D_2 occupancy ≥85% (32). Nevertheless, and as hypothesized by several authors, impairment in other dopamine-dependent functions such as the motivational/incentive salience of the ICSS, can not be excluded (17,37).

Finally, in the case of haloperidol and ziprasidone, an increase of responding over time was found with the lowest dose used. This may be related to the recently described evidence that haloperidol at low doses increases responding both in conditioned and non-conditioned reinforcement (38), revealing a nonspecific stimulant effect of this drug at low doses.

In summary, our results show for the first time that atypical APDs clearly produce within-session decrements on mPFC ICSS behavior and reveal that this is not an exclusive property of typical APDs. The magnitude of these decrements is moderate (sertindole and olanzapine) or comparable (risperidone) to haloperidol and may be related to their relative affinity/lability for the dopamine D_2 receptor. In this respect, to gain an insight into the meaning and mechanisms underlying the phenomenon of antipsychotics-induced within-session decrements, it would be interesting to investigate, in the future, the effects on mPFC ICSS of newer APDs which, like clozapine, have low affinity for D_2 receptors and produce low levels of D_2 occupancy.

6. ACKNOWLEDGEMENTS

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