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Meal patterns of free feeding rats treated with clozapine, olanzapine, or haloperidol

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Abstract

Selective dopamine D_2 antogonists increase meal size and decrease the rate of feeding within a meal. Three experiments investigated the extent to which the atypical antipsychotics, clozapine and olanzapine, and the prototypical antipsychotic, haloperidol, affected meal size and feeding rate. Microstructural analyses of meal patterning were made over a range of drug doses administered to free feeding male Lister hooded rats. Haloperidol and clozapine produced a short-term increase in food intake. Haloperidol (0.05–0.2 mg/kg) enhanced meal size (maximal at 0.1 mg/kg) and reduced feeding rate (monotonic decrease with increasing dose). Neither clozapine (1–10 mg/kg) nor olanzapine (0.3–3 mg/kg) enhanced meal size, although both drugs produced similar reductions in feeding rate to haloperidol. These data suggest that enhancement of meal size may be correlated with a high level of extrapyramidal side effects in an antipsychotic drug. The absence of an increase in meal size by two atypical compounds suggests that the increase in body weight associated with clinical treatment with these drugs cannot be modelled by acute stimulation of meal size in the rat.

Keywords: Haloperidol; Clozapine; Olanzapine; Meal size; Feeding rate; Rat antipsychotic; Weight gain

1. Introduction

In recent years, weight gain has been recognised as a commonplace and potentially serious side effect of antipsychotic treatment for schizophrenia. Indeed, the newer generation of atypical antipsychotics with a reduced level of the extrapyramidal side effects associated with classical antipsychotics, produce a greater treatment-induced increase in body weight, which does not differ in male and female patients (Stanton, 1995; Allison et al., 1999). After only 4 weeks of treatment, average weight gains of 2.3 kg (clozapine) and 3.9 kg (olanzapine) were observed; treatment with haloperidol or placebo produced no change (Kraus et al., 1999). Weight gain of this magnitude is likely to have at least two consequences. Firstly, the patient is more likely to suffer from a range of health problems including heart disease, Type II diabetes, and arthritis. Secondly, weight gain may significantly reduce patient compliance (Wetterling and MuBigbrodt, 1999). However, it should be noted that this tendency might be reduced by greater weight gain in individuals with low BMI prior to treatment (Beasley et al., 1997).

The mechanisms underlying weight gain associated with antipsychotic treatment are not well understood. In broad terms, it might result from endocrine disturbance, during which food intake remains relatively normal but fat deposition is increased. Drug treatment might also provoke an increase in food intake, which, in the absence of appropriate physiological adjustment, would lead to enhanced body weight; these possibilities are not mutually exclusive (Baptista, 1999). There is evidence that dopamine antagonists lead to enhancement of food intake. In rats, antipsychotics, including clozapine, may produce acute increases in food intake (Stolerman, 1977; Antelman et al., 1977). Chronic administration of sulpiride is associated with increase in both food intake and weight gain, though only in female rats consuming a high-fat diet (Baptista et al., 1987). There are also clinical reports suggesting that patients are aware of increased appetite associated with antipsychotic administration (Stanton, 1995).

In a detailed study of meal patterning in rats, pimozide treatment slowed the rate at which food is consumed during a meal but also greatly increased the size of individual meals (Blundell and Latham, 1978). Since meal frequency was also reduced, the drug had only a marginal effect on total

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food intake. More recently, we (Clifton, 1995; Clifton et al., 1991) compared the effectiveness of a range of dopamine D_2 and D_1 receptor antagonists in producing changes in the patterning of ingestive behaviour. The studies showed that: (i) a range of dopamine D_2-like antagonists (YM-09151-2, raclopride, and remoxipride) produced robust decreases in feeding rate and increases in meal size; (ii) dopamine D_1-like antagonists (SCH23390 and SCH39166) produced no increase in meal size, although they produced small decreases in feeding rate and a clear hypodipsic effect; (iii) a dopamine antagonist with limited ability to pass the blood–brain barrier (domperidone) produced no changes in ingestive behaviour until centrally acting doses were reached. Thus, it appears that acute enhancement of meal size is an effect produced at central D_2-like receptors.

Atypical antipsychotics, such as clozapine and olanzapine, have broad pharmacological profiles with affinity for receptor subtypes of a number of different neurotransmitter systems, such as serotonin, noradrenaline, and histamine as well as dopamine (Moore, 1999). These neurotransmitters have been shown to be involved in the regulation of food intake and energy balance. However, the effects of atypical antipsychotics on feeding patterns are largely undocumented.

Here we examine the behavioural action of the atypical antipsychotics clozapine and olanzapine on meal patterns in free feeding rats. Furthermore, we contrast the effects of these two drugs with the classical antipsychotic haloperidol. By examining the microstructure of ingestion across two classes of antipsychotic drug we can probe the facilitation of acute meal size as a potential mechanism underlying the phenomenon of antipsychotic-induced weight gain.

2. Method

2.1. Animals

In each of the three studies, eight experimentally naive male hooded Lister rats were used. The animals were bred at the University of Sussex. Animals weighed between 350 and 400 g at the beginning of each experiment and were housed singly in the meal pattern apparatus, which consisted of a grid-floored chamber ($45 \times 30 \times 30$ cm) containing a wooden open top nest box ($15 \times 10 \times 8$ cm) in one corner. The animals remained in these cages for the entire duration of the experiment. All procedures carried out in these studies conformed to the UK Animals (Scientific Procedures) Act 1986. The rats had continuous access to water and 45-mg Noyes pellets (Formula A/I; Sandown Scientific, Middlesex, UK). These pellets provide a complete grain-based diet containing 372 cal/g.

2.2. Apparatus

The meal pattern chambers were held in a single experimental room, maintained at 21–22 °C and 40–60% RH, in visual but not auditory isolation from each other. The room was maintained on a 12:12-h light/dark (L/D) cycle with lights off at 1700 h. Two 12-W high-frequency red fluorescent tubes provided minimal illumination during the dark phase. Food (45-mg Noyes pellets) and water were freely available throughout the three experiments. Intake was recorded using a microprocessor-based system (Clifton et al., 1991). A single pellet was always available in a small hopper recessed into one wall of the chamber. When the rat took this pellet from the hopper, it was replaced with another pellet within a second and the time was logged by the computer. Only very rarely did the animals drop pellets below the perforated cage floor and no hoarding was possible in these cages. Video analysis of rats feeding in this situation confirms that they removed the pellet with their mouth, then held the pellet in their forelimbs while biting the pellet. Consumption of a single pellet usually takes 10–15 s, and a single meal typically consists of the successive consumption of 20–60 individual pellets. Pellet removals were, therefore, an accurate record of moment-by-moment food intake and the equipment placed no constraint on the determination of meal size, frequency, or feeding rate.

Water was dispensed from a stainless steel nozzle situated 15 cm from the food hopper. The change in capacitance produced by a rat licking the nozzle activated a peristaltic pump that provided water and the times at which the pump was activated were recorded automatically. A maximum current of 2 μA flowed through the spout during operation of this circuit. Water was delivered at a rate of 1 ml every 13 s.

2.3. Procedure

One week prior to the start of each experiment, the animals were placed in the meal pattern cages to habituate to the apparatus and the experimental room. During this time, two sham injections of 0.9% saline were given to familiarise the animals with the experimental regimen. Following the habituation period, the animals were treated with each of the possible doses of the relevant drug in a counterbalanced order. Drug treatments were carried out 30 min before lights out (1700 h) to become effective at a period when food intake is normally high. In addition, body weights were recorded, food hoppers replenished, and water bottles filled during this period. All drug administrations were separated by at least 48 h.

2.4. Drugs

Olanzapine was supplied by Eli Lilly (Windlesham, Surrey, UK) and other drugs were obtained from Sigma/RBI (Poole, UK). Haloperidol was dissolved in a vehicle of 0.5% tartaric acid (w/v in distilled water) and given intraperitoneally at doses of 0.05, 0.07, 0.1, 0.14, and 0.2 mg/kg. Doses over a similar range reduce lever pressing for food

and enhance chow consumption in a choice paradigm (Salamone et al., 1996). Clozapine and olanzapine were dissolved into solution using the same method; the compound was wetted with 400 μl of 10% lactic acid (v/v in distilled water) and then made up to volume using distilled water. The solution was then neutralised with 1 M NaOH to an approximate pH of 6.0. Clozapine was given at doses of 1.0, 3.0, and 10.0 mg/kg. Olanzapine was given at doses of 0.3, 1.0, and 3.0 mg/kg. These are doses that would not be expected to produce nonspecific behavioural effects, but are active in a range of other paradigms (Moore, 1999). All drugs were administered at a volume of 1 ml/kg ip.

2.5. Analysis

The distribution of feeding and drinking patterns were analysed in three ways. First, the number of feeding and drinking responses occurring was summed into 2-h time bins over 22 h. A repeated measures analysis of variance (ANOVA) was performed on these data, with Time and Drug as factors. Where necessary, a one-way ANOVA was carried out on restricted time bins. These analyses indicate the temporal pattern of absolute food and water intake. These analyses were also carried out for the 24–48-h period following drug administration to check for residual drug action. There were no significant effects of drug treatment during this period, and these data are not further discussed.

The second form of analysis examined the microstructure of feeding. This analysis was restricted to the period following drug treatment in which a clear behavioural effect was observed. A meal criterion of 2 min (Clifton et al., 1991) was chosen to separate within- and between-meal interpellet intervals (IPI). After this criterion was applied to the data, meal size was defined as the number of pellets eaten after an initial IPI exceeding 2 min and before the next IPI greater than this value. Meal duration was defined as the time between taking the first and last pellets of a meal. Feeding rate was calculated by dividing the number of pellets taken in a meal by its duration. The intermeal interval (IMI) was defined as the time between taking the last pellet of one meal to taking the first pellet of the next meal. In calculating mean IMI, the latency to the first meal was excluded. Data for drinking were treated in a similar way, except that no measure of drinking rate was obtained. Each meal parameter derived from this microstructural analysis was treated separately in a one-way repeated measures ANOVA. For the final analysis, we plotted the distribution of IPI as a more sensitive indicator of changes in feeding rate that was independent of any particular meal criterion. Occasionally, daily records or partial records for an individual animal were lost due to equipment failure; the subsequent statistical analysis used the missing value procedure of the GENSTAT statistical package (Genstat 5 Committee, 1987) and resulted, in each case, in the loss of a degree of freedom in error term of the ANOVA. Dunnett's test was used to make comparisons between drug and vehicle treatments.

3. Results

3.1. Experiment 1: The effect of haloperidol on food intake and meal patterns

The total number of 45-mg pellets consumed over the 22-h recording period did not vary with any dose of

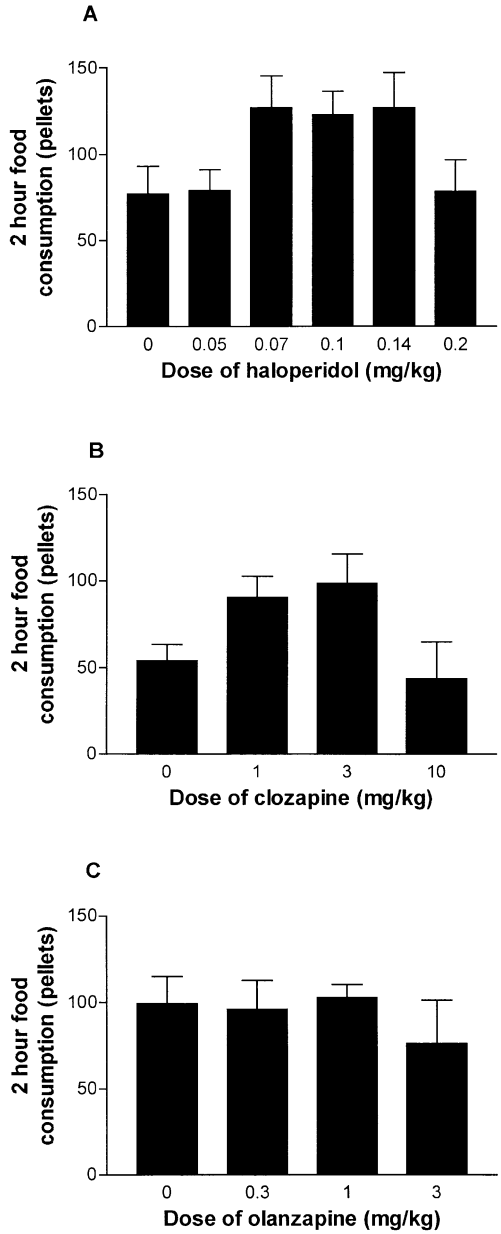

Fig. 1. Total food intake in the first 2-h bin following drug administration. Drug was administered 30 min before behavioural recording commenced. Panels A, B, and C, respectively, show the response to haloperidol (Experiment 1), clozapine (Experiment 2), and olanzapine (Experiment 3).

haloperidol [$F(5,35) = 1.1$, NS; veh = 595.0 ± 26.8, 0.05 mg/kg = 577.3 ± 21.7, 0.07 mg/kg = 561.1 ± 19.3, 0.1 mg/kg = 586.7 ± 31.7, 0.14 mg/kg = 561.2 ± 10.8, 0.2 mg/kg = 600.6 ± 19.1]. When pellet intake was summed into 2-h bins and analysed across the L/D cycle, there was a clear dose-related facilitation of food intake during the initial 2-h time bin [Fig. 1, Drug × Time interaction: $F(50,350) = 1.79$, $P < .001$; one-way ANOVA for the first time bin: $F(5,35) = 2.69$, $P < .05$]. When this analysis was extended to feeding responses during the 6 h immediately following the onset of the dark photoperiod, the hyperphagic action of haloperidol was no longer significant [Table 1: $F(5,34) = 2.46$, NS]. There were no significant effects on water intake, either when totalled over 24 h, or over the initial 6-h (Table 1) time bin after drug treatment. Latency to feed was also unaffected by drug treatment (Table 1), but latency to drink was always substantially greater than latency to feed, reflecting the tendency of animals to feed and then drink at the beginning of the dark period. Latency to drink also increased significantly ($P < .001$) with increasing drug dose. This effect probably resulted from the increase duration of the first meal taken by drug-treated animals (see below).

A detailed analysis of the microstructure of eating in the first 6 h of the night revealed that haloperidol-treatment produced a significant alteration in meal patterning for a longer period than is indicated by changes in total food intake (Table 1). More specifically, an inverted U-shaped dose–response function is apparent for the effect of haloperidol on meal size (Fig. 2A). There was a significant effect of drug treatment on this parameter [$F(5,34) = 4.3$, $P < .005$], with the maximum enhancement of meal size (35% increase compared to vehicle) evident at 0.1 mg/kg (Fig. 2A). For doses greater than 0.1 mg/kg, meal size was reduced slightly although this change was not significant. Similarly, meal duration was extended by doses of haloperidol within the range of 0.05–0.1 mg/kg, while at higher doses (0.14 and 0.2 mg/kg) animals showed no alteration in the duration of meals [Table 1: overall ANOVA, $F(5,34) = 4.41$, $P < .005$]. These effects on meal size were also pronounced when only the first meal of the night was considered [Table 1: $F(5,35) = 6.10$, $P < .001$]. Since there was no change in the first IMI (Table 1), this enhanced meal size of the first meal accounts for the increased total intake in the first 2-h time bin. In contrast to haloperidol-induced changes in meal size and duration, there was a monotonic relationship between the rate of eating and dose of haloperidol (Fig. 3A), with the suppression of feeding rate greatest at 0.2 mg/kg of the drug [Table 1: $F(5,34) = 9.6$, $P < .001$]. The number of meals increases at higher doses of haloperidol [$F(5,34) = 4.02$, $P < .01$], providing a partial compensation for the decreased meal size observed at higher doses. There were no significant effects of drug treatment on the microstructure of water intake.

3.2. Experiment 2: The effect of clozapine on food intake and meal patterns

Clozapine administration caused a transitory increase in the amount of food consumed during the 2 h immediately

Table 1
Haloperidol-induced alterations in meal patterns of free feeding rats during the first 6 h of the dark photoperiod

	Dose of haloperidol (mg/kg)							
	0	0.05	0.07	0.1	0.14	0.2	S.E.D.	*P* value
6-h intake								
Food	223.0	177.8	191.3	259.4	222.3	213.9	25.64	NS
Water	188.6	191.6	152.4	174.6	152.6	132.0	32.9	NS
Latency								
Feed	4.1	5.3	2.2	7.4	5.5	12.2	3.1	NS
Drink	20.1	30.9	80.7	66.2	79.7	73.2	15.2	< .001
Microstructure								
Meal frequency	4.54	3.62	3.75	4.25	5.50	6.00	0.67	NS
Meal size	47.6	54.4	58.8	67.2	42.4	35.3	7.7	.004
Meal duration	437	489	627	718	463	453	77.2	.009
Feeding rate	0.108	0.108	0.093	0.095	0.092	0.076	0.0054	< .001
IMI	65.1	102.5	80.7	63.4	44.5	42.9	24.3	< .05
First meal								
Meal size	67.4	69.0	104.2	115.6	58.6	45.1	15.09	< .001
IMI	114.0	139.8	141.8	125.9	83.4	54.3	31.03	< .05

The 6-h intake and meal size are given in number of pellets and can be converted to grams by dividing by 0.045. Duration of the meal is given in seconds. Feeding rate is calculated in pellets per second. S.E.D. gives the standard error of the difference between means.

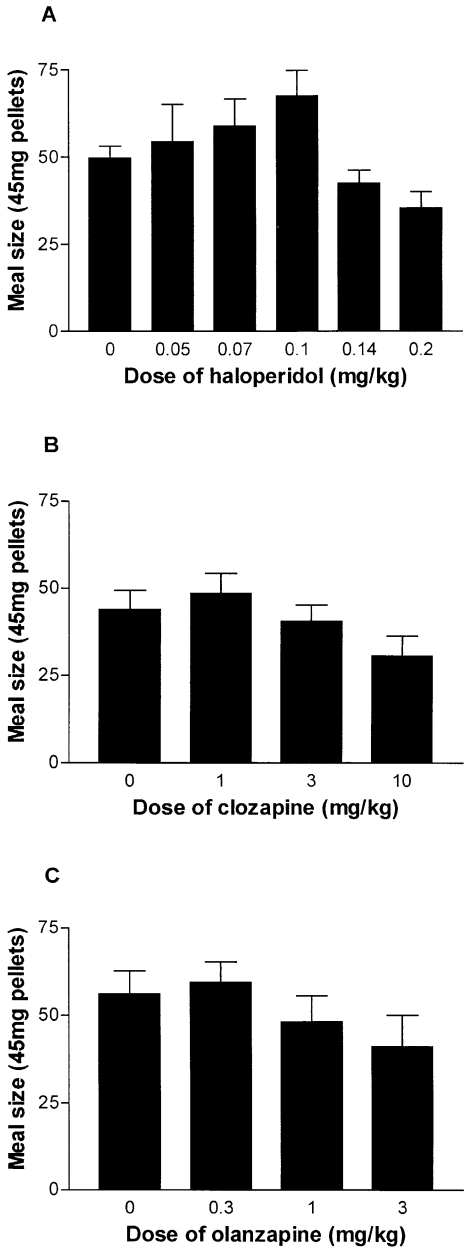

Fig. 2. Changes in mean meal size in the 6 h following drug administration. Drug was administered 30 min before behavioural recording commenced. Panels A, B, and C, respectively, show the response to haloperidol (Experiment 1), clozapine (Experiment 2), and olanzapine (Experiment 3).

following lights out [$F(3,21) = 3.5$, $P < .05$]. At 1.0 and 3.0 mg/kg, food intake was increased by 66% and 81% above vehicle intake, respectively (Fig. 1B). Mean intake in the vehicle condition was slightly lower than expected in this experiment. This was due to a single animal that failed to feed or drink for the first 2 h of the night. ANOVA performed with this animal excluded remained significant. When analysed over longer time periods, the hyperphagic response to clozapine was not significant (at 6 h; see Table 2). There was no difference across the four treatment groups in 22-h food intake [$F(3,21) = 0.02$, NS; veh = 587.1 ± 26.4, 1.0 mg/kg = 588.3 ± 15.9, 3.0 mg/kg = 592.1 ± 26.9, 10.0 mg/kg = 590.0 ± 31.3]. Clozapine treatment had no effect on water intake measured over either 2, 6 (Table 2), or 22 h. There was a small, but significant, increase in the latency to feed following the highest dose of clozapine ($P < .05$), but latency to drink was unaffected by drug treatment.

A meal pattern analysis of carried out for the first 6 h of the dark photoperiod indicated that, in contrast to that seen in haloperidol-treated animals, meal size was not altered by clozapine treatment at any dose [$F(3,21) = 1.7$] (Fig. 2B). Similarly, neither the frequency of meals nor the duration of meals were affected by clozapine, [$F(3,21) = 1.45$, NS, and $F(3,21) = 1.33$, NS, respectively] (Table 2). The rate of eating (Fig. 3B) was suppressed by clozapine in a dose-dependent manner [$F(3,21) = 3.1$, $P < .05$]. At the highest dose of clozapine (10 mg/kg), animals appear to attempt to partially compensate for the marked decrease in feeding

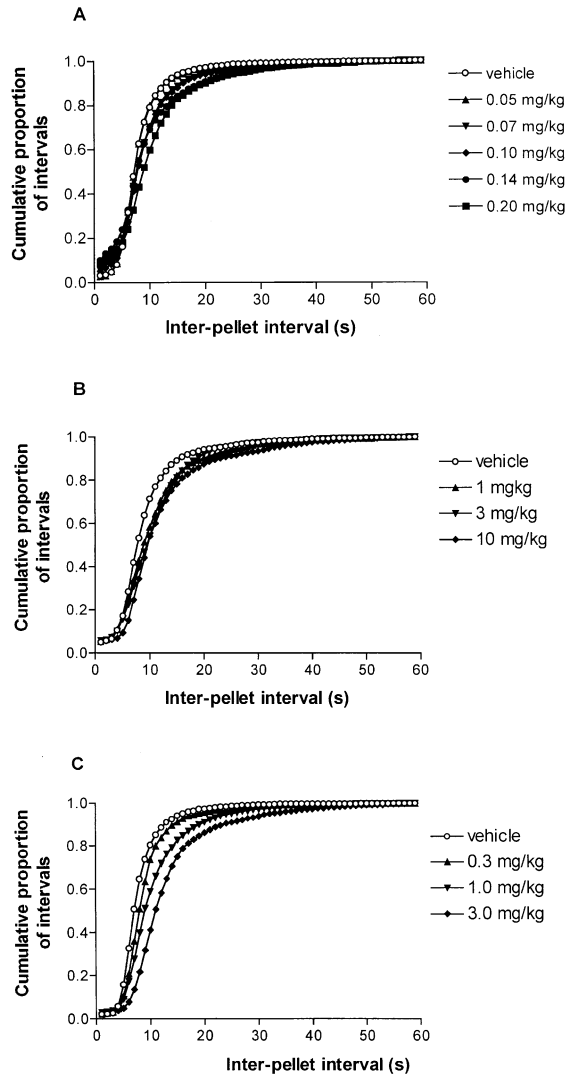

Fig. 3. Changes in feeding rate in the 6 h following drug administration. Drug was administered 30 min before behavioural recording commenced. Panels A, B, and C, respectively, show the response to haloperidol (Experiment 1), clozapine (Experiment 2), and olanzapine (Experiment 3).

rate by reducing the interval between meals [one-way ANOVA: $F(3,21) = 4.2$, $P < .05$; veh vs. 10 mg/kg, $P < .01$, Dunnett's test]. An analysis of first meal size showed no significant effect (Table 2). However, the interval following the first meal did decrease significantly (Table 2). There were no effects of clozapine on the microstructure of water intake.

3.3. Experiment 3: The effect of olanzapine on food intake and meal patterns

Olanzapine also had no overall effect on food intake cumulated into 2-h bins over the 22 h following drug administration [$F(30,100) = 0.89$, NS]. Furthermore, there was no suggestion of increases in food intake at any time point during the dark period following drug administration (see Fig. 1C for 2-h food consumption and Table 3 for 6-h consumption). Olanzapine had no significant effect on total water intake at 2, 6, or 22 h. Olanzapine produced a significant increase in both latency to feed and latency to drink (Table 3). In both cases, this was due to action at the highest dose (3 mg/kg).

There were also no changes in the size of meals (Fig. 2C), the duration of meals, or the frequency of meals evident from a meal pattern analysis of the first 6 h of the night (Table 3). Olanzapine did cause a reduction in the rate of eating [$F(3,21) = 13.07$, $P < .001$], which was particularly marked at the highest dose of 3.0 mg/kg (Fig. 3C). Although no single change was significant, it appears (Table 3) that the rats compensated for the lowered rate of food intake by increasing both meal frequency and duration. Consistent with the failure of olanzapine to increase intake in the first 2 h was an absence of any enhancement of the size of the first meal, or the interval following it, although the highest drug dose did decrease both first meal size and IMI. Olanzapine did not affect the microstructure of water intake.

Table 2
Meal parameters of free feeding rats during the first 6 h of the dark photoperiod following clozapine administration

	Dose of clozapine (mg/kg)					
	0	1.0	3.0	10.0	S.E.D.	*P* value
6-h intake						
Food	179.1	214.3	179.0	153.0	26.41	NS
Water	178.1	221.1	204.4	193.4	25.9	NS
Latency						
Feed	13.7	2.9	22.2	45.8	14.2	<.05
Drink	25.3	19.3	37.1	48.4	10.7	NS
Microstructure						
Meal frequency	4.37	4.62	4.37	6.00	0.917	NS
Meal size	43.9	48.5	40.5	30.7	7.30	NS
Meal duration	472	593	546	432	88.8	NS
Feeding rate	0.092	0.084	0.077	0.068	0.0077	<.05
IMI	65.6	60.7	60.7	36.0	9.24	.018
First meal						
Meal size	58.4	69.2	66.1	35.4	18.12	NS
IMI	138.6	110.9	40.9	50.0	22.73	<.001

Parameters are as for Table 1.

Table 3
Meal parameters for the first 6 h of the dark photoperiod following olanzapine treatment

	Dose of olanzapine (mg/kg)					
	0	0.3	1.0	3.0	S.E.D.	*P* value
6-h intake						
Food	273	253	292	237	29.8	NS
Water	238	221	239	195	26.3	NS
Latency						
Feed	2.8	4.0	3.7	27.0	5.7	<.001
Drink	21.4	27.2	28.6	67.6	10.1	<.001
Microstructure						
Meal frequency	5.25	4.50	7.50	7.62	1.61	NS
Meal size	56.2	59.6	48.2	41.0	8.25	NS
Meal duration	525	617	570	594	89.2	NS
Feeding rate	0.1070	0.0978	0.0818	0.0649	0.00725	<.001
IMI	49.1	57.7	38.6	31.0	9.1	.04
First meal						
Meal size	76.4	74.5	96.4	32.6	15.97	<.001
IMI	102.1	79.3	91.5	41.4	15.4	<.005

Parameters are as for Table 1.

4. Discussion

Our results may be summarised as follows. Haloperidol and clozapine produced a transitory increase in food intake in the 2 h following drug administration; this effect was not observed with olanzapine at the doses tested here. Total intake measured 6 h after haloperidol or clozapine was unaffected indicating a rapid compensatory response to the initial period of hyperphagia. All three drugs produced substantial effects on the microstructure of meal patterns. Haloperidol produced a substantial enhancement of meal size at intermediate doses, whereas higher doses led to a decrease in meal size. In contrast, clozapine and olanzapine showed no tendency to enhance meal size, and the highest doses of olanzapine and haloperidol decreased meal size. These changes in meal size were apparent in both the first meal and in the average size of all meals consumed in the 6 h following drug treatment. Despite the substantial differences between drug effects on meal size, all three drugs produced clear and comparable reductions in feeding rate within meals and a leftward shift in the IPI distribution. None of the drugs had significant effects on either totals or the microstructure of water intake at any dose tested. In addition, there were no substantial increases in the latency to feed and drink, suggesting an absence of sedation, motor impairment, or other nonspecific effects of drug treatment.

The results reported in Experiment 1 for haloperidol are similar to those reported earlier for selective D_2 antagonists including raclopride, remoxipride, and YM-09151-2 (Clifton et al., 1991). Raclopride also produced a short-term enhancement of intake in that earlier study (Clifton et al., 1991). It is therefore of particular interest that neither clozapine (Experiment 2) nor olanzapine (Experiment 3) produced any enhancement of meal size despite a reductions in feeding rate that were comparable to those observed for haloperidol.

4.1. Mechanisms underlying antipsychotic-induced changes in meal patterns

Enhancement of meal size following antipsychotic administration might arise in one of at least several quite different ways. One possibility is that it represents a failure to switch from feeding to other classes of behaviour. The idea that dopamine blockade or depletion, particularly in the ventral striatum, may produce such effects is supported by a variety of evidence. 6-Hydroxydopamine lesions of the ventral striatum are associated with mild hyperphagia in a slightly novel environment and this result has been attributed to an inability to switch from feeding to other behaviour patterns (Koob et al., 1978). Broadly similar accounts of the behaviour of animals with similar lesions have remained influential (Taghzouti et al., 1985; Cousins et al., 1993; Weissenborn et al., 1996). Recent evidence suggests that antagonists at the 5-HT_{2C} receptor may enhance dopamine release in the nucleus accumbens (Barnes and Sharp, 1999). Therefore, on this hypothesis, it is not surprising that drugs that combine dopamine and serotonin (especially 5-HT_{2C}) antagonism, such as clozapine and olanzapine, fail to enhance meal size. In addition, Kapur and Seeman (2001) have recently suggested that atypicality may be related to the dissociation constant of an antipsychotic drug from the dopamine D_2 receptor. Atypical drugs have fast dissociation rates that would allow phasic release of dopamine as a result of normal neurophysiological processes to compete effectively with the antagonist at the receptor. By contrast, typical antipsychotics, such as haloperidol, have low dissociation rates that would not allow phasic changes in dopamine release to generate a postsynaptic signal. Thus, if dopamine has a role in behavioural switching, typical antipsychotics should impair this process whereas atypical antipsychotics should have little effect.

An alternative explanation of the enhanced meal size following treatment with a drug such as haloperidol might be in terms of an impairment of the development of satiety within a meal. In this case, the combination of dopamine D_2-like antagonism with 5-HT_{2C} antagonism in drugs such as clozapine and olanzapine might be expected to produce an additive effect. This prediction would follow from the evidence suggesting that activation of 5-HT_{2C} receptors may enhance within-meal satiety (Vickers et al., 1999). In a clinical context, it has already been suggested that clozapine might have an especially potent effect on food intake through such a mechanism (Goodall et al., 1988). Our data do not allow a clear decision on this point. Clozapine, though not olanzapine, did enhance food intake. However, this increase occurred as a result of increased meal frequency rather than increased meal size.

Our data also provide clear evidence that the effects on feeding rate and meal size are dependent on separate underlying mechanisms. For example, it may be that effects on feeding rate are due to motor impairment and reflect an action on either dorsal or ventrolateral striatal mechanisms, whereas the effects on meal size reflect actions on ventral striatal or prefrontal cortical mechanisms that are of particular importance in switching between one class of behaviour and another (Clifton and Somerville, 1994). Although the measurements were made in a different feeding paradigm than the one used here, ventral striatal infusion of haloperidol has been shown to increase the duration of individual feeding bouts although overall feeding behaviour was not compromised (Bakshi and Kelley, 1991). Ventrolateral dopamine depletion is associated with profound motor deficits that interfere with home cage feeding and lead to sustained loss of body weight (Cousins et al., 1993).

4.2. Meal patterns as predictors of antipsychotic-associated motor side effects

Transitory increases in food intake in the meal patterning paradigm have been obtained with clozapine, raclopride, and haloperidol, but were not observed with YM-09151-2, remoxipride, olanzapine, SCH23390, and SCH39166 (Clifton, 1995; Clifton et al., 1991). Thus, there is no simple relationship between the neurochemical selectivity of a drug for particular dopamine receptor subtypes and the tendency to produce an acute stimulation of food intake in the rat. In addition, since atypical drugs, such as clozapine and olanzapine, are associated with more marked degrees of weight gain in clinical use (Allison et al., 1999), there appears to be no clear predictive relationship between acute stimulation of ad libitum food intake in the rat and weight gain in the clinic. Similarly, enhanced meal size in the rat, which is only apparent following treatment with selective D_2-like antagonists such as YM-09151-2 and haloperidol, is also a poor predictor of weight gain. In the clinic, weight gain associated with antipsychotic treatment may be correlated with histamine H_1 affinity (Wirshing et al., 1999). The effects of histamine agonists and antagonists have not been determined in the present paradigm.

Decreases in feeding rate have been observed with all antipsychotics studied to date and do not appear to be a useful predictor of extrapyramidal side effects. Enhancement of meal size, by contrast, may be a useful and easily measured predictor of such side effects. It is present for relatively selective D_2-like antagonists with which such

side effects are well known, but is absent for atypical drugs. If our tentative explanation of enhanced meal size in terms of a behavioural switching hypothesis is accepted, then enhanced meal size may have both predictive and construct validity as a model of liability to extrapyramidal side effects.

In summary, we have shown that the enhancement of meal size in the rat that follows administration of the relatively selective dopamine D_2-like antagonist haloperidol in the rat is absent for two atypical antipsychotics, clozapine and olanzapine. These results were obtained despite similar reductions in feeding rate by all drugs, and also despite the fact that clozapine, like haloperidol, produced a transitory increase in food intake. We suggest that enhanced meal size arises not from interference with the normal mechanisms that generate satiety within a meal, but instead, from a decreased likelihood of switching from feeding to other behavioural activities. This implies that the presence of enhanced meal size may be a good predictor of tendency to produce extrapyramidal side effects, and that its absence is a further indicator of the atypical profile of drugs such as clozapine and olanzapine.

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