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Long Term Administration of Some Antipsychotic Drugs Increases Body Weight and Feeding in Rats. Are D2 Dopamine Receptors Involved?

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BAPTISTA, T , M PARADA AND L HERNANDEZ *Long term administration of some antipsychotic drugs increases body weight and feeding in rats Are D2 dopamine receptors involved?* PHARMACOL BIOCHEM BEHAV 27(3) 399–405, 1987 —Long term administration of the antipsychotic drugs thioridazine, trifluoperazine, haloperidol, and sulpiride increased body weight in rats This effect was found to be sex dependent, that is, while female rats were prone to gain weight, male rats did not Chlorpromazine and fluphenazine decreased body weight in male rats but did not affect females The mechanism of body weight gain was investigated with sulpiride A linear relationship between dose of sulpiride and body weight gain was found Also, sulpiride increased caloric intake, and both actions were counteracted by bromocriptine, a specific D2 receptor agonist These results confirm that antipsychotic drugs affect feeding and body weight and suggest that hyperphagia and body weight gain might be mediated by blockade of dopamine receptors of the D2 type

Antipsychotic drugs Bromocriptine Body weight Feeding Dopamine D2 receptors

ANTIPSYCHOTIC drugs exhibit marked actions on body weight and feeding behavior in humans For example, one of the complications of chlorpromazine treatment in hospitalized patients is body weight gain [6] As chlorpromazine increases hunger rating, it has been suggested that increased caloric intake might be a causative factor in body weight gain [16] Thiothixene, fluphenazine, haloperidol, and thioridazine have been associated with weight gain [9], and molindone with body weight loss during treatment [12], fluphenazine with no change in body weight, and thioridazine with weight gain [5]

Food intake alterations by neuroleptics have been seen in rats as well Intraventricular or intraperitoneal injections of chlorpromazine had a dual effect on feeding in rats At low doses chlorpromazine increased feeding while at high doses it did not affect feeding Intraperitoneal injections of trifluoperazine and pimozide also increased feeding at low doses but at higher doses significantly decreased feeding Besides these behavioral effects, a good correlation has been found between the peak dose of six neuroleptics that increased feeding and the inhibition of ^{3}H haloperidol binding On these grounds it has been suggested that neuroleptics increase feeding through dopamine receptor blockade in the brain [17]

However, while most of the experimental studies have focused on short term effects of neuroleptics on feeding behavior, most of the human studies have focused on long term effects on body weight Actually there are few reports on long term effects of neuroleptics on body weight in rats, and surprisingly, these experiments yield opposite results to human studies For example daily injections of chlorpromazine decrease feeding and body weight in male rats [4,25], an effect which is contrary to what has been observed in human beings These findings pose the question as to whether or not long term administration of other neuroleptics also decreases body weight in rats For these reasons we studied in the present article the long term effect of six neuroleptics on body weight in rats As it is a well known fact that female rats are more prone than male rats to develop obesity, we used both male and female rats We found a sex difference in body weight change induced by neuroleptics Then we focused our study on one of the neuroleptics that increased body weight We selected sulpiride as the prototype of neuroleptics that increase body

TABLE 1

BODY WEIGHT CHANGES INDUCED BY SOME NEUROLEPTICS IN FEMALE AND MALE RATS

Neuroleptics	Sex	Dose	Percentual Change Respect To Saline	Change
Fluphenazine	M	1 32 mg/dose	−31%	—
		2 65 mg/dose	−112%	▼
		3 90 mg/dose	−112%	▽
	F	1 32 mg/dose	−62%	—
		2 65 mg/dose	−3%	—
		3 90 mg/dose	−4 5%	—
Chlorpromazine	M	1 00 mg/kg	−29 5%	—
		2 50 mg/kg	−48 2%	▼
		5 00 mg/kg	−19 1%	—
	F	1 00 mg/kg	−41 2%	—
		2 50 mg/kg	−70%	—
		5 00 mg/kg	−61%	▽
Thioridazine	M	10 0 mg/kg	+1 6%	—
		20 0 mg/kg	−2 4%	—
	F	10 0 mg/kg	+122%	—
		20 0 mg/kg	+145%	△
Trifluoperazine	M	1 00 mg/kg	−12%	—
		2 00 mg/kg	−37%	—
	F	1 00 mg/kg	+391%	▲
		2 00 mg/kg	+1 125%	▲
Sulpiride	M	10 0 mg/kg	−20%	—
		20 0 mg/kg	−19%	—
	F	10 0 mg/kg	+168%	▲
		20 0 mg/kg	+107%	▲
Haloperidol	M	0 50 mg/kg	−26%	—
		5 00 mg/kg	−88%	▼
	F	0 50 mg/kg	+38%	△
		5 00 mg/kg	+173%	▲

— NS, ▲ $p<0$ 01, △ $p<0$ 05, ▼ $p<0$ 01, ▽ $p<0$ 05

weight in rats The reasons are that sulpiride is a specific blocker of dopamine receptors of the D2 type [15], and that D2 receptors can be identified in the hypothalamus [28], which is a critical area for feeding regulation We reasoned that if sulpiride increased feeding and body weight, then D2 receptors might be involved in feeding and body weight regulation We report here that chronic sulpiride produces body weight gain and hyperphagia, and bromocriptine (a specific D2 agonist) [15] antagonizes these effect Our findings strongly suggest that D2 receptors might play an important role in the weight gain and hyperphagia induced by sulpiride

EXPERIMENT 1 BODY WEIGHT GAIN INDUCED BY NEUROLEPTICS IS SEX DEPENDENT

In this experiment we screened the effects of long term administration of several neuroleptics on body weight of male and female rats

Method

Two hundred and eighty rats of the Wistar strain were individually housed and received Protinal chow pellets and water ad lib Light-dark cycles were 12-12 The rats were divided into 28 groups Each group was formed by 10 weight matched rats Then each group was divided into two subgroups of five rats each One of them received saline and the other one received a neuroleptic

Several doses of each drug were tested in both sexes Fluphenazine decanoate 1 32, 2 65, and 5 mg/dose, chlorpromazine 1, 2 5, and 5 mg/kg, thioridazine 10 and 20 mg/kg, trifluoperazine 1 and 2 mg/kg, haloperidol 0 5 and 5 mg/kg, and sulpiride 10 and 20 mg/kg Chlorpromazine, haloperidol, trifluoperazine, and sulpiride were given intraperitoneally, fluphenazine was given subcutaneously, and thioridazine was administered orally All drugs but fluphenazine were administered daily for 21 days Fluphenazine was administered in two doses The second one was given 21 days after the first one

Body weight was controlled daily Two-way ANOVA followed by Duncan t-test and χ^2 test were made on body weight gain at the end of the drug administration For fluphenazine, the statistical tests were made on body weight gain 21 days after the second dose

Results

The results are summarized in Table 1 The effect of long term administration of neuroleptics on body weight was not homogeneous Out of the 28 groups, only in 12 the results were statistically significant Seven groups gained more weight than their controls, and 5 gained less Interestingly the groups that significantly gained more weight were all formed by females This sexual difference was statistically significant, $\chi^2(2)=9$ 8, $p<0$ 01 The neuroleptics that increased body weight were thioridazine 20 mg/kg, trifluoperazine 1 and 2 mg/kg, sulpiride 10 and 20 mg/kg, and haloperidol 0 5 and 5 mg/kg The neuroleptics that significantly decreased body weight were fluphenazine 2 65 and 3 9 mg/dose, chlorpromazine 2 5 mg/kg, and haloperidol 5 mg/kg in males and chlorpromazine 5 mg/kg in females

Discussion

Chronic treatment with neuroleptics does affect body weight in rats The direction of body weight gain was sex dependent The trend was for female rats to gain body weight while for male rats to lose weight

This is not an uncommon observation in obesity research Cox *et al* [8] found that female rats with ventromedial hypothalamic (VMH) lesions displayed greater hyperphagia and body weight gain than males did A clear explanation of this sex difference has not emerged yet It has been suggested that high prolactin levels after VMH lesions might enhance feeding in females but not in males [24] Despite initial controversial results [10,20] it has recently been shown that high prolactin plasma levels induce behavioral and metabolic changes that enhance fat deposition and lead to body weight gain [23] Neuroleptics increase prolactin secretion [3], therefore, hyperprolactinemia might be the cause of body weight gain and of sex difference Nevertheless female rats which received fluphenazine and chlorpromazine did not increase or rather decreased body weight, although it is well known that these neuroleptics increase prolactin level Therefore, either some side effects of chlorpromazine and

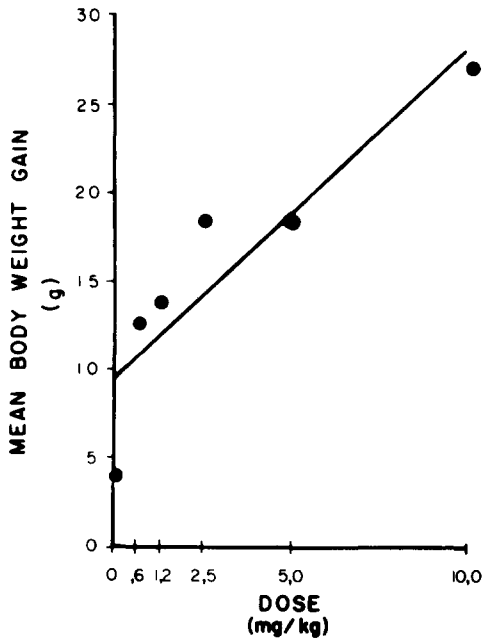

FIG 1 Dose response curve showing a linear relationship between sulpiride dose and body weight gain $Y = 9\,53 + 1\,87X$ $r=0\,89$, $t(4)=4\,06$, $p<0\,02$

fluphenazine prevented body weight gain secondary to hyperprolactinemia, or the dose of these drugs was not the optimal In any event the prolactin role in neuroleptics induced weight gain indeed deserves further research

The neuroleptics that induced weight gain are heterogeneous with respect to their extrapyramidal side-effects [7,27] Some are typical neuroleptics (trifluoperazine and haloperidol), one is an intermediate neuroleptic (thioridazine), and one is atypical (sulpiride)

It has been suggested that anticholinergic potency might be correlated with the weight gaining effect of neuroleptics [26] However, trifluoperazine and haloperidol, two neuroleptics with small anticholinergic effect, increased body weight Thioridazine, a powerful anticholinergic drug, increased body weight in only one group, while chlorpromazine, another neuroleptic with strong anticholinergic action, decreased body weight Therefore there was no correlation between anticholinergic potency and body weight gain

As for the five groups that lost weight, four of them were male rats Our results confirmed previous findings that chlorpromazine decreases body weight in male rats [4,25] In addition, fluphenazine and high doses of haloperidol decreased body weight in male rats too Chlorpromazine was the only neuroleptic that decreased body weight in female rats However, as we said before, the dose of neuroleptics administered to the rats that either did not change or decrease body weight might have not been the optimal dose to produce such body weight gain In fact it has been observed that a dose too high or too low tends to be ineffective or to decrease food intake More extensive dose response studies are required to explore this possibility

Our next step was to study one of the neuroleptics which increased body weight in order to obtain some insight into the mechanism of weight gain Since neuroleptics act by blocking dopamine receptors and two different types of these have been described (D1 and D2 types), we selected sulpiride which is a specific blocker of D2 receptors [15] This drug accumulates mainly in the pituitary gland and also in the hypothalamus [22] D2 receptors can be identified in the pituitary gland and in the hypothalamus, although the exact location of the D2 receptors in the last area is not clear [28] The hypothalamus is a critical area in feeding regulation [19], so we focused on sulpiride in order to assess its effects on body weight and feeding

EXPERIMENT 2 BODY WEIGHT GAIN IS PROPORTIONAL TO THE DOSE OF SULPIRIDE

Method

Female albino rats of the Wistar strain weighing between 190–250 g were individually housed with food and water ad lib We used female rats because the first experiment showed that they were more likely to gain weight than male rats Body weight was measured daily during the whole experiment After 30 days of control, 80 rats divided in groups of 10 animals received daily intraperitoneal injections of saline or sulpiride at the doses of 0 62, 1 25, 2 5, 5, 10, 20, and 40 mg/kg during 21 days Then the injections were suspended and the rats were controlled for 21 more days

Since it had been observed that at day 14 the body weight of the rats receiving sulpiride reached a plateau, the average body weight between days 14 and 21 was taken as the body weight under sulpiride For each rat we calculated the body weight enhancement by subtracting this body weight under sulpiride treatment to the mean body weight that the rat had before treatment In this way we obtained a figure of body weight change for each rat Then we calculated the mean body weight change for each dose of sulpiride, and we analyzed these figures by means of a regression analysis

Results

Again sulpiride increased body weight significantly (Fig 1) The maximal effect was obtained with 10 mg/kg With a dose of 0 62 mg/kg body weight gain was greater than saline The regression analysis showed that body weight gain was proportional to the dose of sulpiride in the dose range from 0 to 10 mg/kg, $r=0\,89$, $t(4)=4\,06$, $p<0\,02$ The doses of 20 and 40 mg/kg did not have an effect greater than 10 mg/kg

Discussion

This experiment confirmed the results of the first experiment as far as sulpiride is concerned, i e , sulpiride injections increase body weight in female rats Also it was shown that a linear relationship does exist between the dose of sulpiride and body weight gain Nevertheless, the cause of this body weight gain is not known In the next experiment we measured food intake and body weight in order to see if sulpiride increases the caloric intake

EXPERIMENT 3 DAILY INJECTIONS OF SULPIRIDE INCREASE FEEDING AND BODY WEIGHT

In this experiment we measured food intake and body weight in order to find out whether or not body weight enhancement by sulpiride was accompanied by food intake disturbance We found that sulpiride induces both body weight gain and hyperphagia

Method

Female albino rats of the Wistar strain weighing between

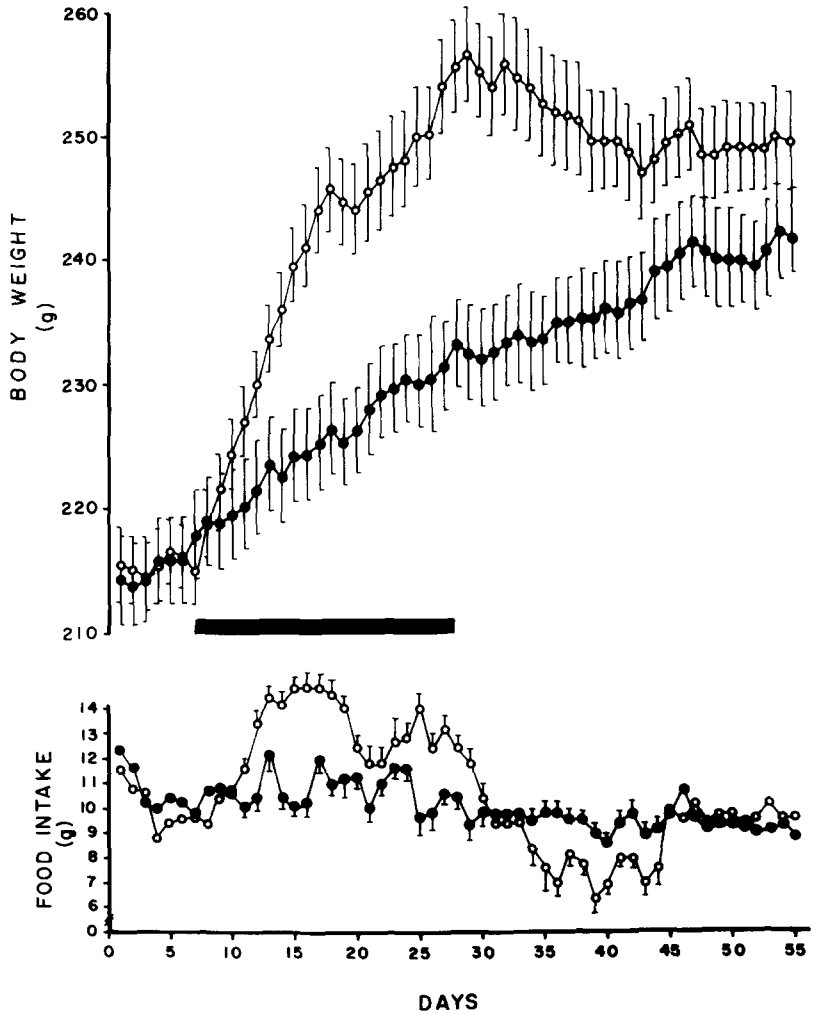

FIG 2 Body weight and food intake before, during, and after daily intraperitoneal injections of sulpiride (20 mg/kg) Open circles sulpiride injected rats Black circles saline injected rats The black bar indicates the lapse of sulpiride or saline injections

200 and 270 g were individually housed and fed with high fat diet (66% powdered rat food and 33% corn oil) The rats had water and food ad lib and a 12-12 light-dark cycle Food was placed in spillage food feeders [11] Food intake and body weight were measured daily After two weeks of control the rats were divided into two groups of 15 rats each One of them received daily intraperitoneal injections of sulpiride, 20 mg/kg during 21 days The other group received saline At day 21 the injections were suspended and food intake and body weight were measured daily for 27 more days

Statistical comparisons were made by two way ANOVA and regression analysis

Results

Intraperitoneal injections of sulpiride increased significantly food intake and body weight (see Fig 2) Preinjection levels of food intake and body weight did not differ significantly when both groups were compared statistically [body weight $F(1,28)=0\ 035$, NS, food intake $F(1,28)=2\ 73$, NS] The first 10 days after the beginning of injections, body weight gain slope increased significantly in the sulpiride group as compared with saline controls [sulpiride 2 88 g/day, saline 0 74 g/day, $t(16)=20\ 4$, $p<0\ 0001$], and food intake increased significantly, $F(1,28)=6\ 66$, $p<0\ 025$ After the 14th day (still on sulpiride treatment), body weight gain slope decreased but food intake remained significantly higher in the sulpiride group [body weight $F(1,28)=15\ 07$, $p<0\ 001$, body weight gain slope sulpiride=1 29 g/day, saline=0 53 g/day, $t(16)=6\ 45$, $p<0\ 0001$, food intake $F(1,28)=6\ 62$, $p<0\ 025$ When the injections were suspended body weight started to decrease [body weight slope sulpiride=$-0\ 6139$ g/day, saline 0 4 g/day, $t(24)=14\ 9$, $p<0\ 001$] and food was below the saline control, $F(1,28)=5\ 48$, $p<0\ 025$

Discussion

This experiment shows that sulpiride enhances caloric intake in rats and that increased feeding is a factor contributing to weight gain

As a matter of fact body weight gain and hyperphagia

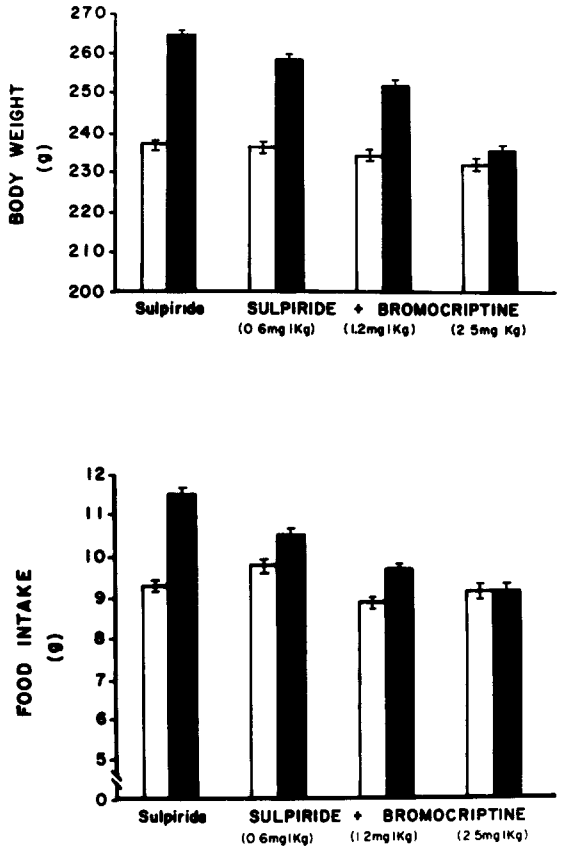

FIG 3 Body weight and food intake of rats receiving injections of either sulpiride (20 mg/kg) or sulpiride bromocriptine (0 6, 1 2, or 2 5 mg/kg) Open bars indicate body weight and food intake before treatment Hatched bars indicate body weight and food intake during treatment

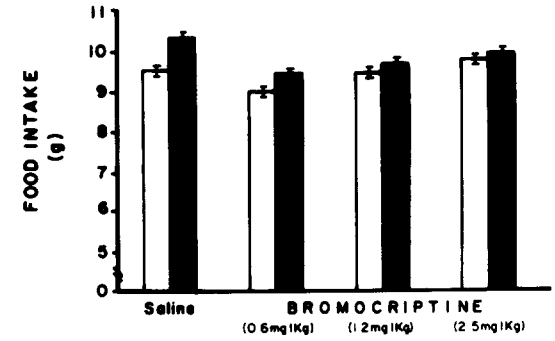

FIG 4 Body weight and food intake of rats receiving injections of either saline or bromocriptine (0 6, 1 2, or 2 5 mg/kg) Open bars indicate body weight and food intake before treatment Hatched bars indicate body weight and food intake during treatment

were closely related When the rats were overeating they gained weight faster than controls When sulpiride injections stopped, the rats lost weight and also ate significantly less than controls

The mechanism underlying sulpiride hyperphagia is not known but there are reasons to believe that dopamine receptor blockade might underlay sulpiride hyperphagia As we mentioned earlier, the potency of the neuroleptics to increase feeding is well correlated with their potency to inhibit ^{3}H haloperidol binding [17] Also, when sulpiride injections stopped the animals underate This might be a rebound phenomenon that could be due to hypersensitivity induced by long term blockade of dopamine receptors.

By using the set point concept in a descriptive way, we could also say that sulpiride shifts the body weight set point of the rats since injection interruption was followed by a lowering of body weight level However, the fact that body weight remained above the control level also suggests that the set point might have shifted permanently to a higher level than the preinjection one

The next experiment was intended to find pharmacological evidence that the body weight gain and hyperphagia by sulpiride might be due to D2 receptor blockade It is known that bromocriptine is a D2 agonist [15] Therefore we tried to counteract with bromocriptine the feeding and body weight effects of sulpiride

EXPERIMENT 4 BROMOCRIPTINE PREVENTS SULPIRIDE HYPERPHAGIA AND BODY WEIGHT GAIN

Since sulpiride is a specific D2 blocker we injected bromocriptine in rats in order to see if this drug counteracted the effects of sulpiride on feeding and body weight

Method

Female albino rats of the Wistar strain, weighing between 200 and 270 g, were individually housed and fed as in experiment 3 Food intake and body weight were controlled for 21 days and then the rats were divided in 8 groups of 10 rats each One of the groups received daily saline injections Another group received daily intraperitoneal injections of sulpiride (20 mg/kg), 3 groups received daily subcutaneous injections of bromocriptine at the doses of 0 6, 1 2, and 2 5 mg/kg The remaining three groups received simultaneously 20 mg/kg of sulpiride plus one of the three doses of bromocriptine The drugs were administered for 21 days The data were analyzed with two way ANOVA and Duncan t-test The analysis was made for each group comparing the mean body weight during the seven days prior to treatment against the mean body weight during the 14th–21st days of treatment For food intake the analysis was made comparing the mean food intake during the seven days prior to treatment against the mean food intake during the 7th–14th days of treatment

Results

Sulpiride again increased significantly body weight, $F(7,42)=289$, $p<0.001$, and food intake as compared with saline [$F(7,42)=11.38$, $p<0.001$, least significant difference 0.96, difference between sulpiride and saline=1.25, $p<0.01$] The dose of 2.5 mg/kg of bromocriptine totally prevented the body weight gain induced by sulpiride (Fig. 3) Also bromocriptine had an action on its own (Fig. 4)—it decreased significantly feeding and body weight

Discussion

Bromocriptine, a D2 specific agonist, prevented the body weight gain and hyperphagia caused by intraperitoneal injections of sulpiride This experiment suggests that sulpiride might be causing body weight gain and hyperphagia by dopamine receptor blockade and that the D2 receptors might play an important role in feeding and body weight regulation However bromocriptine itself decreases body weight and feeding Therefore it is not discarded that bromocriptine blocked unspecifically body weight gain and hyperphagia by sulpiride

In addition, although the involvement of D2 receptors in feeding and body weight seems to be very much straight forward, the participation of D1 receptors has not been yet ruled out Specific D1 agonists and antagonists need to be tested on the same experimental paradigm as sulpiride and bromocriptine were in the present paper

GENERAL DISCUSSION

Long term administration of antipsychotic drugs affected body weight of normal rats Chlorpromazine and fluphenazine decreased body weight It has been reported that fluphenazine does not change body weight in humans We observed the same phenomenon in rats except for the higher doses of fluphenazine in male rats that decrease body weight Chlorpromazine increases body weight in humans, but in rats decreases body weight Since it has been shown that a single injection of chlorpromazine increases feeding it has been proposed that the repeated injections of chlorpromazine produce a metabolite that decreases feeding and body weight in rats [25] Another explanation stems out of the fact that while humans receiving chlorpromazine are in general exposed to highly appetizing diets (the so called cafeteria diets), rats in laboratory standard conditions are not This difference in diets might favor body weight gain in humans but oppose body weight gain in rats Finally, as we discussed before, it is also possible that we did not use the optimal dose to induce hyperphagia and body weight gain

Thioridazine at high doses increased body weight in female rats Also in humans it has been reported that thioridazine increases body weight [5] Trifluoperazine, haloperidol, and sulpiride increased body weight in female rats The gaining effect of trifluoperazine and haloperidol on body weight in rats is contrary to what has been observed in human beings [13] In humans it has been reported that sulpiride increases body weight but only in 3% of a sample of 2851 patients [1] It means that sulpiride is more potent in rats than in humans to increase body weight This difference might be due to species differences in the metabolism of the drug While sulpiride produces 5 metabolites in the rat [2], some of which might be biologically active, it does not produce metabolites in humans [14]

Body weight gain by sulpiride might have been caused by increased caloric intake There was a clear correspondence between feeding enhancement and body weight gain in sulpiride injected rats And sulpiride might be blocking D2 dopamine receptors involved in feeding regulation since bromocriptine prevented body weight gain and hyperphagia caused by sulpiride

A dopaminergic satiety system has been postulated [21] Intrahypothalamic injections of dopamine or its agonists inhibit feeding, and dopamine blockers prevent this effect [18] Our experiments support the conclusion that a dopaminergic satiety system might play an important role in the control of feeding behavior because repeated injections of sulpiride can override the normal satiety mechanisms and set the body weight of a rat at a higher than normal level

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