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Mechanism of the Body Weight Increase Induced by Systemic Sulpiride

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PARADA, M. A., L. HERNANDEZ, X. PAEZ, T. BAPTISTA, M. PUIG DE PARADA AND M. DE QUIJADA. *Mechanism of the body weight increase induced by systemic sulpiride*. PHARMACOL BIOCHEM BEHAV **33**(1) 45–50, 1989.—Long-term intraperitoneal administration of sulpiride induced body weight increase in female but not in male rats. The hypothesis that systemic sulpiride causes an endocrine unbalance which in turn causes body weight gain and hyperphagia was tested in four experiments. First, it was shown that even when they are on a high-fat diet male rats do not show body weight gain induced by systemic sulpiride. Second, sulpiride suppressed the estrous cycle. Third, gonadectomy prevented the body weight gain induced by systemic sulpiride in female rats. Fourth, estradiol simultaneously administered with sulpiride prevented the expected sulpiride-induced body weight gain. These results are discussed in terms of an hypothetical functional castration produced by systemic sulpiride. The well known hyperprolactinemia, induced by the pituitary D2 dopamine receptor blockade, might bring about an impairment of the steroidogenesis with subsequent decrease in estrogens level, which in turn might be responsible for the hyperphagia and body weight increase induced by systemic injections of sulpiride.

Sulpiride Body weight Ovariectomy Estrogens Functional gonadectomy Neuroleptics

IN a previous report it was shown that long-term daily intraperitoneal sulpiride injections resulted in moderate hyperphagia and body weight increase. Bromocriptine administered simultaneously supressed this effect (2). Since sulpiride is considered to be a selective D2 receptor blocker (15, 17, 34) and bromocriptine a D2 receptor agonist (17), these experiments suggested that sulpiride caused hyperphagia and body weight gain by blocking D2 receptors involved in satiety. Later it was shown that introperifornical injections of sulpiride increase feeding in satiated rats, and block amphetamine anorexia in food-deprived rats (29). The fact that a dopaminergic satiety mechanism had already been described in the perifornical region of the lateral hypothalamus (LH) (23,24), and that the dopamine receptors in this region are probably of the D2 type according to the classification of Kebabian and Calne (17), were consistent with the suggestion that intraperitoneal injections of sulpiride blocked D2 receptors in the perifornical hypothalamus yielding a disinhibition of neurones promoting feeding.

However, it was also observed that systemic injections of sulpiride increased body weight in female rats but not in male rats. Since intraperifornical sulpiride increases feeding in males (29), then systemic sulpiride might not be acting within the perifornical hypothalamus to increase feeding and body weight. Besides sulpiride is highly hydrophylic (1), and its scarce liposolubility may interfere with its penetration through the blood-brain barrier (4–6). Therefore, there is at least one other hypothesis concerning the effects of systemic sulpiride on feeding and body weight. According to this hypothesis the effect of systemic sulpiride might be due to an endocrine dysfunction. This interpretation is consistent with the finding that castration increases feeding and body weight in female but not in male rats. Therefore, a hypothetical gonadal suppression by systemic sulpiride would explain the sex-dependent effect on feeding and body weight. This hypothesis seems attractive since prolonged systemic administration of sulpiride causes cytologic modifications of adenohypophysial gonadotrope cells similar to those found in castrated animals (4, 32, 33). The present paper describes a series of experiments conducted to test if the effects of systemic sulpiride on feeding and body weight might be attributed to a functional castration.

EXPERIMENT 1: LACK OF EFFECT OF INTRAPERITONEAL SULPIRIDE ON FEEDING AND BODY WEIGHT IN MALE RATS FED ON A HIGH-FAT DIET

Gonadectomized male rats show a reduction in feeding and body weight gain (12,16). Therefore, the hypothesis of a functional gonadectomy under sulpiride treatment predicts no increase in body weight or food intake in male rats. In fact, the lack of effect of sulpiride on body weight gain in male rats has been shown in a previous report (2). However, sulpiride-induced hyperphagia and body weight gain were potentiated in female rats by feeding them on a high-fat diet. Therefore, the question as to whether or not a

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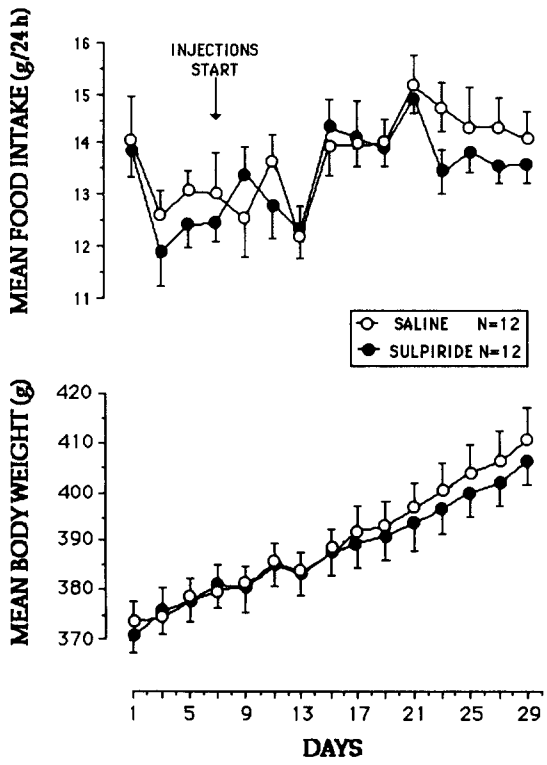

FIG. 1. Food intake and body weight of male rats (± SE) before and during daily intraperitoneal sulpiride injections (20 mg/kg). Only data of the alternate days are presented.

high-fat diet reveals sulpiride-induced hyperphagia in males is still unanswered. The present experiment explores the effect of systemic injections of sulpiride on males eating a high-fat diet.

Methods

Twenty-four male Wistar rats weighing between 350 and 390 g were individually housed and fed with a high-fat diet (66% powdered rat chow and 33% corn oil). The rats had water and food ad lib and a 12-12 light-dark cycle. Food was placed in spillage-proof feeders (11). Food intake and body weight were daily measured. After 10 days of baseline control, the rats were distributed in two groups of 12 rats each, taking care that the body weight means of both groups were roughly equal. The animals of one group received a daily intraperitoneal injection of sulpiride 20 mg/kg during 21 days, and those of the other group received saline. It was considered unnecessary to include female groups in this experiment because it is evident, from experiments previously described (2) and here reported, that systemic sulpiride increases feeding and body weight in female rats.

The body weight data of the initial and the last day of the intraperitoneal treatment were analyzed by two-way ANOVA for repeated measures. The daily body weight gain during the treatment period was calculated; and statistical comparison between the experimental and control groups was done with a *t*-test.

Results

The food intake and body weight data from this experiment are shown in Fig. 1. The bottom graph shows that the daily body weight mean of animals under sulpiride treatment remains under that of the controls since the tenth day of the intraperitoneal treatment. In the first treatment day the mean body weight of the animals receiving sulpiride was 380.8 ± 4.3 g, and that of the controls was 380.9 ± 3.8 g. Twenty-one days later the body weight means were 403.1 ± 4.9 g and 409.4 ± 6.3 g, for the experimental and control groups respectively. These differences were not statistically significant, $F(1,22) = 1.54$.

Discussion

This experiment shows that intraperitoneal injections of sulpiride neither increase food intake nor body weight of male rats fed on a high-fat diet. This result confirms that food intake and body weight increase by systemic sulpiride are sex-dependent phenomena as previously suggested.

EXPERIMENT 2: INTRAPERITONEAL SULPIRIDE INDUCES PROLONGED DIESTRUS IN FEMALE RATS

Specific changes occur in the ovaries, uterus and vagina of female rats during the estrous cycle. The vaginal changes can be followed by means of the vaginal smear technique, and this method is therefore very useful in determing the cyclic estrogenic activity (30). On the day of proestrus occurs a significant rise in estrogen secretion which is responsible for the vaginal cornification typical of the estrous stage (30,31). The sulpiride-induced impairment of the steroidogenesis postulated in this paper predicts the suppression of this cyclical vaginal cornification, and an induction of a prolonged diestrus instead.

Method

Virgin female Wistar rats, about 3 months old and weighing between 220–240 g, were individually housed under a daily schedule of 12 hr of light and 12 hr of darkness, and with water and lab chow pellets ad lib. Vaginal smears were taken daily between 10:00 and 11:00 a.m. for 3 weeks, and 10 rats showing at least 4 consecutive 4-day estrous cycle were selected. On the same day (without taking into account the day of the cycle) these 10 animals began to receive a daily intraperitoneal injection for 16 days. Five of them received sulpiride 30 mg/kg and the other five received saline. Daily vaginal smears were also taken during the treatment interval.

Results

The vaginal smears showed that 7 days after the treatment started all the rats receiving sulpiride were in diestrus and remained in that stage until the end of the treatment. These rats had their last estrus during the first 6 days of treatment. One of them on the second day, other on the third one, another on fourth day and the last two rats on day six. The vaginal smears from the 5 control rats showed that those animals kept cycling normally.

Discussion

The evidence brought by this experiment clearly shows a disruption of the ovarian function induced by intraperitoneal sulpiride. The mechanism for this disruption is still unclear, but it could be triggered, at least partially, by the hyperprolactinemia induced by sulpiride. This possibility is analyzed in the General Discussion section. Strikingly, the time course of the disruption of the estrus cycle parallels the time course of the hyperphagia obseved in other experiments (2). In the next experiment we tested

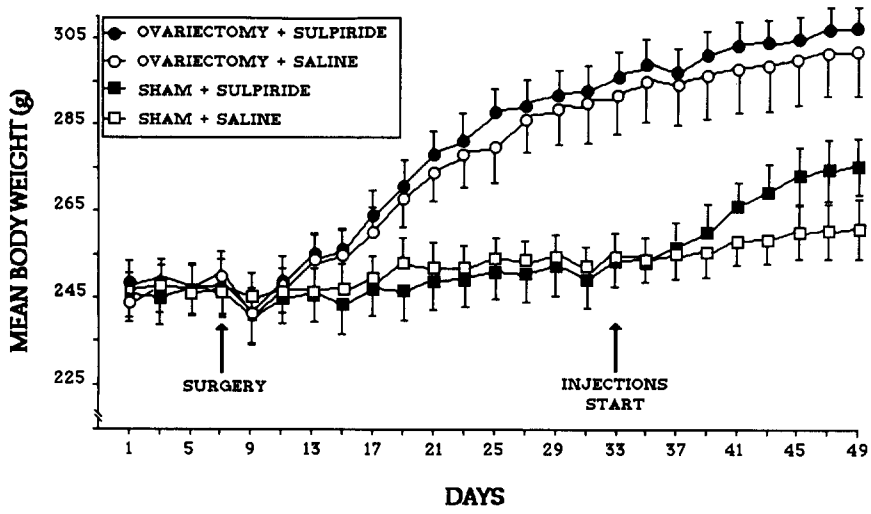

FIG. 2. Body weight of ovariectomized and gonadally intact rats (±SE) before and after daily intraperitoneal sulpiride injections (20 mg/kg). N=11 in each group.

the effect of ovariectomy on body weight gain induced by systemic sulpiride.

EXPERIMENT 3: DOES SULPIRIDE PRODUCE AN ADDITIONAL INCREASE IN BODY WEIGHT OF PREVIOUSLY OVARIECTOMIZED RATS?

It is well known that gonadectomy induces an increase in food intake and body weight in female rats (12,28). If the mechanism by which systemic sulpiride increases body weight was the same as the mechanism by which surgical gonadectomy increases body weight, then both procedures should be substitutive and previous gonadectomy should render sulpiride treatment ineffective.

Method

Forty-four female Wistar rats were kept in the same experimental conditions as the male rats of the first experiment. They were fed a high-fat diet, and food intake and body weight were daily measured. After some days of food intake and body weight control, the rats were divided into 2 groups of 22 animals each. Under ketamine anesthesia the rats of one of the groups were ovariectomized via translumbar incisions, and the rats of the other group were surgically manipulated, but their ovaries were not extirpated. Twenty-eight days after surgery each group of rats was divided into 2 subgroups of 11 rats each, with about the same body weight means. The animals of one of the subgroups received one daily IP sulpiride injection, 20 mg/kg for 15 days, and those of the other subgroup received physiological saline following the same schedule.

The mean daily body weight gain of each subgroup for the 15 days after the beginning of the sulpiride treatment were calculated, and the appropriate comparisons of these data were made with a *t*-test for unpaired samples. The body weight data of the 4 subgroups corresponding to the first and the 12th day of the IP treatment were compared by means of three-way ANOVA for repeated measures, followed by Tukey (a) test.

Results

Figure 2 shows the results of this experiment. Ovariectomized rats increased body weight until they reached a plateau, but later, under the sulpiride treatment, they did not show an additional body weight increase. In contrast, the sham-operated animals did not increase their body weight significantly until the beginning of the sulpiride treatment when their body weight increased as expected. The body weight gain slope of the sham-operated animals was 1.7 ± 0.3 g/day under sulpiride and 0.8 ± 0.2 g/day under saline, $t(20) = 2.4$, $p < 0.01$. In the ovariectomized animals that received sulpiride, body weight increased 0.75 g/day, and in those that received saline 0.54 g/day, $t(20) = 1.09$, ns. The three-way ANOVA for repeated measures applied on the body weight data showed a significant difference, $F(1,40) = 9.39$, $p < 0.005$. According to the Tukey (a) test the least significant differences at $p < 0.05$ and $p < 0.01$ were 5.43 g and 6.79 g respectively, and these differences were only met by the body weight means of both subgroups of sham-operated animals on the 12th day of the treatment (sulpiride: 272.72 ± 7.17 g and saline: 259.72 ± 6.27 g), but not the initial day (253.9 ± 6.28 g and 255.09 ± 5.4 g). The body weight of the ovariectomized animals receiving sulpiride or saline did not significantly differ either the first day (295.9 ± 6.05 g vs. 292.6 ± 7.88 g) or the 12th day of the treatment (304.5 ± 5.91 g vs. 299.5 ± 9.05 g).

Discussion

The hypothesis of the functional gonadectomy has previously been used to explain the sex differences in the effects of VMH lesions on food intake and body weight (16,37). In female rats the reduced estrogen secretion would favour the hyperphagia and the increase in body weight, while in the male rats the androgen reduction would attenuate the weight effects of VMH damage. The functional gonadectomy hypothesis in VMH-damaged animals has been questioned (18) because previous gonadectomy does not attenuate the effects of VMH lesions on body weight in female rats, and because the weight gain of the castrated males was comparable to that found in VMH-damaged females. However, the results of the present experiment are consistent with the functional gonadectomy hypothesis, since sulpiride's effect on body weight was totally abolished by previous gonadectomy in female rats. If systemic sulpiride produces a functional gonadec-

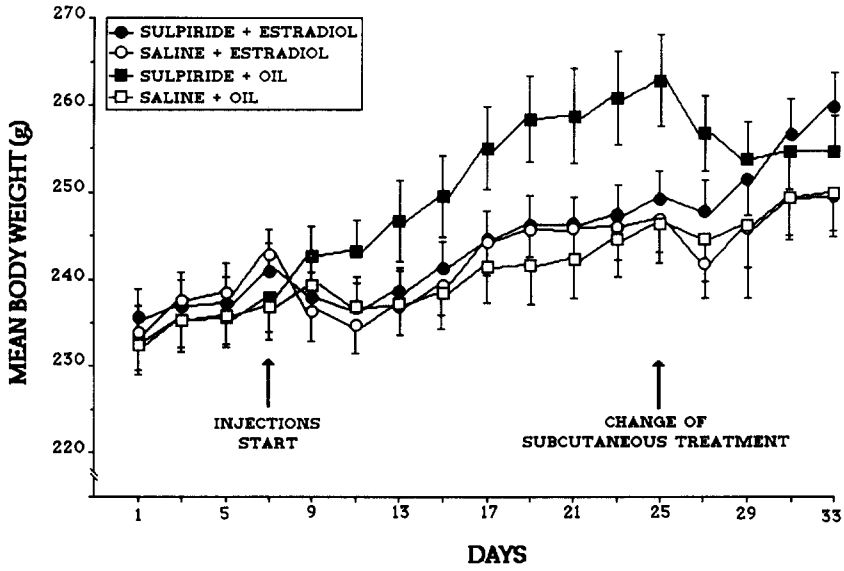

FIG. 3. Body weight of female rats (±SE) after simultaneous daily intraperitoneal sulpiride injections (20 mg/kg) and subcutaneous estradiol injections (2 μg/0.1 ml sesame oil). N=15 in each group.

tomy then the injections of estrogens should suppress the body weight gain and the hyperphagia induced by systemic sulpiride. This proposition was tested in the next experiment.

EXPERIMENT 4: DOES SIMULTANEOUS ADMINISTRATION OF ESTRADIOL SUPPRESS THE SULPIRIDE EFFECT ON BODY WEIGHT IN FEMALE RATS?

It is long known that ovarian hormones influence food intake and body weight (7). Food intake, water intake, and body weight increase during diestrus and decrease during estrus. These fluctuations are well correlated with the ovarian cycle, and disappear during prolonged diestrus or pseudo-pregnancy when animals eat more and maintain higher body weights (36). The subcutaneous (28) or intrahypothalamic (14,39) administration of estradiol benzoate reduces food intake and body weight in previously ovariectomized and obese female rats. Therefore, it is believed that the reduction in estrogenic levels is the primary cause of hyperphagia and body weight increase induced by ovariectomy. Thus, it was reasoned that if sulpiride increases food intake and body weight through some kind of functional castration, then the simultaneous administration of estradiol benzoate (13,37) should render ineffective the sulpiride treatment with regard to body weight increase.

Method

Sixty female rats of the Wistar strain were individually housed and kept under the same conditions as those of the 3rd experiment. After 7 days of food intake and body weight control, the animals were distributed in 4 groups of 15 rats each. Each group received one daily injection of sulpiride or saline, and one daily injection of estradiol or sesame oil for 19 days. The sulpiride solution, 20 mg/kg diluted in saline, as well as the saline solution (0.1 ml) were given intraperitoneally. The β-estradiol-3-benzoate (Sigma Chemical Company), 2 μg/0.1 ml sesame oil, or the oil in the same volume were injected subcutaneously. One group received sulpiride plus estradiol, the second one sulpiride plus sesame oil, a third group saline plus estradiol, and the last one saline and the oil. After the 19th day of treatment, the SC injections were changed, and the animals that had received estradiol first were then switched to sesame oil and vice versa.

The body weight means of the 4 groups of animals, at the first and 12th days of treatment, were analyzed with a three-way ANOVA. The mean daily body weight gains of the 4 groups were calculated for the following time intervals: a) the first 15 days of treatment, b) the week before the reversal of the subcutaneous treatment, and c) the week after this reversal. The body weight slopes of the four groups, corresponding to the first time interval, were analyzed with a one-way ANOVA followed by a Tukey (a) test. The slopes of the second time interval, for each group, were compared with the slopes of the third interval by means of *t*-tests.

Results

Figure 3 shows that the animals receiving sulpiride and oil increased their body weight, while those under sulpiride receiving simultaneously estradiol did not. Body weight slopes during the first 15 days of treatment were significantly different, $F(3,56) = 13.78$, $p<0.00001$. Those differences were located, according to the Tukey test, between the group under sulpiride without estradiol (1.49 ± 0.22 g/day) and the remaining groups (sulpiride + estradiol:0.38 ± 0.1 g/day; saline + oil: 0.40 ± 0.12 g/day; and saline + estradiol: 0.22 ± 0.13 g/day), but not among these last 3 groups. The body weight data of the 12th day of treatment showed a significant difference, $F(1,56) = 11.11$, $p<0.001$, between the group under sulpiride and oil (258.1 ± 5.2 g) and the other groups (sulpiride + estradiol: 246.3 ± 3.3 g; saline + oil: 241.5 ± 4.4 g; and saline + estradiol: 245.8 ± 3.6 g). The group under sulpiride and estradiol did not differ from the control groups. The body weight gain slope of the group that received sulpiride + oil decreased from 0.93 g/day before the treatment reversal, to −0.71 g/day the week after the beginning of estradiol treatment, $t(28) = 5.29$, $p<0.00001$. In contrast, the interruption of estradiol administration in the other sulpiride-treated group induced an increase of the body weight gain slope from 0.65 ± 0.24 g/day to 1.91 ± 0.12

g/day, $t(28) = 4.54$, $p < 0.0001$.

DISCUSSION

The effects of estradiol on body weight increase induced by systemic sulpiride were similar to those of the estrogen on the body weight of ovariectomized rats (37,38). The estradiol alone did not yield any modification in body weight, and that agrees with a previous report (14) showing that the steroid effect is exerted only on body weight of previously ovariectomized rats that have developed obesity. Estradiol seems to alter feeding and weight gain via its action on the medial hypothalamus. Estradiol implantation in this region reduces food intake and body weight of previously ovariectomized rats (14,39). Also, estrogen receptors have been identified on VMH cells (26). Other experiments (3) have shown that VMH lesions considerably attenuate the obesity and hyperphagia induced by gonadectomy in female rats.

GENERAL DISCUSSION

Since sulpiride increases body weight in female but not in male rats, it seems evident that we deal here with a sex-dependent phenomenon.

Sulpiride is a selective D2 receptor blocker (15, 17, 34). Therefore, the increase in feeding and body weight might be attributed to a blocking action of sulpiride on hypothetical D2 dopamine satiety receptors. Such blockade would yield a release of feeding mechanisms. Dopamine satiety receptors, whose blockade by sulpiride might be responsible for the release phenomenon, have been described (23,24) in the perifornical region of the LH. It seems probable that the dopaminergic hypothalamic terminals involved in feeding inhibition belong to cell bodies in the mesencephalic ventral tegmental area (10, 20–22). However, that sulpiride blocks the hypothalamic dopamine receptors is questionable because the drug does not easily pass through the blood-brain barrier (4–6). In contrast, an indirect action of sulpiride on feeding mechanisms is better supported by some findings in this report. Thus, the facts that systemic sulpiride causes diestrus, and that ovariectomy or estradiol injections prevent the body weight increase induced by sulpiride, support the functional gonadectomy hypothesis.

Although they suggest an indirect mechanism of action, the present experiments do not answer the question as to whether sulpiride is acting directly on the ovaries to decrease estrogen production and secretion. It is well known that sulpiride increases the prolactin release through a blocking action on pituitary dopamine receptors normally involved in prolactin release inhibition (4, 15, 17, 35). The hyperprolactinemia induced by sulpiride might be responsible for an impairment of the steroidogenesis. In support of this assertion, it is worth mentioning that the hyperprolactinemia seems to be the cause of 20% of the secondary amenorrhoeas in women, and that the steroidogenesis blockade produced by hyperprolactinemia can partially explain the contraceptive effect of lactation in mammals (27). It has been shown that prolactin acts directly on the granulosa cells to inhibit the estrogens synthesis (40,41), by antagonizing the stimulating effects of FSH on the activity of the enzyme aromatasa (41). Besides, it is possible that prolactin promotes in granulosa cells the production of a nonsteroid oocyte maturation inhibitory factor (8). The hyperprolactinemia itself seems not to be the cause of body weight increase induced by sulpiride; otherwise, the estradiol administration would have been ineffective in suppressing the sulpiride effect. It cannot be suggested either that estradiol reduced the prolactin levels, since it has rather an stimulating effect on the prolactin release (9,25). In this way, the hypothesis that sulpiride blocks D2 pituitary receptors and induces hyperprolactinemia which, in turn, might impair the synthesis of ovarian steroids, yielding a reduction in the estrogen levels with the subsequent increase in food intake and body weight, seems to be in better agreement with the facts reported here than the hypothesis of a direct dopamine satiety receptor blockade.

Finally, other neuroleptics increase food intake and body weight, and these effects have been shown (2) to be also sex-related. While it is tempting to postulate the same action mechanism, a word of caution is needed since these drugs cross the blood-brain barrier, and they could well be acting through blockade of dopamine satiety receptors.

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