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Tamoxifen Prevents Sulpiride-Induced Weight Gain in Female Rats

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BAPTISTA, T., E. ARAUJO DE BAPTISTA, L. HERNANDEZ, M. ALTEMUS AND S. R. WEISS. *Tamoxifen prevents sulpiride-induced weight gain in female rats.* PHARMACOL BIOCHEM BEHAV **57**(1/2) 215–222, 1997.—To evaluate its potential utility in counteracting neuroleptic-induced obesity, the effects of long-term administration of tamoxifen (TAM) on body weight (BW) and food intake (FI) of gonadally intact and sulpiride-treated (SUL) female rats were assessed. In addition, estradiol and prolactin serum levels were measured in rats treated with SUL, SUL plus TAM and SUL plus bromocriptine (BR). TAM, at doses of 10, 50 and 100 μg, significantly decreased BW gain; FI was significantly reduced at the doses of 50 and 100 μg. In addition, doses of TAM ranging from 5-100 μg completely prevented SUL-induced BW gain and hyperphagia. BR also prevented SUL effects on BW and FI. In contrast to BR, concomitant administration of TAM did not prevent SUL-induced hyperprolactinemia. Estradiol levels were not modified by SUL alone or SUL plus BR, but they were significantly increased in the animals treated with TAM plus SUL. Neuroleptic-induced obesity in female rats might be related to an alteration in gonadal steroid balance secondary to hyperprolactinemia. While BR might counteract neuroleptic-induced weight gain by preventing hyperprolactinemia, TAM might directly interact with estrogen receptors, or indirectly increase estradiol levels. The use of TAM in preventing neuroleptic-induced obesity in humans warrants further investigation. © 1997 Elsevier Science Inc.

Neuroleptics Sulpiride Obesity Rats Tamoxifen Bromocriptine Estradiol

NEUROLEPTICS or antipsychotics are a heterogeneous group of drugs that have been used in the treatment of schizophrenia, other psychotic disorders, tics, chorea, vomiting and as pre-anesthesia medication (18). Long-term administration of neuroleptics causes weight gain leading to obesity, which affects the general health of the patient and interferes considerably with treatment compliance (3,10,51).

Correa et al. (16) postulated that neuroleptic-induced weight gain was a neuroendocrine side effect related to hyperprolactinemia. These authors showed that short term administration of amantadine, which is a dopaminergic agonist which reversed hyperprolactinemia, prevented excessive weight gain in neuroleptic-treated patients. Bromocriptine (BR), a D_2 dopamine receptor agonist is also used to counteract hyperprolactinemia (17). Unfortunately, both amantadine and BR can impair the mental state of the patient because of their agonistic aminergic effects (20,22,25,39,43), and it would be unwise to use them in psychosis-prone patients. In addition, amantadine, even at doses as high as 50 mg/kg, did not prevent SUL-induced BW gain and hyperprolactinemia in rats (52), which precludes further exploration of the efficacy of this drug in an animal model. The lack of effect of amantadine in rats, and the deleterious consequences of long-term administration of dopaminergic agonists on mental state and endocrine regulation (52), suggest that new therapeutic strategies are needed to counteract neuroleptic-induced obesity.

Long-term administration of neuroleptics induces significant weight gain and hyperphagia in female rats (4–7). Parada et al. (41) suggested that neuroleptic-induced hyperprolactinemia might impair ovarian estradiol synthesis, which in the long-term can lead to obesity (57). Chronic administration of the neuroleptic sulpiride (SUL) in rats induced a permanent diestrus, which suggests an impairment in sexual hormone function. In addition, SUL-induced weight gain was prevented by the concomitant administration of estradiol (41).

Tamoxifen (TAM) is a drug that belongs to the class of

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nonsteroidal antiestrogens, and it is widely sued in the treatment of all states of breast cancer (32). In addition to preventing growth of estrogen-dependent neoplastic cells, the antiestrogens such as TAM, nafoxidine, and MER-25 block most of the neuroendocrine actions of estradiol such as running wheel activity, estrous and maternal behavior, and gonadotrophin secretion (1,13,28,35). However, regarding BW and FI regulation, nonsteroidal antiestrogens such as TAM behave as agonists of estradiol, because they reduce food intake (FI) and body weight (BW) in ovariectomized rats (13,21,23, 27,28,47,56).

As neuroleptic-induced obesity in female rats appears to be related to an impairment of the estrogenic control of feeding (41,42), TAM, by acting as estradiol on feeding regulation might prevent excessive BW gain during neuroleptic administration. In contrast to monoaminergic agonists such as amphetamine, amantadine, BR, and fenfluramine (22,39,50) TAM does not have a prominent effect on mental state (49) and could be useful in patients prone to psychosis. Therefore, TAM appears to be a potential alternative treatment to counteract weight gain. We report here that in addition to decreasing BW gain in gonadally intact female rats, TAM prevented SUL-induced obesity. TAM also increased estradiol serum levels, while SUL-induced hyperprolactinemia was not affected by the antiestrogen.

METHODS

Animals

Virgin Sprague–Dawley female rats weighing 200–250 g were housed five per cage in wire-bottom cages measuring 20 × 20 in. The animals were maintained on a 12 h light/dark cycle, with lights on at 0700. Food intake was measured by means of spill-proof feeders containing powdered rat food (Bio Serv, NJ). Food and water were available ad lib.

Body Weight and Food Intake Control

BW and FI were recorded daily to the nearest 0.1 g. For each animal, BW gain was calculated every day by subtracting the BW the day prior to starting treatments, from the BW for that specific day of treatment. The daily FI data for the whole period for 7 days prior to treatment, until the end of the treatment, were divided into successive intervals of 7 days each, and expressed as ''mean daily food intake'' for a specific week. Animals were housed in groups of 5 per cage, and each group consisted of 10 rats. The inter-individual variation was not assessed. Therefore, the dispersion of the data reflects the variation of food intake during the days of a particular week of treatment.

Drugs

Racemic Sulpiride (Sigma) was dissolved in 0.1 N HCL; pH was adjusted to 7.0 with 0.1N NaOH. Tamoxifen citrate (Sigma) was dissolved in saline. Bromocriptine (Sigma) was dissolved in a vehicle composed by 40% propylene glycol, 10% ethanol and 50% saline. Injections were given at 0900.

EXPERIMENT 1
EFFECTS OF CHRONIC ADMINISTRATION OF TAM ON BW AND FI OF GONADALLY-INTACT RATS

Seventy rats were divided into 7 groups of 10 rats each. Each group received one of the following treatments IP for 21 days: 0.9% NaCl, or TAM 2.5, 5, 10, 20, 50, and 100 μg.

EXPERIMENT 2
EFFECTS OF CHRONIC ADMINISTRATION OF TAM ON SUL-INDUCED BW GAIN AND HYPERPHAGIA

Eighty rats were divided into 8 groups of 10 rats each. Each group received one of the following treatments IP for 21 days: saline + saline, saline + SUL (20 mg/kg), and SUL plus any of the following doses of TAM: 2.5, 5, 10, 20, 50 and 100 μg. The second injection was given 30 min after the first one.

EXPERIMENT 3
EFFECTS OF TAM ON PROLACTIN AND ESTRADIOL PLASMA LEVELS

Forty rats were divided into 4 groups of 10 rats each. Each group received one of the following treatments over 14 days; saline + saline, saline + SUL, SUL + TAM 50 μg, SUL + BR (3 mg/kg/sc). The second injection was given 30 min after the first one. Six h after the last injection, in a counterbalanced order the rats were decapitated and blood was collected from trunk vessels, and placed in tubes with EDTA. Estradiol and prolactin levels were measured by radioimmunoassay in duplicate for each rat. For prolactin, the antiserum and the standard were provided by he National Hormone and Pituitary Program (Rockville, MD). For estradiol, a commercial kit was used (Diagnostic Products, Los Angeles, CA). The inter- and intraassay variations were for estradiol: 8.5% and 4% and for prolactin 8.7% and 5.2% respectively.

Statistical Analysis

BW and FI data were analyzed by two-factor ANOVA for repeated measures (time and treatment as the factors). For specific comparisons of BW and FI data, and hormone data, the one-way ANOVA followed by the Fisher least-square difference test where appropriate was used. Differences were considered statistically significant when $p < 0.05$ for two-tailed tests.

RESULTS

Experiment 1

BW gain was significantly decreased during treatment with TAM at the doses of 10, 50 and 100 μg: treatment effect: $F(6, 63) = 3.7$, $p < 0.003$; time effect: $F(20,1260) = 58.6$, $p < 0.0001$ (Fig. 1).

FI was significantly decreased in rats during the first week of treatment with TAM at the doses of 50 and 100 μg: treatment effect: $F(6, 42) = 2.5$, $p < 0.05$; time effect: $F(3,126) = 2.8$, $p < 0.05$ (Table 1).

Experiment 2

BW gain was significantly increased by SUL administration; TAM at doses equal to or higher than 5 μg completely prevented this effect of SUL: treatment effect: $F(7, 72) = 5.3$, $p < 0.001$; time effect: $F(20, 1440) = 60$, $p < 0.0001$ (Fig. 2). FI was significantly increased by SUL, and this effect was prevented by TAM at doses equal to or higher than 20 μg (Table 2).

Experiment 3

SUL significantly enhanced BW gain and FI. These effects of SUL were completely prevented by the concomitant administration of TAM (50 μg) or BR (3 mg/kg): BW: treatment effect: $F(3, 36) = 7.7$, $p < 0.0004$; time effect: $F(13, 468) = 10.3$, $p < 0.0001$; FI: treatment effect: $F(3, 52) = 6.8$, $p <$

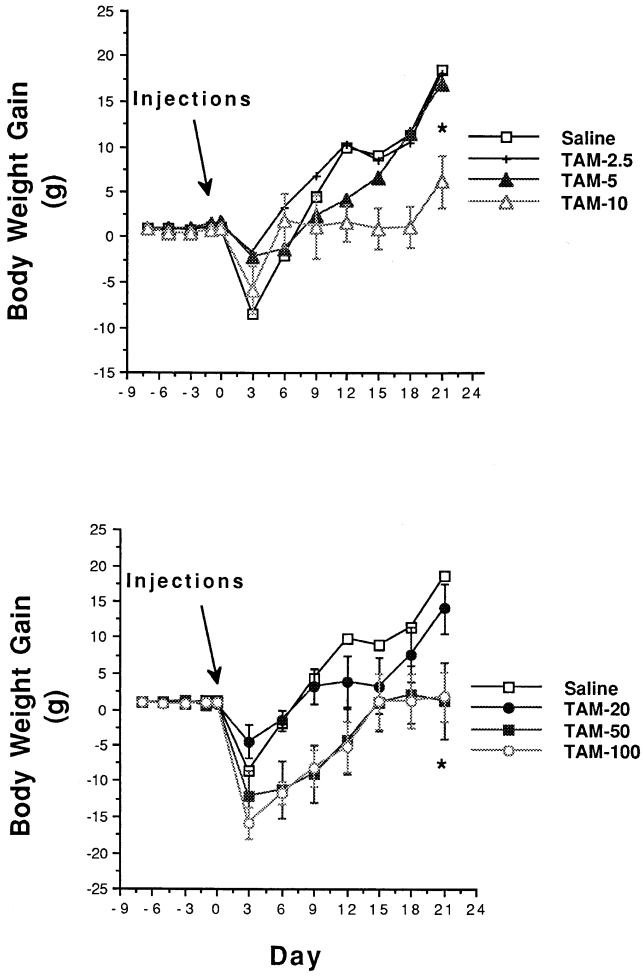

FIG. 1. Body weight gain of gonadally-intact rats treated with TAM. The mean BW gain was significantly decreased in rats treated with TAM at the doses of 10, 50 and 100 μg: for day 21: $*F(6, 69) = 4.02$, $p < 0.001$ (see text for additional statistics).

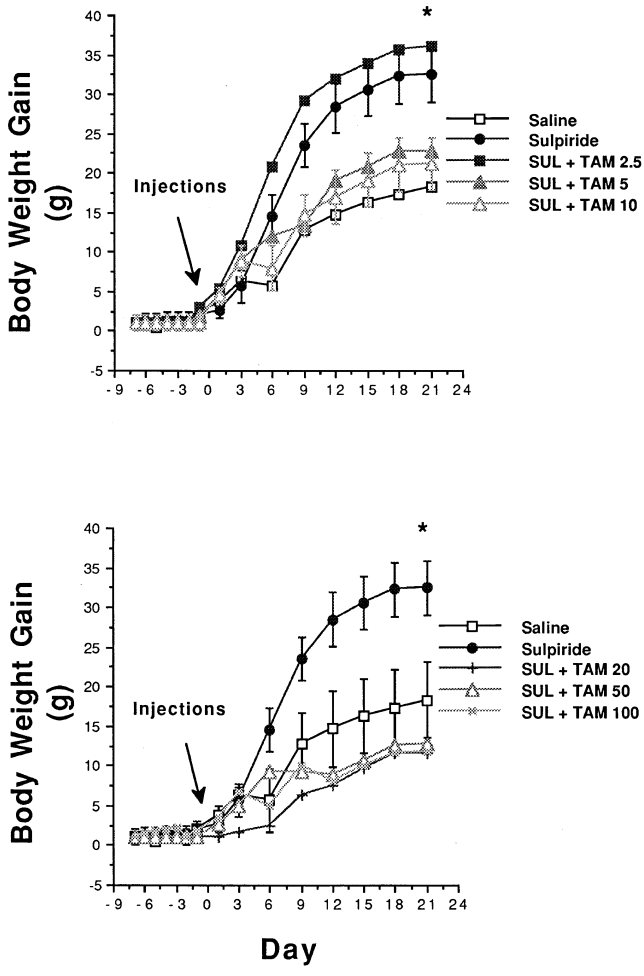

FIG. 2. Body weight gain of rats treated with sulpiride alone or sulpiride plus tamoxifen. SUL (20 mg/kg/IP) significantly increased BW gain. This effect was prevented by TAM at doses equal or higher than 5 μg. For day 21 $*F(7, 79) = 4.5$, $p < 0.001$ (see text additional statistics).

TABLE 1

MEAN DAILY FOOD INTAKE (GRAMS) OF GONADALLY-INTACT RATS TREATED WITH TAMOXIFEN (TAM)

Treatment	Week Before Treatment	During Treatment		
		First Week	Second Week	Third Week
Saline	73.6 ± 0.8	72.1 ± 10.7	68.7 ± 7.0	74.8 ± 3.5
TAM 2.5 μg	74.8 ± 1.2	70.4 ± 8.4	73.1 ± 9.1	70.4 ± 4.3
TAM 5.0 μg	73.9 ± 1.0	70.6 ± 2.2	74.3 ± 6.8	71.7 ± 5.5
TAM 10.0 μg	75.7 ± 0.8	80.8 ± 7.7	67.1 ± 4.7	64.6 ± 3.5
TAM 20.0 μg	74.3 ± 1.0	69.1 ± 4.0	76.7 ± 6.8	70.3 ± 5.6
TAM 50.0 μg	78.3 ± 1.7	54.4 ± 4.7*	65.7 ± 7.2	60.6 ± 4.6
TAM 100.0 μg	74.6 ± 1.0	52.0 ± 6.8*	70.0 ± 8.2	67.0 ± 3.0

Values represent daily food intake of 5 animals per cage, and are expressed as mean ± SEM. The highest doses of Tamoxifen (* = 50 and 100 μg) significantly decreased food intake during the first week of treatment: $F(3, 168) = 2.8$, $p < 0.03$ (see text for additional statistics).

TABLE 2

MEAN DAILY FOOD INTAKE (GRAMS) OF RATS TREATED WITH SULPIRIDE (SUL) ALONE OR SULPIRIDE PLUS TAMOXIFEN (TAM, μg)

Treatment	Week Before Treatment	During Treatment		
		First Week	Second Week	Third Week
Saline + Saline	82.1 ± 2.3	75.9 ± 5.4	71.3 ± 1.7	73.4 ± 2.1
Saline + SUL	81.0 ± 2.1	91.3 ± 3.2(a)	83.1 ± 2.2(a)	87.9 ± 3.4(a)
SUL + TAM 2.5	77.3 ± 2.1	87.2 ± 6.9	87.0 ± 3.1	70.6 ± 3.1
SUL + TAM 5.0	84.7 ± 3.3	87.6 ± 4.4	78.7 ± 4.9	80.1 ± 3.5
SUL + TAM 10.0	79.3 ± 4.6	69.4 ± 3.1	65.9 ± 3.7	70.1 ± 3.9
SUL + TAM 20.0	88.9 ± 4.1	66.7 ± 5.0	67.4 ± 1.8	60.6 ± 2.5(c)
SUL + TAM 50.0	83.1 ± 4.1	66.9 ± 3.7	67.0 ± 3.2	63.9 ± 1.0(c)
SUL + TAM 100.0	82.4 ± 2.3	62.2 ± 3.0(b)	65.9 ± 2.3	73.1 ± 4.7

Values represent daily food intake of 5 animals per cage, and are expressed as daily mean ± SEM. Compared to saline administration, SUL (20 mg/kg/IP) significantly increased FI for the three weeks of treatment: (a) $F(7, 48) = 14.5$, $p < 0.0001$. TAM prevented SUL-induced hyperphagia at the doses of 100 μg during the first week of treatment (b), and at the doses of 20 and 50 μg during the third week: (c) $F(3, 144) = 12.1$, $p < 0.0001$.

0.006; time effect: $F(2, 104) = 8.2$, $p < 0.005$ (Fig. 3). SUL + saline or SUL + BR did not affect estradiol levels. However, estradiol levels were significantly increased in the group treated with SUL + TAM $F(3, 35) = 19.4$, $p < 0.01$. SUL significantly increased prolactin; concomitant administration of BR prevented SUL-induced hyperprolactinemia, whereas concomitant administration of TAM did not: $F(3, 37) = 7.3$, $p < 0.0006$, (Fig. 4).

DISCUSSION

Daily administration of TAM for 3 weeks at doses ranging from 10–100 μg decreased BW gain in gonadally intact female rats. The same doses reduced BW and FI in ovariectomized rats (56). Interestingly, FI was significantly reduced only during the first week of treatment with TAM doses of 50 and 100 μg. Therefore, anorexia is only a conspicuous mechanism of BW reduction during the first week of treatment. Mechanisms other than reduction of FI, such as increases in energy expenditure or changes in lipid metabolism, might be involved in the long term effects of TAM (see below). In addition, TAM prevented SUL-induced obesity at doses as low as 5 μg, which did not affect BW gain or FI in Experiment 1. This phenomenon suggests that TAM prevents some anabolic effects of SUL, and that prevention of SUL-induced obesity is not due to a malady caused by TAM.

In order to gain insight on the mechanisms of actin of TAM on BW and FI, the effects of TAM were compared with the effects of bromocriptine (BR) on prolactin and estradiol plasma levels in rats treated with SUL for 14 days. In contrast to the procedure of Experiments 1 and 2, SUL was administered for 14 days instead of 21, because at the second week of SUL administration the maximal effects on BW and FI are observed (4). BR is a D_2 dopamine receptor agonist (34) that forestalled SUL-induced obesity in rats, probably by preventing hyperprolactinemia (4). As expected, concomitant administration of BR prevented SUL-induced BW gain, hyperphagia and hyperprolactinemia. In contrast, TAM prevented SUL-induced BW and FI changes without suppressing hyperprolactinemia. Estradiol levels were not affected by BR but were significantly increased by TAM. These results must be considered as preliminary, until more information is gathered about the hormonal effects of TAM on gonadally-intact rats.

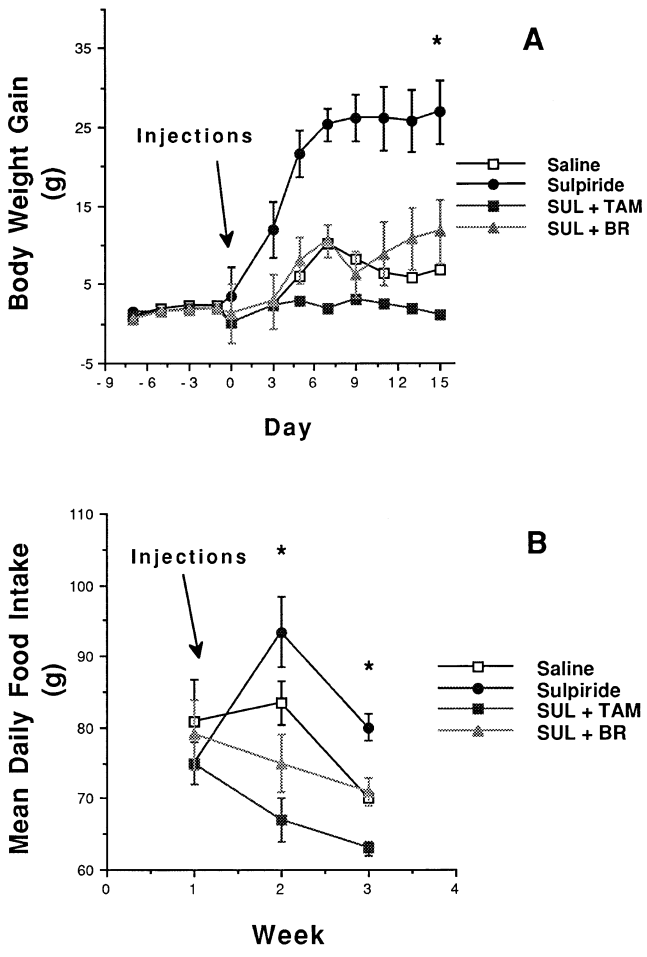

FIG. 3. Body weight gain and food intake of rats treated with sulpiride alone, sulpiride plus tamoxifen or sulpiride plus bromocriptine. SUL (20 mg/kg/IP) significantly enhanced BW gain (A) and food intake (B). This effect was completely prevented by the concomitant administration of TAM (50 μg/IP) or BR (3 mg/kg/sc). Body weight at day 14: $*F(4, 49) = 7.6$, $p < 0.0001$. (For FI see text for statistics).

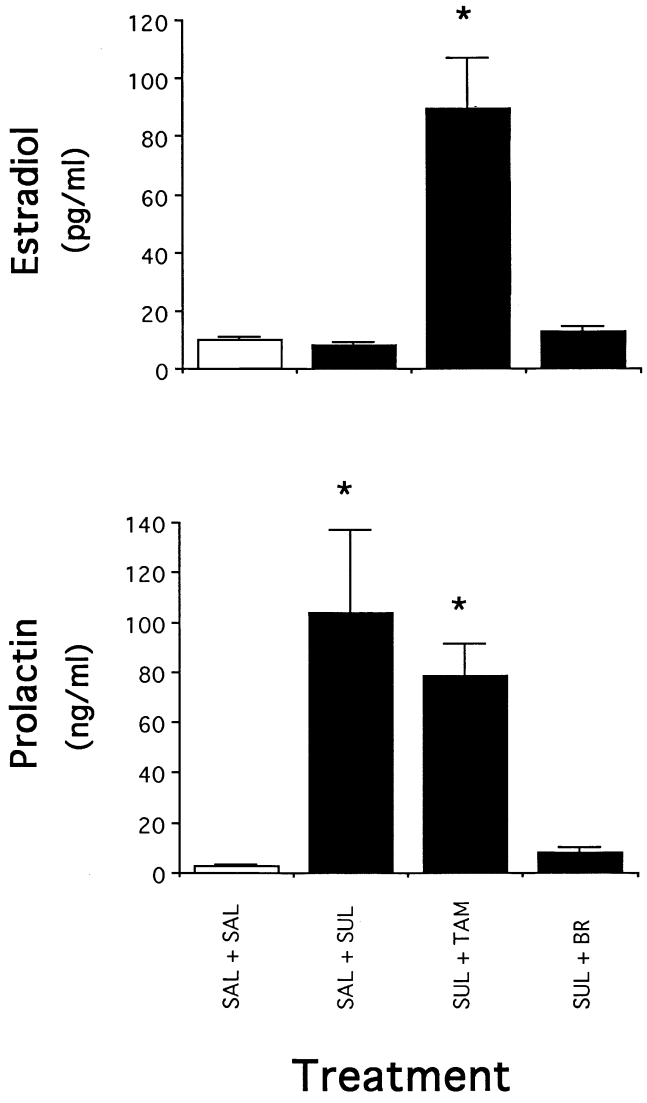

FIG. 4. Serum estradiol and prolactin levels in rats treated with sulpiride alone, sulpiride plus tamoxifen or sulpiride plus bromocriptine. *Estradiol levels were significantly increased in the group treated with SUL + TAM (20 mg/kg/IP, and 50 μg/IP respectively). *Prolactin levels were significantly increased by SUL; the hyperprolactinemia was counteracted by BR (3 mg/kg/sc) but not by TAM (see text for statistics).

In addition, the effects of TAM on prolactin and estradiol in SUL-treated rats were assessed only with high doses of the antiestrogen which themselves affected body weight in gonadally-intact rats (Experiment 1). In future experiments the full range of TAM doses should be explored.

The mechanisms controlling neuroleptic-induced obesity in humans have not been definitively established (18). Correa et al. (16) and Parada et al. (41) suggested that weight gain under neuroleptic treatment might be related to the drug-induced hyperprolactinemia. The effects of prolactin on BW and FI have been attributed to its ability to decrease and increase respectively the gonadal synthesis of estradiol and progesterone (38,53,58). Evidence has accumulated that a decrease in estradiol and/or an increase in progesterone serum levels might be involved in the development of weight gain (see below). Hyperprolactinemia has also been postulated to promote BW gain by additional mechanisms independent from those involving gonadal steroids (38).

Estradiol plays a critical role in the regulation of FI and BW in the female rat, because it acts both on the brain and on nonneural organs and peripheral tissues (such as the liver and adipose tissue) to affect regulatory behaviors, as well as the partitioning and metabolism of metabolic fuels. In the adipose tissue, estradiol decreases lipoprotein lipase activity and in situ lipogenesis, and increases lipolysis and fatty acid release (55–57). Ultimately, all these effects decrease BW. Interestingly, the effects of progesterone on BW and FI are opposite to those of estradiol. Therefore, in gonadally intact female mammals, it appears that it is the estradiol-progesterone balance, more than the absolute levels of each hormone, which affects BW regulation. Any factors that decreases the estradiol/progesterone index, promotes BW gain (56). Hence, it seems apparent that a decrease in the estradiol/progesterone index and/or hyperprolactinemia might be involved in the production of neuroleptic-induced obesity.

Hyperprolactinemia is consistently observed in patients under neuroleptic treatment and in SUL-treated rats. In the present report, estradiol levels were not affected by SUL. In addition, several clinical studies have been consistently unable to show a prominent effect of neuroleptics on absolute estrogen levels in women with mental disorders. For example, Beumont et al., (11,12) reported normal estrogen levels in pre and post menopausal medicated women with chronic mental illnesses, despite variable degrees of menstrual irregularities in the women. Moreover, Ataya et al. (2) reported a normal vaginal cornification index (suggesting normal estradiol impregnation of the epithelium) in most of the patients of a sample of overweight and amenorrhoeic women under chronic neuroleptic treatment. These results suggest that neuroleptic administration, probably via hyperprolactinemia, might impair gonadal function and BW regulation by mechanisms other than the reduction in absolute levels of estradiol. For example, neuroleptic-induced hyperprolactinemia might increase progesterone levels as non-pharmacological hyperprolactinemia does (38). The picture is further complicated by findings which suggest that women with schizophrenia might display low serum estradiol levels regardless of neuroleptic medication (40). Interestingly, the estradiol/progesterone index was lower in this sample of schizophrenic women than in age-matched controls. As neuroleptics are used in several mental and neurological disorders besides schizophrenia, further studies aimed to describe the mechanisms of obesity must take into account the putative contribution of the specific illness afflicting the patient (see 9 for a review).

In discussing the mechanisms by which TAM could have counteracted SUL-induced obesity, the effects of TAM on prolactin, estradiol and progesterone serum levels are particularly relevant.

TAM consistently decreased prolactin levels in rats with mammary carcinoma (30), patients with breast cancer (24,59) and healthy volunteer women (29). The decrease in prolactin which could be critical for the antineoplastic effects of TAM (32), might counteract the tendency to develop neuroleptic-induced hyperprolactinemia, and could also help prevent excessive BW gain. In the experiments reported here, SUL-induced hyperprolactinemia was not prevented by TAM; however, regulation of prolactin levels in patients with breast cancer might be modulated by factors absent in people or rats

without cancer or under neuroleptic treatment. In addition, the high levels of estradiol in rats treated with SUL and TAM could independently increase prolactin levels (19). In contrast, BR prevented both hyperprolactinemia and obesity. It can not be dismissed however, that other effects of BR, such as a direct agonistic effect on dopaminergic receptors in feeding areas of the lateral hypothalamus might also be involved in its ability to prevent SUL-induced weight gain. In fact, we have previously reported that BR at doses as low as 1 and 2 mg/kg tended to reduce BW gain in drug-free female rats (4). In any event, these results show that it is not through the prevention of hyperprolactinemia that TAM prevented SUL-induced weight gain.

As does estradiol, TAM decreased BW, FI, body fat content, parametrial white adipose wet weight and lipoprotein lipase activity in ovariectomized rats (32,57). Specific receptors for estrogen have been described in the brain, some localized in hypothalamic areas involved in FI regulation (32,57). The antiestrogens such as TAM bind competitively to estrogen binding sites (EBS) in both brain and peripheral tissues, and evidence has accumulated that most of the effects of antiestrogens on BW and FI are mediated directly through the EBS system (28). The similarity of effects on BW and FI between estradiol and antiestrogens such as TAM, nafoxidine, MER-25 and CI-628 is surprising, given the well established antiestrogenic effects of these compounds on other estrogen-dependent behaviors such as estrous and maternal behavior, voluntary exercise (57), and growth of estrogen-dependent breast neoplastic cells (32). For these reasons, antiestrogens such as TAM have been labeled as partial agonists/antagonists of estradiol (14). The balance between agonist and antagonist activity varies as a function of the antiestrogen used, the species of animal, and the end point under investigation (32,36).

Preliminary data suggest that there are specific proteic sites with which the antiestrogens, but not the estrogens, interact (antiestrogen binding sties; AEBS) (28). Interestingly, competition studies have shown that both TAM and neuroleptics such as fluphenazine and chlorpromazine were effective competitive inhibitors of [^{3}H]TAM binding to brain AEBS. This finding opens the possibility that neuroleptics could interact directly with neurons receptive to estradiol and antiestrogens in feeding areas in the hypothalamus. However, the physiological and behavioral role of the AEBS has been questioned, because 1–2 week of treatment with TAM or fluphenazine, alone or in combination, did not alter [^{3}H]TAM binding in hypothalamic-preoptic areas (28). This apparent lack of saturability of the AEBS contrasts with the effects of estrogens or antiestrogens on cytosolic EBS using similar binding assays. In any event, TAM could prevent SUL-induced obesity by interacting agonistically with ER or AEBS in neural or peripheral areas involved in BW regulation.

TAM could also decrease BW and FI indirectly, by increasing estradiol serum levels. The rats treated with SUL + TAM displayed very high serum estradiol levels. This has also been reported in female volunteers under chronic TAM administration (29), and in patients with breast cancer (31,45,49). This effect has not been replicated by others (37). The mechanisms by which TAM increased estradiol levels are not clear, but it could be related to a negative feed-back loop activated by the antagonistic effects of TAM on some EBS, or to stimulation of gonadotrophin levels (31).

Regarding progesterone, the absolute levels of this hormone are not affected by chronic TAM administration in women (29,31,49), and this subject has not been studied in rats. Given the relevance of progesterone in body weight regulation, further studies in rats must include the assessment of this hormone.

In summary, the specific mechanism by which TAM prevented SUL-induced obesity can not be definitively established with the results presented here, but it could be related to an increase in the estradiol/progesterone index via increased estradiol serum levels. This effect might counteract any effect of hyperprolactinemia on the hormonal index, or any direct effect of prolactin on adiposity.

The development of pharmacological tools to treat neuroleptic-induced obesity has been hampered by several factors: first, while it is clear that neuroleptic treatment affects gonadal function in humans (2,11,12,51), studies aimed to specifically correlated hormonal changes with BW effects of neuroleptics have not been conducted. Second, the effects of neuroleptics on BW differ in humans and rats, because excessive BW gain is observed in male and female patients (26,51), but only in female rats (4–8, 41,42). Further studies are warranted to clarify the differential effect of neuroleptics on BW in men and male rats.

When considering any pharmacological treatment aimed to counteract neuroleptic-induced obesity, it must be kept in mind that often the patient with mental illness is under treatment with multiple drugs besides neuroleptics, such as lithium salts, anticholinergics, antidepressants or anxiolytic drugs. It is unknown whether it is safe and reliable to add another drug such as TAM. With regard to possible effects on appetite, the effects of TAM on FI and BW in healthy people are basically unknown. TAM has been primarily used in patients with cancer, and BW and FI regulation might be affected by the illness itself or concurrent antineoplastic medication. BW gain under TAM therapy is not a frequent side effect (15,49). However, BW gain has been reported in 4% of patients under chronic administration of TAM (33,46). It remains unclear if this BW gain could rather be a normalization of BW because of the beneficial effect of TAM by controlling recurrence of the illness, or could be related to the hormonal status before treatment. In any event, a trial of TAM in patients under neuroleptic treatment should be conducted after the effects of TAM on BW and FI in people without cancer are delineated.

Ideally, TAM might be used for a short time in patients prone to gain BW, for example in women with brief organic mental disorders, bipolar disorders during a manic episode, or schizophrenia when dosage has to be temporarily increased. Often, these patients gain several pounds during such a brief period, due to the neuroleptic treatment, and that weight gain can interfere with treatment compliance and self-esteem. TAM might be used until the patient regains control over her diet and physical activity. In the short term, TAM at low to moderate doses induces few physical (15) or mental side effects (49). Unfortunately long-term TAM treatment increases the risk of endometrial cancer (54). Regarding possible psychiatric side effects, isolated cases of TAM-induced organic delusional syndrome have been reported (44) and mild depression as observed in 11% of premenopausal women under chronic TAM therapy (49).

In summary, in a preclinical model, TAM prevented neuroleptic-induced obesity and hyperphagia. Given that obesity is an important undesirable side effect of neuroleptic therapy, the potential use of TAM for prevention of neuroleptic-induced weight gain should be investigated.

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