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Antipsychotic Drugs and Reproductive Hormones: Relationship to Body Weight Regulation

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BAPTISTA, T., D. REYES AND L. HERNÁNDEZ. *Antipsychotic drugs and reproductive hormones: Relationship to body weight regulation.* PHARMACOL BIOCHEM BEHAV **62**(3) 409–417, 1999.—Excessive body weight gain is an undesirable side effect of prolonged administration of antipsychotic drugs (AP), which affects health and interferes with treatment compliance. It has been suggested that hyperprolactinemia-induced endocrine and metabolic abnormalities, particularly in the gonadal steroids, might be involved in the development of this type of weight gain. To test this hypothesis, reproductive hormones, cortisol, dehydro-epiandrosterone-sulfate (DHEA-S), thyroid hormones, and body weight gain were assessed in 18 patients (9 men, 9 women) with mental disorders receiving AP who had been medication-free for at least 3 months before the study, and in 27 placebo-treated subjects (10 men, 17 women). In women, hormones were evaluated during several phases of the menstrual cycle. A significant weight gain was observed in men but not in women. Under AP administration, women displayed significantly lower serum levels of estradiol and progesterone, whereas in men the levels of free testosterone and DHEA-S were significantly lower than in controls. Hyperprolactinemia was observed in both sexes. The levels of follicle-stimulating hormone in women and luteinizing hormone in men were significantly elevated by treatment, thus suggesting that the functioning of the hypothalamus–pituitary–gonads was preserved. In men, such an endocrine profile resembles that observed in subjects with primary obesity. Women under AP administration were found to be relatively hyperandrogenic because of decreased serum estradiol levels, whereas women with primary obesity are known to display actual increased levels of androgens. These endocrine abnormalities may contribute to the excessive weight gain observed after AP treatment, and these could be the target of novel pharmacological treatments. © 1999 Elsevier Science Inc.

Antipsychotics Neuroleptics Obesity Reproductive hormones

LONG-TERM administration of typical and atypical antipsychotic drugs (AP) induces excessive body weight gain among patients with chronic mental disorders (17,20,36,37,45,47,65, 69,71,72). Experimental and clinical studies have pointed out several mechanisms that could be held responsible for such a weight gain. First, AP stimulate brain feeding-related areas by interacting with dopaminergic and serotonergic receptors (4,5,13,15,58,64). Second, hyperprolactinemia (a side effect shared by most AP with the exception of clozapine) (19,31,38) impairs gonadal function and decreases estradiol (E_2) and testosterone (T_5) synthesis from the ovaries and testis respectively (14,21,25,26,34,43,54,57,61,70). Moreover, because these gonadal steroids participate in body weight regulation (73,74), the alteration in the E_2/T_5 ratio promotes weight gain (18,44).

The disrupting effects of high serum prolactin levels on the synthesis of the reproductive hormones have been extensively documented in animals (2,8,11,52,61), in patients with pituitary tumors (48,70) and in healthy volunteers with drug-induced hyperprolactinemia (10,43). The status of the endocrine system in psychiatric patients under chronic treatment with AP has also been assessed in depth (3,15,16,60,66). However, these studies present at least four important limitations regarding the relationship between obesity and a drug-induced endocrine unbalance: (a) they were conducted mainly in schizophrenics (60,66), and it is well known that drug-induced weight gain also occurs in patients with other mental disabilities (7); in addition, endocrine abnormalities such as low E_2 (in women) and high E_2 levels (in men) have been reported in

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schizophrenic subjects and these are relatively independent from AP administration (60,66). (b) Some studies have evaluated the reproductive hormones during a single phase of the menstrual cycle (3). This is a methodological flaw because indeed the results of our previous study indicated that E_2 and P_4 levels exhibit significant differences in AP-treated healthy women but only during specific phases of the cycle (10). (c) Most studies have mainly focused on the absolute serum hormone concentrations (3,15,16,60,66), but it has been shown that the E_2/T_5 and E_2/P_4 ratios are more important signals for the feeding areas in the brain than absolute values (74). (d) A relevant role in body weight regulation for the adrenal androgenic hormone dehydroepiandrosterone-sulfate (DHEA-S) has been demonstrated (27,39,59), but it has not been taken into account in previous studies (15,16).

The present study extends the results obtained by the previously mentioned research by evaluating the reproductive hormones and other hormone levels relevant for body weight regulation in a sample of in-patients with various mental disorders under AP administration. Contrary to previous studies in psychiatric patients, then, blood samples were taken at different stages of the menstrual cycle and the hormone serum levels were correlated with the body weight changes observed during the in-hospital treatment. Regarding the studies conducted in healthy women receiving the AP sulpiride during 1 month (10), the present study allowed to assess the effects of higher doses of AP during a longer period (6 weeks). Results were compared with those obtained in a sample of healthy subjects receiving placebo. Indeed, our main objective was to test whether low serum levels of E_2 (in women) and androgens (in men) are observed during prolonged AP administration. Moreover, serial blood samples in women allowed us to assess whether the decrease in estradiol serum levels was held for at least two consecutive menstrual cycles, and to test the hypothesis that women under AP administration display high progesterone serum levels as it occurs in hyperprolactinemic female rats with excessive body weight gain (56).

METHOD

The study was conducted in the in-patient Psychiatric Unit of "Universidad de los Andes" (Mérida, Venezuela). Consecutively admitted adult patients (over 18 years of age) were included if the following inclusion criteria were met: (a) they were free of antipsychotic or contraceptive medication for at least 3 months before the study; (b) they only received antipsychotic drugs during hospitalization (with the single exception of anticholinergic agents) and; (c) they had no history of chronic diseases beside the mental disorder they were suffering from. Female (nonpregnant) patients with regular menstrual cycles were included. The control group consisted of healthy, medication-free subjects who received placebo for 1 month. Nine psychotic women (age 33.1 $\pm$ 7.3 years), 17 healthy women (age 27 $\pm$ 2.6 years), 9 psychotic men (age 29.3 $\pm$ 9 years), and 10 healthy men (age 28.3 $\pm$ 3.9 years) entered the study.

The patients received the type and dosage of antipsychotic medication that the treating staff considered necessary. The research group did not participate in the drug selection. The control subjects were aware that they were taking placebo. In spite of important pharmacological differences among the various drugs, it was not envisaged to control the type of AP because our main hypothesis is related to the endocrine/metabolic effects of hyperprolactinemia, which is induced by all AP used in this study. The diet was similar for all patients, and no attempt was made to monitor food intake or activity levels.

Procedure

Physical and mental examination. The patients and the control subjects underwent a complete physical and laboratory examination. Regarding the mental state, axis I and II diagnoses were assessed according to the DSM-IV criteria (1). Substance pathological use was evaluated with the Diagnostic Interview Schedule (6). The control subjects were also assessed by the Hamilton scales for depression and anxiety (12)

TABLE 1

PSYCHIATRIC DIAGNOSIS, TYPE, AND DOSAGE OF ANTIPSYCHOTIC MEDICATION AND BODY WEIGHT CHANGE IN WOMEN

Subject	Age	Psychiatric Diagnosis (DSM–IV code, Axis 1)	Antipsychotic Medication (Daily Dose, mg)	Initial Body Weight (kg) and Body Mass Index (kg/m^2)	Final Body Weight (kg) and Body Mass Index (kg/m^2)	Body Weight Change (kg)
1	36	Schizophreniform Disorder, first episode (295.40)	Haloperidol 30 Chlorpromazine 100	46.9 (19.5)	43.6 (18.1)	−3.3
2	23	Paranoid Schizophrenia, first episode (295.30)	Thioridazine 200 Sulpiride 100	52.1 (21.9)	53.7 (22.6)	+1.6
3	40	Psychotic Disorder due to Gen. Med. Cond. first episode (293.81)	Haloperidol 15 Levomepromazine 75	56.5 (25.1)	55 (24.8)	−1.5
4	42	Bipolar Disorder, Manic Episode, sixth episode (296.4)	Haloperidol 15 Levomepromazine 75	68.3 (34.4)	68.4 (34.5)	+0.1
5	29	Psychotic Disorder due to Gen. Med. Cond. first episode (293.81)	Haloperidol 15 Levomepromazine 50	55 (22.9)	55.5 (23.1)	+0.5
6	30	Psychotic Disorder No otherwise specified, first episode (298.9)	Sulpiride 100	66.9 (24.1)	70.9 (25.5)	+4
7	26	Mood Disorder due to Gen. Med. Cond. fifth episode (293.83)	Trifluoperazine 40	56 (23.9)	60.4 (25.8)	+4.4
8	43	Schizoaffective Disorder, first episode (295.70)	Haloperidol 20 Levomepromazine 50	53.6 (23.2)	49.6 (21.4)	−4
9	39	Psychotic Disorder due to Gen. Med. Cond. tenth episode (293.81)	Haloperidol 30 Levomepromazine 400	65.5 (25.5)	64.3 (25.1)	−1.2

to exclude subjects with clinically significant levels of psychopathology.

The body mass index (body weight in kg/height in square meters) was calculated on admission. Body weight was assessed every week to the nearest 0.1 kg.

Endocrine Evaluation

Women. The date of the last menstruation of our patients was determined by interviewing them and/or their relatives. Blood samples were collected in three different phases of the menstrual cycle: phase 1, at day 10 after menstruation, which corresponds to the intermediate follicular phase; phase 2, at day 20, which represents the early luteal phase; and phase 3, at day 26, which is the late luteal phase. As all the patients developed amenorrhea during treatment, samples obtained after day 28 were labeled as belonging to phase 4. Samples in phase 4 were obtained until release from the hospital, after 45 days as an average of in-hospital treatment.

For the control subjects, blood samples were obtained at days 3, 10, 20, and 26 after menstruation in two consecutive cycles: before and during placebo administration.

The following hormones were assessed: luteinizing hormone (LH), follicle-stimulating hormone (FSH), 17-β-estradiol (E_2), progesterone (P_4) and prolactin. In the first and last samples the following hormones were assessed as well: thyreotropic hormone (TSH), free tetraiodothyroxine (T_4), cortisol, free testosterone (T_5), and dehydroepiandrosterone-sulfate (DHEA-S).

Men. Blood samples were obtained upon admission and then every 15 days for 1 month. For the control subjects, samples were obtained the day before starting placebo administration and then every 15 days during 1 month.

In all the samples, the following hormones were assessed: LH, FSH, prolactin, and T_5. In the first and last samples TSH, T_4, DHEA-S, cortisol, and E_2 were also assessed.

Hormone Determination

Hormones were determined by radioimmunoassay with commercial kits (DPC, Los Angeles, CA). Intra- and interassay variation was less than 10% for all assays.

Statistical Analysis

An endocrine evaluation in drug-free conditions was not conducted in our patients because blood samples were taken in the in-patient unit, and all the patients had been for at least 3 days in the emergency room where the AP drug treatment was started. For the two groups of treatment in each sex (antipsychotic drugs or placebo), between and within comparisons were conducted. Each time point was considered independent from another. Therefore, after logarithmic transformation, the data were analyzed by a one-way ANOVA followed by a Fisher least-square difference test. Differences were considered significant when $p \leq 0.05$. A correlation coefficient was used to assess the relation between body weight gain during the study (dependent variable) and the serum levels of each of the hormones under study (independent variables).

RESULTS

Tables 1 and 2 show the clinical features and the changes in body weight of the patients under study.

Women

Body weight. Both patients and controls displayed a minimal change in body weight during the study: patients 0.04 ± 0.9 kg; control subjects 0.11 ± 0.2 kg; $t(22) = 0.1$, $p = 0.8$.

TABLE 2

PSYCHIATRIC DIAGNOSIS, TYPE, AND DOSAGE OF ANTIPSYCHOTIC MEDICATION AND BODY WEIGHT CHANGE IN MEN

Subject	Age	Psychiatric Diagnosis (DSM–IV code, Axis 1)	Antipsychotic Medication (Daily Dose, mg)	Initial Body Weight (kg) and Body Mass Index (kg/m²)	Final Body Weight (kg) and Body Mass Index (kg/m²)	Body Weight Change (kg)
1	19	Paranoid Schizophrenia, first episode (295.30)	Haloperidol 30 Levomepromazine 400	53.8 (17.5)	64.9 (21.2)	+11.1
2	34	Psychotic Disorder due to Gen. Med. Cond. third episode (293.81)	Haloperidol 30 Levomepromazine 300	60.1 (20.7)	61.2 (21.1)	+1.1
3	23	Paranoid Schizophrenia, second episode (295.30)	Trifluoperazine 40 Chlorpromazine 300	64.2 (22.2)	76.2 (26.3)	+12
4	42	Bipolar Disorder, Manic Episode, seventh episode (296.4)	Fluphenazine 25 mg/3 weeks Levomepromazine 75	77.8 (27.5)	78.1 (27.6)	+0.3
5	33	Paranoid Schizophrenia, second episode (295.30)	Trifluoperazine 30 Chlorpromazine 50	48.5 (16.9)	56.5 (19.8)	+8
6	29	Psychotic Disorder due to Gen. Med. Cond. first episode (293.81)	Trifluoperazine 30 Thioridazine 300	60 (21.5)	64.5 (23.2)	+4.5
7	27	Paranoid Schizophrenia, second episode (295.30)	Haloperidol 60 Chlorpromazine 300	65.1 (20.2)	71.8 (23.4)	+6.7
8	22	Paranoid Schizophrenia, third episode (295.30)	Trifluoperazine 30	56.8 (20.1)	61.3 (21.7)	+4.5
9	39	Psychotic Disorder due to Gen. Med. Cond. first episode (293.81)	Trifluoperazine 30 Chlorpromazine 200	53 (22.6)	56 (23.9)	+3

TABLE 3

SERUM LEVELS OF PROLACTIN, TSH, T_4, T_5, CORTISOL, AND DHEA-S DURING ANTIPSYCHOTIC MEDICATION OR PLACEBO IN WOMEN

Treatment	Day of the Cycle	Prolactin (ng/ml)	TSH (mIU/ml)	T_4 (ng/dl)	T_5 (ng/ml)	DHEA-S (μg/dl)	Cortisol (μg/dl)
AP	a	220.3 ± 13.8*	0.77 ± 0.1	1.26 ± 0.1	1.5 ± 0.3	91.7 ± 20.3	14.8 ± 3.7
P		24.4 ± 5.7	1.39 ± 0.2	1.16 ± 0.1	2.1 ± 0.4	123.0 ± 23.0	16.1 ± 1.7
AP	b	110.6 ± 22.5*	1.14 ± 0.3	1.39 ± 0.3	2.1 ± 0.5	112.0 ± 24.6	22.7 ± 6.4
P		23.1 ± 5.1	1.46 ± 0.2	1.16 ± 0.1	2.3 ± 0.3	153.0 ± 39.1	16.2 ± 1.7

Values represent mean ± SEM. Day "a" and "b" for the subjects under AP administration represent days 10 and 38 of the menstrual cycles, respectively. For the control group they represent day 26 before (a) and during (b) placebo administration.

Abbreviations: AP = antipsychotic drugs; P = placebo; TSH = thyrotropic hormone; T_4 = tetraiodothyroxine; T_5 = free testosterone; DHEA-S = dehidroepiandrosterone sulfate.

*$p < 0.01$ for comparisons between the groups for a specific day.

Endocrine Evaluation

As expected, prolactin serum levels were significantly higher in the patients receiving AP during the entire course of the study: $F(11,114) = 26$, $p = 0.001$ (Table 3).

As the serum levels of the gonadal steroids (estradiol, E_2; progesterone, P_4) and the pituitary gonadotropins (LH and FSH) in the control group were similar before and during placebo administration, the data were combined to simplify the graphs. In the control subjects estradiol (E_2) and progesterone (P_4) displayed the typical pattern of increment after the intermediate follicular phase. This pattern was not affected by placebo administration. By contrast, in our patients the serum levels of E_2 and P_4 were significantly lower than the control values when comparisons were conducted in equivalent days of the menstrual cycle: for E_2: $F(11, 140) = 6.6$, $p = 0.0001$ (Fig. 1); for P_4: $F(11, 140) = 7.6$, $p = 0.0001$ (Fig. 1).

Regarding the pituitary gonadotropins, the serum levels of FSH were significantly higher in AP-treated subjects: $F(11, 140) = 4.4$, $p = 0.0001$ (Fig. 2). By contrast, the levels of LH tended to be lower than those observed in the controls, but it only reached marginal statistical significance: $F(11, 140) = 1.71$, $p = 0.071$ (Fig. 2).

No significant differences between the placebo and AP group were observed in the serum values of T_5, TSH, T_4, DHEA-S, and cortisol (Table 3). However, because of the low estradiol serum levels, the E_2/T_5 ratio was significantly decreased in the subjects under AP administration: for day 20 of the cycle: $t(17) = 3.9$, $p = 0.0011$ (Table 5).

A negative significant correlation was observed between the body weight gain during the study and the cortisol serum levels at the beginning of AP administration: $r = 0.88$, $F(1, 7) = 21.3$, $p = 0.0036$. No other correlation analysis attained statistical significance.

Men

Body weight. The body weight gain (kg) during the study was significantly higher in the patients under AP administration than in the control subjects: 5.68 ± 1.3 vs. −0.08 ± 0.2, $t(16) = 4.13$, $p = 0.0008$.

Endocrine evaluation. The prolactin serum levels were significantly higher in subjects during AP administration throughout the study: $F(5, 51) = 9.2$, $p = 0.0001$ (Table 4).

Regarding the gonadal steroids, the serum levels of free testosterone (T_5) were significantly lower in the patients

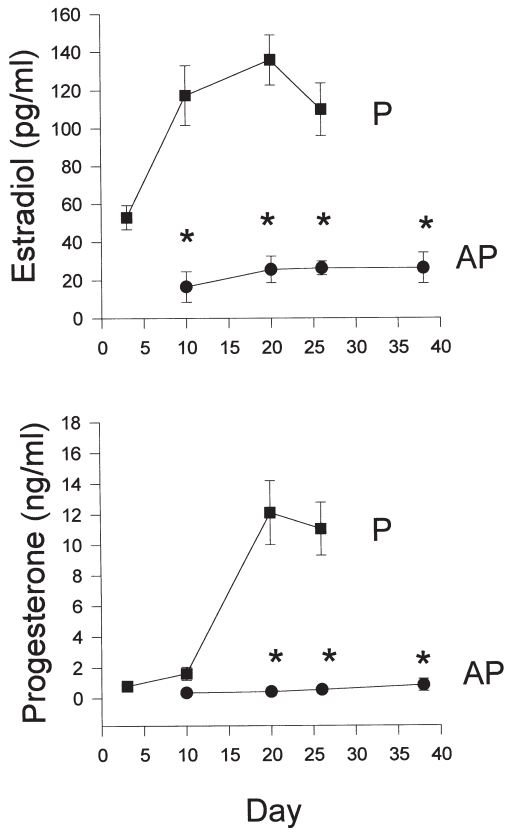

FIG. 1. Estradiol and progesterone serum levels in women receiving antipsychotic medication (AP, $n = 9$) and in healthy women (P, $n = 17$) before and during placebo administration. The serum levels of estradiol and progesterone were significantly lower during antipsychotic than during placebo administration, *$p < 0.01$. Comparisons were conducted in equivalent days of the cycle between the groups. In the AP group, day 38 corresponds to a period of amenorrhea. In the placebo group, hormone values before and during placebo administration were similar. They were, therefore, combined (see text for statistics).

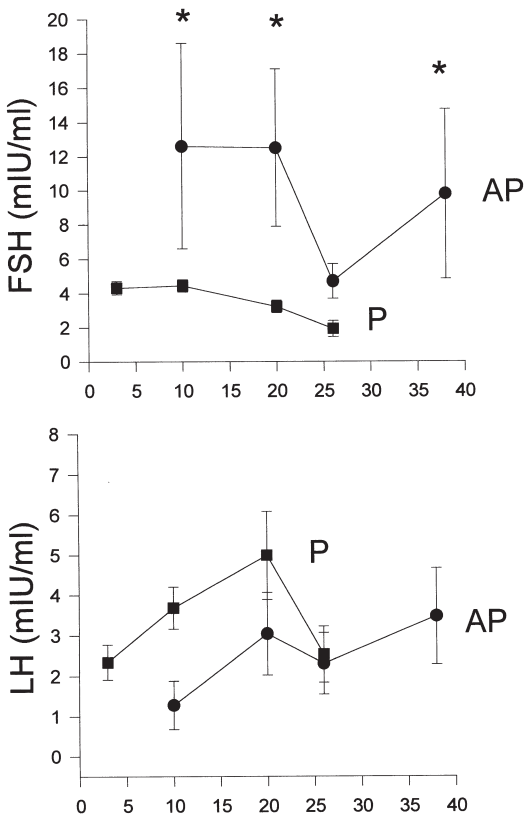

FIG. 2. Serum levels of follicle-stimulating hormone (FSH) and luteinizing hormone (LH) in women receiving antipsychotic medication (AP, $n = 9$) and in healthy women (P, $n = 17$) before and during placebo administration. The serum levels of FSH were significantly higher at days 10, 20, and 38 during antipsychotic administration when compared to all the values in the placebo group, $*p < 0.01$. No significant differences were observed in the serum levels of LH. In the AP group, day 38 corresponds to a period of amenorrhea. In the placebo group, hormone values before and during placebo administration were similar. They were, therefore, combined (see text for statistics).

treated with AP: $F(5, 51) = 3.16$, $p = 0.015$ (Table 4). No significant differences between the groups were observed in the serum levels of estradiol (E_2): $F(4, 43) = 0.8$, $p = 0.5$ (Table 4). However, because of the low levels of testosterone, the E_2/T_5 ratio was significantly higher under AP administration: $F(5, 54) = 3.32$, $p = 0.012$ (Table 5).

The serum levels of LH were significantly higher in the AP group: $F(5, 54) = 3.87$, $p = 0.0049$ (Fig. 3). The levels of FSH also tended to be higher in the AP group, but it only reached marginal statistical significance: $F(5, 51) = 2.26$, $p = 0.063$ (Fig. 3).

The levels of DHEA-S were significantly lower in the AP group: $F(3, 35) = 3.9$, $p = 0.016$ (Table 4) . No significant differences were observed in the levels of cortisol, T_4 or TSH (Table 4).

The correlation analysis only showed significant relationship between weight gain during the study and estradiol levels at day 30 during AP administration: $r = 0.725$, $F(1, 7) = 6.6$, $p = 0.042$.

DISCUSSION

The aim of this study was to assess whether the endocrine unbalance predisposes to an excessive body weight gain in AP-treated patients. The hormone serum levels and body weight of these patients were compared with those obtained in healthy placebo-treated subjects without clinically significant anxiety, depression, and/or substance abuse. As some endocrine abnormalities that are independent of drug treatment may be observed in schizophrenic patients (60,66), our sample was heterogeneous with respect to the psychiatric diagnosis.

Women

The patients under AP medication did not exhibit a significant weight gain, perhaps because of the severity of the psychiatric symptoms. Even though it was not formally assessed, the clinical evaluation showed that their mental disorder was more severe than that observed in males. In fact, a negative correlation was found between weight gain and cortisol serum levels, that is, those patients who gained less weight displayed the highest cortisol levels. Some of these patients were depressed, and decreased appetite (67) and overactivation of the pituitary–adrenal axis (42) are often detected in subjects with major depression.

A marked hyperprolactinemia and a remarkable decrease in the serum levels of E_2 were observed in these patients. The serum levels of P_4 were significantly decreased as well in contrast to hyperprolactinemic female rats (56). The E_2/T_5 ratio was significantly decreased but only because of the low E_2 levels. The levels of FSH were significantly higher in the AP group. This may be related to a negative feedback mechanism activated by the low levels of estradiol (32). Collectively, the abnormalities detected in the gonadal steroids may be important factors in the development of excessive weight gain (36, 72), menstrual irregularities and infertility (3,15,16) often observed in psychiatric patients under chronic AP administration.

Several endocrine/metabolic abnormalities have been described in women with primary obesity, i.e., in clinical conditions not associated with specific endocrine or neurological disorders (62): increased cortisol and insulin secretion, decreased growth hormone production, and increased androgenicity related to high levels of free testosterone and DHEA-S (18,27,39,40,44). In our patients, the serum levels of testosterone and DHEA-S were similar to those observed in control subjects; by contrast, the estradiol serum levels were significantly reduced. Therefore, the E_2/T_5 ratio that reflects the estrogenic/androgenic environment in a dynamic way was also significantly affected towards an increased androgenicity.

Men

A significant body weight gain was observed along with hyperprolactinemia, decreased serum levels of T_5 and DHEA-S and an increase in the LH levels.The E_2/T_5 ratio was also significantly increased but only because of the low T_5 levels. The high LH values may also be related to a negative feedback mechanism activated by the low serum testosterone levels (32). Men with primary obesity display normal serum prolactin levels, increased E_2/T_5 ratio, cortisol, and insulin secretion and low secretion of growth hormone, testosterone, and DHEA-S (18,27,39,40,44,55,59). Therefore, as far as the gonadal and adrenal steroids are concerned, male subjects under AP administration and primarily obese men display a similar profile.

TABLE 4

SERUM LEVELS OF PROLACTIN, TSH, T_4, T_5, ESTRADIOL, CORTISOL, AND DHEA-S DURING ANTIPSYCHOTIC MEDICATION OR PLACEBO IN MEN

Treatment	Day	Prolactin (ng/ml)	TSH (mIU/ml)	T_4 (ng/dl)	T_5 (ng/ml)	Estradiol (pg/ml)	DHEA-S (μg/dl)	Cortisol (μg/dl)
AP	a	52.6 ± 4.99*	1.82 ± 0.58	1.45 ± 0.18	19.1 ± 5.3	47.8 ± 8.1	160 ± 40	23.8 ± 4.1
P		10.2 ± 1.34	1.91 ± 0.31	1.00 ± 0.12	28.9 ± 5.9	37.5 ± 6.1	230 ± 15	23.1 ± 1.7
AP	b	81.9 ± 21.4*	—	—	11.9 ± 2.7*	44.7 ± 13.4	—	—
P		12.1 ± 1.7	—	—	26.7 ± 4.1	27.2 ± 3.9	—	—
AP	c	50.3 ± 9.1*	1.74 ± 0.12	1.42 ± 0.14	15.4 ± 4.9*	42.1 ± 4.1	130 ± 41*	22.2 ± 1.9
P		10.0 ± 1.8	1.55 ± 0.22	1.10 ± 0.11	34.9 ± 5.2	37.7 ± 6.2	270 ± 31	16.1 ± 1.5

Values represent mean ± SEM. Day "a," "b," and "c" for the subjects under AP administration represent the day of admission (a), and day 15 (b), and 30 (c) of treatment. For the control group they represent the day before the beginning of placebo administration (a) and day 15 (b), and 30 (c) under placebo.

Abbreviations: AP = antipsychotic drugs; P = placebo; TSH = thyrotropic hormone; T_4 = tetraiodothyroxine; T_5 = free testosterone; DHEA-S = dehidroepiandrosterone sulfate.

*$p < 0.01$ for comparisons between the groups for a specific day.

Mechanisms of the Endocrine Dysfunction

The mechanisms involved in the decreased serum levels of gonadal and adrenal steroids in men and women cannot be directly inferred from this study, but several findings suggest that they may be related to AP-induced hyperprolactinemia. Prolactin directly interferes with the stimulating effects of the pituitary gonadotropins on steroid synthesis in the ovary (14,25,26,43,54,57). This effect has not been definitely demonstrated in the testis, but low serum testosterone levels have been detected in several hyperprolactinemic conditions in males (21,34,61,70). A direct effect of prolactin or the AP itself on the hypothalamic neurons controlling gonadotropin secretion has been postulated (49,51,53). However, in our subjects the finding of high serum levels of FSH in women and LH in men suggests that the normal negative feedback mech-

TABLE 5

ESTRADIOL/TESTOSTERONE (E_2/T_5) RATIO DURING ANTIPSYCHOTIC MEDICATION OR PLACEBO

Treatment	Sex	Day	E_2/T_5
AP	M	a	3.66 ± 0.81
P			1.73 ± 0.33
AP	M	b	3.62 ± 0.80
P			0.69 ± 0.07
AP	M	c	5.03 ± 1.48*
P			1.62 ± 0.49
AP	F	a	19.3 ± 4.7
P			27.8 ± 6.8
AP	F	b	18.1 ± 3.8*
P			142.7 ± 21

Values represent mean ± SEM. In men, day "a," "b," and "c" for the subjects under AP administration represent the day of admission (a), and day 15 (b), and 30 (c) of treatment. For the control group they represent the day before the beginning of placebo administration (a) and day 15 (a) and 30 (c) under placebo. In women, days "a" and "b" for subjects under AP represents the day 10 and 20 of the cycle. In the control group, they represent day 10 and 20 under placebo.

*$p < 0.05$ for comparison between AP and P groups for that specific day.

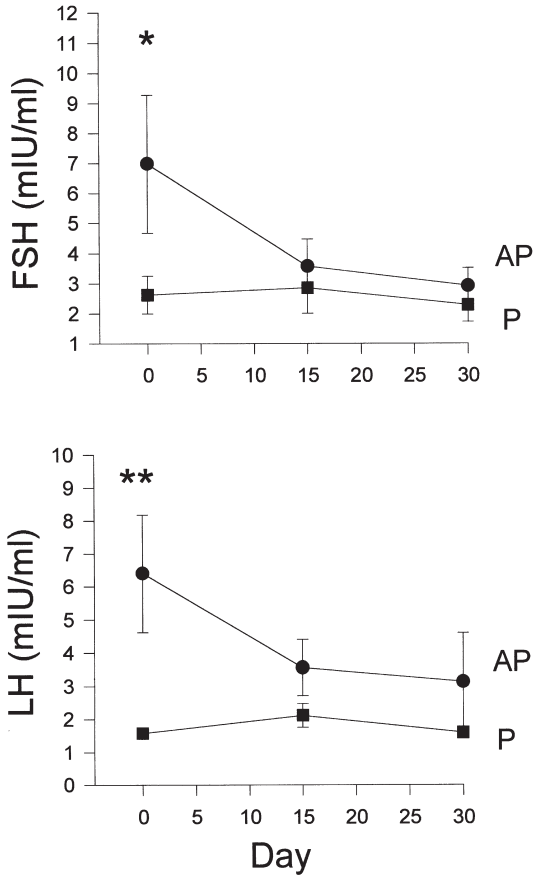

FIG. 3. Serum levels of follicle-stimulating hormone (FSH) and luteinizing hormone (LH) in men receiving antipsychotic medication (AP, $n = 9$) and in healthy men ($n = 10$) before (day 0) and during (days 15 and 30) placebo administration (P). The serum levels of LH were significantly higher at the beginning of antipsychotic administration than the basal levels before placebo administration, **$p < 0.01$. The serum levels of FSH also tended to be higher during AP treatment, but the difference only reached marginal statistical significance, *$p < 0.06$ (see text for statistics).

anism was still preserved. Interestingly enough, studies in nonhuman primates have shown that it is after considerably prolonged hyperprolactinemia that the normal feedback mechanisms are impaired (2). Therefore, it is possible that in subjects chronically treated with AP, a flat pattern of gonadotropins can be detected.

Clinical Implications

Two important differences in the endocrine profile of subjects with primary obesity and AP-treated patients are put forward: first, both men and women under AP administration display hyperprolactinemia [this is not the case in primary obesity (68)], and second, women under AP treatment are hypoestrogenic, whereas primarily obese women display normal or elevated estradiol serum levels (44). These differences have pathogenic and therapeutic implications: besides the effects on gonadal and adrenal steroids, prolactin itself promotes appetite (41) and insulin resistance (10,22,28) that may underlie the excessive body weight observed in hyperprolactinemic conditions detected in both animal (33,56) and clinical studies (24,29,75). These findings support the well-established treatment of AP-induced weight gain with appetite suppressants (13,35) and drugs that counteract hyperprolactinemia, such as bromocriptine (4) or amantadine (8,23).

Regarding the gonadal steroids, the low serum estradiol levels detected in women treated with AP may be the target of novel pharmacological interventions that could enhance the estrogenic milieu. For example, in female rats it has been shown that the antineoplasic drug tamoxifen, which acts as estradiol with respect to body weight and food intake (9), and estradiol itself (63) prevent the obesity induced by the AP sulpiride. But this has only been tested in animal research and, thus, deserves further evaluation under clinical conditions. It is interesting to note that obese women with schizophrenia would benefit even more because of the positive effects of estradiol replacement on schizophrenic symptoms (46).

In men, the effects of testosterone replacement on AP-induced weight gain or psychotic symptoms have not been studied as thoroughly and additional research on that issue is warranted.

Limitations of This Study

This study has several limitations that preclude definitive statements about the mechanisms of AP-induced weight gain: women under AP did not gain weight significantly; our sample was somewhat small; the period of AP administration was rather short, and several hormones and neuroregulators involved in feeding regulation were not assessed (30,50). Despite our reduced sample size, the results of the present study are clear-cut and consistent with those observed in animal research and in studies conducted in healthy volunteers under AP administration (8–11,63). As for the duration of treatment, our results show that endocrine abnormalities that predispose to excessive weight gain may be detected early during AP administration. With respect to the weight changes noted in our female patients, it should be borne in mind that the maximal weight gain under AP administration during inpatient treatment was observed in the first 12 weeks of treatment (37). The present study was only conducted during the first 6 weeks of drug treatment. Therefore, it is possible that a significant weight gain requires more time, particularly after additional clinical improvement. Future research should also determine whether the endocrine profile and body weight changes observed during AP treatment differ between previously obese and nonobese patients, and between depressed and nondepressed subjects.

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