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Mechanism of the Sex-Dependent Effect of Lithium on Body Weight in Rats

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BAPTISTA, T., E. MURZI, L. HERNANDEZ, J. L. BURGUERA AND M. BURGUERA. *Mechanism of the sex-dependent effect of lithium on body weight in rats.* PHARMACOL BIOCHEM BEHAV **38**(3) 533–537, 1991.—Two experiments are reported here. First, the effect of lithium chloride (1, 2 and 4 mEq/kg IP for 21 days) on body weight was assessed in female and male rats. Food intake was measured in the rats treated with 2 mEq/kg. All the doses tested significantly increased body weight in female rats. A linear relationship between body weight gain and lithium dose was also observed. In contrast, in male rats, the low doses of lithium (1 and 2 mEq/kg) did not affect body weight, whereas the high dose (4 mEq/kg) decreased body weight. These results confirm previous reports on a sex-dependent effect of lithium on body weight in rats. In the second experiment, body weight and food intake were assessed in female rats treated with lithium alone, or in combination with insulin or sulpiride, a D2 dopamine receptor blocker. It was found that the effect of lithium on body weight and feeding was additive to the effects of sulpiride and insulin. These findings are indirect evidence that lithium enhances body weight in rats by a different mechanism than the one described for sulpiride or insulin.

Lithium Obesity Sex Rats Insulin Sulpiride

BODY weight gain is a well-known side effect of lithium therapy in human beings. Schou et al. (24) reported weight gain of more than 5 kg in patients treated with lithium for one year or more. Mellerup et al. (17) showed that lithium-treated patients experience a 16 kg increase in body weight relative to the desirable body weight, and Dempsey et al. (10) observed a weight increase in one-third of their lithium-treated patients.

In rats, chronic administration of lithium has produced mixed results. Schou, cited by Mellerup (17), reported weight reduction, whereas Plenge et al. (23), Opitz and Schafer (20) and Vendsborg (29) reported body weight gain.

Some factors may explain these divergent results. When lithium is administered in food, rats tend to eat less and body weight loss is often observed (7). In addition, Plenge et al. (23) showed that maintenance of proper conditions of housing, such as avoiding noise, crowding, and humidity is necessary to observe the weight gain.

A sex- and age-dependent effect of lithium on body weight in rats has also been reported (20,28): two-month-old females significantly gained weight while 5- and 12-month-old females did not (28). In two-month-old males, body weight was not affected, whereas 5- and 12-month-old males lost significant weight (28). In that study (28), an extra sodium supplement was not administered. This might have contributed to the weight loss observed in males, because of the toxic effects of lithium-induced hyponatremia (30). On the other hand, these authors used only one lithium dose (3 mEq/kg day). So far, no relationship between weight change and lithium dose has been reported. The aim of the experiments reported here was to extend previous work, by assessing lithium dose response changes in body weight of 3-month-old female and male rats, given extra-sodium supplement. In addition, to gain further insight into the mechanism by which lithium modifies body weight, we combined lithium with other drugs that induce body weight gain and whose mechanisms of action are well known. Insulin increases body weight because it first produces hypoglycemia that induces hyperphagia, and secondly enhances the transformation of carbohydrates into fat and glycogen stores (15). Sulpiride blocks D2 dopamine receptors in the lateral hypothalamus (4) and the pituitary (14). The blockade in the hypothalamus disinhibits feeding (4) while acting at the pituitary to enhance prolactin secretion which leads to an increase in feeding (22).

We assumed that an additive effect of lithium plus insulin or lithium plus sulpiride would suggest that lithium induces body weight gain by a mechanism different than hypoglycemia or dopamine receptor blockade.

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TABLE 1

BODY WEIGHT (b.wt.) GAIN OF FEMALE OR MALE RATS TREATED WITH LITHIUM CHLORIDE (1, 2 and 4 mEq/kg IP) OR SALINE FOR 21 DAYS

Sex	Treatment	Initial b.wt. (g)	Final b.wt. (g)	b.wt. Gain (g)
F	LI 1 mEq/kg	228 ± 9	249 ± 8	21 ± 1.5*
F	LI 2 mEq/kg	228 ± 8	253 ± 5	25 ± 1.8†
F	LI 4 mEq/kg	228 ± 8	259 ± 7	31 ± 4.3†
F	Saline	225 ± 8	239 ± 7	14 ± 4
M	LI 1 mEq/kg	290 ± 4	356 ± 9	66 ± 7
M	LI 2 mEq/kg	293 ± 4	360 ± 7	67 ± 6
M	LI 4 mEq/kg	293 ± 6	319 ± 9	26 ± 5†
M	Saline	292 ± 3	364 ± 3	72 ± 8

Values represent average ± S.E.M. M = males; F = females; LI = lithium. In female rats all the doses of lithium significantly increased body weight, $F(3,27) = 13.9$, $p<0.01$. In male rats no effect was observed at the doses of 1 and 2 mEq/kg, and a significant reduction in body weight was observed with 4 mEq/kg, $F(3,27) = 12.2$, $p<0.01$. *$p<0.05$; †$p<0.01$ with respect to saline.

EXPERIMENT I. EFFECT OF DIFFERENT DOSES OF LITHIUM ON BODY WEIGHT IN FEMALE AND MALE RATS

Method

Three-month-old adult Wistar rats were used. Forty males, weighing between 270 and 310 g, and 40 females, weighing between 180 and 250 g, were individually housed and fed with high fat diet (66% powdered rat food and 33% corn oil). The rats had water, saline solution (NaCl 0.9%), and food ad lib and a 12–12 light-dark cycle with light on at 7:00 a.m. Food was presented in spillage-proof feeders (11). For each sex the rats were divided into 4 groups of 10 rats each. The body weight was measured daily. The groups were housed for 1 week prior to receiving intraperitoneally at 8:00 a.m., saline 0.9% or LiCl (Riedel-De Haen), (1, 2 and 4 mEq/kg) daily for 21 days. A one-way ANOVA followed by the Newman-Keuls test and regression analysis were used to compare the body weight gain in the four groups over the 21-day test period.

Food intake was measured in the rats treated with saline and LiCl (2 mEq/kg) and the data were analyzed by a two-way ANOVA. Food intake was only measured in the group treated with lithium (2 mEq/kg) because this dose produces serum lithium levels in the therapeutic range for humans (2). The doses of 1 and 4 mEq/kg produce subtherapeutic and toxic serum lithium levels respectively (2). Future studies, however, should assess food intake at these doses of lithium.

Results

In the female rats, LiCl increased body weight significantly (Table 1). The maximal effect was obtained with 4 mEq/kg. With the lower dose of 1 mEq/kg body weight gain was still greater than saline. The regression analysis showed that body weight gain was proportional to the dose of lithium ($r = .87$; $p<0.02$).

In the male rats LiCl at a dose of 4 mEq/kg decreased body weight significantly, whereas no significant effects were noted at 1 and 2 mEq/kg (Table 1).

Food intake was not significantly affected in either females or males at the dose of 2 mEq/kg (Fig. 1).

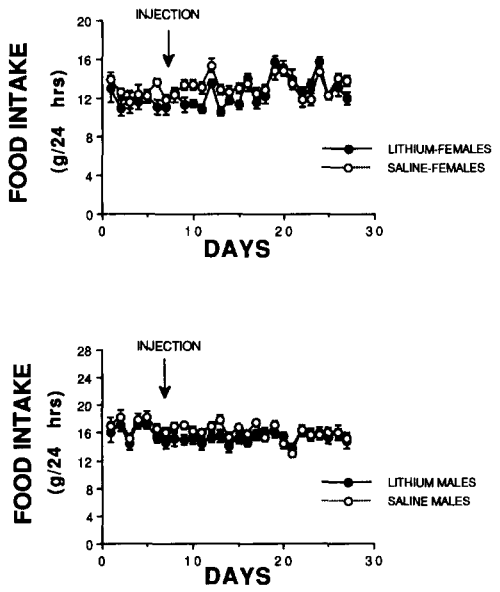

FIG. 1. Daily food intake before and during lithium administration (2 mEq/kg IP) in female (above) and male (below) rats. Data was analyzed by a two-way ANOVA. The arrow represents the beginning of the treatment. No significant differences were observed either in females, $F(1,306) = 0.4$, NS, or in males, $F(1,306) = 0.7$, NS.

Discussion

Lithium exerts a sex-dependent effect on body weight in rats; the trend is for females to gain weight and for males to lose weight. These results confirm the previous work of Opitz and Schafer (20), Texeira and Karniol (28) and Vendsborg (29). In addition, the females showed a linear relationship between lithium dose and weight gain. The weight loss in male rats was only observed with the highest dose of lithium (4 mEq/kg) and it was not prevented by the availability of NaCl. Sex differences are a common observation in obesity research. For example, Cox et al. (9) found that female rats with ventromedial hypothalamic (VMH) lesions displayed greater hyperphagia and body weight gain than did males, and we have shown that neuroleptic drugs increase weight in adult female but not in adult male rats (3). In the case of lithium it has been suggested that the weight loss in male rats is a toxic effect of lithium, because males might display higher serum lithium levels than females (8). We administered LiCl 4 mEq/kg day IP to 10 adult male rats and 10 females. After 10 days of treatment, when the females had gained significantly more weight and males had lost significantly more body weight compared to the saline controls, serum lithium levels were measured 6 hours after the last dose. No differences were observed in lithium levels: females = 0.74 ± 0.08 mEq/l; males = 0.72 ± 0.05 mEq/l, $t(18) = 0.22$, NS (2). However, in that experiment, the time course of serum lithium level was not assessed, but should be assessed in the future. On the other hand, there might be sex-related differences in lithium levels in tissues others than blood that could be relevant to body weight regulation. For example, Suva and Musil (27) reported that male guinea pigs display higher brain lithium levels than did females 4 hours after lithium administration, but not at other times. Further experiments are warranted to assess whether or not this sex-dependent difference in lithium brain levels are relevant to its effect on body weight regulation.

Interestingly, even though the body weight gain of the female rats treated with lithium (2 mEq/kg) was significantly higher than the saline control, their food intake was not enhanced. These findings are contradictory to the results of Opitz and Schafer (20) who found that lithium administration for 4 weeks (1 mEq/kg) significantly increased food consumption in female rats. No clear explanation emerges to account for this discrepancy (see the second experiment for further discussion).

We did not measure linear growth and body composition. Vendsborg (29) showed that female rats under lithium treatment significantly gained body weight. However, its body composition, i.e., the percentage of water, fat, ash and protein, was not affected. This author states that "the influence of lithium seems therefore to be a generalized increase in growth, and not a change in metabolism of some special tissue, e.g., fat tissue" (29). Fluid intake and excretion were not measured either. However, it is unlikely that body weight gain is due merely to fluid retention, because in addition to the finding of normal body composition in lithium-treated rats (29), all our animals developed considerable polyuria and polydipsia. These are well-known side effects of lithium, related to a kidney resistance to the effect of the antidiuretic hormone (30).

The mechanism by which lithium increases body weight in normophagic female rats is unknown (26). The next experiment was designed to gain further insight in this subject, by combining the administration of lithium with either sulpiride or insulin injections.

EXPERIMENT II. ADDITIVE EFFECT OF LITHIUM AND INSULIN OR SULPIRIDE ON BODY WEIGHT AND FEEDING IN ADULT FEMALE RATS

It has been proposed that lithium increases hypothalamic noradrenergic activity which in turn increases ACTH and corticosterone serum levels (26). The higher levels of adrenal hormones cause hyperglycemia that in turn leads to a reactive hyperinsulinaemia. Over the long-term, persistent hyperglycemia and/or hyperinsulinaemia might lead to weight gain (26). This does not explain the sex-dependent effect of lithium on body weight in rats, because hyperinsulinaemia per se increases weight in both sexes (15). Women under lithium treatment also develop hypothyroidism in a higher proportion than men do (19). Were this the case in rats, the lowered metabolic rate could explain why females, but not males, gain weight.

A common method to gain insight into the mechanism of drug action is to combine it with other agents whose mechanisms of action are well known. If the effect is additive, a different action for each drug might be proposed, provided that all the drugs are used at their maximal effective dose.

It has been postulated that exogenous insulin increases body weight by producing hypoglycemia, which in turn enhances hunger, and because it enhances the transformation of carbohydrates into fat and glycogen stores (15).

On the other hand, several experiments suggest that the antipsychotic drug sulpiride increases body weight in female rats by blockade of D2 dopamine satiety receptors in the perifornical lateral hypothalamus (3,4), and blockade of D2 dopamine receptors in the pituitary to cause functional ovariectomy (22).

We report here an additive effect of lithium plus insulin and lithium plus sulpiride on body weight and feeding in rats.

Method

Seventy, three-month-old female Wistar rats were divided into seven groups of 10 rats each. The rats were individually housed and fed as in the first experiment. Each group received one of the following treatments given once daily for 21 days: 1) LiCl, 2 mEq/kg IP; 2) sulpiride (DeLa Grange), 20 mg/kg IP; 3) insulin NPH (Lilly), 5 U/SC; 4) lithium + insulin, (same doses); 5) lithium + sulpiride, (same doses); 6) insulin + sulpiride (same doses), and 7) an isovolumetric dose of NaCl 0.9% IP.

Body weight gain and food intake were measured and analyzed as in the first experiment.

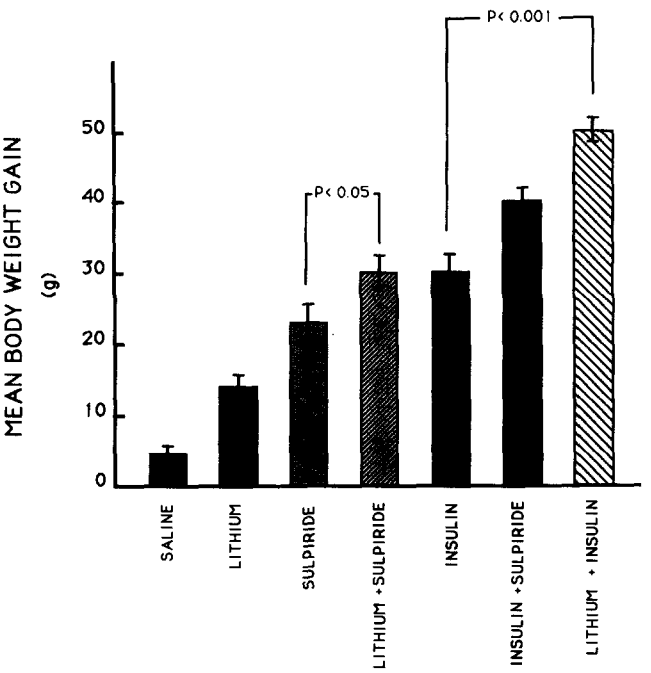

FIG. 2. Body weight gain of female rats treated for 21 days with saline IP, lithium (2 mEq/kg IP), sulpiride (20 mg/kg IP), insulin (5 U/SC), lithium plus sulpiride, lithium plus insulin and sulpiride plus insulin. Data was analyzed by a one-way ANOVA followed by the Newman-Keuls test. All the drugs tested significantly increased weight gain respect to the saline-treated rats: $F(6,54)=40.1$, $p<0.001$. The effect of lithium was additive to the effect of sulpiride and insulin. The effects of sulpiride and insulin were additive as well.

Results

Rats treated with lithium, sulpiride or insulin gained more weight than saline controls (Fig 2). The smallest effect was observed in the lithium group. Food intake was also significantly enhanced by sulpiride and insulin, but not by lithium (Table 2). Food intake was significantly reduced in the lithium group during the first week of treatment.

The effect of lithium on body weight and food intake was additive with the effects of insulin and sulpiride. The effects of insulin and sulpiride were additive as well (Fig. 2 and Table 2). The strongest effect was observed in the group treated with lithium plus insulin (Fig. 2).

DISCUSSION

The mechanisms by which sulpiride and insulin enhance body weight in female rats are well known. Sulpiride blocks D2 dopamine receptors in the lateral hypothalamus involved in satiety (3,4). It also blocks D2 receptors in the pituitary involved in the inhibition of prolactin secretion (14). The resulting hyperprolactinemia causes a functional ovariectomy, which in turn produces

TABLE 2

ADDITIVE EFFECT OF LITHIUM, SULPIRIDE AND INSULIN ON FOOD INTAKE

Treatment	Week Before Treatment (g)	During Treatment First Week (g)	Second Week (g)	Third Week (g)
Saline (n = 10)	12.2 ± 0.3	11.4 ± 0.1	11.9 ± 0.5	11.6 ± 0.4
Lithium (n = 10)	11.3 ± 0.4	9.8* ± 0.6	11.6 ± 0.6	11.4 ± 0.2
Insulin (n = 10)	11.5 ± 0.6	13.6† ± 0.4	17.5† ± 1.2	15.7† ± 0.3
Sulpiride (n = 10)	11.3 ± 0.5	12.6* ± 0.5	13.2* ± 0.9	12.1 ± 0.3
Lithium Plus Insulin (n = 10)	11.2 ± 0.6	14.6† ± 0.7	18.1† ± 1.2	18.5‡ ± 0.2
Lithium Plus Sulpiride (n = 10)	11.8 ± 0.3	11.7* ± 0.6	13.9† ± 0.9	13.4† ± 0.1
Sulpiride Plus Insulin (n = 10)	12.1 ± 0.5	15.1 ± 2.9	19.3† ± 3.8	16.8† ± 3.1

Daily mean food intake (g) of adult female rats before and during treatment for 21 days with lithium chloride (2 mEq/kg/IP), sulpiride (20 mg/kg/IP), insulin (5 U/SC), lithium plus sulpiride, lithium plus insulin, sulpiride plus insulin or saline IP. Means ± S.E.M. are given. The data was analyzed by a two-way ANOVA followed by the Newman-Keuls test. Compared to the saline group, sulpiride and insulin significantly increased food intake. Lithium significantly decreased food intake during the first week of treatment. The food intake of rats treated with lithium plus sulpiride and lithium plus insulin was significantly higher than the food intake of the rats treated with lithium alone. The food intake of the group treated with insulin and sulpiride was significantly higher than the food intake of the group treated with sulpiride alone, $F(18,168) = 3.71$, $p<0.001$. Symbols indicate significant differences within the same week: *$p<0.05$; †$p<0.01$; ‡<0.001.

hyperphagia and obesity (18,22). For several reasons we believe the additive effect of lithium and sulpiride is not due to a common mechanism of action. First, lithium does not block D2 dopamine receptors (6) or causes hyperprolactinemia (1). Second, the dose of sulpiride used here produces maximal increases in body weight and food intake as shown by dose-effect studies (3), whereas lithium does not enhance food consumption. Therefore, the mechanism of lithium-induced body weight gain is not probably mediated by D2 dopamine receptors blockade. For insulin, it has been proposed that food intake is increased in response to the insulin-induced hypoglycemia (15).

Lithium has been suggested as having a mechanism of action which is similar to that of insulin (16). In this model, body weight increase might be secondary to the metabolic effects of lithium and to increased feeding, related to a lithium-induced hypoglycemia. In the two experiments reported here, food intake was not enhanced by lithium, even when a significant body weight gain was observed. Therefore, a mechanism different from an increase in food intake has to be proposed.

It is well-known that lithium increases glycogen synthesis by at least five different mechanisms: a stimulation of glucose uptake into the cells; an activation of the magnesium-activated hexokinase; the inhibition of pyruvate kinase; the inhibition of the protein kinase that promotes the change of the glycogen synthetase to a lesser active form, and the inhibition of adenyl cyclase (17). The net effect of lithium on carbohydrate metabolism, i.e., the enhancement of glycogen synthesis, could explain why a significant weight gain without hyperphagia was observed. Therefore, lithium-induced body weight gain might be a metabolic phenomenon without concomitant hyperphagia.

This kind of nonhyperphagic obesity has also been observed in hypothalamic and other animals models of obesity (13,25). When VMH-lesioned rats were pair fed with normal controls, the VMH rats increased body weight by enlarging their fat compartment (13). However, it is unlikely that lithium increases the fat content because, as it was previously discussed, chronic lithium administration does not change body composition in female rats (29).

Chronic lithium administration enhances serotonin release in the lateral hypothalamus in rats (5). It is well known that serotonin displays anorexic effects in that hypothalamic area (21). Therefore, the metabolic effect of lithium might increase body weight, whereas its agonistic effect on serotonergic transmission in the lateral hypothalamus might decrease feeding. The net effect could be a nonhyperphagic obesity. However, as previously stated, Opitz and Schafer (20) reported that lithium caused weight gain and hyperphagia in female rats. Therefore, further experiments are warranted to clarify this important subject.

On the other hand, the effects of lithium and insulin are additive. This phenomenon does not seem to be due to addition of hypoglycemia. The dose of insulin used in this experiment is the maximal. In our hands, doses larger than this killed most of the rats due to severe hypoglycemia. Therefore, if lithium-induced hypoglycemia was additive to insulin hypoglycemia, increase in mortality rather than feeding should have been observed. In addition, the insulin-treated rats increase their body weight by enlarging the fat compartment (12). As it has been stated, this is not the case in the lithium-treated rats (29).

The effects of sulpiride and insulin on body weight and food intake were additive. These results suggest that these drugs are causing obesity through different mechanisms.

In summary, the results presented here suggest that in the female rat lithium might be increasing the body weight through a mechanism different from dopamine receptors blockade either in the pituitary or in the lateral hypothalamus, and hypoglycemia. In addition, as weight gain is an important side-effect of lithium and antipsychotic drugs in humans, and the effect of both drugs is additive, the combination of these drugs should be cautiously used when obesity is a therapeutically relevant side effect.

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REFERENCES

1. Banerji, T. K. Luteinizing hormone, follicle-stimulating hormone, prolactin and testosterone. In: Johnson, F. N., ed. Endocrine effects of lithium. Basel: Karger; 1988:51–62.

2. Baptista, T. Efecto del litio sobre el peso corporal de ratas. Resumenes de la 37a, Convención Anual de ASOVAC, Maracaibo, Venezuela, 1987:125.

3. Baptista, T.; Parada, M. A.; Hernández, L. Long-term administration of some antipsychotic drugs increases body weight and feeding in rats. Are D2 dopamine receptors involved? Pharmacol. Biochem. Behav. 27:399–405; 1987.
4. Baptista, T.; Hernández, L.; Hoebel, B. G. Systemic sulpiride increases dopamine metabolites in the lateral hypothalamus. Pharmacol. Biochem. Behav. 37:227–229; 1990.
5. Baptista, T.; Hernández, L.; Burguera, J. L.; Burguera, M.; Hoebel, B. G. Chronic lithium administration enhances serotonin release in the lateral hypothalamus but not in the hippocampus in rats: a microdialysis study. J. Neural Transm. 82:31–41; 1990.
6. Berggren, U. Effects of chronic lithium treatment on brain monoamine metabolism and amphetamine-induced locomotor stimulation in rats. J. Neural Transm. 64:239–250; 1985.
7. Bloom, F. E.; Baetge, G.; Deyo, S.; Ettenberg, A.; Koda, L.; Magistretti, P. J.; Shoemaker, W. J.; Staunton, D. A. Chemical and physiological aspects of the actions of lithium and antidepressant drugs. Neuropharmacology 22:359–365; 1983.
8. Cabral, M. A. Influence of the sex factor in weight gain caused by chronic use of lithium. Acta Psychiatr. Psicol. Am. Lat. 29:207–212; 1984.
9. Cox, V. C.; Kakolewsky, J. W.; Valenstein, E. S. Ventromedial hypothalamic lesions and changes in body weight and food consumption in male and female rats. J. Comp. Physiol. Psychol. 67:320–326; 1969.
10. Dempsey, G. M.; Dunner, D. L.; Fieve, R. R.; Farkas, T.; Wong, J. Treatment of excessive weight gain in patients taking lithium. Am. J. Psychiatry 133:1082–1084; 1976.
11. Fregly, M. A. A simple and accurate feeding device for rats. J. Appl. Physiol. 15:539; 1960.
12. Hausberger, F. X. Effect of dietary and endocrine factors on adipose tissue growth. In: Renold, A. E.; Cahill, G. F., eds. Handbook of physiology. Baltimore: The Williams and Wilkins Company; 1965: 519–528.
13. Han, P. W. Hypothalamic obesity in rats without hyperphagia. Trans. NY Acad. Sci. 3:229–243; 1967.
14. Kebabian, J. W.; Calme, D. B. Multiple receptors for dopamine. Nature 277:93–96; 1979.
15. Larue-Achagiotis, C.; Le Magnen, J. Effect of long-term insulin on body weight and food intake: intravenous versus intraperitoneal routes. Appetite 6:319–329; 1985.
16. Mellerup, E. T.; Thomsen, H. G.; Bjorum, N.; Rafaelsen, O. J. Lithium, weight gain, and serum insulin in manic-depressive patients. Acta Psychiatr. Scand. 48:332–336; 1972.
17. Mellerup, E. T.; Rafaelsen, O. J. Lithium and carbohydrate metabolism. In: Johnson, F. N., ed. Lithium: Research and therapy. New York: Academic Press; 1975:381–389.
18. Moore, B. J.; Gerardo-Gettens, B. A.; Stern, J. S. Hyperprolactinemia stimulates food intake in the female rat. Brain Res. Bull. 17: 563–569; 1986.
19. Myers, D. H.; West, T. E. T. Hormone systems. In: Johnson, F. N., ed. Depression and mania: Modern lithium therapy. Oxford: IRL Press Ltd.; 1987:220–225.
20. Opitz, K.; Schafer, G. The effect of lithium on food intake in rats. Int. Pharmacopsychiatry 11:197–205; 1976.
21. Parada, M. A.; Hernández, L.; Schwartz, D.; Hoebel, B. G. Hypothalamic infusion of amphetamine increases serotonin, dopamine and norepinephrine. Physiol. Behav. 44:607–610; 1988.
22. Parada, M. A.; Hernández, L.; Páez, X.; Baptista, T.; Parada, M.; Quijada, M. Mechanism of the sulpiride-induced obesity in rats. Pharmacol. Biochem. Behav. 2:45–49; 1989.
23. Plenge, P. K.; Mellerup, E. T.; Rafaelsen, O. J. Weight gain in lithium-treated rats. Int. Pharmacopsychiatry 8:234–238; 1973.
24. Schou, M.; Baastrup, P. C.; Grof, P.; Weis, P.; Angst, J. Pharmacological and clinical problems of lithium prophylaxis. Br. J. Psychiatry 116:615–619; 1970.
25. Sclafani, A. Animals models of obesity: classification and characterization. Int. J. Obes. 8:491–508; 1984.
26. Storlien, L. H.; Smythe, G. A. Body weight. In: Johnson, F. N., ed. Depression and mania: Modern lithium therapy. Oxford: IRL Press Ltd.; 1987:195–196.
27. Suva, J.; Musil, F. Lithium levels in guinea pigs serum, blood cells and brain. Activ. Nerv. Super. (Praha) 27:265–266; 1985.
28. Texeira, N. A.; Karniol, I. G. The influence of age and sex on weight variation in rats treated chronically with lithium chloride. Acta Pharmacol. Toxicol. 51:1–5; 1982.
29. Vendsborg, P. E. Weight gain and body composition in lithium treated rats. Acta Pharmacol. Toxicol. 46:373–381; 1980.
30. Walker, R. G.; Kincaid-Smith, P. Kidneys and the fluid regulatory system. In: Johnson, F. N., ed. Depression and mania: Modern lithium therapy. Oxford: IRL Press Ltd.; 1987:206–212.