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Effects of Chronic Lithium, Amitriptyline and Mianserin on Glucoregulation, Corticosterone and Energy Balance in the Rat

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STORLIEN, L H , F M HIGSON, R M. GLEESON, G. A SMYTHE AND D M. ATRENS *Effects of chronic lithium, amitriptyline and mianserin on glucoregulation, corticosterone and energy balance in the rat* PHARMACOL BIOCHEM BEHAV 22(1) 119–125, 1985 —Major negative side-effects reported for mood-stabilizing and antidepressant drugs in humans are excess weight gain and carbohydrate craving. The aim of the present study was to establish whether the rat could usefully be employed in investigation of these phenomena Three experiments investigated the effects of chronic lithium (40 mg/kg LiCl), amitriptyline (2 5 mg/kg), mianserin (2.5 mg/kg) and saline administration (15–20 days, one subcutaneous injection/day) on body weight, food intake and fluid intake. Water and food cubes were provided in all experiments Additionally available, as separate fluid sources, in Experiment 2 were 24% sucrose and 0 6% saccharin and in Experiment 3, 0 6% saccharin Blood was collected for plasma glucose and insulin determinations 20–24 hours after the final injections. Lithium administration resulted in a marked increase in weight gain but only if both sucrose and saccharin were available (Experiment 2). Saccharin intake was increased with lithium treatment as was total caloric intake with sucrose available Amitriptyline induced a sweetness craving; however, weight gain was somewhat depressed with just cubes available (Experiment 1) and only normalised by the additional availability of sucrose and saccharin (Experiment 2). With amitriptyline, total caloric intake was never different from controls. Weight gain was slightly suppressed and caloric intake slightly elevated by mianserin but importantly the two effects combined for a decrease in metabolic efficiency which was particularly exaggerated under the condition of carbohydrate availability (Experiment 2) Lithium and amitriptyline both produced hyperinsulinemia with normoglycemia whether or not the rate of weight gain was changed and whether or not intake was increased Corticosterone levels were elevated by all drug treatments in Experiment 1 However, additional availability of carbohydrate dramatically suppressed corticosterone levels to saline control levels in all drug-treated groups Further, carbohydrate availability in saline treated animals further reduced corticosterone levels to 50% of chow-fed saline controls The results demonstrate the usefulness of the rat for the study of the energy balance perturbations attendant upon the use of some mood-stabilizing and antidepressant drugs and focus on carbohydrates as a major contributing factor

Amitriptyline Body weight Corticosterone Food intake, lithium Mianserin Plasma glucose
Plasma insulin Saccharin Sucrose

CLINICAL literature suggests that some antidepressant and mood stabilising drugs produce excessive body weight gain and carbohydrate craving in humans as a side effect of their action. In particular, lithium, [3, 17, 24, 27, 34], amitriptyline [5, 11, 18, 19, 23] and mianserin [7, 25, 40] have been implicated. The recurrent suggestion has been that this undesirable side effect may be due to alterations in insulin/carbohydrate metabolism (see above references plus [12, 30, 37, 41]). However, most reports are anecdotal and often involve the description of a single case.

The general disarray of the clinical literature on the nature and mechanisms of obesity generating effects of antidepressants and mood stabilising drugs suggests the need for controlled laboratory experimentation. Unfortunately, the existing results with laboratory species, mainly rats and mice, are also contradictory. With lithium, weight increase [22, 26, 36, 38], weight loss [32] and no change [36,38] have been variously reported with differing drug dosages, and subject sex and age. The effects of lithium on insulin and glucose tolerance are also inconsistent with reports of increased [37] and decreased [23] tolerance. Amitriptyline does not appear to have been investigated in rats although chronic imipramine has been reported to lead to weight loss [13]. Mianserin treatment was reported to result in a small loss of weight in rats [8] but a small gain in mice treated with a lower dosage [6].

No studies appear to have investigated carbohydrate craving with administration of any of the antidepressant or mood stabilising drugs in animals.

The following is a report of the effects of chronic adminis-

tration of lithium, amitriptyline and mianserin, on body weight, food and fluid intakes, carbohydrate and sweetness craving and plasma insulin, glucose and corticosterone levels in male rats.

METHOD

A total of 85 male Sprague-Dawley rats (Castle Hill Breeding Farms, Sydney) were individually housed in wire-mesh cages in a controlled temperature environment (22±2°C) with a 12-12 light-dark cycle (lights on 0700–1900 hr) Allied Rat and Mouse Cubes (22 7% protein, 6 6% fat, 45.7% carbohydrate) and tap water were available ad lib. During the three week pre-testing period the rats were handled regularly to minimise stress

Drugs used were lithium chloride (40 mg/kg, Ajax Chemicals, Sydney), amitriptyline-HCl (2.5 mg/kg, a gift from Merck, Sharp and Dohme Aust Pty Ltd) and mianserin-HCl (2 5 mg/kg, a gift from Organon, Oss, Holland) All drugs were dissolved in distilled water and administered subcutaneously in volumes of 0.4 ml/kg. Pilot studies indicated that the chosen drug dosages were adequate for producing a pharmacological effect but low enough to minimise iatrogenic confounds

After 2 weeks habituation to individual caging all rats were weighed to the nearest gram between 1000 and 1200 hr on the first day of the experiment and then every third day until three pretreatment measures were obtained. The animals were then divided into treatment groups on a semi-random basis so that on the first injection day all groups had approximately equal mean body weights.

On every third day throughout the experiments the animals were weighed and food and fluid intakes were measured in the following manner. A weighed amount of food cubes in excess of need (approximately 55 grams) was placed in each cage and the cubes remaining were weighed again at the end of the 24 hour period. Spillage, collected on paper towels placed under the individual cages, was dried at room temperature, brushed from the towels and weighed The dry weight of spilled food was subtracted from the difference between the weight in and the weight out of the cubes to give a final food intake figure accurate to the nearest 0 1 grams

Fluid intake was assessed by weighing fluid bottles before and after the 24 hr period and converting the difference to ml consumed or, where graduated cylinders were provided, by simply reading the volume in and the volume out and recording the difference to the nearest ml Loss of fluid due to evaporation or licking-tube leakage was assessed in pilot studies and found to be negligible

Drug injections were administered every day for 15–20 days following baseline. In Experiment 1 eight rats were assigned to a saline (0.9% NaCl) treatment group and seven to each of the three drug treatments (total N=29, mean body weight=546 g) These rats had access to cubes and water throughout with measured quantities on test days

Seven rats were assigned to each of five groups in Experiment 2 (total N=35, mean body weight=511 g) The groups comprised two saline (saline choice and saline) and the three drug treatments All rats had access to cubes and water during baseline testing but from the first injection period the saline choice (Sc) and the drug treatment groups were provided with cubes, water, a 24% sucrose solution and a 0 6% saccharin solution (a gift from Boots Co., Australia) The saline group had only water (from three cylinders) and cubes available The positions of the three fluid containers on each cage were randomised both within and between groups

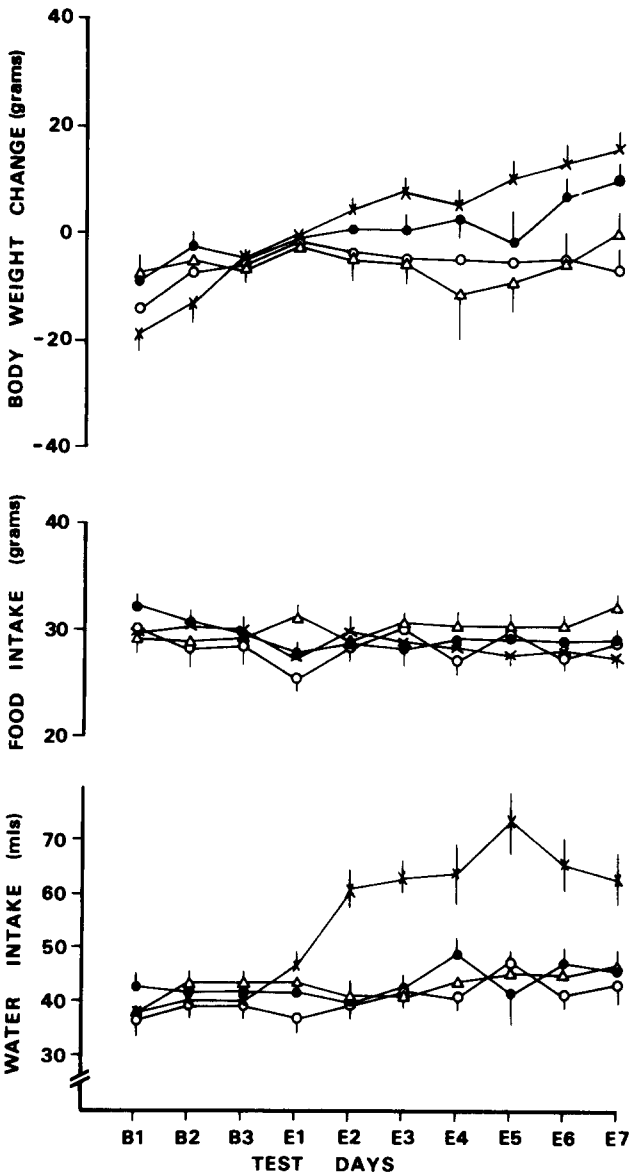

FIG 1 Upper Panel—Experiment 1 mean (±SEM) body weight changes from E1 for lithium (x—x, N=7), amitriptyline (○—○, N=7), mianserin (△—△, N=7), and saline (●—●, N=8) treated rats B1 to B3 and E1 to E7 refer to baseline and experimental 3-day test periods respectively Middle Panel—Experiment 1 mean (±SEM) 24-hr food cube intakes Lower Panel—Experiment 1 mean (±SEM) 24-hr water intakes

Experiment 3 was designed to further investigate the exaggerated saccharin intake displayed by the lithium and amitriptyline treated groups of Experiment 2 Seven rats were assigned to each of three treatments saline, lithium and amitriptyline (total N=21, mean body weight=426 g) Food cubes, water and 0 6% saccharin were provided throughout the experiment with measured quantities on test days and free access at other times

The rats were killed by decapitation 20–24 hours after their last injection and following 4 hr of food deprivation Trunk blood was collected in heparinised tubes and immediately centrifuged The plasma was removed and stored

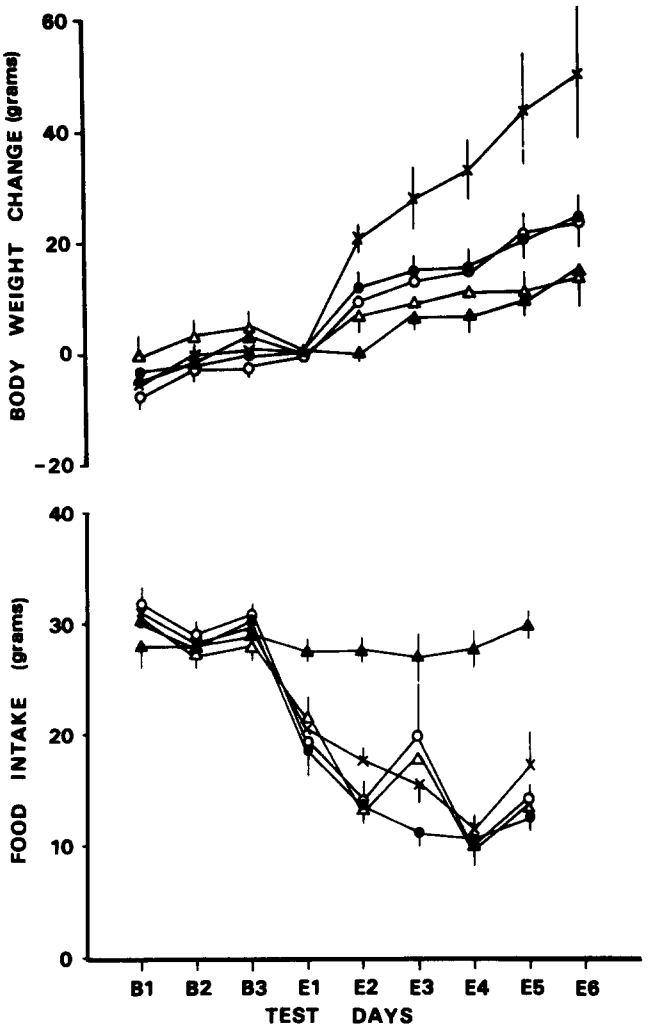

FIG 2 Upper Panel—Experiment 2 mean (±SEM) body weight changes from E1 for lithium (x—x), amitriptyline (○—○), mianserin (△—△), saline choice (●—●) and saline (▲—▲) groups (N=7/group) Lower Panel—Experiment 2 mean (±SEM) 24-hr food cube intakes

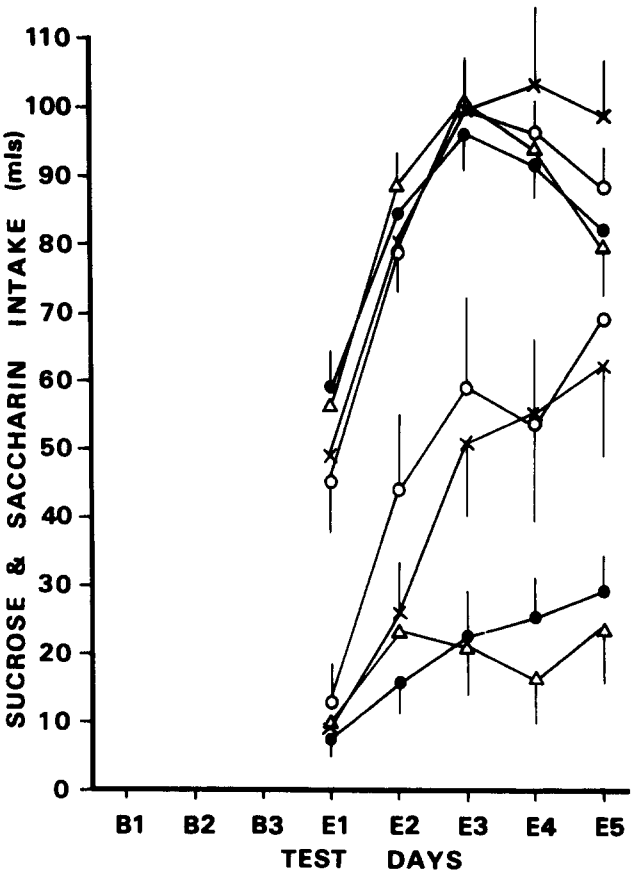

FIG 3 Experiment 2 mean (±SEM) 24-hr sucrose (upper four lines) and saccharin (lower 4 lines) intake for lithium (x—x), amitriptyline (○—○), mianserin (△—△) and saline choice (●—●) groups (N=7/group)

at −20°C for later analysis of glucose, insulin and corticosterone. Glucose was determined on a YSI 23A glucose analyser. Insulin was analysed by radioimmunoassay using rat insulin standard (Novo) and human I^{125} as tracer Corticosterone was also determined by radioimmunoassay as previously described [34]. Blood samples were taken only for the Experiments 1 and 2

All data were analysed with either ANOVA and Tukey's test or Student's *t*-test when appropriate

RESULTS

The major findings of these experiments can be summarised as follows. In Experiment 1 with cubes and water available no body weight increases were observed for any drug group (Fig. 1, top panel) and in fact the only difference was a weight decrease with amitriptyline ($t(13)=2\ 34$, $p<0.05$). Food intake was constant and equal for all groups throughout the experiment (Fig. 1, middle panel) as was water intake (Fig. 1, bottom panel), except for the lithium group which showed the expected hyperdipsia but not the polydipsia often reported for higher dosages [38,43].

In Experiment 2 sucrose and saccharin were additionally available and their availability induced marked effects in the drug treated groups. The lithium treated animals gained weight rapidly with respect to their appropriate saline controls (Fig. 2, top panel). The average gain for the lithium animals by the 15th day of drug treatment was 48.7 g compared to 23.7 g for the Sc group ($p<0.05$). The amitriptyline animals in this experiment had a body weight increase equal to that of the Sc group

Figure 2 (bottom panel) shows the intakes of food cubes. The cube intake declined significantly in all 4 groups given access to sucrose but did not differ between them. Figure 3 shows the sucrose and saccharin intakes of these 4 groups There was no significant difference between groups in sucrose intake but the calories taken as sucrose more than compensated for the reduced food cube calories and the mean daily total caloric intakes of the four choice groups are all significantly higher than that of the saline group. Importantly, lithium treated rats tended to have higher intakes of both food cubes and sucrose and their mean daily total caloric intake over the last three measurement periods was significantly higher than that of the Sc group (145 2±8.42 vs. 123.9±2.23 kcal, $p<0.05$) The mean daily total caloric in-

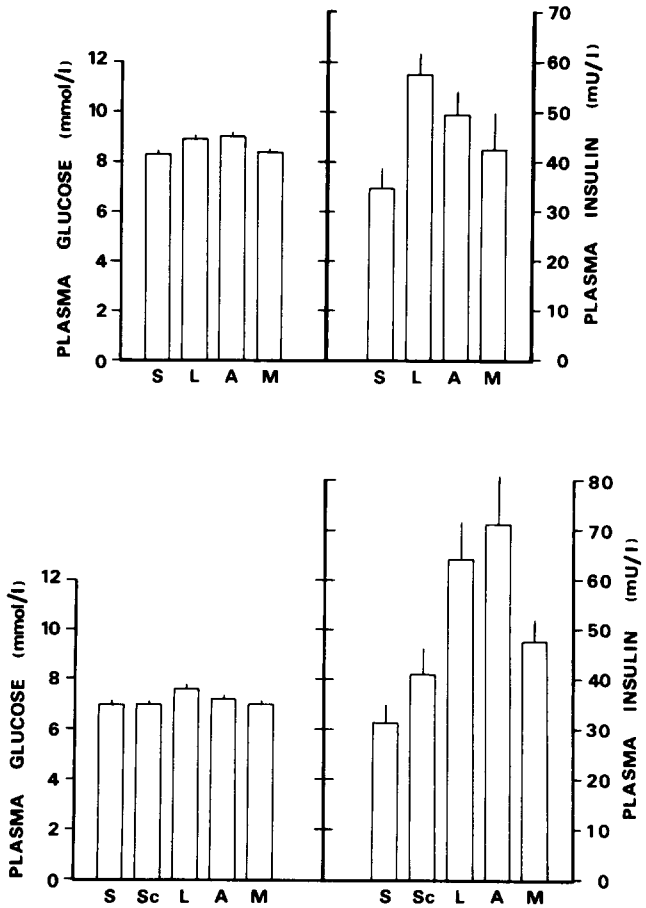

FIG 4 Upper Panel—Experiment 1 mean (±SEM) plasma glucose and insulin levels for saline (S, N=7), lithium (L, N=7), amitriptyline (A, N=6) and mianserin (M, N=6) treated rats Lower Panel—Experiment 2 mean (±SEM) plasma glucose and insulin levels for saline (S), saline choice (Sc) lithium (L), amitriptyline (A) and mianserin (M) treated groups (N=7/group)

takes of the four choice groups were all significantly higher than that of the saline group

Also of prime interest was the more than doubling of intake of saccharin by both lithium and amitriptyline-treated groups compared to groups treated with mianserin or saline (Fig. 3).

The mianserin treated rats of Experiment 2 had a significantly higher total caloric intake than the saline group on a mean daily basis over the injection period (133 9±5 21 vs 93 8±4 77 kcal $p<0$ 001) but showed identical body weight gain (13 0±5.35 vs 14 6±3 44 grams) Looked at another way the mianserin animals were eating more than the Sc animals on the same diet (133 9±5 21 vs 123 9±2 40 kcal) but gaining less weight (13 0±5 35 vs 23 7±4 13 grams) This demonstrates a significant loss of efficiency in the utilisation of available nutrients in the mianserin treated rats

The plasma insulin, glucose and corticosterone levels 20–24 hr following the final injection were determined for Experiments 1 and 2

The insulin and glucose data are presented in Fig 4 In both experiments glucose values did not differ between any of the groups. However, insulin levels differed (Experiment

TABLE 1

PLASMA CORTICOSTERONE LEVELS (nmoles/l) 20–24 HOURS FOLLOWING THE FINAL INJECTION FOR THE GROUPS OF EXPERIMENTS 1 AND 2

Group	Experiment 1 (mean ± SEM)	Experiment 2 (mean ± SEM)
Saline	409 ± 89 6	294 ± 55 5[c]
Saline choice	—	145 ± 38 0
Lithium	928 ± 56 6[a]	378 ± 49 6[c]
Amitriptyline	811 ± 94 3[a]	224 ± 84 1
Mianserin	751 ± 77 1[b]	288 ± 60 7

[a]Different from Saline, $p<0$ 01
[b]Different from Saline, $p<0$ 05
[c]Different from Saline choice $p<0$ 05

1 $F(3,22)=3$ 35, $p<0$ 05, Experiment 2 $F(4,30)=7$ 77, $p<0$ 001) being increased for the lithium groups compared to the appropriate control group in each experiment ($p<0$ 05) Amitriptyline treatment, compared again to the appropriate saline control treatments, also induced a tendency to hyperinsulinemia in Experiment 1 ($p=0$ 08) and highly significant hyperinsulinemia in Experiment 2 ($p<0$ 01) These increased insulin levels were manifested whether or not the drug treated rats were gaining more weight than controls and whether or not their intakes were higher Mianserin did not evoke any insulin level changes in either experiment

The corticosterone data are presented in Table 1 In the first experiment all drug treatments resulted in higher corticosterone levels compared to the saline control group Interestingly in the saline treated groups of Experiment 2 access to carbohydrate significantly reduced corticosterone levels The lithium-treated animals still had corticosterone levels higher than their appropriate saline controls (Sc) but none of the drug treated groups in this experiment had corticosterone levels above that of the saline treated, chow fed group

In the third experiment with cubes, saccharin and water available, the body weight and food intake results were very similar to those of Experiment 1 There were no differences in intakes and only a slight loss of weight was seen again in the amitriptyline group (Fig 5) The non-availability of sucrose in this experiment (compared to Experiment 2) resulted in an increased saccharin intake in saline treated rats but a decrease in both lithium and amitriptyline groups (contrast Fig 3 with Fig 5, lower panel) However, saccharin intake is still somewhat higher in the drug-treated groups

DISCUSSION

From the present results use of the rat will prove productive in the study of many of the energy balance perturbations of mood-stabilising and antidepressant drugs in man

The lithium results are clear. Lithium treatment results in hyperinsulinemia and an increased weight gain and intake with sucrose and saccharin available. This gain was variable but it reached values in excess of 90 g in just 15 days for two rats This represents approximately an 18% increase in body weight for these rats and three of the remaining five rats were showing body weight gains rapidly diverging from control values by the end of the experiment Interestingly, insulin correlates (Spearman rank order) highly with weight gain for

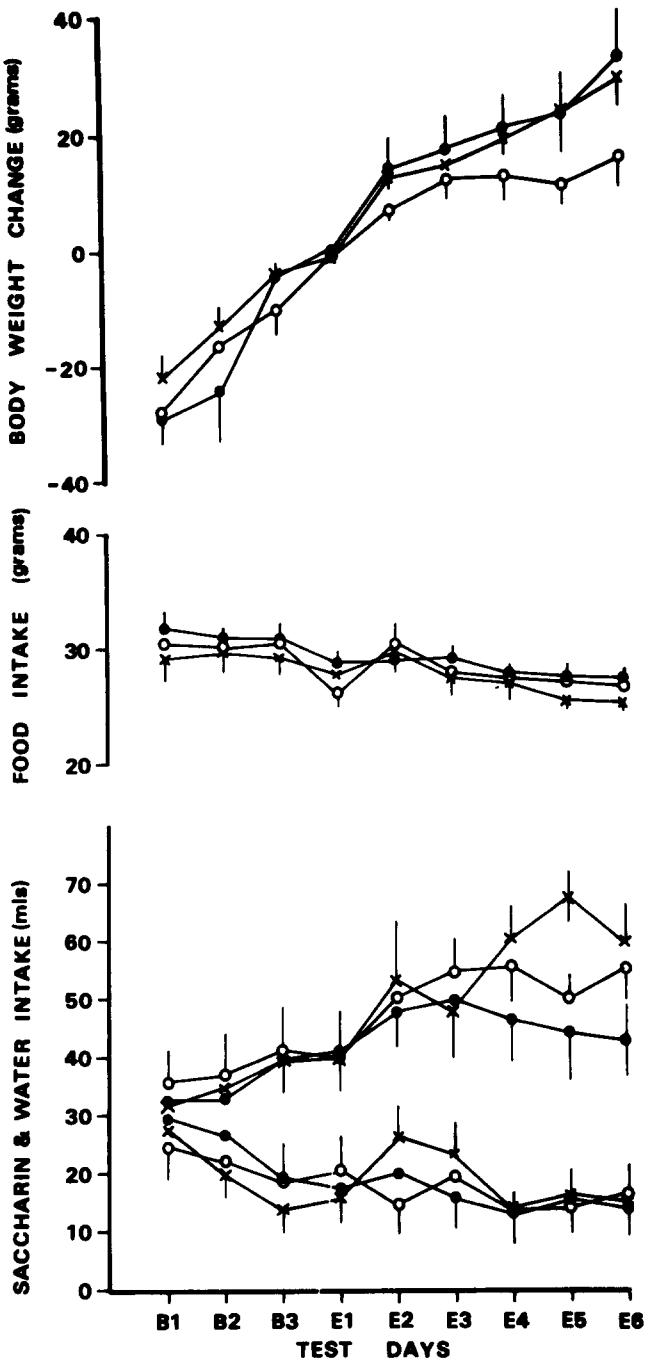

FIG 5 Upper Panel—Experiment 3 mean (±SEM) body weight changes from E1 for lithium (x—x), amitriptyline (O—O) and saline (●—●) treated groups (N=7/group) Lower Panel—Experiment 3 mean (±SEM) 24-hr saccharin (upper 3 lines) and water (lower 3 lines) intakes

the lithium group ($r=0.92$, $t=5.21$, $p<0.01$) which is not true for the other groups (r values from 0 15 to 0.26, all $p>0.20$). It is tempting to compare the large variability in weight gain with the varied response to lithium in humans Previously, three studies [36, 37, 43] had shown small increases in weight gain with female rats maintained only on cubes and water, an effect not seen with male rats in the present experiment. It would be interesting if the female was more susceptible to the obesity-generating influences of the carbohydrate-lithium interaction in rats.

A number of investigators have noted a high fluid intake with lithium treatment in humans (as seen in Experiment 1) and have suggested that weight gain could result from that extra fluid intake if it were in the form of high calorie soft drinks or alcohol (see [9,31]). Our results support such a contention

The increased insulin levels with normal blood glucose in lithium-treated rats also may be interesting with respect to the well-known association between manic-depressive disorders and diabetes mellitus (see [28]) These authors point out the life time risk for major affective disorders is 2–3% and for idiopathic diabetes mellitus less than 2%. Thus the observed 10% diabetes mellitus in manic-depressive patients is far in excess of chance With acute injections of lithium we have observed marked hyperglycemia (unpublished results). It may be that the hyperinsulinemia seen in the present experiments reflects a drive to counter hyperglycemia. In mildly diabetic animals, or in those predisposed to diabetes, frank diabetes may be revealed by lithium administration.

As with lithium, amitriptyline induced a hyperinsulinemia which was particularly pronounced under the condition of additional carbohydrate availability It is interesting that insulin levels correlate significantly with sucrose intake ($r=0.63$, $p<0.025$) for the amitriptyline and lithium groups but not for the saline group ($r=-0$ 22, N.S.) Insulin injections in normal animals result in increased intake and weight gain, the intake being almost exclusively, given the choice, in the form of increased carbohydrate [10]. In Experiment 2 one might have expected not only a significant correlation between insulin and sucrose with lithium and amitriptyline but also a significant increase in sucrose consumption However, the rats of the present experiment consumed such a high proportion of their total intake as carbohydrate that less than seven percent was taken as protein and less than two percent as fat This relative insufficiency of essential amino acids and free fatty acids may have obscured the carbohydrate craving. It is tempting to relate this suggestion to the high levels of saccharin intake seen in both lithium and amitriptyline groups of Experiment 2 Experiment 3 was designed specifically to examine this effect and showed it to be dependent upon an interaction with sucrose. It may be then that the high saccharin intakes of Experiment 2 represented an attempt on the part of the lithium and amitriptyline treated rats to satisfy a carbohydrate craving while avoiding depletion of essential amino acids and free fatty acids by consuming a sweet source which is at least gustatorially similar to sucrose.

On the basis of our results mianserin must be seen as potentially the drug of choice where energy balance perturbations are to be avoided in the pharmacological treatment of depression. Mianserin treatment, when compared to the appropriate saline control treatments, had no significant effect on glucose, insulin, nutrient intake or body weight. Indeed the only effect on these measures seen with mianserin administration was a loss of metabolic efficiency which was most clearly seen in Experiment 2

The changes in corticosterone levels with carbohydrate availability are marked In saline-treated animals, this change was a significant decline to 49% of the chow fed group. In the drug-treated groups the levels were reduced from double control values in the first experiment to within

the control range in the second (see Table 1) If corticosterone levels are seen as an index of physiological stress, it could be argued that carbohydrate intake is a way of ameliorating stress, as indeed has Wurtman [42] Carbohydrate craving is then an adaptive reaction to chronic stress

The brain mechanisms by which various mood-stabilising drugs might act are unclear We have recently shown that the activation of central NE neuronal activity stimulates the release of pituitary ACTH and adrenal corticosterone in the rat and that there is a highly significant correlation between medial basal hypothalamic NE activity and plasma corticosterone [34] The association of reduced corticosterone and presumed reduced NE neuronal activity with increased carbohydrate intake is interesting from two viewpoints First it is consistent with a negative feedback role for glucose on central NE activity [35] Second, an inverse relationship has been demonstrated between hypothalamic NE neuronal activity and 5-HT neuronal activity in normal and stressed rats [34] and, in the present case, this relationship would result in a facilitation of 5-HT activity, especially in the saline choice group Such a facilitation of 5-HT activity would be consistent with the findings of Wurtman and coworkers [4,42] that central 5-HT activity is enhanced after carbohydrate intake The added effects of the drugs complicate the issue since their effect of increasing corticosterone may well imply a relative reduction in net 5-HT activity which is frequently associated with hyperphagia [42] Certainly this is in line with the reported effects of amitriptyline and mianserin which indicate an antagonism of central 5-HT by these drugs [2, 14, 15, 21, 29] However, it must be kept in mind that mianserin, amitriptyline and lithium have a multiplicity of effects on central monoamines (see [1, 16, 20, 32, 33])

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