Effect of Serotonin Reuptake Inhibitor on Syndrome Development in Obese Hyperglycemic Mice (Umeå *ob/ob*)

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These experiments tested the effect of 10 to 30 mg, citalopram/kg body weight on food intake, weight increase, and blood glucose levels in young obese hyperglycemic mice (Umeå *ob/ob*). A leptin defect in *ob/ob* mice results in hyperphagia, hyperglycemia, and increased body weight compared with normal mice. Citalopram had no effect on weight increase in *ob/ob* mice aged 3 to 10 weeks, when the weight increase is most rapid. Citalopram reduced the weight increase at the age 10 to 19 weeks. Food intake reaches a maximum at age 7 to 10 weeks and then decreases. The reduction was more rapid in citalopram-treated mice. The weight of feces paralleled the food intake. Citalopram treatment had no effect on serum insulin levels in 15-week-old mice. Blood sugar values in fed mice reached a peak at age 7 weeks (21.7 ± 1.7 mmol/L in controls and 22.3 ± 1 mmol/L in citalopram-treated mice). After that, blood sugar values decreased. The decrease was more pronounced in citalopram-treated mice ($P < .01$ compared with controls). Blood glucose levels were lower at ages 12 to 15 weeks in female *ob/ob* control mice (13.6 ± 2.5 mmol/L *v* 19.0 ± 0.6 mmol/L in male control mice; $P < .05$). The effect of citalopram was the same in male and female mice. There was a close correlation between accumulated food intake and blood glucose values in individual animals. At age 3 to 10 weeks, *ob/ob* mice have a high β-cell proliferation rate, and they have large islets of Langerhans. This was not affected by citalopram treatment. Our findings show that the serotonergic system plays a role as a regulator of food intake over shorter periods, and this is also true in the absence of leptin.

EATING BEHAVIOR, appetite, satiety, and thus control of body weight are under influenced by the central nervous system serotonergic system. Drugs that enhance serotonergic transmission selectively suppress carbohydrate intake in rats[1] and humans[2] that are given dietary choices.

Serotonin (5-HT) may play a key role in determining emotional state in higher animals, especially humans, and selective serotonin-reuptake inhibitors (SSRIs), including citalopram, represent an important advance in the pharmacotherapy of several psychiatric disorders. SSRIs are used for the treatment of anorexia nervosa and bulimia nervosa, which are eating disorders characterized by disturbances in serotonergic pathways.[3] SSRIs can be useful tools in attempts to reduce body weight in obese patients,[4] but in some cases they also induce weight gain.[5] Citalopram is the most serotonin-selective agent of its class, and its clinical efficacy and tolerability are similar to those of other SSRIs such as fluoxetin and fluvoxamine.[6] More than 20 million patients have been treated with citalopram, and the drug represents a choice for first-line therapy for major depression.[6]

Leptin provides another feedback signal regulating hypothalamic mechanisms that control food intake and metabolic rate.[7,8] Obese hyperglycemic mice are a model for obesity in many studies. The *ob/ob* syndrome is caused by a single mutation in the ob gene, which is normally expressed in adipose tissue with the secreted circulating gene product leptin.[9] The *ob/ob* syndrome is characterized by severe obesity, hyperphagia, hyperinsulinemia, and hyperglycemia.[10,11] A marked islet hyperplasia is also observed and is believed to be secondary to an increased demand for insulin.[12] Mice with the *ob/ob* syndrome are infertile due to the lack of leptin,[13] and breeding must be done using heterozygous lean mice.

The anorectic serotonin uptake inhibitor fenfluramine reduces body weight in adult *ob/ob* mice.[14] Central administration of serotonin also reduces food intake, but the effect is less pronounced in *ob/ob* mice than in lean controls.[15] To further investigate the development of the *ob/ob* syndrome and the effects of the serotonergic system in the control of food intake and weight regulation, we treated obese hyperglycemic mice with the SSRI citalopram. The weight reduction observed is probably caused by reduced food intake rather than increased metabolic rate. The serotonergic system can also regulate eating behavior in leptin-deficient animals.

MATERIALS AND METHODS

Animals and Diets

Male and female *ob/ob* mice from the Umeå strain (Umeå *ob/ob*) were used. Young mice (21 to 23 days old) weighed 16.0 to 29.2 g at the beginning of treatment and were housed in pairs in macrolon cages. They were kept at 22 ± 1°C under a 12/12-hour light/dark cycle with lights on from 6 AM to 6 PM. Their food (Lactamine R3 "rat and mouse breeding food" pellets; Lactamine AB, Vadstena, Sweden) was composed of 21% protein, 5% fat, and 51.5% nitrogen free extracts. Energy content of pellets was 12.60 kJ/g. Food and water were given ad libitum. Effects of citalopram on weight reduction were also tested in 10-week-old *ob/ob* mice.

The Cage

To measure food intake and facilitate collection of feces, animal cages had a punched plate, with 4-mm holes through which food spillage, feces, and urine could be collected. This plate was placed approximately 3 cm above the bottom of the cage. The bottom was

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covered with absorbent tissue (sanitary towels) to keep spilled food and feces dry. Food spillage and feces were isolated and collected once a week with a strainer. After separation, food spillage and feces were dried in air and weighed.

Study Design

Citalopram (kindly provided by H. Lundbeck A/S, Copenhagen, Denmark) was dissolved in saline (0.1 mL/mouse) and administered intraperitoneally every day at 5:30 to 6 PM. Beginning at 3 weeks of age, some animals were given 20 mg/kg daily during the initial 4 weeks of citalopram treatment. Between the 4th and 8th weeks the dose was 25 mg/kg, and during the last 4 weeks the dose was increased to 30 mg/kg. Other animals were injected from 10 weeks of age with 0, 10, or 20 mg/kg citalopram daily for a period of 9 weeks.

At the onset of study, the animals were weighed and earmarked for identification. For obese mice, this was done either between days 21 and 23 or at 10 weeks of age. Blood samples for glucose measurement were obtained from the tail vein once a week in the morning. One male and one female mouse were housed in each cage.

Two hours before animals were killed, they received an intraperitoneal injection of 5-bromo-2′-deoxyuridine, 120 mg/kg body weight (Radiochemical Centre, Amersham, Bucks, England). Pancreas was removed for immunohistochemistry, and serum was taken for analysis of glucose and insulin.

Measurements of Labeling Index and Islet Volume

The pancreases were fixed in 10% formaldehyde, dehydrated, embedded in paraffin, and cut transversely in slices of 7 μm with a microtome. Every 30th slice was placed on a microscope slide. Unless otherwise stated, tris buffer (60.6 g tris, 79.0 g NaCl, and 10 L H_2O, adjusted with 1.0 mol/L HCl to pH 7.6) was used for incubation and rinsing of slides. Tris was from Boehringer Mannheim, Mannheim, Germany. After removal of paraffin, the slides were incubated for 10 minutes with 30% H_2O_2 to reduce endogenous peroxidase activity. The slides were rinsed and incubated with 10 mg/mL bovine serum albumin to reduce background staining. The slides were then incubated overnight at room temperature in buffer containing monoclonal anti–5-bromo-2′-deoxyuridine antibody (Amersham, England), diluted 150 μL/mL. After this, the slides were rinsed and incubated for 30 minutes with anti-mouse immunoglobulin G antibody diluted 1:25, supplemented with 15% normal rabbit serum. After rinsing, the slides were incubated for 30 minutes with alkaline phosphatase anti–alkaline phosphatase complex diluted 1:50. Alkaline phosphatase activity was revealed by incubating for 30 minutes in 5-bromo-chloro-3-indolyl phosphate and nitro-blue tetrazolium, supplemented with levamisole diluted 1:25. Chemicals for immunohistochemistry were obtained from DAKO, Denmark. After rinsing in distilled H_2O, the slides were counterstained for 10 minutes with calcium red (nuclear fast red). Finally, the slides were dehydrated and mounted. Using this technique, labeled nuclei are stained dark blue, and nonlabeled nuclei are stained pink.

Slides were coded and examined under a light microscope using an oil-immersion lens with 1,000× magnification. At least 500 islet cells were counted per pancreas (in most cases > 1,000 cells).

Calculation of Islet Volume

The pancreases from saline-treated (n = 6) and citalopram-treated (n = 6) mice were used for comparisons. Sections were analyzed on a light microscope linked to a digitizing table connected to a computer-aided image analysis device (MOP-Videoplan; Kontron Bildanalyse, Eching/Munich, Germany), and islet volume was calculated.[16]

Blood Glucose and Serum Insulin Analysis

Blood samples were obtained from the tail vein at 1 to 2 PM. The last injection had been given at 5 to 6 PM the previous day. Ten microliters of blood were mixed with 1.600 μL of 1 mmol/L ethylenediamine tetraacetic acid (EDTA) adjusted to pH 7.4 by KOH. These samples were later assayed for glucose content by a single-step assay using the luciferin/luciferase system and a liquid scintillation spectrometer.[17] Luciferin and luciferase were obtained from BioThema, Stockholm, Sweden. Serum insulin was assayed by radioimunoassay using crystalline mouse insulin as standard. Free and antibody-bound insulin was separated by precipitation with ethanol. ^{125}I-labeled insulin was supplied by Eurodiagnostica, Malmö, Sweden.

RESULTS

The weight increase of obese hyperglycemic mice (Umeå *ob/ob*) from 3 to 15 weeks of age is shown in Fig 1. Citalopram treatment had no effect during the first weeks, when the weight increase was most rapid. However, during the last weeks of treatment, the citalopram-treated group were slightly lighter than control animals (Fig 1). The citalopram dose was increased every 4th week, as indicated in the Fig 1. Figure 2 shows that it was only during the last 3 weeks that citalopram-treated mice gained less weight than controls.

When the citalopram treatment started at 10 weeks of age and was continued for 9 weeks, no effect on weight gain was observed with 10 mg/kg citalopram (Fig 3). With daily injections of 20 mg/kg citalopram, however, the initial decrease in weight was more pronounced and the weight gain was slower,

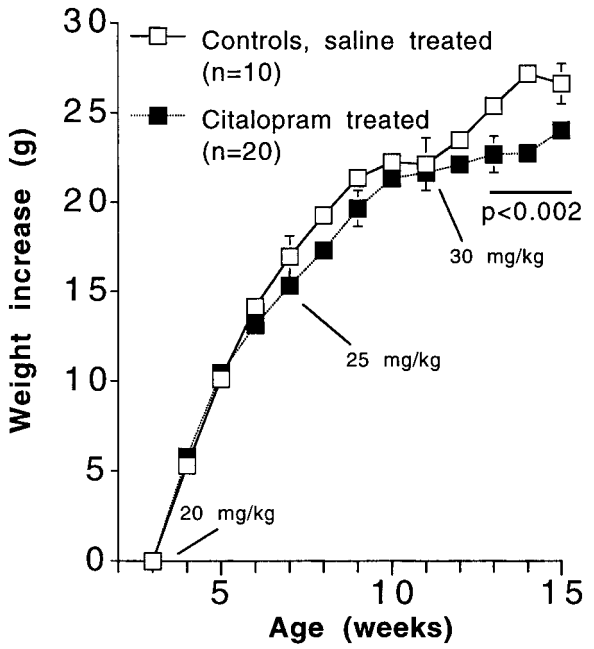

Fig 1. Weight increase in citalopram treated obese mice. Citalopram, 20 to 30 mg/kg, was administered intraperitoneally daily from 3 to 15 weeks of age. Data are presented as means ± SEM (bars) for the weight increase during the observation period. The citalopram dose was adjusted at 7 and 11 weeks, as indicated here. Control mice received saline. Statistical analysis over the period indicated by a bar was done using ANOVA and Student's *t* test for independent samples.

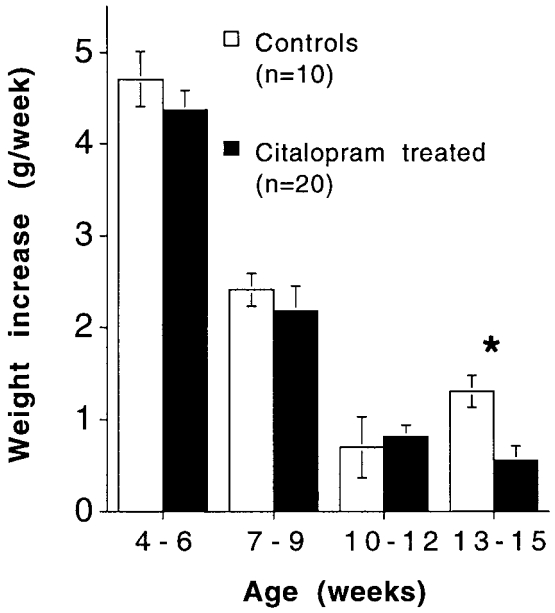

Fig 2. Weight change in citalopram-treated obese mice. Citalopram, 20 to 30 mg/kg, was administered intraperitoneally daily from 3 to 15 weeks of age. Data are presented as means ± SEM (bars) for the weight change during the indicated periods. * *P* < .002 comparing over the period of 13 to 15 weeks.

resulting in a significant weight gain difference at weeks 12 to 19 (Fig 3). This is a lower dose than that given at this age in the experiments presented in Fig 1, suggesting that the response to citalopram is dependent not only on the dose but also on the duration of treatment and the age of the animals. *Ob/ob* mice are sensitive to handling, and there was an initial reduction in weight in all groups, including saline-treated controls (Fig 3). Control mice weighed 18.9 ± 0.9 g (n = 10) at 3 weeks of age. This increased to 46.0 ± 1.7 g at 15 weeks. Corresponding values were 20.3 ± 0.7 g (n = 20) and 44.5 ± 1.1 g in citalopram-treated mice. In the experiment in which citalopram treatment was started in 10-week-old mice, the weight at onset was 48.6 ± 1.2 g (n = 6) in the control group and 48.1 ± 1.0 g (n = 6) in mice treated with 20 mg/kg citalopram. The weight increase during weeks 12 through 19 was 5.9 ± 1.0 g in controls and 3.2 ± 0.8 g in mice receiving 20 mg/kg citalopram ($P < .069$).

Food intake in *ob/ob* mice treated from 3 to 15 weeks of age is shown in Fig 4. There was an increase in food intake between 4 and 7 weeks of age from 70.2 ± 3.4 g/cage (with 2 animals) to 91.3 ± 4.1 g/cage in control animals (ie, 21.1 ± 2.7 g/cage) and from 77.0 ± 1.4 g/cage to 87.1 ± 1.8 g/cage in citalopram-treated mice (10.2 ± 1.9 g/cage; $P < .01$ comparing 21.1 with 10.2). The difference between 70.2 and 77.0 is statistically significant ($P < .05$), suggesting an initial increase of food intake in treated animals. Food intake reaches a maximum at 7 to 10 weeks and decreases slowly after that. The reduction was 21.2 ± 4.6 g/cage in citalopram-treated mice and 7.6 ± 2.3 g/cage in controls ($P < .05$). This is the age at which the weight increase is smaller in citalopram-treated mice (see Fig 1). The weight of feces paralleled food intake, with reduced amounts observed in the test group during the last weeks of study (Fig 5). Serum insulin levels were 62 ± 11 ng/mL (n = 8) in 15-week-old control animals and 57 ± 6 ng/mL (n = 19) in animals receiving citalopram. Food intake was measured in adult lean animals that had already produced one litter. Average food intake was 49.9 ± 4.0 g/cage with two animals (n = 3) and changed little during an observation period of 8 weeks.

Blood glucose values are presented in Fig 6. There was an increase in young animals from 9.7 ± 1.2 to 21.1 ± 1.7 mmol/L (n = 10) in controls and from 11.7 ± 1.0 to 22.3 ± 1 mmol/L (n = 20) in citalopram-treated mice at 7 weeks of age. The increase during the first week was more rapid in citalopram-treated mice, reaching 19.8 ± 1.4 mmol/L ($P < .01$ compared with 15.0 ± 1.2 mmol/L in controls). Blood glucose levels then decreased from 21.1 mmol/L to 16.8 ± 2.1 mmol/L at 15 weeks in controls and from 22.3 mmol/L to 13 ± 1.1 mmol/L in citalopram-treated mice ($P < .01$ for both groups). The decrease was larger in citalopram-treated mice ($P < .01$ *v* controls). There was a close correlation between food intake and blood glucose level in both controls and citalopram-treated animals (Fig 7*B*), with a correlation coefficient of 0.85 ($P < .0001$) for all animals. Figure 7*A* shows that citalopram had no effect on feed efficiency in these animals. Blood glucose/serum

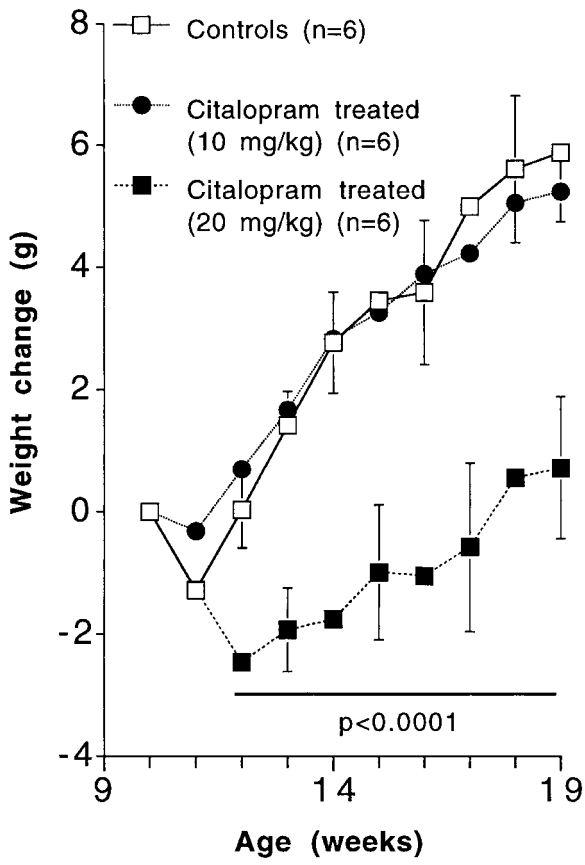

Fig 3. Weight increase in mice treated with daily injections of citalopram from 10 to 19 weeks of age. Control mice received saline. Data are presented as means ± SEM (bars). *P* < .0001 comparing over the period indicated by a *bar.*

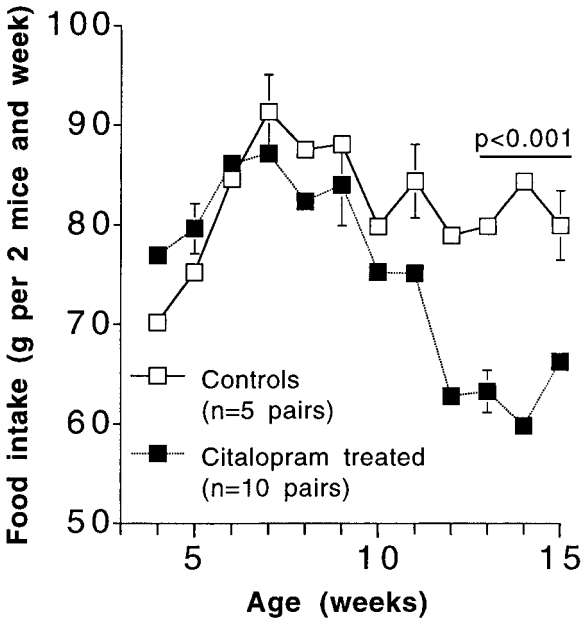

Fig 4. Food intake in citalopram-treated mice. Citalopram, 20 to 30 mg/kg, was administered daily from 3 to 15 weeks of age. Mice were housed in pairs, and food consumption was measured at the end of each week. Data are presented as means ± SEM (bars). Statistical analysis was done using Student's *t* test for independent samples. *P* < .001 comparing over the period indicated by a *bar*.

insulin ratios at age 15 weeks were 0.36 ± 0.07 mmol glucose/μg insulin (n = 8) in controls and 0.28 ± 0.04 mmol/μg (n = 18) in citalopram-treated mice (not significant).

Blood glucose values were the same in male and female control mice aged 3 to 12 weeks, but female mice had lower blood glucose levels at 12 to 15 weeks (13.6 ± 2.5 mmol/L *v* 19.0 ± 0.6 mmol/L in males; $P < .025$, n = 5). The decrease in blood glucose levels in citalopram-treated mice was the same in males and females. Body weight was lower in females at all ages and in both citalopram-treated and control mice, reaching 43.9 ± 2.4 g (n = 5) in 15-week-old female controls and 48.5 ± 2.1 g (n = 5) in male controls ($P < .001$ over the entire age range in control mice using Student's *t* test for paired data). There was no difference in weight gain between citalopram-treated males and females.

Islet cell proliferation was tested in 15-week-old mice at the end of the citalopram treatment period, and islet volume was calculated. In saline-treated *ob/ob* mice, the bromodeoxyuridine labeling index was 0.5% ± 0.1% (n = 6). The corresponding figure in citalopram-treated mice was 0.4 ± 0.1% (n = 6). The islet volume was 1.31 ± 1.4 mm^3 in saline-treated mice and 1.48 ± 1.44 mm^3 in citalopram-treated mice. The large variation in islet size within groups is caused by some animals in both groups that had much larger islets than the majority.

DISCUSSION

Serotonin has been suggested to have a central role in the control of eating behavior and regulation of body weight.[18] The neuropharmacology of serotonin is presented by Cooper et al.[19] Only approximately 1% to 2% of the total serotonin content is found in the brain. Because serotonin cannot readily pass the blood-brain barrier, the serotonergic neurons in the brain must synthesize the transmitter from the dietary amino acid tryptophan. Tryptophan is converted to 5-hydroxytryptophan (5-HTP) by tryptophan hydroxylase and subsequently to serotonin by aromatic L–amino acid decarboxylase. The rate-limiting step for serotonin biosynthesis is the activity of brain tryptophan hydroxylase, but the availability of tryptophan in brain is also important. Carbohydrate meals, by increasing the plasma Trp/LNAA ratio (a phenomenon mediated by insulin), increase brain tryptophan uptake and, consequently, serotonin release.[20] Serotonin then reduces carbohydrate intake relative to that of protein in subsequent meals.[21]

We find that citalopram treatment reduces weight gain in obese-hyperglycemic mice (Umeå *ob/ob*). This effect was observed after prolonged treatment and was accompanied by reduced food intake and feces production. In mice treated from the age of weaning (3 weeks old), the citalopram dose was increased stepwise to enhance the possibility of observing an effect within the observation period. This stepwise increase is in line with the clinical usage of citalopram, in which the dose often must be individually adjusted to give desired effect. The highest dose (30 mg/kg per day) was given from 11 weeks of age, and this was the period during which an effect on weight gain was observed. To be able to distinguish between effects of prolonged treatment and dose dependence, we exposed mice to lower doses of citalopram from age 10 weeks. These experiments showed that lower doses of citalopram can also affect weight increases at this age.

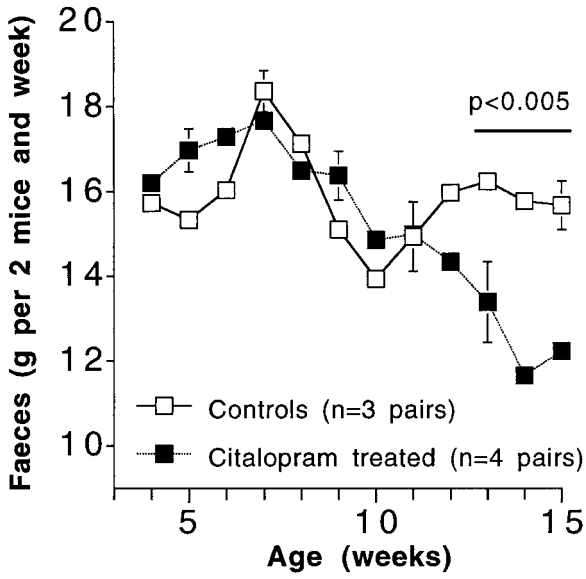

Fig 5. Feces production in citalopram-treated mice. Citalopram, 20 to 30 mg/kg, was administered daily from 3 to 15 weeks of age. Mice were housed in pairs and the amount of feces (dry weight) was measured at the end of each week. Data are presented as means ± SEM (bars). Statistical analysis was done using Student's *t* test for independent samples. *P* < 0.005 comparing over the period indicated by a *bar*.

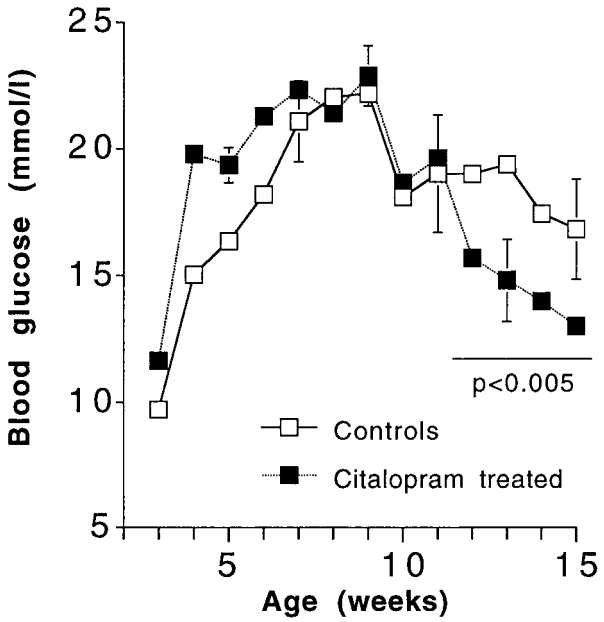

Fig 6. Effects of citalopram on blood sugar levels in young Umeå *ob/ob* mice. Citalopram, 20 to 30 mg/kg, was administered intraperitoneally daily from 3 to 15 weeks of age. Blood samples were obtained once a week from the tails of fed animals at 1 to 2 PM. The last injection was given at 5 to 6 PM the previous day. Data are presented as means ± SEM (bars). There was a significant difference in blood glucose at 12 to 15 weeks ($P < .005$ using ANOVA).

Weight gain in *ob/ob* mice is most rapid in young animals.[22] Westman[23] found that blood glucose levels were decreased after 3 months. We show here that food intake, weight gain, and blood glucose levels all show an age dependence in young, obese hyperglycemic mice (Umeå *ob/ob*) with a tendency to level off at age 7 to 10 weeks. *Ob/ob* mice have increased brain serotonin levels at 4 weeks of age compared with lean mice, but brain serotonin levels are reduced at 8 weeks.[24] Food intake was higher in *ob/ob* mice throughout this period compared with adult lean animals. This indicates that there is a balance between increased food intake attributable to a leptin deficiency and reduced food intake because of increased brain serotonin levels during the first weeks. Soon after weaning, leptin deficiency and reduced serotonin levels act in concert to increase food intake. We show here that this can be partly corrected for by citalopram treatment. Therefore, the serotonergic system probably plays a role as a regulator of food intake over shorter periods, also in the absence of leptin. A dissociation of leptin and serotonin in the regulation of feeding has also been demonstrated in mice with a mutated serotonin 5-HT_{2C}–receptor gene, giving rise to hyperphagia and diabetes type 2.[25] The serotonergic system for control of food intake may play a larger role at an age when the rate of weight increase becomes slower. Part of the effect of leptin deficiency in *ob/ob* mice may be to down regulate this serotonergic system.

Leptin decreases body fat content by reducing food intake, but increased energy expenditure is also an important effect.[26] Leptin increases energy consumption in muscle while reducing energy storage as fat. The increased energy expenditure is already seen in neonatal mice.[27] We find that feed efficiency in terms of weight increase in relation to food intake is the same in control and citalopram-treated mice. This suggests that citalopram reduced food intake but had little effect on metabolic efficiency. There was a strong overall correlation between blood glucose values and food intake. There was also a (weaker) correlation within individual groups of animals.

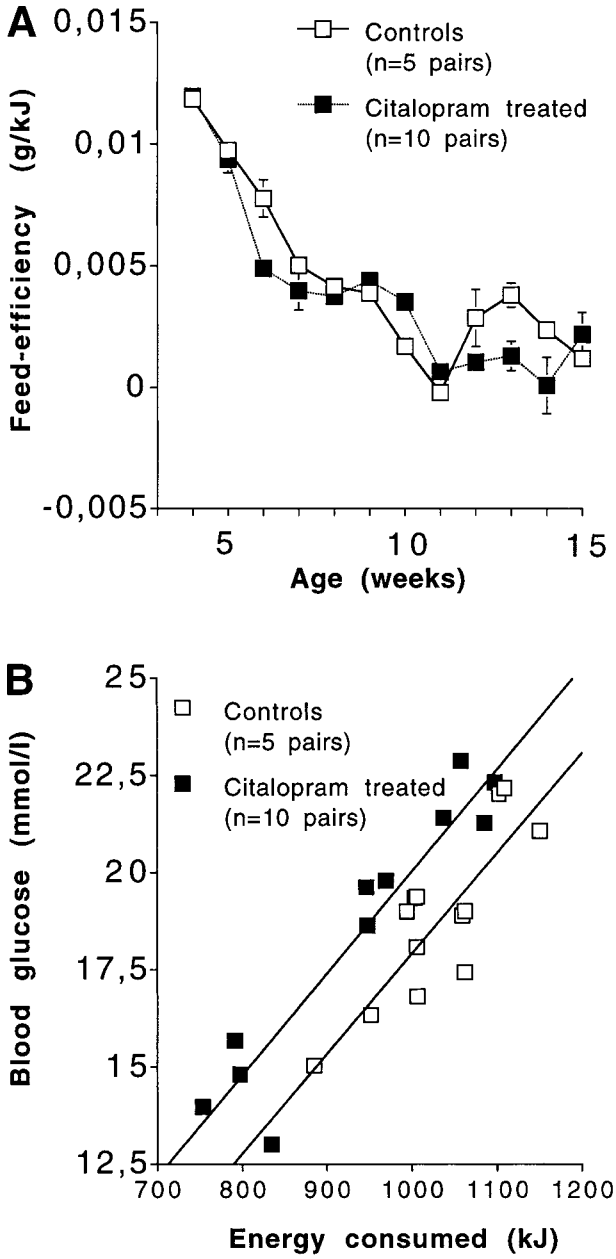

Fig 7. (A) Feed efficiency as weight gained per amount energy (kJ) consumed in citalopram-treated obese mice. Citalopram, 20 to 30 mg/kg, was administered intraperitoneally daily from 3 to 15 weeks of age. Data are presented as means ± SEM (bars). The citalopram dose was adjusted at 7 and 11 weeks. Control mice received saline. (B) Blood glucose plotted against consumed energy; $r = 0.85$ ($P < .0001$) for all data points.

Citalopram is a selective serotonin reuptake inhibitor[28] and is often used as a model drug to test binding to serotonin transporters in mice. Citalopram can affect behavioral models of depression in mice in the dose range used in this study.[29] Citalopram-induced hypophagia may involve activation of 5-HT_{2C} and 5-HT_{1B} receptors.[30,31] Fenfluramine is a less specific serotonin uptake inhibitor with anorectic properties. Fenfluramine acts both as a serotonin releaser and reuptake inhibitor and has neurotoxic effects that can be dissociated from anorectic effects by addition of specific serotonin uptake inhibitors, including citalopram.[32] In a previous study in *ob/ob* mice,[14] fenfluramine was found to reduce food intake. In this study, we have used citalopram to firmly link anorectic effects to increased serotonergic activity. However, citalopram may also have effects on cholinergic[33] and dopaminergic[34,35] signaling, and dopamine receptors may be involved in regulation of food intake.[36]

In summary, our findings suggest that the serotonergic system plays a role as a regulator of food intake over shorter periods in the absence of leptin, although part of the effect of leptin deficiency in *ob/ob* mice may be to down-regulate this serotonergic system. Citalopram reduced food intake but had little effect on metabolic efficiency. The serotonergic system for control of food intake may play a larger role in adult mice when the rate of weight increase becomes slower.

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