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Central Oxytocin Increases Food Intake and Daily Weight Gain in Rats

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BJÖRKSTRAND, E. AND K. UVNÄS-MÖBERG. Central oxytocin increases food intake and daily weight gain in rats. PHYSIOL BEHAV 59(4/5) 947-952, 1996.—The present study was performed to investigate the effects of centrally administered oxytocin on weight gain and food intake in rats. Two substrains of Sprague-Dawley rats (A and B) differing in average daily weight gain were used. Female rats of substrain A gained 2 g per day and males gained 7 g. Female rats of substrain B gained 5 g per day and males gained 8 g. Animals were implanted with a stainless steel guide cannula, allowing ICV injections into the lateral ventricle. ICV injections of 1, 5, or 10 μg of oxytocin or isotonic saline in a volume of 5 μl were given. In females, ICV treatment with either saline or 5 μg of oxytocin caused a transient loss of weight within 24 h of treatment. However, in the more slowly growing females of substrain A depression in body weight was observed after a single treatment with saline, whereas the body weight of oxytocin-treated females showed less marked depression and rapidly returned to the pretreatment weight. After a 3-day treatment period an even greater difference in daily weight gain was seen between oxytocin-treated and saline-treated female rats of substrain A. In contrast, no difference in daily weight gain or food intake was observed between oxytocin- and saline-treated male rats of substrain A, nor in females or males of the more rapidly growing substrain B. Intraperitoneal injections of 5 μg of oxytocin did not influence food intake or daily weight gain in female rats of substrain A. These data suggest that oxytocin may act centrally to influence food intake and daily weight gain in slowly growing female Sprague-Dawley rats.

Oxytocin  Weight gain  Food intake

In rats, lactation is accompanied by a pronounced hyperphagia and an increase in weight (7,22). The suckling stimulus seems to be of importance for these effects and suckling can even stimulate food intake and weight gain in animals in which the milk ducts have been ligated to inhibit the outflow of milk (8,10). The neuroendocrine mechanisms underlying the lactational hyperphagia are not known. Prolactin, which is released by suckling, is a possible mediator of this effect because peripheral administration of prolactin (1–3 mg/kg per day for 10 days) increases food intake and weight gain, and because ICV administration (0.5–2 μg for 10 days) increases food intake in adult female rats (20). However, lesions in the lateral midbrain, including the peripeduncular nuclei, which block the sucking-activated oxytocin release and milk ejection, are followed by a 50% reduction of food intake and a loss of weight (12) in lactating rats. Furthermore, oxytocin in a dose of 10–20 μg given ICV to lactating estrogen-primed ewes increases food intake (14). Taken together these data would imply a role for oxytocin in lactation-induced hyperphagia.

In contrast, oxytocin has been suggested to be a satiety hormone, because oxytocin administered ICV in microgram amounts to male and nonlactating female rats (1,4) has been shown to inhibit food intake up to 3 h after administration.

In the present study, we investigated whether oxytocin might not only induce short-term inhibition of food intake in nonlactating rats, but also increase food intake and weight gain when studied over a longer time scale than 3 h. For this purpose, nonlactating female and male rats were given oxytocin ICV and the effects on weight and food intake were determined 24–72 h after administration.
TABLE 1
NORMAL DAILY WEIGHT GAIN AND FOOD INTAKE
(MEAN ± SD) FOR RATS OF TWO DIFFERENT
SUBSTRAINS (A AND B) OF SPRAGUE-DAWLEY RATS

| Substrain | Daily Weight Gain (g per Day) | n | Food intake (g per Day) | n |
|-----------|-------------------------------|---|------------------------|---|
| Substrain A |                               |   |                        |   |
| Female    | 1.9 ± 2.5                     | 15| 21 ± 3.4               | 19|
| Male      | 6.9 ± 1.3*                    | 11| 25 ± 3.9†             | 11|
| Substrain B |                               |   |                        |   |
| Female    | 5.1 ± 1.5‡                    | 11| 22 ± 7.1               | 12|
| Male      | 7.7 ± 4.3$                    | 12| 23 ± 3.4§              | 12|

In substrain A male rats gained significantly more in weight and ate significantly more than female rats. In substrain B there were no significant differences in daily weight gain or in food intake between male and female rats. Female rats of substrain B weighed significantly more than female rats of substrain A (p < 0.01).

Statistical evaluation were performed by means of the Mann-Whitney U-test.

* p < 0.001.
† p < 0.05.
‡ p < 0.01.
§ p > 0.05.

METHOD

Experimental Animals

Female and male Sprague-Dawley rats (B & K Universal AB, Sollentuna, Sweden) weighing 230–300 g were used in this study. The approximate age of the female rats was 8 weeks and of the males was 6 weeks. Two substrains of Sprague-Dawley rats, defined by differences in spontaneous growth rate (designated as substrain A and B) (see Table 1) were used in this study. Daily weight gain and food intake were calculated. The female rats used in this study were prepubertal and the absence of estrous cycles was confirmed by weekly examinations of vaginal smears. Female rats of substrain A gained 1.9 ± 2.5 g per day and male rats 6.9 ± 1.3 g per day, whereas female rats of substrain B had gained 5.1 ± 1.5 g per day and males 7.7 ± 4.3 g per day (Table 1). The two substrains of rats also have different endocrine profiles, including higher endogenous plasma levels of oxytocin, CCK, and insulin, and significantly lower level of somatostatin in substrain B than in substrain A (Uvnäs-Moberg, in press). There was also a marked difference between these two substrains as regards acquisition of a conditioned avoidance response. Thus, the animals of substrain B were unable to acquire the avoidance behaviour within 3 days of training, during which time substrain A displayed 90–100% of performance (Salmi et al., unpublished observations).

The animals were singly housed in cages in temperature (20 ± 1°C) and humidity (45–55%)-controlled rooms illuminated from 2200 to 1000 h. Pelleted food (Lactamin, Vadstena, Sweden) was used, with a protein content of 18.5% for females and 16.5% for males. Water and food were always available ad lib.

Surgery

Following anesthesia with chloral hydrate (Apoteksbolaget, Stockholm, Sweden) 400 mg/kg body weight IP, the skull was uncovered and a stainless steel guide cannula (21 ga) was stereo-

FIG. 1. Effect of ICV administration of oxytocin (5 μg) or saline on daily weight gain (g) (upper panel) and daily food intake (g) (lower panel) in female rats (n = 9) (left panel) and male rats (n = 10) (right panel). All experiments were performed on animals of substrain A. All animals served as their own controls. Weight gain was calculated as a change from weight of day of injection. The arrow indicates time for injection. The results are presented as means, and statistical evaluation was performed by means of Wilcoxon matched-pairs signed-ranks test. Statistical significances as indicated in the figure. n.s. p > 0.05; ** p < 0.01.
tactically fixed to the skull by means of acrylic dental cement. The coordinates were 1.00 mm posterior and 1.30 mm lateral to bregma. The guides reached, but did not penetrate the dura mater. The injection needles (25 ga) reached 3.8 mm below the dura mater, with the needle tip in the right lateral ventricle. The animals were allowed to recover for 1 week before the experiments. At the end of each experiment, the placement of the guide cannula was checked, by injection of 2 μl of toluidine blue. The brain was removed, frozen, sectioned on a microtome, and the accuracy of the site of injection was confirmed.

Administration of Drugs

Oxytocin was dissolved in 5 μl of 0.9% saline and slowly injected into the lateral ventricle over a period of 1 min. Injections were made via a 25-ga stainless steel injection needle inserted into the guide cannula that was connected by a polyethylene tube to a 50-μl Hamilton syringe. In other studies, oxytocin was injected IP in a volume of 0.3 ml. Control animals received the same volume of 0.9% saline ICV or IP.

Experimental Procedures

Rats and the amount of food in the cage were weighed each morning before the light went off. The accuracy of the scale (Mettler PE200) was ± 0.1 g. Daily weight gain was noted. Food consumption was measured by weighing what was left in the cage of the food given on the previous day. All animals were injected with oxytocin or saline at 0930 h just before the light went off and rats normally start to eat (2). All experiments were carried out in the home cage. Three rats lost their guide cannulas and one died during the course of the experiment. These were excluded from the study, as were two animals that bled through the cannula after injection of drugs.

Statistics and Calculations

Data are presented as mean values ± SD. Comparisons between saline and oxytocin treatment in the same animals were made by the Wilcoxon matched-pairs signed-ranks test. Differences between groups were evaluated with the Mann-Whitney U-test.

RESULTS

Long-Term Effects of a Single Injection of Oxytocin

Female (n = 10) and male (n = 10) rats of substrain A were injected ICV with 5 μg of oxytocin or saline in a crossover design, with a 1-week intermission between injections. All female rats had lost weight 24 h after injection (p < 0.01). Oxytocin-treated rats lost less weight and weighed significantly (p < 0.01) more than their saline-treated counterparts. No significant weight difference could be established 48 and 72 h after administration, although a tendency to a difference remained. The oxytocin-treated females ate significantly (p < 0.01) more than the saline-treated animals during the first 24-h period after injection (Fig. 1).

In male rats no significant decrease in weight was observed in response to injection of either saline or oxytocin, but the increase in weight levelled off. Furthermore, food intake was depressed by the treatment. In males no difference between saline and oxytocin treatment on daily weight gain or food intake could be demonstrated (Fig. 1).

Effect of Daily Oxytocin Injections

Two groups of female rats of substrain A (n = 8) were injected ICV with 5 μg of oxytocin or saline once a day for 3 days according to the experimental design described above. Saline-treated animals lost weight, whereas oxytocin-treated animals did not, and a significant difference in daily weight gain between groups was observed up to 24 h after last injection (p < 0.05) (Fig. 2). During the first 24 h, oxytocin-treated animals ate 21 ± 6 g of food and saline-treated animals ate 14 ± 5 g. However, this difference was not significant. When food intake was calculated during the entire 72-h period, oxytocin-treated rats were found to eat significantly more than saline-treated: 18 ± 4 g and 13 ± 5 g per day, respectively (p < 0.05) (data not shown).

Effects of Oxytocin After Food Deprivation

Female rats of substrain A (n = 8) were injected ICV with either 5 μg of oxytocin or saline after 24 h of food deprivation. Twenty-four hours of food deprivation reduced the weight significantly in both groups (p < 0.01). Oxytocin (5 μg) given ICV was associated with a significantly greater increase in weight after the period of food deprivation than saline: 72 h after injection, oxytocin-treated rats had gained 36 ± 4 g compared to 20 ± 7 g for saline-treated animals (p < 0.05) (Fig. 3). When food intake was calculated during the entire 72-hour period, rats were found to eat significantly (p < 0.05) more after oxytocin treatment than after saline: 26 ± 6 g and 18 ± 2 g per day, respectively (data not shown).

Effects of Three Doses of Oxytocin

Female rats of substrain A received 1 (n = 10), 5 (n = 11), or 10 μg (n = 4) of oxytocin ICV. Separate groups of controls for each dose were given saline. Within this dose range of oxytocin (1–10 μg), a dose-related effect on daily weight gain and food intake was seen. Oxytocin (1 μg) ICV did not affect daily weight gain or food intake. Rats treated with 5 μg of oxytocin showed a significant increase in weight (p < 0.05) compared to rats given saline (2 ± 3 g and 2 ± 4 g, respectively), and oxytocin-treated animals ate significantly more (24 ± 2 g) than saline-treated controls (21 ± 2 g) (p < 0.05). After administration of 10 μg of oxytocin the rats increased weight significantly more than did saline-treated controls (7 ± 4 g and 1 ± 4 g, respectively).
The arrow indicates time for injection. The results are presented as weight gain as a change from weight of day of injection. FIG. 3. Effect of ICV administration of oxytocin (5 μg) or saline on daily weight gain after 24 h of food deprivation. (A) and (B) show results from rats from substrain A (n = 5) and substrain B (n = 6), respectively. Weight gain was calculated as a change from weight of day of injection. The results are presented as means, and statistical evaluation between groups was made with the Mann–Whitney U-test. n.s. p > 0.05; * p < 0.05.

Oxytocin-treated females in the 10 μg group also ate more (20 ± 4 g and 13 ± 4 g, respectively), although the difference in food intake was not significant.

Effects of IP Injections of Oxytocin

Female rats of substrain A (n = 6) were injected IP with 5 μg (weight of rats 282 ± 20 g) of oxytocin or saline in a crossover design, with a 1-week interval between injections. A single dose of 5 μg oxytocin given IP did not influence daily weight gain (5 ± 1 g vs. 4 ± 4 g) or food intake (24 ± 5 g vs. 21 ± 3 g compared to saline-treated controls). Also 48 and 72 h after treatment no difference could be demonstrated (data not shown).

Effect of Oxytocin Injections in Strain B

Female and male rats of substrain B (n = 12) were injected ICV with 5 μg of oxytocin or saline. No weight loss was demonstrated in the saline-treated rats. No difference in daily weight gain or food intake was observed 24 h after injection (data not shown). Female rats were also given 5 μg of oxytocin or saline after 24 h of food deprivation (n = 6). No difference between the groups in daily weight gain was observed 24–72 h after injection [Fig. 3(B)].

DISCUSSION

The present study demonstrates that in comparison to ICV saline treatment, ICV administration of oxytocin in microgram amounts increases food intake and daily weight gain in female Sprague–Dawley rats. The effect could only be demonstrated in animals with the lower growth rate (strain A), because in female rats of a more rapidly growing Sprague–Dawley strain (B) no effect on food intake and weight gain was observed. No effects could be demonstrated in male rats of either strain.

In the slowly growing female rats (substrain A), ICV injections of saline caused a decrease in weight. This decrease was significantly less pronounced after oxytocin treatment. Three days of ICV oxytocin administration caused an even greater difference and more sustained enhancement of daily weight gain in comparison to saline treatment. The effect seemed to be dose-related in the dose interval from 1–10 μg. When oxytocin or saline was applied after 24 h of food deprivation, there was no further decrease in weight after ICV injection but oxytocin-treated rats increased their daily weight gain significantly more and had consumed more food 72 h after injection. In rats treated with systemic injections of the amounts of oxytocin that have effect when administered ICV, no effects on daily weight gain or food intake were observed, which suggests that the effects of oxytocin are exerted centrally.

Oxytocin is generally considered to inhibit food intake in the doses we have used, and several studies have demonstrated an inhibitory effect on food intake in the first hours after administration (1,4,21). However, in these studies no long-term registration of weight gain was performed. Indeed, we were able to record inhibition within 1–2 h of food intake in our experimental model (Uvnäs–Moberg, unpublished data). However, when studied in a longer time perspective (days rather than hours) this effect was overcome by a net increase in food intake and daily weight gain.

The doses used in the present study (microgram amounts) are high in comparison to the doses used to induce some behavioural effects such as induction of sexual behaviour (6) and anxiolytic-like effects (28,29), when nanogram amounts of oxytocin are sufficient. However, the satiety effect previously described to occur in response to oxytocin is obtained in response to microgram amounts of oxytocin. Obviously, different effects of oxytocin are induced depending on the dose given and the effects on feeding—irrespective of the direction—occur in the microgram range.

Why then can two effects on feeding behaviour occur in response to oxytocin? Considering lactation as a physiological model for oxytocin-mediated effects on food intake a dual effect is in fact to be expected. During suckling food intake in the dams has to be suppressed, whereas a compensatory increase has to occur between the suckling periods to allow intake of nutrients for production of milk.

The mechanisms behind the effect of oxytocin on daily weight gain are not known. One possibility would be oxytocin-induced water retention. Oxytocin has complex effects on fluid balance; most often it functions as a diuretic. Thus, oxytocin increases sodium excretion and urine flow by a direct effect in the kidney (13). Intrathecal administration of oxytocin has dose-dependent effects on diuresis—30 ng having a stimulatory and 300 ng an inhibitory effect (25). Nevertheless, it is not likely that the effect of oxytocin on daily weight gain is mediated by a change in diuresis, because the effect tended to be long lasting. Furthermore, in a parallel study performed on the same substrain of rats, water intake was found to be unaffected following SC injections of oxytocin (1 mg/kg), although these treatments caused a similar long-lasting effect on weight gain (Uvnäs–Moberg, in press).

Another simple explanation would be that the weight differences are a direct consequence of the presence of food in the gastrointestinal tract. The long-lasting effects on daily weight gain speak against this simplistic explanation. It is more likely that the differences seen between daily weight gain in oxytocin- and saline-treated animals are related to the actual body weight of
the animals, and are a consequence of the different amounts of food eaten by the two groups. It is also possible that the oxytocin injections have influenced the metabolism in such a way that anabolic metabolism is supported. Indeed, in the experiments mentioned above in which oxytocin was given SC and shown to cause weight gain, no increase in food intake was seen, showing that oxytocin can cause increased weight gain also in the absence of an increased food intake (Uvnäs-Moberg, in press).

Many neurotransmitters have been suggested to influence the regulation of feeding. It is generally accepted that an α-adrenergic mechanism stimulates food intake (15). An inhibitory role for serotonin is suggested (5), but 5-HT₄ agonists increase food intake (9). Dopamine enhances feeding when injected into the lateral hypothalamus (11), but the role of dopamine in feeding behaviour is complicated. Oxytocin could interact with these systems to influence food intake, because exogenous administration of oxytocin is shown to influence central levels of noradrenaline, dopamine, and serotonin (24). Many neuropeptides are suggested to have a stimulatory effect on food intake, including dynorphin, neuropeptide Y, and galanin [for a review see Morley (19)]. Depression of the levels of cholecystokinin (CCK)—a peptide that inhibits food intake—is suggested to contribute to the lactational hyperphagia in the rat (17). Oxytocin may therefore interact with these peptides to influence food intake during lactation.

It has been suggested that prolactin may contribute to the hyperphagia of lactation. Leon has shown an increase in food intake following prolactin administration in virgin female rats (16), and Bates et al. (3) have shown an increase in weight after high doses of prolactin. It has been suggested that the effect of prolactin on food intake is mediated at a central level, but that its effect on weight gain is exerted peripherally (20). There are contradictory results concerning the effect of oxytocin on prolactin. Systemic injections of high doses of oxytocin induce an increase in levels of prolactin in male rats (18). ICV injections of 0.1 μg of oxytocin reduce prolactin levels in rats (18). Prolactin is shown to exert a feedback effect in the hypothalamus, increasing the release of oxytocin by a mechanism that involves dopamine (27). Prolactin has also been shown to stimulate oxytocin release in lactating rats (23). Taken together, these data indicate that prolactin and oxytocin may both contribute to the hyperphagia in lactation, perhaps via a common pathway.

A difficult question to answer is why the effect on weight gain and food intake could not be demonstrated in all rats. It should be mentioned that this phenomenon is not restricted to effects on food intake and weight gain of oxytocin. It has been shown that maternal behaviour is observed after oxytocin administration in some rat strains but not in others (26).

During the course of this study, our animal supplier had to destroy all of their rats because the animals were infected with corona virus; following that the rats from substrain A were no longer available. The growth curve of the new Sprague-Dawley rats (here called substrain B) differs from that of the old ones (substrain A) in that in particular the females of substrain B show a greater average daily weight increase than those of substrain A at the same age. It is possible that oxytocin increases daily food intake and weight gain only in certain animals. A high stress level as a consequence of the corona virus infection or a slightly different genetic profile may have rendered the rats of substrain A sensitive to the oxytocin induced increase of food intake and weight gain. Studies are in progress to further investigate these possibilities.

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