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Short communication

Basal and feeding-evoked dopamine release in the rat nucleus accumbens is depressed by leptin

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Abstract

The involvement of the satiety-controlling hormone leptin in the modulation of the reward-associated dopamine release was investigated by monitoring the extracellular dopamine concentration in microdialysates from the nucleus accumbens of rats during feeding after infusion of leptin or artificial cerebrospinal fluid into the lateral ventricle of rats. Leptin suppressed the basal as well as the feeding-evoked extracellular dopamine concentration and reduced the amount and duration of food intake compared to the pair-feed vehicle-treated controls. These results suggest that leptin is involved in the dopaminergic modulation of feeding-induced rewarding functions.

Keywords: Nucleus accumbens; Dopamine; Feeding; Leptin; Microdialysis

1. Introduction

The brain integrates information about different aspects of feeding, such as the smell and taste of food, previous feeding experiences as well as satiety and hormonal signals related to energy homeostasis. The mechanisms that translate this information into changes of feeding behaviour are only incompletely understood.

Leptin, a blood circulating anorectic hormone secreted by adipocytes (Zhang et al., 1994) and taken up into the brain by a specific saturable transport mechanism, has been considered as a central signal about the size of adipose stores and as a part of the negative feedback regulation of body weight via modulation of food intake and energy consumption. The brain leptin is thought to exert its effects at neurons in the hypothalamic arcuate nucleus stimulating the signalling form of the leptin receptor (Ob-Rb) (Ahima et al., 2000), activating a janus kinase and subsequently changing the gene transcription (Banks et al., 2000).

Pleasurable and rewarding components of feeding are associated with an activation of dopaminergic mesolimbic neurons in the ventral tegmental area (Westerink et al., 1994). The dopamine release from the terminals of these neurons in the nucleus accumbens may facilitate the transposition of the motivational aspects of feeding into goal-directed motor behaviour of food seeking and food intake to reach reward and satisfaction.

Therefore, the question arises whether the enhancement of brain leptin concentration changes the responsiveness of the brain reward circuitry at the level of the mesolimbic dopaminergic transmission in vivo.

2. Material and methods

Male Wistar rats (Wist/Lei, 250–300 g body weight) anaesthetized with ketamine (90 mg/kg) and xylazine (5 mg/kg) were implanted with microdialysis guide cannulas (CMA 12; CMA, Solna, Sweden) placed above the left nucleus accumbens shell relative to bregma A: +1.7 mm; L: 1.5 mm; V: 5.2 mm. A 24-gauge guide cannula for injection of recombinant rat leptin (R&D systems, Wiesbaden, Germany) was implanted above the left lateral ventricle relative to bregma A: −1 mm; L: 1.5 mm; V: 2.5 mm to avoid permanent injury of the ventricle. Both guides were fixed with dental cement.

The rats were trained to eat food pellets (altromin 1326, Altromin, Lage, Germany) after 18 h of food deprivation

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with water ad libitum 7 days after surgery. At 16.00 h on the day before the first training, all food was removed and presented again on the next day from 10.00 until 16.00 h, the beginning of the second 18-h food-free period. At the following day, the microdialysis in the nucleus accumbens was performed to monitor the extracellular dopamine as described previously (Krügel et al., 1999).

Samples were collected every 10 min. After establishment of a consistent extracellular dopamine concentration, 0.5 μl of artificial cerebrospinal fluid as control or 0.5 μl of recombinant rat leptin (1 μg) was infused into the lateral ventricle within 10 min via a 26-gauge injection cannula protruding the guide cannula 1.5 mm beyond its end to reach the ventricle. Forty minutes after the intracerebroventricular injection, all rats had free access to food for 30 min, then the food was removed and the microdialysis experiment was continued.

3. Results

Rats with intracerebroventricular injection of the vehicle ($n = 6$) consumed 4.2 ± 0.4 g food (Fig. 1B) over a mean time of 21.6 ± 1.9 min. Whereas the administration of the vehicle did not change the basal extracellular dopamine concentration, the feeding evoked an increase of the extracellular dopamine concentration by about 35% of the basal level (Fig. 1A) corresponding to a total amount of 24.3 ± 7.3 fmol dopamine (Fig. 1B). The administration of leptin into the ventricle ($n = 6$) reduced the amount and the duration of food intake compared to the vehicle-treated group to 2.2 ± 0.5 g (Fig. 1B) and 12.4 ± 2.3 min ($P < 0.05$). Further, the microinfusion of leptin decreased the accumbal extracellular dopamine concentration before feeding to about 60% of the basal level (Fig. 1A) and also suppressed the feeding-evoked release of dopamine to 4.3 ± 1.2 fmol ($P < 0.05$; Fig. 1B).

4. Discussion

For the first time, it is presented that anorectic concentrations of leptin in the brain reduce the activity of mesolimbic dopaminergic neurons in vivo accompanied by suppression of dopamine-related motivational aspects of feeding. This finding confirms data about the presence of the signalling form of the leptin receptor (Ob-Rb) on tyrosine

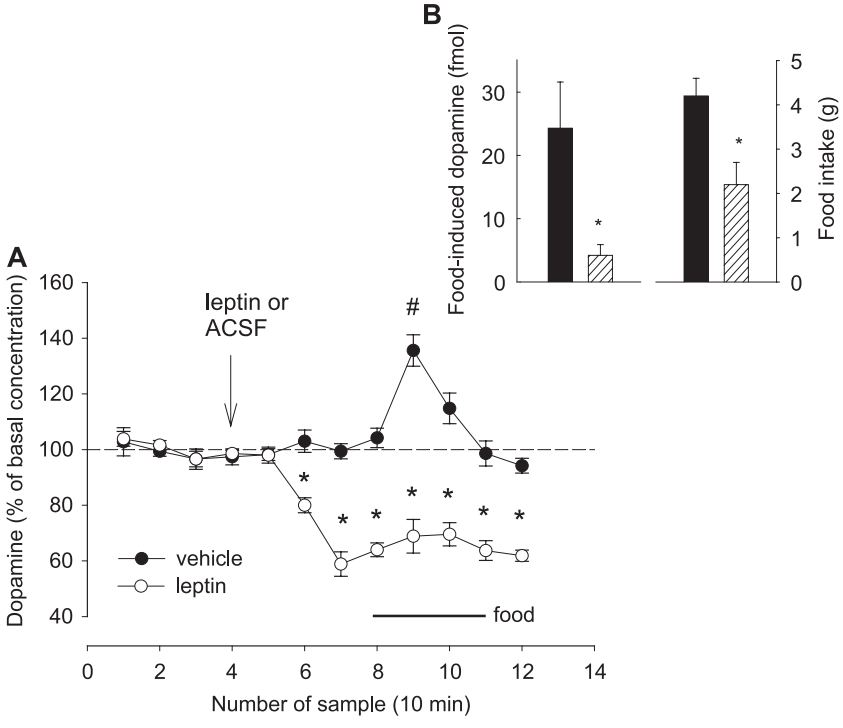

Fig. 1. Effect of leptin on the extracellular concentration of dopamine in the rat nucleus accumbens. (A) Effect of feeding in food-deprived animals on the extracellular concentration of dopamine in the nucleus accumbens of rats microinfused with artificial cerebrospinal fluid (ACSF) as vehicle alone (control, closed circles) or vehicle containing leptin (1 μg; open circles). The horizontal bar indicates the time of food presentation. Data are expressed as a percentage of the basal dopamine concentration (2.0 ± 0.5 nM; $n = 12$) defined as the mean of four consecutive samples with a variation less than 10% and represent the mean ± S.E.M. from six animals. The data were evaluated by using two-way ANOVA with repeated measures over time followed by the Student–Newman–Keuls test. Comparing the leptin group with the control group, the ANOVA reveals the following: for treatment, $F(1,10) = 43.29$, $P < 0.001$; for time, $F(11,55) = 10.7$, $P < 0.001$; and treatment × time interaction, $F(11,55) = 17.80$, $P < 0.001$. *$P < 0.05$, significant differences versus basal values before feeding; $^{\#}P < 0.05$, significant differences induced by feeding. (B) Total amount of dopamine release induced by feeding presented as fmol dopamine recalculated from A (left two columns) and amount of food intake in g (right two columns) after microinfusion with vehicle (black bars) or leptin (striped bars). Each column represents the mean ± S.E.M of six independent experiments. *$P < 0.05$, significant difference versus the control group evaluated by one-way ANOVA.

hydroxylase-positive neurons in the ventral tegmental area (Figlewicz et al., 2003) and about changes in the mRNA expression of this receptor in their accumbal terminal region after restricted feeding (Krügel et al., 2003), suggesting a functional relevance of leptin for the mesolimbic activity. The acute effects of leptin described here cannot be explained by the activation of neuropeptide gene transcription (Niswender and Schwartz, 2003). More likely mechanisms are a hyperpolarization caused by leptin described at hypothalamic neurons via activation of ATP-sensitive potassium channels (Spanswick et al., 1997) and an inhibition of the depolarization-induced dopamine release from mesencephalic neuronal endings shown in the hypothalamus (Brunetti et al., 1999) in vitro.

Though the present microdialysis data give clear evidence that leptin can evoke rapid responses in neuronal transmission which may contribute to the modulation of the mesolimbic dopaminergic activity and food intake, they cannot explain whether the lack of dopamine release in leptin-treated rats during food access is the consequence of the reduced food intake itself or of the diminished dopaminergic activity. However, various studies have shown that motor and motivational aspects of ingestion are dependent on intact dopaminergic transmission. The D1,D2 dopamine receptor blockade by systemic administration of cis-flupenthixol caused a neuroleptic-like suppression of feeding (Pitts and Horvitz, 2000). Mice mutants lacking both, dopamine and leptin, became obese when treated with L-3,4-dihydroxyphenylalanine (L-DOPA); however after termination of this treatment, the animals were capable of movement but did not feed (Szczypka et al., 2000). Therefore, it can be assumed that the depression of the dopaminergic activity may underlie the reduced food intake in the leptin-treated animals.

It remains to investigate whether the centrally administered leptin affects the dopaminergic motivational circuitry by comparable signalling mechanisms directly in the nucleus accumbens or indirectly via multi-synaptic pathways involving the feeding-regulatory hypothalamic nuclei.

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References

Ahima, R.S., Saper, C.F., Flier, J.S., Elmquist, J.K., 2000. Leptin regulation of neuroendocrine systems. Front. Neuroendocrinol. 21, 263–307.

Banks, A.S., Davis, S.M., Bates, S.H., Myers Jr., M.G., 2000. Activation of downstream signals by the long form of the leptin receptor. J. Biol. Chem. 275, 14563–14572.

Brunetti, L., Michelotto, B., Orlando, G., Vacca, M., 1999. Leptin inhibits norepinephrine and dopamine release from rat hypothalamic neuronal endings. Eur. J. Pharmacol. 372, 237–240.

Figlewicz, D.P., Evans, S.B., Murphy, J., Hoen, M., Baskin, D.G., 2003. Expression of receptors for insulin and leptin in the ventral tegmental area/substantia nigra (VTA/SN) of the rat. Brain Res. 964, 107–115.

Krügel, U., Kittner, H., Illes, P., 1999. Adenosine 5′-triphosphate-induced dopamine release in the rat nucleus accumbens in vivo. Neurosci. Lett. 265, 49–52.

Krügel, U., Seidel, B., Spies, O., Kittner, H., Illes, P., Kiess, W., 2003. Chronic food restriction alters purinergic receptor mRNA expression in the nucleus accumbens of the rat. Drug Dev. Res. 59, 95–103.

Niswender, K.D., Schwartz, M.W., 2003. Insulin and leptin revisited: adiposity signals with overlapping physiological and intracellular signaling capabilities. Front. Neuroendocrinol. 24, 1–10.

Pitts, S.M., Horvitz, J.C., 2000. Similar effects of D_1/D_2 receptor blockade on feeding and locomotor behavior. Pharmacol. Biochem. Behav. 65, 433–438.

Spanswick, D., Smith, M.A., Groppi, V.E., Logan, S.D., Ashford, M.L., 1997. Leptin inhibits hypothalamic neurons by activation of ATP-sensitive potassium channels. Nature 390, 521–525.

Szczypka, M.S., Rainey, M.A., Palmiter, R.D., 2000. Dopamine is required for hyperphagia in Lep(ob/ob) mice. Nat. Genet. 25, 102–104.

Westerink, B.H.C., Teisman, A., de Vries, J.B., 1994. Increase in dopamine release from the nucleus accumbens in response to feeding: a model to study interactions between drugs and naturally activated dopaminergic neurons in the rat brain. Naunyn-Schmiedeberg's Arch. Pharmacol. 349, 230–235.

Zhang, Y., Proenca, R., Barone, M., Leopold, L., Friedman, J.M., 1994. Positional cloning of the mouse obese gene and its human homologue. Nature 372, 425–432.