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Special Issue on Galanin

Exaggerated feeding response to central galanin-like peptide administration in diet-induced obese rats

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Abstract

Galanin-like peptide (GALP) is a newly identified neuropeptide implicated in the regulation of metabolism and reproduction. GALP gene expression is decreased in the hypothalamus of genetically obese rodents, such as *fa/fa* rats and *ob/ob* mice, and central administration of GALP increases feeding in satiated rats. The effect of dietary obesity on GALP-induced feeding is unknown, so this study characterized the effects of central administration of GALP on feeding in a rat model of diet-induced obesity. Male Sprague–Dawley rats ($n = 21$) were randomly assigned to receive standard laboratory chow (12% fat as kcal) or high-fat cafeteria diet (35% fat) for 12 weeks before intracerebroventricular (icv) cannulae were implanted. Seven days later, rats received 0, 0.2 or 0.3 nmol doses of GALP in randomized order at least 48 h apart. Food intake was measured at 0.5, 1, 2, 4 and 24 h post administration and body weight was measured at 24 h. Rats were maintained on their respective diets throughout the entire feeding experiment. Implementation of the high-fat diet led to significantly greater caloric intake (230%) and body weight (28%) compared to chow-fed control rats. GALP-induced feeding was rapid and maximal in both dietary groups at 30 min post injection. The 0.3 nmol dose of GALP led to significantly larger increases in caloric intake in high-fat fed rats than in chow-fed controls (35.4 ± 3.7 and 22.1 ± 1.3 kcal, respectively, at 30 min). It is not known if diet-induced obesity alters endogenous GALP levels, but our data suggest that adaptive responses in GALP signaling might occur during chronic overfeeding. One possible explanation is an increased sensitivity and/or number of specific GALP receptors, although actions of exogenous GALP may also represent pharmacological actions at galanin receptors.
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Keywords: GALP; Diet-induced obesity; Food intake; Body weight; Hypothalamus

1. Introduction

Obesity is rapidly becoming a worldwide epidemic and is a major contributor to the increased incidence of cardiovascular disease, diabetes and hypertension. Genetics, diet and lifestyle habits are major factors associated with the development of obesity. Although genetic obesity models (*ob/ob*, *db/db* and *fa/fa*) are useful in discovering the role of endogenous neuropeptides in the regulation of feeding, dietary intervention provides a more physiological obesity model. Ingestion of a high-fat diet promotes body weight gain and increases adiposity in rodents (Storlien et al., 2000; Hansen et al., 2004).

Galanin-like peptide (GALP; 60-amino acids), is a recently identified member of the galanin peptide family (Ohtaki et al., 1999) and since its discovery various studies have implicated GALP in the regulation of feeding, metabolism and reproduction (Gundlach, 2002; Gottsch

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et al., 2004). GALP is discretely expressed in cells of the arcuate nucleus, median eminence and posterior pituitary; and GALP-containing nerve fibres are present in the paraventricular nucleus and lateral hypothalamic area (Takatsu et al., 2001), two areas that are important in the neural regulation of appetite. Central administration of GALP increases acute food intake in rats (Lawrence et al., 2002; Matsumoto et al., 2002; Seth et al., 2003), but not in mice (Gottsch et al., 2004). It has been consistently shown that genetic obesity and dietary intervention alter the expression of mRNAs encoding important feeding mediators in the brain (Mercer et al., 1996; Widdowson et al., 1997; Torri et al., 2002) and a decrease in GALP mRNA expression in Arc was reported in fasted rats (Jureus et al., 2000). Furthermore, studies in obese animals with deficient leptin signaling such as *ob*/*ob*, *db*/*db* mice and *fa*/*fa* rats revealed reduced GALP expression in the hypothalamus (Jureus et al., 2000; Takenoya et al., 2002; Kumano et al., 2003; Shen and Gundlach, 2004).

The effect of dietary rather than genetic obesity on GALP activity has not been studied; hence the present study examined the effect of obesity induced by voluntary intake of a palatable high-fat diet on exogenous GALP-induced feeding in the rat.

2. Study design and methods

Experiments were conducted in 21 male Sprague–Dawley rats housed at 20 ± 2 °C with a 12-h light cycle and free access to food and water. Rats were randomly divided into two groups - controls (193 ± 5 g; $n = 10$) received standard laboratory chow (12% fat as kcal) and a high-fat fed group (195 ± 4 g; $n = 11$) received high-fat chow (35% fat) consisting of powdered chow, sweetened condensed milk and saturated animal fat supplemented with highly palatable cafeteria-style foods (Hansen et al., 2004). Rats were maintained on their respective diets throughout the experiments. Body weight and 24 h caloric intake (kcal) were monitored weekly. After 12 weeks on the diet, rats were implanted with cannulae (Plastics One, Roanoke, USA) into the right lateral ventricle (0.8 mm posterior, 1.5 mm lateral to bregma and 3.5 mm below the surface of the brain; Paxinos and Watson, 1986). Following surgery, rats were housed individually. During a 7-day recovery period, rats were handled daily and acclimatized to the experimental protocol to minimize non-specific stress. As a measure of effective cannula placement, rats were administered 2 nmol angiotensin II and their drinking response was assessed over 30 min. At the end of the study, rats were killed by CO_2 inhalation and decapitation; and cannula placement was verified by visual inspection of coronal brain slices. Interscapular brown adipose tissue (iBAT), reperitoneal (RpWAT) and gonadal white adipose tissue (WAT) were dissected and weighed. All procedures were approved by the University of Melbourne Animal Ethics Committee.

On the experimental day, rats were acclimatized for 1 h with ad libitum access to food and water. GALP (0.2 and 0.3 nmol) or saline vehicle was injected in a volume of 2 μl using a 10 μl Hamilton syringe (SGE, Austin Texas, USA). After injections, pre-weighed food (g) was placed in the cage and food intake was measured at 0.5, 1, 2, 4 and 24 h post injection and body weight at 24 h. All injections were performed between 1000 and 1030 h in random order at least 48 h apart. Repeated injections of each dose were administered where possible and the results were averaged.

3. Results

Animals maintained on a high-fat diet ingested more calories than the chow fed controls immediately after dietary intervention began and this was maintained after cannulation. High-fat fed rats were significantly heavier than chow fed controls 3 weeks after dietary intervention began and were 28% heavier at the end of the study. Consistent with the effects on body weight, adiposity was elevated relative to chow fed controls (2-, 2.5- and 2-fold increases in iBAT, RpWAT and gonadal WAT mass, respectively, Table 1).

Daytime administration of 0.2 and 0.3 nmol GALP significantly increased food intake compared to saline vehicle in both dietary groups at all time points (0.3 nmol data shown in Fig. 1(a), $P < 0.05$ versus saline). The effect of GALP was rapid and appeared to be maximal at 30–60 min post injection for chow control and high-fat fed groups. The high-fat fed group ingested significantly more energy in response to 0.3 nmol GALP at 0.5–4 h post injection (Fig. 1(a), $P < 0.05$) and this remained significant when corrected for individual body weight (Fig. 1(b), $P < 0.05$). More modest increases in feeding were observed following 0.2 nmol GALP in chow control and high-fat fed groups (13.3 ± 1.5 and 17.3 ± 4.0 kcal, respectively, at 60 min); the difference

Table 1
Food intake, body weight and fat mass in different dietary groups at 16 weeks of age

Parameter	Chow control ($n = 10$)	High-fat ($n = 11$)
24 h Food intake (kcal/rat)	111 ± 2	256 ± 5*
Body weight (g)	613 ± 28	782 ± 15*
iBAT (mg)	567 ± 112	1186 ± 123*
RpWAT (g)	6.9 ± 0.8	19.7 ± 1.5*
Gonadal WAT (g)	12.1 ± 1.2	24.1 ± 1.5*

Data are expressed as mean ± SEM and were analyzed using Student *t* test.
* $P < 0.05$ versus chow control.

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