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Galanin-like Peptide Ameliorates Obesity by Control of Food Intake and Energy Metabolism

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Abstract

Galanin-like peptide (GALP) is a 60 amino acid neuropeptide that was first isolated from the porcine hypothalamus. It is produced in the hypothalamic arcuate nucleus by neurons that form networks with other neurons containing peptides involved in the control of feeding behavior. GALP plays an important role in the regulation of feeding, body weight and energy metabolism. Although the physiological actions of GALP are yet to be fully elucidated, it is possible, given the anti-obesity effect of GALP seen in relation to food intake and body weight loss in obese mice, that GALP could be applied clinically to combat obesity in humans. Here we summarize what is known about the regulation of energy metabolism by GALP, and describe results in animals that could possibly lead to the clinical use of GALP to treat obesity.

Keywords: GALP; Clinical implication; Energy metabolism; Anti-obesity; Feeding regulation

Introduction

Metabolic syndrome is composed of a variety of diseases related to obesity, such as glucose intolerance, hyperinsulinemia, dyslipidemia, and hypertension [1-3]. The prevalence of metabolic syndrome is on the rise in many parts of the world, with the main causes of obesity being associated with overeating and lack of exercise [4]. In this context, the control of energy metabolism and regulation of food intake form key pillars in the treatment of metabolic syndrome.

Many neuropeptides in the hypothalamus are involved in modulating feeding behavior and energy homeostasis. It has been reported that the lateral hypothalamus (LH) is a feeding center, the ventromedial hypothalamus (VMH) is a satiety center, and the arcuate nucleus (ARC) is an integrated center for feeding regulation [5,6]. A number of studies have demonstrated that appetite is regulated by many neuropeptides, and that takes place via a neural network linking these brain centers. Neuropeptide Y (NPY), melanin-concentrating hormone (MCH), orexin, galanin, and agouti gene-related protein (AgRP) are typical orexigenic peptides, while α-melanocyte stimulating hormone (α-MSH), corticotropin-releasing hormone (CRH), cocaine- and amphetamine-regulated transcript (CART), neuropeptide W (NPW) and galanin-like peptide (*GALP*) have been described as anorexigenic peptides [7-14]. Moreover, the levels of many neuropeptides are linked to the actions of leptin, in addition to which it has been shown that neurons containing feeding regulating neuropeptides interact with each other via synaptic inputs [15,16]. We previously reported on a number of functional analyses that clarified the actions of many feeding regulating peptides in the brain, among these being GALP [17-21].

In 1999, GALP was isolated from the porcine hypothalamus on the basis of its ability to bind to and activate galanin receptors *in vitro* [22]. GALP is a 60 amino acid peptide, where amino acids 9-21 are identical to the biologically active N-terminal amino acids 1-13 of galanin (Figure 1). Recent studies demonstrated that GALP has physiological actions that are different from those of galanin. In addition to discussing the physiological actions of GALP, this review also summarizes results from studies in which GALP was administered intranasally (i.n.) to obese mice, thereby providing insights into how GALP might be used clinically to treat obesity in humans.

Distribution of GALP and its Neuronal Network

Some studies have demonstrated the localization and distribution of GALP neurons in the brains of rats and mice. In rodents, *in situ* hybridization histochemistry revealed that GALP mRNA is distributed in the periventricular regions of the ARC, in the median eminence, and in the pituitary gland [23-26]. Immunohistochemistry studies have shown that GALP-immunoreactive neuronal cell bodies are observed in the ARC and posterior pituitary gland [27]. Furthermore, GALP-immunoreactive fibers were distributed in the ARC, paraventricular nucleus (PVN), bed nucleus of the stria terminalis (BST), medial preoptic area (MPA), and lateral septal nucleus (LSV) [27].

GALP-containing neurons receive afferent inputs from NPY-containing neurons in the ARC and from orexin-containing neurons in the LH [17,18]. Additionally, GALP-containing neurons project to orexin- and MCH-containing neurons in the LH [19]. GALP-containing neurons thus form neuronal networks with several feeding-related peptide-containing neurons, and have also been shown to co-express the leptin receptor, NPY Y1 receptor, orexin type 1 receptor and serotonin 5-HT_{2c} receptor in rodents and monkey, which suggests that GALP neurons may be under the control of leptin, NPY, orexin and serotonin [17,27,28]. Leptin receptor immunoreactivity in particular was identified in more than 85% of GALP-containing neurons [27]. Further to this, we demonstrated that approximately 10% of GALP-

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containing neurons co-express α-MSH [18]. Taken together, these observations suggest that GALP-containing neurons are intimately connected to various feeding-related neuron types in the hypothalamus and are affected by leptin released from adipose tissues (Figure 2).

Receptor binding experiments suggested that the receptor for GALP is actually the galanin receptor (GALR), which has three known subtypes: GALR1, GALR2 and GALR3. *In vitro* studies showed that GALR3 has the highest affinity for GALP followed by GALR2 and then GALR1 [22,29]. Physiological studies in rats, however, demonstrated that the GALP receptor is not GALR. In this way, the central administration of a GALR2/3 agonist to rats had no effect on food intake and body weight [30]. In addition, the distribution of GALR and c-Fos expression in the brains of rats after the central administration of GALP is different [31]. Furthermore, the physiological effects of GALP did not disappear following the administration of GALP to GALR1 or GALR2 knock-out (KO) mice [32]. These results suggested that the GALP receptor may be GALR3, but the true identity of GALP receptors has not yet been established. Identification of GALP specific receptor is very important in order to understand the physiological functions of GALP.

Regulation of GALP mRNA Expression

In rats, the process of fasting reduces GALP mRNA expression and the number of neurons expressing GALP [27]. Further to this, the relationship between GALP and leptin levels has attracted attention due to the fact that the plasma leptin concentration is reduced in response to fasting. Leptin administration increased the number of GALP expressing cells in the brains of fasted rats compared to control fasted rats that were injected with saline [27]. Conversely, GALP mRNA levels are reduced in leptin-deficient *ob/ob* mice, in leptin receptor-deficient *db/db* mice, and in Zucker obese rats compared to their wild type counterparts [16,33]. Interestingly, it was shown that GALP mRNA expression in *ob/ob* mice can be restored by leptin administration, which suggests that GALP-expressing neurons are a directly regulated target of leptin.

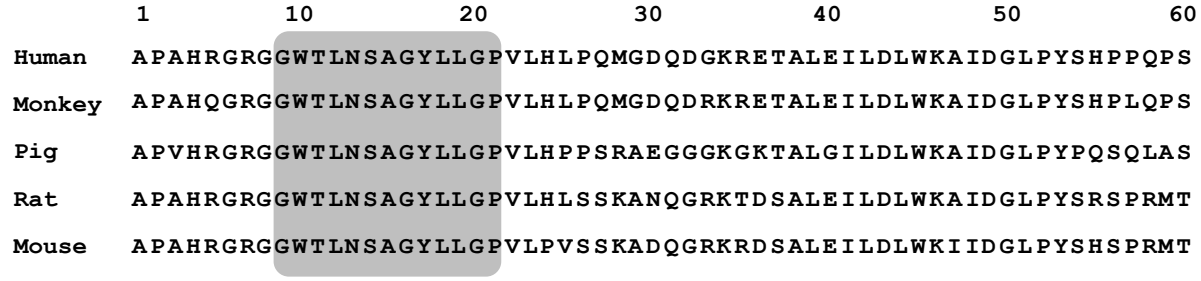
A previous study also reported that GALP expression is regulated by insulin [34]. While GALP mRNA expression in streptozotocin-induced diabetic rats was lower than that of vehicle-treated rats, levels could be restored to normal by administering leptin or insulin. These results suggest that GALP expression is regulated by leptin and insulin.

Anti-obesity Effect of GALP

GALP was initially described as an orexigenic neuropeptide given that administration of GALP into the brain induces food intake for the first hour thereafter in rats [35-38]. We previously reported that c-Fos immunoreactivity is increased in orexin-immunoreactive neurons in the LH after the central administration of GALP [39]. Furthermore, anti-orexin IgG markedly inhibits GALP-induced food intake. Kuramochi et al. [37] reported that the intracerebroventricular (i.c.v.) injection of GALP increases c-Fos expression in NPY-containing neurons in the dorsomedial hypothalamic nucleus (DMH) [37]. Food intake is similarly increased by GALP administered in this way. In addition, the hyperphagic effect of GALP can be suppressed by inhibiting the action of NPY. However, this orexigenic action of GALP in rats is only a short-term effect. In the 24 hours following the i.c.v. administration of 1.6 or 5 nmol GALP, body weight significantly decreased about 5 or 25 g compared with the vehicle treatment [38,40].

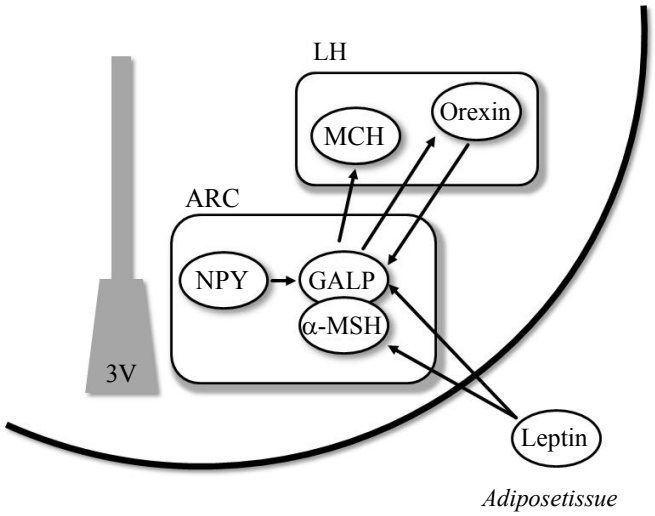
In contrast with that seen in rats, an orexigenic action of GALP is not seen following its administration to mice, where a decreased food intake is seen after two hours and both food intake and body weight are suppressed in the 24 hours following GALP administration [30,32,41,42]. Specifically, in 1.2nmol GALP i.c.v administration, it is the minimum dose in previous reports, body weight was significantly decreased [42]. In *ob/ob* mice, body weight and food intake decreased continuously following chronic GALP administration for 14 days [43].

It has also been reported that GALP regulates energy metabolism (Table 1). The central administration of GALP produces a dose-dependent increase in core body temperature which lasts for 6-8 h after treatment [38]. We found increases in heart rate, oxygen consumption and core body temperature but not skin temperature. GALP-induced thermogenesis is perfectly inhibited by administration of the cyclooxygenase (COX) inhibitor in both our and Lawrence's experiments [38,44]. These studies suggesting that this effect could be dependent on the action of prostaglandin [38,44]. Intracerebroventriclar injection of GALP induced c-Fos expression in astrocytes in the periventricular zone of the third ventricle. In addition, we examined COX1, COX2 and prostaglandin E_2 synthetases (PGESs) mRNA expression after the in primary cultured astrocytes treated with GALP. Both COX2 and cytosolic PGES expression was found to be significantly increased by this treatment, which suggests that GALP evokes thermogenesis via a prostaglandin E(2)-mediated pathway in astrocytes of the central nervous system [44]. The hyperthermia response due to GALP administration is similar to that achieved by the i.c.v. administration of interleukin (IL)-1 [45]. To this end, GALP administration increases IL-1α/β production in microglia and macrophages. As a consequence of this, in IL-1α/β, IL-1β, or IL-1 type1 receptor-deficient mice, food intake reduction, weight loss and thermogenesis are suppressed in response to the i.c.v. administration of GALP. Thus, it is considered that the thermogenesis and food intake reduction effects of GALP are mediated by IL-1 production and



The gray area indicates amino acids sequences of galanin that are identical between species.

Figure 1: Sequence comparison of galanin-like peptide (GALP) from five different species.



GALP neurons send outputs to orexin- or melanin-concentrating hormone-(MCH) containing neurons in the lateral hypothalamus (LH) and receive inputs from orexin neurons in the LH and neuropeptide Y neurons in arcuate nucleus (ARC). GALP-containing neurons also co-localize with alpha-melanin stimulating hormone (alpha-MSH)-immunopositivity. 3V=third ventricle.

Figure 2: Schematic diagram of possible neuronal network involving GALP and other feeding-related peptide-containing neurons in the hypothalamus.

Effect	Reference
Increase of food intake (rat, short-term)	Matsumoto et al. [36] Lawrence et al. [38] Lawrence et al. [35] Kuramochi et al. [37]
Decrease of food intake (rat, long-term)	Lawrence et al. [38] Krasnow et al. [41]
Decrease of food intake and body weight (mouse)	Hansen et al. [43] Krasnow et al. [41] Krasnow et al. [32] Kauffman et al. [42] Man et al. [45]
Increase in heat population	Lawrence et al. [38] Hansen et al. [43] Man et al. [45]
Increase in oxygen consumption	Rich et al. [40]
Enhancement of glucose and lipid metabolism	Ito et al. [46]

Table 1: Effect of GALP for energy metabolism.

the IL-1 type1 receptor [45]. In addition, chronic administration of GALP to *ob/ob* mice increases the uncoupling protein (UCP)1 gene and protein expression in brown adipose tissue (BAT). As BAT is a thermogenic organ innervated by the sympathetic nervous system, it is suggested that the enhanced energy metabolism induced by GALP takes place via sympathetic activation [43].

Further to the above, we reported that a change occurs in the respiratory exchange ratio (RER) in response to the i.c.v. administration of GALP. The RER indicates the amount of oxygen an organism consumes compared to the amount of carbohydrate dioxide it produces, and forms an essential part of the evaluation of metabolic status. The oxidation of carbohydrate results in an RER of 1.0, compared with 0.7 for fat and 0.8 for protein. In non-exercising mice, the RER was reduced 2 hours after GALP administration and increased thereafter, suggesting that the GALP enhances glucose and lipid metabolism under these conditions [46]. We also examined the effect of GALP on gene expression in the liver and in skeletal muscle in relation to glucose and lipid metabolism. The gene expression of hepatic SREBP-1c, which regulates fatty acid synthesis, was reduced by GALP administration, whereas that of GLUT4, which mediates glucose uptake by muscle, was increased. These findings suggest that GALP improves lipid metabolism in the liver and increases glucose uptake by muscle.

Taken together, these findings could explain the anti-obesity effect of GALP.

Possible Clinical Applications of GALP

The use of physiologically active peptides as therapeutic agents may reduce patient compliance and quality of life when these agents are administered parenterally. The intranasal (i.n.) route of administration, however, offers distinct advantages as the nasal mucosa has a rich vascular supply (facilitating drug uptake), and the administration can be performed easily by the patient.

We have considered the i.n. route of administration as a method for the clinical delivery of GALP [47]. In this way, the rate of uptake of intravenous (i.v.-) or i.n.-administered radioactively iodinated GALP (I-GALP) into the brains of mice was measured. I-GALP uptake into the olfactory bulb was very high, and was also elevated in the hypothalamus and hippocampus compared with other brain areas. In this way, the incorporation efficiency of I-GALP via the i.n. route was more than five times that of the i.v. route. Next, we observed the uptake of I-GALP into peripheral tissues, where the i.v. route resulted in much higher I-GALP levels in the spleen than were found for the i.n. route.

Uptake of I-GALP into the brain after i.n. administration was inhibited by unlabeled GALP, which suggests that this route of drug delivery results in the efficient transfer of GALP to the brain without concomitant distribution to the peripheral tissues. Many peptide-based drugs are often administered via the i.n. route in conjunction with the absorption enhancer, cyclodextrin [48-50]. Cyclodextrin is a cyclic glucan that can form inclusion complexes with many substances. I-GALP uptake into the brain was increased threefold by the combined administration of cyclodextrin and I-GALP, a finding that was confirmed autoradiographically and morphologically. We also studied the effect of GALP on feeding behavior in *ob/ob* mice following its administration via the i.n. route and found that food intake and body weight were both decreased. The same effect of GALP on body weight was found for diet-induced obesity (DIO) mice treated i.n with GALP (unpublished findings). As no change in the locomotor activity of these animals was observed, these findings suggest that the weight decrease induced by GALP occurred as a result of increased energy metabolism. The i.n. delivery method may as such be potentially useful to treat life-style-related diseases and obesity in humans.

Conclusion

We have summarized here many of the feeding- and energy metabolism-related functions of GALP. While the physiological mechanisms of GALP's actions are gradually being elucidated, the nature of its receptor is yet to be clarified and remains a key to discovering the widespread actions of this neuropeptide. Recent studies have shown that GALP enhances energy metabolism, and we have demonstrated its capacity to reduce obesity following its administration via the i.n. route. Further studies to reveal GALP's actions may result in it becoming a key player in the fight against obesity.

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