Central nervous system regulation of food intake and energy expenditure: role of galanin-mediated feeding behavior

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Abstract: Galanin is a neuropeptide widely expressed in the brain. It is implicated in energy expenditure, feeding, and the regulation of body weight. Numerous studies have revealed that galanin regulates food intake via galanin receptors, 5-HT_{1A} receptor and adrenergic α -2 receptor. In this review, we summarize recent findings that reveal the essential role of galanin in increasing food intake as well as body weight and that identify the individual galanin receptor subtypes involved in the brain's modulation of food intake and energy expenditure, to provide a theoretical basis for further studies of different aspects of galanin action.

Keywords: galanin; receptor; feeding behavior; central nervous system

1 Introduction

Physiological modulation is often accomplished by release of neuropeptides that change neuronal excitability or activity^[1]. In particular, appetite and satiety modulate feeding behavior in most animals through the actions of neuropeptides. In mammals, the hypothalamus, an important brain region controlling appetite and satiety^[2,3], integrates neuropeptides or hormonal signals such as neuropeptide Y, galanin, and leptin. Numerous studies have revealed that the activation of neurons containing galanin in the paraventricular nucleus (PVN) of the hypothalamus augment food intake and body weight^[4,5]. Galanin, a 29-amino-acid neuropeptide, is mainly distributed in central and peripheral nervous systems^[6]. Currently, it is known that the galanin receptor subtypes include GalR1, GalR2

and GalR3, all of which are G protein-coupled receptors^[7] and are distributed in the hypothalamus, amygdala, hippocampus, thalamus, brainstem, spinal cord and dorsal root ganglia^[7-9]. Both GalR1 and GalR3 act through the Gi/o receptor, inhibiting adenylyl cyclase and causing a decrease of cAMP^[7,9]. Distinct from GalR1 and GalR3, the GalR2 subtype activates the stimulatory pathway of Gq/11, resulting in the hydrolysis of inositol phosphate, activation of atypical protein kinase C, and an increase of intracellular Ca²⁺^[7,10]. Such signaling through galanin subtypes suggests that different receptors are involved in different functions.

2 Effects of galanin on food intake and energy expenditure

In mammals, acute injection of galanin or active fragments such as galanin (1–16), into the PVN, lateral and ventromedial hypothalamic nuclei, and the central nucleus of the amygdala, significantly increases food intake and produces rapid increases in the feeding response and total caloric intake^[4,5,11,12]. The effects of galanin on feeding be-

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haviors are blocked when it is administered with the putative galanin receptor antagonists M40, C7 and galnol^[12–14], suggesting that galanin stimulates acute feeding behavior rather than suppresses satiety. The orexigenic effect of galanin has also been reported beyond the mammals, such as in chicks and goldfish^[15,16].

Chronic intracerebroventricular (i.c.v.) administration of galanin causes variable and complex changes in daily food intake, body weight and level of obesity, depending on the carbohydrate and fat content of the diet^[17]. Galanin preproprotein and galanin are significantly associated with circulating triglyceride levels^[18–20], and increased lipid oxidation and energy expenditure are also associated with markedly decreased levels of hypothalamic galanin^[21]. Mercaptoacetate-induced blockade of fatty acid metabolism reduces the level of galanin expression in the anterior PVN^[22], and rats fed a high-fat diet display a 40% increase in hypothalamic galanin levels^[18]. These results are consistent with previous reports that galanin increases preference for a high-fat diet given a choice of fat, carbohydrate, or protein^[23], suggesting that galanin production is regulated by signals related to fatty-acid metabolism. Moreover, *galanin* knockout (GKO) mice consume significantly less energy than control mice, when only a high-fat diet is available, which further supports the role of galanin in fat intake and preference^[24], while other studies have reported no differences in macronutrient choice^[25].

The complete loss of galanin in GKO mice leads to significant alterations in neuroendocrine homeostasis, whereas targeted overexpression of galanin in the brain does not interfere with normal neuroendocrine function^[26]. A recent study reported a 55% increase in consumption of a fat-rich diet during a 2-h test period in both male and female galanin-overexpressing mice^[27]. These results strongly support the physiological role of this peptide in stimulating the consumption of a fat-rich diet. So it can be concluded that the endogenous galanin system does play a significant role in adjusting food intake and metabolism to acute changes in dietary fat. Furthermore, galanin-transgenic mice exhibit increased body weight, visceral adiposity and total serum triglycerides. The obese phenotype of these

mice is associated with reduced energy expenditure and insulin resistance^[28]. These findings support our previous findings that endogenous galanin contributes to decreased insulin resistance and improved insulin sensitivity in rats^[29–31].

3 Possible mechanisms underlying the effects of galanin on food intake and energy expenditure

3.1 Galanin and GalR1 Recent studies have provided compelling clues for the hypothesis that galanin increases food intake and body weight through the actions of GalR1. First, among the three galanin receptors that are distributed in the central nervous system, GalR1 subtype predominates and accounts for approximately 90% of all ¹²⁵I-galanin-binding sites in the PVN, with the residual 10% being either GalR2 or GalR3^[32,33]. In addition, the expression of GalR1 mRNA is positively correlated with galanin level, but there is no such correlation with GalR2 or GalR3 expression in the hypothalamic nuclei of galanin transgenic mice^[34]. Second, GalR1 knockout (GalR1-KO) mice show abnormal adaptation to dietary challenges under high-fat and high-glucose conditions, while showing normal regulation with chow diets^[35–37]. In response to an acute 3-day high-fat challenge, GalR1-KO mice display impaired adaptation, leading to increased food intake and weight gain, compared with normal food intake and weight modulation in response to low-fat diets^[35]. This latter finding is consistent with the phenotype reported for the GKO mouse, which is more sensitive to leptin treatment^[38]. These results correspond with previous reports that GKO mice have significant alterations in neuroendocrine homeostasis^[26], suggesting that through GalR1, galanin is involved in conditioned neuroendocrine homeostasis. Notably, in contrast to an acute high-fat diet, GalR1-KO mice with a chronic high-fat diet consume less food and daily energy, indicating that GalR1 may oppose positive energy-balance^[35]. Moreover, GalR2 knockout mice show no change in feeding behaviors or body weight^[39]. In summary, these results suggest that GalR1 is involved in reducing feeding behavior, and that the endogenous galanin-GalR1 system does play a significant role in adjusting food intake and metabolism in response to acute changes in dietary fat. Third, a previ-

ous study showed that the GalR1-selective agonist M617 stimulates acute feeding on cookie mash^[40]. This was later extended to show that, through GalR1, galanin is involved in aspects of conditioned feeding^[41]. More recently, it has been shown that i.c.v. administration of M617 markedly stimulates the acute consumption of high-fat milk, and has significant effects on food intake and body weight, whereas the GalR2-selective agonists M1145 and M1153, as well as the GalR2-selective antagonist M871 have no such effects^[42].

Based on these reports, we postulate that galanin increases food intake and body weight via the actions of GalR1, suggesting that GalR1 might be a new therapeutic target for preventing obesity.

3.2 Galanin and 5-HT_{1A} Serotonergic neurotransmitter systems play important roles in the brain. The serotonin receptors, also known as 5-hydroxytryptamine (5-HT) receptors, currently comprise of seven subfamilies, of which six are G protein-coupled receptors and one (5-HT₃) is a ligand-gated ion channel^[43]. It was first demonstrated in the 1970s that the brain 5-HT system has a hypophagic effect in feeding behavior, mainly through the 5-HT_{1A} and the 5-HT_{1B} receptors, while the 5-HT_{1A} subtype appears to play a critical role in decreasing the food intake, making a specific contribution to the regulation of food intake^[44-46]. 5-HT_{1A} receptors are extensively distributed in the PVN, supraoptic, arcuate and ventromedial nuclei and the lateral hypothalamic area^[47]. Recent studies have confirmed that the 5-HT_{1A} agonist 8-hydroxy-2-(di-*n*-propylamino)-tetralin injected into the lateral hypothalamus significantly reduces food intake in female rats^[48]. 5-HT_{1A} plays an essential role in the feeding-related mechanisms of serotonergic control located at the arcuate nucleus and the lateral hypothalamus of female rats^[48].

Serotonin regulates galanin-induced selective macronutrient intake in self-selecting rats, and the galanin-induced increase of total intake regresses to the baseline level when coinjected with 5-HT, implying that galanin has a close association with hypothalamic serotonergic activity^[49]. Besides, i.c.v. injection of galanin shows strong inhibitory actions on 5-HT_{1A} receptor functions^[50]. An

early neurochemical study showed that in limbic cortex, galanin in nanomolar concentrations decreases the affinity of post-junctional [³H]-5-HT_{1A} agonist-binding sites, indicating a potential link between GalR and 5-HT_{1A}^[51]. The modulation by galanin receptors of 5-HT_{1A} agonist-binding sites gave the first clue that GalR/5-HT_{1A} heteromers may exist where galanin receptors antagonize the signaling of postjunctional 5-HT_{1A} via intramembrane receptor-receptor interactions^[51,52]. Remarkably, a recent study confirms that GalR1-5-HT_{1A} heteromers indeed exist^[53]. With a proximity-based fluorescence resonance energy transfer technique, it was demonstrated that GalR1-5-HT_{1A} heteromers are present in HEK cells which were transiently transfected with GFP2-tagged 5-HT_{1A} receptor and YFP-tagged GalR1 receptor^[53]. These results suggest that galanin-induced food intake is probably due to the activation of GalR1-5-HT_{1A} heteromers which inhibit the activation of 5-HT_{1A} and increase food intake. These findings are consistent with previous reports that galanin has important inhibitory actions on central 5-HT neurotransmission by affecting 5-HT_{1A} receptor-mediated events^[54,55].

3.3 Galanin and adrenergic α -2 receptor It is known that the brain adrenergic α -2 receptor is closely associated with the stimulation of feeding behavior^[56,57]. The orexigenic effect of galanin is abolished by inhibiting the synthesis of noradrenaline, indicating that galanin regulates hypothalamic noradrenergic activity^[58]. In addition, acute central administration of galanin stimulates feeding behavior, and this orexigenic effect is mediated by adrenergic α -2 receptor in chicks^[15] and goldfish^[16], suggesting that the mechanism of galanin-induced feeding is mediated through noradrenergic α -2 receptor systems in the brain^[15,16,58,59].

4 Conclusion

Galanin has been reported to increase the preference for a high-fat diet given a choice of fat, carbohydrate, or protein. As research on ingestive behavior has progressed, the regulation of food intake by galanin seems to be more complex. Studies on the role of galanin in promoting food intake started with GalR and gradually expanded to other receptors, such as 5-HT_{1A} and the adrenergic α -2 receptor.

Numerous studies have shown that the endogenous galanin-GalR1 system does play a significant role in adjusting food intake and energy expenditure. In contrast, GalR2 has no effects on feeding behaviors or body weight. These data are compatible with the hypothesis that galanin regulates fat intake, implying that an GalR1 antagonist may be of interest in the treatment of some forms of obesity. Further understanding of these systems involved in feeding behavior will allow researchers to develop effective therapies for overeating.

Obesity is known to be a major cause of insulin resistance. Interestingly, galanin also promotes insulin sensitivity^[28,29]. Most recently, our studies in skeletal muscle and adipocytes preliminarily verified the hypothesis that endogenous galanin notably enhances insulin sensitivity and reduces insulin resistance^[30,31]. As yet it is unknown which of the three receptor subtypes is/are the most effective in enhancing insulin sensitivity. As noted above, GalR1 increases food intake and body weight, but GalR2 plays no role in feeding behaviors or body weight, suggesting that GalR is a significant subject for further exploration in reducing insulin resistance. Current approaches used for the prevention and treatment of type 2 diabetes are not adequately effective. Most of the anti-diabetic drugs induce many adverse effects, in particular obesity, and thus may initiate a vicious cycle of problems. Since GalR2 has no effect on body weight, if it can reduce insulin resistance, it could become a new therapeutic target. These findings first indicate that galanin receptor subtypes may provide new therapeutic targets for preventing obesity and treating type 2 diabetes.

In summary, with the aid of genetic, behavioral and pharmacological methods, the general role of the galanin system and the roles of individual galanin receptor subtypes in the regulation of food intake and energy expenditure can be clarified, thus providing useful hints for the development of novel therapeutic approaches for the treatment of obesity and type 2 diabetes.

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中枢神经系统甘丙肽调节摄食行为及相关机制研究进展

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摘要: 甘丙肽广泛分布于各个脑区, 具有广泛的生理活性, 能够调节能量消耗、促进摄食、增加体重。研究表明, 甘丙肽主要通过甘丙肽受体1、5-HT_{1A}受体以及 α -2肾上腺素能受体调节摄食行为。本文主要对中枢神经系统甘丙肽的调节摄食行为及其相关机制进行综述, 为甘丙肽功能的进一步研究提供依据。

关键词: 甘丙肽; 受体; 摄食行为; 中枢神经系统