The Role of GIP Receptor in the CNS for the Pathogenesis of Obesity

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Glucose-dependent insulinotropic polypeptide (GIP) (also known as gastric inhibitory polypeptide) is a hormone produced in the upper gut and secreted to the circulation in response to the ingestion of foods, especially fatty foods. Growing evidence supports the physiological and pharmacological relevance of GIP in obesity. In an obesity setting, inhibition of endogenous GIP or its receptor leads to decreased energy intake, increased energy expenditure, or both, eventually causing weight loss. Further, supraphysiological dosing of exogenous long-lasting GIP agonists alters energy balance and has a marked antiobesity effect. This remarkable yet paradoxical antiobesity effect is suggested to occur primarily via the brain. The brain is capable of regulating both energy intake and expenditure and plays a critical role in human obesity. In addition, the GIP receptor is widely distributed throughout the brain, including areas responsible for energy homeostasis. Recent studies have uncovered previously underappreciated roles of the GIP receptor in the brain in the context of obesity. This article highlights how the GIP receptor expressed by the brain impacts obesity-related pathogenesis.

Glucose-dependent insulinotropic polypeptide (GIP) is a 42–amino acid polypeptide that is produced by enteroendocrine K cells in the proximal small intestine (1,2). In response to nutrient ingestion, GIP is secreted into the circulation, acts directly on the GIP receptor (GIPR) expressed by pancreatic β-cells, and stimulates insulin secretion. Thus, a major role of GIP is to mediate the postprandial potentiation of insulin secretion. Indeed, GIP and glucagon-like peptide 1 (GLP-1), which is another incretin hormone, account for up to 70% of the postprandial insulin response (1,2).

GIP has long been considered an "obese hormone" (3–5). Early studies showed that obese subjects exhibit an exaggerated GIP secretion response following nutrient ingestion as well as elevated fasting GIP levels (6). In animal models of high-fat diet (HFD)-induced obesity, K cell hyperplasia and increased production of GIP were observed (7,8). Furthermore, GIP promotes fat deposition in the adipose tissues (4). Although favorable data to support this model accumulated for many years, direct evidence supporting a role for GIP as an obesogenic signal initially came from a seminal study by Seino and colleagues (5). They showed that mice with GIPR deficiency displayed relatively normal adiposity and body weight when fed a normocaloric diet; however, when challenged with an HFD, these mice gained less body weight and fat mass and reserved normal insulin sensitivity (5). These observations suggest that GIPR deficiency protects mice from diet-induced obesity and insulin resistance, which has subsequently been supported by many studies. Now, inhibition of endogenous GIP or its receptor is generally accepted to confer resistance to HFD-induced obesity. Many methods of inhibition have been tested, including GIP deficiency (9), ablation of GIP-producing K cells (10), neutralizing antibodies against GIP/GIPR (11–14), GIP vaccination (15–17), and pharmacological inhibition of GIPR (18). In addition, recent genome-wide association studies (GWAS) have identified GIPR variants associated with obesity and BMI, some of which are associated with a lower BMI (19–24). Thus, the currently available data strongly suggest that the endogenous GIP-GIPR system plays a role in the pathogenesis of obesity.

In contrast to its assumed obesogenic role, GIP does not promote food intake or adiposity (25–27). Instead, negative energy balance is induced by administration of long-lasting GIP derivatives (28,29) or transgenic overexpression of *GIP* (30). In addition, GLP-1/GIP hybrid peptides have been shown to induce marked weight loss in preclinical and clinical settings (31,32). The therapeutic

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efficacy of this combination is superior to that of GLP-1 receptor agonists alone, suggesting that GIP agonism has weight-reducing effects in a pharmacological context. The effect of GIP alone or in combination with GLP-1 on food intake requires central GIPR signaling (29). As such, weight loss can be achieved by either GIPR antagonism or agonism. Whereas the exact underlying mechanism remains unknown, a possible explanation for the paradoxical observations is that chronic GIPR agonism desensitizes GIPR, which ultimately results in creating antagonism (24). Although GIPR desensitization in adipocytes has been reported (24), recent studies have shown that this phenomenon does not seem to be applicable to the GIPR in β-cells (33,34). Thus, whether GIPR desensitization occurs in the central nervous system (CNS) and mediates the antiobesity effect of GIPR antagonism remains an open question. Nevertheless, manipulation of the GIP system has a profound impact on energy balance.

In light of the energy balance equation, energy expenditure must exceed energy intake for weight loss to occur. This remains true for GIP-mediated weight loss, which induces increased energy expenditure, decreased food intake, or both (35). As the brain affects both energy intake and expenditure, it is possible that the CNS mediates GIP action. However, early studies suggested that intracerebroventricular (ICV) administration of native GIP does not affect food intake (e.g., [25]) and concluded that GIP does not influence feeding behavior. Although GIPR has been identified in the CNS, very few studies have investigated the CNS role of GIPR in energy homeostasis. Recent findings have renewed interest into whether and how GIPR expressed in the brain mediates its physiological and pharmacological effects on energy balance.

In this Perspective, the role of the CNS in energy balance will be outlined, and discoveries delineating the role of GIP in the CNS will be reviewed. Finally, the potential pathophysiological CNS role of GIPR in obesity will be highlighted.

Hypothalamic Control of Energy Balance

Body weight is tightly regulated by the balance of energy intake and energy output via the neural circuits in the CNS. Neural control of energy balance is achieved through the coordinated integration of multiple neural signals from distinct neural circuits involving the hypothalamus, the hindbrain, the amygdala, prefrontal cortex, hippocampus, and other areas in a complex and redundant manner. The hypothalamus plays a primary role in regulating energy balance, being closely interconnected and reciprocally influencing other neural circuits in the different CNS sites. The hypothalamus is a small region located at the base of the brain and is a highly heterogeneous structure composed of many small nuclei with various functions. Hypothalamic neurons communicate with peripheral organs via circulating factors, such as insulin, leptin, gut hormones, and a variety of nutrients. A key site in the hypothalamus receiving peripheral signals is the arcuate nucleus (ARC) (36). ARC neurons can access the adjacent median eminence, which lacks a functional blood-brain barrier (BBB), permitting ARC neurons to sense blood-borne factors from the periphery (37). This anatomical characteristic makes the ARC an ideal site to respond to peripheral factors and signal to the brain. Within the ARC are two distinct prototypical neuronal populations that yield opposing effects on energy balance: the orexigenic neurons expressing neuropeptide Y and Agouti-related peptide (AgRP/NPY neurons) that promote feeding behavior when activated and the anorexigenic neurons expressing proopiomelanocortin (POMC neurons) that suppress food intake when stimulated (38,39). The ability of orexigenic and anorexigenic neurons to directly respond to circulating hormones and mediate metabolic effects demonstrates that the ARC is a critical site for peripheral metabolic signals.

The central role of the brain in the development and maintenance of obesity has been unequivocally established over the last decades. First, the generation of experimental lesions in the hypothalamus using a stereotaxic apparatus demonstrated that hypothalamic damage causes obesity, firmly establishing the concept of hypothalamic obesity (40). Second, genetic studies of monogenic obesity syndromes support the role of the hypothalamus in human obesity. Many of the genes responsible for human monogenic obesity act through the hypothalamic leptin/melanocortin pathway (41), pointing to the critical role of the hypothalamus in human obesity. Finally, unbiased genetic discovery through GWAS further supports a primary role for the brain in human obesity. GWAS have identified >500 loci associated with BMI and obesity, and the vast majority of the genes located near and/or within the GWAS loci are enriched in the brain or linked to its function (42). Therefore, the CNS is now well established as a critical driver of obesity. Accordingly, studies of central aspects of GIP biology are of increasing importance to fully understand the role of GIP in obesity and its paradoxical antiobesity effects.

GIPR Expression in the Brain

GIPR expression has been observed throughout the brain, including CNS sites responsible for energy metabolism. An early autoradiographic analysis of [^{125}I]GIP identified putative GIPR binding sites in several brain regions (43) but failed to detect GIP binding in the hypothalamus. Other methodologies, such as in situ hybridization, Northern blot, and quantitative PCR (qPCR), also showed broad CNS distribution of *GIPR* mRNA and included the hypothalamus (13,44–47). Elegant work by Adriaenssens et al. (48) recently revealed the anatomical distribution of *GIPR* in the CNS at a cellular resolution. They generated a *Cre*-dependent reporter mouse that enabled the identification of *Gipr*-positive cells and observed *Gipr* expression

throughout the CNS, including the hypothalamic nuclei (the ARC and dorsomedial and paraventricular nuclei of the hypothalamus) and hindbrain areas that are involved in energy balance. Because this model is a germ line reporter, transient expression of Cre recombinase during development may be possible. Nevertheless, these data suggest that GIPR is present in the CNS regions that are responsible for energy homeostasis and support a CNS role for GIPR in the control of energy balance.

The Effect of Pharmacological Activation of GIPR in the CNS on Food Intake and Body Weight

The effect of centrally administered GIP on food intake was studied as early as the 1980s (Table 1). Woods et al. (25) found that a single ICV dose of native GIP at 20 pmol had no effect on food intake in rats. For the next 30 years, the CNS role of GIP in energy balance did not appear in the literature. In 2011, one report demonstrated that chronic ICV administration of native GIP at a supraphysiological dose (2,000 pmol/day) caused significant weight loss in rats, whereas ICV dosing at 20 and 200 pmol/day did not affect body weight or food intake (26). Further, a central bolus injection of GIP suppressed food intake in lean C57BI/6 mice at a higher dose (6,000 pmol) but not at lower doses (1,000 and 3,000 pmol) (27). Similarly, we did not observe changes in food intake or body weight when native GIP was ICV infused at 30 and 3,000 pmol in lean C57BI/6 mice (13,49). Recently, Zhang et al. (29) demonstrated that a long-lasting, fatty acylated GIP agonist suppressed food intake and reduced body weight of diet-induced obese mice when acutely ICV administered at 1,000, 3,000, and 6,000 pmol or when chronically dosed at 20 and 40 pmol/day. Importantly, the weight loss effect of ICV-administered acyl-GIP was blunted in brain-specific GIPR knockout mice (29), suggesting that this effect occurs via GIPR in the CNS. Interestingly, acyl-GIP stimulates c-fos induction (a marker for neural activation) in the ARC (29) where GIPR is expressed (48). Chemogenetic activation of GIPR-expressing cells with Designer Receptors Exclusively Activated by Designer Drugs (DREADD) technology also resulted in suppressed food intake (48). Thus, food intake and body weight can be clearly reduced by supraphysiological doses of native GIP or administration of a long-lasting GIP derivative.

As shown in Table 1, the ICV doses of the native GIP needed to reduce food intake are in the range of several thousand picomoles/brain (i.e., on the order of micromolar concentrations of brain GIP assuming a mouse brain volume of 1 mL). Because the endogenous GIP concentration in the cerebrospinal fluid (CSF) was reported to be at the low picomolar range (13), the effective concentrations of ICV GIP seem to be approximately six orders of magnitude above physiological levels of CSF GIP. Similarly, the

Table 1—Summary of the effects of ICV dosing of the intact GIP and acyl-GIP on body weight and food intake

Peptides	Dose (pmol)	Duration	Species	Diet	Effect on body weight	Effect on food intake	First author (reference no.)
GIP	20	30 min	Rat	NC	—	No	Woods (25)
GIP	20/day	4 days	Rat	NC	No	No	Ambati (26)
GIP	200/day	4 days	Rat	NC	No	No	
GIP	2,000/day	4 days	Rat	NC	Decrease	No	
GIP	1,000	0–24 h	Mouse	NC	No	No	NamKoong (27)
GIP	3,000	0–24 h	Mouse	NC	No	No	
GIP	6,000	0–24 h	Mouse	NC	No	Decrease	
GIP	30	24 h	Mouse	NC	—	No	Kaneko (13)
GIP	3,000	24 h	Mouse	NC	No	No	Fu (49)
GIP	30/day	0–3 days	Mouse	NC	No	No	
GIP	3,000/day	0–3 days	Mouse	NC	No	No	
Acyl-GIP	1,000	0 to ∼90 h	Mouse	HFD	Decrease	Decrease	Zhang (29)
Acyl-GIP	3,000	0 to ∼90 h	Mouse	HFD	Decrease	Decrease	
Acyl-GIP	6,000	0 to ∼90 h	Mouse	HFD	Decrease	Decrease	
Acyl-GIP	20/day	0–12 days	Mouse	HFD	Decrease	Decrease	
Acyl-GIP	40/day	0–12 days	Mouse	HFD	Decrease	Decrease	

NC, normal chow diet.

enormous ICV doses are also required for GLP-1–induced anorectic actions (ICV doses of 750–1,000 pmol of exogenous GLP-1) (27,50,51) vs. the lower end of the picomolar range of endogenous GLP-1 concentration in the CSF (e.g., 52,53). Thus, an enormous amount of exogenous GIPs is required to induce the effect. Furthermore, the effect occurs not only in obese animals but also in normal chow–fed lean animals, which is not typically observed with the inhibition of the endogenous GIP signal. With these observations taken together, it appears that the pharmacological effects may not be induced by the processes and/or sites in the CNS physiologically engaged by the endogenous GIP signal, although the exact underlying mechanisms are unknown. Nevertheless, this important aspect of GIP biology definitely warrants future studies.

The Origin of GIP in the Brain

In establishing the physiological relevance of GIPR in the brain, it is important to determine whether GIP exists in the brain and whether GIP can cross the BBB (2). In support of the physiological role of GIP in the brain, GIP has been detected in CSF in humans (54) and mice (13). However, the origin of brain GIP remains unknown. Two groups have reported centrally produced GIP. Nyberg et al. (55) found that GIP-immunoreactive cells were broadly distributed throughout the brain in rats, which was further confirmed by RT-PCR analysis of *Gip* mRNA. Of note, moderate GIP immunoreactivity was detected in the distinct hypothalamic nuclei (55). Another group also detected widespread *Gip* mRNA by in situ hybridization in the adult rat brain (44). However, centrally expressed GIP was not detected in other studies (13,47,56). We have attempted to clarify whether *Gip* mRNA is expressed in the hypothalamus of mice using RNA sequencing (RNA-seq) and qPCR. We did not detect substantial levels of *Gip* mRNA in the hypothalamus of lean mice or mice with diet-induced obesity mice by qPCR (13); however, we cannot rule out the presence of subdetection levels of *Gip* mRNA. Similarly, *GIP* transcripts were detected at low or nonexistent levels by RNA-seq analysis of the mediobasal hypothalamus (Y. Fu et al., Fukuda laboratory, data not shown). According to publicly available data, such as in the Expression Atlas (57), GIP is not expressed in any brain region in mice. Additionally, the Human Protein Atlas (58) indicates that GIP protein and mRNA are detected in the intestine but not in the brain. Given these conflicting data, the presence of endogenous GIP in the brain remains an open question. In contrast, accumulating evidence suggests that peripherally injected GIP can reach the brain. Peripherally administered GIP analogs exhibit multiple effects on brain function (59), including altered cognition and hippocampal synaptic plasticity. More direct evidence of GIP permeating the BBB comes from a recent study demonstrating that peripherally injected native GIP increases GIP levels in CSF collected from the cisterna magna in mice (13). The ability of GIP to cross the BBB supports its physiological relevance to GIPR expressed by the CNS. Future studies are warranted to clarify the origin of GIP and its interaction with GIPR in the brain.

The Physiological Role of GIPR in the CNS

It is becoming increasingly clear that pharmacological activation of central GIPR influences energy balance. The next key question is whether this has any biological relevance. The first clue came from a study investigating the effect of inhibition of endogenous GIPR in the brain on obesity (Fig. 1). In this study, a GIPR-neutralizing antibody (Gipg013, an antibody with high specificity and potent antagonism of GIPR [60]) was directly infused into the brains of mice with diet-induced obesity (13). The effects of the antibody were robust; at the end of the 15-day treatment, animal weight loss reached ∼15% of the initial weight. Food intake and fat mass were also significantly reduced and glucose homeostasis improved in obese mice receiving ICV GIPR antibody. The observed weight loss was likely achieved via reduced food intake because the treatment did not alter energy expenditure. Consistent with the phenotype of systemic GIPR knockout mice, weight loss was only observed in obese mice and not in lean mice. Interestingly, *ob/ob* mice lacking functional leptin (another animal model of obesity) did not lose weight in response to ICV GIPR antibody, implying a potential connection between brain GIPR and leptin.

Recently, Zhang et al. (29) published genetic evidence supporting the physiological role of central GIPR in energy balance. They generated CNS-specific GIPR knockout mice by crossing *Gipr* floxed mice to Nestin-*Cre* mice, which express *Cre* throughout the brain, including neural and nonneural cells. They found that CNS-specific GIPR knockout mice had lower body weights, reduced fat accumulation, and improved glucose metabolism when fed an HFD. Consistent with the ICV GIPR antibody studies, CNS-specific GIPR deficiency reduced food intake but did not alter energy expenditure. Loss of GIPR in the brain

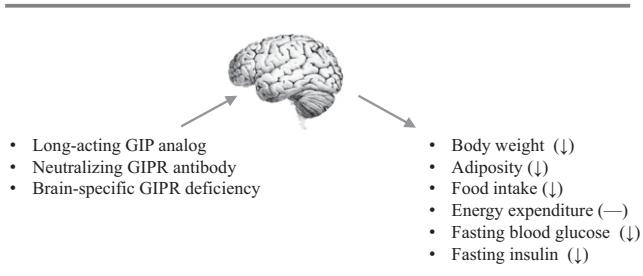

Figure 1—Schematic depiction of the antiobesity effects induced by central GIP agonism or antagonism. The weight loss effect is induced by either central administration of a long-acting GIP derivative, a neutralizing GIPR antibody, or genetic loss of brain GIPR. Interestingly, both central GIP agonism and antagonism have an effect on food intake but not on energy expenditure. Thus reduced energy intake is likely to account for the GIP-mediated weight loss.

did not affect the metabolic profiles of lean animals, which supports the specific role of GIPR in conditions of overnutrition. Collectively, brain-specific inhibition or deletion of GIPR remarkably improves the metabolic consequences of chronic HFD feeding, which typically include increased body weight, adiposity, and glucose imbalance (Fig. 1). CNS-specific loss of GIPR phenocopies the outcomes of systemic GIPR deficiency, suggesting that the CNS is a key mediator of the observed antiobesity effects. Supporting the metabolic role of the GIPR in the hypothalamus, our group has also shown that mediobasal hypothalamic-specific deletion of GIPR improves energy and glucose homeostasis under HFD conditions (K. Kaneko et al., Fukuda laboratory, unpublished data). For a deeper understanding of brain GIP biology, it is important to identify the sites, cell types (neurons, astrocytes, oligodendrocytes, microglia, and endothelial cells), and chemical identities of GIP-responsive neurons. Adriaenssens et al. (48) used single-cell RNA-seq to identify the cell types expressing GIPR and found that GIPR is expressed not only by neurons but also by other nonneural cells such as vascular and glial cells in the mouse hypothalamus. Thus, recent findings reveal the importance of a previously underappreciated site, the brain, in GIP biology.

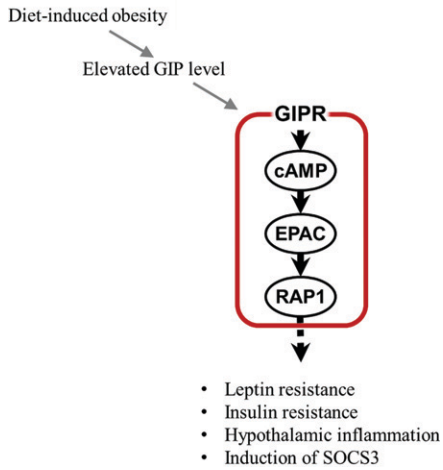

Figure 2—A model depicting a molecular mechanism involved in the actions of brain GIP signaling. Increased GIP associated with obesity activates the GIP receptor expressed by the hypothalamus, which in turn stimulates the cAMP-EPAC-RAP1 signaling cascade. Activation of the pathway results in the induction of SOCS3 and reduces neural leptin and insulin actions, thereby mediating dietary obesity. EPAC, the exchange factor directly activated by cAMP; GIP, glucose-dependent insulinotropic polypeptide (or gastric inhibitory polypeptide); SOCS3, suppressor of cytokine signaling 3.

The Role of CNS GIPR in Obesity-Associated Pathogenesis

In addition to its direct effect on feeding behavior (29,48), GIP may be involved in the physiological responses to diet-induced obesity (Fig. 2). Overnutrition triggers profound cellular and physiological changes in the hypothalamus, which ultimately promote positive energy balance (61,62). Hypothalamic cellular responses to HFD produce hypothalamic inflammation and cellular resistance to exogenous leptin and insulin. Given the critical importance of the hypothalamus in energy balance, hypothalamic reactions to HFD are considered the core of the pathophysiology of obesity. Over the past few decades, accumulating evidence has identified the endogenous GIP-GIPR system as a potential mediator of the physiological response to diet-induced obesity. In this regard, it is worth noting that the weight-reducing effect of genetic and pharmacological manipulation of GIP and GIPR is virtually only seen in obesity. Further, GIP secretion from the gut is potentiated in response to fatty foods, and higher concentrations of serum GIP are observed in obese humans and animals (6). These observations suggest that the GIP system plays a specific role in obesity. Experimental manipulation of GIPR activity in animals also supports this connection. As will be described below in more detail, increasing GIPR activity recapitulates aspects of obesity-associated pathophysiology, such as chronic inflammation and peripheral insulin resistance (63–71). In contrast, decreasing the endogenous activity of GIPR prevents mice from developing symptoms of HFD-induced obesity. Recent studies focusing on brain GIP-GIPR uphold this model by demonstrating that GIP drives a subset of the hypothalamic pathophysiological changes associated with dietary obesity. Taking into consideration the accumulating evidence, it is possible that GIP may promote obesity-related pathophysiological conditions. More specifically, GIP may act as a gut signal that arises from excess caloric intake, signals to the hypothalamus, and drives obesity-related pathophysiological derangements (Fig. 2).

GIP and Leptin Actions in the CNS

The first evidence to suggest a potential role of CNS GIPR in obesity-related pathophysiology emerged from attempts by our group to identify circulating factors inducing hypothalamic leptin resistance. Leptin is a hormone produced and secreted by adipocytes in proportion to fat mass and acts directly on neurons in the CNS (72). Leptin signals from adipose tissue to the brain to promote negative energy balance by decreasing food intake and increasing energy expenditure, which results in weight loss. Although weight loss is robustly observed when exogenous leptin is administered to lean individuals, obese individuals typically have elevated levels of circulating leptin and exhibit resistance to exogenous leptin (72,73). This phenomenon, known as leptin resistance, is a typical characteristic of the common forms of obesity. Although the root cause of leptin resistance is not thoroughly understood, hypothalamic neurons in the ARC are clearly unresponsive to exogenous leptin in the context of obesity, and this characteristic is likely to be key in deciphering leptin resistance.

To identify circulating factors that cause leptin resistance, we adapted a candidate-ligand approach to screen ligands of G-protein–coupled receptors (GPCRs) that link to cAMP-related signaling. Previously, we found that cAMP impairs multiple signaling cascades activated by leptin within the hypothalamus (74,75). Notably, this effect is mediated not by the classical cAMP effector, protein kinase A (PKA), but by a relatively new cAMP effector, EPAC (76), which is a cAMP-regulated guanine nucleotide exchange factor for the small G-protein RAP1 (75). Based on this observation that leptin resistance is potently induced by cAMP-EPAC-RAP1 signaling (75,77), we hypothesized that GPCRs that activate cAMP-EPAC-RAP1 signaling may also drive leptin resistance. Candidate GPCR ligands were selected in the International Union of Basic and Clinical Pharmacology GPCR database (78). During ex vivo screening, GIP came up as a potent cause of cellular leptin resistance. Indeed, GIP treatment of ex vivo hypothalamic explants induces multiple indices of cellular leptin resistance (13). In vivo studies also suggest that centrally administered GIP diminished the cellular and anorectic responses to exogenous leptin (13). In addition, peripheral administration of native GIP for 3 days at levels similar to those observed in obese animals markedly blunted leptin-induced suppression of food intake and weight loss (13). Thus, the increased levels of GIP associated with obesity sufficiently diminish hypothalamic leptin action. Further, mice with systemic GIPR deficiency (5) retain leptin sensitivity even after chronic HFD feeding (13). Obese control mice lose their response to exogenous leptin, suggesting that GIPR is necessary for diet-induced leptin resistance. Interestingly, GIP inhibited leptin-induced phosphorylation of STAT3 (a major signaling molecule mediating the action of leptin), particularly in ARC neurons both ex vivo and in vitro (13). Furthermore, an electrophysiological study demonstrated that GIP blocks leptin-induced neural activation in POMC neurons in the ARC (13). Given that ARC neurons, including POMC neurons, express GIPR (48), POMC neurons and other ARC neurons may be GIP targets in the CNS. Most recently, mice lacking *GIPR* specifically in leptin-responsive cells (LepR cell–specific GIPR KO mice) have been developed. After prolonged HFD feeding, control mice failed to respond to exogenous ICV infusion of leptin as expected, due to the development of central leptin resistance. Under the same conditions, age- and body weight-matched LepR cell-specific GIPR KO mice did respond to ICV leptin, demonstrating significantly reduced body weight and food intake (Y. Fu et al., Fukuda laboratory, unpublished observations). Thus, increased GIP in obesity may mediate cellular leptin resistance by acting directly on GIPR-expressing, leptin-responsive neurons (Fig. 2).

The Role of GIP in Hypothalamic Inflammation and Insulin Response

In alignment with its role as a putative obesogenic factor, GIP has been shown to contribute to peripheral low-grade inflammation and insulin resistance, the hallmarks of obesity. GIP stimulated gene expression of proinflammatory cytokines and chemokines in cultured and primary adipocytes (63–68). In vivo studies infusing GIP into the periphery of animals and humans resulted in increased adipokines and proinflammatory cytokines in adipocytes (67,69,70). Similarly, high plasma GIP levels are associated with elevated proinflammatory gene expression in obese humans (71). Adipocyte-specific deletion of GIPR decreases expression of the proinflammatory cytokine IL-6 (63,68). Together, these findings clearly demonstrate the role of GIP in driving inflammatory responses; however, not all studies support this conclusion. For example, overexpression of GIP (30) or chronic infusion of a long-lasting GIP analog (79) reduces adipose tissue macrophage infiltration and proinflammatory cytokine expression. Moreover, GIPR deficiency in bone marrow myeloid cells increases expression of proinflammatory factors and reduces insulin sensitivity (80). Thus, the impact of GIP on inflammation remains incompletely understood.

Recently, an unbiased RNA-seq analysis connected GIP to hypothalamic inflammation. In this study, hypothalamic transcriptomes from mice with or without central GIP injection (30 pmol/brain) were compared (49). The majority of the top 50 genes upregulated by GIP stimulation were associated with cytokines and chemokines. Further, gene ontology and gene set enrichment analysis of the differentially expressed genes identified inflammatory-related signaling as the most significantly represented molecular pathway. Interestingly, this effect is likely hypothalamic specific because induction of inflammatory-related genes did not occur in the cortex of these mice. Peripheral injection of a long-acting GIP mimetic, [D-Ala^2]GIP (60 pmol), or native GIP (300 pmol) also resulted in increased hypothalamic *IL-6* mRNA. In contrast, GIPR knockout mice had significantly reduced mRNA levels of proinflammatory cytokines and *Socs3* in the hypothalamus. Acute inhibition of GIPR via a centrally delivered neutralizing GIPR antibody also reduced *IL-6* mRNA in the hypothalamus (49). A link between GIP and *IL-6* is further supported by other studies showing GIP-dependent expression of *IL-6* in adipose tissues (63,68). Along with hypothalamic inflammation, GIP impaired the insulin-induced anorectic response and insulin-dependent activation of AKT/glycogen synthase kinase-3β (GSK3β) signaling (49), the crucial signaling pathway of metabolic action of insulin. These observations support the model that GIP contributes to diet-induced hypothalamic inflammation and insulin resistance (Fig. 2).

Of note, supraphysiological dosing of a long-lasting GIP agonist has an opposing effect on neural inflammation. In the context of neurodegenerative diseases, peripheral administration of long-lasting [D-Ala^2]GIP derivatives (2,500 pmol/kg/day) significantly reduces the activation of microglia and astrocytes in the CNS (59). Further, a dual GLP-1/GIPR agonist more effectively

reduces proinflammatory cytokine levels in the brain in a mouse model of Alzheimer disease than the GLP-1R agonist alone (81), suggesting that the GIP moiety potentiates the anti-inflammatory effect of the GLP-1 agonist. It is thus of great interest to determine whether similar antineuroinflammatory effects can be induced by inhibition of endogenous GIPR in the CNS.

Hypothalamic GIPR Signaling

Although GIPR signaling in the brain is not fully understood in the context of obesity, the connection between GIPR and cellular leptin resistance has been established (13). GIP increases cAMP levels in cultured cells (82–84), and cAMP acts through PKA and EPAC. GIP-mediated induction of leptin resistance is completely blocked by specific EPAC inhibitors (ESI-05 and ESI-09) but is not affected by PKA inhibitors ($PKI_{14–22}$ or H89) (13). Moreover, in vivo pharmacological inhibition of EPAC2 blocks GIP-mediated action in mice (13). In support of the involvement of the GIPR-EPAC pathway in leptin resistance, GIP increases the biochemical activity of the small GTPase RAP1, a direct target of EPAC, both ex vivo and in vivo (13). Loss of RAP1 abrogates the effect of GIP on leptin. Thus, hypothalamic GIPR activates the EPAC-RAP1 pathway to exert its action on leptin. How GIPR-EPAC-RAP1 signaling negatively regulates cellular leptin action is the next logical question. Of the direct inhibitors of the leptin receptor, only SOCS3 is sufficiently induced by activation of the GIPR-EPAC pathway (13). In contrast, SOCS3 mRNA and protein levels decline after pharmacological inhibition of EPAC or loss of RAP1 (13). Further, in a *Socs3*-luciferase reporter mouse (85), significantly elevated luciferase activity was detected in hypothalamic explants in response to GIP treatment (E.L. Cordonier et al., Fukuda laboratory, unpublished observations). Thus, GIP inhibits leptin action by activating the EPAC-RAP1 pathway and inducing SOCS3, which directly inhibits the leptin receptor.

Other Roles of the Brain GIP System

Several studies have shown that GIPR in the brain modulates brain functions other than metabolic control. GIPR-deficient mice exhibit impaired memory formation and hippocampus-dependent spatial learning and memory (86). Consistently, loss of GIPR completely abolishes long-term potentiation in area CA1 of the hippocampus as well as reduces the number of neuronal progenitor cells in the dentate gyrus of transgenic mice (87). In addition, mice vaccinated against GIP display significant changes in behavior in the open field test. Conversely, GIP analogs or GIP/GLP coagonists seem to induce several neuroprotective effects, including stimulating progenitor cell proliferation in the hippocampus, improving learning and memory, and enhancing synaptic plasticity in animal models of Alzheimer and Parkinson disease (59). Thus, available evidence suggests that brain GIPR has an impact on brain functions, and further investigation of these psychiatric, emotional, and cognitive aspects will clarify the appropriate use of central GIP-targeting therapies in humans.

Concluding Remarks

Investigation of the GIP-GIPR system in the brain has begun to uncover physiological, pathological, and pharmacological roles of CNS GIPR in energy metabolism. Progress in this area includes but is not limited to mapping of GIPR distribution in the CNS, discovery of the critical role of CNS GIPR in energy balance, and identification of CNS GIPR-mediated regulation of leptin, insulin, and neuroinflammation. These findings highlight the importance of the brain for GIP-based obesity therapies, and future advances in the neurobiology of GIP will further offer a framework for a better understanding of therapeutic actions targeting central GIPR by identifying neural circuits and signaling pathways responsible for the GIP-mediated antiobesity effects. Emerging data also present a new perspective on pathophysiological roles of the endogenous GIP system in the CNS. Gaining further mechanistic insight into the pathophysiological process involving CNS GIPR signaling will provide a foundation for future GIP-based therapeutics for the treatment of metabolic diseases and neurodegenerative disorders.

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