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| Title       | Gastric inhibitory polypeptide/glucose-dependent insulinotropic polypeptide signaling in adipose tissue  |
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| Citation    | Journal of Diabetes Investigation (2019), 10(1): 3-5   |
| Issue Date  | 2019-1   |
| URL         | <a href="http://hdl.handle.net/2433/241649">http://hdl.handle.net/2433/241649</a>  |
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| Type        | Journal Article  |
| Textversion | publisher  |

# Gastric inhibitory polypeptide/glucose-dependent insulinotropic polypeptide signaling in adipose tissue

## INTRODUCTION

Obesity has been recognized as a worldwide problem, especially for developing insulin resistance and increasing the risk of type 2 diabetes. The increased adipose tissue associated with obesity secretes various kinds of cytokines, adipokines and lipokines, and triggers systemic inflammatory response, resulting in the disturbance of metabolic homeostasis.

Gastric inhibitory polypeptide/glucose-dependent insulinotropic polypeptide (GIP) is an incretin secreted from enteroendocrine K cells in response to meal ingestion<sup>1</sup>, and potentiates insulin secretion through the GIP receptor (GIPR) expressed in pancreatic  $\beta$ -cells<sup>2</sup>. Dietary lipid is a very strong stimulant of GIP secretion. For example, the peak value of GIP increase in response to a high-fat meal (450 kcal containing 33.3% of fat) is threefold higher than that in the 75-g oral glucose tolerance test in human subjects, suggesting that fat content in a mixed meal strongly stimulates GIP secretion<sup>1</sup>. Chronic high-fat consumption induces hypersecretion of GIP from K cells<sup>3</sup>, and insulin secretion in response to GIP is enhanced in high-fat diet (HFD)-fed obese mice compared with that in lean mice fed a normal-fat diet<sup>4</sup>, indicating that GIPR signaling plays a critical role in postprandial hyperinsulinemia associated with chronic HFD feeding and the subsequent increase in lipoprotein lipase activity, which results in HFD-induced fat accumulation (Figure 1). Actually, reduction in GIPR signaling using systemic GIPR knockout (GIPR<sup>-/-</sup>) mice<sup>5</sup>, a GIP antagonist<sup>6</sup> and GIP immunoneutralization ameliorates obesity under HFD-fed conditions. In addition, we have reported that genetic deletion of GIP alleviates obesity and lessens the degree of insulin resistance in HFD-fed mice<sup>7</sup>. In contrast, given that functional GIPR is expressed in rodent and human adipocytes, it has been assumed that GIP also has direct effects on adipose tissue and plays some roles in lipid metabolism under HFD-fed conditions.

## GIP SIGNALING IN ADIPOSE TISSUE

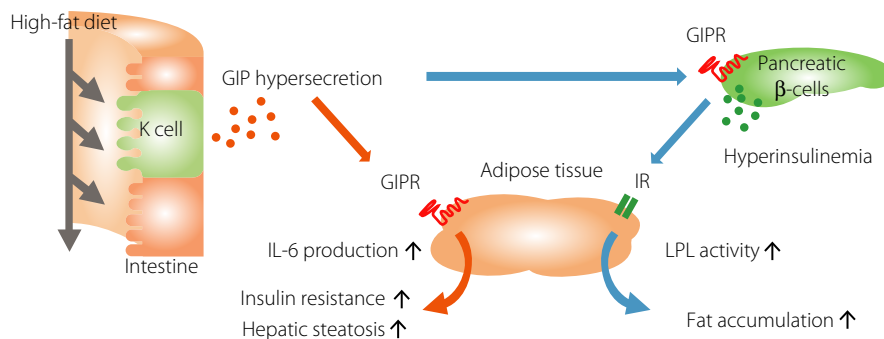
*In vitro* studies have shown that GIP directly induces fat accumulation in adipose tissue by increasing lipoprotein lipase expression through the cyclic adenosine monophosphate response element-binding protein (CREB)-regulated

transcription coactivator 2-mediated pathway, and by increasing lipoprotein lipase enzyme activity and plasma membrane glucose transporter 4 expression through the protein kinase B (PKB)-mediated pathway<sup>8</sup>. However, the physiological significance of GIPR signaling in adipocytes, namely, whether GIPR expressed in adipose tissue plays some roles in HFD-induced obesity and insulin resistance *in vivo*, has remained unproven.

To address this problem, we generated adipose tissue-specific GIPR knockout (GIPR<sup>adipo-/-</sup>) mice<sup>9</sup>. Under HFD-fed conditions, GIPR<sup>adipo-/-</sup> mice had significantly lower bodyweight and lean body mass compared with those in floxed GIPR (GIPR<sup>fl/fl</sup>) mice, although the fat volume was not significantly different between the two groups. Interestingly, insulin resistance, liver weight and hepatic steatosis were reduced in HFD-fed GIPR<sup>adipo-/-</sup> mice compared with those in GIPR<sup>fl/fl</sup> mice. Microarray analysis of adipose tissues showed that expression of interleukin-6 (IL-6), a pro-inflammatory cytokine that induces insulin resistance and hepatic steatosis<sup>10</sup>, was significantly decreased in adipose tissue of GIPR<sup>adipo-/-</sup> mice, and plasma levels of IL-6 were also reduced in HFD-fed GIPR<sup>adipo-/-</sup> mice compared with those in HFD-fed GIPR<sup>fl/fl</sup> mice.

Previous *in vitro* studies have shown that GIP increases IL-6 expression levels in adipose tissue<sup>11</sup>. In astrocytes, CREB activated by  $\beta$ -adrenergic receptor enhances IL-6 expression induced by tumor necrosis factor (TNF)- $\alpha$  receptor signaling<sup>12</sup>. It has been reported that GIP activates CREB in adipose tissue<sup>13</sup>. In our study using differentiated 3T3-L1 adipocytes, IL-6 expression was significantly augmented by GIP in the presence of TNF- $\alpha$ , suggesting that GIP enhances IL-6 messenger ribonucleic acid (mRNA) expression induced by TNF- $\alpha$  in adipose tissue, possibly through CREB activation.

Suppressor of cytokine signaling (SOCS) protein is induced by the activation of cytokine receptors, including the IL-6 receptor, TNF- $\alpha$  receptor and Toll-like receptors, and attenuates cytokine signal transduction<sup>14</sup>. Seven SOCS proteins have been identified, and SOCS1 and SOCS3 were recently reported to negatively regulate insulin signaling by competitively interfering with insulin receptor substrate binding to the insulin receptor<sup>15</sup>, by inhibiting insulin receptor autophosphorylation<sup>16</sup> and by



**Figure 1** | Schematic representation illustrating potential mechanisms by which GIP hypersecretion in high-fat diet conditions induces insulin resistance and hepatic steatosis. GIP, gastric inhibitory polypeptide/glucose-dependent insulinotropic polypeptide; GIPR, gastric inhibitory polypeptide/glucose-dependent insulinotropic polypeptide receptor; IR, insulin receptor; IL-6, interleukin-6; LPL, lipoprotein lipase.

promoting proteasomal degradation of insulin receptor substrate<sup>17</sup>. In particular, SOCS3 signaling is located downstream of the IL-6 receptor<sup>14</sup>, and is associated with insulin resistance and hepatic steatosis<sup>18</sup>. Our *in vitro* experiments showed that GIP induced mRNA expression of IL-6 and SOCS3 in the presence of TNF- $\alpha$  in differentiated 3T3-L1 adipocytes. In addition, expression levels of SOCS3 mRNA were decreased in adipose and liver tissues of GIPR<sup>adipo-/-</sup> mice. These results suggest that a decrease in SOCS3 expression by GIPR deficiency might enhance insulin sensitivity and potentiate PKB phosphorylation in adipose and liver tissues. However, SOCS3 mRNA expression in skeletal muscle was not different between the two groups of mice, although PKB phosphorylation was increased in the skeletal muscle of GIPR<sup>adipo-/-</sup> mice. Further study is required to clarify the mechanism of the increase in insulin-induced PKB phosphorylation in the skeletal muscle of GIPR<sup>adipo-/-</sup> mice.

It has also been reported that SOCS3 binds to the gene promoter of sterol regulatory element-binding protein-1c (SREBP-1c), which has critical roles in fat synthesis in the liver, and increases SREBP-1c mRNA expression<sup>18</sup>. Suppression of SOCS3 expression in *db/db* mice improves the hepatic steatosis through downregulation of SREBP-1c<sup>19</sup>. In our study, SREBP-1c and SOCS3 mRNA expression were decreased in the liver of HFD-fed GIPR<sup>adipo-/-</sup> mice, indicating that deletion of GIPR signaling in adipocytes results in the decrease in IL-6 production from adipose tissue and subsequent fat synthesis in the liver through the IL-6–SOCS3–SREBP-1c pathway.

Although GIPR function in human adipose tissue is still unclear *in vivo*, *in vitro* study shows that GIP induces IL-6 mRNA expression and potentiates IL-6 secretion in the presence of TNF- $\alpha$  in human adipocytes<sup>11</sup>, which is consistent with our data showing that IL-6 mRNA expression is decreased in the adipocytes of HFD-fed GIPR<sup>adipo-/-</sup> mice.

Based on the phenotypes of GIPR<sup>adipo-/-</sup> mice, it can be concluded that GIPR signaling in adipose tissue plays an important

role in HFD-induced insulin resistance and hepatic steatosis *in vivo*, with no direct effect on fat accumulation, through IL-6 signaling (Figure 1).

#### FUTURE PERSPECTIVE

As shown above, there is sufficient evidence to confirm that GIP is an obesity-promoting factor in HFD conditions and that deletion of GIPR signaling causes resistance to diet-induced obesity. Additionally, we have reported that partial reduction of GIP alleviates obesity and lessens the degree of insulin resistance under HFD conditions<sup>7</sup>. These findings suggest that regulation of GIPR signaling, especially after fat intake, is a promising therapeutic approach to obesity and type 2 diabetes. GIP antagonism is one of the candidates for GIP-based treatment for diabetes and obesity. However, the results in mice are not necessarily recapitulated in humans. For example, previously developed (Pro3) GIP as a potent antagonist of GIPR in mice was shown to stimulate GIPR in humans<sup>20</sup>. In addition, given that GIPR is also expressed in various tissues, except for pancreatic  $\beta$ -cells and adipocytes, including the gastrointestinal tract, heart, inner layers of the adrenal cortex and several brain regions, further investigation is required to establish the systemic biological action of GIP before the implementation of GIPR antagonism as an anti-obesity/diabetes therapy to minimize unexpected adverse events.

#### ACKNOWLEDGMENTS

This study was supported by grants from the Ministry of Education, Culture, Sports, Science and Technology (MEXT); Japan Society for the Promotion of Science; Ministry of Health, Labor and Welfare; Ministry of Agriculture, Forestry and Fisheries; Japan Diabetes Foundation; Japan Association for Diabetes Education and Care; Merck Sharp & Dohme (MSD); Novo Nordisk Pharma; and Banyu Life Science Foundation International.

**DISCLOSURE**

The authors declare no conflict of interest.

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Doi: 10.1111/jdi.12942