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Review

# Glucose dependent insulinotropic polypeptide and dipeptidyl peptidase inhibitors: Their roles in management of type 2 diabetes mellitus

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ABSTRACT

This review paper highlights the major advances investigating the roles of glucose dependent insulinotropic polypeptide and its receptors in glucose metabolism and their potential use in management of type 2 diabetes mellitus.

It also focusses on the role of dipeptidyl peptidase-4 inhibitors in the treatment of this disease. This study discussed the recent therapeutic development which have occurred in this field, and also covering the evolvement of the potential treatments for diabetes which can be discovered and implemented in the near future to design an effective therapy for diabetes and prediabetes.



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## 1. Introduction

The disproportion of the enzymatic activity in the body can result in the development of the metabolic disease, as an example, the imbalance between insulin and glucagon secretion and action can cause diabetes mellitus. Postprandial glucose homeostasis is controlled by the two counter regulatory hormones (glucagon and insulin) [1].

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The glucose dependent insulinotropic polypeptide (GIP) and glucagon-like peptide-1 (GLP-1) are incretin hormones, secreted from the intestinal enteroendocrine cells in response to ingestion of various nutrients. They can bind to specific pancreatic β-cell [2] and improve glycemic control through several mechanisms include stimulating insulin release; augmenting glucose sensitivity; promoting beta cell replication and protection from both beta-cell apoptosis and cytotoxic attack [3,4]. The secondary functions or actions of GIP include inhibition of glucagon secretion; gastric emptying and feeding, with additional positive effects on cardiac muscle and improvement of cognition and bone formation [5–7].

The basic process for the conversion of glucagon from proglucagon in islet alpha cells is performed by Proprotein convertase (PC2) enzyme. GIP signaling is performed by their receptors but the malfunctioning of the GIP receptors (GIP-R) result in appreciation of the glucose levels due to the reduction in the secretion of insulin [8–11].

In patients with type 2 diabetes mellitus (T2DM), the levels of incretin hormones are severely reduced impairing their physiological actions including their insulinotropic effects [12]. However, studies showed that replacing GIP will not increase its level in the blood even at high pharmacological doses. An impaired incretin effect is believed to be an early defect in type 2 diabetes mellitus, arising secondarily to the development of insulin resistance [13] thus, the incretin effect is unaltered in people with normal glucose tolerance who have a high risk of developing T2DM at a later stage of their life [14]. While, impaired insulinotropic effects of GLP-1 and GIP are detectable in obese people who have normal glucose tolerance [15].

The currently available pharmacological therapy which target incretin hormones in T2DM include dipeptidyl peptidase-4 (DPP-4) inhibitor. GIP is endogenous substrates for DPP-4 so it is more appropriate to use the DPP-4 inhibitors as an antihyperglycemic agents. Choosing the above pharmacological therapy is of benefits to T2DM patients as GIP and GLP-1 are the most crucial incretin hormones for almost all of the well-established physiological incretin effects and have powerful insulin-releasing and gluco-regulatory properties [16].

On the other hand, glucagon is classically regarded as an important hormone in maintaining normal glucose concentrations through enhanced hepatic glucose production [17]. However, recent evidences suggest that glucagon can be exploited therapeutically as a satiety factor, which also increases energy expenditure and body weight loss [18]. The fact that transgenic mice overexpressing the glucagon receptor in pancreatic beta-cells demonstrated the increased insulin secretion and pancreatic beta-cell mass, with protection against impaired glucose tolerance following high fat feeding [19].

## 2. GIP (glucose-dependent insulinotropic polypeptide)

GIP was the first incretin hormone to be discovered from crude extracts of porcine small intestine and as it had the ability to inhibit gastric acid secretion that is why it was termed as the "Gastric Inhibitory Polypeptide" [20]. Later studies confirmed that GIP was capable of stimulating secretion of insulin in animals and humans. Since the inhibitory effect was revealed at pharmacological doses and incretin effect at physiological level so GIP was renamed as glucose dependent insulinotropic peptide [21] (Fig. 1).

GIP is peptide with 42 amino and having 153 amino acid precursors comprising of post translational processing which are PC1/3-dependent [22] and its gene expression was noticed in K cells of stomach and intestine in human and rodents stimulated just after the nutrient intake. The half-life of GIP is approximately 2 min in rodents [23], 7 min in healthy individuals and 5 min in type 2 diabetic patients [24]. Dipeptidyl peptidase-4 is responsible

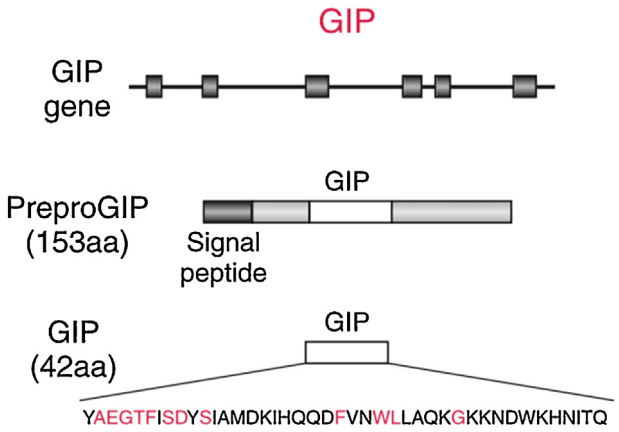


**Fig. 1.** GIP gene consists of 6 exons and located on human chromosome 17. PreproGIP undergoes proteolytic processing for the generation of GIP. GIP comprises of 42 amino acids [31].

for the down regulation of GIP. In type 2 diabetes due to the dysfunction of DPP-4 which is improper functioning or the abnormal behavior. In actual functionality the DPP-4 controls the insulin secretion by inhibiting the activity of GIP but because of type 2 diabetes the activity of the DPP-4 is not inhibited resulting in negligible insulin secretion from GIP disrupting the homeostatic balance of glucose level [23,24].

GIP-R receptor consists of 14 exons with the size of 14 kb located at chromosome 19 and also a member of G protein coupled receptor superfamily with gene expression in pancreas, stomach, small intestine, adipose tissue, adrenal cortex, pituitary, heart, testis, endothelial cells, bone, trachea, spleen, thymus, lung, kidney, thyroid, and multiple regions of CNS.

The GIP binding is the key thing and for a high affinity binding the major things responsible for it are the N terminal domain and the first extracellular loop of GIPR and similarly for receptor activation and cAMP coupling including the N terminal the first transmembrane domain is also a necessary component (Table 1).

### 2.1. Role of GIP and GIP-R in CNS (Central nervous system)

CNS comprises of many parts like cerebral cortex, hippocampus and the GIP expression occurs in hippocampus whereas GIP-R expression is observed in cerebral cortex, hippocampus and olfactory bulb. GIP plays a key role in inducing proliferation of hippocampal progenitor cells when administered exogenously whereas GIP-R works similarly but induces less proliferation of less hippocampal progenitor cells [25].

### 2.2. Role of GIP and GIP-R in adipose tissue

In adipose tissue the expression of functional GIP-R is mainly on the adipocytes and 3T3(3-day transfer, inoculum $3 \times 10^5$ cells) cells [26] whereas GIP plays a role in lipid and fat metabolism control. GIP and GIPR helps in improving the glucose tolerance, enhancing insulin sensitivity and provides the basis for the improvisation with obesity related disease like islet hypertrophy and beta-cell hyperplasia [27].

### 2.3. Role of GIP and GIP-R in bone

Bone and osteoblast like cell lines have the expression of protein and mRNA in relation with GIP-R [28] and it causes the reduction in bone size and mass disrupting its microarchitecture, biochemical proportions and turnover revealing the parameters for