



## **Incretins a hormones increase insulin secretion and useful in the treatment of Type 2 Diabetics**

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### **Abstract**

The incretins are hormones that work to increase insulin secretion. The incretin concept was developed when it was observed that there is substantially more insulin secreted in response to oral glucose versus intravenous glucose, as shown in the graph at right. It was hypothesized that glucose in the digestive tract activated a feed forward mechanism that increased insulin secretion, anticipating the rise in blood glucose that would occur following absorption of ingested carbohydrates. Defective incretin action in T2DM. Some type 2 diabetics show deficient insulin secretion in response to meals. This may be due to a lack of an effect of incretins. Studies have shown that in type 2 diabetics, there is less GLP-1 secretion, and beta cells are less responsive to GIP.

**Keywords:** Incretins, GLP-1, type 2 diabetics, intravenous glucose

### **Introduction**

The incretin hormone glucagon-like peptide-1 agonists and dipeptidyl peptidase-4 inhibitors fill an unaddressed therapeutic gap in the treatment of type 2 diabetes mellitus (T2DM) by potentiating insulin secretion in pancreatic  $\beta$  cells, suppressing glucagon secretion, delaying gastric emptying, and reducing appetite. The incretin therapies, alone or in combination with metformin and/or thiazolidinediones, yield improved glycemic control without risk of hypoglycemia and the potential for weight neutrality or even weight loss. New incretin-based approaches offer promising new strategies for treating T2DM by recruiting new, physiologically based mechanisms of action for glucoregulation in the context of a favorable safety profile<sup>1</sup>.

The metabolic derangement, that is, hyperglycaemia, dyslipidaemia, cytokines and oxidative stress, is believed to cause accelerated b-cell apoptosis, whereas neither b-cell differentiation and replication nor maturation seems to be impaired<sup>2-6</sup>. Thus, the accelerated apoptosis is considered the main cause of the reduction in b-cell mass and as such responsible for the progressive course of type 2 diabetes mellitus. Insulin resistance decreases the stimulation of glucose uptake in skeletal muscle and decreases the suppression of lipolysis in adipose tissue<sup>7</sup>, resulting in an augmented insulin demand and b-cell stress in order to maintain normoglycaemia. The development of insulin resistance is thought to occur as interplay of genetics, obesity, hormones, advancing age and environmental factors such as nutrition and physical activity<sup>8</sup>. B-cell dysfunction in type 2 diabetes is characterized by loss of regular oscillatory insulin secretion, loss of first-phase insulin response to an oral glucose challenge, elevated proinsulin: insulin ratio, abnormal secretion of islet amyloid polypeptide, reduced b-cell sensitivity to glucose and a delay and reduction in the meal-induced insulin secretion – the impaired incretin effect<sup>9</sup>.

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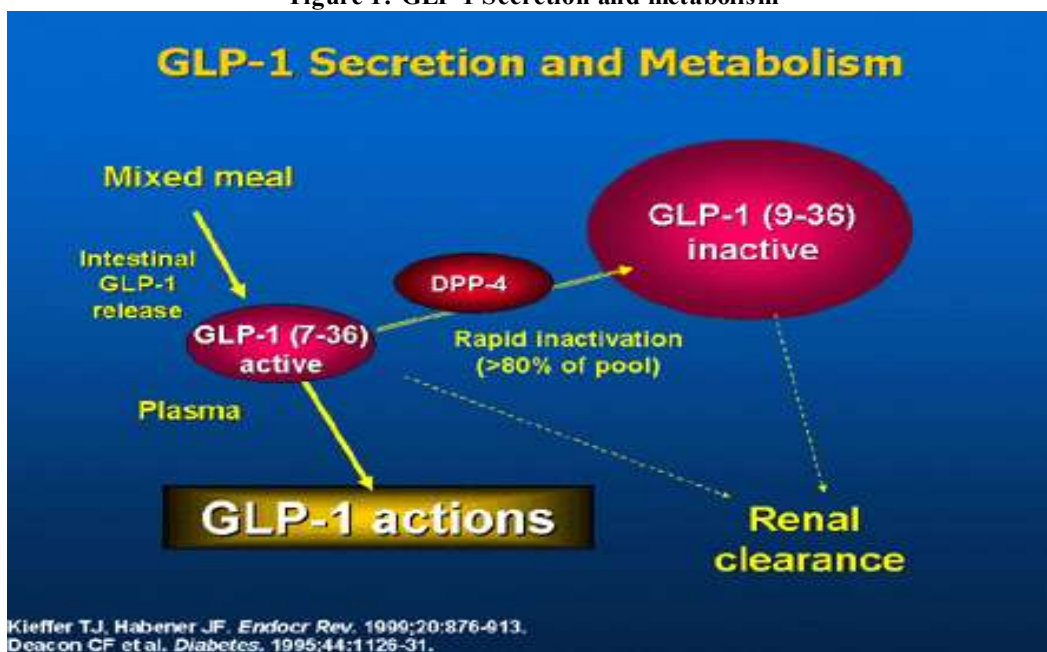
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## Incretin Synthesis and Metabolism

GIP, the larger of the incretin hormones, comprises 42 amino acids and GLP-1 comprises 30. Both GLP-1 and GIP are members of the glucagon peptide family and are derived from the expression of proglucagon and proGIP genes, which code for GLP-1 and GIP (and other proteins), respectively. The proglucagon gene is expressed in the  $\alpha$ -cells of the endocrine pancreas, in the L-cell of the intestine and in certain neurons of the brain stem<sup>10</sup>. GLP-1 is released in two forms: GLP-1 amide and GLP-1; however, the former constitutes the primary type (approximately 80%) of circulating GLP-1<sup>11</sup>. GIP gene expression occurs in the small intestinal K-cells, which are most frequently found in the proximal intestine. Some cells co-express both GIP and GLP-1<sup>12,13</sup>. Both GLP-1 and GIP are susceptible to cleavage at position 2 (alanine) by the ubiquitous dipeptidyl peptidase(DPP)-4 (figure 1). Following secretion, GLP-1 and GIP are both rapidly degraded by DPP-4; indeed, GLP-1 is degraded even before leaving the gut because of the presence of DPP-4 molecules anchored to the luminal surface of the endothelial cells of the mucosal capillaries. GIP is less susceptible to DPP-4 and leaves the gut undegraded<sup>14-17</sup>.

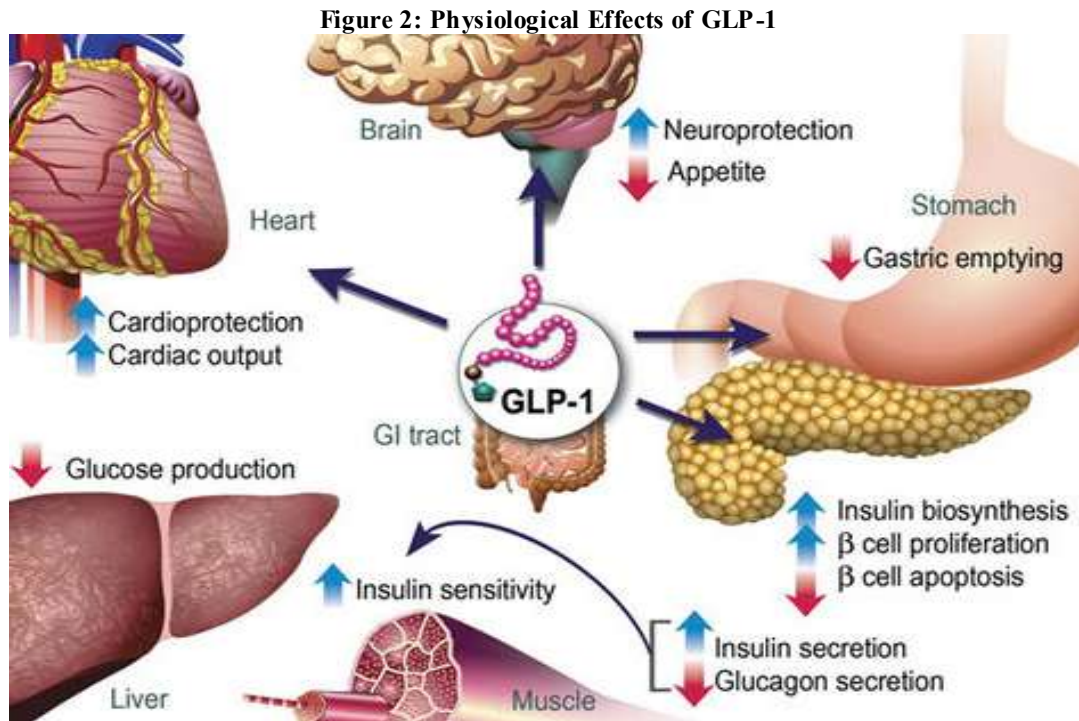
Figure 1: GLP-1 Secretion and metabolism



## Incretin Pathophysiology in T2DM

Incretin hormones are responsible for a variety of biological actions in people without diabetes, although the predominant effect is the lowering of blood glucose. However, the incretin effect is greatly reduced or even lost in patients with type 2 diabetes (a result that has also been seen in other metabolic disorders such as obesity and insulin resistance<sup>17</sup>). The incretin effect further implies a reduced insulin response to ingested carbohydrates and, subsequently, increased blood glucose levels. What remains unclear is why the incretin effect is reduced in type 2 diabetes. Is it the secretion of incretin hormones themselves or is the action of incretin hormones attenuated? Human studies have shown that the GLP-1 response is certainly reduced in patients with type 2 diabetes vs. subjects with normal glucose metabolism<sup>18</sup>. During a 4-h meal test, the GLP-1 response, as measured by the area under the curve of GLP-1 0–240 min after the start of the meal test, was shown to be significantly lower in type 2 diabetes patients vs. subjects with normal glucose tolerance, and it was concluded that this was most likely a consequence of the disease. Until recently, it was unclear whether the reduced incretin effect was a cause or a consequence of type 2 diabetes. A recent study attempted to answer this question by comparing the reduced incretin effect in patients in a

non-type 2 diabetic state (chronic pancreatitis and secondary diabetes, chronic pancreatitis and normal glucose tolerance), patients with type 2 diabetes, and healthy subjects<sup>2</sup>. The incretin effect was significantly reduced in patients in non-type 2 diabetic states vs. healthy subjects, and the study subsequently concluded that the reduced incretin effect was a consequence of the diabetic state and not a primary event in type 2 diabetes. Overall, it appears that the reduced incretin effect seen in patients with type 2 diabetes is attributable to both a decrease in GLP-1 secretion and an attenuated response to both GIP and GLP-1 and that these effects are a consequence, rather than a cause, of type 2 diabetes.

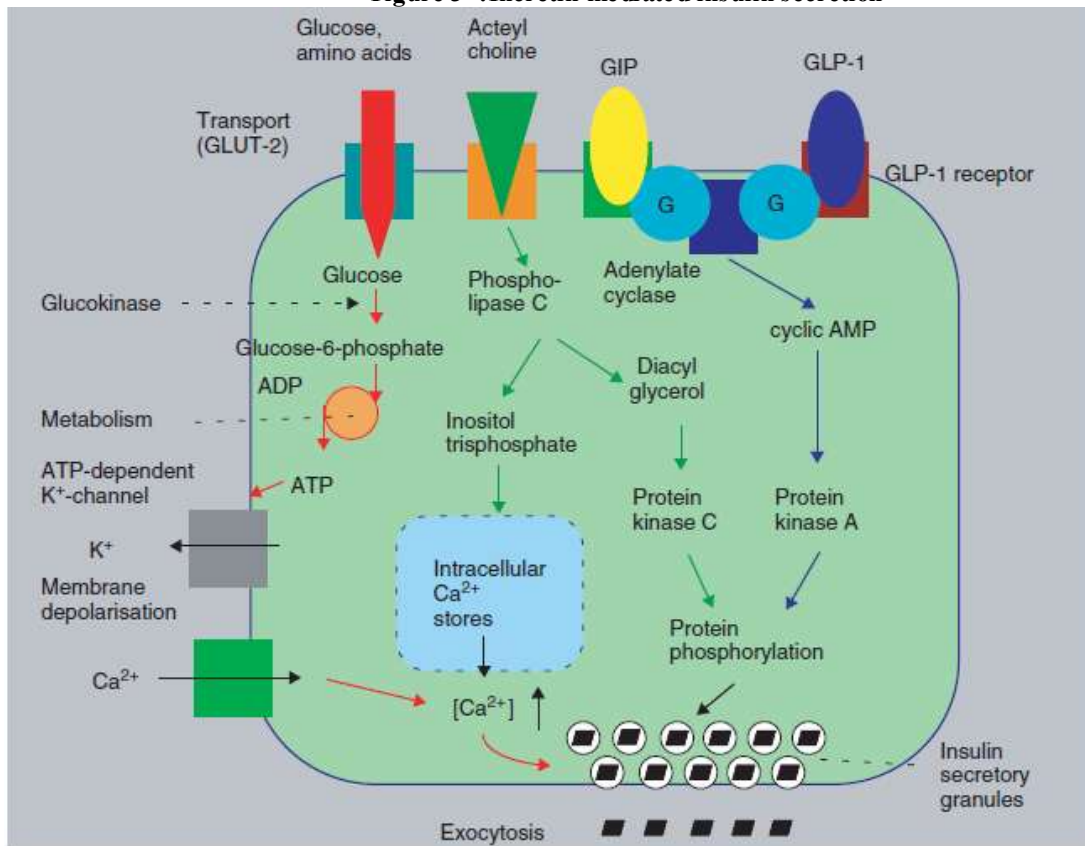


### Modes of Action of Incretins

The stimulation of intracellular pathways through GLP-1R and GIPR can have either synergistic or opposing modes of action. GLP-1 has multiple actions on a number of tissues and on the endocrine pancreas, but its principal action is potentiation of glucose-induced insulin secretion<sup>18–20</sup>. Increased levels of intracellular cAMP stimulate PKA, resulting in the exocytosis of insulin granules from the  $\beta$ -cell. This rise in cAMP is therefore the primary mediator of GLP-1 agonist-induced insulin secretion in  $\beta$ -cells<sup>17</sup>. GLP-1 also encourages insulin gene transcription, increased levels of insulin biosynthesis and stimulation of  $\beta$ -cell proliferation through GLP-1R activation<sup>18</sup>. Unlike GIP, GLP-1 stimulation of  $\alpha$  cells of the pancreas causes a decrease in glucagons secretion<sup>21</sup>. In the stomach, stimulation of GLP-1R by GLP-1 inhibits gastric emptying through a complex mechanism that inhibits the efferent vagus nerve activity through stimulation of afferent receptors<sup>17</sup>. A study in healthy volunteers showed that, when given intravenously, GLP-1 caused a dose-dependent reduction in the rate of gastric emptying<sup>22</sup>. As a result, meal-associated rises in blood glucose were attenuated or even decreased below basal levels. The meal-stimulated insulin response was also reduced or abolished. More recently, a key study investigated the effect of GLP-1R-induced inhibition of gastric emptying following antagonism by erythromycin (an antibiotic and prokinetic agent that increases smooth muscle contractile force and accelerates intestinal transit). With erythromycin, the insulin secretory response was similar to that seen in the absence of GLP-1 infusion<sup>20</sup>. Current opinion suggests that the reduction of postprandial glucose from GLP-1 is largely mediated by a delay in gastric emptying – perhaps involving the vagal nervous system – and is not solely because of insulin release through the endocrine pancreas. GLP-1Rs are expressed in the heart, and effects at this site may be postulated. Studies investigating GLP-1R knockout mice have reported defective left ventricular contractility and diastolic function<sup>21</sup>, and GLP-1 can improve cardiac function in

experimental dog models of cardiac insufficiency<sup>22</sup>, indicating that it may regulate cardiac output. GLP-1 has also been found to reduce infarct size in animal models of myocardial ischemia, suggesting it may play a cardioprotective role<sup>23</sup>. Because GLP-1Rs have been found in the hypothalamic nuclei, which play a role in satiety regulation, brain GLP-1 may have an effect on feeding behavior. In rats, infusion of GLP-1 into the cerebral ventricles reduced short-term Food Intake & meal size, whereas the opposite effect was seen following the administration of GLP-1 antagonists<sup>24,25</sup>. Subsequent studies have confirmed that GLP-1R agonists, when delivered centrally, can reduce short-term food and water intake and result in body weight reduction<sup>25,26</sup>. GLP-1R agonists were also shown to mediate weight loss in human studies by promoting satiety and decreasing food intake when administered peripherally in healthy, diabetic or obese subjects<sup>17</sup>.

**Figure 3 :Incretin mediated insulin secretion**



schematic diagram of a pancreatic b cell. The steps leading to insulin secretion are depicted. Glucose transport via GLUT-2; metabolism of glucose raising the ATP\ADP ratio; closure of ATP dependent K<sup>+</sup> channel causing depolarization of the cell membrane; calcium influx through voltage dependent L –type Ca<sup>2+</sup> channels; GLP -1 can interact by binding to its receptor, promotion of cAMP synthesis, and stimulation of protein kinase A. largely by promoting phosphorylation of proteins, protein kinase A is able to interact with (1) ATP-dependent K<sup>+</sup> channels,(2) L-type Ca<sup>2+</sup> channels (3) Mobilization of Ca<sup>2+</sup> from intracellular storage.

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normal glucose metabolism<sup>28</sup>.

## Conclusion

In recent years, new incretin-based drugs have been developed and approved for the treatment of T2DM. These drugs are meant to be used in conjunction with other anti-diabetic drugs to help patients with T2DM who have had trouble maintaining adequate glycemic control. Exenatide (Byetta; approved in April of 2005) is a peptide GLP-1 receptor agonist that was originally isolated from lizard venom. Exenatide is more effective than native GLP-1 because it is more stable: it is resistant to degradation by DPP-4, the major protease that breaks down GIP and GLP-1. Two newer drugs that are specific inhibitors of DPP-4 have also gained FDA approval: sitagliptin (Januvia; approved in October of 2006) and saxagliptin (Onglyza; approved in July of 2009). An advantage of DPP-4 inhibitors is that they can be taken orally, unlike the peptide drug exenatide, which must be injected.

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