Extrapancreatic Effects of the Insulin Booster, Incretins

S.V. Mythili*, A. Jamunarani
Department of Biochemistry, Sree Balaji Medical College, Chromepet, Chennai, Tamilnadu, India.
*Corresponding author’s E-mail: svmythili@gmail.com

Accepted on: 07-09-2015; Finalized on: 30-09-2015.

ABSTRACT
Incretins, are the intestinal hormones and they are "Glucose dependant Insulinotropic Polypeptide" (GIP) and "Glucagon Like Polypeptide-1" (GLP-1). Their secretion is induced by the presence of food in the stomach and they in turn induce the secretion of insulin from the pancreatic beta cells. A lot of studies have been undertaken on Incretins around the world. They convey interpretations on the characteristics of Incretins, the synthesis, their functions, the mechanism of action etc. Do they have effects on other tissues also? Incretins have been found to have significant effect on other tissues like liver, muscle, heart, bone etc. apart from the pancreas. Results of the Literature search of some such studies on the extrapancreatic effects of incretins are reviewed and presented here.

Keywords: Incretins, extra pancreatic effect, pancreas.

INTRODUCTION
The incretins secreted by the gut mucosa exert their effect mainly on the secretion of insulin. They are two in number, viz. Glucagon like Peptide1 (GLP-1) and Glucose dependant Insulinotropic (GIP) hormone. The entry of food into the stomach induces the neuroendocrine and enteroendocrine cells of the gut mucosa to secrete these incretins. They get distributed in the blood circulation to reach various organs. The incretins, GLP1 and GIP exert their hormonal action through G protein coupled receptor mediated cAMP. There are receptors specific for these 2 hormones on the cells of the Gastrointestinal tract, Liver, adipose tissue, muscle, heart, blood vessels, brain and bone apart from the pancreatic beta and alpha cells of the islets of Langerhans. The major effect is on the pancreas to stimulate insulin secretion from the beta cells of the islets of Langerhans. The other anabolic effects on other tissues may be secondary to that of insulin or independent of insulin. The effects are mediated through specific receptors on the cell surface of the target tissues. The extrapancreatic effects of incretins are reviewed here.

MATERIALS AND METHODS
The nature of incretins, their structure, functions, and the effects of incretins on tissues other than pancreas and their mechanism of action have been studied in animals, cell lines and human beings at large by many researchers worldwide. Results of the Literature search of some such studies on the extrapancreatic effects are consolidated and presented here.

RESULTS AND DISCUSSION
The extrapancreatic effects of GLP-1 mediated through the Receptor(GLP-1R) signaling is studied in various experimental work with animals and cell lines as well as in patients with Type2 Diabetes Mellitus (T2DM), the noteworthy points of which are shown as follows:

Dr. Bernard Thoren from studies with double incretin receptor knockout mice suggested that the first-phase insulin secretion is primarily regulated by an extra pancreatic GLP1-R specific portal vein sensor or via CNS receptor. Of course the first phase of insulin secretion is glucose induced or glucose dependant because the incretins secretion is stimulated only by glucose entry into the gut.

Effects on Gastrointestinal tract
GLP-1 reduces gastric emptying and slows the rate of absorption of nutrients into the blood stream directly, reduces food intake through central actions that signal satiety which then leads to weight loss. GIP inhibits gastric production, reduces intestinal motility, stimulates fluid & electrolyte secretions. GIP does not inhibit gastric emptying.

In Skeletal muscle, incretins promote Glucose uptake.
GLP-1-induced glycogen synthase-a activity through activation of PI3K (Phospho Inositol3 Kinase) / PKB (Protein KinaseB) and MAPKs (Mitogen Activated Protein Kinases) in rat skeletal muscle strips as evidenced by Dr. M. L. Villanueva-Pencarrillo’s laboratory experiments. Later, they also showed that GLP-1 stimulated the redistribution of Protein Kinase C-lambda & alpha isoforms to effect glucose transport and metabolism within the muscle. In their experiments on normal human myocytes also GLP-1 was observed to stimulate glucose uptake like insulin, involving activation of the same enzymes as in rat skeletal muscle strip.

Cardiovascular system
Nikolaids in his study with dogs showed GLP1 to increase myocardial glucose uptake, myocardial insulin sensitivity...
and to improve left ventricular function.\textsuperscript{14} GLP1 has protective effect on myocardium mediated through cAMP activation of antiapoptotic signalling pathways of Phosphoinositide 3 kinase and Mitogen Activated Protein Kinase as studied in rat heart.\textsuperscript{15} This is seen in myocardial infarct patient also.\textsuperscript{16} It improves endothelial function in the blood vessels.\textsuperscript{17}

\textbf{Adipocytes}

Both GLP1 (7-36) amide and GIP stimulate fatty acid synthesis in adipose tissue\textsuperscript{18}. In normal rat adipocytes, GLP-1 increased the activity of PI3K, p44 and p42 MAPKs and possibly PKC, to stimulate glucose uptake. GLP-1 has both lipogenic action by increasing PI3K and MAPKs activity, and lipolytic effect through MAP kinases and PKC.\textsuperscript{19} GIP also regulates fat metabolism in adipocytes, including stimulation of the activity of lipoprotein lipase, fatty acid synthesis and incorporation,\textsuperscript{20} but, reduces the lipolytic effects of glucagon.\textsuperscript{21}

\textbf{Hepatocytes}

In rat hepatocytes, stimulation of glycosyn synthase was induced by GLP1 through activation of phosphorylinsitol 3-kinase (PI3K)/protein kinase B (PKB), protein kinase C (PKC) and protein phosphatase 1 (PP-1).\textsuperscript{12,22} GLP-1 promotes glycogen accumulation through activation of glycosyn synthase-A & inhibition of glycogen phosphorylase-A. Glucagon when added to the media, reduced the accumulation of glycogen. This was also accompanied by a significant reduction in cAMP.\textsuperscript{23}

\textbf{GIP in bone}

Christine and his team compared the effect of total inhibition of GIP signaling on the volume, microarchitecture and quality of trabecular bone in GIP receptor (GIPR) knockout mice by microCT and histomorphometry. The results showed an increase in the number of bone resorbing osteoclasts and also the trabecular bone mass and number with a reduction in mature collagen and mineralization of the bone matrix and bone quality compared to wild type mice.\textsuperscript{24} GIP was shown to reduce etoposide-induced apoptosis of osteoblasts in an experiment with cell line. Thus, GIP through its direct cytoprotective effect on osteoblasts may prevent decreases in density of bone. GIP receptors are present on osteoblasts, osteocytes and osteoclasts. GIP also inhibited bone resorptive activity of osteoclasts.\textsuperscript{25}

\textbf{CONCLUSION}

The incretins namely, GIP and GLP1 are the gut hormones that act to boost the glucose dependant insulin secretion from the beta cells of the islets of Langerhans and depress the secretion of glucagon from alpha cells. Apart from this major effect, they also act on other extrapancreatic tissues like liver, gastrointestinal tract, heart, blood vessels, bone and brain to produce mostly anabolic effects in conjunction with that of insulin.

\textbf{Acknowledgement:} I wish to thank Dr.P. Saikumar, Vice Principal of Sree Balaji Medical College & Hospital for his persistent encouragement. I gratefully acknowledge all the Authors whose articles I have used as references, for their awesome work which only evinced my interest to do the Literature search & write this review.

\textbf{REFERENCES}

5. Usdin T B, Mezey E, Button D C, Brownstein M J, Bonner T I. Gastric inhibitory polypeptide receptor, a member of the secretin-vasoactive intestinal peptide receptor family, is widely distributed in peripheral organs and the brain. Endocrinology. 133(6), 1993, 2861-2870.


