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# The Incretin Axis-Revisiting the Basics: A Review

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## Abstract

Incretin effect is the augmented insulin secretion in response to oral glucose load as compared to intravenous glucose. This incretin axis that has been demonstrated in the gut is mainly mediated by two important gut hormones, namely glucagon-like peptide-1(GLP-1) and glucose dependent insulinotropic polypeptide (GIP). These hormones improve insulin secretion by glucose dependent pathways conferring unique glycemic benefits and safety that has led to their development as pharmacological agents as GLP-1 and dipeptidyl peptidase 4 inhibitors (DPP4-i). Additionally, they have been found to have pleotropic benefits suggesting their presence beyond the gut. This review deals with the advances in the physiology of these incretins and the presence of incretin axes elsewhere.

**Keywords:** Incretin; Glucagon-like peptide-1; Glucose dependent insulinotropic polypeptide; Dipeptidyl peptidase 4 inhibitor

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## Introduction

In the search for pathophysiological targets for type 2 diabetes, there remained the role of gut hormones camouflaged in the pancreatic beta cells' action. The exposure of the gut's role in insulin secretion brought forth an interesting perspective to the type 2 diabetes management. Unlike other insulin secretagogues, these gut derived hormones had glucose dependent actions on the beta cells of the pancreas and inhibitory effects on alpha cells of the pancreas. Additionally, they improved the altered incretin gut axis in type 2 diabetes. Their introduction as pharmacological agents brought forward additional therapeutic evidences which will need a revision of their concept.

## Incretin effect

Gastrointestinal endocrinology dates back to twentieth century when "Moore and colleagues" reported that oral administration of gut extracts reduced glucosuria in juvenile diabetic patients. By 1932 many papers were already submitted regarding the glucose lowering potential of gut extracts. But the problem was how to assess and measure the glucose lowering property of these extracts and were these really attributable to increase in insulin secretion or not? The answer was addressed by the discovery of radioimmunoassay for the first time for Insulin in 1962. It was then reported by Elrick et al. and Mc Intyre et al. that oral glucose leads to higher insulin secretion than intravenous glucose-suggesting the existence of the gut derived factors augmenting insulin secretion. This augmented insulin response is termed as "incretin effect". This was clearly demonstrated by Nauck and his colleagues through the development of 'isoglycemic clamp study' done on 2 separate days and measuring insulin as well as C-peptide. Increase in insulin can be thought under 2 heads:

- Increased secretion: where C-peptide assay helps to stamp endogenous insulin production. We also have to remember that not only glucose but also fats and some amino acids can lead to insulin secretion.
- Decreased insulin breakdown.

Measuring only insulin is problematic as it has high first-pass liver metabolism, reduced hepatic insulin clearance to a considerable extent by oral glucose load, conventional immunoassays cannot differentiate properly between pro-insulin and insulin as both are secreted simultaneously and oral glucose activates beta-cells through many pathways while IV glucose directly only stimulates beta-cells. As per his study the incretin effect lies somewhere between 27.6% to 62.9% (1).

## Normal levels of incretin hormones

The incretin activity seen in health is due to glucagon-like peptide-1 (GLP-1) and gastric inhibitory polypeptide (GIP) (Table 1) (2-3).

**The incretin axis in the gut-the entero-insular axis:** Both the incretins are secreted from two distinct cell types of intestine.

- GIP: Secreted from intestinal k-cells most abundant in duodenum and jejunum.
- GLP-1: Secreted from intestinal L-cells whose presence is heterogeneous throughout the gut with increased amounts being found in distal colon and rectum. Glp-1 is secreted in two distinct forms: the amidated form GLP-1(7-36)and to a

**Table 1.** The normal levels are seen to rise, almost 10-15 min post meals.

| | GIP (pmol/L)* | GLP-1( pmol/L)* |
|---|---|---|
| **Basal** | Approx 10-15 | Approx 2-15 |
| **Prandial** | Approx 150-500 | Approx 15-45 |

lesser extent the Glycine extended form GLP-1(7-37) (4). Both the forms seem to have the same biologic activity (5). Both the incretins undergo rapid proteolytic degradation by the cleavage of their two NH2-terminal amino acids by dipeptidyl peptidadse-4 enzyme (DPP4). Hence both the intact and total (intact plus DPP4 metabolised form) forms have to be measured by using immunoassays requiring specific antibodies to study their in-vivo secretion and processing.

The stimuli for these incretins are: (6-9)

- GIP: glucose, galactose and certain amino acids.
- GLP-1: mainly glucose, free fatty acids (FFA) acting through G-protein coupled receptors, triglyceride.
- Stimulation also comes from bile acids via TGR5 receptor.
- There are also reports of stimulation through sweet taste receptors T1R2/T1R3 which uses artificial sweeteners.
- Recent studies have shown light on Interleukin-6 related stimulation of GLP-1 through alpha-cells through the enhanced production of proglucagon and prohormone convertase 1/3 expression.

Just after secretion these two hormones are rapidly cleaved by DPP4 enzyme found both in circulation as well as all through vascular endothelium. It is seen that 75% of the secreted GLP-1 is inactivated within the gut and upto the rest 40-50% undergoes first-pass liver metabolism so that only 10 – 15% of intact incretin reaches the systemic circulation (10).

There is also another enzyme called neutral endopeptidase 24 (11) contributing to around 50% of the degradation but this enzyme inhibitor has been shown to cause angiodema when used in some studies. Finallythe kidneys eliminate the intact peptide as well as the metabolite for both GLP-1 and GIP (12) as depicted in Table 2.

## Actions post derivation from gut

**GLP-1, Action on islet cells:** **(a)**Robustly increases insulin secretion in hyperglycemic condition while stops action in normoglycemia. The beta-cell effect is coupled with glucokinase enzyme that maintains its glucose dependant action. It has been found to cease work at around 65-70 mg/dl of plasma glucose. The action is mediated through cell-surface receptors which after binding GLP-1 generates cyclic AMP via Protein kinase A favouring closure of ATP-dependant potassium channels and opening of voltage-gated calcium channels leading to exocytosis of Insulin.

**(b)** Other than this direct effect on beta-cells, it also has some other roles on beta-cells:

(i) recruits previously quiescent beta-cells, helps in trans differentiation of exocrine ductal cells to insulin secreting cells, induces beta cell proliferation and reduces its apoptosis(found mainly in infant and neonatal rodent models and data from adult mice is unimpressive)

(ii) increases insulin gene expression via 4 distinct methods (13-16).

- Directly activating CAMP response element
- Augmentation of glucose-stimulated binding of PDX-1(Pancreatic and duodenal homeobox-1)
- Stimulation of transcription of PDX-1 gene
- Augments glucose-stimulated insulin gene transcription by activating NFAT (nuclear factor of activated T cells)

**(c)** Suppresses glucagon level in a glucose-dependant manner. The likely mechanism being secondarily mediated by an increase in somatostatin release from pancreatic delta-cells (17).

**Effect on gastro-intestinal system**: Inhibition of gastric emptying which is thought to be mediated via inhibition of vagal activation. This delays food absorption and also decreases meal related surge of glucose but this effect is subjected to rapid tachyphylaxis if high GLP-1 concentrations are maintained.

**Effect after gastric bypass surgery:** An intriguing finding from a recent study, suggested possible benefit of incretins even in diabetic patients with gastric bypass surgeries. In this study done on 18 patients following Roux-en-Y gastric bypass surgery and intake of low carbohydrate mixed meal test, active GLP-1 showed increased peak and prolonged levels (18).

## GIP

1. The insulinotropic property seems to be same as compared to GLP-1 in health but not in type 2 diabetes mellitus (T2DM) patients. In T2DM patients the response is blunted even at supra-physiological levels. The reason cited being down-regulation of GIP receptors due to chronic hyperglycemia.

2. In normoglycemic conditions there is stimulation of glucagon release (dose-dependant).

3. It does not play a major role in gastric emptying.

4. Rodent and cell culture models showed very good results on triglyceride levels but human studies failed to elucidate this.

5. There is a minor role in bone formation by stimulating osteoblastic action and reducing osteoclastic action (19).

6. Some evidence suggests secretion of cortisol.

**The Incretin axis in the central nervous system:** Supra-physiological levels of GLP-1 has shown to significantly reduce appetite sense and food intake which attributes to the weight reduction property of these analogues when used in type2 diabetes patients. But physiological concentration does not seem to have much role. Three sources have been cited for GLP-1 action in CNS (20):

Peripherally produced GLP-1 crosses blood-brain-barrier through some leaky areas in the brain like area postrema and subfornical organs.

Locally produced GLP-1 in brainstem is transported into CNS through axons.

There are projections from gut mucosa, portal venous bed and vagal nerve via peripheral nerves into hypothalamus (this is a reason why very big GLP-1 analogue moiety might still have some CNS effect even

**Table 2.** t½ and clearance rate of GLP-1 and GIP.

| | Intact GLP-1 | Majormetabolite of GLP-1(9-36 amide) | Intact GIP | Major metabolite of GIP(3-42) |
|---|---|---|---|---|
| **Plasma t ½ (min)** | 2.3+/-0.4 | 3.3+/-0.4 | 5.0+/-1.2 | 22.4+/-3.0 |
| **Metabolic clearance rate(L/min)** | 2.42+/-0.45 | 0.64+/-0.16 | 3.18+/-0.62 | 1.56+/-0.27 |

though their concentrations are less in the hypothalamus compared to the shorter or intermediate acting analogues).

Rodent models of Alzheimer's disease, Parkinson's disease and Huntington's disease have shown neuro-protection and neurogenesis.

**The incretin axis in the cardiovascular system:** Incretins are the first group of anti-diabetic drugs which have been extensively scrutinised for their cardiovascular and renal safety in well-designed robust randomized clinical trials.

Incretins exert their cardioprotective actions mainly through GLP-1 receptors and have been evidenced by the favourable cardiovascular outcomes from two recently concluded CVOTs-the LEADER trial and the Sustain-6 trial (21,22).

Interestingly, native GLP1 have been found to exert cardioprotective actions independent of action on GLP1 receptor (23, 24). These GLP1 receptor independent actions have shown to reduce reperfusion induced injury and increase vasodilatation and coronary flow in murine models. This may confer an additional advantage of DPP4 inhibitors over sulphonyl urea and thereby the results from the CAROLINA trial are earnestly awaited (25).

Incretins have also shown the potential to improve vascular health with explored benefits on lipid profile markers, markers of endothelial dysfunction, and thereby on atherosclerosis, vascular flow and blood pressure (26,27).

These extraglycemic actions have been demonstrated on inflammatory cytokines and markers namely, (TNF-$\alpha$, plasminogen activator inhibitor type-1 (PAI-1), intercellular adhesionmolecule-1 (ICAM-1), and vascular cell adhesion molecule-1 (VCAM-1), interleukin-6 and interleukin-18 (28-39).

**The incretin axis in the kidney:**The availability of DPP4 inhibitors has widened the choice of anti-diabetic drugs in diabetic kidney disease owing to their reasonable efficacy, safety and ease of dosage across stages of renal impairment extending upto renal transplant recipients. Additionally, Incretins have shown potential for renoprotection. Much of these actions have been postulated and evidenced to presence of local Incretin axis in glomerulus which retards AGE-RAGE axis and inhibition of podocyte damage; retardation of glomerular and tubular fibrosis via anti-fibrotic, anti-inflammatory and anti-oxidant action; over and above glycemic control and B.P reduction (40-44).

GLP-1 receptors are found throughout the different organs of the body and are also found in the proximal tubules (45). Animal studies have shown that GLP-1 modulates sodium homeostasis. It has also been demonstrated to stimulate renal excretion of sodium in rats and humans via Na/H exchanger isoform (46).

TGFB-1(tissue growth factor beta-1) is a major fibrogenic growth factor playing an important role in glomerulosclerosis and interstitial fibrosis and can be targeted by Exendin-4. The administration of this molecule in human mesangial cells decreased the level of TGFB-1 protein as well as the mRNA (47).

An animal study showed efficacy of liraglutide in inhibiting oxidative stress and decreasing albuminuria in strptozotocin-induced type1 diabetic rats possibly through inhibition of NADPH oxidase via protein kinase A (48). These animal studies are always good but dedicated human trials are much needed.

## Incretins as a drug class in Type 2 diabetes management (Advantages)

**Glycemic benefits:** (a) Reduction in all glycemic parameters (HbA1c, FPG, PPG, Glycemic variability, improve beta cell dysfunction).

(b) Moderate to good efficacy (DPP4-I has a supra-physiological action, GLP1-RA have a pharmacologicalaction above supra-physiological threshold).

(c) Good durability

**Extraglycemic benefits:** (a) Preserve beta cell mass, reduce apoptosis

(b) Body weight reduction (relative or absolute)

(c) Improvement in cardiovascular risk factors like

- Systolic blood pressure
- Total Cholesterol, Triglycerides
- Low-density lipoprotein cholesterol
- C-reactive protein
- Protective effects on endothelium (anti-inflammatory, anti-oxidant actions)
- Vasodilatation
- Improvement in vascular flow
- Improvement in albuminuria

(d) Cardioprotective role (of GLP1-RA)

(e) Anti-fibrotic role for reducing diabetic kidney disease progression

(f) Possible neuroprotective role

## Conclusion

Incretins have been found to be responsible for postprandial insulin secretion augmentation and decrease in glucagon level in hyperglycemic states and these actions are glucose-dependant. These molecules seem to have many pleotropic benefits which needs further evaluation for addressing them and using these to our help. In this world-wide epidemic of diabetes these molecules have become a cutting-edge weapon due to their least hypoglycemic risk, weight loss property(pharmacological dose of GLP-1) or weight neutral property (DPP4 inhibitors) and sustained, good HbA1c reductions. These hormones can be increased by either exogenously injecting GLP-1 analogue or reducing their breakdown by DPP4 inhibitors. Both these molecules have unique property of lowering glucose in glucose-dependant manner without any weight gain and least chance of hypoglycemia. Hence the physiology of these hormones needs to be clearly understood to apply them in pathological conditions.

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