

## Review

# DRUGS ACTING ON THE ENTEROINSULAR AXIS

Satinath Mukherjee

### ABSTRACT

Enteroinsular axis is involved in the normal homeostasis of blood glucose. Hormones, called incretins, such as glucagon like peptide (GLP -1), glucose dependent insulinotropic peptide (GIP) and cholecystokinin (CCK), have profound effects on insulin secretion and glucose homeostasis. Various gastrointestinal hormones, their analogues or inhibitors of their enzymatic degradation, are being developed for potential use as therapeutic agents. The most promising of these are GLP-1, Exendin-4, DPP-IV inhibitor, CCK -8 and pramlintide. These are briefly discussed.

**KEY WORDS:** Enteroinsular axis; GLP-1; Exendin4; CCK - 8; DPP IV inhibitor; Pramlintide.

### INTRODUCTION

The enteroinsular axis comprises of neural and hormonal pathways that are activated by feeding and that enhance insulin secretion. Parasympathetic nerves supplying the islets can be activated by the sight, smell, taste and the processing of food in the alimentary tract, as well as by the absorption of the digested nutrients.(1-3). The so-called 'cephalic' phase of insulin secretion is well described, but little is known of the neural pathways that convey information from the gut to the islets.

The hormonal arm of the enteroinsular axis has been extensively investigated in the past, with the aim of identifying the 'incretin' hormones. These are secreted during meals and augment the insulin response to levels above that seen when the nutrients are infused parenterally. The incretin hormones are secreted from the endocrine cells in the gastrointestinal tract, in response to the absorption of nutrients. These hormones are then carried in the blood stream to the islets, where they interact with receptors on the  $\beta$  cells and stimulate insulin secretion.

The stimulatory effects of both the neural and hormonal inputs to the enteroinsular axis depend on the ambient blood glucose concentrations. The overall insulin response is a combined effect of the direct action of glucose and other nutrients on the  $\beta$

cells, together with indirect effects of neural and hormonal pathways.

Of the gastrointestinal hormones, vasoactive intestinal peptide (VIP) and gastrin releasing peptide (GRP), act as neuropeptides within the islets, increasing insulin secretion in response to parasympathetic stimulation. Of the remaining gastrointestinal peptides, glucose dependent insulinotropic peptide (GIP), glucagon like peptide (GLP-1 (7-36) amide) and cholecystokinin (CCK), are known to exert definite incretin effect (4,5).

### GIP

It is secreted from the endocrine cells in the upper small intestine, in response to glucose, fructose, amino acids and long chain fatty acids. GIP is a powerful, glucose-dependent, stimulator of insulin secretion. Fructose produces a weaker response (6). GIP binds to its receptor on the  $\beta$  cell plasma membrane, activating adenylyl cyclase and leading to the generation of cAMP. This in turn, increases  $Ca^{2+}$  flux into the cell and increases the sensitivity of the  $\beta$  cell to  $Ca^{2+}$  by protein kinase A activation and phosphorylation of associated proteins.

### GLP-1 (7-36) amide

It is processed from proglucagon in the L cells of the distal ileum and the central nervous system. It is released in the circulation in response to the absorption of the products of carbohydrate, protein and fat digestion. GLP-1 is a potent stimulator of glucose-dependent insulin secretion. It works on specific receptors on the  $\beta$  cell plasma membrane, leading to activation of adenylyl cyclase and elevation of intracellular cAMP. In addition to its incretin effect, GLP-1 profoundly inhibits gastric motility and works as an ileal brake. In the central nervous system, it exerts a satiating effect (7).

### CHOLECYSTOKININ

Most of the C-terminal fragments of CCK stimulate insulin secretion, including CCK-4, which is found in nerves, and CCK-8, which is released from the endocrine cells of the small intestine,

following the absorption of amino acids. CCK stimulates insulin secretion by binding to CCK-A receptors on the  $\beta$  cell surface, activation of phospholipase C, generation of IP<sub>3</sub> and stimulation of protein kinase C activity.

## **DRUGS ACTING ON THE ENTEROINSULAR AXIS**

Both the neural and the hormonal arms of the enteroinsular axis can be activated to enhance insulin secretion in the following ways :

- a. Use of wild type peptides or their stable analogs
- b. Use of enzyme inhibitors to inactivate the peptidases.

Based on these principles, following drugs have been developed to stimulate the enteroinsular axis.

### **GLP-1 (7-36) amide**

As a therapeutic principle, GLP-1 possesses some remarkably attractive properties :

- a. Stimulates insulin secretion
- b. Suppresses glucagon secretion
- c. Delays gastric emptying and acid secretion
- d. Does not cause hypoglycemia
- e. Stimulates proinsulin biosynthesis
- f. Enhances insulin, GLUT 2 and glucokinase gene expression (8).

However, GLP-1 cannot be used in clinical situations because of its rapid and extensive degradation by the enzyme, dipeptidyl peptidase-IV (DPP-IV). The following avenues are thus being explored to circumvent this difficulty :

- a. Development of DPP-IV resistant analogs
- b. Inhibition of DPP-IV
- c. Enhancement of endogenous GLP-1 secretion
- d. GLP-1 delivery systems, using continuous subcutaneous infusion or buccal tablets
- e. Orally active, stable analogs
- f. Ileal transposition

It seems likely that one or more of these approaches would result in a clinically useful drug development program (9). A recent study using a 48 hour continuous subcutaneous infusion of GLP-1 in type 2 diabetes, resulted in lowered fasting as well as meal related plasma glucose and reduced appetite. There were no gastrointestinal side effects or a negative impact on blood pressure (10).

Studies have also shown amelioration of diabetes secondary to chronic pancreatitis and cirrhosis of liver with GLP-1 (11,12).

The insulinotropic effect of GLP-1 is preserved in type 2 diabetes and since it also inhibits glucagon secretion, it effectively lowers blood glucose. When given as an IV infusion, it may completely normalize glucose levels, even in some cases of sulphonylurea failure. Hence efforts are currently on to employ GLP-1 or its analogs in the treatment of clinical diabetes and obesity, as in addition to normalizing blood glucose, it also reduces food intake in humans.

Being a peptide, GLP-1 must be administered by injection, limiting its widespread use. A cell line, genetically engineered to secrete a mutant form of GLP-1 with a longer half life, but similar potency to that of the wild type peptide, is encapsulated in semi permeable hollow viscous fibers for implantation in diabetic hosts for constant, long term, in situ, delivery of the peptide. This approach may be a novel therapy for type 2 diabetes (13).

Obese type 2 diabetics, who undergo bilio-pancreatic-diversion as a treatment for obesity, are cured of diabetes and do not experience a recurrence. A high level of plasma GLP-1 has been recorded even 20 years after jejunio-ileal bypass. Transposition of a short segment of ileum to the duodenum, decreased weight just as effectively as intestinal bypass and could probably cure any coexistent type 2 diabetes as well. In future, ileal transposition could be an ideal operative treatment for type 2 diabetes and obesity (14).

### **Exendin-4**

It is a 39 amino acid peptide, isolated from the salivary secretions of the Gila monster (*Heloderma suspectum*). It shows 53% sequence homology with GLP-1, but unlike GLP-1, has a prolonged glucose lowering action in vivo. Exendin4 treatment is also associated with weight loss and improved insulin sensitivity: Acute and chronic administration of Exendin-4 has demonstrated anti diabetic effect in several animal models of type 2 diabetes (15).

### **DPP-IV inhibitor**

The incretin hormones GLP-1 and GIP are rapidly inactivated by circulating enzyme DPP-IV. Iletiniazolidide, a specific inhibitor of DPP-IV, increases the circulating half life of GLP-1 significantly, resulting in an earlier increase and peak of plasma insulin and a more rapid clearance

of blood glucose. DPP-IV inhibition may have therapeutic potential for the management of type 2 diabetes (16).

### **GLP-1-Gly8**

This is a DPP-IV resistant GLP-1 analog. A single injection of this drug in diabetic mice corrected fasting hyperglycemia and glucose intolerance for several hours, whereas the activity vanished a few minutes after injection. Moreover, normoglycemia was maintained over a period that was longer than the predicted half life of the peptide, suggesting a yet undescribed, long term effect of GLP-1-Gly8. This analog of GLP-1 appears to have a markedly improved therapeutic potential, compared to the wild type peptide (17).

### **Cholecystokinin-8**

Continuous subcutaneous infusion of CCK8 is reported to increase insulin secretion and reduce post meal rise in glucose levels in healthy volunteers, as well as in persons with type 2 diabetes. This effect occurred independent of any change in circulating GIP, GLP-1 or glucagon levels. As the insulinotropic effect of CCK-8 occurs presumably due to a direct effect on the  $\beta$  cell and without any adverse effects, CCK may be a potential treatment of type 2 diabetes (18).

### **Pramlintide**

Pramlintide, an amylin analog, improves glycemic control in type 1 diabetes by suppressing glucagon secretion (19). Use of Pramlintide, however, is not associated with any improvement in insulin mediated glucose disposal (20). It is believed that replacement of the function of both insulin and amylin, may allow for a more complete restoration of the physiology of glucose control (21). In a recent study, subcutaneous administration of Pramlintide for four weeks, in insulin treated type 2 diabetics, resulted in reductions in serum fructosamine, HbA<sub>1c</sub> and total and LDL cholesterol, suggesting that Pramlintide may improve metabolic control in patients with type 2 diabetes using insulin (22).

### **CONCLUSION**

The enteroinsular axis is an important regulator of glucose homeostasis in normal physiology. Of the incretin hormones, GLP-1 is the most powerful insulinotropic agent. In addition, as it also suppresses glucagon secretion and reduces food intake, it appears to be an attractive drug for the treatment of type 2 diabetes. However, rapid inactivation by

dipeptidyl peptidase IV limits its widespread use. Efforts are currently on to circumvent this problem by (1) developing long acting, peptidase resistant analogs, (2) using inhibitors of dipeptidyl peptidase IV, (3) ensuring continuous delivery of GLP-1 into the upper GI tract by ileal transposition, and (4) developing buccal tablets to ensure a steady supply of GLP-1 during meals. One or more of these methods, may offer a novel therapeutic approach to the treatment of type 2 diabetes, in the coming years.

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