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RESEARCH ARTICLE

INCRETIN PATHWAY: NEW APPROACH OF TREATMENT FOR DIABETES

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ABSTRACT

Incretins are the types of metabolic hormones responsible for reducing blood glucose. The two naturally occurring incretins are glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP). They are responsible for amplification of response of insulin to enteral entry of glucose in the body. DPP 4 are the enzymes responsible for the degradation of incretins. This incretin effect is the newer approach to treatment of diabetes. The two groups acting through this pathway are GLP 1 agonist and the DPP 4 inhibitors.

INTRODUCTION

With rising incidence and prevalence of diabetes mellitus there is an ongoing need for better opportunities for the treatment of diabetes. Incretin mimetics and DPP4 Inhibitors are the latest addition in the group of antidiabetics available for the treatment of type 2 diabetes. GLP 1 agonist are the incretins or the gut hormones that increase the secretion of insulin and DPP 4 are the protease group of enzymes responsible for the degradation of incretins

Physiology

Incretins are the types of metabolic hormones responsible for reducing blood glucose. The two naturally occurring incretins are glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP). Receptors for the incretins are present primarily in the pancreas and to a lesser extent in the central nervous system, heart, kidney, lung and gastrointestinal tract (Bullock, 1996; Brubaker *et al*., 2002). In cardiovascular system they are present myocytes, endocardium, vascular endothelium, and cardiac muscle cells.[3,4] Incretins are synthesized and secreted from enteroendocrine cells of large and small intestine. They are released in the blood stream in response to enteral nutrition. Dipeptidyl peptidase 4 are the naturally occuring enzymes responsible for the degradation of naturally occuring GLP 1 and GIP.

Mechanism of Action

Incretin Effect: There are separate mechanisms for blood glucose control depending upon the route of entry of glucose in the body.

If glucose enters into the blood stream through parenteral route then the primary mechanism for glucose control is the direct stimulation of pancreatic beta cells resulting in the release of insulin whereas if glucose enters through the gut then insulin secretion occurs both due to direct effect of glucose on the beta cells and due to release of incretins. This is known as incretin effect (Elrick, 1964). The primary stimulus for the release of incretins is the complex interaction between the luminal nutrients and the enteroendocrine cells in the gut. The released incretins stimulate the release of insulin from the beta cells of pancreas resulting in the uptake of glucose by tissues. In addition, they also reduce glucagon secretion from the alpha cells of pancreas, resulting in decreased glucose production. These two factors ultimately leads to reduced blood glucose level. DPP 4 enzymes are the naturally occuring proteases released in response to the glucose rapidly degrades the naturally occuring incretins. Hence, they are responsible for shortening the duration of action endogenously secreted GLP 1 in response to raised blood glucose. So, the agents that either act as a GLP-1 agonist or enhance endogenous GLP-1 activity by inhibiting the enzyme DPP 4 are approved for the treatment of type 2 diabetes. There are some other minor factors also responsible for reducing blood glucose like slowing of gastric emptying resulting in reduced absorption of glucose and increasing satiety. This effect occurs due to the presence of GLP 1 receptors in the gut and in the CNS respectively. Presence of receptors in the CNS in addition to reducing appetite also have some neuroprotective and antiapoptopic role. They have also been found to be cardioprotective by reducing blood pressure, improving endothelial dysfunction and myocardial function (Nyström *et al*., 2004; Sokos *et al*., 2007; Vilsbøll *et al*., 2007).

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GLP 1 Agonist

Exendin-3 and exendin-4 are the two naturally occurring peptides. The saliva of the lizard *Heloderma suspectum* contains these peptides, which were named exendins as they were isolated from an exocrine gland and were subsequently shown to have endocrine actions.[9] These Exendins exhibit significant biochemical and functional similarity to the human GLP 1. Like all naturally occurring peptides, endogenously occuring GLP-1 is highly susceptible to enzymatic degradation in the gastrointestinal lumen, and thus has a very short half-life. Ideally, to be effective there is a requirement of continous infusion of GLP 1.

To counter this, long-acting analogues of GLP-1 receptor agonists have been identified. Exenatide and Lixisenatide are the short acting GLP 1 agonist available. Exenatide is a synthetic form of exendin-4 and is the first GLP-1R agonist that has been approved by the FDA in April 2005, for the treatment of type 2 diabetes (Kazkoo *et al*., 2011). They are the newly found analogues that are resistant to degradation by Dipeptidyl peptidase 4 and thus have longer half-lives They require twice daily subcutaneous injections just after meal. The duration of action of exenatide is around 2 hours and for Lixisenatide is 13 hours. Due to longer half life in comparison to the native GLP 1, they can be given by bolus injections. But these long acting analogues too require multiple daily injections, which is not possible practically. To overcome this problem, a recombinant GLP 1 agonist has been developed that can be given as once weekly injections. Liraglutide, LAR Exenatide, Albiglutide and Dulaglutide are the long acting formulations available in the market. They are given once a week which improves the compliance of the patient. Currently 5 GLP 1 analogues are available in the market that are exenatide, liraglutide, lixisenatide, albiglutide and dulaglutide. All are given by subcutaneous routes. Now the approach is to develop ultra long acting GLP 1 that can be given once a month. Dosages of the currently available GLP 1 agonist are shown in the Table 1.

Table 1. Dosages for the currently available GLP 1 agonist

Name	Dose	Frequency
Exanetide	5-1omcg	BID
Liraglutide	0.6-1.8 mg	QD
Exanetide LAR	2mg	QW
Albiglutide	30-50mg	QW
Dulaglutide	0.75-1.5mg	QW

DPP 4 Inhibitors

Another class of newly available drugs are the DPP 4 inhibitors. They act by prolonging the effect of endogenously occuring GLP 1 by inhibiting the enzyme responsible for its degradation. The available preparations of DPP 4 inhibitors are Sitagliptin, Saxagliptin and Vildagliptin. They are administered once or twice a day orally. Dosages for the DPP 4 inhibitors are shown in the Table 2.

Table 2. Dosages for the currently available DPP 4 Inhibitors

Name	Dose	Frequency
Sitagliptin	100mg	OD
Vildagliptin	50mg	BID
Saxagliptin	2.5-5mg	OD
Linagliptin	5m	OD

Advantages

They control both fasting and postprandial blood glucose level. It can be combined with other oral hypoglycemics like sulfonylureas, metformin and thiazolidnediones and with insulin also. Studies have also shown that GLP 1 Analogues are also cardioprotective. They reduce blood pressure, improve lipid profile and also improve endothelial function consequently decreasing long term complications of diabetes like cardiovascular disease, cerebrovascular disease and peripheral vascular disease (Monami *et al*., 2014). They also improve myocardial function. They have neuroprotective properties too.

Disadvantages

Earlier the main disadvantage of GLP 1 agonist is the short duration of action which requires multiple daily injections. Now this drawback has been overcome by the introduction of long acting formulations. Secondly, if administered along with insulin it increases the risk of hypolycemia. Milder side effects include nausea and abdominal bloating. Rarely there may be chances of pancreatitis (Idris, 2008). Lastly, the major concern is the high cost which is more for patients on multiple medications.

Table 3 shows the comparison between GLP 1 agonist and DPP 4 Inhibitors.

Table 3. Comparison between GLP 1 Agonist and DPP 4 Inhibitors

S.No		GLP 1 Agonist	DPP 4 Inhibitors
1	Mechanism	Mimics the action of endogenous GLP 1	Prolongs the effect of endogenous GLP 1
2	Effects	Increase Insulin secretion	Increase Insulin secretion
		Decrease glucagon secretion	Decrease glucagon secretion
		Slows gastric emptying	No effecton gastric emptying
3	Route of adminstration	Sub cutaneous	Oral
4	Frequency of administration	Daily or weekly	once or twice daily
5	Effect on weight	Weight loss	Weight neutral
6	Safety in renal insufficiency	Not much	safer
7	Cardioporotective Effect	Yes	No
8	Neuroprotective Effect	Yes	No

Conclusion

Drugs acting through the Incretin pathway are the newer additions in the armamentarium against diabetes. They are classified as GLP 1 agonist and DPP 4 inhibitors. GLP 1 agonist are the analogues of gut hormones and DPP 4 inhibitors are the inhibitors of the enzymes responsible for the degradation of naturally occurring GLP 1. They both reduce blood glucose by increasing insulin secretion primarily. They can be combined with other oral hypoglycemics and insulin but not with each other. Newer GLP 1 agonist can be given once a week also which is a major advancement.

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