DIABETES AND ITS TREATMENT BY GLUCAGON- LIKE PEPTIDE 1 ANALOGS AND DI-PEPTIDYL PEPTIDASE 4 INHIBITORS

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ABSTRACT

The burden of diabetic patients on healthcare has increased over the period of time. Management of diabetes presents a challenge to the physician. The availability of newer drugs, tested in high quality clinical trials, has marked a new era in the treatment of diabetes. Glucagon-like peptide 1 (GLP-1) analogs act by increasing the pancreatic beta-cell mass and subsequent insulin secretion. Dipeptidase-4 (DPP-4) inhibitors inhibit the enzyme that degrades GLP-1, resulting in the augmentation of GLP-1 in the body. Hence, the two drugs can be used synergistically. It was seen that severe hypoglycemia seldom occurred with GLP-1 analogues and DPP-4 inhibitors. Gastrointestinal upset and the development of antibodies to the drug in the body was mainly attributed to GLP-1 analogs. DPP-4 inhibitors showed increased risk of nasopharyngitis, urinary tract infections and headache.

There is a need for further advances in our understanding, through randomized control clinical trials in larger settings, to establish the role and safety of these newer agents in the treatment of diabetes. The initiation of a modern set of medications may help us control type2 diabetes better.

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Glucagon-like Peptide 1 Analogs

Definition

Glucagon- like peptide 1(GLP-1) is derived from the transcription product of the pro-glucagon gene. The major source of GLP-1 in the body is the intestinal L-cells that secrete GLP-1 as a gut hormone, in the lumen of the small intestine, in response to the presence of nutrients like carbohydrates, proteins and lipids. Once in the circulation, GLP-1 has a half-life of less than 2 minutes due to its rapid degradation by the enzyme dipeptidyl peptidase-4 (DPP-4).

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Functions

The common physiological functions of GLP-1 are:

- It increases insulin secretion from the pancreas in a glucose-dependent manner.
- It decreases glucagon secretion.
- It increases beta-cell mass and insulin gene expression.
- It inhibits gastric acid secretion as well as gastric emptying
- It decreases food intake by increasing satiety1.

These physiological properties have led to intensive investigation of GLP-1 and its analogs to ascertain their role in the potential treatment of diabetes mellitus.

GLP-1 and dipeptidyl peptidase-4 inhibitors are primarily cleared by the kidneys. No dosage adjustment of these medications is needed in patients with a creatinine clearance (CrCl) above 50 mL/minute. Their doses should be reduced by half in patients with moderate renal impairment (CrCl 30-50 mL/minute) and by 75% in patients with severe renal impairment (CrCl<30

mL/minute).[2]

Mechanism of glucose homeostasis in diabetes

GLP-1 is a naturally-occurring, incretin compound that possesses biological activity when released from the gut during digestion. GLP-1 and glucagon share the same parent compound, pro-glucagon, but their activities differ. GLP-1 works naturally on several different organs to lower the blood sugar level.

- In the gut it slows down the absorption of glucose.
- In the hypothalamus, GLP-1 attaches to an appetite receptor, which often decreases appetite and gradually decreases weight over time[3].
- GLP-1 increases insulin biosynthesis and gene expression. It also increases the expression of glucose transporter2 (GLUT2) and glukokinase[4].
- Unlike glitazones, which directly reduce insulin resistance (a characteristic of type 2 diabetes), GLP-1 has no effect on it.

Unfortunately, GLP-1 as a drug is not useful because it is broken down within minutes by the enzyme DPP-4 which is present throughout the body. Instead, a class of medications called GLP-1 agonists (not broken down as quickly) has been developed. The sulfonylureas increase insulin production regardless of the glucose levels and can cause hypoglycemia. No hypoglycemia is caused by the use of GLP-1 agonists per se but hypoglycemia can occur if its glucose lowering effects are combined with an excess of sulfonylurea or insulin[3]. Patients with type 2 diabetes have a decreased GLP-1 secretion but a preserved insulinotropic action of GLP-1[5].

Effects of GLP-1 on Blood Brain Barrier (BBB)

Maintaining a constant glucose concentration in brain tissue is important to the preservation of neuronal functioning. Recent research on rodents suggests a protective effect of GLP-1 on brain tissues. A randomized, double-blinded, placebo-controlled, cross-over experiment carried out on 10, healthy, men using positron emission tomography to determine the acute insulin-independent effects of GLP-1 on unidirectional glucose transport in the brain showed that GLP-1 reduces unidirectional glucose delivery across the intact BBB at normoglycaemia[6]. GLP-1 also limits the intracerebral glucose fluctuations when plasma glucose is increased hence protecting the brain tissue by extremes.

Although GLP-1 receptors (GLP-1Rs) are predominantly located on the B-, Δ-, and presumably A-cells of the pancreas, receptors in other tissues may mediate GLP-1's effects outside the pancreas, where gastric emptying and appetite are the well known targets, as are other tissues including heart, kidneys and lungs. By its role in the maintenance of cerebral glucose balance it may have neuroprotective effects linked to both peripheral and cerebral glucose metabolism. During hyperglycemia, GLP-1 is secreted from the gut into the bloodstream and may also be produced in the brain, as central GLP-1 signaling appears to be linked to the control of blood glucose concentrations[6].

Promotion of satiety by GLP-1 Agonists

This mechanism is not very clear. It could be that the GLP-1 receptors located in many regions of the brain, including arcuate nucleus and hypothalamus, are mainly involved in regulating food intake. The inhibitory effect of GLP-1 on food intake and appetite are abolished if there is destruction of arcuate nucleus. Conversely, the formation of GLP-1 from the processing of pro-glucagon in the brainstem inhibits food intake. Furthermore, entry of GLP-1 in the brain might be through the leaks in blood-brain barrier. The hypothalamus might also be involved through an interaction, possibly by means of vagal afferent nerves[7], with sensory neurons in the gastro-intestinal tract or hepato-portal bed[8], although data regarding the hepato-portal bed are conflicting[7]. Recent evidence suggests the importance of a peripheral, relative to central, mechanism. Central administration of GLP-1 receptor antagonist in rodents blocks the anorexia induced by peripherally administered GLP-1[9].

Brief descriptions of GLP-1 analogs

Exenatide has an established role in binding to the GLP-1 receptor more potently than GLP-1 itself. When administered twice daily, especially post-prandially, it reduces blood glucose while simultaneously increasing insulin levels. The advantage is that it rarely leads to hypoglycemia since the production of insulin following its use is dependent on the presence of glucose in the blood[10]. It has a positive relation with Beta cell function and also decreases the release of glucagon by Alpha cells[11]. Moreover, its various glucose-reducing characteristics also include a decrease in food ingestion, slow gastric emptying, a reduced fasting and random glucose level as well as a decrease in body weight[12].

A variety of Exenatide are in phase 3 trials which will allow for once-a-week dosing and a drug delivery which will be easy to manipulate, enabling improved blood sugar management due to constant action of the drug[12]. However, Exenatide

should be avoided in patients with a creatinine clearance of less than 30 mL/minute or in those receiving dialysis[11].

Liraglutide Liraglutide is an acylated human glucagon-like peptide-1 (GLP-1) receptor agonist, which just like GLP-1(7-37), activates the GLP-1 receptor, a membrane-bound cell-surface receptor coupled to adenylyl cyclase by the stimulatory G-protein, Gs, in pancreatic beta cells[13]. It increases intracellular cyclic AMP (cAMP), leading to insulin release in the presence of elevated glucose concentrations. Insulin secretion subsides as blood glucose concentrations decrease and approach euglycemia. It also decreases glucagon secretion in a glucose-dependent manner. Its mechanism of blood glucose lowering also involves a delay in gastric emptying[13]. The pharmacokinetic profile of liraglutide, which makes it suitable for once daily administration, is a result of self-association that delays absorption, plasma protein binding and stability against metabolic degradation by DPP-IV and NEP. The drug does not cause weight gain, and may even cause some weight loss. The adverse effects include nausea, emesis and loose stools which disappear on suspending the drug administration[14, 15].

Dipeptidyl Peptidase-4 Inhibitors (DPP-4 Inhibitors)

Definition

Dipeptidyl peptidase-4 inhibitors (DPP-4 inhibitors) are agents that inhibit the enzyme dipeptidyl peptidase-4 and are a potent treatment for type 2 diabetes. Inhibition of DPP-4 enzyme prolongs and enhances the activity of incretin (GLP-1) that has a significant role in insulin secretion and blood glucose regulation.

Mechanism of Action and Function

Dipeptidyl peptidase-4 (DPP-4), a complex enzyme that exists as a membrane-anchored, cell-surface peptidase, transmits intracellular signals via a short, intracellular tail and as a second, smaller, soluble form present in the circulation. Glucose-dependent, insulinotropic, polypeptide (GIP) and glucagon-like peptide-1(GLP-1) are endogenous, physiological substrates for DPP-4. DPP-4 inhibitors exhibit favorable actions on islet and B-cell mass, their morphology, and survival. The DPP-4 inhibitor des-fluoro-sitaglipitin (DFS) significantly reduced ambient and fed blood glucose and HbA_{1c} levels in diabetic mice, in association with decreased liver weight and reduced levels of hepatic and plasma triglycerides and plasma free fatty acids. DPP-4 has been implicated in the control of lymphocytes and immune function, cell migration, viral entry, cancer metastasis and inflammation[16].

DPP-4 Inhibitors Improve Glycemic Control in Type 2 Diabetes

A once-daily, oral agent that preserves the action of glucagon-like peptide 1 (GLP-1) has been developed. It inhibits the enzymes that degrade GLP-1 and appears to improve glycemic control in patients with type 2 diabetes mellitus who are inadequately controlled with metformin.

The drug, LAF237, is the first in a new class of agents known as dipeptidyl peptidase 4 (DPP-4) inhibitors. Unlike Exenatide (exendin-4), a synthetic version of GLP-1, LAF237 inhibits the action of DPP-4, which rapidly degrades GLP-1[17].

Brief description of dipeptidyl peptidase 4 (DPP-4) inhibitors

Sitagliptin has a half-life of 8-14 hours, a bioavailability of 87%, and an ability to decrease HbA_{1c} levels by 0.6-0.7% in a span of 54 weeks[14, 15]. The dose should be halved in patients with "moderate renal impairment (CrCl 30-50 mL/minute)" and only one fourth of the original dose should be given to patients with severe renal impairment (CrCl < 30 mL/minute)[2].

Vildagliptin**,** a DPP4 inhibitor that augments the secretion of glucagon like peptide-1 (GLP-1), is produced by the intestinal endocrine glands and is responsible for glucose and insulin homeostasis. It has no officially accepted by the Food and Drug

Direct and Indirect Actions of Antidiabetic Agenda on Glucose Homeostasis

Agent	↓ Food intake	↓Gastic Emptying	↓Glucose Absorption	↑ Insulin Secretion	↓ Glucagon Secretion	↑ Glucose Uptake	↓ PPG
GLP-1 receptor agonist	✓	✓		✓	✓	✓	✓
DPP-4 inhibitor				✓	✓		✓

DPP-4, dipeptidyl peptidase-4; GLP-1, glucagon-like peptide-1; PPG, postprandial plasma glucose. Sources: Januvia [prescribing information]/ Whitehouse Station, NJ: Merck & Co., Inc.; 2007. Dricker Dj, et al. Lancent. 2006;368:1695-1705. Hinnen D, et al. J Am Board Fam Med, 2006;19:612-620. Triplitt C, et al. J Manag Care Pharm. 2007;13(9 suppl C):S2-16. National Institutes of Health. Diabetes medications supplement: Wroking together to manage diabetes. http//www.ndep.nih.gov/diabetes/pubs/Drug_tables_spplement.pdf. Accessed April 23, 2008. Byetta [prescribing information]. San Deigo, CA: Amylin Pharmaceuticals, Inc. ; 2008.

Administration, though they have promised to. It has a half-life of approximately 90 minutes though about 50% of the inhibition persists even after 10 hours, enabling the patient to be more compliant with a reduced number of dosing. Vildagliptin plays an integral role in lowering the fasting and random blood glucose levels and ultimately the HbA_{1c} levels in patients with relative recuperation in beta-cell function[9]. Levels of insulin and C-peptide may also rise[18]. The long lasting post-prandial efficacy of the drug is emphasized by the fact that one dose of Vildagliptin, taken at 1730 hours, functions effectively in blocking DPP-4 until the next morning (0800 hours)[18].

ADVERSE EFFECTS ASSOCIATED WITH GLP-1 ANALOGS AND DPP-4 INHIBITORS

Severe hypoglycemia seldom occurred with GLP-1 analogues and DPP-4 inhibitors. Hypoglycemia was more at the start of treatment with *Exenatide* but lessened over time with nausea and emesis being the most common, dose-dependent complaints. The episodes of nausea can be reduced by using a longer acting GLP-1 receptor agonist that takes longer to attain a concentration level in blood. Diarrhea was frequent as well. Several studies reported that a large number of patients (an estimated 67%) under therapy with Exenatide developed antibodies to the drug but these did not have any effect on the function or the side effects of the drug per se[5, 10, 12, 14, 15, 19, 20]. As compared to this, *Liraglutide* does not trigger antibody development[19]. DPP- 4 inhibitors on the whole showed less adverse effects. Nasopharyngitis, urinary tract infection and headache were frequently seen with *Sitagliptin*[14]. The common side effects seen with *Vildagliptin* are headache, cough, inflammation of the nasopharynx, difficult evacuation of faeces, lightheadedness and increased perspiration.

GUIDELINES BY UNITED KINGDOM PROSPECTIVE DIABETES STUDY (UKPDS) GROUP, AMERICAN DIABETES ASSOCIATION (ADA) & EUROPEAN ASSOCIATION FOR THE STUDY OF DIABETES (EASD)

Beta-cell failure has a significant role to play in the advancement of the disease which has been highlighted by the United Kingdom Prospective Diabetes Study (UKPDS) Group.

The UKPDS established that at least half of the beta cells in the pancreas have decreased activity in patients when identified to be suffering from T2DM. However, later researches proposed that as much as 80% of the beta cells may have been destroyed.

Moreover, the group demonstrated that even with strong "monotherapy" there is a high possibility of deteriorating control of blood glucose eventually. While an HbA_{1c} level of less than 7 % was attained by an estimated 50% of the patients subsequent to three years of monotherapy, a mere 25% responded after 9 years. Such observations led to a unanimous decision by the ADA and EASD to initiate the use of multiple drugs, "combination therapy", later in the management of T2DM to provide better control of the blood glucose levels within the near normal range after a few years of monotherapy alone when a decline in its efficacy would be inevitable.

The American Association of Clinical Endocrinologist (AACE) strategy is more precise and advocates that incretins be employed in treating patients, both new and old ones, that have gone through prior treatments.[12] In new patients, the AACE suggests that a DPP-4 inhibitor be used alone for ones that have a baseline HbA_{1c} of 6-7% or a combination of drugs for patients with a baseline HbA_{1c} of greater than 7 %. However, if the HbA_{1c} target of less than 6.5% is not reached then a GLP-1 receptor agonist may be used. One must keep in mind that like many new drugs, these drugs are expensive and may be with time become cheaper and be available for general public at large.

CONCLUSION

The initiation of a modern set of medications may help in better control of type 2 diabetes. GLP1 agonists and DPP4 inhibitors are a new innovation in the treatment of type 2 diabetes mellitus. Further research with randomized, controlled, clinical trials in a larger number of patients should be carried out to test their clinical efficacies, adverse effects and safety. The safe addition of these drugs to the armamentarium of agents presently available to treat diabetes mellitus will go a long way in alleviating the misery of these patients.

REFERENCES

1. Wikipedia, the free encyclopedia. Glucagon-like peptide-1 [Online]. 2010 [citedon 2009 March 13] Available from URL: http://en.wikipedia.org/wiki/Glucagon-like_peptide-1.
2. Karim A, Fleck P, Hetman L. Single-dose pharmacokinetics of the dipeptidylpeptidase-4 inhibitor alogliptin in subjects with renal impairment. Program andabstracts of the American Diabetes Association, 68th Scientific Session. San Francisco, California,2008.
3. Diabetes net [Online]. 2009 [cited on 2009 March 13]. Available from URL: http://www.diabetesnet.com/diabetes_treatments/glp1.php#axzz18JGQkcue.

4. Elahi D, Egan JM, Shannon RP, MeneillyGS, Khatri A, Habener JF, et al. GLP-1 (9–36), amide, cleavageproduct of GLP-1 (7–36) amide, Is a glucoregulatory peptide. Obesity (Silver Spring) 2008;16:1501-9.

5. Stumvoll M,Goldstein BJ, van Haeften TW. Type 2 diabetes: pathogenesis and treatment. Lancet2008;371:2153-5.

6. Lerche S,Brock B, Rungby J, Botker HE, Moller N, Rodell A, et al. Glucagon-likepeptide-1 inhibits blood-brain glucose transfer in humans [Online]. 2009 [citedon 2009 March 13]. Available from URL: http://www.medscape.com.

7. Ruttimann EB, Arnold M, Hillebrand JJ, Geary N, Langhans W. Intra-mealhepatic-portal and intra-peritoneal infusions of glucagon-like peptide-1 reducespontaneous meal size in the rat via different mechanisms. Endocrinology 2009;150:1174-81.

8. Holst JJ. The physiology of glucagon-like peptide 1. Physiol Rev 2007;87:1409-39.

9. Williams DL,Baskin DG, Schwartz MW. Evidence that intestinal glucagon-like peptide-1 playsa physiological role in satiety. Endocrinology 2009;150:1680-7.

10. KimW, EganJM. The Role of incretins in glucosehomeostasis and diabetes treatment. Pharmacol Rev 2008;60:470-512.

11. AmylinPharmaceuticals, Inc. (AMLN) says byetta gets FDA approval for new use [Online]. 2009 [cited on 2010 Dec1]. Available from URL: http://www.biospace.com/news_story.aspx?StoryID=161256&full=1

12. Daniel JD,John BB, Taylor K, Kendall DM, Trautman M, Zhuang D, et al. Exenatide once a weekversus twice daily for the treatment of type 2 diabetes: a randomized,open-label, non-inferiority study. Lancet 2008;372:1240-50.

13. Wikipedia,the free encyclopedia. Liraglutide [Online]. 2009 [cited 2009 March 13]. Available from URL: http://en.wikipedia.org/wiki/Liraglutide.

14. Chia CW, Egan JM. Incretin-basedtherapies in type 2 diabetes mellitus. J Clin Endocrinol Metab 2008;93:3703-16.

15. Drucker DJ,Nauck MA. The incretin system: glucagon-like peptide-1 receptor agonists anddi-peptidyl peptidase-4 inhibitors in type2 diabetes. Lancet 2006;368:1696-705.

16. Daniel J, Drucker M., advances in glucagon-like peptides for the treatment oftype 2 diabetes [Online] 2009. [cited on 2009 March14]. Available from URL: http://www.medscape.com

17. Osterweil N. DPP-4 Inhibitor improves glycemic control in type 2 diabetes [Online]. 2009. [cited on 2009, March14]. Available from URL: http://www.medscape.com

18. Balas B, Baig MR, Watson C,Dunning BE, Saylan ML, Wang Y, et al. The dipeptidyl peptidase ivinhibitor vildagliptin suppresses endogenous glucose production and enhancesislet function after single-dose administration in type 2 diabetic patients. J Clin Endocrinol Metab 2007;92:1249-55.

19. Laferrère B, Teixeira J, McGintyJ, Tran H, Egger JR, Colarusso A, et al. Effectof weight loss by gastric bypass surgery versus hypocaloric diet on glucose and incretin levels in patients with type 2diabetes. J Clin Endocrinol Metab 2008;93:375-7.

20. Amori RE,Lau J, Pittas AG. Efficacy and safety of incretin therapy in type 2 diabetes. JAMA 2007;298:194-206.

CONTRIBUTORS

MOK conceived the Idea, did literature search and wrote the first draft. RM did the literature search and referencing. FS edited the final draft. SF helped in literature search and editing of the manuscript.

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None Declared