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Review Article

HORMONE BASED THERAPY IN TYPE 2 DIABETES MELLITUS

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ABSTRACT

Type 2 diabetes mellitus is a chronic disease mainly characterized by insulin resistance and decrease in the pancreatic beta cell glucose mediate insulin secretion. Hormone Replacement Therapy in type 2 diabetes has attained a great importance in recent days in control of elevated blood glucose levels (Hyperglycemia).The different hormones which are used in this therapy are Insulin, Incretins, Amylin, Leptin, Adiponectin, Testosterone, Estrogen, and Ghrelin. Among these incretins plays very important role in control of diabetes. These are the intestinal hormones i.e. Glucagon like peptide-1(GLP-1) and Gastric inhibitory peptide (GIP) enhances the glucose dependent insulin secretion and inhibits glucagon release. This paper briefly reviews the concept of incretins and other hormones along with their biological effects which are identified so far.

Keywords: Incretins, Hormone Replacement Therapy,

INTRODUCTION

Diabetes Mellitus

It is a chronic hyperglycemic condition mainly associated with abnormally high levels of blood glucose due to the insufficient production of insulin or the inability of cells to use insulin properly which is secreted by the Beta-cells of islets of langerhans of pancreas glands located in the abdomen behind the stomach[1]. Insulin is a hormone that regulates the uptake of glucose from blood and helps in its transport into the cells and tissues of body.

Causes

Abnormal insulin secretion, any disease that cause extensive damage to the pancreas. Disease associated with excessive secretion of insulin antagonistic hormones, drugs which impair insulin secretion and some toxins which damage pancreatic Beta-cells.

Types

Type-1 diabetes mellitus also called insulin dependent or juvenile diabetes. This results from auto immune destruction of insulin producing beta cells of pancreas. This subsequent lack of insulin leads to the increase blood and urine glucose. Abnormal antibodies like anti islet cells, anti insulin antibodies and anti glutamic decarboxylase antibodies have been found as one of the cause.Type-2 diabetes is also called non insulin dependent or adult onset diabetes. It is a metabolic disorder which is characterized by the insulin resistance and insulin deficiency. It is mainly caused by life style and genetic factors[2,3].

Diagnosis

Plasma glucose >11.1 mmol/l (200mg/dl), Fasting plasma glucose level >7mmol/l (126mg/dl)HbA1C[4].

Hemoglobin, in your blood, joins up with glucose to form the chemical called HbA1c. Glucose sticks to the haemoglobin to make a 'glycosylated haemoglobin' molecule, called haemoglobin A1C or HbA1C. The normal range for the A1C test is between 4 percent and 6 percent for people without diabetes. The ideal range for people with diabetes is generally less than 7 percent. It provides an average blood glucose measurement over the past six to twelve weeks and is used in conjunction with home glucose monitoring to make treatment adjustments.HbA1c levels depend on the blood glucose concentration. That is, the higher the glucose concentration in blood, the higher the level of HbA1c[5, 6].

Hormone Replacement Therapy (HRT)

According to a survey of over 14,000 women, only 15% of those with diabetes reported current or previous use of any form of hormone replacement therapy. Possible reasons for these low rates of use are related to concerns raised by many primary healthcare providers and women themselves that hormone replacement therapy may aggravate glycemic control, cause weight gain, elevate blood pressure, and increase the risk of stroke and cardiovascular disease, retinopathy[7].

Hormones

The human bodies possess ductless glands which release their secretions directly into the blood stream. These glands are called Endocrine glands .Their secretions which may stimulate or regulate the functioning of various other organs are known as Hormones. A hormone is a chemically released by a cell or a gland in one part of the body that sends out messages that affects cells in other parts of micro organism. It is a chemical messenger that transports a signal from one cell to another cell. Cells respond to a hormone when expresses a specific receptor for that hormone. The hormone binds to the receptor protein, resulting in the activation of signal transduction mechanisms. Its secretion is can be stimulated and inhibited by other hormones, (stimulating or releasing), plasma concentrations of ions or nutrients, neurons and mental activity, environmental factors.

Effects on the body

Stimulation or inhibition of growth, mood swings, induction or suppression of apoptosis, activation or inhibition of immune system, regulation of metabolism, Preparation of body for a new phase of life such as puberty, parenting, menopause, hunger cravings.

Incretins: A New Hormone in Diabetes

Eating provokes the secretion of multiple gastro intestinal hormones. But in 1990 it was recognized that these hormones have various effects such as disposal of absorbed glucose through stimulation of insulin secretion from the pancreas. Later these hormones are named as “incretins” also called peptide hormones. Recently developed in cretin-based therapies are at-attractive options for adding to metformin the existing regimens in older patients because they have been re-ported to control hyperglycemia with a low risk for hypoglycemia (glucose-dependent mechanism of action)[8,9]. The 2 main hormones that fulfill criteria for an in cretin are “glucagon” like peptide (GLP-1) and glucose dependant insulin tropic polypeptide or (GIP). These 2 hormones are released into the blood stream from L and K cells dispersed through out the gastrointestinal tract in response to ingested nutrients like lipids carbohydrates that stimulate insulin[10]. Normally in cretin hormones are responsible for 70% of post prandial insulin secretion but in diabetic patients the in cretin affects decrease to 30%. The majority of studies agree that glucose is a potent secretagogue for both GIP and GLP-1.Other carbohydrates may trigger the secretion but are reportedly less effective than glucose. It is well known that fat is a good stimulant for both GIP and GLP-1secretion. The response appears to be proportional to the caloric content of the ingested lipid, as secretion is highly sensitive to dose fluctuations. In addition to meal size, secretion of the two hormones is affected by the degree of fatty acid saturation.

Physiological role of incretins

The term ‘‘incretins’’ was first proposed to indicate several gastrointestinal hormones (mainly GIP and GLP-1) released in response to ingested nutrients, such as lipids, proteins and, in first, carbohydrates, that stimulate insulin secretion from pancreatic beta-cells[18]. After being secreted, GLP-1 has a circulating half-life of about 3-5 minutes, and it is rapidly inactivated through the action of some proteases such as dieptidyl peptidase IV (DPP-4). Biological effects on pancreatic beta-cells, increasing post-prandial insulin release and the biosynthesis of glycosidase and GLUT-2 glucose transporters .In addition, GLP-1 is reported to reduce glucagon secretion. GLP-1 receptors were identified in various extra-pancreatic tissues, such as heart, endothelium, lung, kidney, central and peripheral nervous system as well as gastro-intestinal tract[19]. GLP-1 may play an important role in the cardiovascular system, including modulation of heart rate, blood pressure, vascular tone and myocardial contractility. GLP-1 is hypothesized to counteract the beta-cells progressive deterioration by inhibition of beta-cells apoptosis and increase of islet proliferation/replication[20].

GLP-1

Increased plasma GLP levels have been reported in humans after consumption of glucose but not equivalent portions of complex carbohydrates in the form of brown rice or barley. Oral glucose also stimulates GLP-1 secretion more effectively than other mono saccharides such as fructose, although both have been reported to affect appetite similarly[12]. Since secretion of GLP-1 in vitro was shown to be preferentially triggered by long chain monounsaturated fatty acids compared with their saturated equivalents. It has been identified in the intestine, principally in K and L-cells. Its activation by unsaturated long-chain free fatty acids such as α-linoleate, docosahexaenoeate, palmitoleate and oleate, dose-dependently promoted the secretion of GLP-1 both in vitro and in vivo[13]. The primary mechanisms underlying detection of amino acids or small peptides in entero endocrine cells remain uncertain, as a range of potential signaling pathways have been postulated. Hydrolysate or mixtures of essential amino acids, and may provide a link to GLP-1 release. Glutamine promotes the secretion of GLP-1 from rodent primary culture and GLUT cells via two pathways[14]. Electrogenic Na+coupled amino acid uptake appears responsible for initiating membrane depolarization and voltage gated Ca2+ entry, whilst a second pathway in-volves elevation of intracellular cAMP levels. Synergy between these Ca2+and cAMP signaling pathways seems a particularly potent stimulus of GLP-1 release in vitro. It has been found to enhance the pancreatic β cells mass through the stimulation of β cells proliferation and neogenesis. Therefore GLP-1 has become the attractive agent in clinical research studies for the development of new anti diabetic medications[15]. Its secretions is stimulated by glucose, nutrients free fatty acids, peptides, and other forms of sugar.GLP-1 exerts its actions by binding to its receptors in the pancreas brain and heart.

Mechanism of Action

GLP-1 agonists have the same action as native GLP-1 but have longer half-lives. The limiting factor in using native GLP-1 is its very short half-life. The enzyme that breaks down GLP-1 is called dipeptidyl peptidase (DPP-4). DPP-4 inhibitors slow the breakdown of endogenous GLP-1, pro-longing its action DPP4isexpressedinman[11]. GLP-1 in endocrinology and gastroenterology become an important tool for the gastroenterologists to combat metabolic derangements because of over-eating. By inhibiting the gastric emptying, appetite is cut and food intake is diminished .This leads to the weight loss and more favorable metabolic homeostasis thus offering an expansion of therapeutic options for over weight and obese diabetes patients.

E.g.: exenatide and liraglutide (analogues) injection.

Exenatide

It is a glucagon-like peptide-1 agonist (GLP-1 agonist) used to treat diabetes mellitus type 2. It belongs to the group of in cretin mime tics . It is administered by subcutaneous injection (under the skin) of the abdomen, thigh, or arm, any time within the 60 minutes before the first and last meal of the day. Exenatide is a synthetic version of exendin-4, a hormone found in the saliva of the Gila monster. Exenatide is a 39-amino-acid peptide, an insulin secretagogue, with glucoregulatory effects. Exenatide is approved "as adjunctive therapy to improve glycemic control in patients with type 2 diabetes mellitus who are taking metformin, a biguanide, or a combination of metformin and a sulfonylurea.

Mode of action

Exenatide also suppresses pancreatic release of glucagon in response to eating, and prevents hyperglycemia (high blood sugar levels). It helps slow down gastric emptying, It reduces liver fat content. It has a subtle yet prolonged effect to reduce appetite, promote satiety via hypothalamic receptors (different receptors than for amylin).

H-His-Gly-Glu-Gly-Thr-Phe-Thr-Ser-Asp-Leu-Ser-Lys-Gln-Met-Glu-Glu-Glu-Ala-Val-Arg-Leu-Phe-Ile-Glu-Trp-Leu-Lys-Asn-Gly-Gly-Pro-Ser-Ser-Gly-Ala-Pro-Pro-Pro-Ser-NH_2.

GIP

In humans, for example, protein-rich meals were ineffective in altering post-prandial .GIP levels whereas intra duodenal infusion of mixed amino acids or oral consumption of the amino acid glutamine was found to increase GIP release. In animals such as dogs and rats, peptones are considered as potent stimuli for GIP release[16]. Receptors are also found in the islets of β cells to a less extent, in adipose tissue and in CNS. These receptors sites react differently in type-2 diabetes. It leads to activation of both in cretin receptors on β cells leads to rapid release of insulin in a glucose dependant manner.

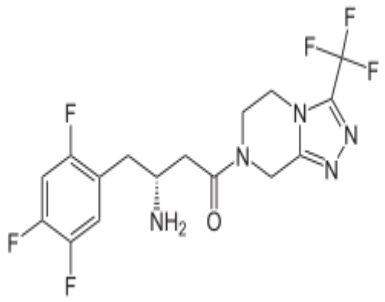
DPP4- inhibitors

The oral DPP-4 inhibitors block the metabolism of GLP-1 and GIP by this enzyme, thereby prolonging the half-lives and increasing the levels of these endogenous incretins. These drugs present the normal rapid degradation of GLP-1. They are selective became they inhibit DPP4 significantly more than the related enzymes DPP8, DPP9[17].

EG: vidagliptin, Sitagliptin

Sitagliptin

It is marketed as sitagliptin phosphate under the trade name Januvia) is an oral anti hyperglycemic (anti diabetic drug) of the dipeptidyl peptidase-4 (DPP-4) inhibitor class. The benefit of this medicine is its fewer side effects (e.g., less hypoglycemia, less weight gain) in the control of blood glucose values. Sitagliptin works to competitively inhibit the enzyme dipeptidyl peptidase 4 (DPP-4). This enzyme breaks down the incretins GLP-1 and GIP, gastrointestinal hormones released in response to a meal By preventing GLP-1 and GIP inactivation, they are able to increase the secretion of insulin and suppress the release of glucagon by the pancreas. Sitagliptin has been shown to lower HbA1c level by about 0.7% points versus placebo. It is slightly less effective than metformin when used as a monotherapy and does not cause a weight gain compared to sulfonylurea.



Role of Insulin in Diabetes

Insulin is an anabolic hormone, causing cells to store energy substrates at times of excess Insulin's action is countered by the catabolic hormones glucagon, adrenalin, noradrenalin and growth hormone. These act primarily through cyclic AMP (cAMP) and

protein kinase A. Insulin is a hormone that is released into the blood by beta cells found in the islets of langerhans in the pancreas in response to rising of blood glucose levels. It is also the principle signal for conversion of glucose to glycogen for internal storage in liver and muscle cells. Lowered glucose levels the reverse conversion of glycogen to glucose. The most common insulin are biosynthetic products produced using genetic recombination technology .Suppliers include Eli Lilly and company, Novo Nor disk, Sanofi Aventis. The phenomenon known as "hypoglycemia unawareness" is more common in diabetic patients with good glycemic control than in those with poor control. Insulin work through activation of protein kinase A with ensuing phosphorylation of key enzymes. Insulin often activates protein phosphates and initiates de phosphorylation of enzymes involved in energy metabolism[38]. Insulin activates glycogen synthetase and pyruvate, dehydrogenase, and inactivates phosphor fructokinase II and hormone-sensitive lipase. The activated insulin receptor speeds uptake of amino acids and glucose, activates protein synthesis from amino acids and glycogen and triglyceride synthesis from glucose. Insulin inhibits breakdown of triglycerides in adipose tissue and gluconeogenesis in the liver. Insulin is a strong predictor within the next five years.

Other Hormones

Amylin

The effect of amylin on suppressing post-meal glucagon secretion is thought to be mediated via amylin's central binding rather than by a paracrine mechanism. suppressive effects of amylin on glucagon are overridden during hypoglycemia, thus not altering this important counter regulatory response[22]. Human amylin exhibits physicochemical characteristics (poor solubility and a tendency to aggregate) that make it unsuitable as a pharmacological agent. This led to the development of pramlintide, an analogue of human amylin, by 25Ala, 28Ser and 29Ser. Amylin is a peptide hormone that is co-secreted with insulin from the pancreatic beta cell and is thus deficient in diabetic people. It inhibits glucagon secretion, delays gastric emptying, and acts as a satiety agent. Amylin replacement could therefore possibly improve glycemic control in some people with diabetes. Amylin is secreted in response to nutrient stimuli. Amylin (also known as islet amyloid polypeptide, or IAPP) is a 37–amino acid peptide hormone[23,24].

Amylin actions

Amylin delays gastric emptying mediated through central nervous system and depends on the intact vagus nerve. It reduces food intake and body weight and also include high affinity binding sites in the area postrema in the hind brain[25]. Human amylin forms islet amyloid and leads to the development of an analogue in which three proline residues were substituted at positions 25, 28, and 29 .This analog, named pramlintide[26]. Pramlintide treatment led to reduce concentrations of glucagon (25%) after a carbohydrate-rich breakfast meal. the addition of pramlintide (q.i.d.) to the insulin therapy significantly reduced HbA1c. Pramlintide, a synthetic amylin analog that can be used in large-scale phase III studies involving more than 3,000 diabetic individuals have demonstrated a beneficial effect of amylin replacement on the HbA1c level in both type 1 and 2 diabetes without an increased number of hypoglycemic events and weight gain[27].

Role of Islet amyloid peptide

Islet amyloid is mainly composed of the beta cell peptide islet amyloid polypeptide (IAPP or amylin). IAPP is a neuroendocrine hormone that is a member of the calcitonin family of polypeptide hormones and is produced and co secreted with insulin in response to beta cell stimulation by both glucose and non-glucose secretagogues[28]. IAPP are shown to inhibit food intake, likely by inhibition of neuro peptide Y; suppress gastric emptying ; and inhibit both basal and stimulated glucagon release from pancreatic alpha cells[29]. Amyloid fibril formation in type 2 diabetes is thought to start with precipitation of soluble IAPP molecules and formation of amorphous aggregates of monomers and small oligomers[30]. Small units that are called proto fibrils and consist of a few oligomers then form larger units called fibrils (4 to 8 nm diameter), which form the foundation of extra cellular islet amyloid[31].

Testosterone

Men in contrast to women display a correlation between low testosterone levels and insulin resistance and type II diabetes, while the same inverse relation is known for insulin resistance.

Low testosterone levels are correlated with type II diabetes, carbohydrate metabolism disorders, and obesity[31]. Testosterone therapy reduced insulin resistance and improved blood sugar control for hypogonadal men with type 2 diabetes. Body fat and cholesterol levels also went down. High testosterone levels had a lower risk of developing diabetes. Testosterone administration in men with type II diabetes has shown the following benefits: Lowered insulin levels, glucose levels, HbA1c levels and decrease glyccolated end products[32]. Testosterone increases the sensitivity of the paroxysmal PPAR gamma receptor and has similar effects as rosiglitazone, androgen deficiency and estrogen excess shifts the carbohydrate metabolism to insulin resistance[33]. The loss of testosterone in middle and older-age, which in turn increases the risk of obesity and insulin resistance.

Estrogen

Type 2 diabetes dramatically increases risk of cardiovascular disease in women. Observational studies have found that estrogen therapy with or without progestin are associated with reduced risk of coronary events. Two observational studies have reported a decrease in risk of myocardial infarction associated with current use of estrogen plus progestin among women with diabetes. Postmenopausal use of estrogen was associated with a 52% reduction in cardiovascular events and current use of estrogen with progestin was associated with a 57% reduction in risk. In small trials of postmenopausal women with diabetes, estrogen has been associated with lower levels of HbA_1, fasting glucose, and insulin, improved insulin sensitivity and decreased hyper androgenicity.

Leptin

Leptin levels, which stimulate the hypothalamus, are secreted by adipocytes. Leptin by itself is a product of the OB gene, the obesity gene, and is an adipose cytokine. It is secreted by white fat cells, and its primary role is in adaptation to negative energy balance .Leptin also plays a role in the regulation of insulin levels and insulin sensitivity[34]. We have higher body fat we also have higher leptin levels and higher insulin levels. This is the correlation between leptin, and fat. Metformin is used to decrease insulin levels in people with type II diabetes. Metformin is the only drug that lowers insulin levels without raising leptin levels[35].

Adiponectin

Another hormone of interest is Adiponectin. It has a direct correlation with insulin. Adiponectin is an adipose-derived peptide and it acts as a systemic regulator of glucose and lipid metabolism. There is a strong relationship between adiponectin, and body composition[36]. If adiponectin levels are low, insulin is not able to phosphorylate the insulin receptor, which normally happens at the tyrosine residuals of the insulin receptors. This phosphorylation stimulates the starting of the insulin effect. This is why we need adiponectin.Low levels of adiponectin have been linked with an increased risk of cardiovascular disease[37].

Ghrelin

Ghrelin is mainly produced in the stomach, and is the only hormone secreted into the blood that stimulates appetite in order to increase the energy balance of the body. Regulate ghrelin receptors in the periphery. Testicles produce Low ghrelin levels in obese men to insulin resistance. Administering testosterone to these men causes ghrelin levels to rise to normal levels[38]. Because hypogonadal men have decreased ghrelin levels they should be very slender because of the reduced appetite. Ghrelin resistance in hypo gonadal men and obese men can be responsible for the low levels of the hormone. Testosterone may activate the androgen receptor, present on the X chromosome, to increase the gene expression of ghrelin.Ghrelin is a

target for posttranslational modifications, which results in two different forms of circulating ghrelin: unacylated ghrelin (UAG) and acylated ghrelin (AG), in which Ser 3 is octanoylated. . Circulating ghrelin concentrations are also reduced in healthy offspring of type 2 diabetic patients indicating the presence of possible genetic component in the regulation of ghrelin plasma levels[39].

CONCLUSION

Majority of people in the world are suffering from type 2 diabetes mellitus. Even though many medications like oral anti diabetics and insulin are available, still the requirement of new medication in diabetes mellitus is more preferable by patients. With safety profile, the glycemic and extraglycemic effects of incretin based therapies make them promising a better therapeutic option in order to reduce the cardiovascular risk, which still represents the major cause of mortality in diabetes. These are well tolerated and enhance glucose induced insulin secretion inhibit glucagons release from pancreatic islets. Further long studies of other hormones like amylin, leptin, adiponectin, ghrelin, testosterone, estrogen etc. are required to determine whether these therapies can protect ß-cell and retard the progression of type 2 diabetes and to be addressed in following years.

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