Available online at www.ijpcr.com
International Journal of Pharmaceutical and Clinical Research 2010; 2(2): 80-89

Review Article

ISSN 0975 1556

New Trends of Diabetes Therapy type II of the Animal Model

Humaira Farooqi[1]; Hamid Nawaz Khan[2]*; Richa Gupta[1]; Anwar Habib[2]; Parwaiz Akhtar[2]; Showkat Rasool Mir[2]; Kamran J. Naquvi

[1]Department of Biotechnology, Faculty of Science, Jamia Hamdard (Hamdard University), Hamdard Nagar, New Delhi 110062; India
[2]Department of Pharmacognosy and Phytochemistry , Research Laboratory, Faculty of Pharmacy, Jamia Hamdard (Hamdard University) Hamdard Nagar, New-Delhi- 110062, India

ABSTRACT
There is a growing consensus that blood glucose control, and postprandial control in particular, must become more aggressive if we are to stem the growing tide of diabetes related complications and mortality. For most people, this means that insulin therapy must begin earlier and that insulin must be titrated sufficiently to achieve tighter glycemic targets. The limitations of traditional treatment regimens, delivery devices and conventional insulin formulations, in conjunction with patient factors, have prevented the majority of people with type-2 diabetes from achieving recommended glycemic targets. Fortunately, incretin mimetics, DPP-4 inhibitors and techniques like bariatric surgery are now available. This review will discuss features and of these new tools, compare the benefits of using these drugs versus conventional drugs and also the use of medicinal plants in this area. Once physicians become familiar with these tools and incorporate them into daily practice, they will be able to better tailor diabetes self-management programs to the needs of individual patients. The result will be that more patients should be able to reach recommended glycemic targets with greater convenience and safety than has previously been available. As this metabolic disorder is like an epidemic, intense research is required and many scientists are working on potential targets to control it.

Keywords : diabetes mellitus , secretagogues , Biguanides , thiazolidinediones , incretins , GLP 1 agonist , DPP 4 inhibitors , bariatric surgery , antidiabetic plants.

INTRODUCTION

Diabetes is a metabolic disease characterized by hyperglycemia resulting from defects in insulin secretion, insulin action, or both (Fig. 1)[1]. After digestion, glucose passes into the bloodstream, where it is used by cells for growth and energy. For glucose to get into cells, insulin must be present. Insulin is a hormone produced by the pancreas, a large gland behind the stomach. When we eat, the pancreas automatically produces the right amount of insulin to move glucose from blood into our cells. In people with diabetes, however, the pancreas either produces little or no insulin, or the cells do not respond appropriately to the insulin that is produced. Glucose builds up in the blood, overflows into the urine, and passes out of the body. Thus, the body loses its main source of fuel even though the blood contains large amounts of sugar.[2]

The three main types of diabetes are (1) type 1diabetes; (2) type 2 diabetes; (3) gestational diabetes Out of these, type 2 diabetes, often called non-insulin dependent diabetes and is the most common form of diabetes, affecting 90% - 95% of the 21 million people with diabetes. 'Metabolic syndrome' encompasses type 2 diabetes (or prediabetes) and a common constellation of closely linked clinical features. Characteristic factors include insulin resistance per se, obesity (in particular abdominal adiposity), hypertension, and a common form of dyslipidaemia (raised triglycerides and low high-density lipoprotein (HDL)–cholesterol with or without elevation of low-density lipoprotein (LDL)–cholesterol). Metabolic syndrome is associated with a markedly increased incidence of coronary, cerebral and peripheral artery disease. Thus, atherosclerotic cardiovascular disease (ASCVD) is responsible for 80% of diabetic mortality and more than 75% of all hospitalizations for diabetic complications. After observing the severe complications posed by this disorder scientists initialized the efforts to control it. There are several conventional treatments that are available in market since 1922[3] But since 2000 the priority of scientist and doctors is changing to treat this syndrome. As a result of which a big revolution came in 2005 with the introduction of new variety drugs which are based on totally new concept of in cretin hormones[4].

METHODS

*Corresponding authors
E-mail: hamidramzan@rediffmail.com, hamidrumi@gmail.com)

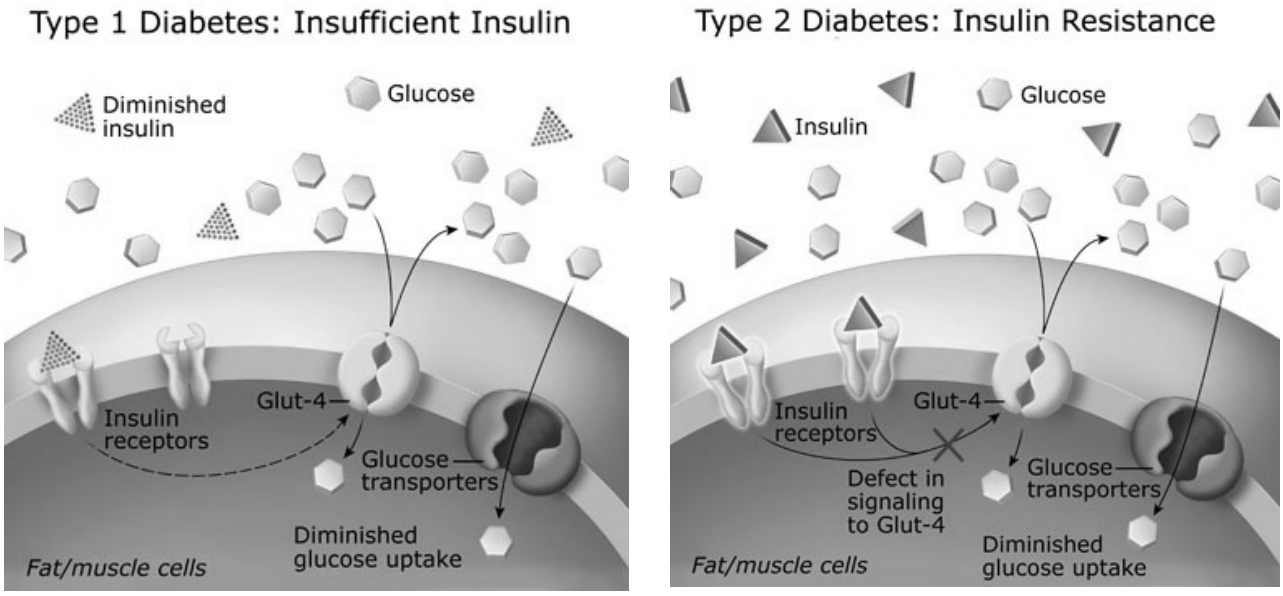

Figure 1: Insulin resistance and insulin absence

We conducted a literature review using the PubMed electronic system. No language restriction was imposed on the search, and articles published after 1999 were identified. Relevant studies published before 1999 were identified through bibliographies of the obtained published articles. For the type II diabetes therapy studies. The food-based intervention trials had to have included a concurrently enrolled control group. Only studies conducted for a minimum of 8 week were accepted, as we consider this the minimum necessary to observe an impact of supplementation on growth

RESULT AND DISCUSSION

CONVENTIONAL TREATMENTS

As therapeutic approaches for type 2 diabetes continue to evolve and improve, the goal of future treatment will be to intervene when very early clinical signs, such as impaired glucose tolerance and other aspects of metabolic syndrome, first manifest. The availability of drugs that affect underlying mechanisms may lead to a new therapeutic paradigm for the prevention of diabetes and its complications[5]. Current therapeutic approaches were largely developed in the absence of defined molecular targets or even a solid understanding of disease pathogenesis. Within the past few years, our understanding of biochemical pathways related to the development of metabolic syndrome has expanded[6]. There is an unprecedented range of molecular drug targets within these pathways. They have been identified on the basis of predicted roles in modulating one or more key aspects of the pathogenesis of diabetes and metabolic syndrome[7]. Several mechanistic categories for new therapeutic approaches can be considered. First are approaches aimed at reducing excessive glucose production by the liver; second, mechanisms to augment glucose-stimulated insulin secretion; third, specific molecular targets in the insulin signaling pathway; and fourth, new approaches to obesity and altered lipid

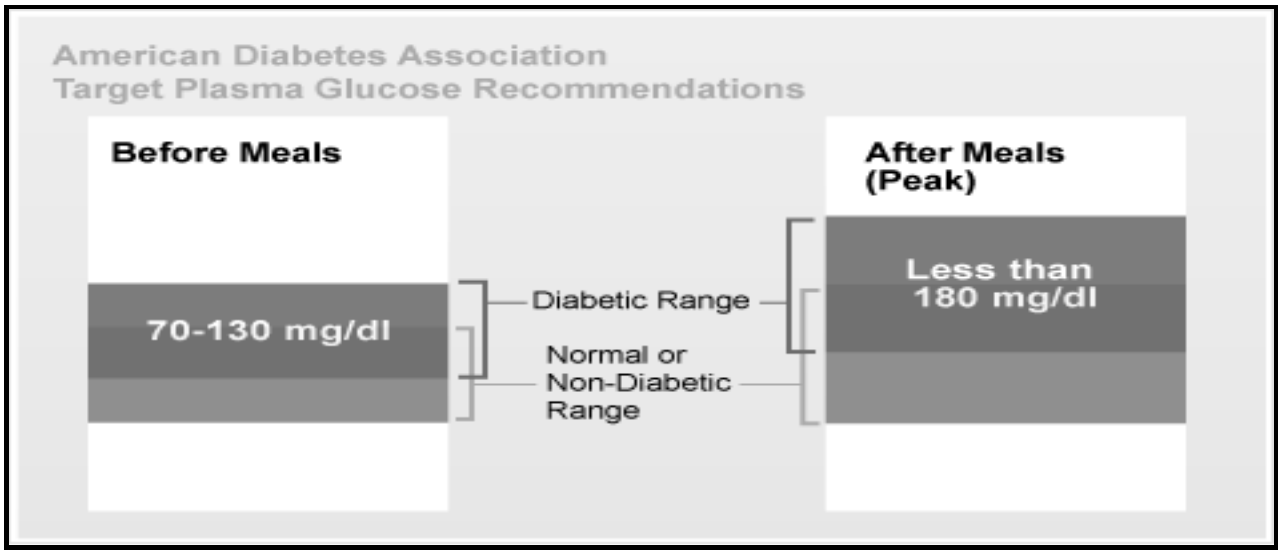

Figure 2: Target Plasma Glucose Recommendations

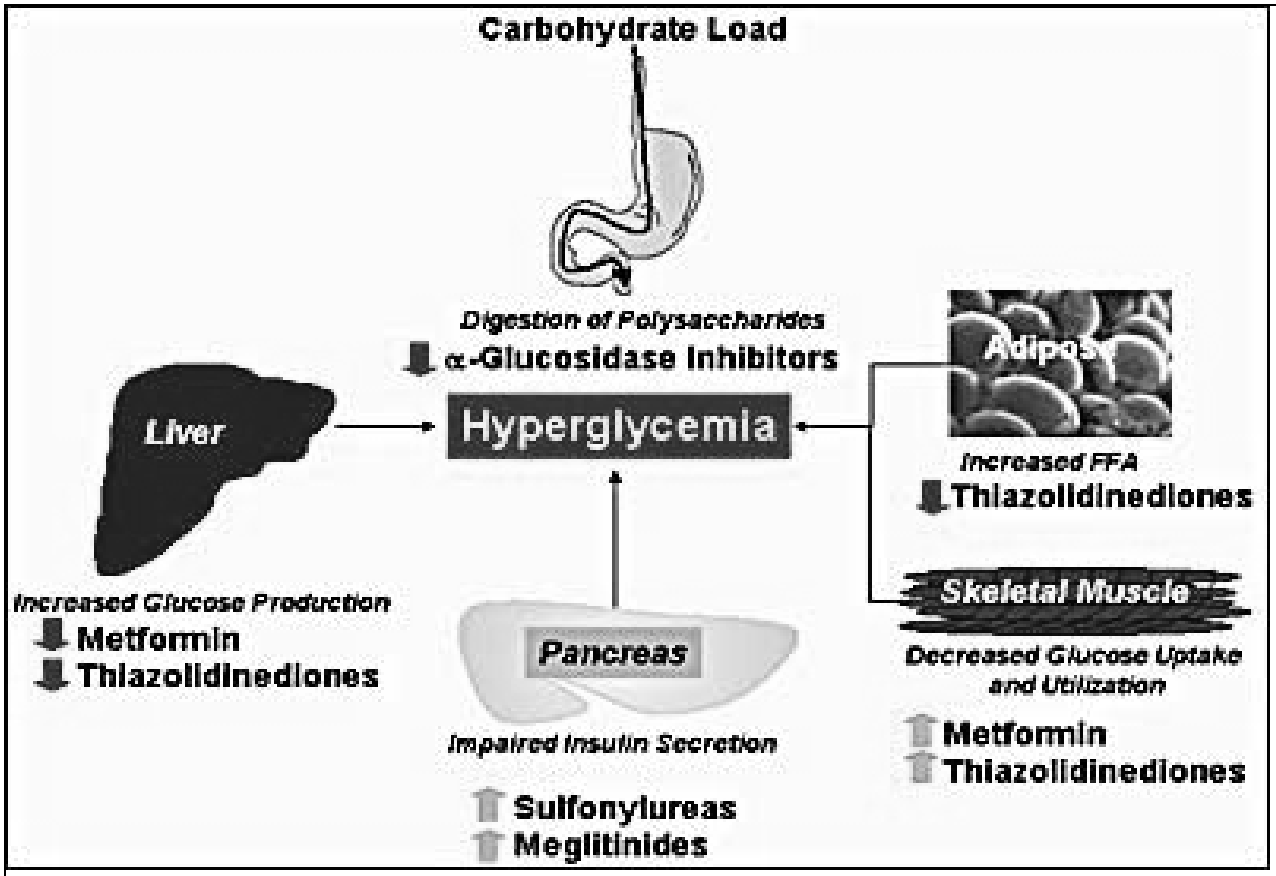

Figure 3: Conventional treatments and their mode of action

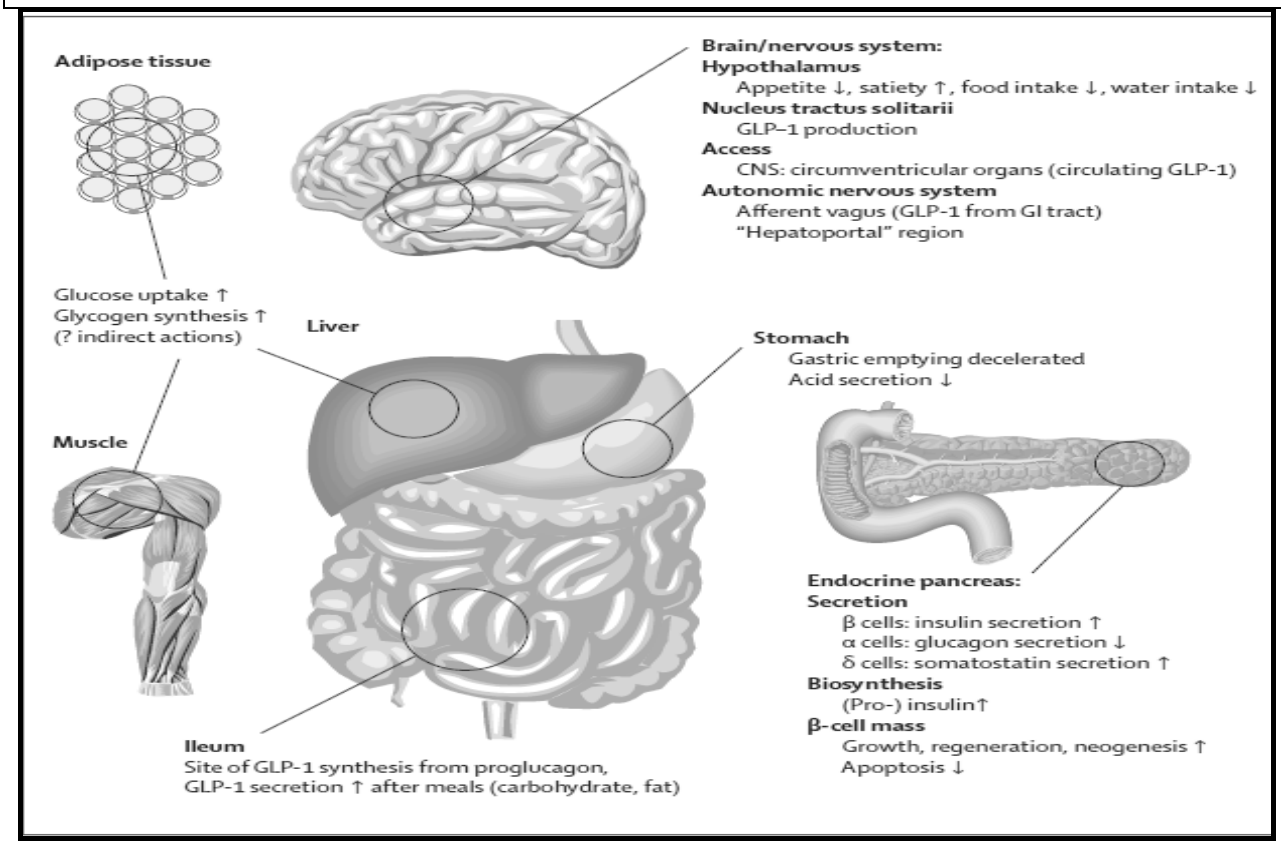

Figure 4: Physiology of GLP 1 Secretion and Action of GLP 1

metabolism, which the major task of diabetes medicines is to keep the blood glucose in the target range (Fig. 2). Starting from insulin there are several other classes of drugs present to control blood glucose levels. Each class has a distinctive mechanism of action (Fig. 3). The insulin secretagogues— sulfonylureas and two nonsulfonyl urea agents (repaglinide and nateglinide)— bind to elements of the ATP-dependent potassium channel complex in membranes of pancreatic B cells. By doing so they potentiate glucose-dependent insulin secretion (especially when used chronically), or provoke insulin secretion independent of current glucose levels with the potential to cause hypoglycemia (especially when used initially or intermittently). They are less effective or ineffective when the mass of B cells is reduced or their function is impaired[8] Biguanides acts mainly at the liver to reduce hepatic glucose production by a mechanism that is not understood completely. In effect, it potentiates the suppressive effects of insulin on hepatic glucose production. Biguanides also can prevent weight gain or lead to weight loss, in some cases as a result of unpleasant gastrointestinal side effects, but also in many patients who do not have such symptoms[9]. AGIs act within the intestinal humen to impair the action of enzymes that digest complex carbohydrates and some disaccharides, thereby delaying their absorption until food has passed further down the small intestine .When the balance of AGI dosage and carbohydrate load is correct, this action blunts postprandial increments of

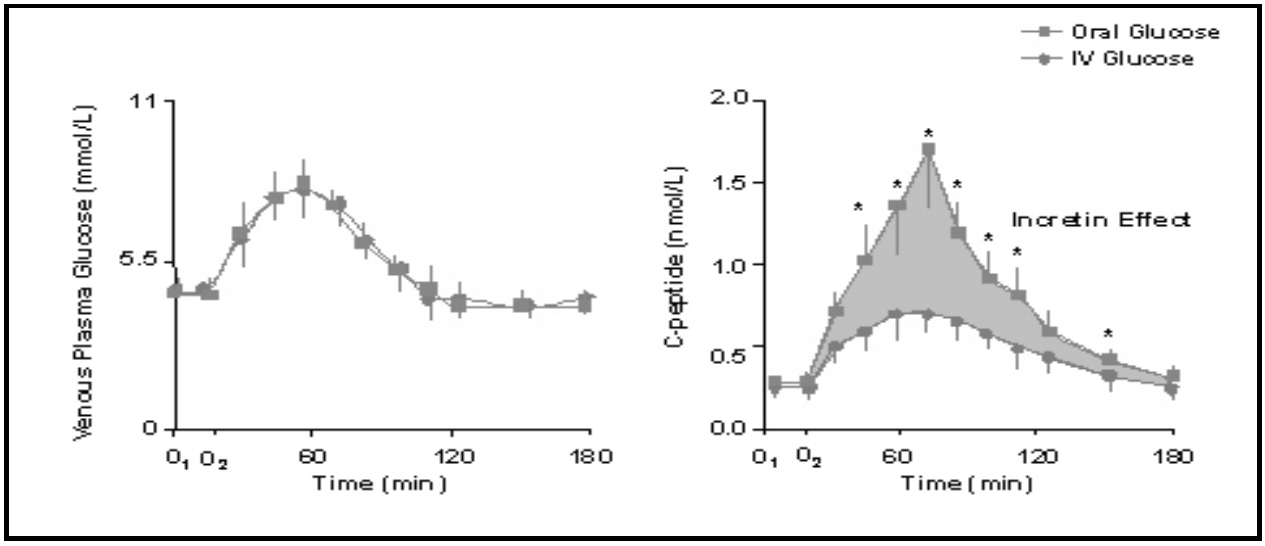

Figure 5 : Incretin Effect

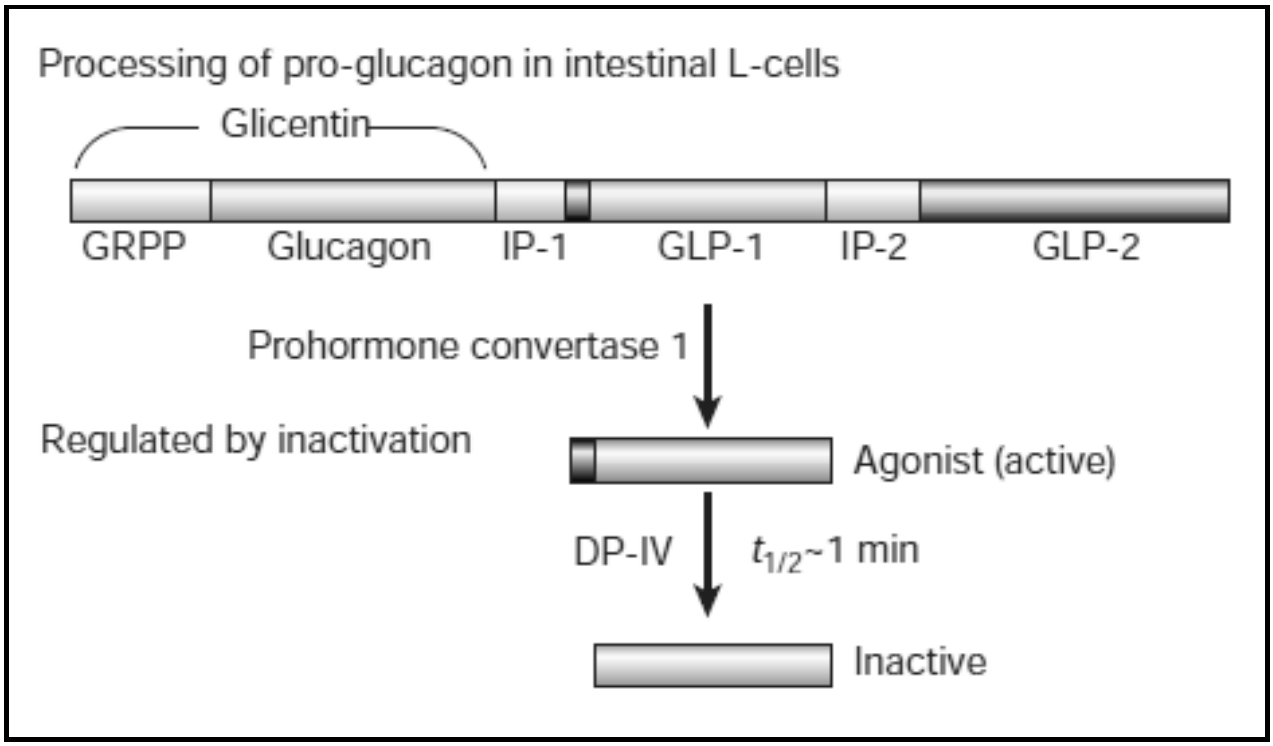

Figure 6 : Incretins and Effect of DPP-4 Inhibitors

glucose without unwanted effects. Beyond their effect on glycemic patterns, AGIs may have favorable effects on the secretion of gut peptides, such as glucagon-like peptide (GLP)-1[10]. TZDs bind to the peroxisome-proliferator–activated receptor-c and the resulting complex alters expression of many genes. The best understood effects of this process are cellular replication and an increase of sensitivity to insulin in adipose tissue. Treatment with TZDs suppresses release of free fatty acids and increases secretion of the hormone, adiponectin, with resulting favorable effects on insulin sensitivity in the liver and in muscle[11].

Injected insulin has multiple effects on fuel metabolism. At low blood levels it suppresses endogenous glucose production (mainly in the liver, but also in the kidney) by direct effects on these tissues and by reducing mobilization of free fatty acids and glycerol from adipose tissue and amino acids from muscle; all of these favor endogenous glucose production. At increased levels, such as are normally seen after meals, insulin promotes glucose uptake by muscle [12]. There are various side effects of these drugs. Out of which the most important are risk of hypoglycemia and weight gain. To circumvent these problems scientist discovered new class of drugs based on totally new concept.

INCRETIN HORMONES: NEW CLASS OF DRUGS FOR DIABETES

Eating provokes the secretion of multiple gastrointestinal hormones involved in the regulation of gut motility, secretion of gastric acid and pancreatic enzymes, gall bladder contraction, and nutrient absorption. Gut hormones also facilitate the disposal of absorbed glucose through the stimulation of insulin secretion from the endocrine pancreas[13]. The observation that enteral nutrition provided a more potent insulin tropic stimulus compared with isoglyceamic intravenous challenge led to the development of the in cretin concept (Fig. 4).

RECEPTORS IN DIFFERENT ORGANS AND TISSUES

The in cretin effect is defined as the ratio between the integrated insulin response to oral glucose and an isoglycemic intravenous glucose infusion. Because insulin itself is taken up by the liver and the amount taken up varies as to the plasma level, you can get a much better indication of the in cretin effect by measuring plasma C-peptides. C-peptides pass through the liver without being taken up; therefore, the difference in C-peptide gives you a very good estimate of the difference in insulin secretion[14]. The in cretin effect of oral glucose is anywhere between 20% and 60%. Interestingly, a number of studies, both older studies and more recent studies, show that one of the defects in diabetes is a decrease in the in cretin effect[15].So, we need to add not only beta-cell insufficiency and insulin resistance to our thinking about the metabolic defects in diabetes, we need to also add an abnormality in the GI hormone control of the in cretin effect (Fig.5).

The first in cretin to be identified, glucose-dependent insulin tropic polypeptide (GIP), was purified from porcine intestinal extracts and had weak effects on gastric acid secretion but more potent insulinotropic actions in human beings[16]. GIP is a 42-amino acid hormone synthesized in duodenal and jejunal enteroendocrine K cells in the proximal small bowel[17]. A second in cretin hormone, glucagon-like peptide-1 (GLP-1) was identified after the cloning of the cDNAs and genes encoding proglucagon (Fig. 6). GLP-1 exists in two circulating equipotent molecular forms, GLP-1 and GLP-1 amide, although GLP-1 amide is more abundant in the circulation after eating. Most GLP-1 is made in enter endocrine L cells in the distal ileum and colon, but plasma levels of GLP-1, like GIP, also increase within minutes of eating.[18]Hence a combination of endocrine and neural signals probably promote the rapid stimulation of GLP-1 secretion well before digested food transits through the gut to directly engage the L cell in the small bowel and colon. More proximally located L cells in the duodenum and jejunum have also been described; however, the precise contributions of the proximal and distal L cells to the early rapid increase in plasma GLP-1 remains unclear. (Schirra, 1998), Biosynthesis and regulation of glucagon-like peptide 1 (GLP-1). GLP-1 is a product of the pre-pro-glucagon gene. Pro-glucagon is cleaved by prohormone convertase 1 to generate active GLP-1, which is released from intestinal L-cells during nutrient ingestion. GLP-1 is rapidly hydrolyzed in vivo (t1/2 ~ 1 min) to produce an inactive product, GLP-1. DPP-IV, a proline-specific serine dipeptidase, is solely responsible for this inactivation[19].DPP-IV inhibitors therefore represent an indirect therapeutic approach to stabilizing endogenous GLP-1 (Fig. 6).

Plasma levels of GLP-1 are low in the fasted state, in the range of 5–10 pmol/L, and increase rapidly after eating, reaching 15–50 pmol/L. The circulating levels of intact GLP-1 and GIP decrease rapidly because of enzymatic inactivation, mainly dipeptidyl peptidase-4 (DPP-4), and renal clearance. Whether additional proteases, such as human neutral endopeptidase 24·11, are also essential determinants of GLP-1 inactivation is being investigated. Both GIP and GLP-1 contain alanine at position 2, and hence are excellent substrates for DPP-4. Indeed, DPP-4 is essential for in cretin inactivation, and mice with targeted inactivation of the DPP-4 gene have raised levels of plasma GIP and GLP-1, increased insulin secretion, and reduced glucose excursion after glycaemic challenge.4 As a result of DPP-4 activity, intact, biologically active GLP-1 represents only 10–20% of total plasma GLP-1[20]. Both GIP and GLP-1 exert their actions by the engagement of structurally distinct G-protein-coupled receptors (GPCRs). The GIP receptor is predominantly expressed on islet β cells, and to a lesser extent, in adipose tissue and in the central nervous system. By contrast, the GLP-1 receptor (GLP-1R) is expressed in islet α and β cells and in peripheral tissues, including the central and peripheral nervous systems, heart, kidney, lung, and gastrointestinal tract. Activation of both in cretin receptors on β cells leads to rapid increases in levels of cAMP and intracellular calcium, followed by insulin exocytosis, in a glucose-dependent manner[21]. 6 More sustained in cretin receptor signalling is associated with activation of protein kinase A, induction of gene transcription, enhanced levels of insulin biosynthesis, and stimulation of β-cell

proliferation.[22] Both GLP-1R and GIP receptor activation also promote resistance to apoptosis and enhanced β-cell survival, in both rodent8 and human islets.9 Consistent with the distribution of GLP-1R expression, GLP-1 also inhibits glucagons secretion, gastric emptying, and food ingestion, and promotes enhanced glucose disposal through neural mechanisms,10 actions that also contribute to the control of glucoregulation.[23]Notably, effects on glucagon secretion, like those on insulin secretary responses, are glucose dependent, whereas counter-regulatory release of glucagon in response to hypo glycaemia is fully preserved even in the presence of pharmacological concentrations of GLP 1.

URE 9: GLP-1 receptor signal transduction pathways in the pancreatic B cell

The physiological importance of endogenous GIP and GLP-1 for glucose homoeostasis has been investigated in studies with receptor antagonists, or gene-knockout mice. Acute antagonism of GIP or GLP-1 lowers insulin secretion and increases plasma glucose after glycaemic challenge in rodents[24] similarly, mice with inactivating mutations in the GIP or GLP-1 receptors also have defective glucose-stimulated insulin secretion and impaired glucose tolerance. GLP-1, but not GIP, is also essential for control of fasting glycaemia, since acute antagonism or genetic disruption of GLP-1 action leads to increased levels of fasting glucose in rodents[25]. Furthermore, GLP-1 is essential for glucose control in human beings: studies with the antagonist expending show defective glucose-stimulated insulin secretion, reduced glucose clearance, increased levels of glucagon, and quicker gastric emptying after disruption of GLP-1 action[26]

The pleotropic actions of GLP-1 and GIP on the control of blood glucose have fostered considerable interest in the use of these agents for the treatment of type 2 diabetes. Whereas in healthy human beings oral glucose elicits a considerably higher insulin secretary response than does intravenous glucose (even if leading to the same glycaemic increments), this in cretin effect is substantially reduced or even lost in patients with type 2 diabetes. As an explanation for the acquired in cretin defect, GIP but not GLP-1 shows noticeably attenuated insulin tropic action in patients with type 2 diabetes. Furthermore, those with type 2 diabetes show a small but significant reduction in meal-stimulated levels of GLP-1.17 since GLP-1 action remains relatively preserved in diabetic patients, most pharmaceutical efforts directed at potentiating of in cretin action for the treatment of type 2 diabetes have focused on GLP-1R agonists[27].

Anti diabetic actions of GLP-1

Short-term intravenous infusions of GLP-1 (1–1·2 pmol kg^{-1} min^{-1}, leading to pharmacological plasma concentrations of total GLP-1 of 70–150 pmol/L and of intact biologically active GLP-1 of 10–20 pmol/L) lowers blood glucose in patients with type 2 diabetes through a transient glucose-dependent stimulation of insulin and suppression of glucagon secretion and gastric emptying. A 6-week subcutaneous infusion of GLP-1 in patients with type 2 diabetes, achieving plasma levels of GLP-1 in the 60–70 pmol/L range, produced substantial improvements in insulin secretary capacity, insulin sensitivity, a reduction in HbA1c of 1·2% and modest weight loss (1·9 kg). Although intravenous or subcutaneous GLP-1 infusions could be useful for the short-term control of hyperglycaemia, the long-term treatment of type 2 diabetes needs a more feasible approach to achieve sustained activation of GLP-1 receptors. The efficacy of inject able GLP-1 receptor agonists (degradation-resistant peptides or larger proteins with more suitable pharmacokinetic properties) and DPP-4 inhibitors (small molecules with good oral bioavailability, web table), has been assessed in clinical trials[28]

GLP-1R agonists

Exenatide

Exenatide (synthetic exendin-4) was discovered in the search for biologically active peptides in lizard venom. Exendin-4 shares roughly 50% of its amino acid sequence with mammalian GLP-1, is encoded by a unique gene in the lizard Gila monster, and is a potent degradation resistant agonist at the mammalian GLP-1R. Exenatide has been developed for the treatment of type 2 diabetes. Exenatide has a circulating half-life of 60–90 min, with increases in plasma exenatide concentrations lasting 4–6 h after a single subcutaneous injection. Exenatide was approved by the US Food and Drug Administration for the treatment of type 2 diabetes in April, 2005[29]

Liraglutide

Liraglutide, a partly DPP-4-resistant GLP-1 analogue, contains a Arg34Lys substitution, and a glutamic acid and 16-C free-fatty-acid addition to Lys26. The acyl moiety promotes non-covalent binding to albumin with 1–2% of liraglutide circulating as the non-albumin bound free peptide[30]. Liraglutide has a half-life of about 10–14 h after subcutaneous administration in human beings, and can be given as a once daily injection. Liraglutide reduces fasting and postprandial glucose, and levels of HbA1c by up to 1·75 %, 33 while preventing weight gain or inducing modest but significant weight loss.

Long-acting GLP-1R agonists

Because one subcutaneous injection of exenatide does not produce effective glucose control for more than 6–8 h, there is considerable interest in the development of long-acting GLP-1R agonists that need less frequent parenteral administration. Exenatide long-acting release (LAR) is a polylactide-glycolide microsphere suspension containing 3% exendin-4 peptide that shows sustained dose-dependent glycaemic control in diabetic fatty Zucker rats for up to 28 days after one subcutaneous injection[31]

Adverse reactions, problems, and concerns

These agents have a favorable side effect profile except for nausea, pancreatitis, fullness, bloating, and vomiting as major side effects[32], which, however, are generally dose-dependent and can be ameliorated by reducing doses and/or doing slow-dose escalation. GLP-agonists on their own do not cause clinically-significant hypoglycemia except when associated with sulfonylureas[33].

DPP-4 INHIBITORS

The observation that GLP-1 is rapidly degraded by DPP-45, 89, 90 has fostered the development of specific protease inhibitors that prevent the rapid fall of GLP-1 in circulating plasma after eating. DPP-4 is a ubiquitous membrane-spanning cell-surface aminopeptidase widely expressed in many tissues, such as liver, lung, kidney, intestinal brush-border membranes, lymphocytes, and endothelial cells. The extracellular domain of DPP-4 can also be cleaved from its membrane-anchored form and circulate in plasma, where it retains its full enzymatic activity[34] DPP-4 preferentially cleaves peptides with a proline or alanine residue in the second amino terminal position. Many gastrointestinal hormones, neuropeptides, cytokines, and chemokines are substrates for DPP-4, among them both GIP89 and GLP-1. In preclinical studies, DPP-4 inhibitors mimic many of the actions ascribed to GLP-1R agonists, including stimulation of insulin and inhibition of glucagon secretion, and preservation of β-cell mass through stimulation of cell proliferation and inhibition of apoptosis.[35] By contrast, DPP-4 inhibitors are generally not associated with a deceleration of gastric emptying or weight loss, perhaps due to the modest stabilization of postprandial levels of intact biologically active plasma GLP-1 (doubled to 15–25 pmol/L) seen after DPP-4 inhibition.Many small-molecule DPP-4 inhibitors have been developed that specifically and potently inhibit DPP-4 activity after oral administration. Typically, these agents reduce serum DPP-4 activity by more than 80%, with some inhibition maintained for 24 h after one dose or with once daily treatment. DPP-4 inhibition is accompanied by a rise in postprandial levels of intact GLP-1. Most published studies used vildagliptin.

VILDAGLIPTIN

Vildagliptin (previously identified as LAF237, trade name Galvus) is a new oral anti-hyperglycemic agent (anti-diabetic drug) of the new dipeptidyl peptidase-4 (DPP-4) inhibitor class of drugs. Vildagliptin inhibits the inactivation of GLP-1 and GIP by DPP-4, allowing GLP-1 and GIP to potentiate the secretion of insulin in the beta cells and suppress glucagon release by the alpha cells of the islets of Langerhans in the pancreas[36]. Vildagliptin has been shown to reduce hyperglycemia in type 2 diabetes mellitus. Novartis has since withdrawn its intent to submit vildagliptin to the FDA, as of July 2008. Vildagliptin has since been approved but USFDA. The Food and Drug Administration had demanded additional clinical data before it could approve vildagliptin including extra evidence that skin lesions and kidney impairment seen during an early study on animals have not occurred in human trials[37]. While the drug is still not approved for use in the US, it has been approved by European Medicines Agency for use within the EU. In India it has been recently launched by USV as jalra.

SITAGLIPTIN

Sitagliptin was approved by the U.S. Food and Drug Administration (FDA) on October 17, 2006[3] and is marketed in the US as Januvia by Merck & Co. On April 2, 2007, the FDA approved an oral combination of sitagliptin and metformin marketed in the US as Janumet[38] Sitagliptin works to competitively inhibit the enzyme dipeptidyl peptidase 4 (DPP-4). This enzyme breaks down the in cretins GLP-1 and GIP, gastrointestinal hormones that are released in response to a meal. By preventing GLP-1 and GIP inactivation, GLP-1 and GIP are able to potentiate the secretion of insulin and suppress the release of glucagon by the pancreas. This drives blood glucose levels towards normal. As the blood glucose level approaches normal, the amounts of insulin released and glucagon suppressed diminishes thus tending to prevent an "overshoot" and subsequent low blood sugar (hypoglycemia) which is seen with some other oral hypoglycemic agents.[39] Sitagliptin also has an effect on appetite. By slowing down gastric motility it induces a feeling of satiety. This reduction of appetite can help patients to lose weight, a useful effect in patients with diabetes.

Adverse reactions, problems and concerns

The long-term consequences of chronic inhibition of DPP-IV in humans are still unclear and are a cause of concern given the ubiquitous nature of the enzyme. Of note is DPP-IV is the major means of degradation of over 20 different peptides including substance P, insulin-like growth factor-1, neuropeptide Y, GLP-2, and GIP. The potential effects of chronically elevated levels of all these peptides that could conceivably result from long standing DPP-IV use are not known.[40] The short term trials thus far have shown good tolerability, with the major reported side effects being pruritus, diarrhea, nausea, dizziness, and diaphoresis. Of particular importance, DPP-IV inhibitors as mono therapy do not appear to be associated with hypoglycemia though it may occur in extenuating circumstances such as heavy alcohol use.

EXERCISE: THE GOLDEN KEY

Exercise plays an important role in controlling diabetes. Specifically a combination of dynamic and isometric exercises is recommended for a diabetic patient.[41]Dynamic exercise burns the calories and isometric exercise increase the muscle mass therefore the combination of two results in increased number if insulin receptors and uniform utilization of sugar molecules

ROLE OF PROPER DIET IN CONTROL OF DIABETES

Diet plays an important role in development and control of type 2 diabetes mellitus. Diet high in simple carbohydrates and fats results in development of diabetes in latter stages of life[42].Also many patients with type 2 diabetes can be controlled by diet alone. Therefore dietary restriction is an essential factor in diabetes management.[43] Dietary guidelines given by American Diabetes Association are as follows:

- Eat a diet low in saturated and total fat.
- Eat a diet moderate in sodium and sugar.
- Eat more of fruits and vegetables.
- Choose a diet rich in whole grains.
- Eat at the same time everyday, at least within 1 hour of regular time.
- Eat about the same amount of carbohydrate with each meal.

- Eat small meals at short intervals of time

BARIATRIC SURGERY

Obesity in one of the major reasons for type 2 diabetes mellitus. Millions of individuals around the world are overweight or obese (severely overweight). When weight increases to an extreme level, it is called morbid obesity.[44] Obesity is associated with diabetes, heart disease, high blood pressure, some types of cancer, and other medical problems. Bariatrics is the field of medicine that specializes in treating obesity. Bariatric surgery is the term for operations to help promote weight loss. Bariatric surgical procedures are only considered for people with severe obesity and not for individuals with a mild weight problem. The body mass index (BMI) is a standard way to define overweight, obesity, and morbid obesity. The BMI is calculated based on a person's height and weight—weight in kilograms (2.2 pounds per kilogram) divided by the square of height in meters (39.37 inches per meter). A BMI of 25 or more is considered overweight; 30 or more, obese; and 40 or more, morbidly obese. Bariatric surgery may be offered to patients with severe obesity when medical treatments, including lifestyle changes of healthful eating and regular exercise, have not been effective.

ANTIDIABETIC PLANTS: HOPE FOR THE FUTURE

Medical plants play an important role in the management of diabetes mellitus especially in developing countries where resources are meager. The plant families, including the species (sp), most studied for their confirmed hypoglycaemic effects include: Leguminoseae (11 sp), Lamiaceae (7 sp), Liliaceae (8 sp), Cucurbitaceae (7 sp), Asteraceae (6 sp), Moraceae (6 sp), Rosaceae (6 sp), Euphorbiaceae (5 sp) and Araliaceae (5 sp). The most studied species are: Citrullus colocynthis (Opuntia streptacantha Lem. (Cactaceae), Trigonella foenum greacum L. (Leguminosea),Momordica charantia L. (Cucurbitaceae), Ficus bengalensis L. (Moraceae), Polygala senega L. (Polygalaceae), and Gymnema sylvestre R. (Asclepiadaceae). Many studies have confirmed the benefits of medicinal plants with hypoglycaemic effects in the management of diabetes mellitus. The effects of these plants may delay the development of diabetic complications and correct the metabolic abnormalities. Moreover, during the past few years some of the new bioactive drugs isolated from hypoglycemic plants showed ant diabetic activity with more efficacy than oral hypoglycemic agents used in clinical therapy. Recently spices and other natural products have been used in control and treatment of diabetes mellitus. Glazer and Halpern who observed that a yeast extract had insulin-potentiating property reported the first evidence that natural products have insulin-potentiating. He reported that activity in 1929. In 1979, Bever and Zahid published a list of plants which had oral hypoglycemic action. Almost a decade later, [45] published lists of several hundred species, which had anti-diabetic properties. Hypoglycemic property of bitter gourd has been reported by many researchers[46-47]. In 1955[48], reported that extract of brewer's yeast could reverse the impaired tolerance to glucose load in formula yeast fed rats. They termed the active substance in brewer's yeast extract as glucose tolerance factor (GTF)[49] reported that the biologically active extract from brewer's yeast contained chromium, nicotinic acid, glycine, cysteine and glutamic acid. They provided further evidence for their claim by synthesizing biologically active complexes comprised of trivalent chromium, nicotinic acid, glycine, cysteine and glutamic acid. Biologically active chromium is that chromium, which potentiates insulin activity measured in vitro. In 1988, working on purification of biologically active chromium[50], discovered that certain spices like cinnamon, cloves, bay leaves and turmeric displayed insulin potentiating activity. They termed this activity as insulin potentiating factor (IPF) present in these spices.[51] reported that jaman seeds, bitter gourd, fenugreek and tea had insulin potentiating activity. The plants which are thought to have anti diabetic activity are sprouted glycine max seeds, aloevera and vinca rosea.

FUTURE PROSPECTS

There has been an influx of new agents in the past several years. Many more are likely to follow in the near future. The evolving understanding of the PPAR system is leading to increased drug discovery in this area.[52-53] The isoxazolidinediones lack the thiol group but affect the same system. The challenge is clearly to achieve reductions in insulin resistance without triggering fluid retention and weight gain[54] The goal of achieving glucose reduction without weight gain is clearly desirable. The disaccharides inhibitors and motorman are the principal agents to accomplish this goal[55] Efforts are under way to attempt to selectively activate those portions of the complex of the PPAR system and the retinoic acid dimmer that lead to increased insulin sensitivity and improved lipid metabolism without triggering the differentiation of adipocytes, which occurs with current-day thiazolidinediones[56]. PPAR-gamma legends, which also behave as partial PPAR-alpha or PPAR-delta agonists, may also be found later to be useful in regulating dyslipemia as well as glucose levels[57] Ligand agents known as retinoid are also being tested to determine whether they interact with the RXR component of the PPAR-gamma-RXR hetero dimmer to modify insulin sensitivity and dyslipemia[58] Amylin is a 37 amino acid polypeptide secreted by the beta cell concurrently with insulin[59]. Amylin slows gastric emptying and inhibits postprandial glucagon secretion. Amylin concentrations, like those of insulin, are reduced in type 1 diabetic patients. The amylin analogue pramlintide has been developed as an injectable agent for treatment. Although the reduction of HgbA1c by pramlintide is modest, there have been reductions in weight in both type 1 and type 2 diabetic patients taking this agent. Beta-3 agonists are under study as antidiabetic agents. Their effect appears to be mediated by enhanced thermogenesis and increased glucose uptake. It is hoped that these agents may reduce glucose levels while decreasing adiposity[61] another hope is the islet neogenesis therapy in which it is proposed that combination of epidermal growth factor and gastrin leads to formation of islet precursor stem cell and ultimately islet cells. This therapy has been proposed by

a company called neither novo nor disk. Our collective knowledge base of pathways and discrete proteins that contribute to distinctive path physiological traits underlying the metabolic syndrome and type 2 diabetes is expanding rapidly. This momentum is fuelled by the quantum leap in potential 'players' provided by the annotated human genome sequence databases and molecular techniques such as DNA microarrays and gene knockouts, and the identification of potential disease genes in humans and model species. The examples of recently discovered drug targets described above strongly suggest that this increase in newly identified components of disease susceptibility will yield an even wider array of potential approaches for therapeutic intervention. In addition to small-molecule modulators of 'classical' receptor or enzyme targets, research could identify additional protein therapeutics, such as GLP-1 analogues, and even more novel approaches, such as antisense oligonucleotide-based therapies. Intensive study of the mechanisms of action of older drugs has provided further validation of several recently identified drug targets. Further efforts in this direction are likely to be fruitful. Given the multifactorial nature of the genetic and environmental factors that contribute to the genesis of metabolic syndrome and type 2 diabetes, it is probable that further efforts to characterize disease 'sub-phenotypes' and specific genetic markers will translate into more selective therapies tailor-made for distinct subgroups of patients or those at risk of developing disease. These individuals may be identified on the basis of specific genotypes or more specific clinical markers of distinct physiological derangements.

REFERENCES

1. American Diabetes Association, "Diagnosis and Classification of Diabetes Mellitus." Diabetes Care 27 (Suppl. 1) 2004; S5–10.
2. Anderson J W, Zeigler J A, Deakins D A, Floore T L, Dillon D W, Wood C L, Oeltgen P R, and Whilley R J. Metabolic effects of high carbohydrate, high fiber diet for IDDM individuals. Am. J. Clin. Nutr 1991; 54: 936-943.
3. Berger J, & Moller D E. Mechanism of PPAR action. Annu. Rev. Med 2009.
4. Bliss M. The Discovery of Insulin Chicago University of Chicago Press 1982; p 155.
5. Cohen N. Oral vanadyl sulphate improves hepatic and peripheral insulin sensitivity in patients with non-insulin dependent diabetes mellitus. J. Clin. Invest 1995; 95: 2501–2509.
6. Connell R D. Glucagon antagonists for the treatment of type 2 diabetes. Exp Opinion There Patents 1999; 9: 701–709.
7. Daniel J, Drucker, Michael A Nauck. The incretin system: glucagon-like peptide-1 receptor agonists and dipeptidyl peptidase-4 inhibitors in type 2 diabetes. Lancet 2006; 368:1696–705.
8. Daniel J, Drucker. The biology of incretin hormones. Cell metabolism 2006; 3: 153–165.
9. Daniel Drucker, Chris Easley and Peter Kirkpatrick, Sitagliptin, Nature Reviews Drug Discovery2007; 6:109-110.
10. David A, D'Alessio and Torsten P Vahl. Am Glucagon-like peptide 1: evolution of an incretin into a treatment for diabetes. J Physiol Endocrinol Metab2004; 286:882-890.
11. DeFronzo R A, Bonadonna R C, Ferannini E. Pathogenesis of NIDDM: a balanced overview. Diabetes Care1992; 15: 318–368.
12. DeFronzo RA, Ratner RE, Han J, Kim DD, Fineman MS, Baron AD. Effects of exenatide (exendin-4) on glycemic control and weight over 30 weeks in metformintreated patients with type 2 diabetes. Diabetes Care 2005; 28: 1092–00.
13. Demuth H-U et al. Single dose treatment of diabetic patients by the DPP IV inhibitor 2003; P32/98.
14. Diabetes 49(supplement 1) 2000; A102.
15. Diabetes overview, U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES. National Institutes of Health NIH Publication 2004; No. 06–3873.
16. Drucker D J. The glucagon-like peptides. Endocrinology 2001; 142:521–527.
17. Drucker DJ. The biology of incretin hormones. Cell Metab 2006; 3: 153–65.
18. Dupre J, Ross SA, Watson D, Brown JC. Stimulation of insulin secretion by gastric inhibitory polypeptide in man. J Clin Endocrinol Metab1973; 37: 826–28.
19. Edwards C M. Glucagon-like peptide 1 has a physiological role in the control of postprandial glucose in humans. Diabetes 1999; 48: 86–93.
20. Evan J, Rushakoff R. Oral Pharmacological Agents for Type 2 Diabetes: Sulfonylureas, Meglitinides, Metformin, Thiazolidinediones, α-Glucosidase Inhibitors,and Emerging Approaches 2005.
21. Exenatide: An incretin mimetic agent. *Pharmacol Indian.* February 2006; 38(1): 76-78.
22. Goodyear L J. AMP activated protein kinase: a critical signaling intermediary for exercise-stimulated glucose uptake Exercise Sport Sci. Rev 2000;28: 113–116.
23. Henriksen E J. Glycogen synthase kinase-3 inhibitors potentiate glucose tolerance and muscle glycogen synthase activity in the Zucker Diabetic Fatty Rat. Diabetes 2001; 50(Suppl. 2):A279.
24. George Holz, Molecular Basis of Antidiabetogenic Hormone Action; March 2006.
25. Rashmi jain, Uday Kabadi, M Kabadi. Is B cell failure in type 2 diabetes mellitus reversible. Int J Diab Dev Ctries 2008;(1) : 1-5.
26. Khan A M, Safdar M, Khattak A K, Khattak K N, and Anderson R A. Effect of cinnamon on blood glucose in diabetic individuals Submitted to FASEB; 2003.
27. Khana P. Insulin from bitter gourd - herbal drug. Eastern Pharmacist 1985; pp: 101-103.
28. Kim J K et al. Prevention of fat-induced insulin resistance by salicylate. J. Clin. Invest. 2001; 108:437–446.
29. Kopelman P G, Hitman G A. Diabetes Exploding Type II. Lancet 1998; 352: SIV5.
30. Lankas G, Leiting B, Roy RS. Dipeptidyl peptidase IV inhibiton for the treatment of type 2 diabetes: potential importance of selectivity over dipeptidyl peptidase 8 and 9 Diabetes 2004; 54: 2988 –94.
31. Lehmann J M. An antidiabetic thiazolidinedione is a high affinity ligand for peroxisome proliferator-activated receptor J. Biol. Chem. 1995; 270: 12953–12956.
32. Maire E Doyle1, Josephine M Egan. Mechanisms of Action of GLP-1 in the Pancreas. Pharmacol Ther 2007; 113(3): 546–593.
33. Meier JJ, Weyhe D, Michaely M. Intravenous glucagon-like peptide 1 normalizes blood glucose after major surgery in patients with type 2 diabetes. Crit Care Med 2004; 32:848–51.
34. Miyawaki K et al. Glucose intolerance caused by a defect in the entero-insular axis: a study in gastric inhibitory polypeptide knockout mice. Proc. Natl Acad. Sci. USA1999; 96:14843–14847.
35. Moller D E. Potential role of TNFa in the pathogenesis of insulin resistance and type II diabetes. Trends Endocrinol Metab 2000; 11: 212–217.
36. Moller D E, Greene D A. Peroxisome proliferator-activated receptor (PPAR) g agonists for diabetes. Adv. Prot. Chem. 2001; (Drug Discovery) 56: 181–212.
37. MMS Ahuja, BB Tirpathy, GP San, HB Moses, AK Chandalia, PV Das, SV Rap, Madhu .Text book of diabetes mellitus; Research society for the study of diabetes in India ;2002.
38. Nauck M, Stockmann F, Ebert R, Creutzfeldt W. Reduced incretin effect in type 2(non-insulin-dependent) diabetes. Diabetologia 1986; 29: 46–54.
39. Nauck MA, Heimesaat MM, Orskov C, Holst JJ, Ebert R, Creutzfeldt W. Preserved in cretin activity of glucagon-like peptide 1 [7-36 amide] but not of synthetic human gastric inhibitory polypeptide in patients with type-2 diabetes mellitus. J Clin Invest1993; 91: 301–07.
40. Nauck MA, Heimesaat MM, Behle K et al. Effects of glucagon-like peptide 1 on counterregulatory hormone responses, cognitive functions, and insulin secretion during hyperinsulinemic, stepped hypoglycemic clamp experiments in healthy volunteers. J Clin Endocrinol Metab 2002; 87: 1239–46.

41. Nauck MA, Meier JJ. Glucagon-like peptide 1 (GLP-1) and its derivatives in the treatment of diabetes. Regul Pept 2005; 124 (suppl): 135–48.
42. Oakes N D et al. A new antidiabetic agent, BRL 49653, reduces lipid availability and improves insulin action and glucoregulation in the rat. Diabetes 1994;43: 1203–1210.
43. Orskov C, Wettergren A, Holst JJ. Biological effects and metabolic rates of glucagons like peptide-1 7-36 amide and glucagons like peptide-1 7-37 in healthy subjects are indistinguishable. Diabetes 1973; 42: 658–61.
44. Petersen K, Sullivan J, Amatruda S J, Livingston J, Shulman G. Diabetologia 1999; 42(Suppl.): A42.
45. Porte D J. Banting Lecture 1990: beta-cells in type II diabetes mellitus. Diabetes 1991; 40:166–180.
46. Schirra J, Sturm K, Leicht P, Arnold R, Goke B, Katschinski M. Exendin (9-39)amide is an antagonist of glucagon-like peptide-1 (7-36) amide in humans. J Clin Invest1998; 101:1421-30.
47. Shah P, Vella A, Basu R, Schwenck W F, Rizza RA. Lack of suppression of glucagons contributes to postprandial hyperglycemia in subjects with type 2 diabetes mellitus. J. Clin. Endocrinol Metab 2000; 85: 4053–4059.
48. Shimomura I et al. Decreased IRS-2 and increased SREBP-1c lead to mixed insulin resistance and sensitivity in livers of lipodystrophic and ob/ob mice. Mol. Cell. 2000; 6: 77–86.
49. Sitagliptin: First DPP-4 Inhibitor for Type 2 Diabetes; Drug update 2007; 53 (4).
50. Treadway J L, Mendys P, Hoover D J. Glycogen phosphorylase inhibitors for the treatment of type 2 diabetes mellitus. Exp. Opin. Invest. Drugs 2001; 10: 439–454.
51. Unger R H. Glucagon physiology and pathophysiology. N. Engl. J. Med.1971; 285:443–449.
52. Unson C G, Andreu D, Gurzenda E M, Merrifield R B. Synthetic peptide antagonists of glucagon. Proc. Natl Acad. Sci. USA1987; 84: 4083–4087.
53. Vilsboll T, Brock B, PerrildtK Levin H H, Lervang K, Kolendorf T, Krarup O, Schmitz M, Zdravkovic T, Le-Thi S, Madsbad. Liraglutide, a once-daily human GLP-1 analogue, improves pancreatic B-cell function and arginine-stimulated insulin secretion during hyperglycaemia in patients with Type 2 diabetes mellitus. Diabetic medicine 2008; 1-5.
54. Williams B, Werner J, Holst JJ, Orskov C, Creutzfeldt W, Nauck MA. Gastric emptying, glucose responses, and insulin secretion after a liquid test meal: effects of exogenous glucagonlike peptide-1 (GLP-1)-(7-36) amide in type 2 (non insulin dependent) diabetic patients. J Clin Endocrinol Metab1996; 81: 327–32.
55. Willson T M, Brown P J, Sternbach D D, Henke B R. The PPARs: from orphan receptors to drug discovery. J. Med. Chem.2000; 43:527–550.
56. Yuan M et al. Reversal of obesity- and diet-induced insulin resistance with salicylates or targeted disruption of Ikkb. Science 2001; 293:1673–1677.
57. Zhang B. Discovery of small molecule insulin mimetic with antidiabetic activity in mice. Science 1999; 284: 974–977.
58. Zhang B, Moller D E. New approaches in the treatment of type 2 diabetes. Curr. Opin. Chem. Biol. 2000; 4:461–467.
59. Zhou G et al. Role of AMP-activated protein kinase in mechanism of metformin action. J. Clin. Invest 2001; 108: 1167–1179.