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Novel therapeutics for type 2 diabetes: Incretin hormone mimetics (glucagon-like peptide-1 receptor agonists) and dipeptidyl peptidase-4 inhibitors

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ABSTRACT

Known treatments of type 2 diabetes mellitus have limitations such as weight gain, and hypoglycaemias. A new perspective is the use of incretin hormones and incretin enhancers. Incretins are defined as being responsible for the higher insulin release after an oral glucose load compared to an intravenous glucose load. The delicate balance of glucose homeostasis, in which incretin hormones are involved, is disturbed in type 2 diabetes mellitus. The incretin GLP-1 helps to maintain glucose homeostasis through stimulation of insulin secretion and inhibition of glucagon release in a glucose-dependent manner. This is associated with reductions in body weight, and no risk of hypoglycaemias. When classical oral agents have failed to maintain adequate glycaemic control, incretin mimetics may be of particular value for obese patients and those who have little control over meal sizes. Exenatide was marketed as a GLP-1 analogue and longer acting incretin mimetics such as liraglutide, albiglutide and others have the same pharmacological profile.

In addition to incretin mimetics incretin enhancers which inhibit/delay degradation of incretins were developed: so-called DPP-4 inhibitors such as sitagliptin and vildagliptin are approved in Europe. Their differences from incretin mimetics include: oral bioavailability, less side effects with overdose, no direct CNS effects (nausea and vomiting) and no effect on weight. In rodent models of diabetes, but not yet in humans, GLP-1 receptor agonists and DPP-4 inhibitors increase islet mass and preserve β-cell function.

Incretin mimetics and enhancers expand type 2 diabetes treatment, are still not first line therapy and it is discussed if they are to be prophylactically used.

Contents

Abbreviations: GLP-1, glucagon-like peptide 1; GIP, glucose-dependent insulinotropic peptide (formerly gastrin inhibiting peptide); DPP-4, (dipeptidyl petidase 4); WNT, cell-secreted glycoprotein ligand); PYY, peptide YY; s.c., subcutaneous; min, minute; TNF-α, tumor necrosis factor alpha; PAI-1, plasminogen activator inhibitor-1; VCAM-1, vascular cell adhesion molecule; ICAM-1, intercellular adhesion molecule; DAPD, dual-acting peptide for diabetes; PACAP, pituitary adenylyl cyclase-activating peptide; GH-RF, growth hormone releasing factor, somatoliberin; SP, substance P; RANTES, regulated on activation normal T cells expressed and secreted; GRH, growth hormone-releasing hormone; IGF-1, insulin-like growth factor 1; HCG, human chorionic gonadotropin.

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1. History

By 2030, the World Health Organization predicts more than 300 million people to be diagnosed with type 2 diabetes (Zimmet et al., 2001). Current treatment modalities of those patients include exercise, diet and a variety of therapeutics. B-cell dysfunction in type 2 diabetes is characterized by reduced B-cell sensitivity to glucose and a delay and–in addition (see below)–a reduction in the meal-induced insulin secretion, a loss of regular oscillatory insulin

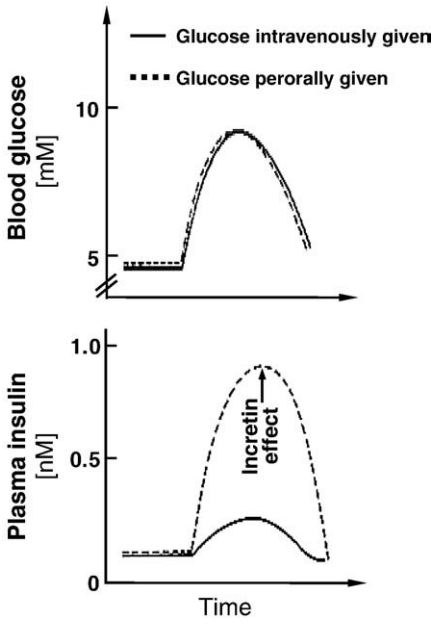

Fig. 1. Incretin effect (schematically shown differences in curves after i.v. and per os application of glucose).

secretion and of first phase insulin response to a glucose challenge, by an elevated proinsulin:insulin ratio, and by an abnormal secretion of islet amyloid polypeptide.

Known treatments have limitations and side effects, e.g. weight gains. The main classes of antidiabetic drugs either suppress hepatic glucose production (biguanides), stimulate insulin secretion (sulfonylureas and glinides), delay digestion and absorption of intestinal carbohydrates (α-glucosidase inhibitors) or improve insulin sensitivity and peripheral glucose uptake (thiazolidinediones and metformin) or insulin (Krentz & Bailey, 2005). Major pathophysiological issues are not addressed by current therapies (Baron et al., 1987; NN, 1995, 1998; Kahn et al., 2006) especially the progressive B-cell failure in type 2 diabetes. Since obesity is the engine that is driving the epidemic of diabetes, it is disappointing that most antidiabetic treatments are associated with weight gain.

New innovative concepts of treatment had to be launched: one new possibility is based on incretins. The incretin concept (the name did not exist yet) was indirectly initiated 100 years ago by showing that duodenal mucosa extracts are effective in inhibiting glycosuria (Moore et al., 1906). An incretin is a compound which is responsible for the higher insulin release in response to an oral glucose load compared to an equal intravenous glucose load (reaching the same glucose level) as shown in Fig. 1. The term incretin, first used by La Barre in 1932, refers to gut derived hormones that stimulate insulin secretion with nutrient ingestion (Elrick et al., 1964; McIntyre et al., 1964; Perley & Kipnis, 1967; Creutzfeldt, 1979; Nauck et al., 1986; Creutzfeldt, 2005; Leon et al., 2006). E.g. glucose was given intravenously and compared with an intrajejunal application (McIntyre et al., 1965). The incretin effect is the most important component of endocrine signalling from the gut affecting pancreatic islet physiology and function.

The incretin effect is believed to be mediated by mainly two incretin hormones: glucose dependent insulinotropic polypeptide (GIP, originally referred to as gastric inhibitory peptide) and GLP-1 (glucagon-like peptide-1) (Holst, 2004). Both hormones enhance insulin secretion to an extent that can fully account for the incretin effect (Kreymann et al., 1987; Nauck et al., 1989; Nauck et al., 1993). It is difficult to state which of both incretins is more important: in normal healthy subjects GLP-1 is several times more potent than GIP on a molar basis at equivalent glycemic conditions (Elahi et al., 1994). Nevertheless GIP may be more effective than GLP-1; this can be indirectly derived from the fact that postprandial concentrations of GIP reach 250-500 pmol/l which is much higher than the minimum concentration affecting insulin release compared to GLP-1 for which postprandial concentrations of 30-50 pmol/l hardly overcome the minimum concentration for insulin release (reviewed by Creutzfeldt and Nauck, 1992). The fact that the physiologic increase after an oral glucose load is much more pronounced for GIP than for GLP-1 was described (Nauck et al., 1993).

More than 40 years ago an enzyme was purified not knowing that it would later be called DPP-4 (DPP-IV, dipeptidyl-peptidase IV; EC 3.4.14.5) (Hopsu-Havu & Glenner, 1966). The enzyme cleaves N-terminal dipeptides with a proline or alanine residue (Fig. 2), an area which is safe with respect to degradation by nonspecific proteases (Yaron & Naider, 1993). DPP-4 cleaves both the incretins GLP-1 and GIP which are substrates (Mentlein et al., 1993) (Fig. 2).

2. The incretin hormones (GLP-1 and GIP)

Eating provokes the secretion of multiple gastrointestinal hormones which have pleiotropic effects such as the regulation of gut motility, secretion of gastric acid and of pancreatic enzymes, induction of gall bladder contraction, and effects on nutrient absorption. Some

Fig. 2. Amino acid sequence of GLP-1 (two types), GIP, exenatide and liraglutide (deviations from GLP-1(7-36)amide are marked by underlining).

gut hormones also facilitate the disposal of absorbed glucose through the stimulation of insulin secretion from the endocrine pancreas: two out of them are incretins, GLP-1 and GIP.

The first incretin to be identified, glucose-dependent insulinotropic polypeptide (GIP), was purified from porcine intestinal extracts; it has weak effects on gastric acid secretion but potent insulinotropic actions (Dupré et al., 1973). The GIP gene is expressed mainly in K cells, enterochromaffin cells of the proximal small intestine (enteroendocrine duodenal and jejunal mucosa). GIP, a 42-amino acid hormone, is stimulated by enteral glucose, lipids and products of meal digestion in a concentration dependent manner (Schirra et al., 1996). Elevated GIP plasma levels augment glucose-stimulated insulin secretion (Nauck et al., 1989). Consistent with the incretin concept, GIP acts as a feed-forward mechanism to signal the endocrine pancreas of impending substrate fluxes from the gut (Ebert & Creutzfeldt, 1987).

The second incretin hormone, called glucagon-like peptide-1 (GLP-1), was identified after the cloning of the cDNAs and genes encoding the human proglucagon (Fig. 3). The human proglucagon gene located on the long arm of chromosome 2 consists of six exons and five introns (Hansotia & Drucker, 2005). The proglucagon gene is expressed in a type of enterochromaffin cells, the L-cells of the intestine ileum and colon. Processing of the expressed peptide by proconvertase 1/3 leads to GLP-1 (Fehmann et al., 1995); another processing of the proglucagon gene product by proconvertase 2 in the A-cells of pancreatic islets leads to glucagon (Fig. 3).

GLP-1(1-37) is produced as an inactive 37-amino acid peptide (Fig. 3). The active form is produced by post-translational cleavage of six amino acids from the N-terminal end. GLP-1 exists in two circulating forms, GLP-1(7-37) and GLP-1(7-36) amide (amidation at the glycine end of the C-terminal) (Fig. 2), from which GLP-1(7-36) amide is more abundant in the circulation after being stimulated by eating (Kieffer & Habener, 1999). Both GLP-1s are equipotent with respect to their receptor interaction as well as their insulinotropic effect.

Cholecystokinin is important for the incretin that did not get clinical importance because its incretin effect is mainly observed in animals (Verspohl et al., 1986a, 1986b; Rushakoff et al., 1987; Rushakoff et al., 1993; Liddle, 1995).

3. Physiology of GLP-1 and GIP (release kinetics, effects, similarities and dissimilarities, kinetics including degradation, receptors and 2nd messengers involved)

3.1. Regulation of incretin secretion (stimuli for incretin release)

Ingestion of nutrients such as carbohydrate, protein and fat leads to release of GLP-1 as well as GIP; of these, carbohydrate ingestion is the best stimulus for GLP-1 secretion. The very rapid increase in plasma levels of GLP-1 after eating implies a combination of endocrine and neural signals well before digested food transits through the gut is able to directly activate the release from L cells; stimulation of GLP-1 secretion may involve vagal pathways (Rocca & Brubaker, 1999). The Rho GTPase Cdc42 is involved in the secretion process of GLP-1 (Lim & Brubaker, 2008).

A rapid gastric emptying, e.g. evidenced by post-gastrectomy dumping syndromes, causes marked increase in GIP and GLP-1 secretion (Ranganath et al., 1998). The impact of circulating free fatty acids on GLP-1 secretion is a matter of controversy: while an inhibition was observed (Ranganath et al., 1999b, 1999c) the opposite was found when the long-chain fatty acid-derivate oleoylethanolamide was investigated which interacts with novel fatty acid receptor (GPR 119) (Lauffer et al., 2009). The effects of α-glycosidase inhibitors are controversial: they increase indirectly GLP-1 secretion (Göke et al., 1994; Qualmann et al., 1995; Seifarth et al., 1998; Ranganath & Morgan, 2000); this was also shown for voglibose (Göke et al. 1995a)

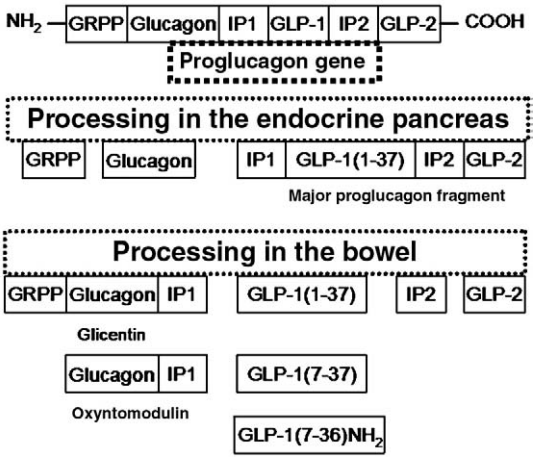

Fig. 3. Proglucagon gene and processing of glucagon and GLP-1.

and miglitol (Lee et al., 2002). However, others did not confirm this effect of acarbose (Hücking et al., 2005). GIP may be reduced by acarbose (Groop et al., 1986).

Plasma levels of GLP-1 are low in the fasted state (5–10 pmol/l), and increase rapidly 3–5 times after eating. Circulating GIP and GLP-1 concentrations rise within 15 min and peak concentrations of GIP and GLP-1 of approx. 200 and 50 pmol/l, respectively, are obtained after 30–45 min, returning to basal values after 2–3 h (Vilsbøll et al., 2001). The concentration of intact GLP-1 after a meal rises proportionally with the size of the meal (Vilsbøll et al., 2003b). Since circulating GLP-1 levels are low, it cannot be excluded that GLP-1 receptors in the portal vein (reached directly after secretion of GLP-1) mediate some effects as alternative to the endocrine signaling (insulin release) (Perabo et al., 2008).

Interestingly insulin and exendin-4 (a GLP-1 analogue, see below) appear to stimulate the proliferation of GLP-1 secreting cells (Miller et al., 2008).

3.2. Effects in vitro (pancreatic islets)

GLP-1 increases insulin secretion and the biosynthesis of important B-cell products besides insulin: glucokinase and GLUT 2 glucose transporters (Wang et al. 1997).

GLP-1 inhibits the secretion of glucagon in a glucose-dependent way (Ørskov et al., 1988; Schirra et al., 2006), but the mechanism is not fully understood and may be a consequence of several factors: since a controversy exists whether receptors for GLP-1 on A-cells exist, intra-islet insulin released from B-cells in response to GLP-1 may locally inhibit glucagon secretion. The resulting improvement in insulin/glucagon ratio may account at least partly for the reduction of insulin resistance in both liver and peripheral tissues such as the skeletal muscle (Ritzel et al., 1995). Surprisingly, GLP-1 does not inhibit, but stimulates glucagon secretion when isolated rat pancreatic A-cells are investigated (Ding et al., 1997), making a direct inhibitory effect on the A-cells unlikely. An important notion is that in vivo, the inhibitory effect of GLP-1 on glucagon secretion fades away at glucose levels just below fasting levels, so that the normal counter-regulatory glucagon secretion at hypoglycaemic levels is preserved even at high GLP-1 concentration (Nauck et al., 2002). Administration of GLP-1 is thus unlikely to be associated with an increased risk of hypoglycaemia (see below).

GLP-1 has been shown to stimulate somatostatin secretion (Ørskov et al., 1988), which in turn may inhibit insulin and glucagon secretion mediated by direct receptor activation of A-cells (de Heer et al., 2005). This indicates a complex interplay between GLP-1 and all the major endocrine cells of the islets possibly being important for the fine-tuning of homoeostatic control of glucose metabolism.

3.3. Effects on non-endocrine cells (stomach, brain, liver) (Fig. 4)

GLP-1 slows gastric emptying (Wettergren et al., 1993;Nauck et al., 1997;Naslund et al., 1999b) using cholinergic pathways (Schirra et al., 2009), and induces gastric relaxation via nitric oxide (Andrews et al., 2007) and satiety (Flint et al., 1998). By delaying gastric emptying postprandial glycaemia is minimized; also the distension of the stomach and peripheral satiety signals are influenced.

The effects of GLP-1 and GIP on gastric acid secretion in vivo at physiological concentrations are disputed. Receptors for GIP and GLP-1 are present in the stomach. The mechanisms involved are not clear, but endocrine or neural mechanisms, or a combination, may be involved. Experiments with vagal deafferentiation of rats and humans show the involvement of vagus (Wettergren et al., 1994; Imeryuz et al., 1997; Wettergren et al., 1997b). Peptide YY (PYY) may participate in inhibitory effects on gastric acid release which is released in parallel with GLP-1 from the L cells (Wettergren et al., 1997a). Both hormones show an additive effect and are able to block, for example, gastrin-stimulated gastric acid secretion (Holst, 1997).

Effects of incretins (and incretin mimetics) on body weight may be mediated through effects on the adipocytes and brain centres controlling food intake and energy expenditure (Kastin et al., 2002). Administration of GLP-1 into cerebral ventricles of rats sharply decreased their energy intake (Turton et al., 1996). GLP-1 effects may be mediated by interactions of central GLP-1 (released from noncatecholaminergic neurons in the solitary tract nucleus) (Larsen et al., 1997) with hypothalamic and extrahypothalamic nuclei in the brain, as well as via peripheral GLP-1, which can reach the area postrema and subfornical organs with access to hypothalamic centres controlling energy intake (Ørskov et al., 1996). Thus, although GLP-1 synthesis was demonstrated in the brain, peripheral GLP-1 may bind to regions of the brain.

GIP receptor expression has also been found in the brain; GIP administration in healthy subjects, however, appears to increase food intake and to decrease energy expenditure, in contrast to GLP-1 (Lui et al., 1990; Ranganath et al., 2007). Beyond acting as an incretin (endocrine axis) other prominent actions are obvious: GIP seems to increase glucose uptake and triglyceride storage in adipocytes (Miyawaki et al., 2002; Gault et al., 2005), and to stimulate possibly bone mass and bone turnover (Tsukiyama et al., 2006; Xie et al., 2007).

In Table 1 the physiologic characteristics of GIP and GLP-1 are summarized and compared. These incretins share a number of similarities: both peptides are released in response to meal consumption with a dose dependent relationship to meal size. Both are inactivated by DPP-4. Early intracellular signaling events following ligand binding to different receptors are comparable. They cause enhanced insulin secretion from B-cells in a glucose-dependent manner. The general conformities shared by GIP and GLP-1 suggest the evolution of redundant systems to mediate the incretin effect. In fact, there is evidence that one system compensates in the absence of normal functioning of the other incretin (Pamir et al., 2003). GIP and GLP-1 have physiologic roles that are complementary and in some aspect distinct.

Despite the many similarities between the incretins there are several dissimilarities. Key points of distinction are site of synthesis and the manner in which nutrient stimuli is coupled to incretin secretion, mechanism of action, and extra-incretin effects. GIP and GLP-1 have only modest degrees of sequence homology as do their receptors. GIP is produced primarily in the upper intestine and there is convincing data connecting K-cell secretion of GIP with the digestion and absorption of lipid and carbohydrate (Falko et al., 1975; Ross & Dupré, 1978; Schirra et al., 1996).

GLP-1 is produced throughout the small intestine but the highest concentrations of producing L-cells are in the distal gut (Eissele et al., 1992). The GLP-1 receptor is expressed in cells of the endocrine pancreas and in many other tissues, mainly those of the central and peripheral nervous systems, heart, kidney, lung, and gastrointestinal tract and GLP-1, therefore, mediates a broader spectrum of effects than GIP. This is why GLP-1 also inhibits gastric emptying, food ingestion, and promotes enhanced glucose disposal through neural mechanisms (Burcelin et al., 2001) which all contribute to glucoregulation. A direct effect on muscle and adipose tissue (Fig. 4) as originally propagated is questionable.

3.4. Receptors and signalling

The actions of both GIP and GLP-1 are mediated by specific and structurally distinct G-protein-coupled receptors (Amiranoff et al., 1984; Wheeler et al., 1995; Thorens & Widmann, 1996). GIP interacts with two subtypes of receptors, GIP receptor 1 and 2, which are predominantly expressed on islet A and B cells, and to a lesser extent in adipose tissue, the upper gastrointestinal tract, adrenal cortex, bone, pituitary and a variety of brain regions (Bollag et al., 2000; Drucker, 2006). The GIP receptor has substantial homology with the secretin-VIP receptor family.

The GLP-1 receptor is expressed in pancreatic A-cells (controversial, see above), B-cells and D-cells. The inhibition of glucagon release by GLP-1 may be a direct effect or an indirect one via somatostatin release (Sinclair and Drucker, 2005b; Leon et al., 2006) (as discussed

Table 1
Summary of the physiological characteristics of glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide-1 (GLP-1): Similarities and differences (modified from Ranganath, 2008; Green and Flatt, 2007).

	GIP	GLP-1
Number of amino acids	42	30/31
Cell of origin in the intestine	K cells/proximal	L-cells/distal intestine/colon
Degradation by	DPP-4	DPP-4
Insulin secretion (glucose-dependent)	Increased	Increased
B-cell glucose responsiveness	Yes	Yes
Lowering of blood glucose	Yes	Yes
Extrapancreatic glucose lowering effect	Yes	Yes
Inhibition of hepatic insulin extraction	Yes	Yes
Gastric emptying	Inconclusive, eventually no effect	Slowed
B-cell proliferation	Stimulated	Stimulated
Glucagon secretion	Unaffected or increased (but not suppressed)	Suppressed
Somatostatin secretion	Unchanged	Increased
Food intake	Increased	Decreased
Reduce body weight	No	Yes
Gastric acid secretion	Decreased	Decreased
Insulin sensitivity	Unchanged	Probably improved
Secretion in Type 2 diabetes	Reduced (questionable)	Reduced (questionable)
Insulin secretion to administration in type 2 diabetes	Impaired	Relatively well preserved

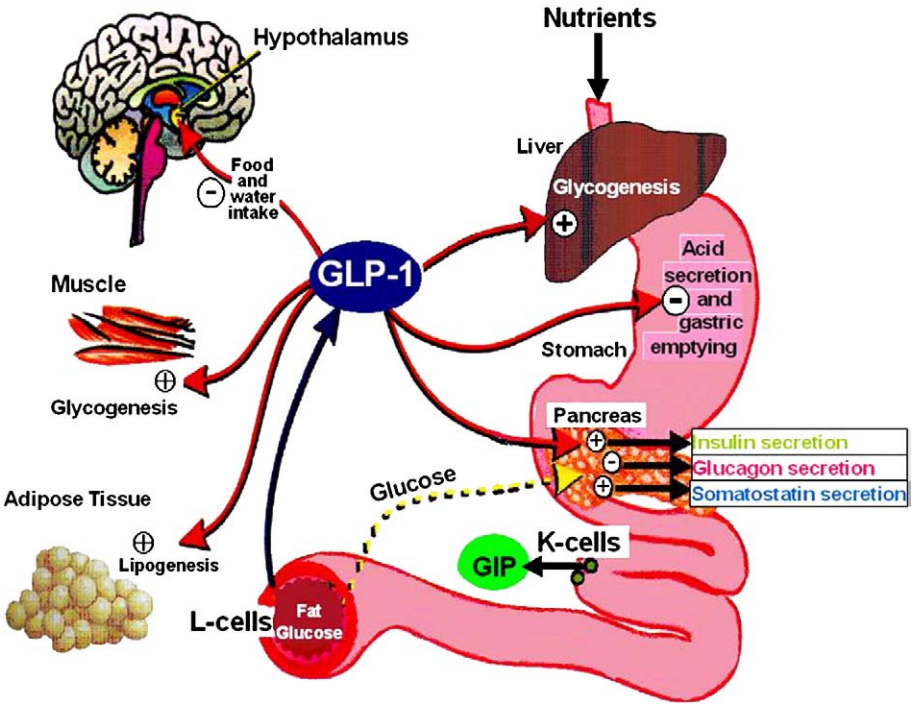

Fig. 4. Physiology of GLP-1 secretion and action on various tissues (modified from Kieffer and Habener, 1999; Meier et al., 2002; Ranganath, 2008). The pleiotropic effects of GLP-1 include the brain (satiety), peripheral organs (anabolic effects), endocrine pancreas (increase of insulin and somatostatin release and inhibition of glucagon release). An effect of GIP on GLP-1 release is not obvious in humans.

above). GLP-1 receptors are also present on mucosal cells in the gastric and small intestinal mucosa, on cardiac myocytes, neurons in the hypothalamus, hindbrain, the vagus nerve and several other brain regions.

Activation of GIP and GLP-1 receptors on B-cells leads to rapid increases in levels of cAMP (Fig. 5) which is glucose-dependent (Drucker et al., 1987) and which is linked to both acute and long-term effects. Acutely a subsequent activation of either protein kinase A (PKA) (Wang et al. 2001) or cAMP-regulated guanine nucleotide exchange factor II (Epac 2) (Holz et al., 2006) alters ion channel activity, handling of intracellular calcium and enhances exocytosis of insulin containing granules (Holz, 2004). The glucose dependency of

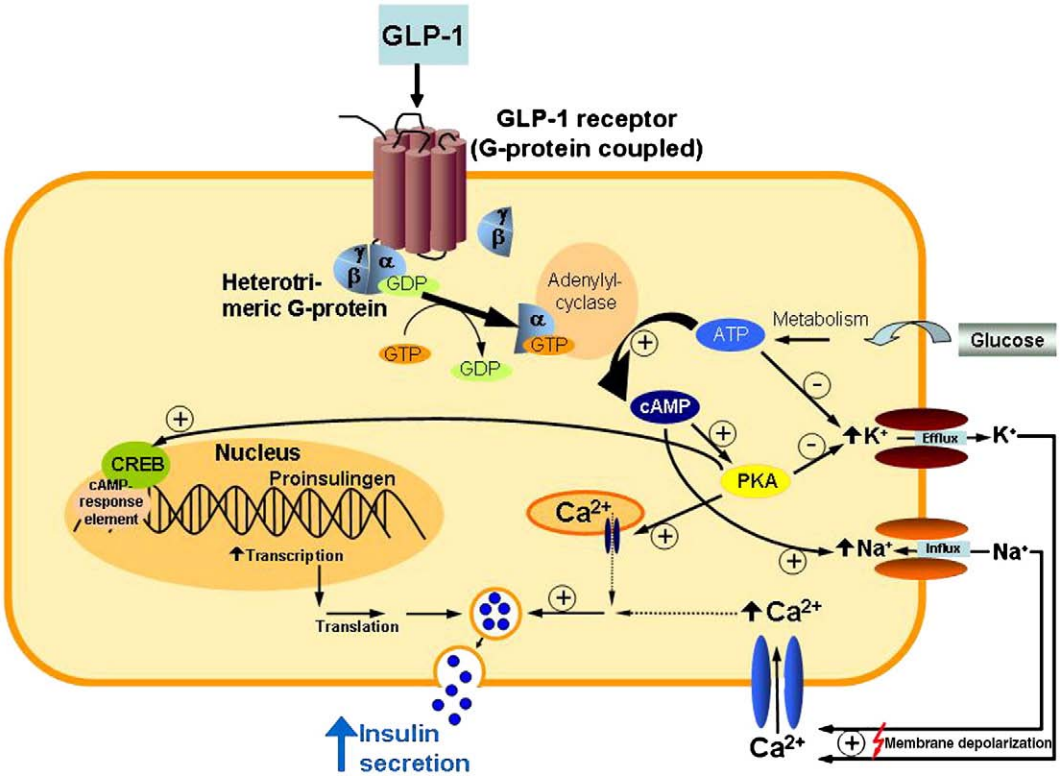

Fig. 5. Mechanisms of action of GLP-1.

insulin release may depend on the KATP channels of the B-cell which close when activated by a rise in the intracellular ATP concentration, hence making them sensitive to the intracellular glucose metabolism and therefore the plasma glucose concentration. The effect of GLP-1 appears to involve further channel closure and membrane depolarization (through accumulation of cAMP and activation of protein kinase A), but apparently, a parallel glucose mediated closure is required for the effect of GLP-1.

GIP receptor signaling in the B-cells shares many similarities with GLP-1 (production of cAMP and activation of PKA, increased intracellular Ca^{2+}, and closure of K_{ATP} channels, causing insulin exocytosis). Like GLP-1, a significant component of GIP signaling is independent of PKA and acts through Epac 2 pathway (Kashima et al., 2001).

3.5. Kinetics

After being secreted both GIP and GLP-1 have a very short circulating half-life of 3–5 min due to the action of proteases such as dipeptidyl peptidase IV (DPP-4) and other endopeptidases, resulting in inactivation (Ørskov et al., 1993). An important organ for GLP-1 clearance is the kidney (Deacon, 2005). Both GIP and GLP-1 contain alanine at position 2 (Fig. 2), where DPP-4 is active (see above and later). The degradation of GLP-1 and GIP occurs through N-terminal removal of the two amino acids histidine and alanine (GLP-1) and tyrosine and alanine (GIP) (Fig. 2), yielding the inactive (with regards to stimulating insulin secretion) truncated form of e.g. GLP-1 (9–36) amide (Mentlein, 1999). As a result of DPP-4 activity, intact, biologically active GLP-1 represents only 10–20% of total plasma GLP-1 (Deacon et al., 1995b). Truncation of GLP-1(7-36)amide to GLP-1(9-36) amide reduces receptor affinity by 1000 and rather completely eliminates its insulin-releasing activity (Knudsen & Pridal, 1996; Deacon et al., 2002; Green et al., 2004). The major significance of DPP-4 for incretin inactivation was shown in DPP-4 gene knock out mice which have elevated levels of plasma GIP and GLP-1, increased insulin secretion, and reduced glucose increases after glycaemic challenge (Marguet et al., 2000). It is not clear to which degree additional proteases, such as a human neutral endopeptidase, are also essential for GLP-1 inactivation. Neutral endopeptidase 24.11 (NEP24.11, also known as neprilysin) is a widespread membrane-bound zinc metallopeptidase (Plamboeck et al., 2005); the molecule is cleaved at the C-terminal region.

The quick degradation by DPP-4 and the short half-life raises the question of whether significant amounts of intact, bioactive, peptide really reach the arterial circulation and target tissues (Hansen et al., 1999) (see above: receptors in the portal vein). In general some uncertainty exists (with this respect) over how GLP-1 mediates its actions at this low concentration.

3.6. Clinical aspects

A short-term intravenous infusion of GLP-1 (1–1.2 pmol kg^{-1} min^{-1}) leading to plasma concentrations of 70–150 pmol/l (total GLP-1) or of 10–20 pmol/l (intact biologically active GLP-1), lowers blood glucose in patients with type 2 diabetes through a transient stimulation of insulin secretion and suppression of glucagon secretion and gastric emptying (Nauck et al., 1993b; Willms et al., 1996; Toft-Nielsen et al., 2001b). A long-term 6-week s.c. infusion of GLP-1 in patients with type 2 diabetes, achieving plasma levels of 60–70 pmol/L, led to substantial improvements in insulin secretory capacity, insulin sensitivity, a reduction in HbA_{1c} by 1.2% and a modest weight loss (1.9 kg) (Zander et al., 2002).

GLP-1 suppresses hepatic glucose production, and promotes insulin independent glucose disappearance (D'Alessio et al., 1994; Egan et al., 2002b). The ability of GLP-1 to lower plasma glucose is preserved even in type 1 diabetic patients (no residual B-cell function) (Creutzfeldt et al., 1996), indicating that a paracrine effect of insulin or other B-cell products is not involved.

The impact of endogenous GIP and GLP-1 on glucose homoeostasis has been investigated indirectly both by using receptor antagonists and by looking at mice with receptor defects. The GLP-1 receptor antagonist exendin (9-39) provokes a defective glucose-stimulated insulin secretion, reduces glucose clearance, increases levels of glucagon and induces a quicker gastric emptying (Schirra et al., 1998). Mutated mice with abnormal GIP or GLP-1 receptors have impaired glucose-stimulated insulin secretion and glucose tolerance and become diabetic (Scrocchi et al., 1996; Miyawaki et al., 1999).

3.6.1. Effects on glucose homoeostasis and HbA_{1c}

Many of the already mentioned effects of GLP-1 are important for glucose homoeostasis during therapy: stimulation of insulin, restoration of first phase of insulin release, suppression of glucagon secretion, inhibition of gastric emptying, and reduction of appetite and food intake. When glucose levels reach normal fasting levels, insulin and glucagon levels return to baseline concentrations despite continued GLP-1 infusion, indicating the glucose-dependent nature of the stimulation of insulin and suppression of glucagon by GLP-1 (Nauck et al., 1993b). The fact that the effects are glucose dependent is a major advantage over sulfonylureas. The question in general is whether therapeutic approaches should be targeted towards relieving the demand on the B-cell to secrete insulin; this option should at least be delayed as long as possible (Aston-Mourney et al., 2008); the primary focus may be to overcome insulin resistance when starting a therapy (see below the relevance of sulfonylureas and incretins for the therapy in the future).

3.6.2. Effects on B-cell mass

Some remodelling of size and function of islet B-cells occurring throughout life may play a role in the maintenance of normal glucose tolerance (Bonner-Weir, 2000). In addition to functional abnormalities destabilizing the islet cell mass primarily through changes in numbers and size of B-cells, a disturbed interplay of division and growth of these cells (neogenesis, rates of apoptosis and even loss) is very important (Finegood et al., 1995; Butler et al., 2003). An inhibition of B-cell apoptosis by GLP-1 is observed in human B cells (Farilla et al. 2003; Buteau et al. 2004). Therefore, any agent that normalizes this balance may delay or prevent the decline in insulin secretory capacity. GLP-1 (including its analogues) possibly has this disease-modifying capability in type 2 diabetes (Xu et al., 1999; Stoffers et al., 2000; Buteau et al., 2001; Baggio & Drucker, 2006; Aaboe et al., 2009).

GLP-1 seems to stimulate the proliferation of developed B-cells. In addition GLP-1 stimulates the differentiation and maturation of foetal islet cells to insulin-producing islet cells (Abraham et al., 2002). In animals a GLP-1 analogue stimulates islet cell differentiation from ductal progenitor cells or exocrine cells (Xu et al., 1999; Zhou et al., 1999). Activation of GLP-1 receptor signaling promotes conversion of human or rat pancreatic ductal cell lines to islet-like cells that produce insulin in a glucose-dependent fashion (Hui et al., 2001; Miyawaki et al., 2002; Bulotta et al., 2002; Drucker, 2003).

The effect of GLP-1 on B-cell differentiation involves the transcription factors PDX-1 and its upstream regulator Foxa2 (formerly HNF3β) (Hui et al., 2001; Miyawaki et al., 2002; Bulotta et al., 2002), and appears to be mediated by MAP kinases (Miyawaki et al., 2002), including extra-cellular signal related kinase (ERK) (Gomez et al., 2002), and an isoform of PKC (Buteau et al., 2001). Besides CREB (Fig. 5), the key intermediary compounds of GLP-1 signaling that mediate more chronic B-cell effects include insulin receptor substrate 2 (IRS-2) and the transcription factor PDX-1 (Drucker et al., 1987; Wang et al., 1997; Skoglund et al., 2000; Wang et al., 2005; Bregenholt et al., 2005). Activation of PDX-1 appears to be involved in all cytoprotective effects of GLP-1. Enhanced PI-3K activity as a result of IRS-2

phosphorylation or EGFR transactivation leads to the upregulation of PDX-1 via nuclear exclusion of Fox01 (Buteau et al., 2006). Transactivation of epidermal growth factor receptor (EGFR) is involved in inducing PI-3K activity (proliferation) (Buteau et al., 2003). Support for involvement of the transcription factor NFAT (nuclear factor of activated T-cells) has been presented (Lawrence et al., 2002; Heit et al. 2006). The data are summarized in Fig. 5.

The role of neogenesis of endocrine precursors from pancreatic duct cells has been questioned as a significant mechanism for changes in B-cell mass in vivo (Dor et al., 2004; Dor, 2006; Teta et al., 2007).

GLP-1 and similar receptor agonists reduce apoptosis in primary rodent islets or islet cell lines exposed to cytotoxic agents, such as cytokines, free fatty acids, hydrogen peroxide, or streptozotocin (Perfetti et al., 2000; Pospisilik et al., 2002; Buteau et al., 2003; Hui et al., 2003; Bregenholt et al., 2005).

The data raise the interesting possibility that activation of the GLP-1 receptor could increase B-cell mass, a novel and potentially effective approach to inhibit the progression of diabetes. It has to be differentiated between in vitro/animal studies and the extrapolated clinical outcome. It is important to note that despite the accumulation of an impressive body of evidence the GLP-1 receptor signaling promotes the expansion or protection of B-cell mass; this information is limited to studies of cultured cells or rodent models. There are important differences in rates and capacity for islet cell turnover and growth between rodents and humans (Butler et al., 2007), such that extension of findings from animal studies cannot be assumed. The mechanisms of prolonged effects are summarized in Fig. 6 (Brubaker & Drucker, 2004; Li et al., 2005). Some of these effects may have a therapeutical implication (see details later). Thus basic research in this area has proceeded over the past years, albeit translation of this work to human application has not yet been accomplished. Because it is not currently possible to evaluate B-cell mass non-invasively in humans the question of GLP-1 effects on B-cell proliferation and apoptosis cannot be reliably addressed in longitudinal or intervention studies.

Chronic effects of GLP-1, such as gene transcription through the actions of CREB (Fig. 5), activation of cellular growth and inhibition of apoptosis, can be attributed to PI-3K downstream pathways possibly including PI3-K, protein kinase B (PKB) and protein kinase C (PKC) (Buteau et al., 2001; Wang & Brubaker, 2002; Buteau et al., 2003) enhancement of insulin biosynthesis (Drucker, 2006), increased resistance to apoptosis and enhanced B-cell survival (Li et al., 2003; Farilla et al., 2003).

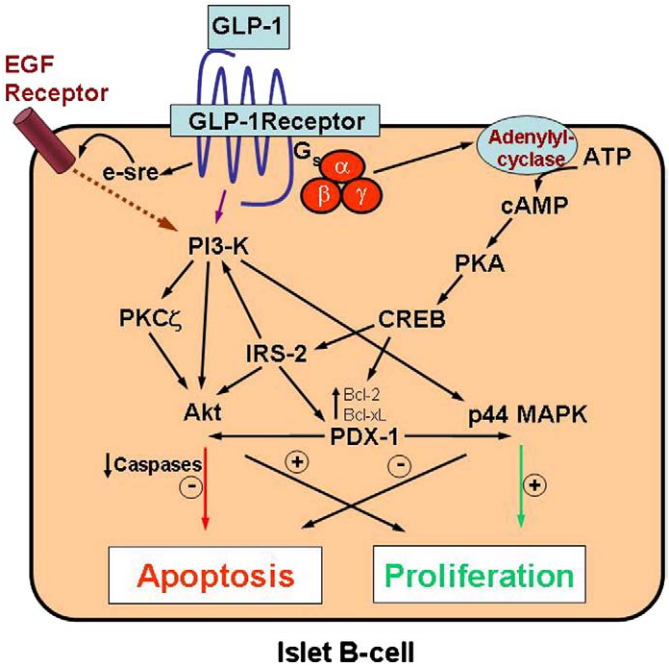

Fig. 6. Mechanisms involved in apoptosis and proliferation with respect to GLP-1 (modified from Brubaker & Drucker, 2004). (Bcl-2 and Bcl-xL are antiapoptotic proteins; PDX-1 is pancreatic and duodenal homeobox 1, a transcription factor; c-src is a protein with tyrosine kinase activity).

WNT signalling (WNT = cell-secreted glycoprotein ligand) is a key pathway for B-cell growth and differentiation. There are some hints that GLP-1 is linked as a direct activator of the WNT pathway (Gustafson & Smith, 2008).

The other incretin GIP has similar proliferative and anti-apoptotic effects on B-cells using rather the same intracellular mechanisms (PKA activation, PI-3K/PKB activity and p38 MAPK) (Trumper et al., 2001; Wideman & Kieffer, 2004). Administration of a GIP-antagonist for 11 days to *ob*/*ob* mice partially reversed islet hypertrophy with a concurrent improvement of hyperinsulinemia and insulin resistance (Gault et al., 2005). There are yet no studies of chronic effects of GIP receptor agonists in humans; thus the intriguing results of these animal studies have not been extended to possible clinical applications as it holds for GLP-1 receptor agonists.

3.6.3. Effects on the gastrointestinal tract and exocrine pancreas

GLP-1 inhibits gastrointestinal secretion and motility (Wettergren et al. 1993; Nauck et al. 1997). It has further been established that GLP-1 inhibits pancreatic exocrine secretion independently of its inhibition of gastric emptying (Groger et al. 1997).

3.6.4. Central effects with respect to appetite and food intake

GLP-1 receptors in the brain are expressed particularly in the regions responsible for the regulation of food intake. Intracerebroventricular administration of low GLP-1 doses results in inhibition of food intake (Göke et al., 1995b; Tang-Christensen et al. 1996; Turton et al., 1996). Interestingly also peripheral administration of GLP-1 enhances satiety and reduces food intake in normal subjects (Flint et al., 1998; Verdich et al., 2001), as well as obese subjects (Naslund et al., 1999a) and type 2 diabetic patients (Gutzwiller et al., 1999a; Zander et al., 2002). The local mechanisms of these effects are unclear. As the enhancement of satiety and decrease of hunger is preserved in fasting subjects (Gutzwiller et al., 1999b), it is unlikely that the mechanisms are direct, i.e. related to the effect on gastric emptying and motility. This is corroborated by experiments when exendin 9-39 is given intracerebroventricularly.

3.6.5. Cardiovascular effects (GLP-1)

It is evident from in vitro and in vivo experiments that GLP-1 has beneficial effects on myocardial function: in rat models of myocardial ischemia a reduction in infarction size has been demonstrated (Bose et al., 2005). GLP-1 improves myocardial contractility and glucose uptake in normal and postischemic rat hearts (Zhao et al., 2006). In humans with type 2 diabetes and congestive heart failure, GLP-1 may improve myocardial function (Thrainsdottir et al., 2004; Nikolaidis et al., 2004).

GLP-1 has been shown to induce an endothelial-dependent reduction in vascular tone of rat lungs (Golpon et al., 2001) and improves endothelial function in a salt-sensitive rat model (Yu et al. 2003). In type 2 diabetic patients with established coronary artery disease an expression of GLP-1 receptors in coronary artery endothelial cells was observed and a beneficial effect of GLP-1 infusion on endothelial function was demonstrated (Nystrom et al., 2004).

4. Pathophysiological impact of the incretin concept (similarities and differences between the incretins GLP-1 and GIP in pathophysiological terms)

Failure of incretin effect leads to a relative insulin deficiency and hyperglycaemia. The incretin effect (oral glucose elicits a considerably

Table 2
Pathophysiological state of type 2 diabetes and related biological effects of GIP and GLP-1.

Feature of type 2 diabetes	GIP	GLP-1
⇓ Insulin secretion	Ineffective in type 2 diabetics	Effectiveness preserved in type 2 diabetes; ⇑ Insulin secretion
⇓ Insulin synthesis		⇑ Insulin synthesis
Hyperglucagonaemia (⇑ Glucagon secretion)		⇓ Glucagon secretion (possibly indirectly)
⇑ B cell apoptosis	⇓ B cell apoptosis	⇓ B cell apoptosis
⇓ B cell mass	⇑ B cell replication (humans?)	⇑ B cell replication (humans?)
Obesity		⇓ Food intake, ⇓ body weight
⇑ ⇓ ± gastric emptying	No effect	⇓ gastric emptying
Hyperlipidemia	No effects	⇓ triglycerides, ⇓ free fatty acids
Insulin resistance	No effects	No immediate effect (⇑ Insulin sensitivity (probably))

(⇑ increase, ⇑ decrease, ± no effect) (adapted from Van Gaal et al., 2008).

higher insulin secretory response compared to the same amount of intravenous glucose; see above) was believed to be substantially reduced in patients with type 2 diabetes (Nauck et al., 1986; Nauck et al., 2004b). Studies have reported that plasma GLP-1 levels are increased (Ørskov et al., 1991; Fukase et al., 1995), decreased (Vaag et al., 1996; Vilsbøll et al., 2001; Toft-Nielsen et al., 2001a; Vilsbøll et al., 2003b), and not changed (O'Donovan et al., 2004; Ryskjaer et al., 2006; Knop et al., 2007) in this situation. These differences are probably due to technical discrepancies using different assays and due to the relatively small sample sizes studied. Regardless, in studies where GLP-1 secretion has been reported to be reduced in diabetic subjects the relative decrease was modest, suggesting that GLP-1 deficiency probably does not contribute significantly to B-cell dysfunction in type 2 diabetes. The GLP-1 release, but not that much the GLP-1 effect is hampered in type 2 diabetics (Højberg et al., 2007) which, however, can be improved by a 4-week normalization of blood glucose (Højberg et al., 2007, 2008). Supplementing the incretin GLP-1 can overcome this type of defect in type 2 diabetics.

There is no evidence for reduced GIP secretion as an explanation for a reduced incretin effect in diabetes. GIP and fortunately not GLP-1 shows attenuated insulinotropic action in patients with type 2 diabetes (Nauck et al., 1993a). GIP, by contrast, has proved to be disappointing in terms of therapeutic use since its intravenous administration is not associated with unequivocally improved insulin secretion and glucose tolerance (Elahi et al., 1994). GIP is an insulin secretagogue in healthy subjects but is relatively inactive in patients with type 2 diabetes. The defect in GIP is acquired rather than representing a primary feature of type 2 diabetes (Meier et al., 2003b). The defect is reversible, and GIP responsiveness can be restored by sulfonylureas or by improving blood glucose control (Menelly et al., 1993; Aaboe et al., 2007; Højberg et al., 2007). Studies in type 2 diabetes report decreased, normal and increased GIP secretion (Ebert & Creutzfeldt, 1987; Krarup, 1988; Nauck et al., 1993a; Fehmann et al., 1995; Toft-Nielsen et al., 2001a; Vilsbøll et al., 2003a).

GLP-1 secretion is reduced in non-diabetic obese subjects, suggesting that incretin secretion may be altered early in the natural history of diabesity (Ranganath et al., 1996). Since GLP-1 actions remain relatively preserved in diabetic patients, the pharmaceutical efforts have mainly focused on GLP-1 receptor agonists since they are of higher therapeutic relevance than GIP.

It now has to be concluded that the impaired incretin effect is a result of the diabetic state rather than a primary pathogenic factor (Vaag et al., 1996; Meier et al., 2005b). The paradigm has changed: it is now clear that diabetes affects the incretin hormones.

In Table 2 the pathophysiological situation in type 2 diabetes including the influences of GIP and GLP-1 is summarized.

Increased circulating glucagon levels are not suppressed in type 2 diabetics after a carbohydrate-rich meal and occurs early in prediabetes (Muller et al., 1970; Unger et al., 1970; Åhren and Larson, 2001). The resultant hyperglucagonaemia contributes both to an inability to suppress hepatic glucose production postprandially and to excessive plasma glucose excursions. Therapies currently available do not influence the hyperglucagonaemia; an approach that targets glucagon suppression (Table 2) would offer a valuable mechanism to improve glycaemic control.

Gastric emptying may be more rapid in type 2 diabetes and may be a key determinant of postprandial glucose excursions (Phillips et al., 1992; Horowitz et al., 1994). A slowing in gastric emptying occurs to improve the match between rise in glucose due to nutrient absorption and glucose disappearance from the circulation, despite which, the gastric half-emptying time is significantly shorter in patients with type 2 diabetes. GLP-1 inhibits the gastric-emptying rate (Table 2).

Effects as a result of an incretin lack and therapeutic effect of incretins are summarized in Table 3.

One characteristic of diabetic islet function is the classic absence of first-phase insulin release (Table 4), an apparent loss of B-cell sensitivity to glucose (Byrne et al., 1996), and delayed insulin secretion in response to oral glucose (Table 4). This may be partly due to a decrease in the actions of GI hormones and neural signals, engaged after meals, to potentiate the insulin response (Quddusi et al., 2003). Additionally there may be a disruption of normal pulsatile insulin secretion (Polonsky et al., 1988), abnormal potentiation of non-glucose secretagogues, and a decreased maximal secretory capacity (Ward et al., 1984).

Two different approaches can be used: one would be to administer incretin(s) exogenously (incretin mimetics). An alternate strategy would be to enhance endogenous incretins by inhibiting their degradation (= incretin enhancers).

There are some aspects (pathophysiological factors) in type 2 diabetes addressed now (Table 4), but not fully addressed by other antidiabetic treatments (Table 5) except incretin mimetics (avoiding weight gain and metformin (hyperglucagonaemia).

5. GLP-1 receptor agonists (exenatide)

GLP-1 itself is rapidly degraded and could only be used as a continuous infusion (Neilsen & Baron, 2003). Chemically modified degradation-resistant peptides with an acceptable pharmacokinetic profile have been developed. In the search for those peptides GLP-1 was compared with known structures from databanks. Exendin-4 (36 amino acids) was discovered in a lizard (salivary gland venom of the Gila monster) and found to be more stable and less rapidly degraded than GLP-1 (Eng et al., 1992; Göke et al., 1993; Raufman, 1996). Although exendin-4 (synthetic = exenatide) is transcribed from a distinct gene, it has a 53% overlap of the amino acid sequence with mammalian GLP-1 (Chen & Drucker, 1997) (Fig. 2). Exendin-4 has an in vivo potency up to 5-10 times higher than GLP-1 itself.

As a GLP-1 agonist, exenatide binds to the pancreatic GLP-1 receptor and improves glucose homeostasis by mimicking the actions of naturally occurring GLP-1: it stimulates insulin release in a glucose-dependent manner (Egan et al., 2002a; Kolterman et al., 2003; Degn et al., 2004a), improves first phase insulin release (Fineman et al.,

Table 3
Consequences of incretin deficiency and substitution (modified from Ranganath, 2008; Holst et al., 2008).

Presumed phenotype	Incretin actions correcting this
Weight gain	Decrease in food intake
Postprandial hyperglycaemia	Delay in gastric emptying, increase in glucose-induced insulin secretion
Hyperglucagonaemia	Increase in glucose-mediated suppression of glucagons
Increase in loss of B cells	Increase in B cell neogenesis, proliferation snf decrease in apoptosis
Delayed insulin response (lacking first phase insulin release) (partly mediated)	Reversed

Table 4
Comparison of defects in type 2 diabetes and biological actions of GLP-1, incretin mimetics, and DPP-4 inhibitors (partly modified from several authors: Drucker & Nauck, 2006; Åhrén, 2007; Handelsman, 2008).

Defect in type-2 diabetes	Biological action of compounds	GLP-1, Exenatide, Liraglutide	Sitagliptin, Vildagliptin (DPP-4 inhibitors)
⇓insulin secretion	⇑ insulin secretion (glucose-dependent	Yes	Yes
Lack of first phase insulin secretion	Restoration of first phase insulin secretion	yes[a]	Not known
⇓ incretin effect	Replacement of incretin effect	yes	Yes
⇑ glucagon secretion	⇓ glucagon secretion	yes	Yes
Hypoglycemia counterregulation	⇑ Glucagon secretion at low glucose	yes	Not known
⇓ßcell insulin content	⇑ proinsulin biosynthesis	yes	Yes
⇓ ßcell mass	⇑ proliferation of ßcells	yes	Not known
⇑ ßcell apoptosis	⇓ ßcell apoptosis	yes	Not known
No pathophysiological equivalent	⇓ velocity of gastric emptying	yes	No (nearly not detectable)
⇑energy/food uptake	⇓ energy/food uptake	Yes	No
⇑ weight gain	⇓ weight gain or even weight loss	Yes	No

Note: the outcome of data presented in the table is in part from animal studies. The first phase insulin release is a measure of clinical diagnosis albeit artificial because not seen after an oral glucose load (slow glucose increase).
[a] Not known for liraglutide.

2003; Quddusi et al., 2003; Fehse et al., 2005), induces a delay of gastric emptying (Kolterman et al., 2003, 2005; Blase et al., 2005) and decreases food intake. It improves the GLUT-4 expression in target cells of STZ-diabetic rats (Tornero-Exteban et al., 2007). On a long run B-cell function is improved for which a permanently ongoing treatment is necessary (Bunck et al., 2007).

5.1. Clinical aspects

The incretin mimetic exenatide has been developed for the treatment of type 2 diabetes (Polonsky et al., 1988; Gerich, 1989; Rachman et al., 1997; Quddusi et al., 2003; Degn et al., 2004a; Fehse et al., 2005; Kolterman et al., 2005). The efficacy of adding exenatide to ongoing therapy in patients suboptimally controlled by oral antidiabetic agents has been investigated: metformin (DeFronzo et al., 2005), sulfonylureas (Buse et al., 2004) including a combination of both (Kendall et al., 2005) or thiazolidinediones (Zinman et al., 2006). Exenatide is indicated as an adjunctive therapy to improve glycaemic control in patients with type 2 diabetes mellitus who are already receiving metformin, a sulfonylurea, or both but continue to have suboptimal glycaemic control. Exenatide is approved only for the use in combination with metformin, a sulfonylurea, a thiazolidinedione or the combination of metformin with either a sulfonylurea or with a thiazolidinedione. Exenatide nevertheless is effective as monotherapy, but this is not an immediately attractive option for most patients with respect to the type of administration. Not surprisingly, there also is some interest in using GLP-1 mimetics for weight loss in patients without diabetes, but this has not yet been approved.

Appropriate doses were derived from various studies (Buse et al., 2004; DeFronzo et al., 2005; Kendall et al., 2005; Heine et al., 2005; Zinman et al., 2006). 5 or 10 μg exenatide by two subcutaneous injections per day shows reductions in fasting and postprandial glucose concentrations and in weight loss (2–5 kg). Given chronically it enhances hepatic insulin sensitivity and splanchnic glucose uptake (Cersosimo, 2007). Exenatide reduces HbA_{1c} concentrations by 0.8–1.0% (Buse et al., 2004; DeFronzo et al., 2005; Heine et al., 2005; Kendall et al., 2005; Kim et al., 2006; Zinman et al., 2006) for a long time (over 30 weeks), with prevention of weight gain or even induction of a modest weight loss of 1.5–3 kg which may be higher (4–5 kg) after 80 weeks (Riddle et al., 2006).

Sixteen-week treatment with exenatide added to existing thiazolidinedione treatment in type 2 diabetic patients suboptimally controlled with or without metformin reduced HbA_{1c} by 0.98% from a mean baseline value of 7.8–8.0%, with a weight loss of 1.51 kg (Zinman et al., 2007). The addition of either insulin or exenatide in patients not sufficiently controlled by sulfonylurea and metformin resulted in a better reduction of HbA_{1c} in the exenatide-group and in a weight reduction only in this group (weight increase in the insulin-group) (Nauck et al., 2007a) although a more stringent insulin regime might have equalized the differences. Among patients with type 2 diabetes requiring insulin therapy, exenatide exhibits less potent HbA1c reduction compared with its combination with oral agents (Davis et al., 2007); this observation was expected because such individuals tend to be more insulin deficient with less available insulin secretory reserve.

The main metabolic benefits demonstrated from exenatide therapy have been on indexes of glycaemic control.

On a long term exenatide has additional effects: it also improves markers of hepatic functions such as ALT and AST (Okerson et al., 2007); nonalcoholic fatty liver disease often coexists with diabetes. The observed weight reduction over time may have an indirect benefit on cardiovascular risk, including blood pressure, cholesterol levels, inflammatory markers, and insulin resistance. One clinical report on exenatide suggests a modest benefit on certain cardiovascular risk factors (Buse et al., 2007). GLP-1 receptors have been demonstrated in cardiac myocytes and in those regions of the brain that regulate autonomic function (Bullock et al., 1996). The observed effects on blood pressure are controversial: GLP-1 may decrease (Avogaro, 2008) or increase (Yamamoto et al., 2002) blood pressure in humans. Rat

Table 5
Drugs used in type 2 diabetes and effects on factors with pathophysiological relevance (+ = improved or increased; - = reduced; 0 = not changed; ? = questionable; -/? = reduced or questionable effect) (adapted from Ranganath, 2008).

	Bigua-nide (Met-formin)	Thiazoli-dindione	α-Glucosi-dase inhibitor	Sulfo-nylurea	Glinides	Insulin	Amylin	Glucagon-like peptide-1 mimetics	Dipeptidyl peptidase-4 inhibitors
Insulin deficiency	0	0	0	+	+	+	0	+	+
Insulin resistance	+	+	0	0	0	0	0	+?	0
Hepatic glucose output	+	+	0	0	0	0	0	-?	0
Excess glucagon	0	0	0	0	0	0	-	-	-?
Gastric emptying	0	0	-	0	0	0	-	-	-/?
Body weight	0	+	0	+	0	+	-/?	-	0
B-cell mass	0	+	0	0	0	0	0	+	+
B-cell function	0	+	0	0	0	0	0	+	+

experiments (antihypertensive or hypertensive effect of GLP-1 (Barragán et al., 1996, 1999; Yu et al., 2003; Okerson et al., 2008)) especially those using the intracerebroventricular application (increase in blood pressure by GLP-1) may not be helpful (Isbil-Buyukcoskun and Gulec, 2004). The heart rate may be increased indirectly (Yamamoto et al., 2002) as well as a positive inotropic effect may be induced. Liraglutide decreases blood pressure. It is still a matter of speculation whether GLP-1–based drugs might be useful as adjunctive therapy in patients with decompensated heart failure. Improvements in high density lipoprotein cholesterol and triglycerides were reported (Blonde et al., 2006) but need further verification.

Exendin-4 has also extrapancreatic effects: increase in glucose transport in muscle (Moreno et al., 2007), glucose transporter expression and glycogen synthesis in liver (Arnés et al., 2008).

5.2. Pharmacokinetics (note: some data information were only available from a company)

The s.c. absorption of exenatide is quick. Its relative bioavailability is 93–97% and similar when exenatide is injected s.c. into the upper arm, abdomen or thigh (Calara et al., 2005). The starting dose of exenatide is 5 μg twice daily for 4 weeks, followed eventually by an increase to 10 μg (Fineman et al., 2002, 2004). Since exenatide is DPP-4 resistant, its pharmacological action lasts for 4-6 h after a single subcutaneous injection (Nielsen & Baron, 2003; Nielsen et al., 2004). It reaches peak plasma concentrations after approximately 2 h, its circulating half-life is 2.4 h, and it is predominantly eliminated by glomerular filtration (N.N., 2005; Kolterman et al., 2005). The pharmacokinetics of exenatide is linear with respect to AUC (dose-dependency), albeit not with respect to C_{max} (reviewed by Iltz et al., 2006). The V_d is 28.3 l (after a single s.c. dose).

Since exenatide will be degraded enzymatically in the kidneys, it is not recommended for patients with severe renal insufficiency (creatinine clearance<30 ml/min); no dose adjustment, however, is necessary in patients with mild to moderate renal insufficiency. Hepatic dysfunction is not expected to influence exenatide pharmacokinetics (see elimination pathways above). Obesity does not appear to modify the pharmacokinetic profile of exenatide. The fetal maternal exenatide concentrations are <0.017 (*ex vivo* study) (Hiles et al., 2003).

5.3. Side effects

Nausea is the most commonly (45-51%; placebo 7-23%) (Mikhail, 2008) reported adverse effect of exenatide (see also other GLP-1 receptor agonists), which lessens over time. It is more obvious in fasting subjects and is probably a direct central effect. Other adverse events occurring in >10% of patients are diarrhoea (12.8%), and vomiting (12.8%) (Buse et al., 2004; DeFronzo et al., 2005; Kendall et al., 2005). The etiology of nausea is not fully clear, but may be partly related to the delay in gastric emptying. Nausea is not the major reason for weight loss induced by exenatide, since there was no correlation between change in body weight and the duration of nausea (DeFronzo et al., 2005; Kendall et al., 2005).

Hypoglycaemic events are mainly observed when combinations are used: in 20–30% of the patients when being treated together with a sulfonylurea and in 13% of the patients treated in combination with a thiazolidinedione (Buse et al., 2004; Kendall et al., 2005; Zinman et al., 2007). When sulfonylurea doses were reduced, the incidence of hypoglycemia decreased from 26.9 to 6.1 events/patient–year (Nauck et al., 2007a). When exenatide produces hypoglycaemia (especially in combination therapy) the counter-regulatory responses to hypoglycaemia are unimpaired (Degn et al., 2004a). Hypoglycaemias were not observed when it was given together with metformin (DeFronzo et al., 2005).

Other side effects of exenatide are feeling jittery (12-15%), dizziness (9-15%), constipation (9%), sweating (8%), and backache (6%) (Mikhail, 2008).

Exenatide was rarely (5-10%) discontinued because of side effects (Buse et al., 2004; DeFronzo et al., 2005; Kendall et al., 2005, Heine et al., 2005; Mikhail, 2008).

40–50% of patients develop anti-exenatide antibodies with low binding affinity and low titres (Buse et al., 2004; DeFronzo et al., 2005; Kendall et al., 2005) which, however, did not affect patients' clinical glycaemic control in most cases. About 6% of patients had high titres of antibodies; in about one half of these the glycaemic response to exenatide appeared to be diminished (N.N., 2005).

In 2006 the first case of acute pancreatitis was reported in a patient, who had been treated with exenatide and neutral protamine Hagedorn insulin (Denker & Dimarco, 2006). Recently, the US Food and Drug Administration reviewed 30 post-marketing reports of acute pancreatitis in patients: an association between exenatide and acute pancreatitis has been suspected in some of these cases (N.N. Food and Drug Administration Information for Healthcare Professionals Exenatide, 2008); it is, however, not clear whether the incidence of acute pancreatitis in patients receiving exenatide is higher than expected in diabetic patients for which it is known to be increased generally. Most of the patients had an additional risk factor for pancreatitis such as gall stones, severe hypertriglyceridemia or alcoholism. A causal association with exenatide is not clear. Nevertheless US manufacturer labelling was updated in this respect giving the advice: "Patients should be informed that persistent severe abdominal pain, which may be accompanied by vomiting, is the hallmark symptom of acute pancreatitis. If pancreatitis is suspected exenatide and other potentially suspect drugs should be discontinued, confirmatory tests performed and appropriate treatment initiated." The problem of pancreatitis is unsolved and still to be discussed (Ahmad & Swann, 2008).

5.4. Drug and food interactions (absorption problems)

Exenatide should be administered 60 min before a meal (in accordance with its mechanism of action); it should not be administered after a meal.

Due to the delay of gastric emptying induced by exenatide, a modified absorption of oral compounds simultaneously given can be expected. A decrease of e.g. paracetamol (acetaminophen) plasma concentrations can be seen (Kolterman et al., 2003; Blase et al., 2005; Iltz et al., 2006). Compounds of which the effectiveness relies on a minimal drug concentration (e.g. oral contraceptives, antibiotics) should be given 1 h before an exenatide injection. Acid resistant preparations (e.g. proton pump inhibitors) should not be given simultaneously with exenatide. When e.g. digoxin (Kothare et al., 2005), lisinopril (Iltz et al., 2006) or warfarin are given 30 min after exenatide, the t_{max} values are delayed by 2 h; in the case of lisinopril, however, no clinical effect was observed. Exenatide decreases the AUC and C_{max} of lovastatin severely.

Exenatide does not appear to influence the pharmacokinetics of sulfonylureas or of metformin, used for a combination therapy (see above).

Erythromycin reverses the delay of stomach emptying induced by GLP-1 (Meier et al., 2005a).

5.5. Contraindications

Contraindications are ketoacidosis and kidney failure (see above).

Exenatide should not be used in type 1 diabetics although it was very recently claimed to have promising effects (interesting because of weight loss, see information above) (reviewed by Aaboe et al., 2009).

5.6. Comparison with other therapy regimes (insulin glargine) or replacement of insulin by exenatide

Exenatide has been compared with insulin glargine when either compound was added to metformin and a sulfonylurea because an

effective glucose control was not reached (Heine et al., 2005): fasting glucose concentrations were reduced more effectively by insulin glargine, albeit postprandial glucose reduction was better with exenatide. Patients receiving insulin glargine gained an average of 1.8 kg compared with a 2.3 kg weight loss observed in exenatide-treated patients; no significant differences were seen in levels of HbA_{1c} (reduction by 1.1% over 26 weeks) or in hypoglycaemias as a side effect (7.3 events/patient–year) compared with insulin glargine patients (6.3 events/patient–year) (Heine et al., 2005).

Replacing insulin treatment by exenatide therapy does not seem to be advisable (Davis et al., 2007). In a crossover non-inferiority study, the overall incidences of hypoglycaemia were <15% in patients on exenatide compared with 25% on insulin glargine treatment (Barnett et al., 2007). This was rather the same with respect to hypoglycaemias when it was compared with insulin aspart.

5.7. Aspects for the future

Several therapeutic implications need clinical confirmation: the durability of the weight loss, the ability to preserve functional B-cell mass and the applicability to other patients than type 2 diabetics. Long-term studies especially with cardiovascular end-points are needed to confirm the probable benefits of this new class of anti-diabetic drugs.

6. Longer acting GLP-1 analogues

Although intravenous or subcutaneous GLP-1 application could be useful for the short-term control of hyperglycaemia (Meier et al., 2004; Nauck et al., 2004c), long-term treatment of type 2 diabetes is necessary and application therefore, should be less than twice a day as for exenatide.

6.1. Liraglutide

Liraglutide (NN 2211) is a long-acting GLP-1 analogue with the following chemical modification (Arg34Lys substitution, and a glutamic acid and 16-C free-fatty-acid addition to Lys26) (Fig. 2) (Knudsen et al., 2000; Juhl et al., 2002). The fatty-acyl-GLP-1 structure binds to interstitial albumin at the injection site and the GLP-1 resembling structure is released slowly from the albumin complex to be absorbed into the circulation.

Liraglutide inhibits appetite (Hansen et al., 2001). The counter-regulation by glucagon induced by a hypoglycaemia is not impaired by liraglutide (Nauck et al., 2003).

Liraglutide inhibits apoptosis (Bregenholt et al., 2001) and increases B-cell mass (Rolin et al., 2002).

6.1.1. Clinics

The clinical effects of liraglutide are similar to those of GLP-1 (Saad et al., 2002; Juhl et al., 2002; Degn et al., 2004b). In phase II studies 14 weeks of treatment as monotherapy with 2 mg (the highest dose) reduced fasting plasma glucose and HbA_{1c} was lowered up to 1.75% from a baseline value of 8.1–8.5%. Liraglutide reduces HbA_{1c} by 0.7% (Madsbad et al., 2004; Mikhail, 2008). Patients experienced a weight loss of approximately 3 kg (1.2 kg corrected for placebo) (Vilsbøll et al., 2007) or at least weight gain was prevented (Nauck et al., 2004a, 2006). Overall liraglutide has similar effects like the incretin mimetic exenatide. Recently several studies called LEAD (Liraglutide Effect and Action in Diabetes) were presented on congresses and/or were published (Marre et al., 2009; Nauck et al., 2009): higher doses (1.2 and 1.8 mg) were much more effective than 0.6 mg with respect to various parameters such as HbA_{1c} in absolute terms and as a percentage of improvements with respect to the envisaged goal. Nausea did not increase in a dose-dependent manner. Liraglutide was superior to rosiglitazone (either compound was combined with glimepiride), liraglutide was superior to glimepiride (when both were combined with metformin) with respect to reduction of body weight and the occurrence of hypoglycemias whereas the glycemic control was the same.

Furthermore, liraglutide has been shown to significantly lower systolic blood pressure by 7–9 mm Hg (Vilsbøll et al., 2007). Atherosclerosis is a major contributor to morbidity and mortality in diabetes. Liraglutide improves parameters which are associated with atherosclerosis: it inhibits TNFα-induced PAI-1, VCAM-1, ICAM-1, and E-Selectin mRNA and protein secretion in an in vitro model of vascular endothelial cell dysfunction (Dear et al., 2007): E-selectin is involved in inflammation, recruiting leucocytes, VCAM is important for the immune system, recruiting monocytes to atherosclerotic sites, ICAM is an intercellular adhesion molecule and is involved in subarachnoid hemorrhage, and PAI-1 has an impact on thrombosis and cell migration.

6.1.2. Pharmacokinetics

Liraglutide (modified GLP-1–albumin complex) results in a favourable pharmacokinetic profile because it resists DPP-4 metabolism, is slowly absorbed from injection site with a maximum after 9-12 h (Jonker et al., 2008), and its renal clearance is reduced. It is first absorbed in zero-order kinetics and later within first-order kinetics, the absolute bioavailability is 51% (Jonker et al., 2008), the V_d is very low indicating that the compound is concentrated mainly in the central compartment, and the clearance is in the range of 6 ml/h × kg and not dose-dependent (Jonker et al., 2008). After s.c. injection, liraglutide has a half-life of 10–14 h allowing once-daily injection (Agerso et al., 2002; Elbrond et al., 2002; Jonker et al., 2008). The acyl moiety promotes non-covalent binding to albumin with 1–2% of liraglutide circulating as the non-albumin bound free peptide (Knudsen et al., 2003). The variations of plasma levels are lower when liraglutide is given once compared to when exenatide is given twice a day (Jonker et al., 2008).The liraglutide dose is between 0.45 and 0.75 mg daily (Madsbad et al., 2004; Nauck et al., 2006, Vilsbøll et al., 2006).

Liraglutide kinetics is not significantly modified in patients with renal kidney insufficiency (Jacobsen et al., 2007, 2008) or liver impairment (Flint et al., 2008).

6.1.3. Side effects

As expected from exenatide, GI symptoms (e.g., nausea, vomiting) are prominent adverse effects of liraglutide and led to discontinuation in 3% of patients (Vilsbøll et al., 2007). Side effects are generally mild and transient (Nauck et al., 2006; Vilsbøll et al., 2006). No patient experienced any hypoglycaemic episodes, and there was no anti-liraglutide antibody induction (Vilsbøll et al., 2007) as it was observed for exenatide (see above).

In Table 6 liraglutide is compared with exenatide. Long term data are needed to fully assess the potential of liraglutide in treatment of type 2 diabetes.

The impact of liraglutide on the absorption of simultaneously administered drugs is summarized and appears to be low (Zdravkovic et al., 2008).

Table 6
Comparison of effects with respect to exenatide and liraglutide (adapted from Ranganath, 2008).

Exenatide	Liraglutide
Twice daily injection	Once daily injection
Plasma levels: rise to a peak and then a fall	More or less peakless plasma levels
Significant weight loss	Weight loss
Good effect in HbA_{1c}	Good effect on HbA_{1c} and fasting glucose
Antibodies to exenatide	No antibodies to liraglutide
Injection site reactions occur	Neglible injection site reaction

6.2. Exenatide long-acting release (exenatideLAR)

The action of one subcutaneous injection of exenatide lasts for only 6–8 h. Exenatide long-acting release (LAR) is a special preparation containing a polylactide-glycolide microsphere suspension with biodegradable microparticles (polymers: Medisorb®) with 3% exenatide peptide. This leads to a sustained dose-dependent glycaemic control in diabetic rats, for up to 28 days after only one s. c. injection (Gedulin et al., 2005). It was planned to be given once weekly to patients (Kim et al., 2006).

Experience with this dose regime of exenatideLAR indicates a much greater reduction in fasting glucose concentrations and HbA1c compared with normal exenatide administered twice daily (Kim et al., 2006). In a small, trial with patients suboptimally controlled by metformin and/or diet, 15-week treatment with 2.0 mg LAR once a week showed a reduction in HbA_{1c} by 1.7% from a baseline value of 8.5% and a weight loss of roughly 4 kg (Kim et al., 2007).

Altogether the efficacy with respect to fasting blood glucose and postprandial glucose appears to be similar and the side effects are not different compared to normal exenatide. The pharmacokinetics will be different (Trautmann et al., 2008) although many details are not yet available. It has to be mentioned that 14 injections of normal exenatide is now reduced to once each week, that the exenatide levels in the periphery are kept a little bit lower (to avoid peak values mainly responsible for above mentioned side effects), that there is no tachyphylaxis (vanishing of effects) as often recorded after continuous application of hormones, and that the time point of injection is not important at all.

6.3. Albiglutide (Albugon)

Recombinant albumin-GLP-1 fusion proteins have been developed that mimic the full range of GLP-1 actions (Baggio et al., 2004). Albiglutide is one example: it stimulates GLP-1 receptor–dependent pathways coupled with glucose homeostasis and gastrointestinal motility, improves insulin secretion, and reduces blood glucose (Baggio et al., 2004). Little clinical information is currently available regarding this drugs safety in humans (Kim et al., 2003; Baggio et al., 2004). Albiglutide has less potent anorectic effects in animal studies compared to exenatide and liraglutide, and it is not clear whether this disparity is secondary to the impaired blood–brain barrier's permeability due to the larger molecule and not to albiglutide itself (Baggio et al., 2004).

6.4. Taspoglutide (Ro 1583)

Taspoglutide is a matrix free sustained release formulation for GLP-1 and is just going to be converted to phase III studies.

6.5. Other compounds (Table 7)

The following strategies are used to circumvent rapid renal filtration: modification of the molecule so that the incretin binding to circulating plasma proteins is increased; this is performed by acylation, i.e. attachment of a fatty acid side-chain; see liraglutide, or by PEGylation, i.e. attachment of polyethylene glycol chains. An N-terminal modification will result in prevention of degradation by DPP-4; this is done by attaching chemical groups or by substituting amino acids with others. Another way is C-terminal modification which will reduce renal clearance; this is done by either attaching fatty acids or PEG moieties to facilitate binding to blood proteins or a direct fusion with a blood protein like albumin or transferrin.

CJC-1131 (Conjuchem) is a synthetic GLP-1 analogue produced by a single amino acid substitution and by attachment of a chemical reactant at the carboxyterminal end; it allows for covalent binding to endogenous serum albumin and is protected against DPP-4 degradation (Guivarch et al., 2004). Its half-life is similar to that of circulating albumin, approximately 10–15 days (Sinclair & Drucker, 2005a; Leon et al., 2006). It does not seem to be of further clinical interest.

CJC-1134 is a similar conjugate of albumin, albeit with exendin-4 (Baggio & Ducker, 2006; Baggio et al., 2006; Kim et al., 2003).

Because of the naturally limited intestinal absorption of GLP-1 a series of GLP-1 analogues via site-specific conjugation of biotin-NHS and/or of biotin-poly(ethylene glycol)-NHS at Lys26 and Lys34 of GLP-1 (7–36), respectively, was developed. The resultant GLP-1 analogues, Lys26,34-DiBiotin-GLP-1 (DB-GLP-1) and Lys26-Biotin-Lys34-(Biotin-PEG)-GLP-1 (DBP-GLP-1), were investigated. DB-GLP-1 and DBP-GLP-1 show enhanced GLP-1 intestinal bioavailability. DBP-GLP-1 concentration in plasma rapidly increased 30 min after oral administration in rats. Both DB-GLP-1 and more DBP-GLP-1 had markedly better proteolytic stabilities than native GLP-1 and preserved their biological and pharmacological activities (Chae et al., 2008).

It was reported that site-specific PEGylated GLP-1 at the Lys34 position profoundly improves its enzymatic stability while retaining its biological activities, and thus enhances its therapeutic potential in type 2 diabetic *db*/*db* mice (Lee et al., 2005, 2006; Youn et al., 2007). Both show potent in vitro insulinotropic effects which resemble that of native GLP-1. Altogether these orally active bioconjugated GLP-1 drugs might be considered as potential oral antidiabetic agents for type 2 diabetes mellitus.

In general site-specific bioconjugation offers a convenient means of developing also orally active peptide drugs. In general many different types of peptide bioconjugation, with vitamins, fatty acids, bile acids, and PEG, have been used to develop orally active peptide agents (reviewed by Chae et al., 2008). For an oral application of GLP-1 Eligen™ technology is under investigation (Arbit et al., 2007). Eligen is a drug delivery agent due to a conformational complex with the peptide which can protect against degradation and helps the peptide to be absorbed. In HTS (high throughput screening) for an oral incretin mimetic Boc5 (a substituted cyclobutane) was identified (Chen et al., 2007).

Even intranasal administration of exenatide and pulmonary administration of GLP-1 as a Technosphere powder are under investigation (Blase et al., 2008; Cassidy et al., 2008).

For the GLP-1 receptor agonist ZP10 a prolonged-release formulation exists (Thorkildsen et al., 2003). For the novel, rationally designed peptide ZP10A (H-HGEGTFTSDLSKQMEEEAVRLFIEWLKNGGPSS-GAPPSK KKKKK-NH2) the binding affinity for the human GLP-1 receptor is 4-fold higher than that of GLP-1 (7-36) amide (Thorkildsen et al., 2003). An antiapoptotic effect was demonstrated (Thews et al., 2008).

Albiglutide is generated by genetic fusion of a DPP-4 resistant GLP-1 dimer to human serum albumin (Stewart et al., 2008).

More modifications/substitutions of GLP-1 are summarized in a review (Green & Flatt, 2007) (Table 7).

Table 7
Other compounds.

Compound	Chemistry
CJC-1131	GLP-1 plus Gly^{37} replaced with Lys^{37}, Lys^{37} contains a reactive chemical linker, Ala^{8} replaced with D-Ala^{8}
CJC-1134-PC	same molecule as CJC-1134 except that it originates from exendin-4(1-39) instead of GLP-1
ZP 10 (AVE0010), ZP 10A	going to be tested positively (Rosenstock et al., 2008a) exendin-4(1-39) plus C-terminally extended with 6 Lys residues
BIM51077	structure not disclosed
LY307161	31 amino acid analog of GLP-1; long acting
LY315902	GLP-1 plus C8 fatty acid chain linked to Lys^{34}, Lys^{26} replaced with Arg^{26}, His^{7} replaced with des-His^{7} → half-life of 3-6 hours
PEG-DAPD	PEGylated DAPD; DAPD stands for dual acting peptide for diabetes = GLP-1/glucagon hybrid peptide containing a maleimide-polyethylene glycol polymer
Taspoglutide (Ro 1583)	Matrix free sustained release formulation for GLP-1

Additionally a GLP-1/glucagon hybrid peptide was engineered that acts both as a GLP-1 receptor agonist and as a glucagon receptor antagonist; it is named "dual-acting peptide for diabetes" or DAPD.

6.6. Gene therapy with respect to GLP-1

A single administration of rAd-GLP-1 (recombinant adenoviral vector expressing GLP-1) via the tail vein into diabetic (streptozotocin) nonobese mice with severe combined immunodeficiency (NOD/SCID) resulted in remission of diabetes within 10 days, and normoglycaemia remained until the experiment was terminated (Liu et al., 2007). Intramuscular gene transfer of the plasmid coding for the GLP-1/Fc peptide in *db/db* mice demonstrated that its expression normalized glucose tolerance by enhancing insulin secretion and suppressing glucagon release (Kumar et al., 2007). Hence gene therapy leading to overexpression of GLP-1 related peptides may have a potential in the future.

7. DPP-4 (dipeptidyl-4) inhibition as a drug target

GLP-1 as an endogenous peptide is characterized by a very short half-life of 2-3 min due to the hydrolysis by DPP-4 (Fig. 2). Thus DPP-4 came into the focus as a relevant drug target (Holst & Deacon, 1998) since specific inhibitors would prevent the rapid fall of GLP-1 in circulating plasma. Two inhibitors of DPP-4 enzyme activity are in the market and many more are going to be developed.

7.1. DPP-4 enzyme characteristics

DPP-4 was already described in 1966 (Hopsu-Havu & Glenner, 1966); it is also known as CD26 regarding its activity in the immune system (see below). It is a 110 kDa plasma membrane-spanning cell-surface glycoprotein ectopeptidase ubiquitously expressed in tissues such as liver, lung, kidney, intestinal brush-border membranes, lymphocytes, and endothelial cells (Barth & Schulz, 1974; Elovson, 1980; Kreisel et al., 1984; Mrazkova et al., 1986; Imai et al., 1992; Darmoul et al., 1994; Kozakova et al., 1998; Mentlein, 1999; De Meester et al., 2000, 2003). The enzyme is also present in the circulation since the extracellular domain of DPP-4 can be cleaved from its membrane-anchored form and protrudes from endothelial cells into plasma, thereby retaining its full enzymatic activity. DPP-4 is also present in other fluids besides serum (Iwaki Egawa et al., 1998): in urine, seminal (Wilson et al., 1998) and amnion liquid (reviewed by Hildebrandt 2004). Serum DPP-4 can also bind plasminogen and streptokinase (Gonzalez Gronow & Weber, 1998).

The enzyme DPP-4 preferentially cleaves peptides with a proline or alanine residue in the second last aminoterminal position (see above, Fig. 2) and removes X-Pro and X-Ala dipeptides from the N-terminal end of peptides and proteins which may have relevance in inhibiting degradation by unspecific proteases (Yaron & Naider, 1993; Mentlein et al., 1993; Kieffer et al., 1995;Deacon et al., 1995a, 1995b;Holst & Deacon, 1998;Kieffer & Habener, 1999; Deacon et al., 2000; Deacon, 2004). DPP-4 inhibitors act by binding to the enzyme pocket, leaving the incretins GLP-1 and GIP circulating in intact (active) form. The modification of a protein in the proline region (DPP-4 enzyme) has a general impact since protein influences the secondary structure of a protein and, therefore, its biological activity (reviewed by Hildebrandt, 2004).

Many substrates of DPP-4 have been identified (Table 8): gastrointestinal hormones, neuropeptides, cytokines, and chemokines possessing a proline in the right position are in vitro substrates of DPP-4 (Mentlein, 1999; De Meester et al., 2000, 2003).

The expression of DPP-4 may be increased by a proline diet (Suzuki et al., 1993) and by interferon-γ (Dang et al., 1991; Schmitz et al., 1996).

DPP-4 is not only responsible for inhibition of peptide degradation, but has also an effect on immunomodulation, cell adhesion and cell movement. These effects are mediated by the rather identical functional protein, also called T-cell antigen CD26, but not by its enzymatic activity (Bednarczyk et al., 1991). It has an impact on the immune system with respect to T-lymphocyte memory cells activity and movement (Masuyama et al., 1992, 1999), differentiation of lymphocytes as a thymic maturation marker in differentiation of lymphocytes, and the anchoring of the ecto-adenosin deaminase in the lymphocyte membrane (involved in lowering extracellular adenosine) (Blanco et al., 1996; Iwaki Egawa et al., 1998).

Table 8
Substrates of DPP-4 (Mentlein, 1999; De Meester et al., 2000, 2003),

Substrates which may have clinical relevance	GLP-1, GLP-2, GIP, NPY, PYY, PACAP (pituitary acenylate cyclase-activating polypeptide), Substance P, RANTES (regulated on activation normal T cells expressed and secreted).
Substrates with questionable clinical relevance	GRH (growth hormone-releasing hormone), IGF-1, Prolactin, HCG (human chorionic gonadotropin), Bradykinin, Interleukin-1ß, Interleukin-2

The enzyme may be released from activated T-lymphocytes (Uematsu et al., 1996) and hepatomas of rats (Hanski et al., 1988). Cell adhesion (Hanski et al., 1985), and cell movement across the extracellular matrix (reviewed by Hildebrandt, 2004) were observed. This means that DPP-4 plays an important role in immune system, being a T-cell co-stimulator (Barnett, 2006), activating T-lymphocytes and cleaving numerous physiological peptides (Gorrell, 2005; Green et al., 2006). Note: all these additional effects may be relevant for unselectivity of DPP-4 inhibitory drugs as discussed later.

Clinically DPP-4 may also be linked to some immune diseases: low serum DPP-4 in patients with systemic lupus erythematodes (Stancikova et al., 1992), in synovial fluid of patients with rheumatoid arthritis (Kamori et al., 1991), and in Morbus Crohn patients (Th-1 cytokine profile) (Willheim et al., 1997). The clinical data are not conclusive since DPP-4 has contradictory effects, increasing and inhibiting immune responses (reviewed by Hildebrandt, 2004).

Interestingly, mice lacking the DPP-4 gene appear to be protected against obesity and insulin resistance (Conarello et al., 2003).

7.2. DPP-4 inhibitors

DPP-4 inhibitors increase the effects of above mentioned enzymes. The therapeutic focus is on increasing the activity of GLP-1 for type 2 diabetics. They are not incretin mimetics such as GLP-1, but incretin enhancers. DPP-4 inhibitors mainly act indirectly via incretin hormones which is evident from animal studies: their beneficial effect is lost in mice lacking the GLP-1 and GIP receptors (Hansotia et al., 2004) or lacking the DPP-4 enzyme (Mitani et al., 2002).

Small-molecule DPP-4 inhibitors have been developed that can be used orally. Typically, the inhibitors reduce serum DPP-4 activity to a high degree with some inhibition maintained for 24 h after one dose which allows once daily treatment (Åhren et al., 2004a, 2004b; Herman et al., 2005). There is evidence that plasma DPP-4 must be inhibited by rather 80% for an effectively high and sustained GLP-1 level increase since it has to be kept in mind that DPP-4 is also present in tissues with still potentially degrading activity for GLP-1.

Many effects different from incretin mimetics exist (Table 4).

7.2.1. Clinics

The DPP-4 inhibition is accompanied by a rise in postprandial levels of intact GLP-1 (Åhren et al., 2004a, 2004b; Herman et al., 2005; Nauck & El-Quaghlidi, 2005) and GIP. Though the total pool of the peptides is decreased during DPP-4 inhibition (El-Ouaghlidi et al., 2007) (probably a negative feedback mechanism of GLP-1 on its secretion), the levels of active hormones are increased (Mari et al., 2005). DPP-4 inhibitors mimic the therapeutic effects of the incretin mimetics including stimulation of insulin secretion, inhibition of

glucagon secretion and possibly preservation of B-cell mass (Deacon, 2004) and inhibition of apoptosis (see above Fig. 5) (Drucker et al., 1987; Deacon 2004). Two compounds are in the market (Fig. 6). As shown for sitagliptin DPP-4 inhibitors improve HOMA-ß, a marker of fasting insulin secretion, the proinsulin-to-insulin ratio, and the insulinogenic index. The moderate increase in GLP-1 by DPP-4 inhibition is probably not sufficient for a direct central effect on satiety. In contrast, DPP-4 inhibitors are so far not believed to alter gastric emptying (Vella et al., 2007) and are generally not associated with weight loss (reviewed by Aaboe et al., 2009) (Table 9). However, compared with sulfonylureas, thiazolidinediones, and insulin, DPP-4 inhibitors have the advantage that patients at least do not gain weight. Sitagliptin reduces weight by approx. 1.5 kg or is weight neutral whereas the sulfonylurea glipizide increases weight by approx. 1.1 kg.

Sitagliptin rather doubles the GLP-1 levels after a meal for a long time (Herman et al., 2005, Åhren et al., 2004a; Pratley et al., 2006; Rosenstock et al., 2006a; Garber et al., 2006).

Incretin enhancers do not pass the blood-brain barrier which may be the reason that there is rather no effect on satiety compared to GLP-1. The in vivo effect of exenatide is much greater than that of sitagliptin in rodents with respect to inhibition of food intake, amelioration of weight gain, and better inhibition of gastric emptying (Gedulin et al., 2007).

Sitagliptin and vildagliptin therapy in comparison with placebo resulted in an HbA_{1c} reduction of approximately 0.7%. There is no major difference in decreasing HbA_{1c} by either exenatide or the DPP-4 inhibitors sitagliptin and vildagliptin being 0.8 and 0.7% (Mikhail, 2008).

DPP-4 inhibitors are not associated with weight gain or oedema (except for combination with glitazones).

Clinical studies with both vildagliptin (Åhren et al., 2004a, 2004b; Åhren, 2006; Rosenstock et al., 2008b; Dejager et al., 2006; 2007; Pi-Sunyer et al., 2007) and sitagliptin (Scott et al., 2007; Aschner et al., 2006a; Charbonnel et al., 2006) have shown their efficacy in the treatment of type 2 diabetes. Compared with metformin (52 weeks) (Dejager et al., 2006;) and rosiglitazone (24 weeks) (Rosenstock et al., 2007b) in drug-naive type 2 diabetic patients, treatment with vildagliptin as monotherapy showed slight inferiority and non-inferiority, respectively, with regards to lowering HbA_{1c}. DPP-4 inhibitors can be used as monotherapy (patients with type 2 diabetes uncontrolled by diet) and in combination (Mikhail, 2008). A combination of either sitagliptin or vildagliptin with metformin was recently approved; the HbA_{1c} is decreased by an extra of 0.7% compared to metformin alone. The addition of sitagliptin to glimepiride reduced the HbA_{1c} more effectively (0.89% versus 0.57%). As add-on therapy, both DPP-4 inhibitors induce additional lowering of HbA1c with approximately 0.8–1.0% (Charbonnel et al., 2006; Bosi et al., 2007; Fonseca et al. 2007; Garber et al. 2007).

In general DPP-4 inhibitors seem to have positive effects on B-cell mass (Pospisilik et al., 2003; Mu et al., 2006).

DPP-4 inhibition seems to be well tolerated. Few adverse effects in humans have been demonstrated thus far in clinical trials (Raz et al., 2006; Rosenstock et al., 2006c; Åhren et al. 2004a). No characteristic pattern of adverse events has been associated with the use of vildagliptin (Åhren et al., 2004a; Åhren et al., 2004b) or other DPP-4 inhibitors (Scott et al., 2005; Hanefeld et al., 2005; Brazg et al., 2005).

There is practically no risk for hypoglycaemias (Nauck et al., 2007b; Aschner et al., 2006a; Charbonnel et al., 2006) which is due to the fact that the therapeutic effect of indirectly elevated GLP-1 is dependent on the glucose concentration (Nauck et al., 2007b) (for comparison e.g. glipizide (32%)). The risk of hypoglycaemic episodes during monotherapy with a DPP-4 inhibitor or a DPP-4 inhibitor in combination with metformin is negligible.

7.2.2. Sitagliptin (MK-0431)

Sitagliptin is the first compound of its class introduced in the market as a DPP-4 inhibitor. Its chemical structure is (2R)-4-Oxo-4[3-(trifluoromethyl)-5,6-dihydro[1,2,4]triazolo[4,3-a]pyrazin-7(8H)-yl] 1-(2,4,5-trifluorophenyl]butan-2-amide (Fig. 6). It has an IC_{50} of 18 nM.

It is approved as a monotherapy in the U.S. and as an add-on therapy to metformin or glitazone, when metformin plus diet are not sufficient (Aschner et al., 2006c; Charbonnel et al., 2006). In Europe a monotherapy with sitagliptin primarily for newly diagnosed diabetes or during therapeutic failure of other oral antidiabetics is not allowed; approved and effective are combinations of sitagliptin with metformin, insulin sensitizers (glitazones), and a sulfonylurea or in a triple combination with both metformin and a sulfonylurea, but not with a glinide (Karasik et al., 2006; Raz et al., 2006; Rosenstock et al., 2006b). The combination with metformin shows an improvement of the B-cell function (Xu & Williams-Herman, 2007; Migoya et al., 2007); probably different mechanisms are involved.

Table 9
Comparison of GLP-1 and DPP-4 inhibitors.

GLP-1 receptor agonists (GLP-1 mimetics)	DPP-4 inhibitor
Parenteral administration (s.c.), administration 60 min before morning and evening meal	Oral administration
Short acting*	Long acting
Strong effect	Effect less strong compared with incretin mimetics (except decrease in HbA_{1c})
Selective (one single target = GLP-1 receptor)	Nonselective (multiple targets: other enzymes, many DPP-4 substrates) Non-specific: GLP-2, NPY, SP, PACAP and others
Add-on therapy (metformin, sulfonylurea or to a combination of metformin and a thiazolidinedione)	Monotherapy or adjunctive therapy (combinations as shown left)
Increase in levels of exogenous GLP-1 (supraphysiologic, sustained)	Increase in endogenous GLP-1 concentrations (close to physiologic, retained diurnal pattern) and GIP
Stimulated insulin secretion	Stimulated insulin secretion
Inhibited glucagon secretion	Inhibited glucagon secretion
No change in fasting glucose	No change in fasting glucose
Marked reduction prandial glucose	Slight reduction in prandial glucose
Reduction in HbA_{1c} (~ -0.8%)	Reduction in HbA_{1c} (~ -0.7%)
Inhibition of gastric emptying	No effect on gastric emptying
May induce early satiety	No clear effect on satiety
Drug overdosage problematic	Drug overdose is non-toxic (except liver toxicity and QT prolongation for vildagliptin)
Potential of CNS side effects	No CNS side effects (no passing the blood-brain barrier)
Weight loss	Weight neutral (no effect)
Side effects well known (e.g. probably pancreatitis)	Side effects still to be evaluated (completely)
Increased hypoglycaemias, especially in combination with sulfonylureas	Low/no incidence of hypoglycaemias
Dose-related nausea	No nausea or vomiting
Not recommended in severe renal failure	Dose adjustment in severe renal failure (for only some compounds)

* Effect may be extended by pharmaceutical technology manipulations (once weekly injections).

The normal dose is 100 mg once a day (Raz et al., 2006; Aschner et al., 2006a, 2006b, 2006c; Kipnes, 2007; Karasik et al., 2006; Rosenstock et al., 2006b).

7.2.2.1. Pharmacokinetics (note: some data were obtained from a company). Sitagliptin is well absorbed and its oral bioavailability is 87%. The maximum plasma concentration after intake of 100 mg sitagliptin is reached after 1 to 4 hours. Binding to plasma proteins is low (38%), the V_d is 198 litres. 70-80% of a dose are renally excreted unchanged, and only a small amount is metabolized in which mainly CYP3A4 and CYP2C8 are involved. Its plasma half-life is between 8 and 14 hours.

The dose should not be changed when it is combined with other antidiabetic drugs (e.g. metformin or glitazones). In kidney malfunction or even renal failure the dose of sltagliptine has to be reduced one half or one fourth or sitagliptin should even no longer be used.

7.2.2.2. Side effects and contraindications. Medication with DPP-4 inhibitors appears to be reasonably safe. Side effects of sitagliptin are cold (running nose), stuffy nose and diarrhoea, also sore throat, headache and arthralgias were observed. Recently, postmarketing reports of anaphylaxis, angioedema, and rashes, including Stevens-Johnson syndrome, in sitagliptin-treated patients have emerged. A causal link to the drug, however, is not known in some cases.

Contraindications are rarely known except severe kidney malfunction.

7.2.2.3. Drug interactions. The combination of sitagliptin with pioglitazone results in peripheral oedema (4%). Glitazones probably posses a cardiotoxic effect (increased heart attack) and worsening of heart failure (Slørdal & Spigset, 2006). It is not sure whether the increase of cardiotoxic effects is only a result of this combination therapy.

Though CYP3A4 and CYP2C8 are partly involved in the degradation of sitagliptin, no drug interactions are expected except when this metabolizing way is extremely because of a kidney failure. In this case ketoconazole, Itraconazole, ritonavir, clarithromycin and possibly other CYP3A4 inhibitors may be relevant with respect to drug interactions.

Plasma digoxin is slightly increased by sitagliptin; an adaptation of doses of either drug is not necessary.

An interaction with any antidiabetic drugs has not been observed (Mistry et al., 2008).

7.2.3. Vildagliptin (LAF237)

Vildagliptin is the second DPP-4 inhibitor being approved in Europe. Sitagliptin and Vildagliptin are different in molecular structure (Fig. 7) and in pharmacokinetics. Sitagliptin is a competitive antagonist at the enzyme, and vildagliptin (as saxagliptin, see below) is a substrate for DPP-4 and inhibits the target (receptor or enzyme) molecule. Vildagliptin has a high affinity (Åhren et al., 2007; Villhauer et al., 2003; El-Ouaghlidi et al., 2003).

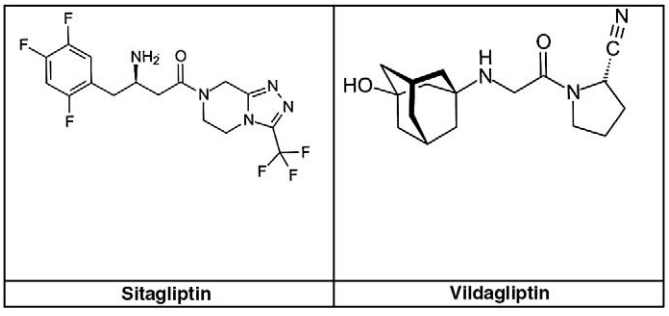

Fig. 7. Chemical structures of sitagliptin and vildagliptin.

7.2.3.1. Clinical aspects. Note: 100 mg doses of vildagliptin have been used in many studies, but only 50 mg are approved. Some above mentioned clinical results as well as some side effects (see below) have to be recognized under this aspect.

The in vitro actions have translated into significant effects in improving glycaemic control in type 2 diabetic patients, as illustrated by the clinically meaningful reductions in HbA_{1c} (by 0.8%) observed over 24 weeks (Rosenstock et al., 2007a) and 1 year (Schweizer et al., 2007) when a monotherapy of 100 mg/day is used. This was also observed using over 52 weeks a combination of vildagliptin 50 mg/day with metformin (Åhren et al., 2004a). Vildagliptin is used as a monotherapy or in combination with metformin (50 mg together with 850 mg metformin). Vildagliptin (as sitagliptin) may be used as monotherapy in patients who cannot tolerate metformin or sulfonyureas. Sitagliptin may be used as alternative to metformin in modest renal insufficiency. 100 mg vildagliptin can be combined with metformin or glitazone, but only 50 mg should be combined with a sulfonylurea (no higher effect when 100 mg are used.

Mechanistic studies in type 2 diabetics indicate that vildagliptin increases fasting and postprandial GLP-1 levels, improves B-cell sensitivity to glucose, A-cell functions, and insulin sensitivity, reduces postprandial lipaemia but exerts no clinically important effect on gastric emptying (Garber et al., 2006; Pratley et al., 2006; Rosenstock et al., 2006a). These effects lead to improved glucose tolerance and a reduction in fasting plasma glucose levels. At a dose of 100 mg once daily, fasting and postprandial glucose concentrations were reduced after 4 weeks of vildagliptin treatment and plasma glucagon concentrations were suppressed and the ratio of insulin to glucose was increased (Åhren et al., 2004b). An increased insulin secretory rate was observed with vildagliptin (Balas et al. 2007): calculation of the insulin secretory rate area under the curve (ISR) divided by the glucose AUC showed significantly improved insulin response at 0–30 min, 0–120 min and 0–840 min. Vildagliptin improves glucose-dependent pancreatic A-cell function in type 2 diabetes mellitus, as shown by reduced glucagon levels in the postmeal period (Åhren et al. 2004b; Azuma et al., 2008). The reduction in glucagon/insulin ratio is associated with reduced endogenous glucose production during both the postprandial period and the postabsorptive period (Balas et al. 2007). These results illustrate the dual effects of vildagliptin to improve glucose tolerance during meals and to directly reduce fasting hepatic glucose production. Clinical trials indicate that these mechanisms of action are associated with clinically significant improvements in glycaemic control as assessed by HbA_{1c} when vildagliptin is used alone or in combination, in patients with type 2 diabetes. Insulin sensitivity is significantly improved following meal ingestion for up to 52 weeks (Åhren et al., 2005). Such improvement could be an indirect effect of improved glycaemia, or related to glucagon reduction, but it may also be a direct effect shown in a hyperinsulinaemic euglycaemic clamp study in which vildagliptin improved insulin sensitivity under conditions where neither glucagon nor glucose toxicity could explain the improved insulin-mediated glucose disposal rate.

Vildagliptin has no effect on gastric emptying or rate of entry of ingested glucose into the systemic circulation (Vella et al., 2007) which is in contrast to GLP-1 (Naslund et al., 1999b; Kolterman et al 2000; Meier et al., 2003a; Kolterman et al., 2005). DPP-4 inhibitors are generally not associated with a deceleration of gastric emptying, perhaps due to the modest increase of postprandial plasma levels of intact (biologically active) GLP-1 (doubled to 15–25 pmol/l). For vildagliptin there exists one opposing outcome demonstrating an inhibition of gastric emptying (Dardik et al., 2003).

Like sitagliptin vildagliptin therapy does not result in weight gain.

B-cell function is improved by vildagliptin treatment over 1 year in patients with type 2 diabetes, indicated by measuring C-peptide secretion after meal ingestion, (Åhren et al., 2005). Levels of proinsulin during meal ingestion are reduced by vildagliptin (Åhren et al., 2007); proinsulin is an additional marker of abnormal B-cell function.

Fasting lipolysis is decreased by vildagliptin (Azuma et al., 2008). Postprandial hypertriglyceridaemia is an important metabolic abnormality in many patients with type 2 diabetes mellitus; animal studies suggest that incretin enhancement may reduce intestinal triglyceride absorption (D'Alessio & Tso 2005). Postprandial triglyceride-rich lipoprotein levels were reduced (Matikainen et al., 2006): this happens with respect to total serum triglycerides and chylomicron triglycerides, reflecting reductions in chylomicron apolipoprotein B-48 and chylomicron cholesterol.

As already shown for GLP-1 alone a combination of GLP-1 with a DPP-4 inhibitor has positive effects on B-cell viability and proliferation in a model of B-cell regeneration (partially pancretectomized rats) (Joanny et al., 2007).

Vildagliptin monotherapy, either 50 mg twice daily or 100 mg once daily, showed in preliminary reports of longer phase III sustained efficacy but non-inferiority compared with metformin after 1 year of therapy, (Dejager et al., 2006); it has to be emphasized that vildagliptin was better tolerated than metformin. Similarly, vildagliptin was as effective as rosiglitazone in direct comparison monotherapy study (Rosenstock et al., 2006a) and also produced significant reductions in HbA_{1c} when used in combination with metformin (Garber et al., 2006). Since metformin increases GLP-1 being a GLP-1 secretagogue and not a DPP-4 inhibitor (Sinha Roy et al., 2007), the clinical observation to combine metformin with a DPP-4 inhibitor is reasonable.

The DPP-4 inhibitor vildagliptin enhances the HbA_{1c} reduction when already induced by insulin in type 2 diabetic patients (Fonesca et al., 2007).

7.2.4. Side effects and contraindications

Hypoglycaemias are rare in response to vildagliptin combined with pioglitazone (0.3%) but were higher with pioglitazone being used alone (1.9%). Pioglitazone increased body weight (1.4 kg) which is further increased using a combination with 100 mg vildagliptin (2.7 kg).

Adverse effects of sitagliptin and vildagliptin were nasopharyngitis (6.4%), urinary tract infection (3.2%), and headache (5.1%), although placebo effects are close to these values (Mikhail, 2008). There are some hints on skin lesions.

The combination with pioglitazone increased the incidence of peripheral oedema.

Vildagliptin should not be used by patients with impaired kidney function or being dialysed or having a severe liver disease.

7.2.5. Drug interactions / combinations

A vildagliptin dose of 100 mg (approved are 50 mg in Germany) daily should be reduced to 50 mg when combined with other drugs such as sulfonylurea and can later be increased again but not to more than 100 mg. There is no interaction with food.

The metabolism of vildagliptin is not influenced by P450 enzymes so that drug interactions by this mechanism can not be expected.

7.3. Nonselectivity as a problem

In view of the widespread expression of DPP-4 on many cell types (see above), unselective effects have to be expected. Taking into account the large number of potential substrates for DPP-4 (Table 8) (Mentlein, 1999; De Meester et al., 2000) the aspect of nonselectivity is a major issue with respect to long-term safety. Since DPP-4 enzymes metabolise a wide variety of peptides, they potentially affect other regulatory systems and have pleiotropic additional effects (Hildebrandt et al., 2000; Durinx et al., 2000; Gorrell, 2005).

PACAP (pituitary adenylyl cyclase-activating peptide) is one of the DPP-4 substrates (Mentlein et al., 1993), but the inhibition of PACAP degradation in porcine pancreas is not associated with an acute effect on endocrine secretion (Hjøllund et al., 2007).

Other substrates of DPP-4 are trypsinogen (Erlanson Albertsson & Larsson, 1988; Heymann et al., 1986) and procolipase (which has impact on enterostatin by which the lipid uptake is regulated) (Bouras et al., 1996). The inactivation of GH-RF (somatoliberin) and of other mitogens may be inhibited by DPP-4 inhibitors.

GLP-2 degradation will be inhibited by DPP-4 inhibitors which will increase its activity (Mentlein et al., 1993); it has effects on intestinal trophic activity (proliferation), suppresses parathormone, decreases bone resorption and increases gut motility.

The inhibition of NPY (neuropeptide Y) degradation has an impact on its orexigenic effect since intact NPY stimulates food intake and feeding motivation (Karl et al., 2003b). The not degraded NPY is one of the most orexigen peptides (Bray, 1993; Chance & Fischer, 1993; Karydis & Tolis, 1998), and by truncating this peptide its receptor preference is modified (Grandt et al., 1993). It would be expected that diminishing NPY interaction with NPY1 receptors will not only modify hunger and satiety, but also the GI motility (Chen et al., 1997). It is also involved in modifications of behavioural tests; DPP-4 deficient rats exhibit increased pain indicative of a reduced stress-induced analgesia (Karl et al., 2003a). Psychoneuroendocrine effects may perhaps been underestimated by not concerning the less degradation of NPY (also substance P) (Myers, 1994; Hildebrandt, 2004). Rats lacking DPP-4 like activity have a reduced behavioural stress response which may be linked to NPY processing. Cleavage of NPY by DPP-4 results in NPY (3-36) which lacks affinity for the NPY-1 receptor mediating the anxiolytic-like effects of NPY. The nonspecific effect of DPP-4 inhibitors on NPY degradation (truncated from NPY(1-36) (original) to NPY(3-36)) may influence the antilipolytic effect (Kos et al., 2007).

Possibly the impact of an inhibition of above mentioned compounds degradation is underestimated.

Long-term safety based on CD26 effects remains unknown, but to date no significant alterations of immune function have been observed (Richter et al., 2008a) except a nonspecific increase of infections after sitagliptin (Richter et al., 2008b).

Non-selectivity with respect to actions on the related enzymes DPP-8, DPP-9 or both, could be of particular importance (Lankas et al., 2005). The relevance of DPP-8/9 inhibition is not clear yet, although skin lesions observed in primates have to be reevaluated, the FDA says. DPP-8 and DPP-9 are active in hematologic and immune cells (Gorrell, 2005). DPP-4 inhibitors do not substantially inhibit cell proliferation in experiments with human lymphocytes in vitro (Lankas et al., 2005). The toxicity of DPP-8/DPP-9 inhibitor that were reported as 100% mortality in mice, alopecia, thrombocytopenia, reticulocytopenia, enlarged lymph nodes, splenomegaly and 20% mortality in rats was not confirmed by others (Burkey et al., 2008).

7.4. Comparison of properties of GLP-1 receptor agonists and DPP-4 inhibitors (Table 9)

Exenatide (GLP-1 receptor agonist) is an incretin mimetic, while sitagliptin and vildagliptin (DPP-4 inhibitors) are incretin enhancers. No difference is observed with respect to HbA_{1c} values: exenatide is associated with reduction by approximately 0.8% that with either sitagliptin or vildagliptin is 0.7%; no difference was observed with respect to hypoglycaemias.

Exenatide treatment leads to a mild weight loss of approximately 2 kg after 30 weeks, whereas sitagliptin and vildagliptin have generally a neutral effect on weight. Weight loss is a common outcome of therapy with native GLP-1 (Zander et al., 2002), exenatide (DeFronzo et al., 2005; Buse et al., 2004; Kendall et al., 2005), and liraglutide (Nauck et al., 2006; Hansen et al., 2001), whereas treatment with DPP-4 inhibitors is associated with prevention of weight gain (Åhren et al., 2004a; 2004b; Scott et al., 2005; Hanefeld et al., 2005).

GLP-1 mimetics markedly inhibit gastric emptying whereas DPP-4 inhibitors have no such effect. This is of major importance for the glycaemic effect of the two strategies because a main mechanism of GLP-1 mimetics is to reduce prandial glucose, which is achieved mainly by reduction in gastric emptying, whereas DPP-IV inhibitors

reduced the overall 24-hour glucose with no marked difference in reduction in fasting versus prandial glycaemia.

GLP-1 mimetics heavily activate GLP-1 receptors whereas DPP-4 inhibitors moderately increase endogenous GLP-1 levels, which will retain the diurnal pattern and the primary portal action (Vahl et al., 2007) of the incretin. The difference of effects of incretin mimetics and DPP-4 inhibitors might be partly because of the relative low increase in GLP-1 levels by the enzyme inhibitors. This is explained in part by the relatively modest stabilisation of postprandial GLP-1 seen after DPP-4 inhibition, compared with the high increases in circulating levels of GLP-1 receptor agonists exemplified by exenatide. Gastrointestinal side-effects, predominantly nausea, are often reported after treatment with injectable GLP-1 receptor agonists but have not been described for DPP-4 inhibitors (Åhren et al., 2004a, 2004b; Demuth et al., 2005; Scott et al., 2005; Hanefeld et al., 2005; Brazg et al., 2005). Although nausea is a common side-effect of in exenatide therapy, many patients lose weight independently of nausea. The lack of a weight loss by DPP-4 inhibitors obese patients compared to lean subjects probably due the low activity of DPP-4 in fat cells of obese patients (Kos et al., 2007).

When exenatide is compared with sitagliptin, the effectiveness of exenatide is higher with respect to inhibition of food uptake and in inhibiting gastric emptying (Herrmann et al., 2008) which may be linked to weight reduction (mentioned above).Twice daily exenatide through subcutaneous injection is indicated for the treatment of patients with type 2 diabetes mellitus in whom one or more oral agents do not work, often as an alternative to insulin treatment. By contrast, once daily DPP-4 inhibitors could be used alone or as add-on therapy to patients failing one or more oral agents.

In contrast to incretin mimetics, DPP-4 inhibitors do not exclusively act via pharmacological concentrations of GLP-1 like activity, but raise the concentration of other peptide hormones possibly involved in metabolic control.

Differences between GLP-1 agonists and DPP-4 inhibitors are summarized in Table 9.

7.5. DPP-4 inhibitors under investigation

In addition to the mentioned two drugs being in the market, more are going to be developed as DPP-4 inhibitors. Concerning the chemical differences of distinct DPP-4 inhibitors it seems likely that one or more of these agents could be associated with unexpected adverse effects. Some characteristics of new compounds are summarized in Table 10.

The dose of saxagliptin (BMS-477118; active metabolite; developed by Bristol and Astra Zeneca) has to be changed due to kidney functioning (Augeri et al., 2005, List et al., 2007). Denagliptin (developed by Glaxo Smith Kline, albeit no longer clinically investigated for being approved) (Demuth et al., 2005) show significant differences in their pharmacokinetic profiles, side-effects, or clinical activity which are not investigated in detail.

Table 10
Comparison of some DPP-4 inhibitors.

	Sitagliptin	Vildagliptin	Alogliptin	Saxagliptin	BI 1356[b]
Enzyme inhibition in vivo after 24 hours (ED_{50} as mg/kg)	>30	14	10	2.7	0.9
IC_{50} (nM)	19	62	24	50	1
Dissociation velocity from enzyme		2.1×10^{-4} sec^{-1}			3.0×10^{-5} sec^{-1}
Selectivity versus DPP-8 and DPP-9		Approx. 300 and 30 fold, respectively[a]			10000 fold

[a] Burkey et al., 2008.
[b] Thomas et al., 2007, 2008b.

Alogliptin (SYR-322; developed by Takeda) is a novel quinazolinone-based dipeptidyl peptidase-4 (DPP-4) inhibitor (IC_{50} ~ 6.9 nM) and exhibited a >10,000-fold selectivity for DPP-4 over the closely related serine proteases DPP-2, DPP-8, DPP-9, fibroblast activation protein/seprase, prolyl endopeptidase, and tryptase (IC_{50}>100,000 nM); the absolute oral bioavailability of alogliptin is between 45% and 88% (Lee et al., 2008). Alogliptin has a kinetic profile which may allow a once-a-day dosing regime (Takeuchi et al., 2007; Christopher et al., 2007). Alogliptin improves the glycemic control (Fleck et al., 2008).

P32/98 (Isoleucine thiazolidide) increased B-cell mass in animal studies (Pospisilik et al., 2003).

BI 1356 ((R)-8-(3-amino-piperidin-1-yl)-7-but-2-ynyl-3-methyl-1-(4-methyl-quinazolin-2-ylmethyl)-3,7-dihydro-purine-2,6-dione; developed by Boehringer-Ingelheim, proposed tradename Ondero®) differs from those in the market (Thomas et al., 2008a, 2008b) since it is a xanthine derivative, has higher in vitro potency (IC_{50}) combined with a stronger in vivo effect, has a lower dissociation velocity from the enzyme DPP-4, which means it binds merely to the target at rather low plasma levels in humans. BI 1356 has a longer duration of action in vivo so that a once a day regimen is possible (Thomas et al., 2007). BI 1356 increases the basal GLP-1 level, but not the plasma insulin levels in rats after 24 hours. Under specific conditions it may (yet not proved) improve a regeneration of B-cells (see above for GLP-1). BI 1356 induces a more than 80% enzyme inhibition at plasma concentration of 5.3 nM (Dugi et al., 2007). It is not renally excreted and, therefore, a modification of the dose in kidney failure may not be necessary.

BI 1356 competitively inhibits DPP-4 activity in vitro with an IC_{50} of approximately 1 nM (Thomas et al., 2008a, 2008b), compared with sitagliptin (19 nM), alogliptin (24 nM), saxagliptin (50 nM), and vildagliptin (62 nM). The calculated k(off) rate for BI 1356 was $3.0\times10(-5)/s$ (versus $2.1\times10(-4)/s$ for vildagliptin). BI 1356 is >/= 10,000-fold more selective for DPP-4 than DPP-8, DPP-9, aminopeptidases N and P, prolyloligopeptidase, trypsin, plasmin, and thrombin and is 90-fold more selective than for fibroblast activation protein in vitro (Thomas et al., 2008a, 2008b).

PHX1149 (developed by Phenomix Corporation) is water-soluble, not metabolized, excreted renally, and has a half-life of 10 to 13 hours (Guler, 2007). The SK-0405 characteristics are an IC_{50} of 3.3 nM, high selectivity (17000 fold selectivity over DPP8, DPP9, FAP = fibroblast activation protein), and a longer lasting inhibition compared to vildagliptin (Yasuda et al., 2007).

There are even many more DPP-4 inhibitors including P93/01, NVP-DPP728, 815541A, GSK23A and valine-pyrrolidide.

Up to 50% of GLP-1 entering the circulation may be degraded by NEP-24.11; therefore combined inhibition of DPP-4 and NEP-24.11 is superior to DPP-4 inhibition alone in preserving intact GLP-1, which potential therapeutic effect (Plamboeck et al., 2005).

7.6. Additional remarks and general comment with respect to DPP-4 inhibitors

Some antidiabetic compounds (e.g. pioglitazone), which are in the market for a long time, partly may have DPP-4 inhibitory effects (Lenhard et al., 2004), also atorvastatin (Taldone et al., 2006). In addition to the well known direct insulinotropic effect of nateglinide via KATP channels, also an inhibition of GLP-1 degradation may have some minor relevance (McKillop et al., 2007). Metformin may inhibit DPP-4 activity (Lindsay et al., 2005) which could be valuable for a combination with incretin hormones. A confirmation of these data by other laboratories is awaited.

Generally speaking, the DPP-4 inhibitors are modestly effective glucose-lowering drugs although HbA_{1c} values lowering effect is sufficient and it has to be admitted that mainly patients with not extremely high HbA_{1c} values were included in some trials and could not show up with higher effects. This new class of antidiabetic agents

(incretin enhancers) expand B-cell mass in preclinical studies. However, long-term clinical studies are needed to determine the benefits of targeting the incretin axis for the treatment of type 2 diabetes.

A flat dose–response curve for DPP-4 inhibition was observed in trials of vildagliptin and sitagliptin and is sufficient. On the other hand an inhibition of at least 70-80% is necessary.

So far, no study reported on patient-oriented parameters like mortality, diabetic complications, costs of treatment and health-related quality of life. When compared to placebo treatment sitagliptin and vildagliptin improved metabolic control. Comparison with other already established blood-glucose lowering drugs did not reveal major advantages of DPP-4 treatment. DPP-4 inhibitors like sitagliptin and vildagliptin probably have advantages over existing therapies with oral antidiabetic compounds (Table 5), s e.g. with respect to absence of hypoglycaemia, weight gain etc. Long-term data on cardiovascular outcomes and safety are urgently needed before widespread use of these new agents. More information on the benefit-risk ratio of DPP-4 inhibitor treatment is necessary especially analysing adverse effects on parameters of immune function although not the enzymatic component of the enzyme (DPP-4, CD 26) is responsible for this effect. Also, long-term data are needed investigating patient-oriented parameters like health-related quality of life, diabetic complications and all-cause mortality.

7.7. Developments to be expected in general with respect to incretins and future perspectives

Much effort continues to be directed towards improvement of the pharmacokinetic profile of GLP-1 receptor agonists, to minimise peak levels of the drug and thus reduce the extent of nausea. Longer-acting GLP-1 receptor agonists should ideally provide more uniform and sustained GLP-1 receptor activation over a 24-h period while requiring less frequent administration (as mentioned before). Furthermore, there is great interest in determining whether chronic therapy with GLP-1 receptor agonists will be associated with sustained long-term control of HbA_{1c} and improvement in B-cell function beyond that achievable with existing agents. Similar questions pertain to the DPP-4 inhibitors, which also (indirectly) target B-cells.

Several issues remain to be elucidated. The durability of the weight loss induced by GLP-1 receptor agonists needs to be established, and even though both GLP-1 receptor agonists and DPP-4 inhibitors improve B cell function, the ability of either treatment to preserve functional B cell mass in humans needs clinical confirmation. The optimal role on B-cell mass has to be established. However, it is important to note that new drugs that act by blocking the action of DPP-4 increase levels of GIP as well as GLP-1. Therefore, manipulations that increase islet mass in rodents by reducing DPP-4 action are potentially due to actions of both incretins (Pospisilik et al., 2002; Conarello et al., 2003).

This leaves no direct means for testing direct effects of incretin based drugs on B-cell mass in diabetic patients. Given this limitation, the best alternative currently available to gain insights into the effects of GLP-1 receptor agonists and DPP-4 inhibitors on the course of B-cell function in diabetes may be careful natural history studies. An excellent example of this is the recently published ADOPT study (Kahn et al., 2006). In this trial, patients were followed for 4 years to the relative rate of decline in glycemic control. The reflected data worsened glycemic control on stable therapy, which is thought to be at least partially the result of loss of islet mass. Therefore the first step in ascertaining whether incretin based drugs can affect islet mass in humans is likely to come from clinical trials such as ADOPT. Comparison of the course of diabetes in patients treated with GLP-1 receptor agonists or DPP-4 inhibitors, using durability of effect on glycemic control as the primary outcome, would provide some insight into whether these agents have chronic effects on B-cell health. While such studies cannot prove that the effects of incretin-based stimulation of islet mass in animals also pertain in humans, they would go a long way towards establishing the optimal role for these drugs in clinical medicine.

In patients with newly diagnosed type 1 diabetes in remission phase, treatment with intravenous infusions of GLP-1 without concomitant insulin injection displays beneficial effects on postprandial glucose excursions and glucagon suppression, and in patients with long lasting type 1 diabetes and no residual insulin secretory capacity, administration of exenatide together with insulin has similar effects (Behme et al., 2003; Dupré et al., 1995, 2004). But, further investigations are needed to fully evaluate the ability of GLP-1 to prolong the remission period, to reduce the insulin requirements and to evaluate the overall efficacy of incretin based treatments in the field of type 1 diabetes.

The observation that GLP-1 receptor agonists improve myocardial function in human patients after myocardial infarction and reduce blood pressure highlights the need for studies with cardiovascular end-points, especially as short-term studies with GLP-1 receptor agonists show promising results. Because patients with type 2 diabetes have increased risks of cardiovascular morbidity and mortality, the observation that GLP-1 receptor agonists improve myocardial function in human patients after myocardial infarction (Nikolaidis et al., 2004) even more strengthens the need for studies that assess cardiovascular endpoints in patients treated with DPP-4 inhibitors or GLP-1 receptor agonists, which will help to get a greater understanding of the true benefits and role of these drugs for the treatment of diabetes mellitus.

Interestingly a non-peptide GLP-1 receptor agonist was developed which is also an allosteric modulator of GLP-1 binding (6,7-dichloro-2-methylsulfonyl-3-N-tert-butylaminoquinoxaline).

Besides using GLP-1 analogues and inhibitors of GLP-1 degradation, a third strategy aims at enhancing the endogenous GLP-1 secretion by using α-glucosidase inhibitors (controversy about this possible effect as mentioned above under 3.1. These drugs induce a lasting improvement in the GLP-1 response to oral sucrose in both patients with type 2 diabetes (Seifarth et al., 1998) and in healthy volunteers. They result in a more than 90% increase in the GLP-1 concentration after a meal (Göke et al., 1995a). However, a clinical relevance (similar effect on GLP-1 secretion) in patients with type 2 diabetes has not been demonstrated yet (Hücking et al., 2005). Inhibition of intestinal a-glycosidase has been shown to augment secretion of both GIP and GLP-1. The biological consequences of GLP-1 enhancement by α-glycosidase inhibition are also not characterised beyond their ability to minimise postprandial glucose fluctuations and delay in gastric emptying.

Suppression of circulating NEFA by inhibition of adipose tissue hormone sensitive lipase may augment circulating GLP-1 concentrations (Ranganath et al., 1999a).

7.8. Overall clinical aspects

It is currently not clear at which point in the natural history of type 2 diabetes incretin therapy should be initiated and more research is needed to address this issue. Logic dictates that since incretin failure may occur early and can address many pathophysiological features of type 2 diabetes that lead to progression despite use of existing treatments, incretin therapy should be used early. However, most current data on incretin therapy are to be found in combination with existing treatments often when type 2 diabetes is well advanced. The optimal agent(s) that may mimic and replace the endogenous incretin effect is not fully known and awaits the outcome of ongoing clinical trials. Important issues with regard to practicalities such as oral or parenteral route of administration, long term safety and efficacy may determine which of the proposed options to increase the incretin effect is preferred in clinical practice.

In view of the above limitations, metformin will be the drug of choice for initial treatment of type 2 diabetes.

Incretin mimetics and enhancers may be established as first-line treatment; however, the exact place in therapy remains to be explored.

DPP-4 inhibitors could eventually be used in prediabetic stages and in early stages of diabetes in order to prevent the progression of type 2 diabetes (prophylactic use).

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