

Glucagon-Like Peptide-1 Synthetic Analogs: New Therapeutic Agents for Use in the Treatment of Diabetes Mellitus

George G. Holz* and Oleg G. Chepurny

New York University School of Medicine, Department of Physiology and Neuroscience, New York, NY, USA

Abstract: Glucagon-like peptide-1-(7-36)-amide (GLP-1) is a potent blood glucose-lowering hormone now under investigation for use as a therapeutic agent in the treatment of type 2 (adult onset) diabetes mellitus. GLP-1 binds with high affinity to G protein-coupled receptors (GPCRs) located on pancreatic β -cells, and it exerts insulinotropic actions that include the stimulation of insulin gene transcription, insulin biosynthesis, and insulin secretion. The beneficial therapeutic action of GLP-1 also includes its ability to act as a growth factor, stimulating formation of new pancreatic islets (neogenesis) while slowing β -cell death (apoptosis). GLP-1 belongs to a large family of structurally-related hormones and neuropeptides that include glucagon, secretin, GIP, PACAP, and VIP. Biosynthesis of GLP-1 occurs in the enteroendocrine L-cells of the distal intestine, and the release of GLP-1 into the systemic circulation accompanies ingestion of a meal. Although GLP-1 is inactivated rapidly by dipeptidyl peptidase IV (DDP-IV), synthetic analogs of GLP-1 exist, and efforts have been directed at engineering these peptides so that they are resistant to enzymatic hydrolysis. Additional modifications of GLP-1 incorporate fatty acylation and drug affinity complex (DAC) technology to improve serum albumin binding, thereby slowing renal clearance of the peptides. NN2211, LY315902, LY307161, and CJC-1131 are GLP-1 synthetic analogs that reproduce many of the biological actions of GLP-1, but with a prolonged duration of action. AC2993 (Exendin-4) is a naturally occurring peptide isolated from the lizard *Heloderma*, and it acts as a high affinity agonist at the GLP-1 receptor. This review summarizes structural features and signal transduction properties of GLP-1 and its cognate β -cell GPCR. The usefulness of synthetic GLP-1 analogs as blood glucose-lowering agents is discussed, and the applicability of GLP-1 as a therapeutic agent for treatment of type 2 diabetes is highlighted.

Keywords: GLP-1, diabetes mellitus, insulin secretion.

A. INTRODUCTION

Glucagon-like peptide-1-(7-36)-amide (GLP-1, also known as t-GLP-1 or GLIP) is an intestinally-derived insulinotropic hormone that has attracted considerable attention by virtue of its proven ability to act as a blood glucose lowering agent. The efficacy with which GLP-1 lowers concentrations of blood glucose in type 2 diabetic subjects (adult onset diabetes mellitus) has prompted clinical investigations whereby the therapeutic value of GLP-1 as an antidiabetogenic agent has been substantiated. Earlier studies revealed that GLP-1 is an effective stimulator of insulin secretion from pancreatic β -cells located in the islets of Langerhans. More recently, it has become appreciated that GLP-1 also exhibits trophic factor-like properties, acting to stimulate β -cell growth and differentiation. These effects of GLP-1 are complemented by its ability to suppress appetite and to delay gastric emptying. Since GLP-1 is a naturally occurring hormone, and because GLP-1 is not reported to exert deleterious side effects, new efforts are currently under way to develop GLP-1 synthetic analogs that exhibit an optimal pharmacokinetic and pharmacodynamic spectrum of

action commensurate with their use as therapeutic agents. The intention of this review is to highlight recent advances in this field and to provide an overview of the potential usefulness of GLP-1 and its synthetic analogs for treatment of type 2 diabetes mellitus. For a detailed discussion of previous studies concerning GLP-1, the reader is referred to earlier in-depth reviews of this subject matter [1-9].

B. GLP-1 AS A BLOOD GLUCOSE-LOWERING AGENT

The blood glucose-lowering hormone GLP-1 possesses insulinotropic properties that indicate its usefulness as a therapeutic agent in the treatment of diabetes mellitus. When administered by intravenous infusion to type 2 diabetic subjects, GLP-1 stimulates pancreatic insulin secretion and blunts the postprandial hyperglycemic excursion that is typically observed following ingestion of a meal [10-12]. Short term or continuous infusion of GLP-1 restores fasting glycemia in type 2 diabetic subjects [13-19], and available evidence indicates that GLP-1 remains an effective blood glucose lowering agent under conditions in which subjects are not responsive to administered sulfonylureas such as tolbutamide, glyburide, or glipizide [20-22]. Antidiabetogenic actions of GLP-1 in type 2 diabetic subjects are manifest as an improvement of pancreatic β -cell function, as measured by a clear restoration of the missing

*Address correspondence to this author at the Department of Physiology and Neuroscience, MSB 442, New York University School of Medicine, 550 First Avenue, NY 10016, New York, USA; Tel: 212-263-5434; Fax: 212-689-9060; E-mail: holzg01@popmail.med.nyu.edu

first phase component of glucose-dependent insulin secretion [10,15,19,23]. Also observed is an augmentation of second phase insulin secretion [14] and an increased amplitude of pulsatile insulin secretion [24,25]. Simultaneously, levels of fasting blood glucose are reduced (typically by 4-5 mmol/L) [19]. Such beneficial actions of administered GLP-1 may be a consequence of its ability to compensate for a major deficit of endogenous GLP-1 synthesis, secretion, or metabolism in diabetic subjects [26,27]. The long term therapeutic value of GLP-1 is evident given that it is reported to reduce circulating hemoglobin A_{1c} levels by as much as 1.3% [19].

From the standpoint of its usefulness as a blood glucose lowering agent, an attractive pharmacodynamic property of GLP-1 is that it stimulates insulin secretion only under conditions in which the concentration of blood glucose is elevated. As concentrations of blood glucose fall in response to administered GLP-1, the insulin secretagogue action of GLP-1 is self-terminating [10]. Therefore, unlike administered insulin, a natural safeguard exists whereby GLP-1 is less likely to induce hypoglycemia in type 2 diabetic subjects [28,29]. These antidiabetogenic properties of GLP-1 are observed not only with intravenous infusion, but also following subcutaneous administration [19,23,29,30-33,] or oral administration via a buccal tablet [34].

Although not fully understood, there is evidence that the blood glucose lowering action of GLP-1 is also attributable, at least in part, to its ability to suppress pancreatic glucagon secretion [11,12,23,35]. This action of the hormone reduces hepatic glucose output and may explain, at least in part, an ability of GLP-1 to lower levels of blood glucose in type 1

(juvenile-onset) diabetic subjects [11,36]. Interestingly, the ability of GLP-1 to suppress pancreatic glucagon secretion also appears to be glucose-dependent. Under conditions of hypoglycemia, no suppression is observed [37]. Therefore, available evidence suggests that GLP-1 does not impair the ability of glucagon to act as a counter regulatory hormone in support of hepatic glucose output under conditions of hypoglycemia.

It is important to note that GLP-1 is also an inhibitor of gastrointestinal secretion and motility, not only in healthy individuals [38], but in type 2 diabetic subjects as well [21,31,39]. GLP-1 slows gastric emptying and delays nutrient absorption, actions that are likely to play a major role in determining the effectiveness of GLP-1 as a regulator of blood glucose concentration during the time immediately following ingestion of a meal [40]. The inhibition of gastric emptying by GLP-1 appears to reflect its normal physiological role as an intestinal hormone because new evidence exists that it mediates the "ileal brake" phenomenon [41]. Concomitant with this gastrointestinal action, GLP-1 also acts within the central nervous system as a mediator of satiety [42]. Evidence has been presented that GLP-1 suppresses appetite [43,44], an effect of the hormone that appears to involve hypothalamic appetite control centers where GLP-1 is synthesized [45,46] and where GLP-1 receptors are expressed [46,47].

Although controversial, there is limited evidence that GLP-1 exerts an insulinomimetic action to directly facilitate glucose uptake in peripheral tissues such as liver, fat or muscle. Early on it was recognized that GLP-1 increases glucose disposal in type 1 diabetic subjects [11] and healthy

A

GLP-1	H A E G T F T S D V S S Y L E G Q A A K E F I A W L V K G R - N H₂
Glucagon	H S Q G T F T S D Y S K Y L D S R R A Q D F V Q W L M N T
Secretin	H S D G T F T S E L S R L R E G A R L Q R L L Q G L V - N H₂
GIP	Y A E G T F I S D Y S I A M D K I R Q Q D F V N W L L A Q K G K K N D W K H N I T Q
PACAP 27	H S D G I F T D S Y S R Y R K Q M A V K K Y L A A V L - N H₂
VIP	H S D A V F T D N Y T R L R K Q M A V K K Y L N S I L N - N H₂

B

GLP-1-(1-37)	H D E F E R H A E G T F T S D V S S Y L E G Q A A K E F I A W L V K G R G
GLP-1-(7-37)	H A E G T F T S D V S S Y L E G Q A A K E F I A W L V K G R G
GLP-1-(7-36)-NH₂	H A E G T F T S D V S S Y L E G Q A A K E F I A W L V K G R - N H₂
GLP-1-(9-36)-NH₂	E G T F T S D V S S Y L E G Q A A K E F I A W L V K G R - N H₂

Fig. (1). (A) Alignment of the secretin-like family of peptide hormones including GLP-1-(7-36)-amide. (B) Precursor GLP-1-(1-37) aligned with mature forms of the hormone consisting of GLP-1-(7-37) and GLP-1-(7-36)-amide as well as the immediate degradation

subject [48], while simultaneously reducing the postprandial glycemic excursion [35,36,49]. Of particular interest is one report that in the OLETF rat model of type 2 diabetes, GLP-1 stimulated uptake of 2-deoxy-D-glucose in skeletal muscle while exerting no effect on hepatic glucose output [50]. Therefore, alterations of glucose disposal in response to GLP-1 may not be explained simply by a suppression of glucagon secretion. This conclusion is supported by a recent report in which GLP-1 was shown to increase insulin sensitivity in depancreatized dogs [51]. Similarly, GLP-1 was reported to increase insulin sensitivity and insulin-mediated glucose uptake in elderly and obese diabetic subjects [52,53]. Despite these observations, no firm conclusion can as yet be made concerning the possible existence of GLP-1 receptors on hepatocytes, adipocytes, or skeletal muscle, and furthermore, such findings have been contradicted by several alternative reports [54-58].

C. GLP-1 AND GLP-1 RECEPTOR-MEDIATED SIGNAL TRANSDUCTION

In order to appreciate exactly how GLP-1 may exert pancreatic and/or extra-pancreatic effects, it is useful to review current concepts concerning GLP-1 biosynthesis and action. GLP-1 is one member of a large family of structurally-related hormones and neuropeptides that include glucagon, secretin, glucose-dependent insulintropic polypeptide (GIP), pituitary adenylyl cyclase activating polypeptide (PACAP), and vasoactive intestinal polypeptide (VIP) (Fig. 1A). GLP-1 is synthesized by enteroendocrine L-cells of the distal intestine, and it is released into the systemic circulation concomitant with a meal. Secretion is stimulated by carbohydrates, fat, hormones, and neural reflexes [59-61]. The intestinal L-cells synthesize and process proglucagon such that the principal post translational end product is GLP-1 rather than glucagon. *In vitro* analyses of GLP-1 biosynthesis have been facilitated by the availability of cell lines (GLUTag, NCI-H716) that exhibit regulated secretion of the hormone [62-64]. The specificity of post translational processing within L-cells distinguishes them from pancreatic α -cells where glucagon is the principal end product. The immature form of GLP-1 is GLP-1-(1-37), and it is thought to be biologically inert (Fig. 1B). Processing of GLP-1-(1-37) generates the biologically active isopeptides GLP-1-(7-37) and GLP-1-(7-36)-amide, with the amidated peptide representing the fully mature form of GLP-1. Circulating levels of GLP-1 rise to the low picomolar range after ingestion of a meal [65], and GLP-1 is rapidly inactivated by serum dipeptidyl peptidase IV (DDP-IV; EC 3.4.14.5) [66-68]. This generates GLP-1-(9-36)-amide, a degradation product devoid of agonist activity at the GLP-1 receptor (Fig. 1B). No evidence exists demonstrating a significant difference in pharmacological action when comparing GLP-1-(7-37) and GLP-1-(7-36)-amide.

The GLP-1 receptor cDNA was first identified by use of an expression cloning strategy [69]. Subsequently, it was established that GLP-1 receptors are expressed in pancreatic islets of Langerhans, stomach, lung, heart, kidney, and brain [47]. GLP-1 receptors have also been located to vagal sensory afferent nerve endings constituting a hepatportal vein glucose sensor [70-71]. This pattern of tissue specific

expression of receptors underlies the ability of GLP-1 to act as a stimulus for insulin secretion, to slow gastric emptying, and to suppress appetite. The GLP-1 receptor genomic sequence identifies it as a member of Class II (Family B) heptahelical GPCRs. Receptors of this family are structurally-related and recognize GLP-1, glucagon, GIP, secretin, PACAP, VIP, calcitonin, parathyroid hormone (PTH), and corticotropin releasing factor (CRF).

A common feature of Class II GPCRs is their ability to mediate stimulatory actions of peptide hormones on cAMP production, Ca^{2+} signaling, and exocytosis. This is also true for GLP-1 receptors expressed on pancreatic β -cells. By stimulating production of cAMP, GLP-1 acts as a modulator of the β -cell glucose signaling system (Fig. 2). The GLP-1 receptor is positively coupled to adenylyl cyclase by heterotrimeric G_s proteins [72]. Evidence also exists for coupling of GLP-1 receptors to G_i and $G_{q/11}$ proteins [73]. GLP-1 receptor occupancy stimulates cAMP production, whereas very little evidence exists for a major effect of GLP-1 on β -cell inositol phosphate production. PKA is a downstream effector of the GLP-1 receptor, and it is activated by an increase of $[\text{cAMP}]_i$. Evidence exists for the targeting of PKA to specific subcellular compartments via A-kinase anchoring proteins (AKAPs) [74,75], thereby offering one potential explanation for how the cAMP-dependent actions of GLP-1 may be spatially restricted within the β -cell. An additional target of cAMP action is the newly recognized family of cAMP-binding proteins known as cAMP-regulated guanine nucleotide exchange factors (cAMPGEFs, also referred to as *Epac*) [76-79]. The cAMPGEFs couple cAMP production to the activation of Rap1, a small molecular weight G protein. Novel signaling properties of the GLP-1 receptor include its ability to activate immediate early genes (IEGs) [80], to increase the number of insulin receptors on insulin-secreting cells [81,82], to stimulate mitogen-activated protein kinases (p38 MAPK, ERK), phosphatidylinositol 3-kinase [83], atypical protein kinase C- ζ [84], Ca^{2+} /calmodulin-regulated protein kinase [85], protein kinase B (*Akt*), and hormone-sensitive lipase [86]. It seems likely that at least some of these effects result from activation of *Epac* by GLP-1. Available evidence also indicates an important action of GLP-1 to regulate β -cell ion channel function. GLP-1 has been reported to inhibit ATP-sensitive K^+ channels (K-ATP) [87-89] and to facilitate the opening of voltage-dependent Ca^{2+} channels (VDCCs) [3]. Intracellular Ca^{2+} release channels are also targeted by GLP-1 in a cAMP-dependent manner [74,90,91]. They include the type-2 isoform of ryanodine receptor (RYR-2) Ca^{2+} release channels located on the endoplasmic reticulum.

D. GLP-1 AS A β -CELL GLUCOSE COMPETENCE HORMONE

It is now established that GLP-1 acts as a competence hormone in support of glucose-dependent insulin secretion [1,87,92,93]. Under conditions in which β -cells are metabolically compromised, GLP-1 acts to restore the sensitivity of these cells to glucose. Since type 2 diabetes mellitus is a metabolic disorder in which β -cells lose their ability to respond to glucose, the induction of glucose competence by GLP-1 may be of major therapeutic

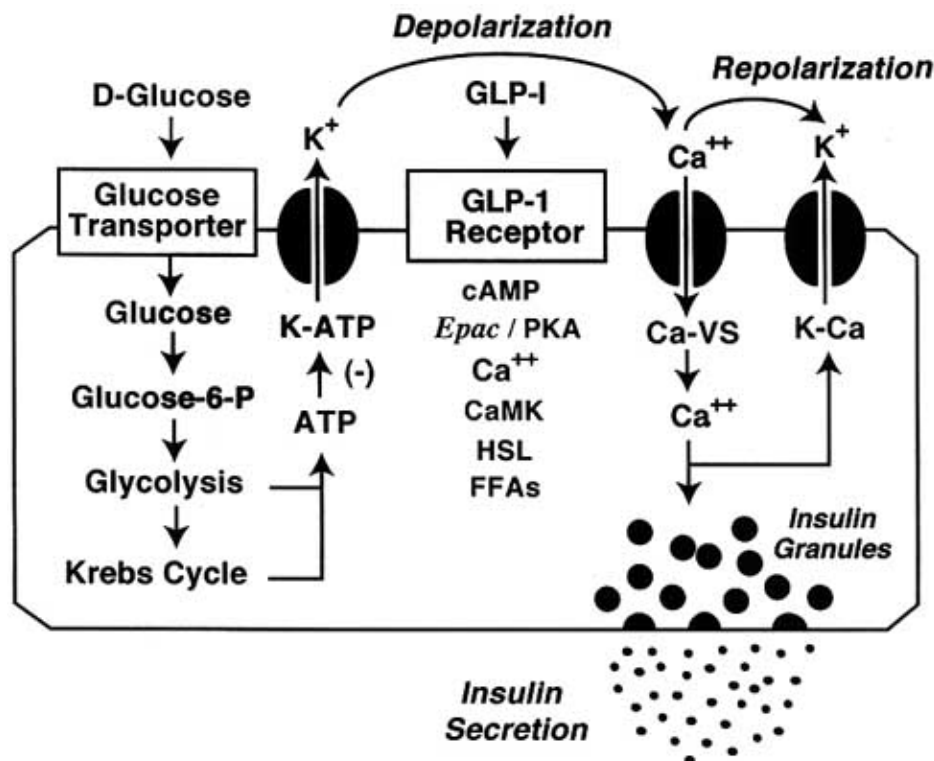


Fig. (2). Illustrated is the role GLP-1 plays as a modulator of the β -cell glucose signaling system. Glucose stimulates insulin secretion, and GLP-1 potentiates the action of glucose by activating multiple signal transduction pathways important to Ca^{2+} -dependent exocytosis. Uptake of glucose is mediated by the type-2 glucose transporter (Glut2) and glucose is converted to glucose-6 phosphate by glucokinase, a type-IV hexokinase that is rate-limiting for β -cell glucose sensing. Aerobic glycolysis generates metabolic coupling factors, one of which is ATP. An increase of the cytosolic ATP/ADP concentration ratio results in the closing of ATP-sensitive K^+ channels (K-ATP), thereby producing membrane depolarization and activation of Ca^{2+} influx through voltage-sensitive Ca^{2+} channels (Ca-VS). Ca^{2+} influx produces an increase of $[\text{Ca}^{2+}]_i$ and triggers fusion of insulin secretory granules with the plasma membrane. Repolarization of the membrane is due, in part, to the Ca^{2+} -dependent activation of K^+ channels (K-Ca). GLP-1 modulates this sequence of events via second messengers (cAMP, Ca^{2+}), protein kinase A (PKA), guanine nucleotide exchange factors (*Epac*), Ca^{2+} -calmodulin-regulated protein kinase (CaMK), hormone sensitive lipase (HSL), and lipid metabolites including free fatty acids (FFAs).

importance. Recent studies suggest that glucose competence results from the ability of GLP-1 to act as a glucose-sensitizer. The central locus for this effect appears to be intermediary metabolism where GLP-1 facilitates glucose-dependent mitochondrial ATP production [94]. This key observation provides a clear explanation for why the insulin secretagogue action of GLP-1 in β -cells is entirely glucose-dependent. An initiating event for induction of glucose competence is likely to be the release of Ca^{2+} from intracellular Ca^{2+} stores. This is Ca^{2+} -induced Ca^{2+} release (CICR), and it is stimulated by GLP-1. Available evidence suggests that endoplasmic reticulum-derived Ca^{2+} interacts with cAMP to facilitate mitochondrial oxidative phosphorylation. Intramitochondrial targets of Ca^{2+} include Ca^{2+} -sensitive dehydrogenases, whereas the targets of cAMP may include mitochondrial PKA and *Epac*, although this remains to be determined. Regardless of the precise signal transduction mechanism involved, it is reasonable to hypothesize that the induction of β -cell glucose competence by GLP-1 might contribute to its ability to lower

Indeed, the restoration of first phase insulin secretion by GLP-1 in diabetic subjects is understandable in view of this hormone's ability to augment glucose-dependent ATP production, thereby closing β -cell K-ATP channels. This action of GLP-1 at K-ATP is analogous to the effect produced by sulfonylureas (tolbutamide, glyburide, glipizide), however it is unique in that it is entirely dependent on metabolism of glucose rather than being the consequence of a direct pharmacological inhibition of K-ATP.

E. THE INSULIN SECRETAGOGUE ACTION OF GLP-1

GLP-1 stimulates pancreatic insulin secretion under conditions in which β -cells are exposed to concentrations of glucose typical of the postprandial state (> 7.5 mM). Insulin secretion occurs in a pulsatile manner, and GLP-1 increases the amplitude of each pulse without changing the pulse frequency [24,25,95]. These effects of GLP-1 are

islets due to the generation of action potentials [96]. Evidence exists indicating that GLP-1 facilitates both the triggering (first phase) and augmentation (second phase) pathways of glucose-dependent insulin secretion [3]. Stimulatory effects of GLP-1 on insulin secretion appear to be mediated primarily by cAMP [3]. New findings indicate that GLP-1 and cAMP target insulin granule-associated proteins including *Epac* [76] and *Rim2* [77], thereby increasing the likelihood that a readily releasable pool of secretory granules will undergo exocytosis in response to an increase of intracellular Ca^{2+} concentration. Simultaneously, GLP-1 appears to stimulate refilling of the readily releasable pool, an effect attributed to the mobilization of a reserve pool of secretory granules [97]. Such direct effects of GLP-1 on the exocytotic secretory apparatus are complimented by the ability of GLP-1 to increase β -cell electrical activity, thereby facilitating influx of Ca^{2+} through VDCCs [87]. Simultaneously, GLP-1 mobilizes Ca^{2+} from intracellular Ca^{2+} stores via CICR, thereby amplifying the exocytosis triggered by Ca^{2+} influx [98]. The Ca^{2+} stores mobilized by GLP-1 appear to correspond to those that are sensitive to ryanodine, caffeine, and thapsigargin [75,98]. Indeed, evidence has been presented that β -cell RYR Ca^{2+} release channels are important intermediaries linking GLP-1-stimulated cAMP production to Ca^{2+} mobilization and the initiation of Ca^{2+} -dependent insulin granule exocytosis [98].

F. STIMULATION OF INSULIN GENE EXPRESSION BY GLP-1

GLP-1 stimulates insulin gene expression by virtue of its ability to increase transcription of the insulin gene while simultaneously stabilizing preproinsulin mRNA [99-103]. GLP-1 also increases translational biosynthesis of proinsulin. These effects of GLP-1 resemble the previously described action of glucose to increase β -cell insulin content. The ability of GLP-1 to stimulate insulin gene transcription has been studied in isolated islets of Langerhans and in a variety of insulinoma cell lines. In general, GLP-1 exerts multiple stimulatory influences on insulin gene promoter activity, as expected given that it activates more than one signal transduction pathway. These signaling pathways converge at the promoter to regulate the function of

transcription factors that interact with specific response elements (Fig.3). Although a conventional cAMP signaling mechanism involving PKA, CREB, and the insulin gene cAMP response element (CRE) has been suggested to play a significant role in this effect, it now appears more likely that actions of GLP-1 at the CRE are PKA-independent. This conclusion is based on studies of the INS-1 insulin-secreting cell line where it was demonstrated that pharmacological inhibitors of PKA (H-89, KT 5720) failed to block stimulatory actions of GLP-1 at a luciferase reporter incorporating -410 bp of the rat insulin I gene promoter (RIP1-Luc). Interestingly, the action of GLP-1 was shown to be blocked by the serine/threonine protein kinase inhibitor Ro 31-8220, by transfection of INS-1 cells with a dominant negative isoform of CREB (A-CREB), or by introduction of inactivating mutations at the CRE. On the basis of these observations, it was suggested that stimulatory actions of GLP-1 at the CRE are mediated by basic region leucine zipper (bZIP) transcription factor related in structure to CREB, and that the transactivation function of such bZIPs might be upregulated by an Ro 31-8220-sensitive MAPK-activated kinase such as RSK and/or MSK.

Evidence has also been presented that the pancreatic/duodenal homeodomain transcription factor PDX-1 mediates stimulatory actions of GLP-1 at A-elements of the insulin gene promoter. PDX-1 translocates to the nucleus in response to GLP-1, an effect mediated by PKA [104]. Levels of PDX-1 mRNA are increased by GLP-1 [105,106], and binding of PDX-1 to A1 elements of the rat insulin I and II gene promoters is facilitated. The transactivation function of PDX-1 is stimulated by GLP-1 [107], and GLP-1 also stimulates a luciferase reporter incorporating synthetic multimerized E2/A4/A3 elements of RIP1. Given that the A-elements of the insulin gene promoter are established to be mediators of glucose insulinotropic action, they appear to be a locus at which nutrient metabolism and hormonal signal transduction interact.

Recently, it has been suggested that NFAT transcription factors (nuclear factor of activated T-cells) mediate stimulatory effects of GLP-1 on insulin gene transcription [108]. Three NFAT binding sites have been identified in the rat insulin I gene promoter (RIP1), and it was suggested that GLP-1 facilitates binding of NFAT to the promoter in a

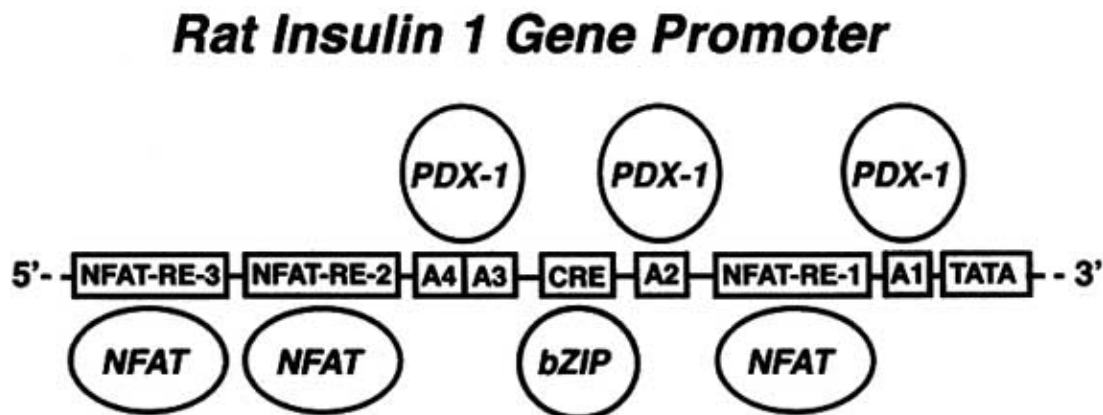


Fig. (3). Response elements and transcription factors that are targeted by GLP-1 for increased insulin gene transcription. Within the first -400 bp of the promoter are found 3 predicted response elements for NFAT (NFAT-RE-1-3). Also present are A4/A3 elements that bind the homeodomain transcription factor PDX-1. A non-palindromic cyclic AMP response element (CRE) mediates stimulatory

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