Review

Mono-ADP-ribosyltransferase as a Potential Pharmacological Drug Target in the GLP-1 Based Therapy of Obesity and Diabetes Mellitus Type 2

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Abstract

Glucagon-like peptide-1 (GLP-1) based therapy is well established for treating diabetes mellitus type 2. Moreover, GLP-1 receptor agonists influence weight loss, and have potential for treating obesity. GLP-1 receptor agonists should be administered in low doses, together with drugs that potentiate insulin release, to avoid some minor side effects. We have focused on incretin hormones, especially GLP-1 and its analogues. Here we discuss the effect of the third intracellular loop-derived peptide of GLP-1 receptor on intracellular mono-ADP-ribosyltransferase and its role in regulating the receptor. We suggest that this intracellular mono-ADP-ribosyltransferase could constitute a possible novel pharmacological target in the treatment of diabetes mellitus type 2 and obesity.

Keywords: Peptide drugs; glucagon like peptide-1 receptor; mono-ADP-ribosylation; mono-ADP-ribosyltransferase, obesity, diabetes

1. Introduction

Advances in synthetic chemistry, solid support materials, purification technology, large scale production and biological drug delivery strategies have all contributed to expanding interest in peptide drugs. In the commercial sector, even with the global economic recession, the market for Good Manufacturing Practice (GMP) peptides continues to grow,[1] albeit at a reduced rate, with the progress of established therapeutic peptide projects, through clinical development, with the emergence of new peptide drug candidates from discovery research. In the research sector, demand for peptides also continues to rise, particularly for peptides used in structure-activity studies, drug screening, target validation, epitope mapping, etc. Natural peptides are being used as active substances such as insulin the first peptide to be isolated and administered therapeutically. Peptides for therapeutic use can be chemically modified in several ways. The most usual changes are additions, deletions or substitutions of standard amino acids thereby creating peptide analogues. Peptides can however contain other, non-standard, amino acids, and can thus be covalently bound to fatty acids or other organic compound by acylation or PEGylation. These modifications are made to optimize the pharmacokinetic properties and biological efficacy of the peptide drug.[2] Treatment with peptide drugs is already being used successfully in various fields of medicine such as allergy, anti-infection, diabetes, cardiovascular, obesity, arthritis, cancer. Their advantages are high activity and specificity, high potency, minimal drug-drug interactions, low level of accumulation in tissues and consequentially low toxicity, great biological and chemical diversity, which eases treatment with and administration of these drugs However, peptides are limited in that they are metabolically unstable in environments with extreme pH values and high protease activity, have low bioavailability, in part due to low membrane transport characteristics. They use specific drug-delivery systems and their synthesis is demanding and expensive.[3]

In this minireview, we focus on the development on new therapies for treating obesity and diabetes mellitus type 2. We introduce the incretin hormones, with special emphasize on glucagon-like peptide-1 and its analogues that are associated with the treatment of these two diseases. Finally, we discuss the evidence for a novel pharmacological target, mono-ADP-ribosyltransferase, and its potential role in treatment of both incretin dependent diseases.

2. GLP-1 Based Ttherapy of Obesity and Diabetes Mellitus Type 2

There are pathogenic and epidemiological correlations between diabetes mellitus type 2 and obesity. Both diseases are at least partly associated with the pleiotropic effects of endogenous incretin hormones.[4] Incretins are a group of gastrointestinal hormones that are released from intestinal cells into the circulation in response to nutrient ingestion.[5] They are responsible for the so-called »incretin effect« in which the plasma insulin response to oral glucose is a much greater than the insulin release after intravenous glucose administration.[6,7] These diseases usually have a common cause, malfunction of the incretin hormones, so it is appropriate that they be considered together. The most important incretin hormones are glucagon-like peptide-1 (GLP-1), secreted by L-cells of the distal small intestine and glucose-dependent insulinotropic polypeptide (GIP), secreted by K-cells that are localized to more proximal regions of the small intestine.[8,9,10] They have been reviewed in detail.[5]

Excess body weight has become the fifth most important contributor to the global burden of disease (World Health Organization, 2009). Obesity directly or indirectly affects a number of health problems such as cardiovascular diseases, psycho-social and psychological problems, arthritic problems, obstructive sleep apnoea, and others.[4] Although environmental factors are clearly important for its development, obesity has a high heritability.[11,12] Incretins play perhaps the most important role in regulating body weight.[13] It is clear that GLP-1 has direct effects (inhibition of glucagon release from α-cells, stimulation of insulin release from β-cells, an inhibitory effect on the appetite center in the hypothalamus) and an indirect effect (inhibition of appetite by delayed emptying of stomach contents) on individual food behaviour.[14,15,16] Obesity is treated with a non-peptide drug Orlistat. But several GLP-1 receptor agonist peptide drugs, such as exenatide and liraglutide, which are primerly used for treatment of diabetes also suppress appetite, reducing body weight.[17]

Diabetes mellitus type 2 in the developed world is also on the rise and is a major health problem throughout the world. It results from insulin resistance in peripheral tissues and impaired insulin secretion. Insulin resistance is a consequence of obesity, physically inactive lifestyles and aging. An established treatment involves diet, exercise and pharmacological agents such as insulin, biguanides, sulfonylurea derivatives and thiazolidinediones.[18] However, these drugs have side effects, including hypoglycemia, weight gain and edema. Treatment usually requires a combination of several different drugs simultaneously, so the need for novel therapeutic approaches is urgently required. One such approach for glycemic control that can complement existing therapies is based on the action of the incretins, particularly GLP-1, as it stimulates insulin gene expression, promotes insulin biosynthesis, indirectly increases insulin sensitivity, stimulates the proliferation of existing β-cells, stimulates the maturation of new β-cells and inhibits their apoptosis.[19]

GLP-1 has positive effects, both in the treatment of obesity and diabetes mellitus type 2. However, its application is not very effective. It is rapidly metabolized in blood by the enzyme dipeptidyl peptidase IV (DPP-IV). This enzyme removes the two N-terminal amino acids histidine and alanine from GLP-1, so that its half-life is only 1 to 2 minutes. The resulting GLP-1 (9-36)amide is not only inactive, but probably acts as a weak antagonist of GLP-1 receptor.[20] In addition, GLP-1 based therapy thus includes drugs, which are divided into two groups: DPP-IV resistant GLP-1 receptor agonists and DPP-IV inhibitors. Since inhibitors of DPP-IV are not peptides, but rather small organic molecules, they will not be discussed in more detail here; they are clearly described elsewhere.[18,21] Just three significant differences between the two groups require mention. (A) While GLP-1 receptor agonists influence weight loss, the DPP-IV inhibitors do not, and are therefore fit only for the treatment of diabetes type 2.[22] (B) DPP-IV inhibitors are not very selective. They can also inhibit DPP-II, DPP-VIII, DPP-IX, prolyl endopeptidase and fibroblast activating protein α.[20] (C) DPP-IV is pleiotropic enzyme that inactivates a variety of peptide hormones, neuropeptides and chemokines. Furthermore, it binds several proteins such as adenosine deaminase and fibronectin. Therefore, inhibition of DPP-IV may have some severe side effects in diabetes treatment, which are not seen with application of GLP-1 receptor agonists.[20] On the other hand, they lower levels of glycoslated haemoglobin HbA1c, have positive effect on β-cells and prevent the risk of hypoglycemia posed by sulfonylureas.[23]

GLP-1 receptor agonists design is based on the structure of native GLP-1 (GLP-1 analogues), or exendin-4 (exendin analogues), which is a peptide isolated from the salivary gland in the lizard *Heloderma suspectum*. Resistance to DPP-IV inactivation and minimal excretion by the kidneys are essential prerequisites. For this reason, GLP-1 receptor agonists can, in addition, be bound to albumin to prolong its biological action.[22]

Exenatide was the first GLP-1 receptor agonist in the market to be approved, in 2005, for treatment of diabetes mellitus type 2 and has potential in the treatment of obesity.[22,24] It is a synthetic equivalent of exendin-4. In spite of the fact that it shows only 53% homology with GLP-1, it binds to GLP-1 receptor with an affinity comparable to that of native GLP-1 (Table 1).[25] Amino acid in position two is substituted by glycine and, because of this, it is resistant to DPP-IV inactivation. Thus, its half-life is significantly longer (about 2 hours) than that of GLP-1 (1-2 min). Exenatide side effects occur in approximately 40% of patients, as primarily nausea, diarrhea and vomiting;[26] the nausea is usually reduced during on-going treatment. About 20–40% of the patients develop low titer antibodies against the drug with no apparent clinical con-

Table 1. Amino acid sequences of the GLP-1, GLP-1 analogues and exendin-derived GLP-1 receptor agonists.

Peptide	Structure	EC_{50} (nM)
GLP-1	HAEGTPTSDVSSYLEGQAAKEPIAWLVKGR HAEGTPTSDVSSYLEGQAAKEPIAWLVRGRG	1.0
Liraglutide	| E–C16 fatty acid	*
Albiglutide	$(HGEGTPTSDVSSYLEGQAAKEPIAWLVKGR)_2$ – genetic fussion with human albumin	*
Taspoglutide	HXEGTPTSDVSSYLEGQAAKEPIAWLVKXR (X = 2-aminoizobutirična kislina)	*
Exendin-4 Exenatide™	HGEGTPTSDLSKQMEEEAVRLPIEWLKNGGPSSGAPPPS	0.5
Lixisenatide	HGEGTPTSDLSKQMEEEAVRLPIEWLKNGGPSSGAPPSKKKKKK	*

*Data not available.

sequences.[22] The worst side effect is acute pancreatitis, although the causal link is difficult to attribute solely to exenatide, since this disease in patients with diabetes mellitus type 2 is three times more frequent *per se*.[21] Exenatide is a good supporting drug of existing anti-diabetic therapy with metformin. It significantly improves glycaemic control and shows greater decrease in body weight if used in combination with metformin.[27]

The first GLP-1 analogue to be approved for treatment of diabetes mellitus type 2 was liraglutide in 2009.[28] It improves glycaemic control, lowering the levels of HBA1c in patients treated in combination with metformin (LEAD program).[29] It also shows positive effects in the treatment of obesity.[30] Liraglutide differs from GLP-1 and is characterized by (a) a palmitoyl acyl chain linked to lysine 20 via a γ-glutamic acid spacer, (b) substitution of lysine in position 28 of native GLP-1 with arginine and (c) an additional C-terminal glycine (Table 1). An acyl chain allows non-covalent binding to albumin, which increases resistance to DPP-IV and delays renal clearance. Side effects are similar to those of exenatide, with the exception of lower concentration of antibodies in the blood.[31]

The other three peptides in Table 1 are in late stages of clinical testing, and there are no reliable data yet. Lixisenatide is an exenedine-4 based compound in which proline 38 is removed and the molecule extended by six lysine at the C-terminus.[32] This prolongation enables the lixisenatide to be administered just once daily, less compared than twice daily for exenatide. Albiglutide and taspoglutide are GLP-1 analogues; the former being the result of genetic fusion of modified GLP-1 dimer (alanine in position 2 is substituted by glycine) and human serum albumin. In taspoglutide, amino acids 2 (alanine) and 29 (glycine) of native GLP-1 are replaced by 2-aminoisobutyric acid. These modifications of native GLP-1 prolong the biological action, because molecules are both DDP-IV resistant and bound to albumin. It is therefore possible to administer peptide drugs only once weekly or even once monthly.[33,34] A new exenatide LAR (long-acting release) or exenatide once weekly Ex(OW) was approved for marketing in Europe in 2011 and in US in 2012. Ex(OW) results in greater improvements in glycemic control compared with exenatide twice daily, but shows lower HbA1c reductions compared with liraglutide once daily (DURATION program).[35,36]

3. Mono-ADP-ribosyltransferase as a Potential Pharmacological Target in the Treatment of Obesity and Diabetes Mellitus Type 2

GLP-1 receptor agonists have proved to be good supportive tools of existing therapies in treating diabetes mellitus type 2 and obesity. However, these drugs have some minor side effects such as vomiting, transient nausea, high blood pressure, increased heart rate and risk of developing acute pancreatitis, mainly because they are administered subcutaneously at high doses. These high doses should be avoided by employing a combination therapy with new drugs that reduce the need for high dose application of GLP-1 receptor agonists. At the same time they potentiate insulin secretion. The enzyme mono-ADP-ribosyltransferase (ART) might overcome this problem and thus interesting for pharmaceutical industry as a new drug target.

Mammalian ARTs are divided into two groups, extracellular ecto-ARTs and intracellular endo-ARTs.[37,38] Intracellular ARTs, but not phosphatidylinositol (GPI)-anchored enzymes, are plasma membrane associated. They are less well characterized regarding gene and protein structure than their ecto-enzyme family members but their potential physiological roles have been explored.[39] Moreover, mammalian intracellular mono-ADP-ribosylation has been reported for different protein substrates, chaperone GRP78/BiP, mitochondrial glutamate dehydrogenase, poly-ADP-ribose polymerase PARP1[40,41,42,43] and for the β-subunit of heterotrimeric G-proteins.[44] The mono-ADP-ribosylation reaction is catalyzed by an arginine-specific endo-ART that transfers an ADP-ribose moiety from β-NAD^+ to a specific arginine at position 129, a crucial amino acid residue in the common effector-binding surface of the β subunit. Mono-ADP-ribosylation of this residue pre-

vents β subunit-dependent modulation of effectors such as type 1 adenylyl cyclase,[44] phosphoinositide 3-kinase-γ and phospholipase C-β2.[45] Further, mono-ADP-ribosylated β subunit is a substrate for a cytosolic mono-ADP-ribosylhydrolase that releases bound ADP-ribose from modified protein.[44] These enzyme activities are thus part of an intracellular mono-ADP-ribosylation and de-mono-ADP-ribosylation cycle, which regulates the function of the βγ dimer. The physiological role of this reaction has been supported further by the demonstration of its hormonal control exerted by thrombin, serotonin and cholecystokinin *in vitro*[45] and by thrombin in intact cells.[46] Moreover, mono-ADP-ribosylation of G-protein β-subunit can be initiated by activation of specific G-protein coupled receptors[45] and, more so, by specific synthetic peptides such as Mas 7, a structural analogue of mastoparan.[47]

GLP-1 mediated activation of endo-ART has not been determined. However, in our previous work, we used synthetic peptide IC_3, whose sequence corresponds to the third intracellular loop of the GLP-1 receptor that mimics the activated GLP-1 receptor. We found a) that the third intracellular loop of GLP-1 receptor is the main switch that mediates signaling via GLP-1 receptor to heterotrimeric G-proteins – The other two intracellular loops are responsible for specific coupling to different types of G-protein[48] – and b) we showed specific mono-ADP-ribosylation of the third intracellular loop of GLP-1 receptor *in vitro*.[49] The latter finding indicates the probable existence of a novel type of receptor activity regulation by endo-ART, and, independently, the ability to use the IC_3 for effective treatment of diabetes mellitus type 2 and obesity.

GLP-1 receptor has been described in detail elsewhere,[5,50] so we will mention only the essential features that are required for understanding the hypothetical model we proposed in Figure 1. GLP-1 receptor mediated signaling involves activation of at least two signaling pathways. i) The adenylyl cyclase/cAMP/protein kinase A pathway, that increases the level of cAMP and consequently activates EPAC 1 and 2, results in glucose-stimulated insulin secretion.[51,52,53] ii) The phosphatydilinositol 3-kinase/extracellular signal-related kinase/protein kinase Cζ pathway affects β-cell insulin gene transcription, β-cell proliferation and inhibit β-cell apoptosis.[54,55,56] Neither signaling pathway is understood completely but they may converge and overlap at some points.[5] A plasma membrane bound intracellular ART from β-cell has not yet been cloned. However, mammalian intracellular ARTs are seen in the class III HDACs (histone deacetylases) or sirtuins.[57] Human sirtuins consist of seven members (Sirt1-7) homologous to Sir2 and are located in the cytoplasm, mitochondria and nucleus. Apart from intracellular localization, Sirt1, 3, and 5 differ from Sirt2, 4, and 6 in the type of reaction they catalyse. In particular, Sirt2, 4, and 6 exert NAD^+-dependent ART activity. Sirt4 inhibits the activity of glutamate dehydrogenase in β-cells by ADP-ribosylation, thereby down-regulating insulin secretion.[42] Moreover, Sirt4 is expressed in the islets of Langerhans and colocalizes with insulin-expressing β-cells. Depletion of Sirt4 from insulin producing cells results in increased secretion of insulin from these cells, suggesting that Sirt4 negatively regulates insulin release.[58] These results fit well with our model. GLP-1 binding causes receptor conformational changes and activates the heterotrimeric G_s-protein. G_s-protein α-subunit dissociates from β dimer and receptor. Both α-subunit and β dimer are able to modulate the activity of adenylate cyclase.[44,59] The result is a locally increased concentration of cAMP, which mediates its stimulatory effect on insulin release. Mono-ADP-ribosylation by intracellular ART prevents G protein βγ dimer dependent modulation of adenylyl cyclase and consequently inhibits insulin secretion. IC_3 peptide acts as a competitive inhibitor of intracellular ART,[49] meaning that βγ dimer is now free to activate adenylyl cyclase type 2 and to potentiate insulin release in patients with diabetes mellitus type 2. Additionally, if mono-ADP-ribosylation is actually the mechanism of regulation of GLP-1 receptor *in vivo*, insulin release would be even more potent. The IC_3 peptide would prevent mono-ADP-ribosylation of β subunit, but also the third intracellular loop of GLP-1 receptor, which

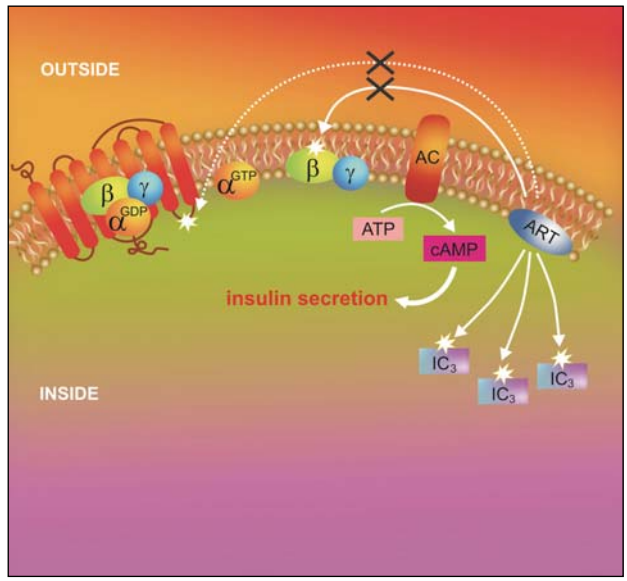

Fig. 1: Schematic representation of the cAMP-dependent GLP-1 receptor signaling pathway in β cells with a yet undefined intracellular mono-ADP-ribosyltransferase. The crucial intermediate molecule in glucose-stimulated insulin secretion from β cells is cAMP. The concentration of cAMP could be modulated by the mono-ADP-ribosylation of the third intracellular loop of GLP-1 receptor and β subunit of G-proteins. Explosion (✷) indicates the site of mono-ADP-ribosylation by intracellular ART. The dashed arrows indicate the possible regulation of GLP-1 receptor signaling pathway by ART in β cells. The cross (✕) indicates ART inhibition by IC_3 (see text for details). ART: intracellular mono-ADP-ribosyltransferase; AC: adenylyl cyclase; IC_3: third intracellular loop-peptide of GLP-1 receptor. The Figure is not applicable to an *in vivo* situation and represents the *in vitro* results with the IC_3 peptide. Mono-ADP-ribosylation of GLP-1 receptor *in vivo* still awaits identification.

is the main switch that mediates signaling to G-proteins.[60] Finally, IC_3 peptide mimics the activated GLP-1 receptor and activates G_s-proteins without use of an agonist,[48] meaning that receptor desensitization and internalization might be bypassed completely.[61]

Where should we look for an undefined plasma membrane bound intracellular ART in β-cells? Sirtuins could be considered good candidates, since one of their members, Sirt4, negatively regulates insulin release. More recently, PARP10, a member of the poly-ADP-ribose polymerases that are responsible for poly-ADP-ribosylation of cellular proteins, has been identified as functioning as an intracellular ART.[62] With the discovery of a mono-ADP-ribosylating class of PARP enzymes, the intracellular mono-ADP-ribosylation within PARP family can now be studied in more detail. A further possibility is that the still-not-yet-identified new isoforms or splice variants of the ecto-ARTs that lack the GPI-anchor might function as endo-enzymes.[63]

4. Conclusions

Peptide drugs, especially GLP-1 receptor agonists, are excellent choices to complement existing therapies. However, transmission of information depends not only on the presence of agonist. There are several other intermediate control points, such as receptor phosphorylation or mono-ADP-ribosylation that could prevent insulin secretion. Previous approaches to the treatment of diabetes mellitus type 2 and obesity are based primarily on increasing the amount of GLP-1 receptor agonist over a longer time period, which could lead to severe side effects and increased immunogenicity. The long-term consequences of such a therapy on β cell function remain unknown. IC_3 peptide, as a competitive inhibitor of mono-ADP-ribosyltransferase and its analogues (Table 2),[64] would therefore be useful in combination with GLP-1 receptor agonists. Consequently, ART peptide inhibitors would lower the amount of agonist necessary for GLP-1 receptor activation, which is certainly very desirable because of the side effects noted above. GLP-1 receptor agonists and ART inhibitors might provide a new tool for all those who are interested in the treatment of diabetes mellitus type 2 and obesity, especially in therapies with long-acting GLP-1 receptor agonists; such are albiglutide, taspoglutide and lixisenatide.

Table 2. Peptide IC_3 corresponding to sequence derived from the third intracellular loop of GLP-1 receptor (329–351) and its analogues.

Peptide	Structure
IC_3	CIVIAKLKANLMCKTDIKCRLAK
IC_3(R348A)	CIVIAKLKANLMCKTDIKCALAK
IC_3(C341A)	CIVIAKLKANLMAKTDIKCRLAK

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6. References

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Povzetek

Glukagonu podobni peptid-1 (GP-1) se je že uveljavil kot sredstvo pri zdravljenju sladkorne bolezni tipa 2. Še več, nekateri agonisti receptorja GP-1 vplivajo na izgubo telesne teže in imajo tako potencial tudi pri zdravljenju debelosti. Seveda pa imajo agonisti receptorja GP-1 lahko stranske učinke, zato jih je potrebno dati v čim nižjih koncentracijah, skupaj z novimi zdravili, ki pomagajo pri izločanju insulina. V članku se bomo osredotočili na delovanje inkretinskih hormonov, s poudarkom na GP-1 in njegovih analogih. Na koncu bomo predstavili učinek peptidov, ki izhajajo iz tretje znotrajcelične zanke receptorja GP-1, na encim mono-ADP-riboziltransferazo in v povezavi s tem predstavili nov model regulacije receptorja GP-1. Zato predlagamo, da znotrajcelična mono-ADP-riboziltransferaza lahko predstavlja novo farmakološko tarčo pri zdravljenju sladkorne bolezni tipa 2 in debelosti.