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Review

Glucose-lowering therapies in type 2 diabetes: Opportunities and challenges for peptides

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ABSTRACT

This overview considers the opportunities and challenges that face the use of gluco-regulatory peptides to treat type 2 diabetes. New insulin analogues and formulations are being developed with pharmacokinetic properties to speed-up or prolong transfer from a subcutaneous injection site to the target tissues, or to selectively favour effects on the liver. Alternative routes of insulin administration continue to attract attention, and advances in the integration of glucose monitoring with insulin pump devices are improving miniaturised 'closed loop' artificial pancreas systems. Proof of concept has been established for non-cellular glucose-responsive insulin delivery ('smart insulins') to release insulin from implants or circulating depots in proportion to circulating glucose. The many peptides involved in blood glucose control offer diverse therapeutic opportunities. Exploitation of multiple selected receptor targets using constructs of hybrid and chimeric peptides, especially those based on glucagon and gastrointestinal hormones, has gained much credence from initial preclinical studies. Peptide templates identified from comparative endocrine studies have also provided valuable insights in this respect and indicated novel approaches to address associated conditions such as obesity and infections at the same time. Nevertheless, there are many challenges to the use of therapeutic peptides that impose on every step in the complex pathway from design and testing through to making a fully characterised therapeutic product, and optimising administration, tissue targeting and degradation. Stability of peptides and immunological uncertainties of novel structures require particular consideration as well as the need to avoid over-reduction of blood glucose into hypoglycaemia.

1. Introduction

Hormonal peptides play a decisive role in the control of blood glucose homeostasis from the activation of feeding behaviour and the intestinal digestion of carbohydrates through to the storage, mobilisation and utilisation of glucose as a vital source of energy. Blood glucose concentrations are normally maintained within a narrow range of 4–9 mmol/L, due mostly to peptide hormones that balance fluctuations in the prandial supply and tissue storage of nutrients with the varied demands of normal metabolism and the extremes of exercise and fasting. Excess glucose accumulates in the liver and muscle as glycogen or is converted to triglyceride in adipose tissue, and the liberation of these nutrient stores is highly regulated. Low blood glucose concentrations (hypoglycaemia) below about 3 mmol/L cause symptoms of neuroglycopenia and concentrations below 2 mmol/L can be fatal. Conversely, exposure to high circulating glucose concentrations (hyperglycaemia) above about 10–12 mmol/L causes glucosuria, osmotic diuresis and risk of dehydration, while persistent hyperglycaemia (diabetes) causes glucotoxic damage to the endothelium of capillaries which typically manifests as nephropathy and retinopathy as well as nerve cell damage responsible for neuropathies. Glucotoxic damage to the endothelium in large vessels also contributes to the long-term increased risk of cardiovascular disease in type 2 diabetes [1].

The persistent hyperglycaemia of diabetes is predominantly due to defects in the secretion and/or action of insulin, but many other regulatory peptides are intimately involved, especially with type 2 diabetes. Lack of insulin and impaired insulin action (insulin resistance) deprive major insulin-sensitive tissues such as active skeletal muscle of adequate glucose. Inadequate insulin is also responsible for unrestrained output of glucose by the liver and fatty acids released from adipose tissue, resulting in the elevated concentrations of these nutrients in the circulation. Beyond disruption of insulin-glucose dynamics, altered production, secretion and activity of many other peptide hormones contribute to the metabolic disturbances and the pathogenic sequelae in diabetic states. These include other pancreatic hormones and regulatory peptides of the alimentary tract, other neuroendocrine glands, adipose tissue and further peptide-secreting tissues [Table 1]. This chapter will focus on the breadth of opportunities and

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Table 1
Gluco-regulatory peptides with established or potential therapeutic use in the management of hyperglycaemia in type 2 diabetes. ↑ increase; ↓ decrease.

Peptide hormone	Main gluco-regulatory effects	Type 2 diabetes therapeutic potential
Pancreas		
Insulin	↓ Hepatic glucose output ↑ Peripheral glucose uptake and utilisation ↓ Lipolysis ↑ Protein anabolism ↑ Growth and differentiation	Lowers blood glucose but can cause hypoglycaemia. Default glucose-lowering therapy in severely insulinopenic type 2 diabetes. Many available analogues, formulations and delivery systems. Extensive developments in progress
Glucagon	↑ Hepatic glucose output ↑ Energy expenditure ↑ Satiety	Raises blood glucose: key counter-regulatory effect. Relative hyperglucagonaemia in type 2 diabetes is potential therapeutic target.
Somatostatin	↓ Glucagon and insulin secretion ↓ Growth hormone secretion Many other neuro-endocrine roles, especially in GI tract	Analogues used therapeutically to treat excess GH, but suppression of insulin reduces suitability for type 2 diabetes
Pancreatic polypeptide	↓ Food intake Various GI effects	Possible value in treatment of obesity
Amylin (IAPP)	↑ Satiety ↓ Gastric emptying ↓ Glucagon secretion	Analogue (pramlintide) available in some regions for use with insulin: assists glucose lowering and weight loss
Alimentary tract		
GLP-1	↑ Nutrient-induced insulin secretion ↓ Glucagon secretion ↓ Gastric emptying ↑ Satiety and ↓ body weight Emerging CV and neuroprotective effects	Established blood glucose-lowering therapy in overweight and obese type 2 diabetes, especially with metformin and insulin. Fixed ratio combinations with insulin
GIP	↓ Gastric acid secretion ↑ Nutrient-induced insulin secretion ↑ Glucagon secretion Emerging roles in adipogenesis and bone remodelling	Research into potential therapeutic role: effects of agonists and antagonists vary with physiological state. Potential therapeutic role supported by bariatric procedures that reduce contact of food with duodenum
Peptide YY	↓ Gastric emptying ↑ Satiety ↓ body weight	Potential anti-obesity therapy
Oxyntomodulin	↑ Nutrient-induced insulin secretion ↓ Gastric emptying ↑ Energy expenditure ↑ Satiety and ↓ body weight Overall effects on glucagon? Emerging effects on liver and adipose tissue	Potential therapy for type 2 diabetes. Agonist at receptors for GLP-1 and glucagon: uncertain balance of glucose lowering effect via GLP-1R versus glucose-raising effect via glucagon receptor. Possible ↓ ghrelin, ↑adiponectin and ↑ FGF21
Cholecystokinin	↑ Gall bladder contraction ↑ Pancreatic digestive enzymes ↑ Satiety ↓ Gastric emptying Various neural effects	Fragments and analogues that preferentially promote satiety considered for therapeutic purposes. Possible effect on islet beta-cell growth
Gastrin	↑ Gastric acid secretion ↑ Gastric motility	Possible effect on islet beta-cell growth
Secretin	↑ Pancreatic juice and enzymes	Possible islet effects unclear
Ghrelin	↑ Appetite ↑ Adipogenesis ↑ Growth hormone	May decrease insulin secretion. Research into potential therapeutic role of antagonists
Obestatin	↓ Appetite Emerging metabolic effects	Therapeutic interest in possible effect on islet beta-cell growth and antagonism of ghrelin
Adipose tissue		
Adiponectin	↑ Insulin sensitivity ↑ Energy expenditure Various metabolic, anti-inflammatory and vascular effects	Therapeutic application of adiponectin itself limited by physicochemical properties, but other agonists of adiponectin receptors and agents to stimulate adiponectin secretion being studied
Leptin	↓ Appetite and ↓ body weight ↑ Insulin sensitivity ↑ Energy expenditure Neurally mediated effects that improve glucose homeostasis	Short-term therapeutic value of metraleptin to reduce body weight and lower blood glucose is limited by increasing leptin resistance
Resistin	↑ Insulin resistance?	Target candidate for antagonism?
Omentin	↑ Insulin sensitivity Emerging vascular effects?	Target candidate for agonism?
Visfatin	Insulin-like effects?	Possible target candidate?
Apelin	Emerging vascular and metabolic effects	Possible target candidate?
Liver		
Fibroblast growth factor-21	↑ Insulin sensitivity	FGF-21 resistance may occur in obesity and type 2 diabetes
Insulin-like growth factors	Weak insulin-like effects	Assist glycaemic control if severe defects of insulin receptors
Fetuins	Emerging evidence of impaired glycaemic control	Possible target candidates?

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