North Asian International Research Journal of Pharmaceutical & Medical Sciences

IRJIF: 5.012

ISSN: 2456-8287 Vol. 7, Issue-3 March-2023

Index Copernicus Value: 64.15 Fulfill MCI Criteria Indian Citation Index

NAIRJC A Peer Reviewed Refereed Journal

DOI: 10.5859/2456-8287/nairjc_6.9.2

TREATMENT OPTIONS FOR DIABETES

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INTRODUCTION

Diabetes is an increasingly common metabolic disorder distinguished by lack of production or dysfunction of the insulin hormone, resulting in raised blood glucose levels, known as hyperglycaemia (Bailey 2015). In 2015, it was recorded that approximately 415 million individuals had diabetes worldwide, which is expected to increase to 642 million individuals by 2040 (International Diabetes Federation (IDF) 2015). Financially, it was estimated that the total cost for both the direct and indirect care associated with diabetes within the UK is currently £23.7 billion. This is expected to rise to £39.8 billion by the year 2035-2036 (Diabetes UK 2016).

There are two main forms of diabetes mellitus, Type 1 (Insulin-Dependent) and Type 2 (Non-Insulin Dependent). Type 1 is a chronic autoimmune disease which develops following the destruction of the Î²-cells within the islets of Langerhans throughout the pancreas. The Î²-cells function by synthesising and secreting insulin in the response to the maintenance of glucose levels. (Bluestone et al 2010) (Kulkarni 2003). When these cells are destroyed, this results in the loss of blood glucose control. Therefore, insulin replacement is the main treatment therapy in order to maintain optimum blood glucose levels (Bacha and Klinepeter 2015) (Bailey 2015). Type 2 (Non-Insulin Dependent) diabetes is the most common type, affecting approximately 85-90% of individuals with diabetes (Hex et al 2012). This type occurs when the Î²-cells produce defective insulin or when insulin secretion is reduced resulting in insulin resistance and hyperglycaemia (Nyenwe et al 2011). Certain therapeutic treatments can be given to maintain blood glucose levels (Bailey 2015).

At present there is no single drug available that can treat all aspects of diabetes mellitus, due to the complexity of the Î²-cells within the pancreas. However, there are various medications currently available that can be used in combination with lifestyle changes to reduce hyperglycaemia and maintain blood glucose homeostasis (Bailey 2015) (Breuer et al 2010). Treatment therapy is selected according to the pathophysiology of the individual. More recent approved treatments include SGLT-2 inhibitors, bile acid sequestrants and incretin mimetics (Bailey 2015). More focus being brought to peptide treatment therapy relating to neurotensin (Chowdhury et al 2013).

TYPE 2 DIABETES (NON-INSULIN DEPENDENT)

The maintenance of blood glucose homeostasis is performed by two hormones secreted from the islet of Langerhans cells in the pancreas. Insulin, secreted from the Î²-cells and glucagon, secreted from the Î±-cells (Meece 2007).

Type 2 Diabetes Mellitus develops when the Î²-cells within the pancreas become dysfunctional and the volume of insulin released is inadequate to maintain glycaemic control (Kasuga 2006) (Nyenwe et al 2011). Hyperglycaemia ensues, increasing the demand for insulin, and to compensate the Î²-cells excessively release insulin to lower the blood glucose level and over time these cells lose their function (Kasuga 2006).

CURRENT TREATMENTS

The occurrence of Type 2 diabetes continues to increase globally; and whilst the pathophysiology and further complex issues are understood, treatment therapy can be difficult (Nyenwe 2011). Currently approved diabetic drug therapies are listed in Table 1**.**

Table 1. Current approved drug therapy used in the treatment of Type 2 diabetes to aid in the maintenance of blood glucose homeostasis.

DRUG	ROUTEÂ	MECHANISM OF ACTION	IMPLICATIONS
BIGUANIDE Metformin	Oral	Suppresses hepatic glucose production and increase insulin sensitivity within the muscle tissue	Linked to lactic acidosis. Gastrointestinal side effects. Should be avoided in deteriorating renal function or liver impairment.
SULFONYLUREAS Gliclazide Glimepiride Tolbutamide	Oral	Increases insulin secretion by binding to sulfonylurea receptor-1 on Î²-cells resulting in depolarisation and calcium influx	Weight gain is possible. High risk of hypoglycaemia – need for close blood glucose monitoring.
DPP-4 INHIBITORS Saxagliptin Sitagliptin Vildagliptin	Oral	Inhibits enzyme DPP-4, prolonging incretin hormones (GLP-1 and GIP) half-lives	Association with pancreatitis
SGLT2 INHIBITORS Dapaglifozin	Oral	Inhibit Sodium-Glucose-Co-transporter-2 proteins to increase glucose elimination in urine	High risk of developing genital and urinary tract infections. High risk to hypoglycaemia.

GLP-1 MIMETICS	Subcutaneous injection	Binds to GLP-1 receptors causing an increase of insulin secretion, reduce glucagon secretion, delay gastric emptying and appetite suppression	Association with pancreatitis and can cause gastrointestinal side effects. Should be avoided in deteriorating renal function.
Bile Acid Sequestrants	Oral	The mechanism is still uncertain. It is thought that this drug interferes with the enterohepatic circulation of bile acids to lessen their effect; increasing glucose metabolism and advance GLP-1 secretion	Association with gastro intestinal disorders and elevated triglyceride levels.

METFORMIN

This is the preferred first-line drug choice to treat Type 2 Diabetes Mellitus. This drug is part of the biguanide class and its main role is to reduce and maintain blood glucose levels without the risk of hypoglycaemia (extremely low blood glucose levels) and weight gain (Chatterjee 2015). It reduces glucose levels by suppressing hepatic glucose output and increasing insulin sensitivity in muscle cells (Bailey 2015). This drug can be used with used alone, but may be more effective when used in combination with other diabetes therapies, such as DPP-IV inhibitors, sulfonylureas and insulin. (Chatterjee 2015) (Ahren 2008).

SULFONYLUREAS

This drug stimulates the secretion of insulin from pancreatic Î²-cells, by binding to the sulfonyurea receptor subunit of ATP sensitive potassium channel, closing it (Prors 2002). This closure causes depolarisation of the membrane, producing an influx of calcium, activating insulin secretion (Bailey 2015). This drug can only work correctly depending on sufficient Î²-cell function within the pancreas to assist in the release of more insulin (Bailey 2015).

DPP-IV INHIBITORS

This drug functions by inhibiting the action of enzyme DPP-IV from breaking down incretin hormones, in particular GLP-1. Prolonging the life of the incretin hormone allows it to perform its role and stimulate insulin secretion of the pancreatic Î²-cells (Seino 2010).

Sodium Glucose Transporter-2 (SGLT-2) Inhibitors

SGLT-2 proteins present in the proximal convoluted tubule of the kidney are responsible for renal glucose filtration and reabsorption (Rizos and Elisaf 2013). Inhibitors of SGLT-2 competitively bind to and block the proteins reducing the amount of glucose reabsorption in the blood but increasing the amount of glucose excreted in urine (Bailey 2015). Associated with the elimination of glucose in urine, the use SGLT-2 inhibitors increase the risk of genital and urinary tract infections (Bailey 2015).

BILE ACID SEQUESTRANTS

Bile acids are produced in the liver and upon release promote the absorption of fatty acids (Hansen 2014). However, it has been found that bile acids are associated with the regulation of glucose homeostasis (Nguyen 2008). The exact mechanism of the bile acids sequestrants is unknown, but it has been investigated that this drug

inhibits the binding of bile acids to the corresponding receptors, TGR5 and Farnesoid-X-receptor (FXR) interrupting the enterohepatic bile acid circulation and increasing the utilisation of glucose. (Hansen 2014) (Bailey 2015).

COMBINATION TREATMENT THERAPY

More recently combination drug therapy has been analysed and proved to have beneficial effects in rodents, such as GLP-1-GIP-GCG triple incretin agonists (Gault 2013).

GUT PEPTIDES

The intake of food generates the release of two primary incretin hormones; Gastric inhibitory polypeptide (GIP) and Glucagon-like peptide (GLP-1) (Seino et al 2010). Secreted from the intestinal K-cells and L-cells respectively (Bailey 2015), these hormones are released to stimulate insulin secretion to aid in glycaemic control and have a positive effect on the survival of Î²-cells (Brubaker 2006).

GLP-1

These 31 amino acid hormone chains, not only inhibits glucagon release and stimulates insulin secretion, also has been discovered in the Central Nervous System promoting satiety (Seino et al 2010) (Gallwitz 2005).

GLP-1 agonists are more recently used as peptide drug to treat type 2 diabetes mellitus (Fosgerau 2015).

NEUROTENSIN

A neuropeptide secreted from endocrine cells in the gastrointestinal tract, was found to have two important roles in glycaemic control by increasing the release of insulin in low glucose concentrations and decreasing the release of glucose-mediated insulin (Gruundal et al 2016) (Béraud-Dufour 2010). Neurotensin also functions to protect the pancreatic Î²-cells from apoptosis in patients with Type 2 diabetes (Mazella 2012).

XENIN

Xenin, a 25 amino acid gut peptide derived from the K-cells in the small intestine (Wice et al 2012). This peptide was initially identified in the human gastric mucosa, and it was further discovered in the liver, pancreas, hypothalamus and stomach (Parthsarthy 2016). It is co-secreted from the K-cells along with GIP following the consumption of high-fat meal increasing the concentration of this peptide in the plasma (Martin et al 2012) (Wice 2012). Natural occurring xenin has been known to have a restricted therapeutic effect due to break down by plasma enzymes (Martin et al 2016). A hybrid peptide Xenin-25(gln) was generated by substituting Arginine and Lysine amino acids present on natural Xenin-25 with Glutamine (Parthsarthy et al 2016).

MODIFIED GUT PEPTIDE

Hybrid peptides have been generated via fusion of vital sequences in amino acid chains (Hasib et al 2016). These modified peptides increase the therapeutic ability of antidiabetic drugs, which can be given in one drug combined, rather than separate forms (Hasib 2016).Â Recent studies assessing the therapeutic activity of the hybrid peptide

xenin-8-gln, in the treatment of Type 2 diabetes (Hasib et al 2016) compared to constituent parent peptides, indicate a potential for the use of hybrid peptides in the treatment of diabetes.

BRIN BD11 CELLS

Electrofusion of rat pancreatic islet cells and RINm5F cells produced a hybrid cell line known as BRIN-BD11 cells (McClenaghan et al 1996) (Davies et al 2000). It was found that this cell line had similar properties and responses when compared to normal Î²-cells (Davies et al 2000).

CONCLUSION

Recent research has demonstrated that new therapeutic treatments are needed as the incidence type 2 diabetes mellitus is increasing globally. Hybrid peptides are becoming more popular in the field of diabetes treatment. By generating a long-acting modified peptide ($Q^8Q^9W^{11}$) neurotensin-K^6-L-glutamyl-PAL it will be investigated how effective it will be at stimulating insulin secretion compared to non-acetylated constituent peptides. This modified peptide, along with control peptide counterparts will be commercially synthesised and purified using HPLC. The insulin secreting properties of the modified peptide will be measured, recorded and analysed at various glucose concentrations within BRINBD-11 cells. This could further develop treatment for type 2 diabetes.

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