A Review on Insulin-Producing Beta Cell: Regenerative Role of Drugs Acting on DYRK1A, GLP-1 and DPP-4 Receptors

By

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A thesis submitted to the Department of Pharmacy in partial fulfillment of the requirements for the degree of
Bachelor of Pharmacy

Department of Pharmacy
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Declaration

It is hereby declared that

1. The thesis submitted is my own original work while completing degree at Brac University.
2. The thesis does not contain material previously published or written by a third party, except where this is appropriately cited through full and accurate referencing.
3. The thesis does not contain material which has been accepted, or submitted, for any other degree or diploma at a university or other institution.
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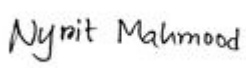

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Approval

The thesis titled "A Review on Insulin-Producing Beta Cell: Regenerative Role of Drugs Acting on DYRK1A, GLP-1 and DPP-4 Receptors" submitted by Nyrit Mahmood (17146013) of Spring, 2017 has been accepted as satisfactory in partial fulfillment of the requirement for the degree of Bachelor of Pharmacy (Hons) on 29th May 2021.

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Ethics statement

This study does not involve any kind of human or animal trial.

Abstract

Approximately 422 million people have diabetes all over the world. The regeneration of the beta cell has been investigated for a longer time by scientists with the hope of newer potential opportunities, thus contributing to the treatment of diabetes. Beta-cell regeneration is a mechanism of producing new beta cells in the pancreas, which is responsible for the secretion of insulin, currently on pre-clinical trials. In this study, the action of each three receptors – GLP-1, DPP-4, and DYRK1A has been discussed. Their possibility of combination in the regeneration of damaged beta cells for the welfare of diabetic patients by comparing the ability of each of the receptors to regenerate beta cells as well as the combination of actions on these receptors produce any better effect or not has also been analyzed. However, millions of people with diabetes have a ray of hope as the current use of GLP-1 and DYRK1A indicates a prospective technique based on DYRK1A inhibition with the GLP-1 receptor. Moreover, it is also a fact that still there is no evidence of any potential combined treatment with the use of GLP-1 and DPP-4 for diabetic patients.

Keywords: Glucagon-like peptide-1, Dipeptidyl peptidase-4, Dual specificity tyrosine-phosphorylation-regulated kinase 1A, Beta-cell regeneration, Diabetes

Dedication

Dedicated to my Parents

Acknowledgment

I would like to thank them who have contributed significantly to my academic success. I would like to express my gratitude to the Almighty for keeping me healthy and allowing me to pursue my dreams with the knowledge I have gained throughout my life.

First and foremost, I would like to thank my father for his unwavering support and motivation in helping me to follow my dreams.

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Table of contents

List of tables

List of figures

List of acronyms

SGLT2	Sodium-glucose cotransporter 2
OGTT	Oral glucose tolerance test
HbA1c	Hemoglobin A1c or glycated hemoglobin test
GDM	Gestational diabetes mellitus
ADH	Antidiuretic hormone
AVP	Arginine vasopressin
GLP-1	Glucagon-like peptide-1
DPP-4	Dipeptidyl peptidase-4
DYRK1A	Dual specificity tyrosine-phosphorylation-regulated kinase 1A
GSIS	Glucose-stimulated insulin secretion
VG	Vildagliptin
5-IT	5-iodotubercidin
Pdx	Pancreatic duodenal homeobox-1
FGF21	Fibroblast growth factor 21

Chapter 1

Introduction

1.1 Diabetes

Diabetes is a heterogeneous category of syndromes that are distinguished by excessive blood glucose due to a relative or absolute insulin deficiency (Whalen et al., 2019). The number of cases and the prevalence of diabetes has gradually increased in recent times. At the same time, it has been observed that about approximately 422 million people have diabetes. In reality, most of the people are from those countries where the income of people is not that high. From different statistics, it has been observed that about 1.6 million deaths are preciously responsible for diabetes. Around, 8.5 percent of adults over the age of eighteen years were diabetic in 2014. From 2000 to 2016, premature mortality from diabetes increased 5 percent (M. Chan, 2016). The premature mortality rate for diabetes in high-income countries dropped between the years 2000 and 2010 and was raised by 2010-2016. Diabetes may affect any part of the body. Similarly, some areas of our body are more vulnerable to severe than others. The more poorly regulated the diabetes is, the greater the likelihood of complications. However, complications can be kept in check and avoided by having a consistent control on blood sugar and cholesterol levels. Upon this variety of possible consequences, one will find heart attack, renal failure, amputation, and neuropathy. Additionally, lower back pain and eye infections, urinary tract infections, cataracts, and erectile dysfunction are very common among diabetic people (Chawla et al., 2016) (Fiagbe et al., 2017).

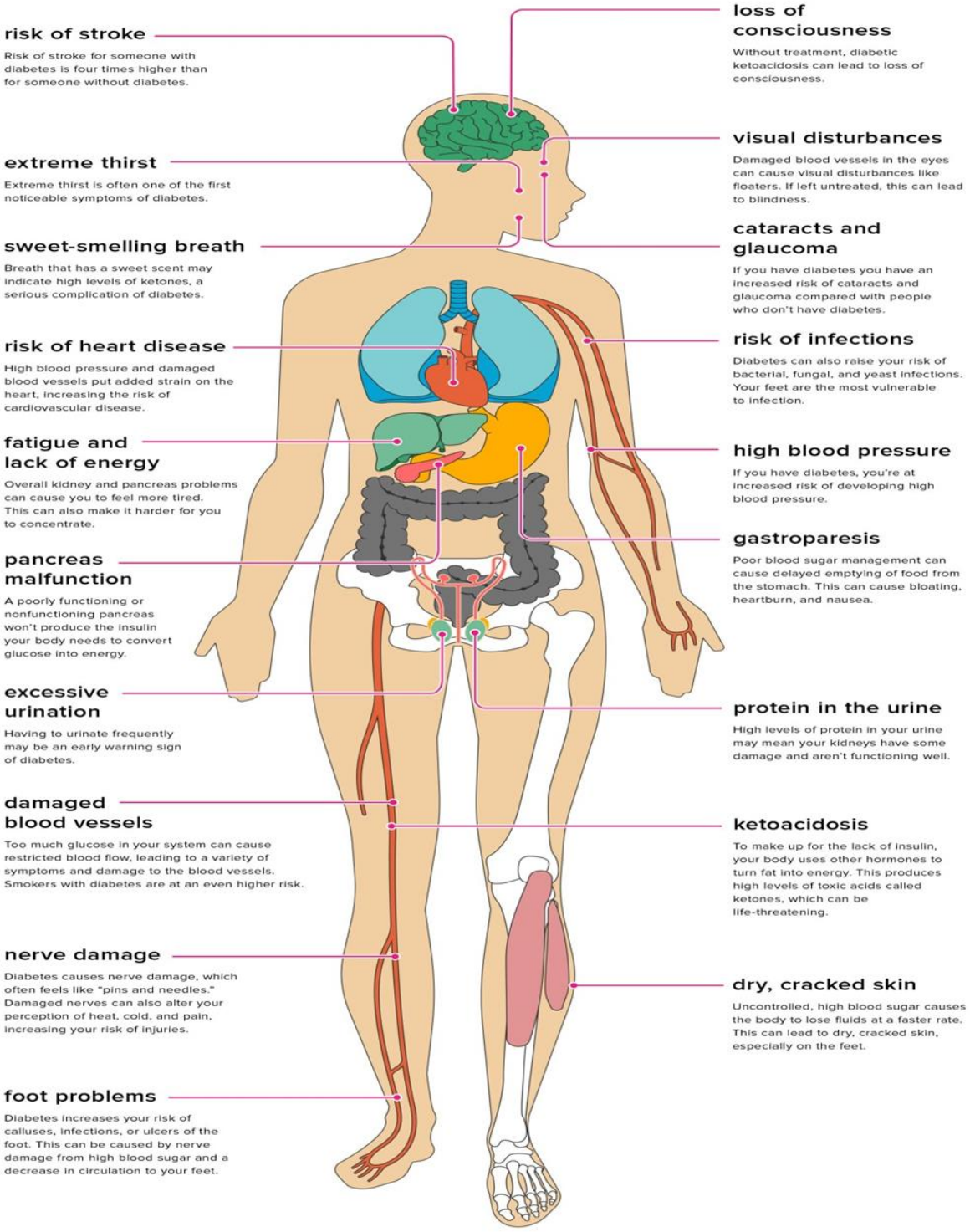

Figure 1 : The effect of diabetes on the body (Ann Pietrangelo, 2017)

1.2 Causes, the prognosis of diabetes

There are many causes of diabetes.

Prediabetes:

Prediabetes is diagnosed when an individual's fasting glucose, impaired glucose tolerance, and increased glucose levels are elevated. HbA1c levels range between 5.7 percent and 6.4 percent. According to the World Health Organization, it has a narrower threshold between 110 and 125 mg/dL (Zand et al., 2018).

Type I diabetes:

Without functional β cells, the pancreas does not respond to glucose, and a person with type I diabetes has classic insulin deficiency symptoms for example; polydipsia, polyphagia, polyuria, and weight loss. However, people with type I diabetes without functioning cells cannot sustain basal insulin secretion or respond to changes in the circulating amount of glucose. Constant β-cell secretion retains low basal levels of circulating insulin during the usual post-absorptive era. This inhibits lipolytic, proteolytic, and glycogenolytic cleavage. Insulin secretion surges within two minutes of meal ingestion in response to transient changes in blood glucose and amino acid levels. It takes up to 15 minutes and is caused by postprandial insulin secretion (Whalen et al., 2019)

Type II diabetes:

In type II diabetes, the pancreas maintains some of its β-cell activity but insulin isolation is not enough to preserve glucose homeostasis due to the increase in peripheral insulin tolerance, which is characterized by the loss of insulin sensitivity of the target organ. Beta-cell mass can decrease gradually in the case of type II diabetes. In contrast to type I diabetes patients, people

with type II diabetes are often obese. Obesity increases resistance to insulin, which is considered the most fundamental dysfunction in type II diabetes (Whalen et al., 2019).

Gestational diabetes;

Gestational diabetes is characterized as carbohydrate aversion with onset or first diagnosis throughout pregnancy. Important to realize, uncontrolled gestational diabetes will contribute to fetal macrosomia a condition of an abnormally large body. As per international consensus criteria for OGTT, when fasting plasma glucose levels reach 92 mg/dL,1h exceeds 180 mg/dL, or 2 h after glucose loading exceeds 153 mg/dL, it can be understood that the patient is suffering from gestational diabetes mellitus. For diagnosis, a single increase in value is sufficient as well as strict metabolic monitoring is mandatory. OGTT is not recommended following bariatric surgery due to the possibility of postprandial hypoglycemia (Kautzky-Willer et al., 2019).

1.3 Types of diabetes

Diabetes insipidus

Diabetes insipidus is likely due to impaired secretion of arginine vasopressin (AVP) or renal tubular with no responsibility to arginine vasopressin. It is also widely called pituitary (central insipidus diabetes) antidiuretic hormone (ADH). If the patient is deprived of fluid, this leads to polyuria, hyposthenuria polydipsia, which cause dehydration and hypernatremia (Saifan et al., 2013).

Diabetes mellitus

The most common type of diabetes is diabetes mellitus. It results in higher blood sugar levels. The body splits food into glucose, the fuel for normal metabolic processes in cells (Hisham M Darwish, 2015). If the body cannot effectively absorb glucose, high levels of sugar contribute to severe health problems, such as kidney failure, vision loss, and amputation.

Diabetes mellitus is of two types:

Type I diabetes: Type I, though most commonly occurring in children and youth, may grow at any age (Saifan et al., 2013).

Type II diabetes: Type II, that means, adult diabetes accounts for an estimated 90% of diabetes cases (Saifan et al., 2013).

1.4 Treatments for diabetes

The key aim of diabetes therapy for avoiding complications of the condition is to regulate blood sugar (glucose) levels. Type I diabetes is treated with insulin, as well as dietary changes and exercise. Non-insulin drugs, insulin, weight loss, or lifestyle changes can be used to regulate type II diabetes (Robert Ferry Jr., 2020). Prediabetes may indeed be controlled with improved lifestyles, perhaps with a balanced diet, loss of weight, and regular exercises.

Insulin treatment: Type I diabetes

Anyone with type I diabetes requires insulin treatment for a lifetime. Multiple insulin forms include short-acting insulin, fast-acting insulin, intermediate-acting insulin, and long-acting insulin.

Table 1: Examples of insulin in the treatment of diabetes (Otto-Buczkowska & Jainta, 2018)

Short-acting insulin	Novolin R Humulin RN
Fast-acting insulin	Insulin lispro (Humalog) Insulin glulisine (Apidra)
Intermediate-acting insulin	Insulin glargine (Lantus, Toujeo Solostar) Insulin degludec (Tresiba) Insulin detemir (Levemir)
Long-acting insulin	Insulin NPH (Novolin N, Humulin N)

Diabetes medications: Type II diabetes

The following include prescription therapies for type II diabetes.

Metformin: Metformin primarily works by decreasing liver glucose and increasing the body's insulin tolerance, resulting in more effective insulin use. The first medication used for type II diabetes commonly consists of metformin (Fortamet, Glumetza, others) (Whalen et al., 2019).

Sulfonylureas: Glipizide, and Glimepiride, DiaBeta and Glynase, Glynase and Amaryl are examples of sulfonylureas (Whalen et al., 2019). Sulfonylureas stimulate the liver to produce more insulin.

Glinides: Glinides stimulate more insulin secretion from the pancreas. Repaglinide and nateglinide are some examples. They function faster than sulfonylureas and have a shorter effect on the body (Otto-Buczkowska & Jainta, 2018).

Thiazolidinedione: Thiazolidinediones make the tissues of the body more insulin-sensitive. Rosiglitazone (Avandia) and pioglitazone (Actos) are examples of thiazolidinedione (Otto-Buczkowska & Jainta, 2018).

SGLT2: Inhibitors of SGLT2 affect blood vessels in kidneys by inhibiting the bloodstream's return of glucose. As a consequence, glucose is excreted from the urine. These medications can help reduce the risk of heart disease and stroke in people who are predisposed to these conditions (Otto-Buczkowska & Jainta, 2018). Examples of SGLT2 inhibitor include dapagliflozin (Farxiga), and empagliflozin (Jardiance).

Other medications: Apart from medications for diabetes, the doctor will prescribe medicines for blood pressure and lowering cholesterol and low-dose aspirin for the prevention of heart and blood vessels (Robert Ferry Jr., 2020).

1.5 Additional aspects on controlling diabetes

Diet for diabetes

Food strategies are customized to the requirements, routines, and eating habits of each person. Proper nutrition is key to all people with diabetes. Regulation of blood glucose levels is indeed one goal of a balanced diet schedule. The intake of insulin and other diabetes medication must be balanced in each diabetes diet plan. Whole grain, fruit, non-fat milk, beans, lean meats, vegetarian alternatives, poultry, or poultry fish provide different foods in a balanced diet. Consideration about serving portions and preparing for meals will make diabetic people enjoy the same meals as anyone else (Asif, 2014).

Glycemic index and glycemic loading

The glycemic index is a measure of the ability of various carbohydrate-containing foods to increase blood glucose levels within two hours. Again, the glycemic load can be calculated by multiplying the content of carbohydrates in a given food by the number of carbohydrates in a serving of that food. For a standardized calculation, the glycemic index applies, whereas the glycemic load considers the average size of the component. Glycemic index and glycemic load are more significant when evaluating a diabetes meal plan. Low glycemic index and load foods increase more progressively than high glycemic index or load foods, thus increasing blood sugar (Monro & Shaw, 2008).

Reduction of weight and exercise

Weight reduction and physical exercise boost the body's insulin reaction, assisting in the regulation of blood sugar elevations. However, everyone needs daily physical exercise, and people with type I diabetes are no different from this. Weight loss and physical activity are also good treatments for type II diabetes (Swift et al., 2014).

Carbohydrate, fat, and protein counting

A dietician will be urged to consume less of these things, like white bread and cookies, or processed carbs. This balanced eating schedule is recommended even for people without diabetes. A licensed dietitian will help to build a food schedule that is suitable for their needs (Hibbert-Jones, 2016)

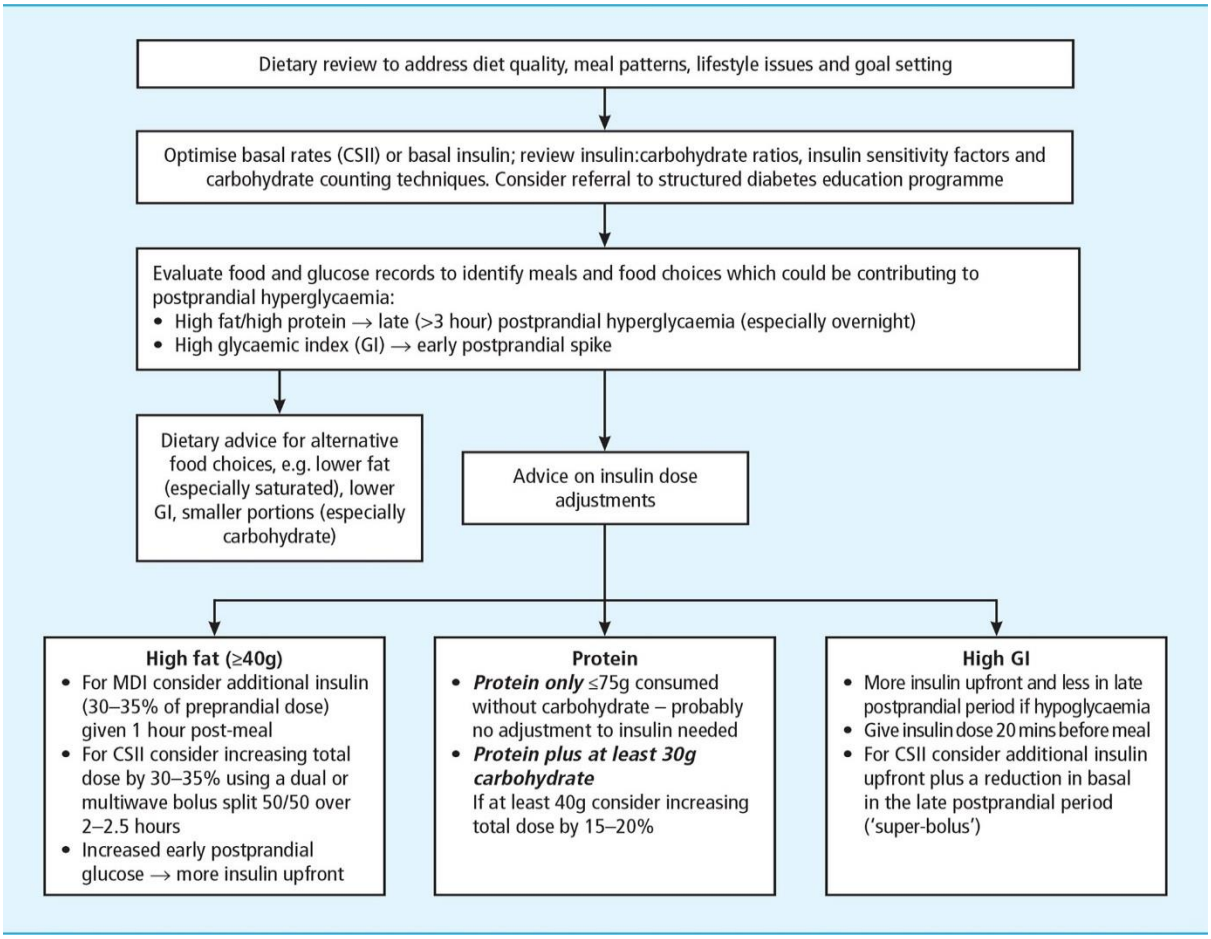

Figure 2 : Nutritional intervention to improve postprandial glycemia (Chen et al., 2020)

1.6 Need for new treatment options

Diabetes impairs the regulation of insulin, a hormone essential for glucose uptake in cells, resulting in elevated blood sugar levels. The two major forms of diabetes evolve differently, but there are certain apparent similarities in symptoms. Type I autoimmune disorder in which beta-pancreatic insulin cells are destroyed. By contrast, individuals with type II diabetes develop insulin resistance, which ensures that it has little effect on blood sugar levels (Fernandez, 2019). In some cases, it has been observed the current treatments that are already present in treating diabetes are not sufficient enough. For this purpose, scientists are finding newer opportunities for this condition.

1.7 Challenges of antidiabetic drugs and insulin supplements that are needed to overcome

Subcutaneous injections are the most reliable and traditional method of administering insulin. This method is often painful, which discourages patient compliance, especially when multiple dose injections are required four times a day. There have also been reports of hypoglycemic episodes after multiple insulin injections. To reduce the suffering of diabetic patients, several new approaches to the method have been adopted, including the use of supersonic injectors, infusion pumps, sharp needles. While some of them helped diabetic patients with pain, they were insufficiently convenient. Even though the ultimate goal is to eliminate the need for exogenous insulin delivery and restore patients' ability to produce and use their insulin, new concepts for delivering insulin via oral, pulmonary, nasal, ocular, and rectal routes are currently being investigated. The effectiveness of a route of administration is determined by its ability to produce a consistent and effective reduction in blood glucose levels. There are several challenges to overcome when using formulation and application device technology (M. M. Al-Tabakha & A. I. Arida, 2008).

1.8 Newer opportunities for treating diabetes

Type I diabetes

A. **Replacement of missing cells with cell therapy:** The most advanced alternatives have been offered by the Diabetes Research Institute in the US for creating a bioengineered mini-organ where insulin-producing cells are encapsulated inside a protective barrier (Fernandez, 2019). Cell therapy is one of the most common methods that makes it easy for accelerating the discovery of a cure for diabetes, especially type I diabetes. This will potentially substitute missing insulin-producing cells, regenerating normal insulin

supply, and curing patients. Earlier efforts at pancreatic cell transplantation have mostly declined, owing to immune responses that both prevent and kill the implanted cells. The Belgian company Orogenesis is seeking a method where cells from the liver of the recipient are converted into cells that contain insulin to prevent donor cell recruitment problems. Again, Islexa is also trying to design a related technique in the United Kingdom to procure pancreatic cells.

B. **Immunotherapy used for attacking origin:** In the case of type I diabetes, the immune system gradually kills the insulin-producing cells. This process is needed to be stopped as early enough for providing a solution. ActoBio Therapeutics, a Belgian company based, is currently conducting a phase I and phase II clinical trial with an unconventional pathway to evading type I diabetes. Imcyse, another Belgian firm, has performed a clinical trial aimed at preventing type I diabetes by deliberately targeting the immune cells that trigger pancreas injury (Fernandez, 2019). Via the activation of regulatory T cells, cheese-producing bacteria instruct the immune system not to attack insulin-producing cells.

C. **Automated treatment with an artificial pancreas:**

A much more immediate form of treatment for patients who have already impaired their insulin-producing cells could be an 'artificial pancreas,' a completely functioning device capable of measuring glucose levels and injecting the required amount of insulin into the bloodstream, just like a healthy pancreas does. However, several challenges must be addressed before insulin therapy can be fully simplified. To begin, faster forms of insulin are needed to react quickly enough to changes in blood sugar (Fernandez, 2019).

Type II diabetes

A. **Insulin synthesis stimulation:** GLP-1 or its inhibitors are available on the market in all major pharmaceutical companies like Sanofi, Eli Lilly, Roche, AstraZeneca, and Boehringer Ingelheim. However, Novo Nordisk is making a move further with the first widely viable oral form of the GLP-1 medication. The French company Poxel aims at a new approach for a drug that targets the pancreas, liver, and muscles specifically for lower sugar levels (Fernandez, 2019). By the same token, German Morphosys is now focusing on the obesity component of type II diabetes in phase II antibody tests designed to reduce weight, suppress insulin tolerance. One of the major advancements in the treatment of type II diabetes is the agonists of the GLP-1 peptide-like receptor, which increases insulin output in beta-pancreatic cells and suppresses glucagon secretions, the hormone of the opposite insulin activity.

B. **Targeting the microbiome:** To emphasize, within the last decade, new research reveals that bacteria inside us play an important role in our survival. Patients with diabetes, who has a less stable gastrointestinal microbiota than healthier ones, have an unbalanced microbiome structure (Fernandez 2019). Multiple chronic diseases, including diabetes, have been related to the human microbiome, and especially the gut microbiome. Researchers from the University of Amsterdam recently found that fecal transplants, used to move the microbiota of a healthy person to the gut of one with diabetes, can result in a short-term reduction of insulin resistance in obese patients with type II diabetes.

C. **The needle-free revolution:** According to MediWise, Panos Kosmas' co-founder, the facility can minimize healthcare expenses, which exceed €90 billion annually in Europe for diabetes Furthermore, new developments are expanding, such as the use of laser

light to monitor blood sugar levels and radiation signals in London's GlucoSense (Fernandez2019).

Chapter 2

Aim and objective

The aim of this review is to –

- Find out an effective treatment to regenerate beta cells and to increase the quality of life of diabetic patients.

The objective of this review is to-

- Find out the most potential receptors among the three receptors (GLP-1, DPP-4, and DYRK1A) and how they can participate in the regeneration of beta cells from the pancreas.
- The other objective is to understand the mechanism of each receptor to be proven as a beneficial approach in the treatment of diabetes.

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Chapter 3

Beta-cell regeneration

3.1 The perspective of beta-cell regeneration

Beta-cell regeneration is a normal mechanism that produces new beta cells in the pancreas that contain and secrete insulin (Robert S. Dinsmoor, 2020). Pre-existing beta-cell replication is a significant mode of beta-cell replenishment that contributes to postnatal homeostasis in rodents and humans. However, the basal replication rate of beta-cells decreases exponentially with age. In mice, β-cells are amplified, although somewhat genetically immature, in the early postnatal phases, and gradually β-cells become more capable of glucose-stimulated insulin secretion and lose their proliferating ability (Jia et al., 2020). Correspondingly, in the postnatal cycle, human β-cells often exhibit a brief replicative process, peaking in the first year, followed by a long refractory state that lasts throughout life. Therefore, while the molecular origins of the decline associated with age in basal β-cell replication are demonstrated, further studies are critical for understanding molecular targets and signal pathways that regulate the dynamics of proliferation and the functioning of β-cells (Jurczyk et al., 2014).

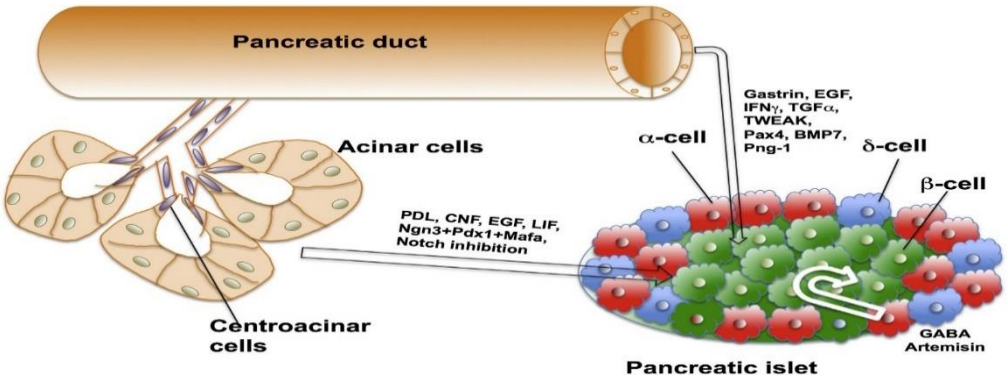

Figure 3 : Cell Sources within the Pancreas that Have Been Shown to Differentiate into b cell (Aguayo-Mazzucato & Bonner-Weir, 2018)

3.2 Hurdles and controversy regarding beta cell regeneration

The widespread belief of beta-cell proliferative ability declines with age has caused controversy. Consequently, one study found that the beta-cell population is formed early in life in humans, but that beta-cell mass is maintained as time passes. When old mice were placed in a young mouse setting, their beta cells proliferated rapidly, implying that age-related proliferation loss is caused by factors outside the beta-cell. In old mice, proliferative factors such as diphtheria toxin-mediated beta-cell ablation or glucokinase activation enhanced beta-cell proliferation, meaning that beta-cell regenerative ability is maintained (Jurczyk et al., 2014). The therapeutic potential of incretins for increasing beta-cell mass in diabetics is still debated. It has been predicted that incretins have a proliferative effect on human beta-cells, according to studies. The insulin granule SNARE Vamp8 has been shown to inhibit GLP-1-induced proliferation (Garber, 2011). Although there have been valid criticisms of this work, and rodent studies have not shown the same effect, more research is needed to determine the safety of these agents (Aston-Mourney et al., 2013). Meanwhile, a report recently linking inconsistent use of pancreatic neoplasms overshadowed the promising prospect of conflicting treatment.

3.3 Methods of drug discovery in beta cell regeneration

Numerous approaches have been used to classify drugs or growth factors capable of promoting beta-cell proliferation in humans. Since juvenile beta cells and human insulinomas proliferate at the fastest concentrations *in-vivo*. These cell types have been used as data mines for human beta-cell replication by researchers. As a result of their combined efforts, these methods have established a slew of novel drug targets and drug groups (Aguayo-Mazzucato & Bonner-Weir, 2018) (Kondegowda et al., 2015). These inhibitors stimulate human beta-cell development at a rapid rate (P. Wang et al., 2015).

3.4 Optimistic thoughts regarding beta cell regeneration

Beta-cell replacement therapy with human islet transplantation is probably the only alternative for regenerating beta cells, despite major obstacles such as donor shortages and high immune rejection. Recent advancements in regenerative medicine, as well as the establishment of a standard operating procedure for cell therapy, particularly T-cell-based immune therapy, can serve as a motivating reference in this context. To turn insulin-producing cells into a therapeutic breakthrough, contamination, immunogenicity, and tumorigenicity problems should be resolved *in-vitro*. The lack of an antigenic target capable of convincingly and safely increasing beta-cell mass through self-replication or regeneration is a major hindrance to *in-vivo* beta-cell regeneration efforts. The discovery of the betatrophin receptor and its human homolog will meanwhile have a significant impact on the development of particular genes (P. Wang et al., 2015).

Chapter 4

Receptor

4.1 The basic concept of receptor

A receptor can be loosely classified as a molecule that accurately recognizes a second small molecule whose binding enables the unbound cell process to be regulated (Lambert, 2004). To describe the molecular mechanisms underlying the impact of a ligand on physiological or therapeutic cell activity, a series of basic principles of receptor theory is to be understood. This includes the effectiveness, and potency, target's affinity, the rates of activity and dissociation (residence time) as well as the number of receptors inhabited (John C. Foreman, 2010). Though physicians are concerned with exogenous ligands, receptors in human tissues have evolved to bind endogenous ligands such as neurotransmitters, hormones, and growth factors. However, the formation of a drug-receptor complex is often reversible, and the percentage of the receptor occupied is proportional to the drug concentration. For this reason, the term “receptor” is typically used to refer to proteins whose sole objective is to bind a ligand, other types of drug targets, such a transporter protein, enzymes, voltage-sensitive ion channels are occasionally more often used in pharmacology. Reversibility provides an opportunity to modulate biological responses and ensures that related ligands can fight for access to the receptor.

4.2 GLP- 1 receptor

GLP-1 is a peptide hormone that raises the secretion of insulin and reduces the secretion of glucagon. The pancreas also depends on glucose (Trujillo et al., 2015). It improves leptin and weight loss by raising glucose-related insulin secretion, decreasing glucagon secretion, delaying gastric emptying and satiety. Many of the GLP-1 receptors are delivered

subcutaneously. The drugs vary significantly in terms of molecular structure, pharmacokinetics, dosage, administration and handling, effectiveness, tolerability, and patient satisfaction. Although medication varies with adverse reaction frequencies, the most often reported adverse reactions in the GLP-1 class are gastrointestinal, like nausea, vomiting, diarrhea, and injection site reactions. Each agent should be assessed separately rather than by a class consequence, depending on the degree of heterogeneity and complexity in the GLP-1 class (León et al. 2006).

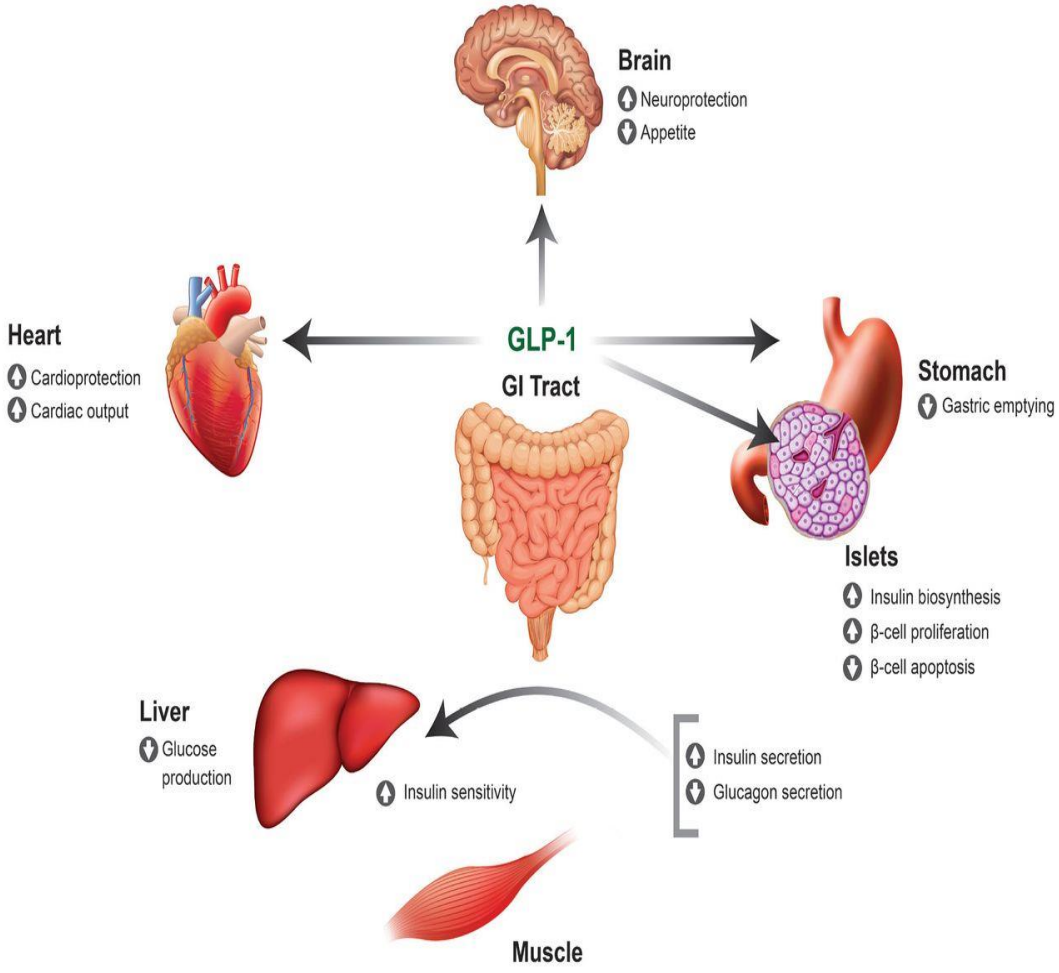

Figure 4 : Glugacan like peptide 1 receptor (Andersen et al., 2019)

Role of GLP-1 on beta cell regeneration

Glucagon-like peptide-1, which is secreted by intestinal L-cells in response to nutrient absorption, plays a critical physiological function. It facilitates the secretion of glucose-stimulated insulin, stimulates transcription of the insulin gene and insulin biosynthesis, increases proliferation of β-cells, and prevents apoptosis of β-cells (Lee et al., 2018). Moreover, in the pancreatic islets, GLP-1 has an impact on pancreatic beta-cell regeneration, differentiation, and neogenesis, primarily by producing glucagon hormone cells. Recent research has shown that cells are capable of producing GLP-1 (Barragan et al., 1994) (Mayer et al., 2020). Their capacity to transdifferentiate into beta-cells under conditions of severe damage to beta cells is another inherent characteristic for alpha cells. Increased physiological demand for insulin can also contribute to the increased proliferation of cells. These findings indicate that cells may be a source of newly produced cells that produce insulin. GLP-1 can serve as a trigger by autocrine signaling (Montanya, 2014). Additionally, glucagon receptor mouse models develop beta-cell hyperplasia, which correlates with an increase in plasma FGF21 levels in these mice. In contrast, a GLP-1 analog increases FGF21 expression and activity in insulin-resistant mice. As a response, it can be hypothesized that GLP-1 could increase FGF21 production. This secretion would be crucial by which GLP-11 generates new beta cells from alpha cells (Yang et al. 2019) (Lee et al., 2007).

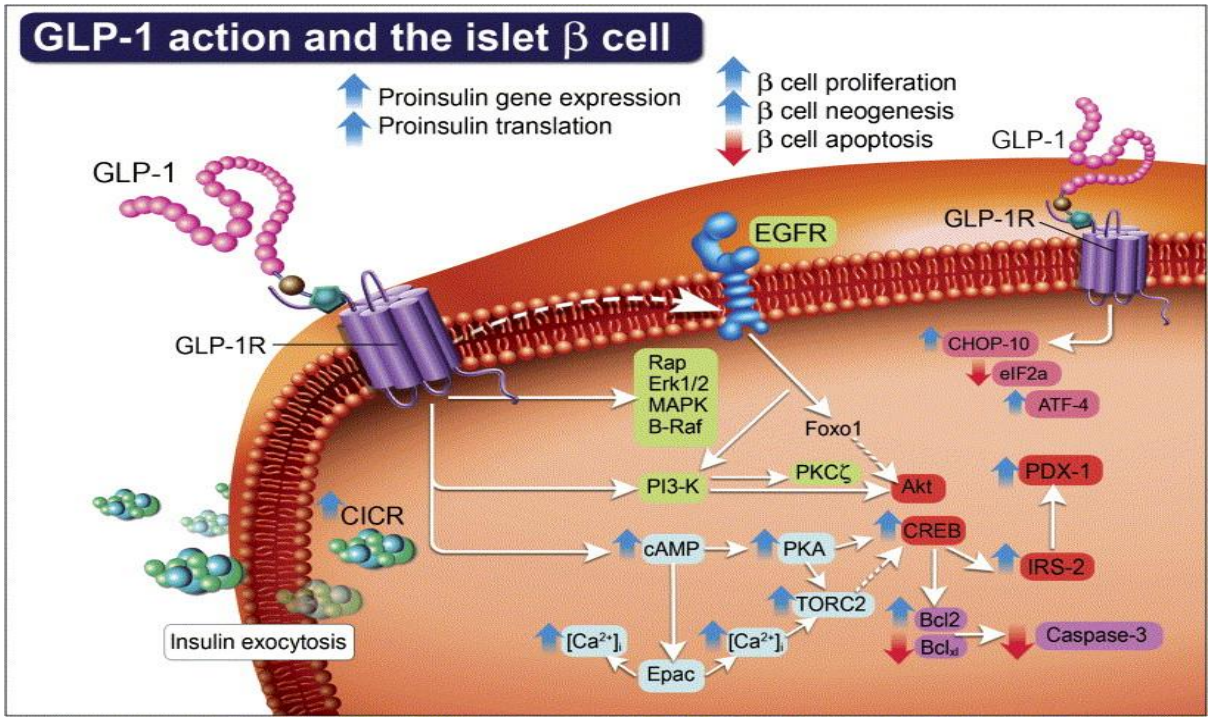

Figure 5 : GLP action on Beta-cell (Drucker, 2006)

4.3 DPP-4 receptor

DPP-4 is a transmembrane peptidase that is widely distributed in the body, and it has a high expression in the liver. Inhibition of DPP-4 has been commonly used in type II diabetic patients to reduce blood glucose because the inhibitors are well absorbed and have no apparent side effects. DPP-4 inhibitors mainly exert their anti-hyperglycemic role by blocking incretin degradation (Li et al., 2020)). Furthermore, DPP-4 contains a normal signal peptide, which is essential for targeting the endoplasmic reticulum and inducing translocation across the cell membrane, as a part of the type II transmembrane proteins. The signal peptide is not cut off, but acts as a membrane anchor, in contrast to the classically secreted proteins. Studies imply the circulating form of DPP-4, which lacks the cytoplasmic domain and transmembrane region, can be isolated from the membranes of human adipocytes and smooth muscle cells through a process called shedding in the presence of matrix metalloproteases (Röhrborn et al., 2015).

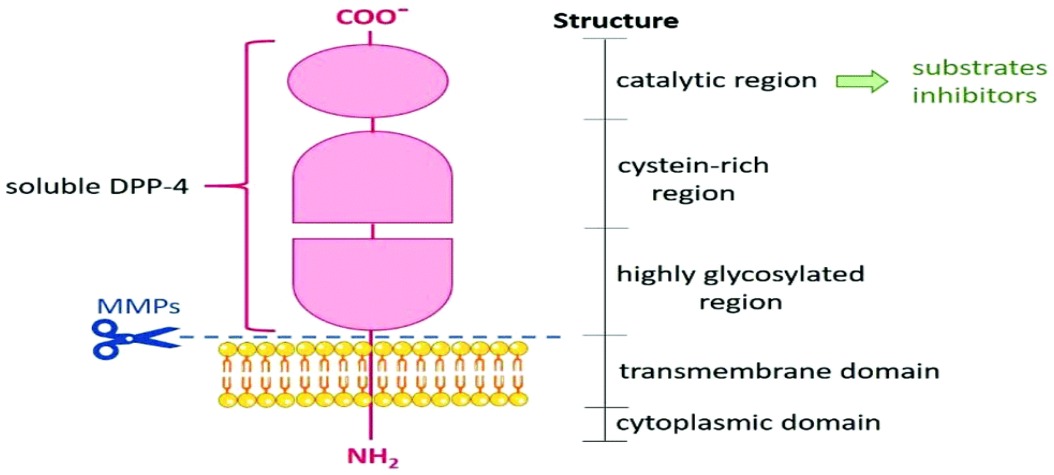

Figure 6 : Domain structure of DPP4 (Proencą et al., 2019)

Role of DPP-4 on beta cell regeneration

The control of high levels of blood insulin and the regeneration of beta cells in the pancreas have been linked with DPP-4 inhibitors (A Duchon & Herault, 2016). Vildagliptin is an agent of diabetes and has extensively been examined for GLP-1 repression, plasma glucose reaction to insulin secretion, and plasma circulating GLP-1 increases, which significantly control plasma glucose levels. The pancreatic duodenal homeobox-1, which activates a wide range of unique cell genes, was mainly expressed in adult beta cells. Similarly, pancreatic duodenal homeobox-1, pancreatic growth, and defining transcript factor are all important cell markers (Mastracci & Sussel, 2012). Cells of pancreas islet were hypothesized to give birth to progenitor cells intra- and extra-islet.). The findings explore the effects of vildagliptin on beta-cell regeneration and DDR-1 expression to show that beta-cell progenitor cells can induce vildagliptin. DDR-1 is a plasma membrane transmembrane protein that, by its association with collagen molecules, controls the proliferation, transcription, differentiation, and remodeling of the extracellular matrix. DDR-1 has been identified primarily in kidney, liver, gastrointestinal tract, brain, and bone cells.

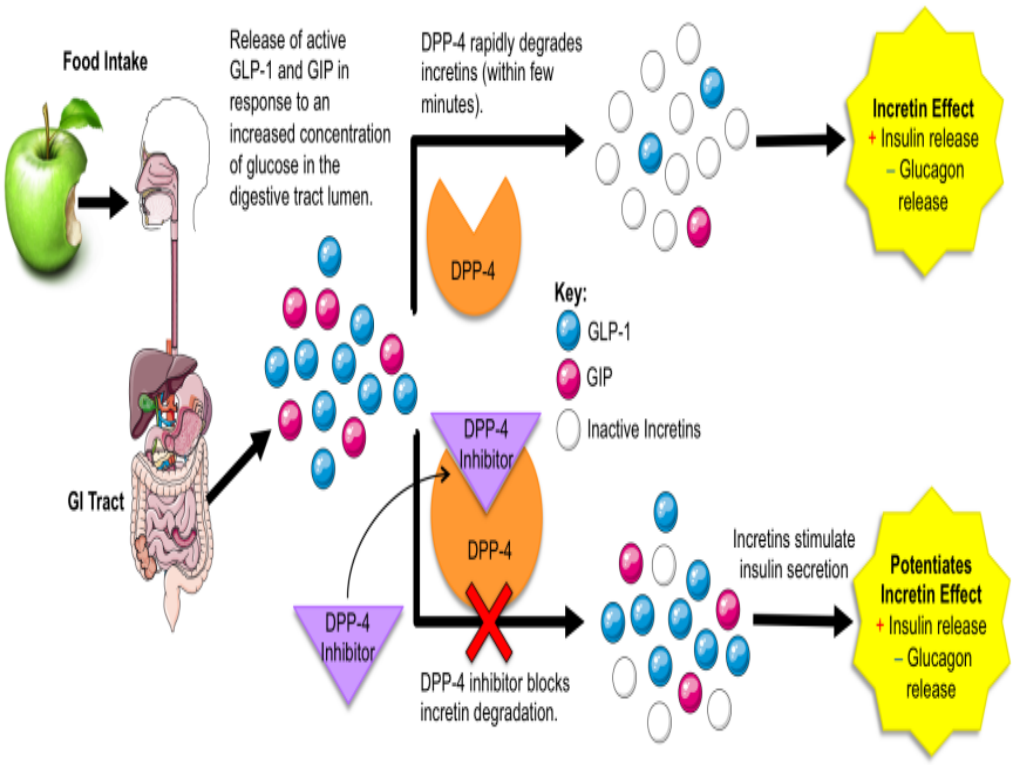

Figure 7 : Inhibition of DPP4 (Aertgeerts, 2004)

4.4 DYRK1A receptor

Most of the DYRK1A protein (nearly 80%) in the human and mouse brain is correlated with the cytoskeletal fraction, and the remaining protein is found in the cytosolic and nuclear fractions (Duchon & Herault, 2016). DYRK1A is a component of the Tyrosine Phosphorylation-Regulated Kinase (DYRK) dual-specificity family. This portion includes a series of nuclear signal targeting, a domain of protein kinase, a modification of leucine zipper, and a highly conservative 13-consecutive-histidine repeat. Autophosphorylation catalyzes the residue of serine, threonine, and tyrosine. It can play a vital role in controlling cell proliferation through a signaling pathway and can be involved in the development of the brain (Belgardt & Lammert, 2016).

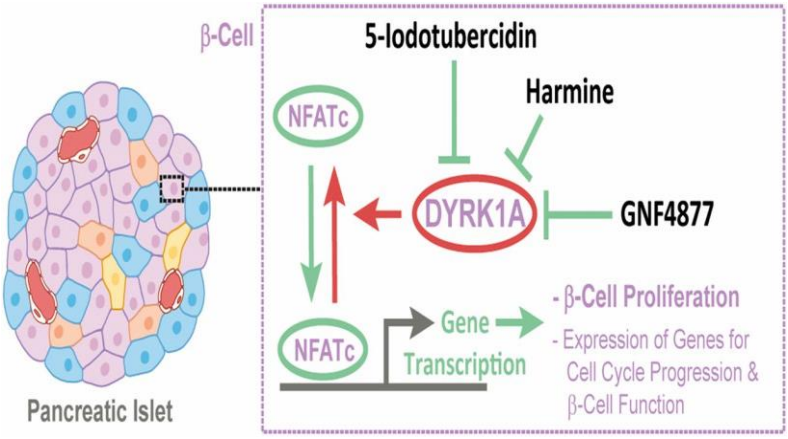

Figure 8 : Pancreatic islets are composed of different endocrine cells in insulin-secreting beta-cell (Belgardt & Lammert, 2016b)

Role of DYRK1A on beta cell regeneration

There is scientifically no evidence for DYRK1A function in beta cells, especially during neural growth (Rachdi et al., 2014). The current study examined the effect of DYRK1A haploinsufficiency on the regulation of beta-cell mass in mice. The current study's findings demonstrate the crucial role of DYRK1A in beta-cell proliferation and indicate that DYRK1A dose could be a critical goal in type II diabetes mellitus. 5-IT inhibits another enzyme in the human environment to promote beta-cell proliferation, as most chemical compounds, especially kinase inhibitors, never demonstrate exclusive specificity for a single target. A test for kinases affected by 5-IT treatment showed that it inhibited DYRK1A as well as a significant number of other high-affinity-associated kinases. Previous studies with genetically modified mice established that partial deletion of DYRK1A inhibits beta-cell growth and results in diabetes (Dirice et al., 2016a). Recently, it was shown that the adenosine kinase inhibitor 5-iodotubercidin enhanced the proliferation of rodent and porcine beta-cells. These results corroborate previous observations that DYRK1A inhibition promotes human beta-cell proliferation. A recent study confirms that small molecule-induced human beta-cell proliferation is feasible, providing great promise for regenerative medicine's diabetes treatment goals (A Duchon & Herault, 2016).

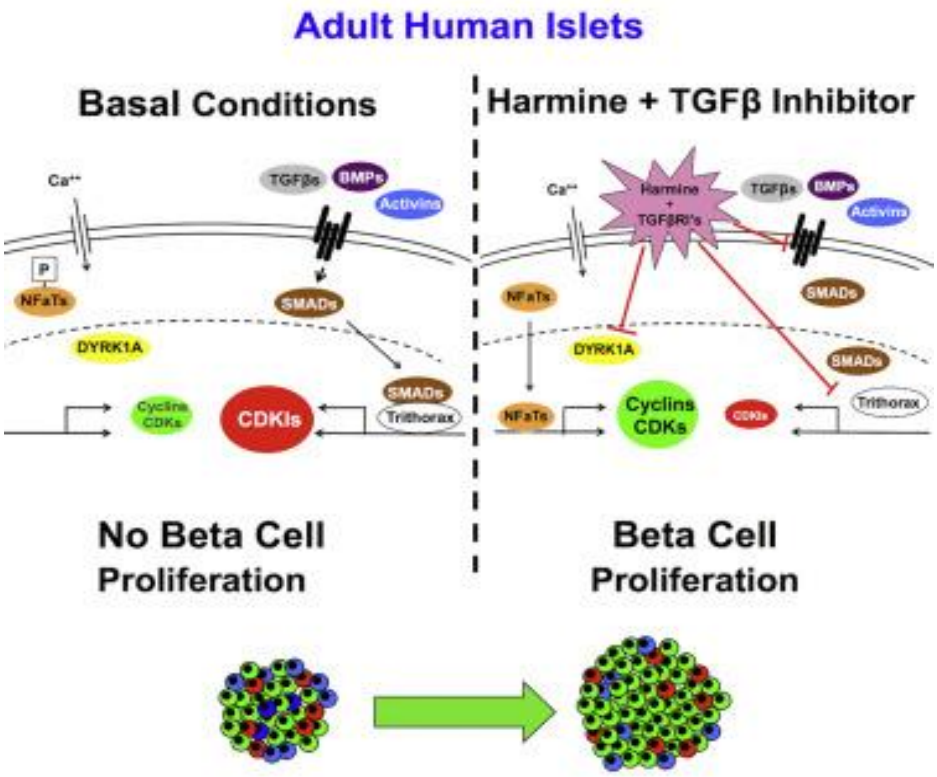

Figure 9 : Synergistic inhibition of DYRK1 receptor (P. Wang et al., 2019)

Chapter 5

Combination of drug effects

Inhibitors of dipeptidyl peptidase-4, such as sitagliptin, prevent GLP-1 degradation, thus increasing the endogenous hormone incretin's levels (H. Wang et al., 2017). The widespread usage of GLP-1 agonists in millions of people worldwide with diabetes suggests that a technique combining the DYRK1A inhibitor and GLP-1 could be possible. It can be adaptable and have a significant impact on diabetes worldwide if its efficiency and consistency are maintained. Oral medication administration is scientifically beneficial, especially in the long-term management of chronic diseases. Sitagliptin administration increased plasma GLP-1 levels in the mouse model, as predicted (Hald et al., 2012). As a result, some other peptide hormones can be degraded by DPP-4. Further research is necessary to determine if additional DPP-4 substrates contribute to the beneficial metabolic additive impact observed in the combined therapy experiments (Röhrborn et al., 2015).

5.1 Combination effects of drugs acting on both GLP-1 and DPP-4

DPP-4 antagonists block the breakdown of GLP-1 resulting in increased amounts of the active hormones. In clinical studies, DPP-4 antagonists have a negligible impact on glycemic control. They are generally well-tolerated, have a negligible impact on weight, and pose little chance of hypoglycemia. GLP-1 receptor agonists are exendin-4 or human GLP-1 peptide derivatives that have been designed to survive DPP-4 action and hence have a longer half-life (Nauck et al., 2011). They have also shown superior efficacy in clinical studies to a variety of oral antihyperglycemic medications, as well as improved weight reduction and a decreased likelihood of hypoglycemia. However, there have been reports of stomach adverse effects such as nausea, vomiting, and diarrhea. Both DPP-4 inhibitors and GLP-1 receptors are healthy in large-scale cardiovascular outcome trials, and certain GLP-1 has been shown to reduce the

likelihood of significant adverse cardiovascular outcomes in type II diabetes mellitus patients who already have cardiovascular disease (Holst et al., 2020). Numerous clinical studies have been conducted to compare the effectiveness and protection of DPP-4 inhibitors and GLP-1 receptor antagonists. Furthermore, these reports concluded that GLP-1 receptors provided superior glycemic regulation and weight loss to DPP-4 inhibitors. GLP-1 treatment has historically been correlated with a higher rate of gastrointestinal side reactions, even though both drugs have a minimal and similar rate of hypoglycemia. A few trials have examined the effect of switching patients from DPP-4 inhibitors to GLP-1, with promising outcomes in terms of improved glycemic regulation and weight loss. According to current clinical recommendations, GLP-1 and DPP-4 antagonists are both prescribed for the glycemic control of patients with type II diabetes. Due to the larger reductions in hemoglobin A1c and weight loss found in clinical studies, glucagon-like peptide-1 could be preferred for some patients over DPP-4 inhibitors (Nauck et al., 2011).

5.2 Combination effects of drugs acting on both DPP-4 and DYRK1A

Recently, there have been studies of human cell labeling indications in the range of 1% to 3% for inhibitors of the DYRK1A small molecule class, such as INDY, leucettine, GNF4877, 5-iodotubericides, and CC401 (Dirice et al., 2016a). Notably, it was shown that when a superfamily (TGF, SF) transformer is combined with a DYRK1A inhibitor, human cell labeling indexes are increased further into the 5–8% range (Santulli, 2019). Additionally, DYRK1A inhibitors stimulate nuclear factor of activated T cells (NFaT) proliferation in human cells by repressing both cell cycle inhibitory and triggering genes. This strategy still lacks a sense of cell specificity, but there is a noticeable improvement over DYRK1A inhibitors, as both DYRK1A and TGSF receptors and signaling molecules are pervasive (Sui et al., 2018). There seems to be a pressing need to find medications that have both increased growth of human cells

and enhanced specificity of cells (Ding et al., 2016). Still, there is not much research on the combination of these receptors. But, in the nearer future, there are potential possibilities that can be predicted regarding these on improving the beta cell regeneration.

5.3 Combination effects of drugs acting on both GLP-1 and DYRK1A

Medicines that block glucagon-like peptide-1 receptors directly or indirectly are among the most popular diabetes medications available worldwide, reaching millions of people with type II diabetes. While GLP-1 agonists do not induce human cells to proliferate, GLP-1 has a restricted tissue distribution in humans and is highly expressed in cells, providing it with a special cell specificity (Nauck et al., 2011). However, except for pancreas transplantation, none of these treatments is clinically available, and neither of them, like pancreas transplantation, is scalable to the hundreds of millions of people who have type I or type II diabetes (Stephens et al., 2012). Nonetheless, osteoprotegerin, as well as parathyroid hormone-related protein, serpin B, aminobutyric acid, and the peptide TLQP21, are all being investigated as possible molecules for human cell regeneration (Sui et al., 2018). Although GLP-1 agonists do not induce human cell proliferation, the GLP-1 receptor is highly expressed in cells and has a restricted tissue distribution in humans, offering an unprecedented, although incomplete, degree of cell specificity at the moment. Currently, no medications are accessible that enable human cells to reproduce. As a result, an urgent need exists for drugs that facilitate human cell proliferation while also enhancing cell specificity (El Ouaamari et al., 2016).

5.4 Combination effects of drugs acting on all three receptors

The GLP-1 receptor can be converted to active receptors using small-molecule DYRK1A inhibitors. They turn "inactive" medicines into highly proliferative agents for cells (Guo, 2016). Thus, these powerful cell proliferation agents allow the regeneration of cells. The resulting proliferation rates are greater than those of DYRK1A inhibitors separately, which could allow

for cell mass regeneration in type I and type II diabetic patients. In both DYRK1A and cAMP signaling activation, harmine GLP-1 synergistically activated PKA and EPAC2 signaling, and nuclear abundance increased combined cell proliferation more in addition to harmine or GLP-1 (Purwana et al., 2014). Additionally, these results show that any DYRK1A inhibitor may be used in conjunction with any GLP-1 agonist commonly used in people with type II diabetes, as well as any DPP-4 inhibitor drugs that substantially increase GLP-1 levels in the blood and are capable of generating substantial human cell proliferation rates. The relative specificity of GLP-1 family molecules in beta cell therapeutic paradigms is one of their advantages. Cells, the ductal pancreas, central nervous system nuclei, cardiac tissue, smooth gastric muscle, and T-sections all include GLP-1 receptors. As a result, it increases the average level of speech of the harmine target DYRK1A (Dirice et al., 2016b). Apart from that, their beneficial therapeutic effects on diabetes are a result of their incretin effect, which stimulates cell secretion of insulin in response to elevated blood glucose levels, as well as their nourishing properties (Holst et al., 2020).

Chapter 6

Challenges

This analysis has certain barriers.

First, newly generated β cells need to be defended from constant immune attacks in people with type I diabetes. However, it is not a barrier for the wider group of diabetic patients of type II who require both cell β expansion and better β-cell differentiation and are already using GLP-1 agonists (Santulli, 2019).

The second massive issue is the potentiality of cells to experience oncogenic transformation outside the islet. This ultimately affects both forms of replacement and regenerative treatments, most notably pancreas and islet transplantation, which is believed to increase lymphoma and other cancers. For example, CRISPR-Cas9 targets specificity of stem cell-derived therapy that carries a teratoma risk, genetic modification therapies with imprecise off-target deletion, and distributor criteria for viral vectors with broad, nonspecific, and potentially oncogenic chromatin modifiers (Lino et al., 2018). Although long pre-clinical studies will be optimal to assess these potentials for all forms of βcell regeneration therapy, including GLP-1 agonist hybrid DYRK1A inhibitor (Chen et al., 2020).

Again, the consequences of harmine on humans have not been directly investigated. From this viewpoint, the doses of harmine with little to no effect on human β-cell proliferation *in-vitro* or *in-vivo* were converted along with GLP-1 or exenatide into an effective agent for human β-cell proliferation. Around the same time, some findings indicate that preclinical and human model pharmacokinetics and toxicity can be studied. Harmine is psychoactive owing to its involvement in ayahuasca, psychoactive medication, and injection of banasteriopsis.

The following crisis is to increase the specificity of beta cells by selectively and directly adding modifications to target regenerative drugs and imaging agents in human beta cells. At the moment, there is no appropriate target molecule for delivering a therapeutic agent directly to a human beta-cell. In this case, when combined with some GLP-1 receptor agonist dosage, the synergistic effects of low-dose damage, which do not affect beta-cell proliferation alone, increases the likelihood.

Lastly, transplantation, stem cell, and gene therapy are costly and resource-intensive and are expected to be implemented in hundreds of millions of diabetes patients (Coppieters et al., 2012).

Chapter 7

Conclusion

In this review, the function of each of the three receptors (GLP-1, DPP-4, and DYRK1A) has been addressed and their relationship to diabetes, as well as their involvement in the regeneration of impaired beta cells, has also been discussed to benefit diabetic patients. The review has been conducted in the hope that illustrating the role of these receptors on beta cells would advance regenerative medicine and result in the development of a standard operating procedure for cell therapy, especially immune therapies based on beta cells. Beta-cell regeneration is currently being evaluated in a preclinical environment. Insulin-producing cells produced *in vitro,* in particular, must resolve the safety concerns of cross-contamination, immunogenicity, and tumorigenicity during the clinical progression. This may be motivated by recent advancements in regenerative medicine and the creation of a standard operating procedure for cell therapy, specifically beta cell-based immune therapies. A potentially negative effect of the absence of significant beta cell regeneration in autoimmune diabetes must be mitigated. These advancements would have a direct impact on early-stage drug discovery for beta cell regeneration. Nonetheless, due to the lack of a circulating component, this process's drug potential remains small. Additionally, there are currently no guidelines for the combination of a GLP-1 agonist and a DPP-4 inhibitor. Though it was originally believed that this mixture of drug groups would be effective, with the GLP-1 agonist increasing incretin levels and the DPP-4 inhibitor enhancing the influence of endogenous incretins. The widespread use of GLP-1 agonists in people with diabetes raises the prospect of a procedure combining a DYRK1A inhibitor with the GLP-1 receptor. DPP-4 antagonists, such as sitagliptin, prevent GLP-1 degradation, thus increasing the endogenous hormone incretin levels. Additional research is necessary to determine if other DPP-4 receptors contribute to the

beneficial metabolic additive impact observed in the combination therapy experiments. From the review, it has been observed that the combination of a GLP-1 agonist and a DPP-4 inhibitor is not currently recommended due to a lack of prominent evidence. Additionally, each of these groups of medicines is more costly than diabetes medications. This is far more than what would be possible for DYRK1A alone, rather than within a spectrum of thresholds that may result in the regeneration of natural beta-cell mass in both type I and type II, diabetes patients.

Chapter 8

Future perspective

There is a great need to identify the specific and reliable function of GLP-1, DYRK1A, and DPP-4 receptors for the treatment of diabetes. To determine the effectiveness of the GLP-1 receptor, molecular combinations of dosages, treatment schedules, and further research are needed. To make an accurate assessment of the potential hazards of DPP-4 inhibitors, the retable data should be analyzed. Correspondingly, additional information about the impact of *in vivo* elevation of DPP-4 substrates is needed to complete the currently promising analysis on stability. These studies would need to be very broad and prolonged to resolve the remaining unresolved issues. If these problems are resolved favorably, DPP-4 inhibitors might have a strong chance of replacing sulphonylureas in diabetic treatment. Moreover, It would be important to assess the capacity of the DYRK1A receptor to efficiently, selectively, and reversibly promote human-cell proliferation in the future. As well as, it is required to find out in the future whether there is any other way to predict the efficacy of these receptors. Short-term and long-term adverse effects of these receptors need to be further evaluated in clinical trials. However, GLP-1 and DPP-4 are FDA approved but there is no confirmation regarding DYRK1A approval by FDA. As a consequence, it is expected that further investigation will be conducted regarding the potential approaches of treatment that were reviewed in this paper. Thus, it can be proven as a beneficial method of treatment for diabetic patients for minimizing their suffering in the future.

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