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HDAC Allostery: A Therapeutic Target for the Management of Diabetes and Its Complications

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Abstract

A few decades ago, Diabetes Mellitus (DM), as well as its complications was and till date, remains, a threat to the medical and economic sectors of the world. DM is a polygenic metabolic syndrome with varying types, which include type 1 DM, type 2 DM, and Gestational Diabetes Mellitus (GDM). These have different etiologies but share similar symptoms. Though the full pathogenesis of DM is yet to be unraveled, it is of great importance to note that a strong genetic correlation exists between HDAC and DM and its associated complications. HDAC is a superfamily of enzymes that function in the catalytic removal of acetyl groups from Ɛ-amino groups of lysine residues. It is believed that targeting HDAC with the use of HDAC inhibitors will be a key tool to regulate the catalytic function of HDAC towards ameliorating or reversing the complications associated with DM. In this review we summarize the forms of dabetes, classes of HDAC relationship between etiology of diabetes and HDACi Insulin resistance and HDACi and pharmacological target of HDAC.

Keywords: Diabetes Mellitus (DM); HistoneDeacetylase (HDAC); Histone Deacetylase Inhibitor (HDACi); Type 1 DM, type 2 DM,Gestational Diabetes Mellitus (GDM).

Abbreviation: DM: Diabetes Mellitus; GDM: Gestational Diabetes Mellitus; T1DM: Type 1 diabetes mellitus; T2DM: Type 2 Diabetes Mellitus; HDAC: Histone Deacetylase; HDACi: Histone Deacetylase Inhibitor; ADA: American Diabetes Association; WHO: World Health Organization; BMI: Body Mass Index; GAD: Glutamic Acid Decarboxylase; GLUT: Glucose Transporter; GEF: GLUT4 Enhancer Factor; MEF: Myocyte Enhancer factor.

Introduction

It is of great importance to note that, diabetes remains a threat to the health and economic sectors due to the complex nature of this chronic disease, which imposes a devastating health status on its victims, and due to the cost of treatment of this disease and the management of its complications [1]. Diabetes mellitus is a complex and chronic metabolic dysfunction characterized by an abnormal rise in blood glucose levels caused by a defect in pancreatic insulin secretion, insulin action, or a combination of the two. Socio-economic development, urbanization, sedentary lifestyles, and unhealthy diets are major factors that precipitate this devastating disease. It should be noted that these factors also contribute to an increase in BMI [2]. The long-term complications of this metabolic aberrance are renal failure, neuropathy, retinopathy, foot ulcers, and complications of the heart. Both microvascular and macro-vascular complications exist following the diagnosis of diabetes. Microvascular complications occur at the onset of diabetes, *i.e.,* when the fasting plasma glucose level equals or exceeds 126 mg/dL of blood. The affected organs are majorly the kidneys and eyes, while macro-vascular complications are associated with the cardiovascular system. A correlation exists between diabetes and cardiovascular problems such as hyperlipidemia, atherosclerosis, and hypertension [3]. Symptoms of this disease include polyphagia, polydipsia, polyuria, reduced body weight, hyperosmolar coma, diabetic ketoacidosis, and defects in sight [4]. In the diverse forms of diabetes, there is a probability of this disease affecting up to about 590 million people [5]. With respect to the statistics made in 2013, globally, 382 million people had DM. A forecast was made that in 2035, 592 million people might have died of DM [6]. According to WHO, it is expected that over 19% of the global adult population will have become diabetic patients in 2030 [7]. In 2015, more than 415 million people were diagnosed with DM, and this is expected to rise to about 642 million people by 2040 [8]. The International Diabetes Federation (IDF) reported in 2017 that 451 million adults worldwide were suffering from diabetes, and it is estimated that up to 693 million people will be diabetic by 2045. This highly-increasing rate of diabetic patients globally is a major threat or challenge to the healthcare sector. Metabolic aberrances in diabetes are not limited to abnormal glucose metabolism, but also involve defects in the metabolism of lipids and amino acids. Different types of diabetes mellitus have different etiologies but share similar symptoms [9].

Literature Review

Type 1 diabetes mellitus: This type of diabetes mellitus was previously known as Insulin Dependent Diabetes Mellitus (IDDM) or juvenile-onset diabetes mellitus. It affects about 5–10% of the human population, especially the European population [10]. The global occurrence and wide spread of T1DM is fast increasing, with about a

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the autoimmune breakdown of the B-cell present at the islet of Langerhans in the pancreas [11]. This destructive process is initiated by the T-cells of the immune system. As a result, the strong odor of acetone is one of the symptoms of diabetes in children, which is known as ketoacidosis. Athar et al. reveal that factors such as genetics, auto-immune dysregulation, and lifestyle (nutrition) are predisposing parameters in the etiology of T1DM [12], but it should be noted that viral infection also plays a critical role [13]. Coxsackie B4 virus, an RNA virus, has been implicated in the destruction of the B-cells of the islet of Langerhans. The molecular mechanism of this process can be illustrated as follows: an enzyme located on the surface of the islet of Langerhans, called Glutamic Acid Decarboxylase (GAD), has a similarity to the protein present in coxsackie virus B4, called Protein 2C (P2C). Due to this similarity, p2C is seen as self and left un-attacked by the T-cells, thus enhancing the destruction of B-cells. This isn't usually the case in T2 DM [14].

Type 2 diabetes mellitus: This form of DM is more prevalent than type 1 DM. This form of DM is characterized by an elevated level of both insulin and glucose in the blood [15]. Unlike in T1DM, where there is a breakdown of B-cells, the physiology of B-cells in T2DM is usually kept intact. Like T1DM, the etiology of T2DM can be traced to genetic, lifestyle, and environmental factors [16]. In T2DM, there is insulin secretion, but the Glucose Transporters (GLUT) at the membrane surface of most cells are resistant or non-responsive to this secreted insulin, leading to insulin resistance. This is exacerbated due to no further production of insulin to compensate for the resistivity of the insulin earlier produced [17]. There is elevated blood glucose in patient affected by T2DM for a period of time but shows no symptoms of diabetes, in this individual, there is usually no need of insulin injection for survival. T2DM has a prevalence of about 90–95% of DM cases globally. A correlation exists between T2DM and obesity, lack of physical exercise, and increased caloric intake [18].

In addition, genetic, environmental and lifestyle factors are not only responsible for the incidence of T2DM, but factors such as immune dysfunction, adipokine dysfunction, and aberrance in gut microflora are all precipitating factors for T2DM. It should be noted that patients with T2DM have a higher probability of developing cardiovascular disease, which can be precipitated by obesity, elevated blood glucose, dysfunction in lipid metabolism, inflammation, hypertension, and resistance to insulin [19]. Patients with a history of GDM are likely to develop T2DM later in life.

Gestational diabetes mellitus: There is a proportionality between the prevalence of T2DM and GDM owing to the fact that T2DM is a predisposing factor to GDM [20]. At present GDM is the most common clinical aberration associated with pregnancy and has been in existence since over 50 years ago. It can be precipitated by several factors, which include advanced age of childbearing, previously diagnosed with GDM, family background of T2DM, obesity, and lack of physical activity [21]. The incidence of GDM is diagnosed in the second or third trimester of pregnancy. Any diagnosis noticed prior to conception or in the first trimester should be classified as T2DM rather than GDM. Several hormones such as cortisol, progesterone, leptin, estrogen, placental lactogen contribute to the insulin resistance state that occurs during pregnancy [22]. One of these hormones called the human placental lactogen, produced by the placental increases the level of glucose thereby reducing the sensitivity of the body to insulin. Study reveals that during the third trimester the sensitivity to insulin is reduced by about 56% and there is an increased endogenous production of glucose by 30% [23].

International Association of Diabetes and Pregnancy Study Group (IADESD) has classified any increased in blood glucose level when detected post conception as GDM or overt diabetes. The World Health Organization (WHO) in 2013 made a recommendation that any rise in blood glucose level noticed in pregnant women should be termed as "diabetes mellitus in pregnancy" or GDM.

Histone deacetylase: The removal of acetyl group from an Ɛ-amino group of lysine residue of histone and non-histone protein e.g. cytokine-induced Signal Transducers And Activators Of Transcriptions (STATs), a tumor suppressor gene p53, tumor inducing Nuclear Factor-kappa β (NF-kβ)(Kramer) is mediated by a metal-dependent enzyme called HDAC (Lombardi et al). In addition to the de-acetylation function of HDAC, Histone Acetylase (HAT) is concerned with the acetylation of chromatin tails, thereby inducing the expression of genes. For this reason, inhibition or induction of activity of either of these enzymes appropriately can restore the cellular homeostasis from pathological state e.g. the induction of HDAC activity to inhibit tumor promoting factor nuclear factor kappa β or inducing the HAT activity towards promoting p53 gene expression.

Chromatin is a highly complex and organized structure. It is composed of a supercoiled DNA-protein aggregate. The protein moiety is a special type of protein called histones, which are tightly wrapped around the DNA moiety. The fundamental unit of chromatin is referred to as the nucleosome. A nucleosome consists of an octamer of core histones, which are about five in number. The octamer is made up of a tetramer of H3/H4, located at the front side of the nucleosome, and a pair of H2A/H2B dimers, situated at the back side of the nucleosome, and is surrounded by 146bp of DNA (Rujiter et al.). H1 and H5, which are analogous to each other, serve as intermediary or linkers for the coiled core structure of chromatin.

Classification of HDAC

HDACs are a complex family of enzymes that are evolutionarily conserved whose function is to catalyze the removal of an acetyl from Ɛ-amino group (McClura). HDAC is broadly classified into two:

- The NAD+-dependent mammalian sirtuins, which as members range from SIRT 1-7, This class is also a homolog of the yeast's (Saccharomyces cerevisiae) Silent Information Regulator 2 (SIR p2).
- The classical HDAC for the sake of this review, this reveals the subject of attention.

Based on phylogenetic analysis, the classical HDAC can be classified into four classes.

l, lla, llb, and lV are the classes. The class l shares a relationship with Reduced Potassium Deficiency 3 (RPD3P) of *Saccharomyces cerevisiae* and consists of HDAC 1, 2, 3, and 8; the class lla consists of HDAC 4, 5, 7, and 9. Class lla shares similarity features with the Hda1p of Saccharomyces cerevisiae. These similarity features are true for class llb, which consists of HDAC 6 and 10.

The class consists of HDAC 11. All classes l, lla, llb, and lV are zinc independent for their catalytic action.

HDAC's mechanism of action

The natural and primary function of HDAC and HAT is the regulation of acetylation and deacetylation processes to control gene

expression and maintain the homeostasis of the cell. Acetylation, methylation, and phosphorylation are the modification factors that regulate the process of transcription, but the most understood among these processes is the acetylation process [24]. Deacetylation or methylation increases the net positive charge of histone which represses the binding of transcriptional factors, and thus downregulating the process of gene expression. On the hand, acetylation increases the net negative charge of histone proteins, thereby reducing the affinity of DNA for histone and this gives chance for the accessibility of RNA polymerase ll.

A stretch of about 390 amino acids makes up the catalytic domain of HDAC. The active site of HDAC, is made up of evolutionarily conserved amino acids and consists of a slightly curved pocket-like structure with a tubular shape and has an extensive basement. The enzymatic function of HDAC is carried out by a charge-relay system. This system consists of two histidine residues which are adjacent to each other, a pair of aspartate residues (that are separated by about 6 amino acids and distant from the histidine residues by 30 amino acids), and a single tyrosine residue which is present downward by about 123 amino acids from the aspartate residues. The charge-relay system has a critical component essential to its function. The component is the Zn^{2+} ion, which is bound to a site called the Zn binding site at the extended bottom. Other metals, especially the transition elements, e.g., Fe^{2+}, can take the role of Zn^{2+}.

Crosstalk between the aetiology of diabetes mellitus and HDACI

As earlier stated, lifestyle and genetic factors play a key role in the etiology of DM, especially T1DM and T2DM. Study reveal that the pro-inflammatory cytokines namely Tumor Necrotic Factor-α (TNF-α), γ-interferon (IFN-γ) and Interleukin-1β (IL-1β) are involved in the pathogenesis of β-cell which is apoptotic-mediated. The β-cell apoptosis involve the action of IL-1β while TNF-α and IFN-γ function in aggravating the cytotoxic effect of IL-1β. This can be circumvented by the use of HDACi inhibitors, e.g., SAHA and TSA, against cytokine-mediated apoptosis.

The molecular mechanism for this involves the inhibition of NF-kβ mediated β-cell apoptosis and the impairment in the expression of NF-kβ-dependent genes. There is a strong correlation between 6q21 (which is the location of the HDAC 2 gene on the chromosome) and DM. Generally, members of class ll HDAC are involved in glucose metabolism. It was reported that the widespread of T2DM among the Chinese Han population is due to the expression of class l HDAC, specifically the HDAC 3.

Discussion

HDACi and insulin resistance

For the influx of glucose to occur through the action of myocytes (cardiac and muscle cells) and adipocytes (fat cells), there is a critical need for insulin. In this process of glucose uptake, when a carbohydrate meal is ingested and the blood glucose level becomes elevated, insulin is produced by the β-cell of the pancreas and binds to the insulin receptor. On successful binding, auto-phosphorylation of the insulin receptor occurs, which leads to the phosphorylation of the Insulin Receptor Substrate (IRS) family in a stepwise and cascading fashion.

Afterwards, IRS binds to and activates an enzyme called phosphatidyl calledenzyme Inositol-3-Kinase (PI3K) which enhances the phosphorylation of the Akt protein kinase. GLUT4 is used by both adipocytes and myocytes and is present on membrane vesicles inside the cell and on the plasma membrane in some cells. Akt ignites the export of GLUT4 from vesicles to the cell surface (plasma membrane). At this level, increased and continuous uptake of glucose occurs until the level of blood glucose resumes back to normal. The GLUT4 is then re-sequestered into the vesicles inside the cell. These steps of processes represent the insulin signaling pathway and any alteration or abnormality in the process of this step-wise cascade will lead to insulin resistance. It is represented by Figure 1.

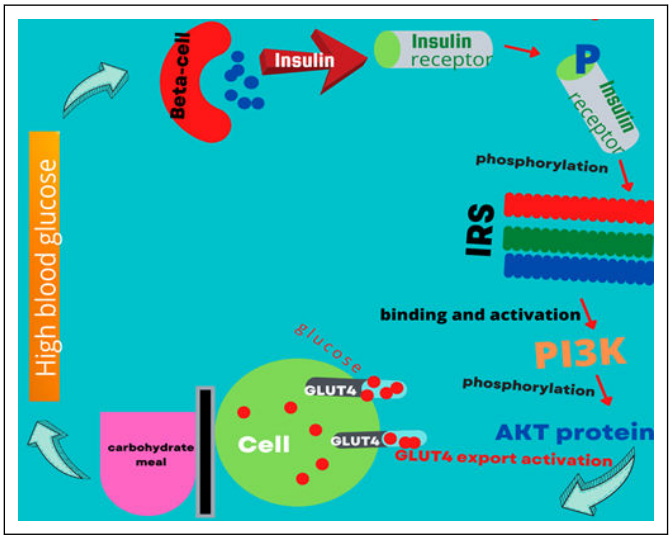

Figure 1: Insulin signaling pathway.

It has been suggested that HDAC is involved in the regulation of the insulin signaling cascade. For this reason, HDACi inhibitors will induce increased translocation of GLUT4 and increase both insulin-mediated and basal uptake of glucose into the adipose tissues and skeletal muscles. Both GLUT4- Enhancer Factor (GEF) and Myocyte-Enhancer Factor (MEF)-2 are the regulators for GLUT4 transcriptional processes and HDAC5 is said to be involved in the suppression of GLUT4 gene expression. This can be circumvented by the phosphorylation of HDAC5 by Calcium/Calmodulin Stimulated Protein Kinase (CaMK) and AMP-Activated Protein Kinase (AMPK). A correlation exists between class 1 HDAC and insulin resistance, while HDAC1 specifically is involved in the down regulation of GLUT4 action. In addition, class lla HDAC, especially the HDAC4 and 5 are implicated in the repression of gene coding for GLUT4, thereby contributing vastly to insulin resistance.

Pharmacological targets of HDAC

It is of great importance to note that a strong relationship exists between the chemistry and function of four biomolecules, not excluding the catalytic ones such as enzymes. For this reason, targeting the mechanism of action of catalytic enzymes through the allosteric site is of great advantage to regulating or having control over the activities of these enzymes. For decades, the use of HDAC inhibitors to target the allosteric sites of the enzymes has been the better option. HDACi are chemical compounds that down regulates the catalytic function of Zn^{2+} dependent HDAC enzymes.

They are believed to be a key agent in drug discovery for ameliorating several disease conditions. With respect to their chemical structures, they are classified into the following groups:

- Short-chain fatty acids, which include Sodium Butyrate (NaB), Vaporic Acid (VPA), phenyl butyric acid;
- Benzamides such as MS-275
- Hydroxamic acid-based e.g. Vorinostat, Panobinostat (LBH589), Trichostatin A (TSA)
- Cyclic peptides such as Romidepsin.

The majority of these groups of HDACi are made up of about 3 distinct structural parts, which include; the surface recognition domain that aids the interaction with the residues located at the active site; a warhead domain that serves as the group that binds to the Zn^{2+} present at the active site; and a linker which aids in connecting the other two components. Vorinostat (SAHA) was the first hydroxamic-based HDACi to be synthesized, though its group (the Hydroxamic group) was the pioneer in HDACi development and marketing. In 2006, Vorinostat was granted approval for use against refractory Cutaneous T-Cell Lymphoma (CTCL) by the Food and Drug Administration (FDA). It was initially thought to be effective against all classes of HDAC, but not until later research showed that its inhibitory effect was restricted to class I HDAC. Vorinostat has a high potency degree up to the extent of being effective in the nano-molar range (IC50<86 nM). A study reveals that TSA, a hydroxamic-based inhibitor, is a potent inhibitor of HDAC1 and 6.

Also, Panobinostat, which is marketed under the trade name Farydak, is approved by the FDA for the treatment of multiple myeloma, while Romedepsin was approved in 2009 for curing CTCL. Belinostat, which is marketed under the trade name Beliodaq was approved in 2014 for the cure of Peripheral T-Cell Lymphoma (PTCL).

Limitations and future perspectives

Generally, HDACi, especially the hydroxamic-based-types, lack specificity, *i.e.,* they are non-selective inhibitors of HDAC classes, which brings about the inability to target a particular or specific class of HDAC for therapeutic intervention. Also, there are poor pharmacokinetic properties and associated severe toxicity with the use of hydroxamic-based HDACi. It is important to note that the poor pharmacokinetic property of HDACi does not exclude poor bioavailability, which makes the active compound of the drug less available for its pharmacological function.

Vorinostat is said to have adverse effects which include; nausea, thrombocytopenia, diarrhea, dehydration, fatigue, vomiting with an incident of at least 20%. Study reveals that Vorinostat is a non-reversible inhibitor of some of the enzymes involved in metabolism such as CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6 as well as CYP3A4 (Iwamoto et al). The common adverse effects experienced with the use of MS-275 are vomiting, diarrhea, dehydration, amenorrhea, astheinia, nausea, and asymptomatic hypophosphatemia. The health related adverse effects associated with the use of Panobinostat are the toxicities associated with hematological and gastrointestinal aberrances such as diarrhea, fatigue, thrombocytopenia, nausea, and vomiting.

Since it has been established that only the non-hydroxamic based HDACi shows specificity for HDAC isozymes, it is of great importance to focus on the discovery of HDACi, especially the hydroxamic-based ones that have excellent specificities for individual HDACi isozymes. Also, due to the poor pharmacokinetic properties of HDACi which are currently in use, it is worthwhile to focus on the discovery of improved therapeutic agents with better pharmacokinetic properties, extremely low and considerable toxicities, and also excellent specificity for both class and individual HDACi isozymes.

Conclusion

During the course of this review, we realized that HDACi has inhibitory effects on HDAC, a complex group of enzymes with the ability to catalytically remove acetyl groups from evolutionarily conserved lysine residues. This catalytic action helps to achieve the regulation of processes involved in the transcription of genes associated with metabolism of sugars, fats and proteins. It is important to note that the side effects associated with the use of HDACi are poor pharmacokinetic properties and non-selectivity. We hereby implore scientists in the world of research to develop HDACi with high specificities and the least toxicities possible. We conclude that, HDAC are implicated in the aetiology of DM and its complications, therefore, targeting their allosteric sites with the use of HDACi can restore the physiological state of the body to normal.

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