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The Familiar and the Unfamiliar: Is there a Practical Neurodegenerative Connection between Diabetes Mellitus and Riboflavin Transporter Deficiency?

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Abstract

Diabetes mellitus is a prevalent disease and commonplace in children and young adults. Conversely, riboflavin transporter deficiency is a rare, neurodegenerative, autosomal disorder, which primarily affects children and younger adults. Due to this disparity in prevalence and "notoriety", relatively scant research has been performed on riboflavin transporter deficiency, in contrast to diabetes mellitus; and virtually no research has been done exploring a possible commonality between the two diseases. However, there may be a connection between the two. This paper investigates and explores a possible confluence between riboflavin transporter deficiency and diabetes mellitus and makes a case that an etiological common ground may exist. If a connection does exist, medicine may discover a way in which to diagnose better and treat the extraordinary, neurodegenerative, riboflavin transporter deficiency; and, perhaps in doing so, shed new light on addressing certain causations of diabetes mellitus.

Keywords: *Advanced Glycated End Products; Diet-Induced Obesity; Diabetes Mellitus; Solute Carrier 52A; Huntington's Disease; Insulin Resistance; Parkinson Disease; Riboflavin Transporter Deficiency Syndrome; Reactive Oxygen Species*

Abbreviations

AGEs: Advanced Glycated End Products; AD: Alzheimer's Disease; DIO: Diet-Induced Obesity; FAD: Flavin Adenine Dinucleotide; IL-1: Interleukin-1; IL-6: Interleukin-6; PD: Parkinson Disease; mRAGE: Membrane Receptor for Advanced Glycated End Product; ROS: Reactive Oxygen Species; RTD: Riboflavin Transporter Deficiency; TNF-α: Tumor Necrosis Factor Alpha

Introduction

Diabetes Mellitus (DM) is a well-known and prevalent disease, which can occur from a cluster of metabolic disorders that affect the homeostasis of major macromolecules (carbohydrates, proteins, and fat) in the body. Hyperglycemia is a major hallmark of DM [1]. DM results from a deficiency of insulin caused by an autoimmune assault on the beta cells in the islet of Langerhans of the pancreas [2] and by metabolic dysfunctions. Historically, DM typically affected middle-aged or older adults. However, currently, obesity is common in children and young adults; hence, the prevalence of diabetes in both groups.

In contrast to DM, riboflavin transporter deficiency (RTD) is a rare, neurodegenerative, autosomal disorder which results from a mutation of a specific gene, identified as solute carrier 52A (SLC52A) [3]. The symptoms of RTD are seen mostly in children; however, some adults have been diagnosed with RTD. Common symptoms of RTD include sensorineural deafness, infantile- or early-childhood onset nystagmus, sensory ataxia, atrophy of the upper limbs, respiratory insufficiency, and tongue fasciculations [3].

There are several biological factors at play that predispose a person to DM as well as RTD. The focus of this research was to investigate the possible role of or connection to DM in RTD and vice versa. To that end, the involvement of key cellular factors, such as insulin, glucose, and reactive oxygen species (ROS), have been examined.

Discussion

RTD is a newly acknowledged and rare neurodegenerative disorder. According to Cure RTD Registry, there are only 214 confirmed individuals with RTD, as of 2019. There is a minimal body of research available to understand the scope of its pathological impact on the various organ systems of the human body. Exome sequencing has shown that the mutation of the gene that codes for the riboflavin transporter occurs due to autosomal recessive inheritance [4,5].

The malfunctioning of the riboflavin transporters (RFVT) in this disorder impedes the entry of riboflavin into the cell. As a result, essential cofactors of flavoenzymes, such as FMN and FAD (active forms of riboflavin), are inadequate for normal cellular processes [6]. One downstream recipient of such deficiency is the mitochondria. FMN and FAD indirectly affect mitochondrial activities, thereby reducing its oxidative metabolic capability. The interruption of this metabolic pathway can result in several metabolic and neurodegenerative diseases, two of these being DM and RTD, respectively.

The causality of DM or RTD cannot be solely attributed to the interruption of the biological 'crosstalk' between flavoenzymes and the mitochondrial network. Research has shown the genetic involvement in the genesis of these two pathologies. What has not been clinically demonstrated thus far—particularly in the case of RTD—are the epigenetic factors that can complicate these diseases or predispose the body to these two disorders. Also, no known study, as yet, has investigated RTD as a potential underlying risk factor in DM, nor DM as an underlying risk factor for RTD. However, a comorbidity among these two distinct diagnoses seems plausible. Other neurodegenerative diseases, such as Alzheimer's (AD), Parkinson (PD), and Huntington's diseases (HD) [3,10], demonstrate a comorbidity with DM in the specific ways in which they impact the human body. Theoretically, at least, RTD appears to predispose the body to DM [5]. RTD and DM involve the neurons and the metabolic machinery of the mitochondria. At the biological crossroad between these two disorders are common risk factors and mediators, such as glucose, obesity, ROS, inflammation, and metabolic dysfunction [7-10].

The following sections will address the similar factors and expressions in the development of DM and RTD, primarily focusing on obesity, ROS, insulin, and glucose, in that order.

Obesity and RTD

RTD is, relatively, a very rare neuropathy and its phenotypical manifestation of symptoms varies from person to person [4]. Some are wheelchair users later in the disease process, while others suffer that fate much earlier. In any case, a chronic lack of physical activity and inappropriate diet management not only lead to excess abdominal fatty deposits but may also lead to atrophy of skeletal muscle [11]. Skeletal muscles require energy and glucose metabolism. Skeletal muscle is a significant site of postprandial glucose uptake. Interruption of this physiological process can play a role in the pathogenesis of DM. Excess abdominal fat, calculated as a ratio of waist circumference (WC) over waist-to-height ratio (WHTR) is a contributing risk factor in DM. In general, obesity destabilizes the homeostasis of the body and places it at risk for DM.

Obesity, diabetes, and neurodegenerative diseases, such as Parkinson and potentially RTD, are implicated in the inflammatory process that follows dysfunctional metabolic activities [12]. The hallmark of obesity is usually the presence of prominent visceral adiposities and adiposity in ectopic tissues. Within these tissues are proinflammatory cytokines (FK-kB) produced by macrophages. Currently, there are no reliable means to inhibit the onslaught of these cytokines.

Preclinical trials on diet-induced obesity (DIO) in rats suggest rhesus theta defensin (RTD-1) as a promising novel therapy; especially as it is nonimmunologic, nonimmunosuppresive, and nontoxic [13]. Physiologically, by way of an obesity-diabetes axis, RTD interferes in metabolic processes with adverse consequences. Therefore, RTD may be implicated in certain metabolic abnormalities and the ensuing inflammatory processes of such.

Conversely, mitochondrial dysfunction, oxidative stress, ROS, and inflammation are strongly implicated in the pathogenesis of these two neurodegenerative diseases, RTD and PD [14]. As mentioned previously, no known study has demonstrated definite causation from or correlation with obesity, glucose, RTD, ROS, and inflammation. However, it has been established that glucose and energy metabolism of the brain are adversely affected by the obesity-induced proinflammatory modulators TNF-α, IL-1 and IL-6. Such neuro-inflammations invariably affect the neuronal function and its internal molecular machinery and, subsequently, lead to neurodegeneration.

Certain studies have proposed that diabetes could be caused by neurodegeneration in the brain. It has been argued that the identification of obesity-based neurodegenerative disorders, such as Prader-Willi syndromes and Alstrom, affirms this hypothesis [8]. The hypothesis that considers the interplay of obesity, diabetes, insulin, glucose, ROS, inflammation, and neurodegeneration as factorial in RTD is plausible; and, thus, deserves further investigation.

The Role of ROS in Neurodegenerative Disorders and DM

ROS, which are precipitated by metabolic dysfunction, can lead to oxidative stress [15,16]. Contrary to general perceptions, ROS serve various vital physiological roles, which include the initiation of the mitogenic response, defense against antigens, and pathway signaling [9,10,15,17]. Nevertheless, excess production of ROS and the dysfunction of the antioxidant machinery may lead to cellular oxidative damage. Such damage generally affects proteins, lipids, DNA and RNA oxidation, and post-translational modification, all of which are common characteristics of many degenerative disorders, including RTD.

ROS are also implicated in the pathogenesis of diabetes and other diseases [10,18]. ROS are typically comprised of free radicals with the ability to oxidize and damage DNA, proteins, and carbohydrates. Hyperglycemia appears to induce oxidative stress in the metabolic pathway and inadvertently leads to the production of free radicals and, thus, their concomitant effects. Epigenetic modification of proteins, referred to glycosylation, is profoundly affected in the hyperglycemic state. Also, hyperglycemia plays a significant role in the non-enzymatic incorporation of glucose (glycation) into various biological proteins, thereby diminishing their functional abilities. Any abnormality in post-translational modification, coupled with ineffective cellular scavengers brought on by a neurodegenerative disorder, can result in neuronal death (Figure 1).

The Role of Insulin in RTD

Except for a few tissues in the human body, the homeostatic interplay between extracellular and intracellular glucose uptake is principally modulated by insulin and its transporters. Insulin is a peptide hormone. It is secreted by the beta cells of the islet of Langerhans in the pancreas. Defects in signal transductions, brought about by several aberrant biological factors, lead to insulin resistance. Insulin resistance is a complex phenomenon that may be induced by obesity-related metabolic syndrome [1,4].

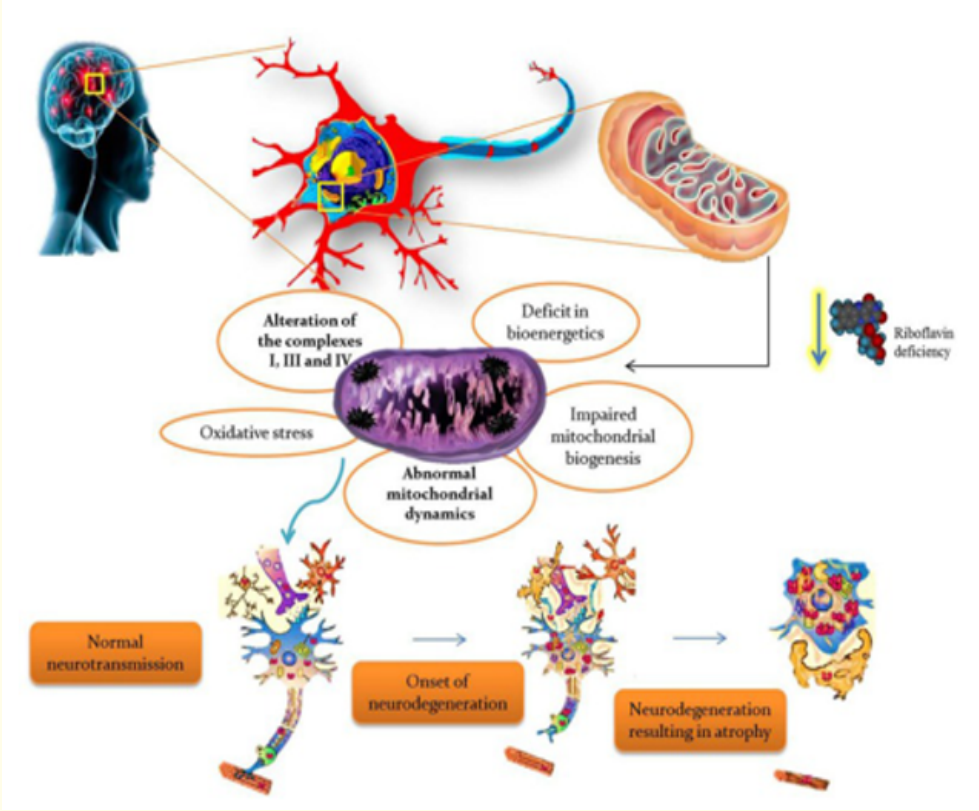

Figure 1: *A depiction of the effects of riboflavin deficiency on metabolic activities, by Udhayabanu T., et al (2017) [6].*
Note. The sequelae of riboflavin deficiency are self-perpetuating anomalies: genetic mutation, RTD, a deficiency of riboflavin, abnormal mitochondrial dynamics, and the cascading effects that end in neurodegeneration and its phenotypic symptoms.

Before the clinical detection of hyperglycemia in the plasma, insulin resistance could very well take a cellular presence in the body for as long as two decades. The biological dynamics that may lead to a point of convergence between insulin and RTD has not been genetically or clinically established, as yet. However, the epigenetic factors of RTD are implicated in insulin resistance and vice versa. Genetically, the mutation of riboflavin transporter genes results in a deficiency of riboflavin transporter proteins. This transporter deficiency leads to a decrease in the active forms of riboflavin, FMN, and FAD. Functionally, the downstream recipient of these insufficiencies is the mitochondria.

Molecular analysis has shown that FAD and its reduced form, FADH2, are among the critical cofactors in the metabolic functions of the mitochondria and its oxidative phosphorylation role. Research also shows that chronic metabolic dysfunction leads to undesirable consequences, such as mitochondrial complex 1 dysfunction, ROS, and inflammation.

It is posited that any condition that causes a decrease in mitochondrial activity or contributes to mitochondrial dysfunction can lead to a decrease in ATP. A decrease in ATP is particularly harmful to neuronal cells since they, like skeletal muscle cells, utilize a significant amount of ATP for their cellular activities. It is worth reiterating that most of the body's ATP is generated in mitochondria via oxidative phosphorylation.

Conversely, insulin resistance appears to modulate biological aging by aiding in the formation of advanced glycation end products (AGEs), as illustrated in Figure 2 [16,17,19]. ROS are again implicated in the inactivation of protein tyrosine phosphatases (PTPs) in the liver, which then activate rogue pathways. These rogue pathways subsequently promote fatty liver disease and exacerbate the development of obesity and DM.

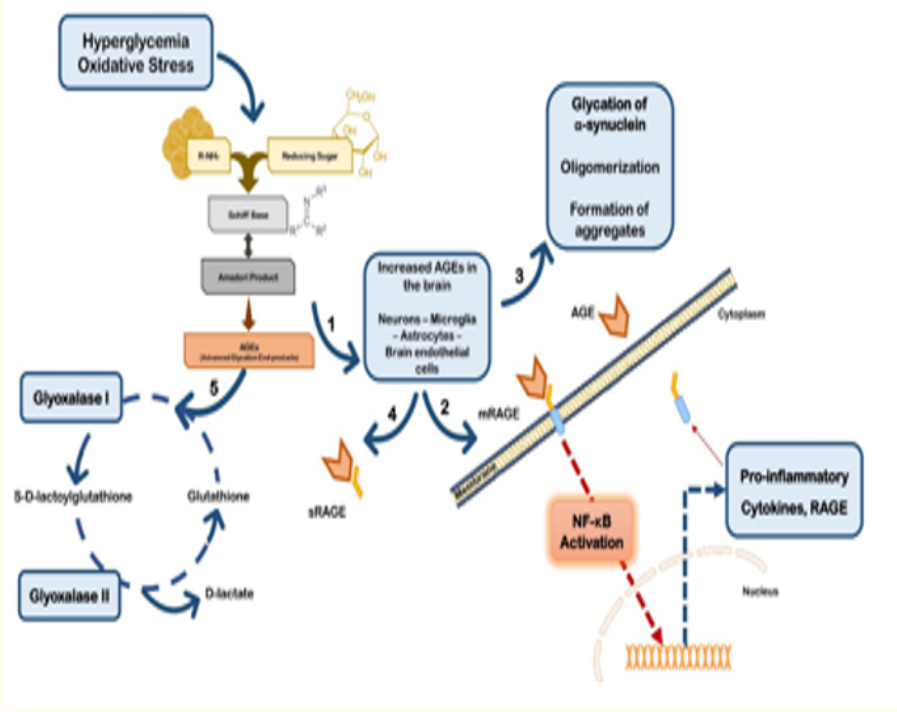

Figure 2: *Depicting the Maillard reaction pathway, by Videira P and Castro-Caldas M.(2018) [17].*

Note. Hyperglycemia and oxidative stress are implicated in the formation of AGES in a non-enzymatic modification of cellular protein, in a process called glycation. These glycated proteins have receptors to which they can bind at the cell membrane mRAGE. Such binding elicits the activation of NF-Kb and indirectly leads to the expression of pro-inflammatory mediators.

Glucose and RTD

The role of glucose in neuronal activities has been studied extensively, but its role in neurodegenerative diseases, such as RTD, has not yet been succinctly articulated. There is sufficient evidence that neurons utilize a vast amount of ATP for transcriptional, translational, and posttranslational activities as neurons are postmitotic cells with no chance for self-regeneration, repair, or replacement. Any sustained decrease in ATP availability can adversely affect neuronal cell activities, dramatically.

The physiological hallmark of RTD is the malfunctioning, structurally and functionally, of the transporter proteins; thus, hindering the entry of riboflavin into the cell. As a result, essential cofactors of flavoenzymes, such as FMN and FAD (the active forms of riboflavin), are inadequate for cellular processes. The mitochondria are the subsequent cellular recipients and 'victims' of such a deficiency. FMN and FAD indirectly affect mitochondrial activities, thereby reducing its oxidative metabolic capability.

A review of available data on this subject reveals that this interruption in the metabolic pathway may, among other sequelae, result in hypometabolism. Hypometabolism is characterized by decreased cellular glucose level in the brain. Hypometabolism could be an epigenetic factor that has the potential to contribute to RTD neuropathy. However, despite the seemingly logical molecular pathway that indicates a link between RTD and hypometabolism, there is an absence of any clinical symptoms in support of decreased glucose uptake in the brain. Thus, the hypometabolism hypothesis in RTD remains a salient supposition for now.

Hypofunction (low glucose uptake in the brain) is a typical feature of hypometabolism [20]. In RTD, hypofunction does not appear as a factor in the phenotypic display of symptoms. Most patients with hypofunction, such as those with Alzheimer's and Parkinson diseases, have progressive cognitive decline. RTD patients have no known cognitive impairment [5].

Neurons have a high level of intolerance for inadequate glucose supply [21]. Any disruption of the energy supply (via ATP) typically predisposes the brain to a variety of diseases with severe symptoms [21]. As mentioned previously, one noticeable characteristic of RTD is the absence of cognitive abnormalities [5] Thus, it is presumed, that in RTD, there is no interruption of the glycolytic pathway, which is the primary source of energy supply to the brain. To the contrary, the large quantity of ATP, which is required for post-translational modification, neuronal, and axonal synthesis, is affected due to the non-glycolytic metabolic pathway (oxidative phosphorylation) being interrupted [22]. FADH2 and ROS (DM-or RTD-related) can trigger several such feed-forward cascading metabolic events.

Thus, the destabilization of glucose homeostasis in the body can be preceded by hyperglycemia and end in neuronal death, with RTD implicated as a possible exacerbating neurodegenerative disorder. Conversely, RTD's pathology can lead to neuronal death with hyperglycemia implicated as the underlying exacerbating disorder [20].

Biological elements	RTD (reference)	DM (reference)
ROS	[9]	[10]
Oxidative Stress	[3]	[3]
Inflammation	[7]	[22]
AGEs	[3]	[16,17]
Antioxidant Enzymes	[10]	[18]

Table 1: *Biological elements common to RTD and DM, by Christopher C Ukpong (2019).*
Note: These elements are also considered by many as risk factors for RTD and DM.

Conclusion

Currently, there is no clear clinical or epidemiological footprint detailing whether riboflavin transporter deficiency is a risk factor for DM or vice versa. However, research has established a network of cellular interplay that shows a close association between these two pathologies. Therefore, given the risk factors and cofactors (glucose, insulin, obesity, ROS, and metabolic dysfunction) shared in RTD and DM, further investigation into the possible association and comorbidity of these two conditions seems warranted.

Conflict of Interest Statement

The authors declare that this paper was written in the absence of any commercial or financial relationship that could be construed as a potential conflict of interest.

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