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Molecular Modulation by Magnesium and Inflammatory Factors in the Pathophysiology of Diabetes and Depression

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Abstract

Type 2 diabetes (T2DM) and depression are widespread pathologies throughout the world, with increasing growth. The diagnosis and treatment of both pathologies is affected by their silent presentation and by the lack of adherence to treatment. The molecular pathways involved in its pathogenesis seem to be associated with each other, not only due to the presence of comorbidity but also due to the common nutritional, inflammatory, and metabolic factors. Likewise, being chronic pathologies, the inflammatory component becomes a common phenomenon in these pathologies, where the circulating elevation of tumor necrosis factor-alpha (TNFα) has downstream action, both insulin receptor signaling pathways like neurotransmitters. A deeper understanding of these biomolecular processes can improve the correct diagnosis of two diseases that occur in people with increasing frequency, and that do not distinguish socioeconomic status or age. Furthermore, the search for biomarkers that allow the identification of pathological stages and clinical differentiation will provide tools for the search for early and multidisciplinary therapeutic targets.

Keywords: Depression; Diabetes mellitus; Magnesium; TNFα; Inflammation; Metabolism

Abbreviations: NMDA: N-Methyl-D-Aspartic Acid; Fyn: Proto-Oncogene Tyrosine-Protein Kinase; Src: Proto-Oncogene c-Src; GLUT-4: Glucose Transporter Type 4; PI3K: Phosphoinositol 3-Kinases; Akt: Serine/Threonine-Specific Protein; TRPM6: Transient Receptor Potential Cation Channel Subfamily M Member 6; hs-CRP: High-sensitivity C-reactive Protein; NF-κB: nuclear factor kappa-Light-Chain-Enhancer of Activated B cells

Introduction

The prevalence of diabetes has increased by at least 3.8% in the past 4 decades. It is estimated that there are around 422 million people in the world with this disease, to which 1.5 million deaths are attributed in a year [1]. While depression affects around 264 million people worldwide and is associated with the 800,000 suicides that occur annually [2]. In addition, it is the third cause of years lived with disabilities [3]. The comorbidity of these two diseases is estimated to be 28% globally [4]. Having depression confers a Risk ratio of 1.18 for suffering from type 2 diabetes, this increases if it is estimated only in terms of the use of antidepressants, risk ratio 1.33 [5]. Similarly, having diabetes confers an OR of 1.33 (95% CI, 1.18–1.51) to having depression. This bi-directional association shows that increasing the degree of depression also increases the risk of diabetes in a linear way, as reported in a longitudinal study with a hazard ratio of 1.33 [6]. Having depression also increases the risk of death in those with type 2 diabetes with a hazard ratio of 1.52 for death from all causes, and with an hr of 2.15 for death unrelated to cancer or atherosclerotic cardiovascular disease [7]. In another longitudinal study that followed 1,465 people found that anhedonia predicts short survival time in people with diabetes (HR 1.82) [8]. These conditions affect men and women differently, in the case of depression, being a woman confers almost twice the risk (OR 1.95) in adults. This risk is higher during adolescence, increasing to 2.69 OR at ages 16 to 19 years [9]. Regarding diabetes, gender differences have also been studied, and it has been found that the prevalence is higher in men [10], while in women there is a higher risk of complications [11].

Psychological stress is a nodal point between these two pathologies. A longitudinal study that followed for 35 years more than 800 participants observed that those who reported permanent stress at work or at home had a higher risk of developing diabetes with a hazard ratio of 1.45 [12]. While stressful life events are considered causal with respect to depressive episodes [12,13]. Depression has also been reported to increase insulin resistance [14], which is partly attributed to cortisol, which is another common point of both pathologies since it has been found that in people with the disorder major depressive, this raises more than in people without the disorder when recovering from a stressor [15] and in diabetes, the degree of cortisol secretion is associated with the number of complications [16].

Diabetes is considered an inflammatory disease in which components of the immune system such as macrophages and TNFα are associated with insulin resistance [17]. On the other hand, in depression high levels of TNFα and other cytokines are found in peripheral blood in contrast to healthy subjects [18]. Furthermore, TNFα has been described as an activator of serotonin transport [18,19].

Discussion

Magnesium, a common denominator between diabetes and depression

Magnesium (Mg) deficiency in the brain reduces serotonin levels, and antidepressant drugs have been shown to have the effect of raising Mg in the brain. Excessive intake of calcium, glutamate, and aspartate can greatly worsen Type 2 Diabetes (T2DM) [20,21]. There are certain biomarkers described in patients with depression and in populations of "high risk by family line" [22]. Among them is the increased activity of the adrenal hypothalamic-pituitary axis (HPA) known as the axis of stress [23]. In this context, the aldosterone axis has a regulatory role in magnesium. Adrenocorticotrophic hormone (ACTH) regulates both aldosterone and cortisol, so there is likely to be an association between the two phenomena [24]. Magnesium is the main regulator of phosphate transfer in the cellular metabolic pathways. Also has recently been shown to participate in brain regulation in the limbic system, implying a possible role for magnesium in the etiology and progression of depression [25,26]. The known biological mechanisms between low serum magnesium levels and depression may involve the central nervous system, the stress axis, and oxidative pathways [27]. Magnesium is particularly known for its importance as an antagonist of the glutamate receptor NMDA, a key element in synaptic enhancement, learning, and memory [24,28]. NMDA receptors can be phosphorylated by the serine/threonine kinases protein kinase C (PKC), protein kinase A (PKA) and calcium/calmodulin-dependent protein kinase II (CaMKII), as well as by the tyrosine kinases Src and Fyn. In general, phosphorylation enhances NMDA receptor function [29]. NMDA channels primarily carry calcium and sodium currents, so depletion of magnesium could allow an excess calcium current. Evidence supports the possibility that magnesium deficiency disrupts neuronal function by increasing neuronal calcium flux, resulting in increased nitric oxide, acting as a reactive oxygen species, causing neuronal inflammation and death [30-32]. On the other hand, among the common mechanisms involved in the pathogenesis of diabetes and depression, is magnesium modification in the face of stress. Magnesium's ability to reduce the release of ACTH and modulate adrenocorticotropic sensitivity to ACTH is preventive against hyperactivation of the HPA axis [33]. In the adult population with dysregulation of the HPA axis, it has been related to stress and depression, which translates into an elevation of elevated cortisol. Thus, unbalanced HPA activity has frequently observed in depressed populations [34]. Glucocorticoids have been continuously shown to cause neurotoxic adverse effects in the hippocampus, suggesting that excess glucocorticoids may be responsible for hippocampal cell death observed in depression [35,36]. When the HPA axis is activated on a sustained basis, it may lead to dysregulated cortisol secretion [37,38]. In addition, glucocorticoid receptors are expressed in pancreatic β cells, where cortisol stimulation directly influences insulin sensitivity and decreases insulin secretion, so that neuroendocrine dysfunction promotes T2DM pathogenesis [39].

The effect of magnesium on insulin sensitivity has been extensively studied [40]. Mainly participating in the signaling pathway for translocation of the GLUT-4 receptor [41]. Mg is an important regulator of many enzymes involved in glycolysis because it acts as a cofactor for adenine nucleotides. Insulin itself can also regulate Mg homeostasis [42]. Upon activation of the epidermal growth factor receptor (EGFR) and insulin receptor, the intracellular signaling cascade that includes PI3K / Akt and ras-related botulinum C3 substrate 1 is activated, causing increased expression of TRPM6 membrane and channel activity [43]. Furthermore, it has been observed that when Mg concentrations are low, signal transduction decreases, and as a consequence insulin resistance (IR) occurs [43]. On the other hand, chronic hyperinsulinemia, secondary to IR, promotes an increase in renal excretion of Mg with renal losses greater than those of intake, which perpetuates a pathological cycle [44].

Inflammation present in diabetes and depression

Depression is an inflammatory disorder involving proinflammatory cytokines, interleukin-1, interleukin-6, TNF-alpha, soluble interleukin-2 receptors, interferon-alpha, interleukin 8, interleukin-10, hs-CRP, acute phase proteins, haptoglobin, toll-like receptor 4, interleukin-1beta, mammalian target of the rapamycin pathway, substance P, cyclooxygenase -2, prostaglandin-E2, levels of lipid peroxidation and acid sphingomyelinase [45]. High levels of TNFα and other peripheral blood cytokines are found in depression in contrast to healthy subjects [18]. It has also been found that TNF alpha receptors

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sTNFR1 and sTNFR2 are found in a smaller proportion in people with depression, compared to those without it, which suggests that it is involved in the reduction of tissue regeneration and neurogenesis [46]. Furthermore, TNFα has been described as an activator of serotonin transport [19,47]. This cytokine upregulates the enzyme indoleamine 2, 3-dioxygenase, whose function is the breakdown of tryptophan, generating metabolites such as kynurenine and quinolinic acid that have neurotoxic effects and lead to damage to cortical neurons which generates depressive symptoms [48]. Both diabetes and depression are considered an inflammatory disease in which components of the immune system such as macrophages and TNFα are associated with insulin resistance [17]. The reduction in the mass and function of beta cells contributes to the development and progression of type 2 diabetes mellitus. Proinflammatory cytokines TNF α and interleukin (IL) -1β have been associated with the genesis of this pathology [49].

TNFα signaling has shown a controversial role [50]. IL-1β and TNFα bind to different receptors. However, both cytokines can activate transcription factor NFκB and c-Jun N-terminal kinase (JNK) [51-54]. Various studies suggest that JNK activation contributes to insulin resistance induced by the inflammatory process present in obesity, decreasing the function and mass of beta cells [54-56]. On the other hand, it is established that TNF-α induces insulin resistance [14,15]. Following insulin binding to its receptor, TNF-α reduces IRS-1 phosphorylation and decreases nitric oxide (NO) release via the PI3K / Akt / eNOS pathway [57]. TNF-α is closely related to the regulation of tumor suppressor protein phosphatase (PTEN), which plays an important role in downstream transduction of the insulin receptor [58]. A recent study showed that PTEN haploinsufficiency is a monogenic cause of deep constitutive insulin sensitization [59].

Conclusion

The current knowledge about the pathophysiological phenomena involved in diabetes and depression are not approached as a single pathological entity, that is, they are treated independently of each other. However, current evidence from both molecular biology and neuropsychoimmunology allows us to deepen our understanding of the mechanisms involved in common with the ability to become targets for action in both treatment and prevention. Evidence suggests that magnesium as an ion plays a regulatory role in brain and metabolic functions, so analyzing its behavior in the patient with diabetes who is suffering from depression will probably reduce the processes involved in the progression of the disease. Likewise, by recognizing that depression is an important factor for the development of chronic diseases, it is possible to consider that the inflammatory processes that accompany this pathological entity are responsible for short and long-term organic damage, for which reason the correct monitoring of Inflammatory biomarkers will expand clinical and diagnostic strategies for their treatment. The inflammatory and metabolic mechanisms have common denominators in chronic diseases that affect not only glucose levels but also adaptive neurological processes. .

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