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Ultrastructural aspects of cranial and peripheric nerves of cronically diabetic and malnourished rats: a short biochemical panorama

REVIEW

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Abstract

Diabetes Mellitus is one of the most common causes of neuropathies, which can be caused by molecular imbalances that impair metabolic pathways. Studies in rats showed the importance of sirtuins (SIRT), deacetylases that use NAD^+ as a cofactor, which have a widespread function in metabolism, and their relation when food deprived or calorie restricted. Additionally, diabetic neuropathy presents different structural biomarkers that cause morphological alterations in fibers that can be partially treated. SIRT1 is the principal sirtuin, which acts on hypothalamus, liver, kidney, among other organs, up regulating or down regulating the expression of some genes or enzymes crucial in the process of glucose absorption.

Keywords
Diabetes Mellitus, Neuropathy, Sirtuins, Calorie Restriction

The prevalence of diabetes mellitus has been increasing worldwide over recent years. Long-term diabetes results in vascular changes and dysfunction; diabetic complications are the major causes of morbidity and mortality in diabetic patients [1]. It affects 243 million worldwide people of which 30 million suffer from some form of diabetic neuropathy (DN) [2, 3]. Experimental models involving diets and peripheral nerves are indispensable to assist in current research, since peripheral

neuropathies, particularly diabetic neuropathy is a devastating common comorbidity in diabetic patients. [4, 5, 6]

Nowadays, Diabetic Neuropathy (DN) is considered the most common cause of peripheral neuropathy in clinical practice. It can affect sensitive, motor or autonomic nerve fibers, with symmetric, asymmetric, acute or chronic presentations. DN is not just a functional disease, but a complication of diabetes with molecular and pathological substrates caused by hyperglycemia [2]. A buildup of myoinositol is observed on diabetic's urine and its reduction on injured tissue. This is the most widely known metabolic mechanism involved on DN [4]. Therefore, normalization of blood glucose is a fundamental step towards the successful prevention and treatment of DN [2].

The structural biomarker of DN can be considered as the atrophy and loss of myelinated and non-myelinated fibers, followed by Wallerian Degeneration, paranodal and segmental demyelination, associated to a weak regenerative response [7, 8]. In chronically diabetic rats treated with intensive insulin replacement, only part of the nerve conduction can be restored (first detectable neuronal alteration in experimental models). [7, 9, 10].

Long term experimental diabetes caused important morphological and morphometric alterations in the aortic depressor nerve of *Wistar* rats for both myelinated and unmyelinated fibers. These alterations were more severe on the distal segments, exhibiting a ''dying back'' type neuropathy. These alterations were not dependent on the endoneural blood vessels lesions and treatment with insulin delayed, but did not stop or correct the observed lesions. Also, these alterations were more evident in the distal segments of the nerves and were moderated by insulin treatment. These results indicate that the baroreflex impairment described in the literature for chronic diabetic patients or experimental animals is due not only to efferent neuropathy as widely accepted, but also to an afferent diabetic neuropathy [11].

Also, thiamine, whose deficit is more often than thought, is involved in the genesis of the peripheral nerve system damage in diabetes mellitus [2]. There is a high deficit frequency (17-79%) of thiamine in diabetics, due to low intestinal absorption caused by insulin action deficit. This same thiamine deficit reduces insulin production in pancreatic beta cell. Finally, the proximal tubular reabsorption of thiamine in diabetic people does not increase, compensatorily, with deficit [2].

CR (calorie restriction) promotes longevity and slows aging. However, further restriction of food intake, leading to malnutrition, reduces the lifespan [1, 12]. One possible mechanism by which CR exerts such beneficial effects involves the actions of sirtuins (SIRT) [1, 14], which are conserved mediators of longevity [13]. In mammals, SIRT1, SIRT6, and SIRT7 are nuclear; SIRT3, SIRT4, and SIRT5 are mitochondrial; and SIRT2 is cytoplasmic [13]. SIRT1 is associated with the regulation of a wide variety of cellular processes, such as apoptosis, metabolism, mitochondrial biogenesis, autophagy [1, 15], and stress tolerance [9]. SIRT1 also interacts with the Notch signaling pathway in the nervous system, and has a role in neural development and age-related diseases such as Alzheimer disease [15].

SIRT3 enhances lipid catabolism by deacetylating and activating long-chain-specific acyl-coenzyme A dehydrogenase (LCAD), a key enzyme in the fatty acid oxidation pathway [16]. SIRT3 might also regulate the TCA cycle itself, as it interacts with the TCA enzymes succinate dehydrogenase and isocitrate dehydrogenase 2 [17-19]. Mechanisms that reduce levels of reactive oxygen species (ROS), such as activation of SIRT3, might be beneficial against age-related diseases [15].

Sirtuins are the class III histone deacetylase family, and use NAD^+ as a cofactor [20]. SIRT1 deacetylates not only histones, but also many transcriptional regulators, thereby modulating diverse biological processes. SIRT1 exerts renoprotective effects by conferring resistance to cellular stress

such as hypoxia, reducing fibrosis, inhibiting apoptosis and inflammation, inducing autophagy, and regulating blood pressure [1]. CR is also renal-protective in a diabetes model in rats, and this is associated with activation of SIRT1 and deacetylation of NF-kB [21]. SIRT2 mitigates oxidative stress in HK-2 cells [22].

SSIRT1, which expression has strong links to insulin sensitivity [23], deacetylates circadian clock proteins BMAL1 (transcription factors CLOCK and ARNTL [15]) and PER2 [24] to influence their function, by amplifying expression of BMAL1 [25]. SIRT1 deacetylates PGC-1α in neurons to increase activation of BMAL transcription [25]. SIRT1 in the hypothalamus is key to the observed extension of life span in transgenic mice by virtue of its activation of the orexin type 2 receptor in the Lateral Hypothalamus (LH) and Dorsomedial Hypothalamus (DMH) [26]. Additionally, calorie restriction results in upregulation of SIRT1 in some regions of the brain (such as the hypothalamus) and downregulation in others [27, 28, 29]. In mice undergoing calorie restriction, there is an attenuation of beta-amyloid content in the aging brain, suggesting that SIRT1 upregulation might be protective under some types of nutritional stress [27].

In conclusion, sirtuins have a crucial impact on glucose and age-related metabolism and the arising of neuropathies. SIRT1 is the most responsible for regulating all those processes. Other sirtuins, including the mitochondrial sirtuins SIRT3, SIRT4 and SIRT5 and the nuclear sirtuins SIRT6 and SIRT7, may have important roles in cytoprotective functions, their molecular targets and biological functions, and possible roles in renoprotection, are largely unknown [1]. So it is important to check the molecular and microscopic level the role of these proteins in the peripheral nerves in models of experimental diabetes and malnutrition, in order to corroborate more with the proposed study. [30]

This manuscript is dedicated to visionary and humanist medical researcher Naíde Regueira Teodósio (1915-2005) by his birth centenary and pioneering.

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