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Review

Downregulated Brain-Derived Neurotrophic Factor-Induced Oxidative Stress in the Pathophysiology of Diabetic Retinopathy

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ABSTRACT

Brain-derived neurotrophic factor (BDNF), a member of neurotrophin growth factor family, physiologically mediates induction of neurogenesis and neuronal differentiation, promotes neuronal growth and survival and maintains synaptic plasticity and neuronal interconnections. Unlike the central nervous system, its secretion in the peripheral nervous system occurs in an activity-dependent manner. BDNF improves neuronal mortality, growth, differentiation and maintenance. It also provides neuroprotection against several noxious stimuli, thereby preventing neuronal damage during pathologic conditions. However, in diabetic retinopathy (a neuromicrovascular disorder involving immense neuronal degeneration), BDNF fails to provide enough neuroprotection against oxidative stress-induced retinal neuronal apoptosis. This review describes the prime reasons for the downregulation of BDNF-mediated neuroprotective actions during hyperglycemia, which renders retinal neurons vulnerable to damaging stimuli, leading to diabetic retinopathy.

RÉSUMÉ

Le facteur neurotrophique dérivé du cerveau (BDNF pour *brain-derived neurotrophic factor*) est un facteur de croissance, membre de la famille des neurotrophines, qui médie physiologiquement l'induction de la neurogenèse et la différenciation neuronale, promeut la croissance et la survie des neurones, et maintient la plasticité synaptique et les interconnexions neuronales. Contrairement au système nerveux central, sa sécrétion dans le système nerveux périphérique apparaît d'une manière dépendante de l'activité. Le BDNF améliore la mortalité, la croissance, la différenciation et le maintien des neurones. Il offre également une neuroprotection contre plusieurs stimuli nocifs, empêchant ainsi les dommages neuronaux au cours des états pathologiques. Cependant, lors de rétinopathie diabétique (un trouble de la neuromicrovascularisation impliquant une dégénérescence considérable des neurones), le BDNF n'offre pas assez de neuroprotection contre l'apoptose des neurones rétiniens induite par le stress oxydatif. Cette revue décrit les raisons principales de la régulation à la baisse des effets neuroprotecteurs médiés par le BDNF durant l'hyperglycémie, qui rend les neurones rétiniens vulnérables aux stimuli dommageables, et qui mène à la rétinopathie diabétique.

Introduction

Brain-derived neurotrophic factor (BDNF) is a protein that belongs to a family of growth factors, called neurotrophins, whose other mammalian members include nerve growth factor (NGF), neurotrophin-3 (NT-3) and neurotrophin-4 (NT-4). Neurotrophins are basically involved in regulating the development, survival and functioning of neurons. Among all neurotrophins, the physiology of BDNF is the most well defined and well characterized (1). It is encoded by the BDNF gene and is known to control vital physiologies of the vertebral nervous system, encompassing mainly the monitoring of differentiation and growth of neurons as well as their maintenance. Moreover, subsequent studies have revealed more complex functions of BDNF in the nervous system, including regulation of synaptic plasticity, dendritic arborization, mediation of long-term potentiation and establishment of neuronal circuits to modulate complex behaviours. Also, its involvement in other pivotal roles, such as in hippocampal-dependent cognitive functions and the control of hyperactiveness, has also been demonstrated. Owing to the vehemence of BDNF-mediated functions, any deviation from its normal physiology leads to psychiatric disorders (such as bipolar disorder, schizophrenia, anxiety and cognitive dysfunctions), stroke, spinal cord injuries and several disorders concerning neuronal degeneration (2,3). (Figure 1)

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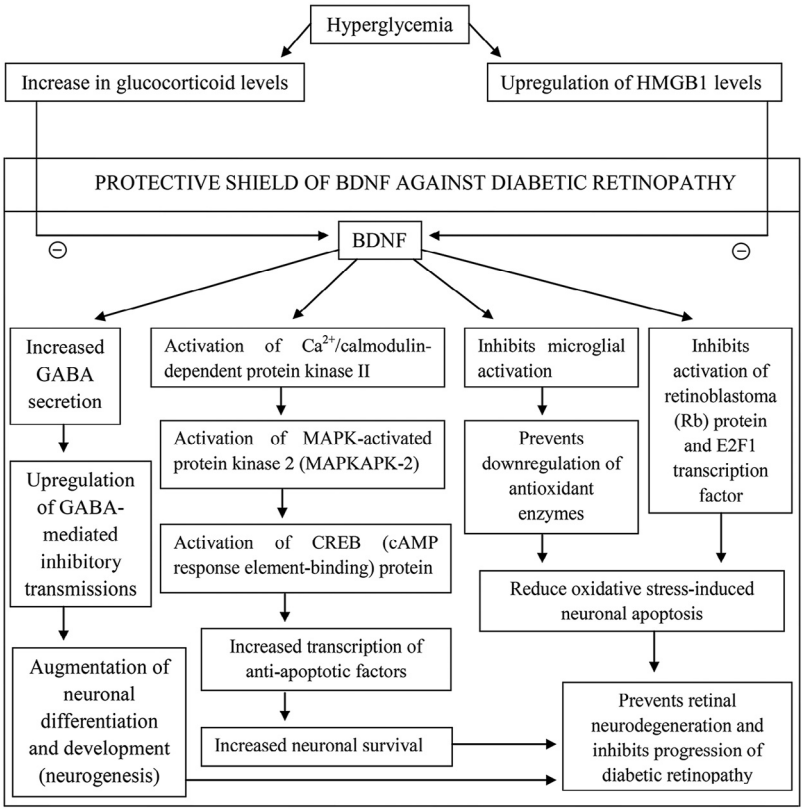

Figure 1. Hyperglycemia-induced downregulation of protective effects of brain-derived neurotrophic factor (BDNF) against oxidative stress-induced retinal neurodegeneration and progression of diabetic retinopathy.

Diabetic retinopathy, earlier considered merely a microvascular complication, is now widely recognized as a neuromicrovascular complication, with damage to the neuronal system that plays an integral part in its pathophysiology. BDNF is acknowledged for its role in neurogenesis and in protecting neurons from several damaging stimuli. This review describes the effects of various hyperglycemia-induced alterations on the neuroprotective mechanisms offered by BDNF, which render the latter incapable of preventing retinal neurodegeneration during diabetic retinopathy.

Retinal Anatomy, Neuronal Damage and Diabetic Retinopathy

Diabetic retinopathy is a severe sight-threatening complication of diabetes mellitus, and it accounts for a large number of cases of acquired, yet potentially avoidable, blindness. The principal mechanism of its pathogenesis appears to be alterations in the microvasculature of retina as the result of hyperglycemia. The elevated concentration of blood glucose is a harbinger of numerous molecular changes. These lead to various responses that result in neuropathy and microangiopathy.

Retinal detachment is the ultimate reason for the irreversible blindness associated with the advanced stages of diabetic retinopathy. Retinal detachment is caused by the destruction of the anatomic structure of the retina as well as the hyperosmolar pathologic conditions created in the retina during hyperglycemia. Recent studies conducted to explore the role of retinal neurodegeneration in the pathophysiology of diabetic retinopathy have revealed that oxidative stress-induced destruction of retinal neurons leads to disruption in normal retinal physiology and, thus, compromises vision. The anatomic structure of the retina basically comprises neuronal tissue containing several layers of different types of cells, namely, ganglionic cells, amacrine cells, Müller glial cells, bipolar cells, horizontal cells and the photoreceptor layer of rods and cones (4). Lipids are widely found to be associated with the retina. Studies employing matrix-assisted laser desorption/ionization (MALDI) imaging mass spectroscopy have shown the presence of plasmalogen phosphatidylethanolamine lipid-containing docosahexaenoic acid in the inner retina and docosahexaenoic acid-containing glycerophosphatidylcholine and other phosphatidylethanolamine lipids in the photoreceptor cells (5). These whole units collectively make up the retinal screen, which is sandwiched between the posterior wall of the vitreous chamber and the retinal pigment epithelium. The inner limiting membrane formed by the Müller glial cells adjoins the posterior chamber, whereas the photoreceptors are present at the other extreme end, adjoining the retinal pigment epithelium.

The retinal pigment epithelium comprises the outer blood-retinal barrier and interacts with the choroidal blood supply for the exchange of oxygen and vital nutrients, besides serving several other functions (6). Because neurons are the basic structural units of the retina, any damage to these cells would directly hamper retinal physiology. Inflammation, oxidative stress and hypoxia-ischemia are the 3 major hyperglycemia-induced pathologic conditions that account for retinal neuronal damage. The causes of all 3 mentioned pathologic states are interlinked and ultimately lead to similar damaging outcomes. Hyperglycemia-induced mitochondrial dysfunction may be regarded as an initial trigger for the induction of these conditions.

The human body responds to excessive blood glucose primarily by upregulating 2 major glucose-metabolizing pathways—glycolysis and the citric acid cycle. In both these pathways, reduced forms of nicotinamide adenine dinucleotide and flavin adenine dinucleotide (NADH and $FADH_2$, respectively) are formed as