

Genistein is a Promising Intervention Therapy for Diabetic Vasculopathy and Gliopathy

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Received date: February 5, 2018; Accepted date: February 14, 2018; Published date: February 18, 2018

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Introduction

Diabetic retinopathy (DR) is one of the serious secondary consequences of diabetes. It is the leading cause of blindness in individuals of working age. Diabetes mellitus (DM) patients characterized by the state of hyperglycemia are prone to some long-term complications like nephropathy, neuropathy and retinopathy [1]. Clinically, DR is characterized by vasculopathy [2]. Retinal gliopathy (Müller cells, astrocytes and microglia) occurs in both early and advanced phases of almost every retinal vascular disease. Glial cells act as communicators between vessels and neurons [3]. In this review, we would like to overview the role conferred by genistein on vasculopathy and gliopathy in the course of DR, where glial and vascular abnormalities play a critical role.

Diabetic Vasculopathy and Gliopathy

Pathogenesis of micro vascular retinopathy could be caused by abnormal glucose metabolism, activation of protein kinase C (PKC), formation of advanced glycation end products (AGE), increased production of Reactive Oxygen Species (ROS), release of proinflammatory cytokines from Müller cells or microglia in the retina [4]. A decrease in pericyte coverage of retinal capillaries might represent the first pathological changes in diabetic retinopathy.

An increase in number and activation of Müller cells occurs in diabetic patients and animal models, as reflected by strong up regulation of glial fibrillary acidic protein (GFAP) and nestin [5]. Müller cell proliferation might be detrimental as it requires functional uncoupling from neurons and blood vessels. Inducible nitric oxide synthase is increased in human diabetics and animal models, which colocalizes with vascular endothelial growth factor (VEGF) overexpression in Müller cells and appears to be associated with breakdown of the blood retina barrier (BRB) in diabetes [6]. Müller cells might undergo further morphological changes during diabetes, including hypertrophy, increased glycogen granules, swelling and increased density and frequency of the processes which enclose the neuronal processes and blood capillaries and mitochondrial swelling and accumulation in their end-feet [7].

Astrocytes dysfunction is also reported in DR, which is critical in the maintenance of blood brain barrier integrity [5]. This might result in a synergistic effect, whereby the barrier-maintaining properties of macroglia are lost, coupled with the enhanced production of permeability factors. Morphologically astrocytes exhibited rounded form with large euchromatic nuclei, a scanty cytoplasm and infrequent processes containing numerous glycogens.

In response to signals from dying cells, activated microglia evolves into phagocytes capable of clearing debris. In ultrastructure, reactivated microglia possessed dense hypertrophied cell bodies with

small ovoid nucleus, a prominent chromatin pattern and a few thick processes containing numerous dense bodies and lipofuscin granules [7].

The blood capillaries of diabetic retina undergo dilatation and endothelial mitochondrial swelling, apoptotic degeneration, chromatin fragmentation and/or loss of the endothelial and the pericytic cells nuclei [7]. Breakdown of the blood brain barrier in DR, induces gliosis which potentially further exacerbate vascular dysfunction. Gliosis might be initiated by oxidative stress and activation of the polyol pathway, as pharmacological inhibition of these pathways inhibits GFAP up regulation [8].

Genistein and Diabetic Retinopathy

Genistein is a naturally occurring protein tyrosine kinase inhibitor, which is a class of phytoestrogens mostly found in legumes. It may be a natural antidiabetic agent which exhibits anti oxidative properties by protecting against lipid peroxidation and by scavenging hyperoxide and superoxide anion [9].

Genistein inhibits DNA topoisomerase II and S6 kinase [10] which contributes to growth arrest in vascular endothelial cells, resulting in inhibition of angiogenesis [11]. Retinal neovascularization can be inhibited by genistein by suppressing HIF1alpha protein and VEGF expression in an oxygen-induced retinopathy model [12]. Retinal vascular leakage has been significantly reduced by chronic oral genistein in an animal model of diabetic retinopathy [6]. Genistein treatment improved the integrity of the retinal capillaries [7] possibly by reducing iNOS as blocking iNOS decreased hyperglycemia induced micro vascular anomalies in dogs, rats, and mice [13].

Physically, genistein ameliorated morphological changes of the retina of streptozotocin-induced diabetic rats regarding Müller cells glycogen contents in the cytoplasm, frequency and electron density of their process around nerve fibers and blood capillaries and the mitochondrial structure and accumulation in their end feet. Astrocytes were more or less of normal architecture with long process which partially enclosed the blood capillaries, external to Müller cell processes. The retinal capillaries were partially enveloped by Müller and astrocyte cell processes.

Consistently, the increased numbers and activation of microglia reported in diabetic animals [7,14] appears pathological as minocycline, an inhibitor of microglia, reduced the progression of DR. Release of soluble cytotoxins from activated retinal microglia in diabetic rat model contribute ultimately to the progression of DR [15]. Reduced activation of microglia following genistein treatment indicated reduction in the pathogenic molecules.

The possible retinal anti-inflammatory effects of genistein have been distinguished from its activity as an antidiabetic (insulin releaser).

Intravitreal injection of genistein decreases the expression of proinflammatory cytokines in retina of STZ-injected rats and decreases microglial activation [16].

Being a multifunctional compound, genistein may be a new intervention therapy that might be expected to be effective in inhibiting progress in vasculopathy and retinopathy and there by modulating early pathological pathways long before the occurrence of vision loss among diabetics.

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