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Mini Review

Hyperglycemia Damages the Endothelial Glycocalyx: Implications for The Blood Brain Barrier

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Abstract

The glycocalyx is a matrix of proteoglycans, glycoproteins, glycosaminoglycans, glycolipids and soluble proteins that coats the endothelial cells, together with the endothelium, the astrocyte end feet and basement membrane, contributes to the blood brain barrier, which prevents large molecules, neurotoxins, inflammatory factors and pathogens into the brain. It has been demonstrated that hyperglycemia results in damage to the glycocalyx through mechanisms that are still being elucidated. This means that the brain may be exposed to harmful agents that can cause multiple diseases. More studies are therefore needed to understand and prevent brain disease due to hyperglycemia.

Keywords: Hyperglycimia; Diabetes; Brain; Blood brain barrier; Endothelium; Glycocalyx; Cerebrovasculature

Introduction

It is well established that diabetes can lead to cerebral vasodegeneration, manifested principally by blood brain barrier (BBB) dysfunction [1]. The BBB consists of a tight capillary network that protects the brain from most circulating molecules while providing access to necessary nutrients required for function. These capillaries are formed by an inner layer of endothelial cells that are joined together via tight junctions and adherent junctions followed by a less dense layer of pericytes (ratio 4:1) that form socket like structures at the point of contact with endothelial cells, and a layer of astrocytes, whose end feet are in close proximity with the endothelium and allow for the diffusion of metabolites and neurotransmitters from the brain tissue to the endothelium and vice-versa [2]. The tightness of the barrier is mainly determined by the integrity of the endothelium, which provides the major resistance to transport across the vessel walls [3].

Homeostasis of the endothelium not only depends on the adequate transmission of biochemical signals but also on dynamic interactions due to the circulating blood. The release of metabolic molecules, as well as changes in gene and protein levels have been attributed, among other stimuli, to fluid flow shear stress (FFSS) [4]. Endothelial cells sense and respond to such stimuli due to the presence of a mechanosensing machinery that includes the glycocalyx (GCX) at the luminal side of the vessel that connects to the integrin binding domains and focal adhesions and basal GCX at the abluminal side via the cytoskeleton [5]. This mechano-signaling modulates vasculogenesis, permeability, vasoconstriction, cell death and other physiological and adaptation responses [6]. The GCX is denser in the brain, covering the entire luminal surface of cerebral capillaries, suggesting that it may be an important component of the BBB [7].

The GCX is a matrix of proteoglycans (PG), glycoproteins, glycosaminoglycans (GAGs), glycolipids and soluble proteins coating the endothelial cells. The most abundant GAGs are heparan sulfate (HS), chondroitin sulfate and hyaluronan (HA). The main PGs are syndecan (SDC)-1, -2 and -4 and glypican-1(GPC1).For reviews on the GCX composition and function see Reitsma et al. and Curry and Adamson [8,9]. The integrity of the GCX is critical for sensing FFSS caused by the circulating blood [10]. Interestingly, FFSS can modulate the GCX barrier properties against cellular infiltration and molecular transport across the vascular wall [11-

13]. In addition, the GCX is negatively charged due to the presence of anionic oligosaccharides, thereby forming an electrical barrier [14,15]. In vitro experiments have shown that high glucose leads to the degradation of the HS component of the GCX in bovine aortic endothelial cells (BAEC) [16] and in human endothelial cell lines [17]. In BAEC, this resulted in an abnormal response of FFSS dependent hydraulic conductivity across the cell layer. In vivo experiments have shown that either neutral or anionic dextrans with molecular weights of 70-kDa and higher, do not penetrate the GCX and are therefore retained in the vasculature [18], however, short-term hyperglycemia can impair the ability of the GCX to exclude 70-kDa dextran [19] possibly due to enzymatic shedding of some of its components. This was partially supported by the observation that the GCX of mice deficient in hyaluronidase 1, an enzyme that cleaves HA, was preserved from damage in streptozotocin-induced diabetes [20]. In type 1 diabetes patients and in acute hyperglycemia, plasma HA and hyaluronidase are increased [21,22]. In type 2 male patients, sublingual and retinal GCX thickness was reduced as measured by angiography, with a concomitant increase in markers for HA catabolism (HA and hyaluronidase) and an increase in transcapillary efflux of albumin, that was partially restored following administration of sulodexide [23], a purified GAG combining HS and dermatan sulfate with affinities for antithrombin III and for heparin cofactor II respectively [24,25]. It is well established that reactive oxygen species (ROS) and advanced glycation end products (AGE) are involved in diabetic complications. ROS can depolymerize GAGs [26] and AGE degrade and inhibit the production of HA [27]. Besides the presence of ROS and AGE, the activation of heparanase and hyaluronidase lead to the deterioration of the GCX during diabetes [28]. The GCX therefore has been suggested as a target in diabetic vascular complications [29]. In hyperglycemic conditions, heparin or insulin preserves GAGs; insulin is an effective diabetic therapy since it both lowers blood glucose and protects the endothelium [30].

The GCX, the endothelium, the astrocyte end feet and basement membrane contribute to the BBB [31] preventing large molecules, neurotoxins, inflammatory factors and pathogens into the brain. A compromise in the BBB precedes many neurological disorders and is related to diabetes-associated comorbidities such as cognitive impairment and depression [32]. Hyper and hypoglycemia have been associated with oxidative stress in the brain, that may upregulate and activate the receptor for AGE, which also transports amyloid-beta from the blood into the brain, thus, establishing a relationship between type 2 diabetes mellitus and Alzheimer's disease (also referred to as "type 3 diabetes"). Degradation of the GCX at the BBB may imply that there is a lower FFSS-induced endothelial nitric oxide production [33] which can impair vasodilation. According to the International Diabetes Federation (www.idf.org), in 2019, approximately 463 million adults were living with diabetes and it is estimated that by 2045 this number will rise to 700 million. Therefore, more research is necessary to understand the mechanisms by which hyperglycemia damages the GCX. Such studies will likely provide a key to prevent complications in micro and macrovascular beds of the brain and other organs.

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Conflict of Interest

We would like to declare that no conflict of interest exists related to this article.

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