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Critical role of microvasculature basal lamina in ischemic brain injury

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Abstract

Cerebral vascular system can be divided into two categories: the macrovessels and microvessels. The microvessels consist of arterioles, capillaries and venules. There are three basic components in the microvasculature: endothelial cells, basal lamina and end-feet of astrocytes. The basal lamina is situated between the endothelial cells and the end-feet of astrocytes, and connects these two layers together. Damage to the basal lamina causes the dismantlement of microvascular wall structures, which in turn results in increase of microvascular permeability, hemorrhagic transformation, brain edema and compromise of the microcirculation. The present article reviews microvascular changes during ischemic brain injury, with emphasis on basal lamina damage.

Keywords: Basal lamina; Microvessel; Ischemic brain injury

Contents

1. Introduction

The main arteries that supply blood to the brain are the internal carotid arteries and the basilar artery which is formed by the confluence of the two vertebral arteries. Anastomotic connections between the carotid and basilar artery systems

Abbreviations: BBB, blood brain barrier; CSF, cerebrospinal fluid; ECM, extracellular matrix; HSPG, heparan sulfate proteoglycan; MCA, middle cerebral artery; MMPs, matrix metalloproteinases; tPA, tissueplasminogen activator.

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occur through the Circle of Willis, which allows reversal of flow and cross-filling of deep brain structures. Primary blood flow to the cerebral hemispheres is supplied primarily by the internal carotid arteries and the basilar artery. Some blood also reaches the cortices via the external carotid artery through a number of anastomoses. Subcortically, the penetrating branches of the middle cerebral artery (MCA, the major branch of the internal carotid artery), also irrigate the corpus striatum, whereas the penetrating branches of the basilar artery serve the midbrain and pons of the brainstem. The effective supply of blood flow to these brain structures depends on the absence of vascular injury within the large arterial system and the target microvessels.

The cerebral vascular system is the primary site of involvement in many diseases. Stroke is one such disease affecting approximate 15 million people worldwide. Stroke is also the third leading cause of death in the majority of industrialized countries and also in many developing countries (Green and Shuaib, 2006; He et al., 1995). Ischemic brain injury accounts for more than 85% of all strokes while hemorrhagic brain injury is responsible for the remaining cases. Ischemic brain injury results from the occlusion of major cerebral artery by a thrombus or embolism. This occlusion results in loss of blood flow and a major decrease in the supply of oxygen and nutrients to the affected region. Hemorrhagic injury, on the other hand, is the result of blood vessel rupture either in the brain parenchyma or on its surface. Over the past decade, substantial knowledge has been gained on the sequence of events following an ischemic insult, particularly neurochemical changes. As stroke is a vascular disorder affecting neuronal function, attention has also been given to the vascular changes following stroke, particularly in the recent years.

2. Anatomy and physiology of microvessels

2.1. Structures of microvessels in the brain

The cerebral vascular system can be arbitrarily divided into two major categories, the macrovascular and microvascular systems. Cerebral microvessels consist of arterioles, capillaries and venules. The wall of microvessels are composed of an endothelial cell layer, basal lamina derived from extracellular matrix (ECM), myointimal layers of smooth muscle cells encased in ECM, and adventitia which includes pericytes and end-foot processes of astrocytes and neurons. The capillaries, however, are only ternary structures and consist of the endothelial cell layer, basal lamina and adventitia (del Zoppo et al., 1998; Takahashi and Macdonald, 2004).

The basal lamina is a specialized part of the ECM that connects the endothelial cell compartment to the subjacent cell layers, end-feet of astrocytes and smooth muscle. The basal lamina is composed of collagen type IV, laminin, fibronectin, entactin, thrombospondin and various proteoglycans (Abrahamson, 1986; McArdle et al., 1984; Mohan and Spiro, 1986; Petty and Wettstein, 2001; Yurchenco and Schittny, 1990). The components of the basal lamina are generated by endothelial and astrocytes. Collagen type IV chains form a covalently stabilized polygonal framework. Laminin self-assembles to form a second polymer network and it also serves to connect the basal lamina with the surrounding structures. Entactin binds laminin and collagen type IV, bridging the two. Heparan sulfate proteoglycan (HSPG) is a dichotomous structure, a protein coupled to a unique glycosaminoglycan chain characterized by a linear array of alternating disaccharide units (Iozzo, 2001). The HSPG protein component binds to collagen type IV whereas the HS chain interacts with laminin (Forsberg and Kjellen, 2001). Perlecan is a major HSPG found in the basal lamina and its expression is prominent in the endothelial cell basement membrane (Iozzo, 1998; Whitelock et al., 1999). The major ECM components in the microvasculature and those around neurons are very different. Laminin, fibronectin and collagen type IV are largely undetectable around neurons and glia (Hamann et al., 2002; Sanes, 1989; Sobel, 1998).

2.2. Functional role of the microvascular components

Mechanically, the microvascular wall is an elastic tube that can collapse under the influence of pressure differences across the wall (Cook et al., 1975; Kresch and Noordergraaf, 1972; Lambert, 1991; Lambert and Wilson, 1972). Components of basal lamina play important roles in the strength of microvascular walls. For instance, collagen (stiffest of the ''soft'' tissues in the body) is organized as a network and is responsible for the mechanical resistance of the basal lamina (Dehan et al., 1997; Lambert, 1991). HSPG is firmly anchored in the basal lamina, and it binds laminin and collagen type IV (Petty and Wettstein, 2001). Therefore, it has been postulated that HSPG also plays a role in the strength of microvascular walls. Laminin is the main noncollagenous protein of the basal lamina and it connects the two layers, endothelial cells and end-feet of astrocytes, to collagen and HSPG of the basal lamina (Schnittler et al., 1993). *In vitro* studies have shown that laminin contributes to the resistance of the endothelium to mechanical stress (Franke et al., 1989; Schnittler et al., 1993) and evidence from *in vivo* studies supports this notion in that reduced laminin content after ischemia/reperfusion is associated with reduced mechanical resistance (Hamann et al., 2004). Integrins also subserve cellular adhesion of vascular cells and astrocyte end-feet to the basal lamina, which requires the interaction of cellular integrin receptors to their matrix ligands, laminin and collagen type IV (del Zoppo et al., 1998).

3. Ischemia affects the microvascular basal lamina

3.1. Dissolution of basal lamina during ischemia

Altered basal lamina architectures induced by ischemia have been evidenced by experimental studies (Fig. 1). In animal models of transient stroke, apparent dissolution of basal lamina starts at 2 h after the onset of ischemia and continues during reperfusion (Hamann et al., 2004). Change of basal lamina was observed as early as 10 min after reperfusion following MCA occlusion (Yepes et al., 2000). Using an awake stroke model in baboons, it has been shown that cerebral microvessel walls became gradually bleached and basal membrane constituents