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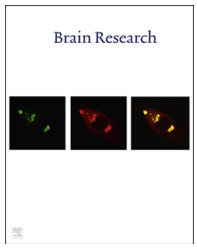

Review

Cerebral microvascular pericytes and neurogliovascular signaling in health and disease

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ABSTRACT

Increases in neuronal activity cause an enhanced blood flow to the active brain area. This neurovascular coupling is regulated by multiple mechanisms: Adenosine and lactate produced as metabolic end-products couple activity with flow by inducing vasodilation. As a specific mechanism to the brain, synaptic activity-induced Ca^{2+} increases in astrocytes, interneurons and neurons translate neuronal activity to vasoactive signals such as arachidonic acid metabolites and NO. K^+ released onto smooth muscle cells through Ca^{2+}-activated K^+ channels on end-feet can also induce vasodilation during neuronal activity. An intense communication between the endothelia, pericytes and astrocytes is required for development and functioning of the neurovascular unit as well as the BBB. The ratio of pericytes to endothelial cells is higher in the cerebral microcirculation than other tissues. Pericytes play a role in distribution of microvascular blood flow in response to the local demand as a final regulatory step after arterioles, which feed a larger cohort of cells. Pericyte–endothelial communication is essential for vasculogenesis. Pericyte also take part in leukocyte infiltration and immune responses. The microvascular injury induced by ischemia/reperfusion plays a critical role in tissue survival after recanalization by inducing sustained pericyte contraction and microcirculatory clogging (no-reflow) and by disrupting BBB integrity. Suppression of oxidative/nitrative stress or sustained adenosine delivery during re-opening of an occluded artery improves the outcome of recanalization by promoting microcirculatory reflow. Pericyte dysfunction in retinal microvessels is the main cause of diabetic retinopathy. Recent findings suggest that the age-related microvascular dysfunction may initiate the neurodegenerative changes seen Alzheimer's dementia.

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1. Cerebral circulation

The brain surface is covered by a network of pial arteries and veins (Duvernoy et al., 1981). Arteries branching off the pial network dive in the brain, while intracortical veins surface and join to pial veins (Duvernoy et al., 1981; Lauwers et al., 2008) (Fig. 1). The honeycomb-like structure of pial arterial/arteriolar network allows redistribution of blood during activation of cortical columns to match the increased focal demand of the activated brain area via penetrating arteries (Blinder et al., 2010; Schaffer et al., 2006). Penetrating arteries branch into arterioles and terminate in an extensive network of capillaries (Fig. 2). There is a circular capillary-free space surrounding intracortical arteries (Fig. 1). Capillaries are not required around large vessels possibly because they can supply the surrounding tissue by passive diffusion of O_2 and glucose (Duvernoy et al., 1981; Kasischke et al., 2011; Sakadžić et al., 2014) (Fig. 2B). Away from these perivascular areas, there is a microvessel located within 15 μm of every neuron soma (Mabuchi et al., 2005; Tsai et al., 2009). Unlike other organs where temporary closing or recruitment of capillaries matches the varying tissue O2 demand, in the brain, this is likely regulated by varying red blood cell (RBC) transit times across capillaries (Jespersen and Østergaard, 2012; Pawlik et al., 1981; Villringer et al., 1994). Heterogeneous RBC transit times among capillary branches decrease O_2 extraction during resting conditions. On neuronal activation, RBC transit times are homogenized and the mean RBC flux increases, allowing more O_2 to be extracted (Jespersen and Østergaard, 2012; Ostergaard et al., 2013) (Fig. 2C and D). Altogether these observations suggest that, whereas regulation of the blood flow in intraparenchymal arterioles may be sufficient for the perivascular tissue, a control at arteriolar level is solely not adequate to match the local tissue O_2 demand at capillary level. Recent evidence suggests that pericyte-mediated capillary dilatation in response to neurotransmitters released from nearby active neurons demanding oxygen may yield higher oxygen extraction (Peppiatt et al., 2006). The capillary dilation is followed by dilation of pre-capillary arteriole in one second to meet the increased downstream blood volume need (Hall et al., 2014). The capillary endothelia, pericytes and the surrounding astrocyte end-feet are thought to transmit the dilatory signals upstream to the pre-capillary arterioles (Itoh and Suzuki, 2012; Peppiatt et al., 2006; Puro, 2007).

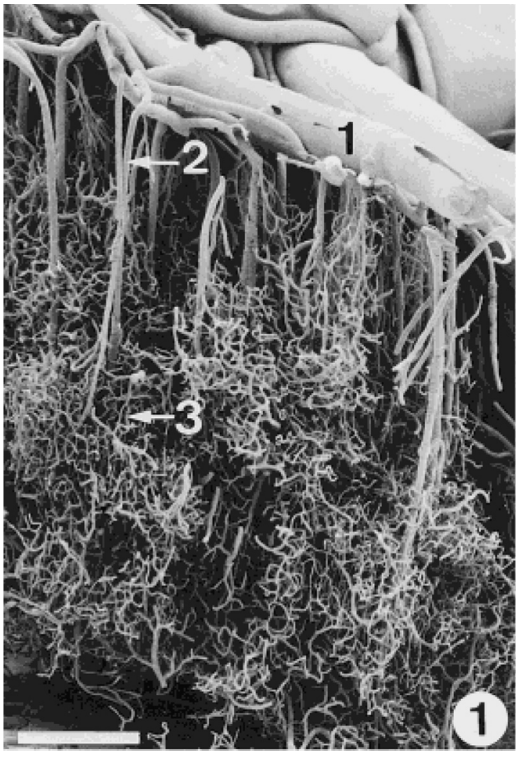

Fig. 1 – Vascular cast of the human occipital cerebral cortex. Pial vessels (1) and the cortical arterioles (2), which course through the cerebral cortex give rise to the cortical capillary network (3). Note the capillary-free area around arterioles. Scale bar = 500 μm. Reproduced from Rodriguez-Baeza et al. (1998) with permission.

2. Neurovascular unit and neurovascular coupling

The neurovascular unit (NVU), which is composed of the endothelia, pericytes, neurons and astrocyte end-feet, plays an integrating role in matching the metabolic demand with the blood flow in addition to the vasodilation induced by adenosine and lactate produced as end-products of the metabolic activity and by NO of endothelial origin (Fig. 3) (Abbott et al., 2006; Attwell et al., 2010; Iadecola, 2004; Ko et al., 1990; Li and Iadecola, 1994). Recent studies suggest that astrocytes play an important part to translate neuronal activity to vasoactive signals (Attwell et al., 2010; Cornell-Bell