Mechanisms of Development xxx (2015) xxx–xxx

Contents lists available at ScienceDirect

Mechanisms of Development

journal homepage: www.elsevier.com/locate/mod

Control of cerebrovascular patterning by neural activity during postnatal development

Baptiste Lacoste, Chenghua Gu *

Department of Neurobiology, Harvard Medical School, 220 Longwood Avenue, Boston, MA 02115, USA

ARTICLE INFO

Article history:
Received 1 November 2014
Received in revised form 26 May 2015
Accepted 16 June 2015
Available online xxxx

Keywords:
Cerebrovascular patterning
Neural activity
Neurovascular unit
Brain
Endothelial cells

ABSTRACT

The brain represents only a small portion of the body mass and yet consumes almost a quarter of the available energy, and has a limited ability to store energy. The brain is therefore highly dependent on oxygen and nutrient supply from the blood circulation, which makes it vulnerable to vascular pathologies. Key vascular determinants will ensure proper brain maturation and function: the establishment of vascular networks, the formation of the blood–brain barrier, and the regulation of blood flow. Recent evidence suggests that the phenomenon of neurovascular coupling, during which increased neural activity normally leads to increased blood flow, is not functional until few weeks after birth, implying that the developing brain must rely on alternative mechanisms to adequately couple blood supply to increasing energy demands. This review will focus on these alternative mechanisms, which have been partly elucidated recently via the demonstration that neural activity influences the maturation of cerebrovascular networks. We also propose possible mechanisms underlying activity-induced vascular plasticity.

1. Control of cerebrovascular patterning by neural activity

1.1. Meeting energy demands: neurovascular interactions in the mature versus immature brain

In order to function properly, the brain relies heavily on the delivery of oxygen and nutrients from the blood stream (Attwell and Laughlin, 2001; Peters et al., 2004), requiring an adequate matching between metabolic demands of neural cells and blood supply. In the central nervous system (CNS), neural and vascular cells form a functionally integrated network, whereby neural activity and vascular dynamics are tightly coupled (Hamel, 2006; Lecrux and Hamel, 2011).

The anatomical substrate of neurovascular interactions in the brain is known as the 'neurovascular unit' (NVU), a complex multicellular system where neurons, astrocytes, microglia, pericytes and endothelial cells communicate to control the diameter of brain vessels and ensure an adequate delivery of oxygen and nutrients to neural tissues through the blood stream (Attwell et al., 2010; Cauli and Hamel, 2010; Chen et al., 2014; Fernandez-Klett et al., 2010; Hall et al., 2014; Hamel, 2006; Howarth, 2014; Lecrux and Hamel, 2011; Lo and Rosenberg, 2009; Petzold and Murthy, 2011). The NVU is also the anatomical substrate of the blood–brain barrier (BBB), a system which provides a tightly controlled environment, free of various toxins, pathogens, and with adequate chemical composition, for proper brain function (Andreone et al., 2015; Ben-Zvi et al., 2014; Saunders et al., 2014).

In the mature brain, the functional coupling between neural activity and cerebral blood flow (CBF) has been known for more than a century (Roy and Sherrington, 1890), as recently revisited (Sandrone et al., 2014). The increase in CBF following neural activity, also known as "neurovascular coupling", has far-reaching implications in health and disease (Cauli and Hamel, 2010; Drake and Iadecola, 2007; Iadecola, 2004; Zlokovic, 2010), and represents the basis of functional brain imaging using blood oxygen level-dependent (BOLD) signals (Devor et al., 2005, 2007; Hillman, 2014). In the immature brain, however, recent studies in rodents and humans have shown that the phenomenon of neurovascular coupling is not functional until few weeks after birth. While in adults sensory stimulation leads to a positive BOLD signal, reflecting a local increase in CBF, the identical stimulus in newborn infants or rat pups was shown to result in an inverted response with negative BOLD signals (Anderson et al., 2001; Born et al., 2002; Kozberg et al., 2013; Muramoto et al., 2002; Yamada et al., 2000). In these studies, negative BOLD signals were suggested to result from either decreased perfusion or increased oxygen consumption in response to sensory stimulation. The absence of a neurovascular coupling response to neuronal activation implies that, during early postnatal development, the immature brain must rely on alternative mechanisms to adequately match oxygen and nutrients supply with increasing energy demands. One potential mechanism during postnatal development could be the control of cerebrovascular patterning by neural activity.

* Corresponding author.
E-mail addresses: Baptiste_Lacoste@hms.harvard.edu (B. Lacoste), Chenghua_Gu@hms.harvard.edu (C. Gu).

http://dx.doi.org/10.1016/j.mod.2015.06.003
0925-4773/

1.2. Activity-induced vascular plasticity during postnatal development

Both the nervous and vascular systems comprise highly branched and complex networks, and their patterning is initiated during development in a highly stereotyped fashion that is controlled by genetic programs, as reviewed elsewhere (Adams and Eichmann, 2010; Andreone et al., 2015; Carmeliet and Tessier-Lavigne, 2005; Tam and Watts, 2010). However, both networks exhibit a certain degree of plasticity and undergo dynamic remodeling after birth (Norman and O'Kusky, 1986). As early as embryonic day 10.5 (E10.5), the neural environment plays a critical role in the initial ingression and pruning/stabilization of blood vessels (Daneman et al., 2009; Haigh et al., 2003; Hogan et al., 2004). Along development, multiple cell types including neuroblasts, neuroepithelial radial glia, pericytes, microglia and astrocytes associate with blood vessels and influence their density/branching patterns (Arnold and Betsholtz, 2013; Lee and McCarty, 2014; Ma et al., 2012, 2013). For instance, reducing the proliferation of radial glial or astroglial progenitors during embryonic development led to a severe reduction in vascular density and branching frequency in the CNS at peri- and postnatal stages (Ma et al., 2012, 2013).

Whether electrical activity of neural cells influences the postnatal maturation of cerebrovascular networks remained elusive and controversial until recently. Almost 30 years ago, William T. Greenough and colleagues postulated that, during postnatal development, the brain adapts to increased metabolic demands by creating new vessels (Black et al., 1987, 1990, 1991). These milestone studies introduced the concept of vascular remodeling during maturation of the brain, however they did not establish a direct link between neural activity and vascular patterning after birth.

From studies in the rat cerebral cortex, the unique prevailing view was that requirements from expanding neural tissues influence the maturation of underlying capillary networks (Black et al., 1987; Sirevaag et al., 1988), and that high metabolic activity correlates with higher vascular density (Riddle et al., 1993). Moreover, several studies proposed the existence of anatomical relationships between neuronal and vascular modules within cortical columns in the rat somatosensory cortex (Cox et al., 1993; Patel, 1983). Such anatomical parallelism suggests that neuronal and vascular modules may instruct each other to build a precise wired network for optimized local interactions, similar to the neurovascular congruency observed in the peripheral nervous system (Mukouyama et al., 2002). However, it was later demonstrated in the same species that cortical microvascular domains do not display any direct topological relationship with underlying columns (Woolsey et al., 1996). In line with this observation, recent studies using novel imaging and computational techniques, with three-dimensional (3-D) reconstructions of cerebrovascular networks, further demonstrated that the microvascular topology does not match the neuroarchitecture in the mouse cerebral cortex (Blinder et al., 2013; Lacoste et al., 2014; Tsai et al., 2009). Thus, in light of the fact that cortical columns are shaped after birth by neural activity (Erzurumlu and Kind, 2001; Li et al., 2013a; Narboux-Neme et al., 2012), it is possible that vascular network structure can also be influenced by neural activity.

The concept of neural activity-induced cerebrovascular plasticity during postnatal development was first introduced by earlier studies which postulated that sensory stimulation had a positive effect on brain angiogenesis (Argandona and Lafuente, 1996, 2000; Black et al., 1987; Sirevaag et al., 1988). Therefore, after birth, sensory-related neural activity may refine cerebrovascular networks into their mature form, as it does for neuronal circuits (Katz and Shatz, 1996; Zhang and Poo, 2001). With the ability to simultaneously visualize and analyze neuronal and vascular modules, the direct effect of sensory neural activity on postnatal cerebrovascular development in the healthy brain was recently demonstrated in a study from our laboratory (Lacoste et al., 2014). We found that vascular density and branching, as well as endothelial cell proliferation, were decreased in layer IV of the primary somatosensory cortex when sensory input was reduced either by a complete deafferentation, by a genetic impairment of neurotransmitter release at thalamocortical synapses, or by a selective reduction of sensory-related neural activity. In contrast, enhancement of sensory inputs led to an increase in vascular density and branching. Therefore, sensory-related neural activity appears necessary for vascular patterning, and changes in neural activity are sufficient to trigger changes in vascular structure. This implies that the postnatal maturation of brain vascular networks not only relies on angiogenic programs, but is also influenced by environmental stimuli.

Under pathological conditions in which neural activity is affected, the brain vascular structure may be regulated differently, particularly when these conditions occur during critical developmental periods. Excessive neural activity following hyperactivation of sensorimotor systems was recently shown to impair cerebrovascular network formation during a critical postnatal time (Whiteus et al., 2014). Whiteus et al. found a severe reduction of angiogenesis in the cerebral cortex following either intense locomotor exercise, persistent auditory stimulation, or following chemically-induced seizures in mice. This led the authors to propose that excessive neural activation during early childhood may trigger long-term deficits in microvascular networks with important consequences for brain function. In the adult rat brain however, previous studies with such hyperactivation paradigms evidenced increased angiogenesis in the cerebellum following vigorous locomotor exercise (Isaacs et al., 1992) or in the hippocampus after electroconvulsive seizures (Newton et al., 2006), thus emphasizing the difference between the "immature" and the "mature" brain in terms of vascular plasticity. Importantly, this angiogenic capability of the adult brain might be of interest in ischemic conditions such as stroke. Indeed, it has been demonstrated that angiogenesis is increased in the penumbra of the ischemic adult mouse barrel cortex following enhancement of sensory-related neural activity by whisker stimulation (Whitaker et al., 2007), an effect which involves *vascular endothelial growth factor* (VEGF)/VEGFR2 signaling (Li et al., 2011) and which can be amplified by inhibition of de novo cholesterol synthesis by statins (Zhang et al., 2012).

2. Possible mechanisms underlying activity-dependent cerebrovascular plasticity

2.1. What cell types could be involved?

The question remains whether neural activity affects angiogenesis directly via neurotransmitter and/or growth factor release by incoming axons, or indirectly via local pathways activated following neural activation that involve various cellular components of the NVU (Table 1).

Table 1
Contribution of different cell types in the neurovascular unit to cerebrovascular development.

Cell type	Released factors	Effect on vascular patterning	References
Pericytes	Ang1	Vessel stabilization	Suri et al., 1996
Astrocytes	VEGF-A	Pro-angiogenic	Stone et al., 1995; Munzenmaier and Harder, 2000; Zhang and Harder, 2002; Potente et al., 2003; Pozzi et al., 2005; West et al., 2005; Li et al., 2013a, 2013b
	EETs		
	Shh		
	Ang1	Vessel stabilization	
Neurons	Ang1	Vessel stabilization	Cao et al., 2004; Joyal et al., 2014
	VEGF-A	Pro-angiogenic	
Microglia	TNFα	Pro-angiogenic	Stefater et al., 2011; Arnold and Betsholtz, 2013; Li et al., 2014
	VEGF-C,D	Pro-/anti-angiogenic	
	Wnt5a,Wnt11	Anti-angiogenic	

Ang1, angiopoietin-1; EETs, epoxyeicosatrienoic acids; Shh, sonic hedgehog; VEGF, vascular endothelial growth factor; Wnt, wingless integration site.

Please cite this article as: Lacoste, B., Gu, C., Control of cerebrovascular patterning by neural activity during postnatal development, Mechanisms of Development (2015), http://dx.doi.org/10.1016/j.mod.2015.06.003