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Review article

Microvascular anomaly conditions in psychiatric disease. Schizophrenia – angiogenesis connection

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ABSTRACT

Schizophrenia (SZ) is a severe mental disorder with unknown etiology and elusive neuropathological and neurobiological features have been a focus of many theoretical hypotheses and empirical studies. Current genetic and neurobiology information relevant to SZ implicates neuronal developmental and synaptic plasticity abnormalities, and neurotransmitter, microglial and oligodendrocytes dysfunction. Several recent theories have highlighted the neurovascular unit as a potential contributor to the pathophysiology of SZ. We explored the biological plausibility of a link between SZ and the neurovascular system by examining insights gained from genetic, neuroimaging and postmortem studies, which include gene expression and neuropathology analyses. We also reviewed information from animal models of cerebral angiogenesis in order to understand better the complex interplay between angiogenic and neurotrophic factors in development, vascular endothelium/blood brain barrier remodeling and maintenance, all of which contribute to sustaining adequate regional blood flow and safeguarding normal brain function. Microvascular and hemodynamic alterations in SZ highlight the importance of further research and reveal the neurovascular unit as a potential therapeutic target in SZ.

1. Background: role of angiogenesis during neurodevelopment and CNS function

Schizophrenia (SZ) is a disabling psychiatric disorder that affects multiple brain functions, impairs real-world functioning and is only partially responsive to pharmacological treatments.

Although multiple pathological processes in the neurobiology of SZ have been identified to date, including neurotransmitter system dysfunctions (e.g., dopaminergic systems and the glutamatergic system), myelin, immune-response and infectious origins (Arion et al., 2007; Hakak et al., 2001; Harrison and Weinberger, 2004; Lewis et al., 1999; Meltzer, 1987; Wolf et al., 1993), none have accounted for heterogeneous array of clinical symptoms consistently, making pharmacological intervention difficult and only partially efficacious.

Vascular involvement in the pathophysiology of SZ (Bleuler, 1911) has gained some salience in recent years to explain and unify physiologic abnormalities seen in SZ (Hanson and Gottesman, 2005; Moises et al., 2015; Schmidt-Kastner et al., 2012). These hypotheses place impairment of the brain microvascular system as the central mechanism in the pathophysiology of SZ.

A fundamental physiological process in development and maintenance of the microvascular system is angiogenesis. Angiogenesis is the process of formation of new capillaries from existing vessels and it is the pivotal event in neovascularization during embryogenesis and throughout the life span. Angiogenesis is also engaged in response to brain injury, brain function demands and it is responsible for coupling the capillary endothelium with astroglial cells and neurons.

During brain development neurovascular coupling mechanisms assure simultaneous generation of neuroblasts and blood vessels. The primary perineuronal vascular network that surrounds the ventral neural tube is established very early during embryogenesis, in mice this occurs at approximately E7.5–E8.5 days (Risau, 1997). Vascularization of the neuroepithelium occurs via sprouting angiogenic endothelial progenitor cells from the pial surface to the periventricular areas by E11 and generates a vascular plexus (Risau, 1994). Formation of the blood brain barrier (BBB) is likely to begin at this time. Tracer-injection studies in embryos demonstrate permeability of brain endothelial cells in the first few days of vessel formation, but it becomes tightly restricted by E15.5 (Ben-Zvi et al., 2014) suggesting that the BBB has already formed. Diverse angiogenic factors including PDGF, IGF-1,

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TGFB, GDNF, BDNF, bFGF etc. secreted by neuroblasts, most notably VEGF are required to induce angiogenesis (Hellbach et al., 2014; Raab et al., 2004; Virgintino et al., 2003). Accumulated evidence from animal models also reveals that a preexisting vasculature is a necessary physical substrate for oligodendrocyte (OLG) precursor cells migration during early brain and spinal cord development. Interestingly, OLG precursor cells migration *in vivo* was disrupted in mice with defective vascular architecture, but was normal in mice lacking pericytes (Tsai et al., 2016). Thus, endothelial-OLG precursor cells interactions appeared to be critical for coordination of migration and differentiation of these precursors into OLG. Astrocytes migration, however, is different from OLG precursors during early development. Astrocytes progenitors migrate following radial glia without secondary tangential migration and, therefore, occupy restricted spatial domains related to their developmental site of origin (Tsai et al., 2012).

As brain circuitry matures during adolescence and attains adult levels of myelination-dependent saltatory action potential conduction, adequate access to blood supply and oxygen tension become central factors in the processes of the formation and compaction of myelin segments. Hypoxia inducible factors (HIF1/2a) stabilization in OLG progenitors as a result of oxygen strain inhibits their differentiation into OLGs. Remarkably, these undifferentiated OLG progenitors possess paracrine activity that induces robust postnatal angiogenesis *in vivo* and directly stimulate endothelial cell proliferation *in vitro* (Yuen et al., 2014). Given the strong evidence for the involvement of OLGs and myelin abnormalities in the pathophysiology of SZ (reviewed in (Haroutunian et al., 2014)), the functional impact of oligodendroglial by endothelial cell (EC) interactions may be fundamental to the pathophysiology of SZ and may explain, at least partially, the observed gene expression changes specific to OLG and ECs in SZ.

This review aims to assess the accumulated evidence for the involvement and role(s) of the brain microvasculature in SZ and answer the following questions: (1) is there evidence for regional brain hemodynamics changes in SZ? (2) What are the morphological abnormalities in BBB/microvascular structure in the brains of individuals with SZ? (3) Does microvascular/BBB gene expression signature associated with SZ show changes in angiogenesis/vascular remodeling and offer support for an anomalous BBB in SZ? (4) Could the genes involved in angiogenesis and associated with it signaling pathways be potential risk factors in SZ from the genomic and transcriptomic perspective? (5) Do animal models aimed at revealing the mechanism of cerebral angiogenesis demonstrate cognitive and socioemotional deficit similar to those observed in individuals with SZ?

2. Regional brain hemodynamic changes associated with SZ clinical symptoms

That the neurovascular system is involved in SZ has been repeatedly documented by neuroimaging studies. Extensive reviews of structural and functional neuroimaging in SZ (Buchsbaum and Hazlett, 1998; Lopes et al., 2015), including discordant monozygotic twins (Weinberger et al., 1992), have demonstrated that abnormalities in brain hemodynamics are generally consistent with historical concept of hypofrontality in individuals with SZ (Berman et al., 1986) and reflect functional deficit of frontal cortex (Davidson and Heinrichs, 2003; Taylor, 1996; Weinberger et al., 1986). Frontal hypoperfusion has been consistently documented in clinical cases involving first episode, neuroleptic-naïve (Andreasen et al., 1997; Catafau et al., 1994; Erkwoh et al., 1997; Rubin et al., 1994) and untreated individuals with chronic SZ (Kim et al., 2000) suggesting that this characteristic is independent of the length of disease, its treatment and duration. Other regions, where hypoperfusion in SZ has been extensively documented, include middle and anterior cingulate, temporal and parietal regions (Ojeda et al., 2002; Schultz et al., 2002; Yucel et al., 2002) and thalamus (Clark et al., 2001). More recently, MRI based investigation of alterations in the volume of small arterial (pial) and arteriolar vessels in brains of individuals with SZ suggested that microvascular abnormalities maybe more widespread across the entire brain (Hua et al., 2016). Reduced CBF has been also associated with psychotic symptoms. For example, it has been shown that reduced CBF was associated with greater severity of negative symptoms in frontal, cingulate and superior temporal cortices (Pinkham et al., 2011). In contrast, positive symptoms have been associated with increased CBF in temporal, cingulate and superior frontal gyri (McGuire et al., 1993; Pinkham et al., 2011) and in subfields of hippocampus (Schobel et al., 2013). Although most neuroimaging studies have made the underlying assumption that the SZ hypofunction in CBF reflects neuronal hypometabolism, a more direct association of SZ with cerebrovascular circulation and function is equally plausible.

The evolutionary increase of cortical neuronal complexity, massive expansion of the cortical surface and cell number in humans depends on higher blood supply due to oxygen and nutrients requirements. Not surprisingly cerebral cortical vascularization is dramatically enhanced in humans relative to monkeys and cats (Lauwers et al., 2008). Moreover comparison of newborn and adult cerebral cortical depth in non-human primates using 3D-imaging has shown that relative cortical vascular volume nearly doubles in adults compared to newborns and that this increase occurred predominantly at the capillary level (Risser et al., 2009). Increase in capillary volume is sustained by the lengthening of pre-existing segments and by the formation of new segments, while the contribution of capillary diameter is minor and only marginal at the perforating vessel level. These findings indicate that structural adaptations of the cerebral vascular system induce multiple changes that include: vessel density and segment length, a decrease in intercapillary distances and, to a lesser extent, vessel diameter increase. Therefore, postnatal cortical maturation typically described in terms of synaptogenesis, gliogenesis and interconnectivity is accompanied, and perhaps preceded, by an intensive remodeling of microvascular architecture.

Moreover, recent studies in mice using combination of high-throughput histology and computation models also suggest that the known changes in cortical blood flow (CBF) induced by changes in the neurotransmitter microenvironment are controlled at the level of microvessels (Blinder et al., 2013), likely through constriction or stiffening of contractile proteins in pericytes. The restricted lateral perfusion of cerebral cortical tissue is an additional distinctive parameter of brain hemodynamics. Although the microvasculature forms interconnected loops with a topology that follow organization of cortical columns, blood flow sourced by penetrating arterioles is effectively drained by penetrating venules limiting lateral perfusion. Experimental results for pathological condition such as local ischemia are also consistent with restricted lateral perfusion within the cerebral cortex, which prevents blood in neighboring penetrating vessels from entering the area previously sourced by the occluded vessel (Blinder et al., 2013), thus limiting damaging impact on neural cells proximal to supplying impaired vessel and sparing those in neighboring columns. Therefore, it is anticipated that reduced blood perfusion documented in individuals with SZ and possibility of associated with it, mild hypoxia will be restricted to cortical columns with reduced CBF.

Astrocytes, which encase by their end-feet, almost the entire parenchymal arterioles and capillaries also play a pivotal role in regulating CBF. By contrast, the processes from neurons are rarely in direct contact with brain blood vessels (Koehler et al., 2009). Astrocytes sensing synaptic activity and the release of calcium and major neurotransmitters, such as glutamate, may additionally influence CBF by modulating the vascular smooth muscle tone around larger vessels, such as arterioles. Spill over glutamate elicits NMDA receptor signaling that engages the calcium syncytium by raising intracellular Ca^{2+} concentration in astrocytic end-feet modulating vascular tone via several pathways. The first involves the vasodilator-nitric oxide release by neurons, which activates smooth muscle guanylate cyclase. This activation results in a rise in cGMP levels causing dilatation of vessels.