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Review article

The astrocytic contribution to neurovascular coupling – Still more questions than answers?

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ABSTRACT

Cerebral blood flow adequate for brain activity and metabolic demand is maintained through the processes of autoregulation and neurovascular coupling. Astrocytes undoubtedly make an important contribution to these processes. The critical factors that determine the polarity of astrocytic response include: metabolites (e.g., arachidonic acid and its derivatives, lactate and oxygen concentrations), ions (H^+, Ca^{2+} and K^+), gliotransmitters (glutamate, Glu; gamma-aminobutyric acid, GABA; D-serine; adenosine 5′-triphosphate, ATP and brain derived neurotrophic factor, BDNF), neuronal activity and vascular tone.

Although the astrocytic contribution to neurovascular coupling has been intensively studied, a few important questions still remain, such as: (1) the modulatory function of astrocytes in tripartite synapses, including effects related to the strength of synaptic stimulation and the particular signaling pathway (astrocytic or neuronal) that becomes activated, (2) the significance of the vasoconstrictive reaction evoked by arachidonic acid metabolites (e.g., 20-hydroxyeicosatetraenoic acid, 20-HETE) under both physiological and pathological conditions, (3) the relationship between brain activity level and metabolic processes occurring in astrocytes, which is studied using neuroradiological techniques and (4) the astrocytic contribution to the neurovascular response under pathological conditions. Hence, the function of astrocytes in neurovascular coupling remains ambiguous. The function of astrocytes is beneficial and integrative in physiological conditions, but under definitive pathological conditions may become detrimental and involved in the development of diseases like ischemic stroke, arterial hypertension and Alzheimer's disease.

Contents

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1. Introduction

One of the most important features of cerebral circulation is its ability to maintain adequate blood flow for neuronal activity. Because there is no oxygen or energy reserves in the brain, changes in cerebral blood flow (CBF) must be immediate and precisely attuned to the physiological demand, which may be achieved with autoregulation and neurovascular coupling (NVC). This latter process, also known as functional hyperemia, describes the ability of the cerebral vessels to enlarge their diameter in response to increasing metabolic demands and synaptic transmission (Filosa and Blanco, 2007; Carmignoto and Gómez-Gonzalo, 2010; Cauli and Hamel, 2010). Changes in CBF can be initiated by neurons directly contributing to the vascular wall, or indirectly through glial cells. Astrocytes are well positioned for the integration of synaptic signals with those from the extracellular space (Haydon and Carmignoto, 2006; Gordon et al., 2007). The characteristic elements of astrocytic morphology, such as the perinodal processes that establish contacts with neighboring neurons and their axons and the subpial endfeet and perivascular endfeet that are in close spatial relationship with cerebral vessels, enable the integration of signals that determine the vascular response (Fig. 1). Numerous processes are involved in the astrocytic control of CBF: (1) neuron–astrocyte reciprocal signaling, (2) changes in the concentration of metabolites and electrolytes and (3) changes in vascular tone. However, the interactions between these processes and signaling pathways, although intensively studied, remain far from completely elucidated. It is evident from the large number of publications studying the NVC and astrocytes that both of them have been the focus of scientific interest for many years. Moreover, recently published data clearly indicate that the role of astrocytes in regulating CBF has been underestimated and is still growing.

The regulation of CBF requires the cooperation of neuronal, vascular and glial components, which make up the functional neurovascular unit (NVU). Comparing the function of astrocytes with the function of the other elements of the NVU, astrocytes, and in particular their modulation of the function of the pre- and postsynaptic elements of the "tripartite synapse", appear to contribute most significantly to NVC under physiological conditions. However, under pathological conditions the role of astrocytes is ambiguous. Because they are more resistant to oxygen and glucose depletion than neurons, astrocytes may retain their abilities pertaining to CBF regulation longer than the remaining elements of the NVU. In conditions in which pathological processes are developing, astrocytes may be involved in the pathogenesis of many diseases, including ischemic stroke, arterial hypertension and Alzheimer's disease (AD; Stanimirovic and Friedman, 2012).

The aim of this review is to highlight the most important aspects of the function of astrocytes in NVC and CBF regulation, under both physiological and pathological conditions. We also present important, although still unanswered, questions regarding the role of astrocytes in NVC.

2. Morphology and physiology of cerebral vessels – the neurovascular unit

Parenchymal and intracerebral arteries are surrounded by astrocytic endfeet and the terminals of intracerebral neuronal projections that come from the locus coeruleus, raphe nuclei or basal forebrain (Hamel, 2006). In contrast to the pial vessels of the subarachnoid or Robin–Virchow perivascular space, parenchymal arteries are influenced neither by the neurotransmitters and neuromodulators present in the cerebrospinal fluid, nor by the sympathetic, parasympathetic and sensory projections of extracerebral origin (Bleys and Cowen, 2001).

Classical neurotransmitters such as dopamine (DA), serotonin (Ser), norepinephrine (NE) and acetylcholine (Ach) are found in neuronal terminals supplying the cerebral vessels (Fig. 2). In addition, numerous neuromodulators, such as substance P (SP), neurotensin (NT), vasoactive intestinal peptide (VIP), somatostatin (SOM) and neuropeptide Y (NPY), as well as nitric oxide (NO), colocalize in those fibers (Hamel, 2006; Drake and Iadecola, 2007). Their physiological effect on cerebral vasculature is due to vasoconstriction (e.g., after stimulation by NE, DA, NPY or SOM) or vasodilation (e.g., after stimulation by ACh, NO, or VIP) (Vaucher and Hamel, 1995; Tong and Hamel, 2000; Vaucher et al., 2000; Drake and Iadecola, 2007; Kleinfeld et al., 2011).

Excluding the direct effect of neuron-derived signals on the cerebral arteries, some indirect signals may also act on those vessels by stimulating astrocytes. Considerable evidence suggests that noradrenergic neuronal terminals make extensive contacts with astrocytes (Cohen et al., 1997). Moreover, NE and DA release is correlated with changes of intracellular Ca^{2+} concentration in astrocytic endfeet and leads to the pronounced constriction of cerebral microvessels (Krimer et al., 1998; Mulligan and MacVicar, 2004).

The regulation of CBF requires the coordinated and precise activation of the neuronal, vascular and glial elements that constitute the functional NVU. Hence, the most important elements of the NVU are the neuronal fibers and terminals, endothelial and smooth muscle cells of the vascular wall, endothelial glycocalyx and basement membrane, pericytes, astrocytes and microglia (Abbott et al., 2010; Carmignoto and Gómez-Gonzalo, 2010; Neuwelt et al., 2011).

The integrative function of astrocytes with the remaining components of the NVU is clearly illustrated by the concept of the "tripartite synapse", according to which astrocytes, because they are integrated with pre- and postsynaptic neuronal structures, can be affected by synaptic activity, but at the same time, can modulate the strength of synaptic connections (Araque et al., 1999; Halassa et al., 2009; Perea et al., 2009). After astrocytic stimulation, the numerous perivascular endfeet can cause the immediate release of vasoactive substances (Ventura and Harris, 1999). Morphologically well documented, the concept of the tripartite synapse provides an interesting hypothesis of NVC regulation (Petzold and Murthy, 2011). The strength of stimulation may determine the type of signaling pathway that is activated. Stimulation of the astrocytic element by the presynaptic neuronal ending is thought to be the prevalent pathway in the case of weak and moderate excitation, whereas stimulation of the postsynaptic neuronal element is thought to be responsible for the physiological effects induced by strong stimulation. This interesting hypothesis provides some new possibilities for the regulation of CBF and situates the astrocytic component of the tripartite synapse very high among possible regulatory mechanisms. On the other hand, this hypothesis points to new areas of study regarding the molecular mechanisms responsible for the activation of particular regulatory pathways. There is no information available regarding the types of neurotransmitters,