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Astrocytes and ischemic injury

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Abstract

Ischemic injury is traditionally viewed from an axiomatic perspective of neuronal loss. Yet the ischemic infarct encompasses all cell types, including astrocytes. This review will discuss the idea that astrocytes play a fundamental role in the pathogenesis of ischemic neuronal death. It is proposed that stroke injury is primarily a consequence of the failure of astrocytes to support the essential metabolic needs of neurons. This 'gliocentric view' of stroke injury predicts that pharmacological interventions specifically targeting neurons are unlikely to succeed, because it is not feasible to preserve neuronal viability in an environment that fails to meet essential metabolic requirements. Neuroprotective efforts targeting the functional integrity of astrocytes may constitute a superior strategy for future neuroprotection.

Introduction

Over the past decade, a virtual revolution has occurred in our understanding of the physiology of astrocytes, and of their interactions with neurons in the normal brain [1, 2]. For example, astrocytes actively propagate Ca^{2+} signals to neighboring neurons, whose level of synaptic activity they can actively modulate [3, 4]. Key mediators of astrocyte-neuron signaling are glutamate [5] and ATP/adenosine [6]. While much current work is focused on the role of gliotransmitters in synaptic transmission, the potential harmful effects of glutamate/ATP release from astrocytes in the ischemic penumbra has not been defined. Also, astrocytes have recently been implicated in the local control of blood flow [7-9], but it is not established how ischemia affects the ability of astrocytes to modulate vascular tone. We will here critically evaluate astrocytes as a potential new therapeutic target in stroke. Although the contribution of astrocytes to the process of ischemic infarction has not been clearly defined, an abundance of data already suggests the importance of astrocytes in both the initiation and propagation of secondary ischemic injury.

Pathology of focal stroke

Focal ischemia, or prolonged occlusion of a cerebral vessel, initiates the process of ischemic infarction, in which all tissue elements are affected. Ischemic infarcts are sharply demarcated and the transition between the infarct and the surrounding tissue is frequently less than 100 μm. All cell types, including neurons, astrocytes, and the vasculature are dead in a chronic infarct, whereas cells in the per-infarct areas are preserved. No evidence for neuronal loss outside chronic infarcts has been identified in either human or rodent brain [10, 11]. In contrast, transient artery occlusion is frequently associated with selective neuronal injury with little, if any loss of astrocytes [12]. Functional recovery after prolonged or permanent artery occlusion

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is often poor, indicating that ischemic infarcts have a much worse prognosis than transient ischemic attacks (TIA) associated with selective neuronal injury.

Supportive functions of astrocytes

Astrocytes are the principal housekeeping cells of the nervous system. Their main supportive tasks are to scavenge transmitters released during synaptic activity, control ion and water homeostasis, release neurotrophic factors, shuttle metabolite and waste products, and to participate in the formation of the blood-brain-barrier [13]. Failure of any of these supportive functions of astrocytes will, either alone or in combination, constitute a threat for neuronal survival. In fact, the all-and-none pattern of ischemic infarction indicates that neurons are not capable of surviving in the absence of astrocytes. Unfortunately, our current understanding of how ischemia affects basic astrocytic functions is incomplete [14]. It has not been established to which degree astrocytic glutamate uptake is impaired in the ischemic penumbra. It is therefore not possible to predict whether impairment of astrocytic glutamate uptake contributes more significantly to neuronal death, than for example a decrease in astrocytic K+ buffering capacity.

Astrocytes Ca^{2+} oscillations and Ca^{2+} waves

A growing body of evidence has in the last decade documented that astrocytes are more than the supportive cells of CNS. Astrocytes express neurotransmitter receptors and respond to neuronal activity by increases in cytosolic Ca^{2+} [15]. Astrocytes display two distinct types of Ca^{2+} signaling modalities: Ca^{2+} oscillations and propagating Ca^{2+} waves [16]. Ca^{2+} oscillations are repetitive monophasic increases in cytosolic Ca^{2+} limited to a single cell. Ca^{2+} oscillations can be evoked by exposure to several different transmitters, including glutamate, GABA, and ATP [17]. They can also be triggered by removal of extracellular Ca^{2+}, or by exposure of cultured astrocytes to hypoosmotic solutions [18]. An extensive literature has documented that astrocytic Ca^{2+} oscillations involves activation of PLA, IP_3 production, and release of Ca^{2+} from intracellular stores, rather than Ca^{2+} influx through membrane channels [17].

The second modality of astrocytic Ca^{2+} signaling, propagating Ca^{2+} waves, can be stimulated by focal electrical stimulation, mechanical stimulation, lowering extracellular Ca^{2+} levels, or by local application of transmitters (glutamate or ATP). High frequency neuronal spiking has been shown to induce astrocytic Ca^{2+} waves in organotypic slices and in anesthetized mice following sensory stimulation [19, 20]. In general, Ca^{2+} waves propagate with a velocity of around 8−20 μm/s and expand over a maximum radius of 100 to 300 μM, including 10 to 50 astrocytes per wave. Initially, it was proposed that propagation of Ca^{2+} waves was conducted through the diffusion of IP_3 and/or calcium through intercellular gap junctions [21]. Using pharmacologic approaches, it was demonstrated that an extracellular agent, ATP, was the actual diffusible messenger [22]. Similar studies have in parallel shown that ATP mediates Ca^{2+} waves in several non-excitable cells, including epithelium, liver, heart, and osteoblasts (see Berridge 2000 [48]). Wave propagation is mediated by P2Y receptors, likely including multiple purinergic receptor subtypes in astrocytes, including P2Y1, P2Y2, and P2Y4 [23]. Ca^{2+} waves can be viewed as a pathway for amplification of astrocytic activation. When an astrocyte reaches a certain level of activation, it will release ATP that in turn increases Ca^{2+} in its neighbors resulting in a spatial expansion of astrocytic activation [49]. Purinergic signaling plays important roles in coordination and synchronization of astrocytic responses to synaptic transmission. Accordingly, inhibition of astrocytic P2Y receptors reduced and delayed Ca2+ increases in cortical astrocytes following whisker stimulation [20]. Little is known with regard to the effect of ischemia on purinergic signaling. However, traumatic spinal cord injury is associated with prolonged increases in astrocytic ATP release. Motor neurons express multiple purinergic receptors, including P2×7 receptors. Administration of P2×7 receptor antagonists reduces

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tissue injury and improves functional recovery suggesting that excessive purinergic signaling contributes to secondary damage following spinal cord injury [24].

Mechanisms of ATP release

Purinergic signaling represents the most important pathway by which astrocytes communicate with other cells in CNS. A key step to understand the modulation of astrocytic function is therefore to define the mechanism by which these electrically unexcitable cells release ATP. Several pathways of ATP release have been proposed, including channel-mediated release, exocytosis of ATP containing vesicles, connexin (C×) hemichannels, and P2×7 receptor hemichannels, possibly linked to pannexins (reviewed in [25]. Several observations indicate that C×-hemichannels are the most significant mechanism of ATP release from astrocytes. It has been shown that: C×-deficient glia cell lines increased ATP release 3 to 10-fold after transfection with C×43 [22]; C×-channel blockers (NPPB and FFA) potently inhibited ATP release [26]; and single channel recordings indicate that ATP can exit through C×43 hemichannels [27]. Cultured neurons do not release ATP in response to K+ or receptor activation, suggesting that release of ATP from synaptic vesicles is low [28]. Although neurons express the gap junction protein, C×36 [29]., this connexin has a small single channel conductance and is impermeable to larger molecules, including Lucifer yellow and ATP [30]. Astrocytes can release many other transmitters, including PGE2, glutamate, TNF-α, and d-serine, which play a role in paracrine signaling between astrocytes and neurons, endothelial cells, and microglial cells. The pathways for release of these gliotransmitters have not been established. Nevertheless, excessive release of gliotransmitters in the setting of ischemia is likely contributing to additional cellular damage, similar to the observations of increased ATP release in spinal cord inury.

Astrocytic Ca^{2+} signaling as an integral part of brain function

Purinergic signaling represents the primary pathway for astrocyte-astrocyte signaling. Emerging evidence indicates that astrocytes also modulate the function of other cell types in brain by release of ATP and other gliotransmitters including glutamate, PGE2, and d-serine. Several methods by which astrocytes modulate brain function are described here:

Synaptic transmission—A flurry of studies has over the past few years documented that astrocytes can modulate neuronal Ca^{2+} levels and synaptic transmission by means of Ca^{2+} signaling. For example, spontaneous astrocytic Ca^{2+} oscillations and subsequent glutamate release can drive NMDA-receptor-mediated neuronal excitation in the rat ventrobasal thalamus [31], and astrocytes can potentiate inhibitory transmission in the hippocampus through a pathway that is sensitive to kainate-receptor antagonists [32]. These and other studies have pointed to glutamate and ATP/adenosine as key mediators of astrocyte-to-neuron signaling [33]. Astrocytic release of ATP leads to the production of adenosine in the extracellular space by the action of highly expressed nucleotidases that degrade ATP with a rapid time constant (~200 ms) [34]. Adenosine then acts as is a potent neurotransmitter, with pervasive and generally inhibitory effects on neuronal activity [34]. Several recent lines of work have demonstrated that astrocytes can control network activity in both cortex and hippocampus through adenosine resulting from astrocytic ATP release [28, 35]. Adenosine has both presynaptic and postsynaptic effects. Presynaptically, adenosine A1 receptors inhibited Ca^{2+} channel opening resulting in reduced transmitter release, whereas postsynaptically, A1 receptors opened K+ channels resulting in hyperpolarization and decreased neuronal activity [34]. In a resting state, low levels of extracellular adenosine tonically dampened neural activity, and the A1 receptor antagonist, DPCPX, increased spontaneous cortical activity. Conversely, adenosine or the A1 specific agonist CCPA potently suppressed local activity [34]. Interestingly, adenosine and ATP have recently been implicated in the depression of synaptic activity associated with increased

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concentrations of CO_2 [36], and one report found that extracellular ATP was increased in rat striatum following MCA occlusion [37].

Control of local microcirculation—Given that cerebral microvessels are extensively ensheathed by astrocyte processes, thereby physically linking the intraparenchymal vasculature with synapses, it is tempting to speculate that astrocytes are involved in activity-induced hyperemia [38, 39]. Several studies suggest that astrocytes participate in activity-dependent parenchymal blood flow regulation. One study demonstrated that astrocytic activity can influence vascular tone, by observing that direct stimulation of perivascular astrocytes in cortical slices caused vasodilation [7]. It was demonstrated that mGluRs on astrocytes were activated by synaptic release of glutamate and that the resultant astrocytic Ca^{2+} signaling was linked to changes in vascular diameter. This study concluded that a cyclooxygenase product was involved, since acetylsalicylic acid blocked astrocyte-mediated vasodilation [7]. A subsequent study, which selectively targeted astrocytes by Ca^{2+} photolysis, found that astrocytic Ca^{2+} signaling triggered cerebrovascular constriction [40]. Similar to the first report, arachodonic acid (AA) metabolites were generated in astrocytes, but were proposed to diffuse into smooth muscle cells, where they are converted to 20-HETE, a potent vasoconstrictor [40]. The two papers raised considerable interest and it was speculated that use of L-NAME or differences with regard to brain regions (cortex versus hippocampus) could explain the opposing results. Importantly, both studies were performed in non-blood perfused brain slices, which has obvious limitations when studying functional hyperemia. Using 2-photon imaging of intact cortex in live adult mice, it was later demonstrated that photolysis of caged Ca^{2+} in astrocytic endfeet invariably triggered vasodilation [8]. Astrocytic activation lead to an 18% increase in arterial cross-sectional area corresponding to an almost 40% increase in local perfusion. A specific COX-1 inhibitor (NS-398), as well as indomethacin, attenuated astrocyte-induced vasodilation. Furthermore, COX-1 immunoreactivity was strongly expressed around penetrating cortical arteries, suggesting that COX-1 vasoactive products mediated vasodilation [8]. Recent work has supported the concept that COX-1 is the primary mediator of vasodilation involving astrocytes [41].

Microglial cell activation—Recent reports using 2-photon imaging have shown that astrocytes release ATP in response to local injury, this, in turn, activated local microglial cells [42, 43]. Microglial P2Y12 and P2Y6 receptors are critical for movement and phagocytosis, respectively [44, 45]. Together, these reports highlight the importance of astrocytic ATP release and position purinergic signaling in as an important initial step of inflammatory responses.

Human astrocytes are more are larger, more complex, and more diverse than rodent astrocytes

The relative ratio of glial cells to neurons increases algorithmically with phylogeny, manifestly as a function of increasingly complex information processing [6]. The human brain also contains subtypes of GFAP positive astrocytes that are both human and primate specific, suggesting their importance in the evolution of the human brain [46] . Additionally, human protoplasmic astrocytes are significantly larger in diameter and more complex that the rodent counterpart represented by a 2.5 fold increase in diameter and 10-fold more main GFAP positive processes. Human protoplasmic astrocytes are organized into domains in which there is little overlap adjacent cells processes, resulting in autonomous territories of neuropil that are influenced by a single astrocyte. The domain of a single human astrocyte has been estimated to contain up 2 million synapses as well as vasculature, significantly greater than the estimated 20,000 to 120,000 synapses in rodent astrocytic domains [46]. Therefore, human astrocytes can integrate a larger contiguous set of synapses in conjunction with the vasculature creating a larger glioneuronal unit linking neuronal activity with blood flow. Therefore, in adult humans then, stroke may be more a disease of astrocytes than in our experimental rodent models.

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CONCLUSION

During evolution, neurons have lost many essential metabolic pathways as they became increasingly specialized and gained the ability to generate action potentials and communicate by synaptic transmission. As a consequence, neurons in the adult brain depend on metabolic support from surrounding astrocytes. For example, neurons do not express the mitochondrial enzyme glutamine dehydrogenase and cannot produce the chief excitatory transmitter, glutamate, which in the adult CNS mediates 70% of neurotransmission. Since glutamate does not pass through the blood-brain-barrier, excitatory transmission heavily depends on glutamate produced by astrocytes [33]. Similarly, synapse formation requires multiple lipids, including cholesterol, produced by astrocytes [47]. It is clear that neuron survival in both the normal and the diseased brain relies heavily on surrounding astrocytes. A striking example is ischemic infarcts, in which neurons do not survive if neighboring astrocytes are lost. While large gaps exist with regard to our understanding of how ischemia affects the supportive function of astrocytes, it is likely that failure of glutamate uptake, K+ buffering, water homeostasis, vascular control, etc, all contribute to the massive loss of neurons in focal stroke. A challenge for the future is to develop experimental tools to manipulate and monitor dynamic changes in the supportive function in ischemic astrocytes.

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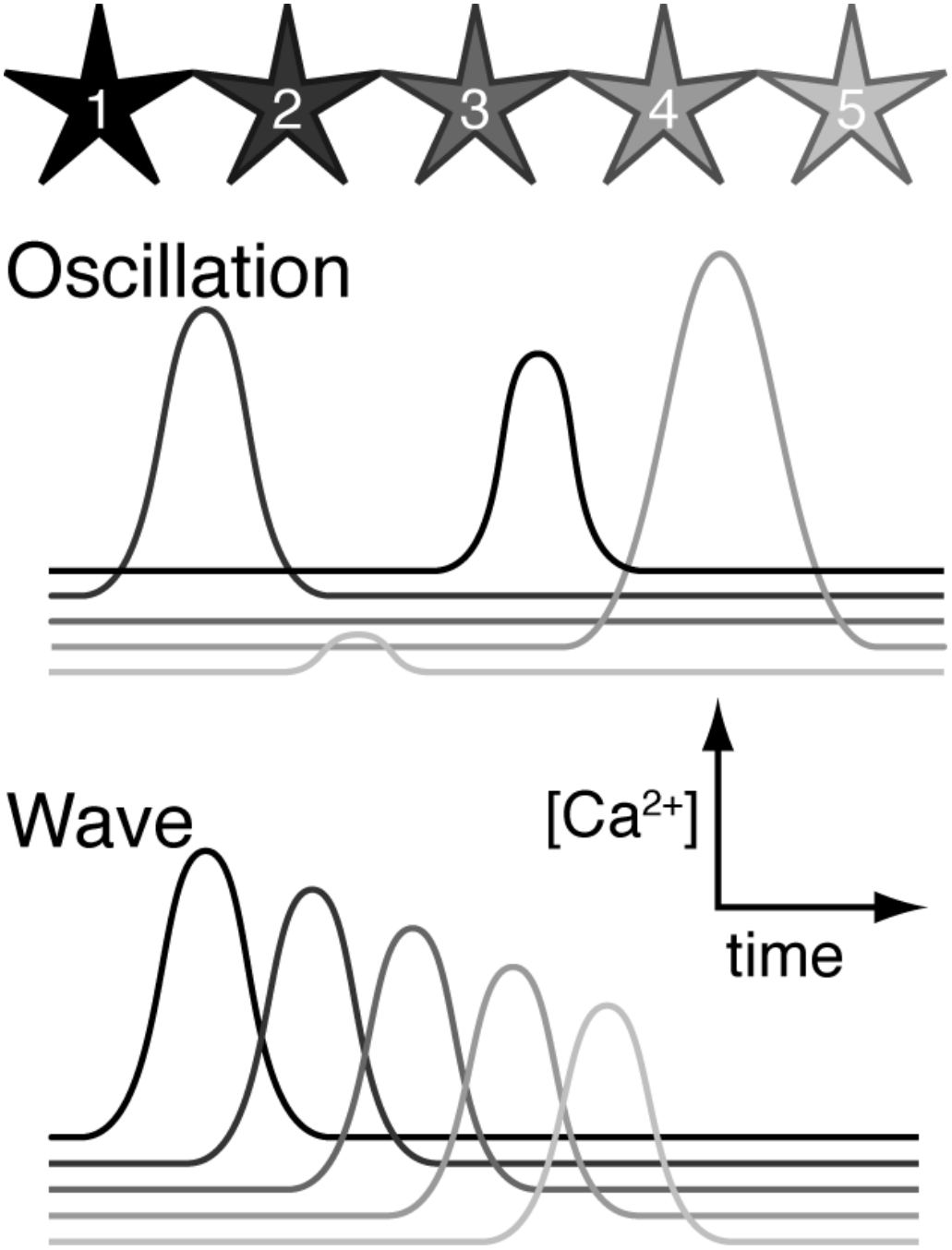

Fig. 1.
Ca2+ oscillations and Ca2+ waves represent two different modalities of astrocytic Ca2+ signaling

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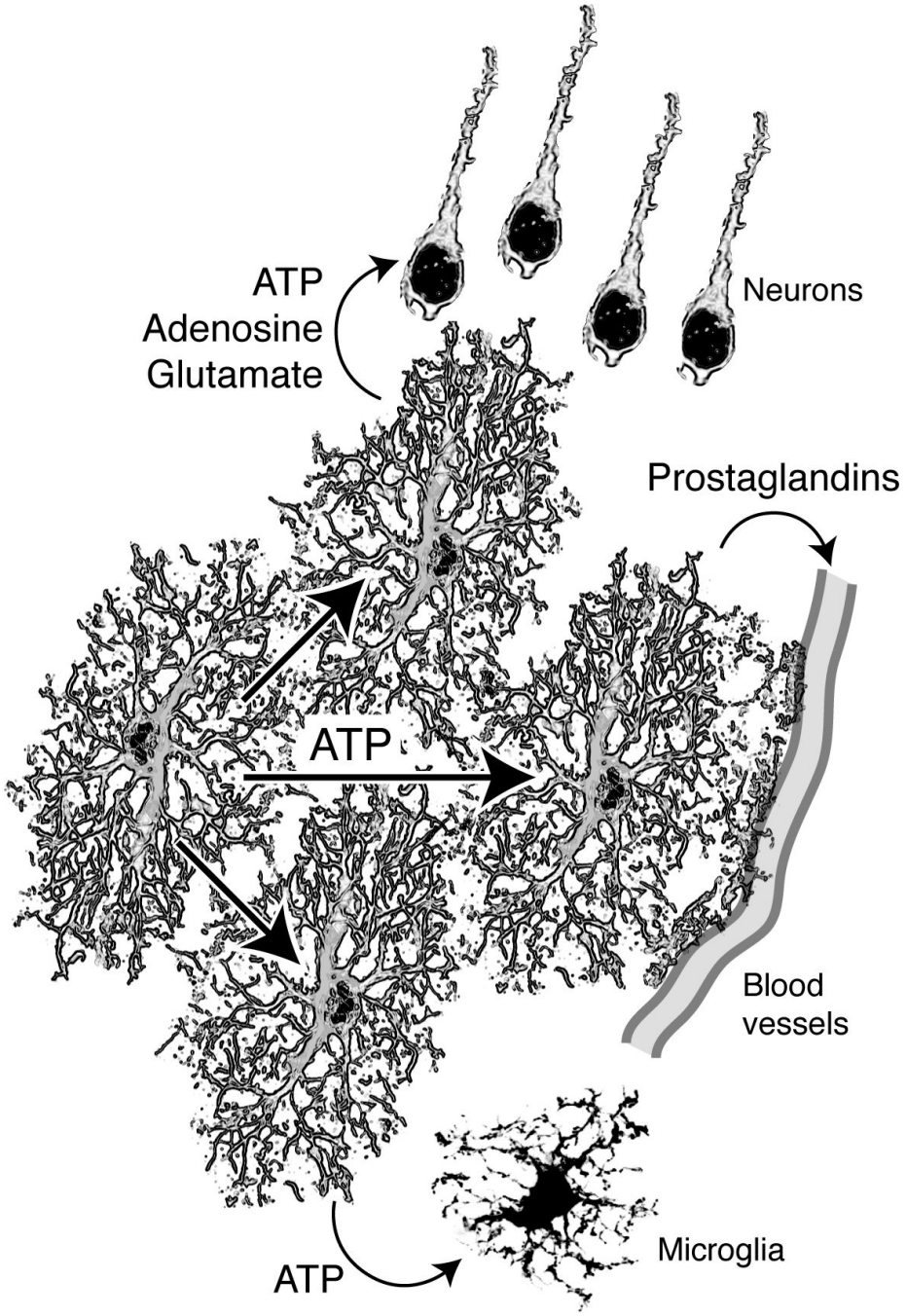

Fig. 2.

ATP is the main transmitter by which astrocytes communicate with neighboring astrocytes. ATP is also an important paracrine transmitter in signaling to neurons, vessels, and microglial cells. Other gliotransmitters include glutamate, d-serine, and prostaglandins,