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A major role for adenosine A_{2A} receptor in the interaction between astrocytes and myelinated neurons: possible implications for the therapy of neurodegenerative disorders

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Article summary

It has been widely demonstrated that astrocytes regulate multiple functions in the grey matter of the central nervous system (CNS), but less is known about their role in the white matter. By combining immunohistochemistry, electrophysiology, and computer modelling, Lezmy et al. [1] investigated how astrocytes modulate neuronal circuit function in the white matter, focusing on myelinated pyramidal neurons of the cortical layer V, which project into the corpus callosum. The authors found that astrocytes regulate the properties of myelinated axons through Ca^{2+}-dependent release of vesicular ATP. The latter is extracellularly converted to adenosine, which activates A_{2A} receptors (A_{2A}Rs) that were demonstrated for the first time to be expressed at the axon initial segment (AIS) and nodes of Ranvier. This led in turn to a local increase in cAMP, hyperpolarization-activated cyclic nucleotide-gated channel (HCN2) activation, and induction of an inward current in these axonal compartments. A_{2A}R activation has a double effect: at the AIS, it evokes an increase in axon excitability, whereas at the nodes of Ranvier, it decreases the conduction speed of the action potential. Thus, it is conceivable that physiological changes in extracellular adenosine levels influence information processing and cognition. Furthermore, A_{2A}R ligands could represent suitable pharmacological tools to reinstate normal excitability and conduction speed in myelinated axons in pathological conditions characterized by altered adenosinergic signalling.

Commentary

The role of astrocytes in the CNS in supporting neuronal function has been extensively characterized. In the grey matter, astrocytes regulate formation and pruning of synapses, clear the extracellular space of neurotransmitters, keep extracellular K^+ and glutamate levels low, thus facilitating fast, repetitive neurotransmission, control the dynamics of cerebral blood flow and provide energy to neurons [2]. Less is known about white matter astrocytes, except for the distinctive morphological differences that identify the grey matter cells as "protoplasmic" and the white matter as "fibrous" astrocytes. Even though their role in clearing glutamate and maintaining oligodendrocyte (OL) health has been demonstrated in vitro, the functional relevance of the interaction in vivo between astrocytes and myelinated neurons in the white matter is far from being fully understood. The possibility that unidentified modulatory functions of astrocytes can influence the excitability and conduction speed of myelinated axons in the white matter provided the rationale behind the present study.

Adenosine is a purine ribonucleoside, ubiquitous in the body, which modulates a variety of cellular functions. In the CNS, adenosine plays an important role in controlling synaptic plasticity, cognition, sleep, motor function and neuronal survival [3], and its physiological extracellular levels are regulated by enzymes and transmembrane transporters

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(ENTs) [4]. Among the four G-protein-coupled receptors (A_1, A_{2A}, A_{2B} and A_3) [5] involved in adenosine signalling, A_{2A}Rs, which activate the AC-cAMP-PKA pathway, are effective modulators of neuronal damage in various pathological conditions, and both their activation and blockade were neuroprotective in different experimental models [6]. Therefore, maintaining appropriate physiological levels of adenosine in the brain is fundamental.

By using a combination of immunofluorescence and the patch-clamp technique in mouse coronal brain slices, the authors found that astrocyte processes were associated with both internodal and nodal regions of myelinated axons of layer V cortical pyramidal cells. They observed that the depolarization of a pyramidal cell and the consequent induction of action potentials evoked an increase of $[Ca^{2+}]_i$ in astrocyte processes near the neuronal dendrites and axon. Uncaging Ca^{2+} in the astrocyte soma produced the same effect and induced ATP release into the extracellular milieu. By using immunohistochemistry, the authors identified, for the first time, adenosine receptors on myelinated axons of layer V excitatory neurons. Very interestingly, considering the role of endogenous adenosine and A_{2A}Rs in modulating OL development and myelination [7], only the A_{2A} subtype of adenosine receptors was detected. Furthermore, A_{2A}Rs were found in small amounts in cerebellar white matter, while they were absent at the AIS of cerebellar Purkinje cells, suggesting a neuron type-specific expression of A_{2A}Rs in myelinated axons. A_{2A}R stimulation, inducing an increase in cAMP levels, can affect cell excitability by promoting the opening of HCN K^+ channels present in axons. In particular, the authors found an overlap between A_{2A}Rs and HCN2 channels at the AIS and nodes of Ranvier. Following pharmacological A_{2A}Rs activation at the AIS, they observed depolarization of the pyramidal neurons cell soma and a consequent action potential response, increased or reduced in frequency depending on whether low or high input injected currents were applied. Unexpectedly, A_{2A}R activation at the nodes of Ranvier produced instead a significant reduction of conduction velocity.

The same effects—somatic depolarization upon activation of A_{2A}Rs and reduced axonal conduction speed—were reproduced in computational models of either a neuron with soma, AIS and an initial axonal tract and a corpus callosal axon. Adenosine-activated I_h currents were modelled by adding appropriate extra currents at the distal AIS and at the nodes of Ranvier, respectively. Finally, uncaging Ca2+ in an astrocyte with processes close to the AIS led to the depolarization of the pyramidal neuron and to an action potential response, exhibiting a higher firing rate to low injected currents and a lower firing rate to high injected currents, similar to what previously obtained by pharmacological A2ARs stimulation at the AIS.. The authors ruled out the involvement of glutamate released from astrocytes in this response, which was instead confirmed to be mediated by A_{2A}Rs and HCN channels.

This study elucidates a new mechanism of fine-tuned cross-talk among neurons and astrocytes in the white matter potentially involved in disorders in which the adenosine extracellular level and the neuronal or astrocytic density/affinity of A_{2A}Rs are altered. Worthy of note, adenosine levels are significantly reduced in Huntington's disease (HD) [8], epilepsy [9] and Niemann-Pick type C1 (NPC1) [10]. Therefore, enhancing adenosine levels reduces cognitive/plasticity impairments in models of HD [8], seizures in a mouse model of temporal lobe epilepsy [11] and cognitive deficits in a mouse model of NPC1 [12].

Interestingly, upregulation of A_{2A}R expression has been observed in cerebral white matter of progressive multiple sclerosis (MS) patients, also correlating to high disability scores [13]. Accordingly, A_{2A}R inactivation reduces memory deficit in a lysolecithin-induced demyelination model of MS [14]. Otherwise, A_{2A}R deficiency exacerbates white matter lesions and cognitive deficits in mice model of chronic cerebral hypoperfusion [15] and worsen experimental autoimmune encephalomyelitis (EAE) pathology [16]; conversely, SCH58261, an A_{2A}R selective antagonist, is protective against EAE development [17] when administered after its onset [18]. Thus, it appears clear that any variation in adenosine level and signalling could affect white matter's ability to correctly control information flow and neural circuit function.

Finally, adenosine and A_{2A}Rs exert an indirect influence on axon excitability and conduction speed by modulating myelination through their ability to affect migration, proliferation and maturation of OLs [19, 20]. In addition, the paper confers a new and unexpected function to adenosine and A_{2A}Rs in the direct control of excitability and conduction speed in the axons of myelinated neurons.

In conclusion, these data report for the first time a novel modulatory role played by astrocytes on the neuronal circuit occurring in the white matter, raising many interesting questions that deserve further investigation. It would be of great interest to determine if, and eventually, how, this mechanism is altered in the above-mentioned pathological conditions and if the pharmacological modulation of adenosine levels and A_{2A}Rs could reinstate it and improve myelinated neurons properties.

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Declarations

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