SMGroup

SM Journal of Neurological Disorders and Stroke

Editorial

Dysfunction of Astrocytic Syncytium in Neurological Disorders

Baofeng Ma*, Shiying Zhong

Department of Neuroscience, the Ohio State University Wexner Medical Center, United States

Article Information

Received date: Nov 09, 2015
Accepted date: Nov 10, 2015
Published date: Nov 10, 2015

***Corresponding author**

Baofeng Ma, the Ohio State University Wexner Medical Center, United States, Email: ma.499@osu.edu

In the nervous system, astrocytes are organized to form a giant syncytium through gap junctions, which are intercellular membrane channels. This organization by gap junctions is rarely seen in mature neurons and provides the basis for the difference in function between astrocytes and neurons. Astrocytes use gap junctions to redistribute molecules[1]and, more importantly, to confer is potentiality on the syncytium[2], thus providing homeostatic function, including the clearance of elevated K^+ and glutamate in extracellular space. Whether or how dysfunction of astrocytes syncytium causes neurological disorder is still uncertain despite extensive studies. This brief review focuses on recent neurological disorder findings and provides a view about is potentiality in an astrocytic syncytium and its relation to disorder based on these findings.

The K^+ spatial buffering mechanism has three steps: K^+ uptake in regions where K^+ is elevated, intercellular transfer, and release in distant regions [3]. Based on Ohm's law, the K^+ uptake or release rate (I) is determined by both membrane resistance (the inverse of membrane conductance, R_M or $1/G_M$) and driving force, which is the difference between equilibrium and membrane potentials in individual astrocytes (E_M-V_M), or $I = (E_M\text{-}V_M)G_M$. The intercellular transfer rate (I_T) is determined by both gap junction resistance (the inverse of gap junctional conductance, Rg, or 1/Gg), and the transfer driving force that is the difference in equilibrium plus membrane potential between neighbors ((E_{M1}-V_{M1}) - (E_{M2}-V_{M2})), or $I_T = [(E_{M1}\text{-}V_{M1}) - (E_{M2}\text{-}V_{M2})]Gg$. At a given distribution of extracellular K^+ concentrations in a syncytium, physiologically or pathologically, the ability of clearing K^+ could be simplified to be determined by only two components: gap junctional coupling between neighbors and K^+ conductance in individual cells [2]. In other words, those two components, together with two driving forces determined by the same components [2], affect K^+ clearance in each step of buffering.

Isopotentiality facilitates all three steps [2]. If isopotentiality is disrupted due to one or two components, K^+ buffering would be impaired and neurological disorders would likely develop. The first component is gap junctional coupling that is extremely strong in an astrocytes syncytium. Therefore, when gap junction coupling decreases, even at a small scale, both driving forces may decrease greatly, this in turn slows K^+ clearance. Additionally, weakening coupling can decrease K^+ transfer rate, thus resulting in further decrease of K^+ clearance. Altogether, K^+ flow rate decreases in each step after coupling becomes weak. In mature mouse astrocytes, the main gap-junction proteins are Cx43 and Cx30. Genetic deletion of these Cxs causes K^+ elevation in brain slices [4] and neurological disorders in mice [5] such as memory deficit. Gap junction uncoupling underlies human temporal lobe epilepsy [6]. Therefore, some neurological disorders result from deficit of gap junctions; however, their relative contribution is not clear.

The second component affecting syncytial function is K^+ conductance, which is also highly expressed in astrocytes and is contributed to mainly by Kir4.1 channels. When K^+ conductance decreases, for example by Kir4.1 down-regulation, both uptake and release rates decrease directly. This results in decrease of K^+ clearance. This decreasing conductance would strengthen the coupling within the syncytium [2], and thus enhance both driving forces that would facilitate K^+ clearance. Therefore conductance has two opposite sides affecting K^+ clearance. The side that prevails will determine the net effect on K^+ clearance. A recent study using Huntington's disease model mice shows that Kir4.1 deficits elevate striatal extracellular K^+ and contribute to dysfunction of striatal medium spiny neurons [7]. Those data suggest the net effect is impairment of K^+ clearance, evidenced by data that forced Kir4.1 expression rescued some neuron deficit. However, it is not clear whether gap junction deficits exist and contribute to the impairment of K^+ buffering in this study. If K^+ conductance is lowered further, such as knock out of Kir4.1 in astrocytes [8], there is more severe impairment of K^+ buffering [7].

In terms of K^+ homeostasis through buffering, many neurological disorders may have a common mechanism, for example, local K^+ elevation and consequent epileptic activity. Therefore, to determine which component is predominant, it is desirable to investigate those two components together. Also, the above analysis shows gap junction coupling may be used to compensate for Kir4.1 deficiency because of opposite effects on syncytial function. It should be interesting to test this experimentally in neurological disorders, exploring therapeutic intervention in a new direction.

References

1. Rouach N, Koulakoff A, Abudara V, Willecke K, Giaume C. Astroglial metabolic networks sustain hippocampal synaptic transmission. Science. 2008 ; 322: 1551-1555.
2. Ma B. Gap junction coupling confers isopotentiality on astrocyte syncytium. Glia. 2015.
3. Kofuji P, Newman EA. Potassium buffering in the central nervous system. Neuroscience. 2004; 129: 1045-1056.
4. Pannasch U. Astroglial networks scale synaptic activity and plasticity. Proceedings of the National Academy of Sciences of the United States of America. 2011; 108: 8467-8472.
5. Theis M. Accelerated hippocampal spreading depression and enhanced locomotory activity in mice with astrocyte-directed inactivation of connexin43. The Journal of neuroscience: the official journal of the Society for Neuroscience. 2003; 23: 766-776.
6. Bedner P. Astrocyte uncoupling as a cause of human temporal lobe epilepsy. Brain. 2015; 138 : 1208-1222.
7. Tong X. Astrocyte Kir4.1 ion channel deficits contribute to neuronal dysfunction in Huntington's disease model mice. Nat Neurosci. 2014; 17: 694-703.
8. Djukic B, Casper KB, Philpot BD, Chin LS, McCarthy KD. Conditional knock-out of Kir4.1 leads to glial membrane depolarization, inhibition of potassium and glutamate uptake, and enhanced short-term synaptic potentiation. The Journal of neuroscience: the official journal of the Society for Neuroscience. 2007; 27: 11354-11365.