MSc Coursework Submission Form

Programme (*please tick your programme*)

- ☐ MSc Psychological Research Methods
- ☐ MSc Psychological Research Methods and Advanced Statistics
- ☐ MSc Cognitive and Computational Neuroscience
- ☐ MSc Cognitive Neuroscience and Human Neuroimaging
- ☐ MSc Systems Neuroscience

Registration Number	2	3	0	1	6	3	8	4	3

Module Number	**P**	**S**	**Y**	6	3	0	6

Title	The role of astrocytes in neurovascular coupling

If you are taking part in the University's 'sticker' system for students with SpLD's please enter 'D' here:	

Word count	2039

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Grade:

Fail	Pass	Merit	Distinction
1) Introduction			
A very limited introduction/outline of the topic. Writing is unclear.	A satisfactory introduction/outline of the topic. Writing may be somewhat repetitive or unclear.	A clear and concise introduction/outline of the topic, succinctly written.	An excellent, very clear and concise introduction/outline of the issue. Critical and logical writing.
2) Main answer content			
The answer provides a limited key theories/data with no criticism and limited descriptions of the material.	The answer provides a satisfactory evaluation of the relevant material. Criticism is lacking, limited evidence of reading beyond lecture material.	The answer provides a competent and satisfactory evaluation of the relevant material. There is evidence of broad reading.	The answer provides an excellent succinct evaluation of the relevant material in a thorough and coherent way. There is evidence of extensive reading.
3) Structure and Evaluation			
The structure is satisfactory, but too descriptive, repetitive or superficial. Some errors in grammar and spelling.	A satisfactory presentation with some omissions of crucial arguments. Satisfactory grammar and spelling with some errors.	A coherent presentation with some evidence of critical reasoning. Good grammar and spelling.	A highly coherent presentation with independent critical writing style based on relevant literature. Excellent grammar and spelling.
4) Discussion and Conclusions			
Unclear, with limited relevance to the presented material.	Somewhat unclear, but partly supported by the content of the answer.	Clear and concise, related to the presented material, succinctly written.	Very clear and relevant to the content of the answer. Critical and logical writing.

Further comments:

The role of astrocytes in neurovascular coupling

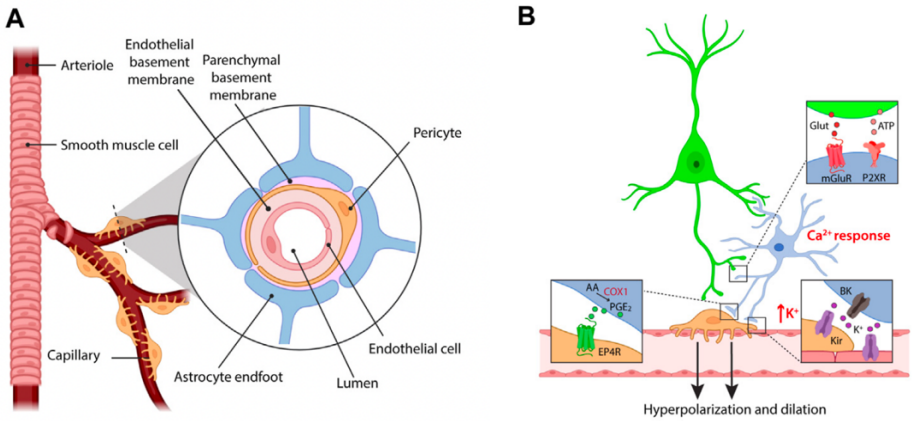
Neurovascular coupling (NVC) is a critical process in the brain which associating neuronal activity and cerebral blood flow complicatedly. It is essential to ensure the blood supply to meet the metabolic demands of certain region of the brain experiencing heightened neural activity. The dynamics of NVC is sophisticated, involving a series interaction of cells and signaling pathway. During this process, astrocyte play a significant role in NVC. It is a type of cell exist in the central neural system (CNS), characterized by its star-like appearance. Normally, astrocyte provide support and protection for neuron. However, it also has interacting with neurons and other glial cells. This essay will illustrate some discussion of research in this field and their related evidence to have a comprehensive view of the role of astrocytes in NVC. To be specific, the role of astrocytes in NVC will demonstrate from several aspect: involved ions, the communication between astrocytes and blood vessel, the communication between astrocytes and neurons, different vascular response depends on astrocytes, and other function of astrocytes in NVC.

Firstly, astrocyte as a signal transduction mediator in NVC, its function depends on signal transduction mechanism involving two kinds of chemical ions in astrocyte: calcium (Ca^{2+}) and potassium (K^+). Concerning Ca^{2+}, research in 2003 found that perfusing mGluR agonist will activate the metabotropic glutamate receptors in astrocytes which infect the endoplasmic reticulum release Ca^{2+} promoting the increase of concentration of Ca^{2+} in astrocytes. This kind of surge of Ca^{2+} is associated with the dilation of artery (Zonta et al., 2003b). However, some research queries the essential of Ca^{2+} to the vasodilation. In some experimental model, vasodilation has been observed in the Gene knock out (KO) mice with their transaction of Ca^{2+} have been inhibited. This indicated that there may be alternative pathway and compensation mechanism. (Nizar et al., 2013). In this research, the Ca^{2+} did not show significant effect, which may account for did not reach the requirement of trigger its action. As the development of technology, the following research explored deeper adopting the genetically encoded Ca^{2+} indicators (GECIs). While the results indicated there are week signal of Ca^{2+} can be detected in the (KO) mice, which partly deny the conclusion of previous research. (Srinivasan et al., 2015). However, the residual Ca^{2+} remain in the mice may produce by other metabolic process instead of NVC. Except of Ca^{2+}, the role of K^+ in mediating vasodilation also arouse the interest of researcher. Some research indicated the activation of big potassium (BK) channels in the terminal of stellate cells is a crucial factor. This kind of activation account for the release of K^+ ions of astrocytes, and K^+ ions in turn activate the inward rectifier potassium (Kir) channels in smooth muscle cells (SMCs) of vessels. The activation of (Kir) channels in critical in vasodilation, therefore, emphasize the significance of the dynamic of K^+. (Filosa et al., 2006).

Secondly, the specific sites of this complex communication of signal are ongoing subject of research and discussion, especially the start site. Initial research mainly focuses on the vasodilation happened in the level of penetrating arteries and ignore the potential of engaging of capillaries. One part of the reason is that, compared to penetrating arteries which is encapsulated by smooth muscle cells (SMC), capillaries is lack of this kind of anatomical

structure, therefore it been consider having limited function on regulating blood flow. However, subsequent research dramatically changes this sort of perspective which reveal the exist of contractile pericytes along capillaries, and it have a capacity like smooth muscle cells, regulate the blood vessel diameter. (Biesecker et al., 2016). More particular research suggests the temporal aspect of this kind of vascular response. This research indicate that capillaries show expansion before the response of penetrating arteries in repones to neural activation. The finding suggest that the signal of astrocytes is initially target capillaries but not penetrating arteries. (Hall et al., 2014).

After the discussion of the start sites, there are plenty of research investigate the detail regarding how these signals been transport between astrocytes and vessel. One of the research projects involve how capillary endothelial cells interact with the external K+ ions released from astrocytes. These cells express inward rectifier potassium (Kir) channels which can detect the presence of K+ ions and been activated by K+ ions. Once been activated, these channels will transfer the hyperpolarizing signal along the vascular tree, therefore infect the upstream upstream arterioles and downstream capillary beds. (Longden et al., 2017). This finding has a different understanding of how K+ function compared to the above research, which make this process more complicated. There is another research concerning the detail of how Ca2+ ions transport to the vessel. This research indicated that the increase of internal level of Ca2+ in astrocyte will result in the production of prostaglandin E2 (PGE2), which is a kind of molecule can act on EP4 receptor in capillaries and induce dilation of capillaries. (Mishra et al., 2016). The mechanism of Ca2+ and K+ is different, which may indicate the distinction between their role in promoting vasodilation. In contrast to the phenomenon in capillaries level, the mechanism of vasodilation of arterial vessels is controlled by a different process. It is notable that research emphasized the role of nitric oxide (NO) in regulating the lumen of arterial vessels through activation of N-mehtyl-D-Aspartate receptors (NMDARs) and nitric oxide synthase (NOS). (Lu et al., 2019). More in detail, the function of NO is various depend on different region of brain. In the cerebral cortex, NO inhibit the synthesis of vasoconstrictor 20-HETE to facilitate vasodilation. However, NO directly facilitate vasodilation in the cerebellum. (Lourenço and Laranjinha, 2021). However, the significance of this sort of distinction between brain region is not clear. There is also uncertain whether this activation from NO is related to the hyperpolarizing signal transfer by (Kir) channel.



Concerning the communication between astrocytes and neuron, astrocytes have various receptor for diverse neurotransmitter, which empower astrocytes to respond to neuron activity. During the process, there are two critical neurotransmitters: glutamate (Glu) and gamma-aminobutyric acid (GABA). In terms of Glu, when it combines to the class I metabotropic receptors on astrocytes, it will activate phospholipase C and inositol trisphosphate (IP3). This will result in the release and following oscillations of Ca2+ in astrocytes. In addition, Glu can initial

the production of arachidonic acid (AA) and its metabolites through activating phospholipase A. Both of Ca2+ and AA is critical in regulating neurovascular dynamics. (Haydon and Carmignoto, 2006). There is another research indicated that the Ca2+ transients in astrocytes in the hippocampal stratum radiatum are dependent on TRPA1 channels (Shigetomi et al., 2013). However, this sort of dependency was not observed in the astrocytes located in the stratum lucidum (Haustein et al., 2014). This might suggest astrocytes utilize the variation of channel to achieve different signal transformation mechanism in regions. Concerning another transmitters GABA, it also affects the activation of astrocytes. In a vitro study, there is an increase of Ca2+ mediated by GABA_B receptor observed in hippocampal slices after repetitive intraneuronal firing. (Kang et al., 1998). In addition, there is research indicate that astrocyte have different reaction to various inhibitory neurons. In specific, this research found the distinction between parvalbumin-positive GABAergic interneurons (PVIN) and GABAergic interneuron subtypes (VGATIN). The response of astrocytes activated by PVIN is instant while it is relatively delayed when the same response activated by VGATIN (Krogsgaard et al., 2023).

There is also research indicate that the role of astrocytes in NVC is not restrict in promote vasodilation but induce vasoconstriction in certain condition. This sort of dual function depends on various factor, including the resting arteriolar tone and the metabolic state of brain issue. Concerning the arteriolar tone, the behavior of astrocytes seems to depend on the degree of tension with the smooth muscle cells of arterioles. When the smooth cells maintain moderate tone (around 30% to 40%), the astrocytes mainly promote vasodilation, and enhance the blood flow to brain region in demand. However, when the tone of smooth cells is relatively low, astrocytes is more possible induce vasoconstriction and reduce the blood flow (Blanco et al., 2008). However, the reason causes the change in tone of smooth muscle is not clear, which might associate with neuron activity. In another hand, the metabolic state of brain issue, especially the oxygen level, also determine the activity of astrocytes. In general oxygen level, astrocyte promote vasodilation to ensure enough oxygen and nutrition to support brain activity. However, when it come to the excessive oxygen level, astrocyte will induce vasoconstriction. The reason is one of the enzymatic reactions is sensitive to oxygen concentration, and the reaction involved controlling the synthesis of vasoactive metabolites from arachidonic acid (AA). The vasoactive metabolites will determine the happen of vasoconstriction or vasodilation. (Gordon et al., 2008). This might indicate excess of oxygen have negative impact on neuron activity, therefore NVC would regulate the intake of oxygen by vasoconstriction.

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Except of regulate the vasodilation and vasoconstriction in the brain, astrocytes also play a critical role in other several aspects of NVC. First aspect involves insulin receptor (IR) of astrocytes, which regulate brain glucose uptake. Research involved mice provided an important understanding of this mechanism which found that those mice lack of insulin receptors (especially in the astrocytes) present impaired glucose metabolism both centrally and peripherally. Except of glucose metabolism, this imperfection also causes the defects of their glial transport functions, which is important for transportation of various nutrients and molecules maintained the brain activity (Fernandez et al., 2022).

Secondly, recent research found that astrocytes also have bidirectional signaling capacity, which mean they not only transmit signals to blood vessels but also convey information back to neurons. Astrocytes collect various physiological parameters like blood pressure, CO2 levels, or osmolality from blood vessels. After that, this information is transmitted to neurons contributing to the regulation of neurons. (Filosa et al., 2016). There is another research indicate that astrocytes can infect the response of neuron activity to changes in vascular flow and pressure. (Kim et al., 2015). The mechanism and effect of this sort of neuronal response to vessel

mediated by astrocytes still need to be investigate. This might relate to regulation and long-term change of mechanism of individual NVC, which account for chronic disease.

Thirdly, except of the role in cerebral NVC, recent research also suggests that astrocytes play an important role in spinal NVC. There is research utilizing fluorocitrate to probe the influence of astrocytes on spinal cord blood flow (SCBF), which is a selective inhibitor of astrocyte metabolism. The result of research indicates that the appliance of fluorocitrate will induce substantial decrease of SCBF, which is up to 40%. However, there is no respective change of neuron activity, which indicate this effect is not directly relate to neuron activity but astrocytes activity (Paquette et al., 2021).

Finally, the operation of NVC rely on the integrity of the blood-brain barrier (BBB). There is research indicated that astrocytes have a significant role in maintain BBB. In this research, astrocytes in mouse were selectively removed by a drug called tamoxifen. After the removing of astrocytes there is evidence suggest the leakage of Cadaverine (a small molecule) and fibrinogen (a large plasma protein) into the brain, which indicate the BBB damage. This phenomenon last for several week, the astrocytes did not replace by new ones, which indicate the BBB cannot repairing by itself. (Heithoff et al., 2021)

Generally, astrocytes play a role as mediator during the signal transformation between neuron and vessel in NVC. In this way, astrocyte promote vasodilation and vasoconstriction to meet the metabolic requirement of neuron activity, and it also reversely promote the regulation of neuron depend on vessel activity. During this process, the signal transform through various ions and substance, like Ca^{2+}, K^{+}, Glu, GABA, NO. However, astrocytes also play an important role in other aspect of NVC, like regulating brain glucose uptake and vascular function, transforming bidirectional signaling, spinal NVC and maintaining the integrity of BBB. All this research suggests astrocytes play a significant role in NVC. Even though there are many experiments using mice model, in terms of brain of human the situation might involve more factor concerning more complicated cerebral activity.

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