Proceedings of the 2nd International Conference on Biological Engineering and Medical Science (ICBioMed 2022), Part I
DOI: 10.54254/2753-8818/3/20220465

Role of Astrocytes in Epilepsy and Schizophrenia

Jiaming Liang

SSFBC:The High School Affiliated to Shaanxi Normal University, Xian, China

631512345678@mails.cqjtu.edu.cn

Abstract. The dangers of epilepsy and schizophrenia are increasingly being noticed. Its economic burden, social harm and harm to patients cannot be ignored. However, little is known about the pathogenesis of psychiatric disorders. Relevant treatment is limited to symptomatic treatment. Research suggests astrocytes play a role in seizures and schizophrenia. In the occurrence and development of mental diseases such as epilepsy and schizophrenia, astrocytes cannot be ignored. The article introduces the current findings and theories on role and function of astrocytes, and their connection with epilepsy and schizophrenia. It describes the positive effects and negative effects of astrocytes and their basic mechanisms that are now believed. And those mechanisms include glutamate-glutamine cycle which is related to the synthesizing of gama-aminobutyric acid (GABA), blood brain barrier which is controlling the matter exchange between vessels and brain, several molecules and inflammatory factors' effect on the channel expressing on the surface of astrocytes and other main paths that could contribute to neuronal disorders. The article also includes several chemicals and their effects on inhibiting astrocytes of isolated sample, from chliroquine, calmodulin-trifluoperazin, gamma globulin and anticardiolipin antibodies. Last, the present study on the relationship between epilepsy and schizophrenia is discussed.

Keywords: epilepsy, schizophrenia, glia, astrocyte.

1. Introduction

The mental diseases have puzzled humanity for centuries. Even today the science has not found the perfect solution. The symptoms of two of those mental diseases, epilepsy and schizophrenia are torturing the patients cruelly by disturbing their life in a large scale. Though there are medicines like phenobarbital luin inal, Sodium Valproate NavpA for curing by regulate the neuron transmitter GABA, gama-aminobutyric acid a more effective and general acceptable therapy must be introduced in order to improve patients' living standards. In the studies on patients with epilepsy or schizophrenia, the role of astrocytes in brain functioning is gradually being perceived. It is reported that the foci of brain tissue causing seizures has an increased quantity of astrocytes [1]. It is also pointed out that the cause of schizophrenia is contributed by inappropriate interactions between different areas in brain, and it is accomplished by glial cells including astrocyte. The fact to mention is that the astrocytes make up approximately 17% of glial cells [2]. And astrocyte is the most abundant cell in central nervous system, 5 times more than neurons on quantity [3]. More important, astrocytes seem to play a role in inhibiting neurons and also excitement of neurons. And those diseases are exactly about neurons. So, it can never ignore the astrocyte in the development of medicine of mental diseases like epilepsy and schizophrenia.

© 2026 The Authors. This is an open access article distributed under the terms of the Creative Commons Attribution License 4.0 (https://creativecommons.org/licenses/by/4.0/).

DOI: 10.54254/2753-8818/3/20220465

Furthermore, the medicine on regulating astrocyte can be the answer, even the end of a period of therapies of the neuronal disorder.

Before more studies, it is needed to be clearly understood which kind of function of astrocyte overweight the other one, excitement or inhibition. This concept is vital for development of medicine using astrocytes as targets. Otherwise, the curing method can be incorrect since the role of astrocyte is not clear and all those phenomena of abnormal quantity of astrocyte in foci will be meaningless.

2. Astrocyte functioning

The astrocyte is a kind of glial cells, which is related to excitation and inhibition of neurons. The glutamate (Glu) is responsible for excitation and the gama-aminobutyric acid (GABA) is responsible for inhibition of neurons [3]. The Glu released from neurons will be accepted by alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA), which is made up of GluR1 to GluR4 on astrocyte and, undergo glutamate-glutamine cycle [1]. After the procedure, the glutamine synthetase (GS) resided in astrocyte will use glutamine to synthesize glutamine (GLn) for transporting to glutamatergic neurons to form Gama-aminobutyric acid (GABA) by glutamic acid decarboxylase [4]. At the same time, astrocyte is capable of releasing inflammatory factors like TNF-alpha, which is used for inhibiting tumor or defensive protection [4]. It is reported that the presence of TNF-alpha will decrease the mRNA for synthesizing subunit of excitatory amino acid transporters (EAATs), EAAT 1 [5]. However, the EAAT 1 takes part in the process of astrocyte taking up of the glutamate, and conducting of chloride ions, which is participating in depolarization of neurons. Accordingly, the glutamate remain between neurons will have a numerical increasing to decrease the synthesis of GABA as there is less glutamate was transported into astrocyte to further synthesize less GABA and also cause the damage to neurons [2](Figure 1). Moreover, the TNF-alpha can induce astrocyte to release glutamate into space between neurons [3]. After the injury of astrocytes, they open calcium channel and the maximum concentration of calcium ions inside astrocyte will be reached in 10 seconds [7]. Another factor released after injury is transforming growth factor-beta1, which is thought to be an important factor for healing [8]. The transforming growth factor-beta1 can be accepted by two protein receptors TGF-beta RI and TGF-beta RII on the membrane. To accept transporting growth factor-beta1, both TGF-beta RI and TGF-beta RII must to be presented because the TGF-beta RI is not able to recognize free transforming growth factor-beta1 alone as the experiment found that TGF-beta RI can only bind with the TGF-beta RII- transforming growth factor complex. And the phenomenon further showed that TGF-beta RI and TGF-beta RII bind with transforming growth factor-beta1 to form a strong complex even can persist under pH of 2.5. However, it showed that TGF-beta RI can only recognize the complex formed after transforming growth factor-beta1 bind with TGF-beta RII [9]. In normal brain, the presence of transforming growth factor-beta1 is low, and its presence increases apparently on the second day after penetrating injury on the cortex.[8] During the process of the recovering of injury, the transporting growth factor-beta 1 mainly comes from astrocytes and microglia though neurons also have the ability to make transporting growth factor-beta 1. And presence of transforming growth factor-beta1 came to normal level on the third day after injury [8]. Accordingly, it is proved that transporting growth factor-beta1 is essential in healing and recovering. However, it is also found that transporting growth factor can inhibit overgrowth of astrocyte after injury to prevent astrocyte scars to further prevent neuronal disorder that could be induced. While some researches showed the presence of transporting growth factor in astrocyte from hippocampus of status epilepticus (SE)-experienced mice, which makes some scientists believed that the transporting growth factor-beta 1 contributes to and aggravates excitation of neurons to cause epilepsy and seizures [10](Figure 1). In the experiments conducted on mice, it is found that overexpression of transporting growth factor-beta 1 in astrocytes has positive effects like preventing spreading of damage, and experiment showed that it prevents losing of synaptic markers after experiencing of acute and chronic injury. Also, it argued that there is no causing of hydrocephalus under the condition of overexpressing of transporting growth factor-beta 1. It also pointed out that sufficient quantity of transporting growth factor-beta 1 is important for repairing against wound [11].

DOI: 10.54254/2753-8818/3/20220465

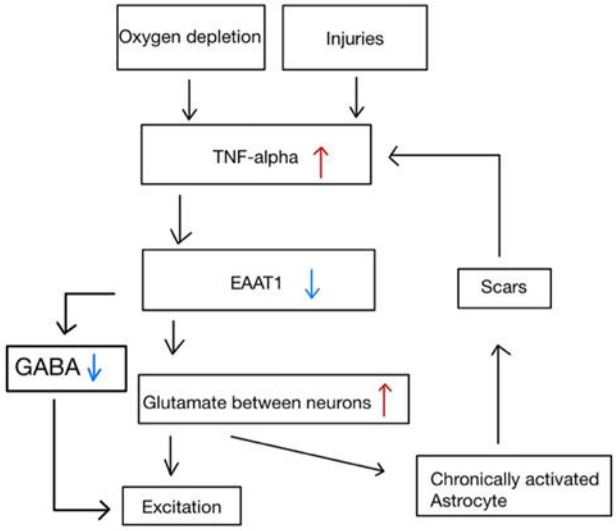

Figure 1. The pathway of inducing dysfunction of astrocytes and seizures. The arrows in box refer to increasing or decreasing of the content in the box. The arrows outside the box refer to the consequence of each change to the content in the box by the given change from the arrow in each box.

3. Blood brain barrier

Blood brain barrier has a key function of preventing brain from threats of damaging brain tissue and disrupting brain normal function brought by every molecule that may get into brain and it is thought to be constructed by astrocytes and microvascular endothelial cells [12,13]. After either injuries or serious seizures, the function of blood brain barrier will be affected and disrupted to have undesirable effects which may contribute to further seizures and epilepsy. In the experiment, the albumin is used to detect the leakage the blood brain barrier. In the autopsy of patients died when happening acute status epilepticus unfortunately, the albumin is found to be presented in neurons and astrocytes near the blood vessels, which implies to the leakage of blood brain barrier. And the presence of albumin in hippocampus is clear 1 or 2 days after status epilepticus. Also, the albumin presented in a smaller scale in the epileptic mice has been found, all proved that epilepsy induces blood brain barrier to be not protective enough and its dysfunction [14]. However, the inflow of albumin will activate a pathway of signal transmitting mediated by receptor of transporting growth factor-beta in astrocytes. And it mentioned that opening blood brain barrier disturbing the glial cells includes astrocytes to lead to epilepsy [10]. Interestingly, the inflammatory damage will be the consequence of dysfunction of blood brain barrier after traumatic brain injuries, and the inflammatory damage will chronically activate the astrocytes to induce epilepsy. They are also undeniable truths that epilepsy will cause more damage to blood brain barrier and more scars on astrocytes, then lead to more and more seizures and damages. The vascular endothelial growth factors are responsible for proliferation and growth of endothelial cells, and it is thought that vascular endothelial growth factor is capable of increase the permeability of blood brain barrier by showing that the giving of vascular endothelial growth factor antibodies can lower the level of leakage of blood brain barrier [15]. Moreover, the knockout of receptor-2 of vascular endothelial growth factor can lower the level of disturbance to blood brain barrier brought by permanent ischemic damage, which also proved that vascular endothelial growth factor is playing a negative role in protective function of blood brain barrier. From one point of view, the loss of

DOI: 10.54254/2753-8818/3/20220465

connection between blood and astroglia will lead to blood brain barrier disturbance while from the other point of view, that knock out of one of the isoforms of astrocytic sodium ion/proton exchanger will lead to decreasing of astrogliosis and enhancing of function of blood brain barrier after ischemic stroke in rats. Also, it is found that vascular endothelial growth factor is presented in astrocytes in animals and human with sclerosis, and it is proved that the disturbance to blood brain barrier will be reduced if the vascular endothelial growth factor in astrocytes is inactivated [16].

4. Astrocyte with epilepsy

As the glutamate is essential for GABA synthesis, it is responsible for epilepsy induction due to the inhibiting function of GABA. The receiving of GABA of neurons can open chloride channel to undergo hyperpolarization in order to decrease the voltage further from the threshold to prevent overexcitation of neurons. Apparently, the astrocytes fail to synthesize the GABA for inhibiting neurons in epileptic brains. The overexcitation will then lead to seizures, which are common symptoms of epilepsy. Along the path, it is also found that the inhibiting of GS can cause epilepsy, and astrocyte can finally deplete glutamate between neurons in order to prevent epilepsy [3]. It is found that the inhibiting on receptor of GABA can enhance the quantity growth of proliferative glial fibrillary acidic protein-expressed cells like astrocytes [17]. The Kir channel on the astrocyte can take up potassium ions, which is used to excites neurons. It adjusts the concentration of potassium ion inside the astrocytes by taking up water by aquaporin 4 AQP4 channel to create chemiosmosis gradient to take up potassium ions and accordingly inhibit neurons [1,3]. The epilepsy patients were found to have reduced expression of potassium ions channel and AQP4 channel in sclerotic hippocampus. The research found that the astrocytes in sclerotic hippocampus respond to glutamate with more corresponding intracellular calcium ion responding. However, the calcium ions are required to process the pathway of releasing glutamate, calcium ion dependent exocytotic release of glutamate [1]. Therefore, it leads to over accumulation of glutamate to induce seizuring. However, the dysfunction of blood brain barrier, of opening of it, will leak albumin and transporting growth factor-beta 1, which will decrease the expressing of channel of Kir4.1 and AQP4. And the down regulation of Kir4.1 and AQP4 channel at the end feet of astrocytes will cause the ability of regulating the concentration of potassium ion to decrease, make the epilepsy inducing is more possible [10].

5. Medicine test on curing epilepsy by affecting astrocyte

Chliroquine is believed to have effects on inhibiting epilepsy of mice, and test of Chliroquine on isolated samples of astrocyte at hippocampus of mice is possible for providing clues of the mechanism of the Chliroquine on inhibiting pentylenetetrazole induced epilepsy of mice [9]. The pentylenetetrazole is found to bind with receptor of GABA and cause epilepsy, and in the many experiments conducted on animals by injecting pentlenetetrazole, the epilepsy is induced [10]. So the incorrect number of GABA out of the neurons can mislead this system and promotes to synthesize more GABA. In effect, it is mentioned that that pentylenetetrazole will chronically active the astrocyte and damage cells. Also, the activated astrocyte can release inflammatory factors to induce epilepsy. The test examines the activity of astrocyte after adding Chliroquine to samples, and the result shows that the Chliroquine can inhibit astrocyte activity that is activated by pentylenetetrazole. At the same time, the Chliroquine can prevent increasing of astrocyte tumor and releasing of inflammatory factors like TNF-alpha [9]. In this case, the astrocyte is more likely to play a role on resulting in inducing of epilepsy.

In another experiment, the calmodulin-trifluoperazin dihydrochloride, which can maintain low calcium ion concentration, was added in controlled group of isolated samples of mice. And the sample tissue is cut, the group without calmodulin-trifuoperazin dihydrochloride had an overgrowth of astrocyte. The group with calmodulin-trifuoperazin dihydrochloride prevented the overgrowth of astrocyte [7]. However, the repairing of astrocyte is beneficial after injury, and it will then become scars, harming the normal function of astrocyte.

DOI: 10.54254/2753-8818/3/20220465

In mice brain, the proliferation is reduced by gamma globulin and anticardiolipin antibodies by detecting of thymidine incorporated into astrocytes from isolated sample cultured. The collected data showed that the gamma globulin increases the proliferation of mice astrocytes in first day and then decreases in the next two days below the proliferation value of the controlled group. For anticardiolipin antibodies, they inhibited the proliferation of mice astrocytes in a greater scale than that of the effect of gamma globulin from the first day, and they make the value of the proliferation to be approximately 20 percent compared to controlled group. More importantly, 22%-70% of systemic lupus erythematosus patients have neuronal disorders and the anticardiolipin antibodies are possibly transferred from serum to central nervous system through blood brain barrier that is damaged [18].

The nitrogen oxide has a sophisticated way to disrupt blood brain barrier function by cyclic guanosine monophosphate pathway. Angiopoietin-1 is thought to play protective role after injuries of brain because it can alleviate the leakage of blood brain barrier after injuries by overexpressing angiopoietin-1 and can gain better recovery after intracerebral hemorrhage [15].

6. Astrocyte with schizophrenia

It is found that the expression of fasciculation and elongation protein zeta-1(FEZ1) has reduced in hippocampus after injury of frontal lobe and FEZ1 mainly resides in astrocyte. So, it claims the FEZ1 in astrocyte taking part in repairing injured tissues. Also, the glutamate caused overexcitation can lead to symptoms of schizophrenia. It is pointed out that astrocyte participates in expression of dopamine reception and dopamine can increase the quantity of EAAT 1 to increase taking up of glutamate to maintain balance between neuron transmitters [5]. It is also found that the expression of glial fibrillary acidic protein is increase in astrocyte [9]. Glial fibrillary acidic protein is responsible for growth of astrocytes [12]. Other than that, S100-beta(can combine with calcium ions) is found to have numerical increase in schizophrenia patients [5]. Unfortunately, the mechanism of S100-beta remains unknown. It does report that the presence of S100-beta is more in kids who has more serious brain injuries than those who has lighter. And in the other group, the death rate is eight times more along patients who has more percentage of S100-beta than the patients have less percentage of S100-beta resided [13]. It is possible that the damage of astrocyte and neurons leads to the increasing of percentage of S100-beta in schizophrenia patients. And the experiment that is going to find the effect of knockout of S100-beta needed to be conducted to give further remarks on the specific role of S100-beta.

7. Epilepsy and schizophrenia

It mentioned the presence of white matter, astrocyte, in schizophrenia patients than in epilepsy patients, and it thought they may have opposite relationship [7]. And that is how electric shock treatment is conceived. According to the opinion of the experiment in the book, the astrocyte increasing was induced by abnormal function of neurons, the overexcitation. Also, it implies that schizophrenia is caused by ineffective communicating between neurons or over accumulation of glutamate if it does. And it is found later that 1684 of schizophrenia patients emerged 45 of them having epileptic seizures after electric shock treatment. This result seems to be proving for the glutamate- mechanisms mentioned above. Also, for other treatments to schizophrenia patients which can damage brain tissue in any ways, it is also causing epilepsy. For epilepsy patients, they can also have symptoms of schizophrenia, but what need to point out is that when those symptoms are induced, the symptoms of epilepsy will be alleviated. It will be strong evidence to that one of the function of astrocyte can overweight the other one if assuming that schizophrenia is associated with less Astrocyte and epilepsy with more. Generally, there is no definite or clear explanation to this until more evidence is collected. Moreover, it reported that some patients are with both symptoms of schizophrenia and epilepsy [8]. A group of scientists believe the relationship between epilepsy and schizophrenia is antagonism.

Apparently, the conclusion of experiments is controversial as in one trial, the astrocyte is thought to be insufficient, and in the other one, the astrocyte overgrows. And it is requiring discussion about conducting experiment to find what determines how the astrocytes participate in inducing of epilepsy

DOI: 10.54254/2753-8818/3/20220465

or schizophrenia. Another point is that the structure of astrocytes in brain will vary after abnormal functioning of neurons, which is what happened when epilepsy or schizophrenia is induced.

8. Conclusion

No matter the positive effects or negative effects of astrocytes, the deeper and more investigations are required for coming up proper and efficient ways to cure or alleviate the harm from epilepsy and schizophrenia to patients. That is because astrocytes are never absent from the pathway of inducing or stop of neuronal injury and dysfunction. The new medicine can work on the aspect of neuronal transmitters, blood brain barrier, inflammatory factors, channels on astrocytes. It is better that it could found new treatment on stopping the undesirable loop of damage-activation-seizure-damage. And it is expected to unearth more details and functions of astrocytes from investigating the relationship between epilepsy and schizophrenia. Still, there is no whole picture of astrocytes, its function and role need further study.

References

[1] C.D. Nihal, et al. (2010). Astrocytes and epilepsy. Neurotherapeutics.
[2] N. C. Andreasen, et al. (1991). Schizophrenia: the characteristic symptoms. Schizophrenia Bulletin, 17(1), 27-49.
[3] D. Fields, (2021). Electric Brain. (Nanjie Ruan). Beijing:CITIC Press Corporation. (Original work published 2020).
[4] Q.H. Yu, et al. (1995). Jingshenfenliezheng yu dianxian[schizophrenia and epilepsy][J]. Shanghai jingshen yixue, 1995, 7(4):
[5] L.L Xing, et al. (2011). Lvkui yizhi tiwaipeiyangxingxingjiaozhibaode jihuo[chliroquine inhibit the activation of isolated sample of astrocytes][J]. Basic and Clinical Medicine,31(10), 5.
[6] R.Q. Huang, et al. (2001). Pentylenetetrazole-induced inhibition of recombinant gamma-aminobutyric acid type a (gaba(a)) receptors: mechanism and site of action. Journal of Pharmacology & Experimental Therapeutics, 298(3), 986-995.
[7] B. Iaaa, et al. (2020). Decreased il-1β-induced ccl20 response in human ipsc-astrocytes in schizophrenia: potential attenuating effects on recruitment of regulatory t cells. Brain, Behavior, and Immunity, 87, 634-644.
[8] M. A. Mccall, et al. (1996). Targeted deletion in astrocyte intermediate filament (gfap) alters neuronal physiology. Proceedings of the National Academy of Sciences, 93(13), 6361-6366.
[9] L.Y. Liao, (2007). S100 danbaide yanjiujinzhan[development of study on S100 protein], 004(003), 182-184.
[10] X. Gu, et al. (2009). Xing xing jiao zhiibao gaitiaodanbai zai sun shang hou jiang zhi ban hen xing cheng Zhong de zuo yong[The role of gfap in scar formation of astrocytes after injury][J]. Chong qing yi ke da xue xue bao, 34(5), 4.
[11] D. Lindholm, (1992). Transforming growth factor-beta 1 in the rat brain: increase after injury and inhibition of astrocyte proliferation. Journal of Cell Biology, 117(2), 395-400.
[12] J. Massagué. (1994). Mechanism of the Activation of TGF-Beta Receptor.
[13] U. Heinemann, et al. (2012). Blood‐brain barrier dysfunction, tgf β signaling, and astrocyte dysfunction in epilepsy. Glia, 60(8), 1251-1257.
[14] T. C. Brionne, et al.. (2003). Loss of TGF-β1 Leads to Increased Neuronal Cell Death and Microgliosis in Mouse Brain.
[15] E. A. van Vliet et al. (2007). Blood-brain barrier leakage may lead to progression of temporal lobe epilepsy. Brain, 130(2), 521-534.
[16] B. B. Weksler, et al. (2005). Blood-brain barrier-specific properties of a human adult brain endothelial cell line. Faseb Journal Official Publication of the Federation of American Societies for Experimental Biology, 19(13), 1872.
[17] S. Michinaga, et al. (2019). Dual roles of astrocyte-derived factors in regulation of blood-brain barrier function after brain damage. International Journal of Molecular Sciences, 20(3).

DOI: 10.54254/2753-8818/3/20220465

[18] K. H. Sun, et al. (1992). Inhibition of astrocyte proliferation and binding to brain tissue of anticardiolipin antibodies purified from lupus serum. Annals of the Rheumatic Diseases, 51(6), 707-712.