The Role of Glial Cells in Epilepsy and Possible Anti-Epileptic Drug Designs

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Abstract. Epilepsy, affecting about 1% of the population, comprises a group of disorders of brains characterized by periodic and unpredictable occurrence of seizures. Seizures are medically intractable in about 30% of patients suffering from epilepsy, they have no response to anti-epileptic drugs (AED) which are currently being used in clinical field. Decades of efforts of scientists has demonstrated glial cells' very crucial role in neuron network. They not only serve to maintain homeostasis, but also interfere communication and general regulation. As the consequence, glial cells also go through damage and lesion during seizures and epilepsy, which further exacerbate pathological condition. This hypothesis can account for lots of AED refractory cases because most of AEDs target only neurons' lesion. In a number of experiments, scientists have demonstrated this hypothesis by finding various striking lesion in glial cells before; during; after epilepsy. Blocking water channels and potassium channels over-expressed by astrocytes; blocking gap junction to decrease diffusion in glial networks; locating these lesion of glial cells and then neutralize the dysfunction are very promising ideas of designing drugs alleviating epilepsy. This paper introduces basic characters of glial cells, putting emphasis on their abnormalities within epileptic brains, corresponding therapy will be discussed.

Keywords: Astrocyte, gap junction, cytokine, glutamate, hyper-excitation.

1. Introduction

Epilepsy, characterized as periodic and unpredictable seizure occurrence, nowadays is a very remarkable and prevalent brain disease which is medically complicated, TLE (temporal lobe epilepsy) is the most common form of epilepsy found in adult, in which most of patients suffer from. In about 38%-58% percent of TLE cases, hippocampal sclerosis occurred. Previous studies have demonstrated that most of types of epilepsy originated from hippocampus. In lots of cases, refractory epilepsy is found. Researchers cannot conclude the relationship between seizure and epilepsy. Besides, scientists cannot fully acknowledge all the pathogenic principles of epilepsy. Basically, it is roughly precise to understand epilepsy at a very preliminary extent, that is, to some reasons including free radicals' attack or brain cells' aging, homeostasis in a specific area is disrupted. Thus, neurons and glial cells go through a disordered discharge also named as seizure, which give rise to several lesions in glials and neurons. Continuously, these lesions exacerbate the debacle pf homeostasis, thus, the whole system get trapped into vicious cycles.

Glial cell is another type of cell other than neurons in our brain. There are three types of glial cells: astrocyte; microglia; oligodendrocyte. In obsolete conception, glial cells are supportive roles for neuron communication. However, scientists' opinions have greatly changed. Researchers have found glial cells play complicated role in brain function. They not only participate in communication, but also regulate the whole network. Astrocytes participate in extracellular space regulation and glutamate regulation; dysfunction of astrocyte regulation can lead to excessive glutamate and hyper-excitation. Microglias participate in brain immune systems, they are observed to play double sided role in epilepsy because microglias can exert brains high pressure during seizure's occurrence. Oligodendrocytes participate in myelination and are relatively less relevant to epilepsy.

In brains, there are millions of inhibitory neurons and excitatory neurons. In healthy brains, they function together within a balance to regulate effectors. As the consequence, contemporary anti-epileptic drugs mostly aim at recovering the balance of neurons to prevent abnormal discharge. There are basically two main types of AEDs: Inhibiting neuronal voltage-gated sodium channels and

calcium channels and glutamate receptors in order to decrease neuron excitability; boosting c-aminobutyric acid (GABA) systems in order to inhibit neurons from excessive firing. Contemporary AEDs have lots of defects. About 30% of patients show refractory to AEDs [1]. Besides, AEDs inevitably impair memory and other brain functions at the same time because their neutralization to specific hyper-excitation is no selective. What is more, today our AEDs all function to neutralize excessive or abnormal function generated by epilepsy, finding ways to recover tissues to their normal condition and function is necessary. In this paper, author will emphasize glial cell's importance as targets of AEDs.

Putting emphasis on glial cells, this paper introduces pathogenic principles of epilepsy. Lesions which disrupt homeostasis within sophisticated networks in brain will be discussed in details. Accordingly, author will summarize and offer several possible pharmaceutical pathways in order to cure or alleviating epileptic syndrome.

2. Glial cell

2.1. Astrocyte

2.1.1 Regulation of water and potassium

Astrocyte is a subgroup of glial cells which is most populated in our brain. They not only serve as supportive cells of neurons, but also participate in complex regulation and reuptake, which is very crucial for neurons' normal function. Astrocytes possess numbers of channels which are able to reabsorb potassium along with water released by repolarization of neurons. Kir4.1 and AQP4 are frequently expressed together on membranes and able to redistribute potassium and water from extracellular space to areas which are devoid of potassium and water [2]. Such process is operated via gap junction among astrocytes conducted by osmosis pressure. Same principle is also appropriate for calcium transportation in astrocytes. Gap junctions among astrocytes allow kinds of ions and messengers to penetrate including glucose and ATP in astrocyte networks.

2.1.2 Glutamte regulation

Glutamate is a type of excitatory neurotransmitter in people's brain, which is cytotoxic at high concentration in neuronal clefts [3]. Astrocytes are responsible for removal of glutamate in neuronal cleft by glutamate transporters, then, transferring glutamate into glutamine-by-glutamine synthetases in cell bodies. After the redistribution by gap junctions in astrocyte-networks, glutamine will be transported into presynaptic terminals. This process is assumed to obey same principle as discussed in preceding part. Besides, glutamate receptors located on astrocyte membranes can initiate release of calcium ions as signal molecules to activate glutamate release from astrocytes into extracellular space [4].

2.1.3 Gliotransmission

Gliotransmission is a relatively mew conception because for a very long period scientists regarded glial cells as only supportive cells and lack of ability to communicate. Such communication is characterized by release of neuron transmitters. Nevertheless, a study published in 1994 led to an overthrow of this theory [5]. The researchers tested cultured astrocytes and surprisingly uncover their ability to release glutamate, which considered as a hallmark of communication in neuron systems. Scientists assumed that the release of glutamate in astrocytes is triggered by extracellular calcium ions as signal. The mechanism of gliotransmission still remain controversial. What is more, studies have found electrical stimuli can trigger the release of calcium in astrocytes, whose function and physiological meaning is still unclear.

2.1.4 Immunology function

A series of inflammation events are associated with epilepsy, and such inflammations play counterproductive and controversial role during epilepsy. This process is considered to exert exceeding oxidative pressure to brains and give rise to further damage.

Astrocytes participate in inflammation largely via release of various cytokines which can initiate microglia migration and increase release of glutamate. It is remarkable that inflammation process can activate several gene mutation in astrocytes [6], which directly influence the expression of channels and receptors of astrocytes, thus disturb normal function of astrocytes and induce epilepsy. It is important that genetic alterations are involved in such process. Such alteration offers new clues and targets for scientists to reveal mechanisms behind epilepsy, as will be discussed in later part. Basically, astrocytes can release kinds of cytokines: interleukin-1-beta (LK-1b), tumor necrosis factor-alpha (TNF-a).

Besides, astrocytes also express toll-like receptors, which can recognize and react to microbes [7]. The activation of this receptor can lead to release of NF-kB and trigger an increase of glutamate. The glutamate release mentioned here is considered as one of causes of hyperexcitation.

2.2. Microglia

Microglia is a kind of glial cell which actively patrol brains continuously even when brains are in static status. They patrol brains as immune cells. Their activity is highly associated with calcium concentration's fluctuation correlated to neuronal activities. After excitation or inhibition of neurons, coming after a short delay, the activity of microglia will also go through same process, which refers to synchronized excitation and inhibition. researchers believe that such delay is a result of signal extension.

After an insult to brain like seizure occurrence, microglia will be activated by astrocytes and go through a process called "microgliosis". This process is characterized by a range of alteration: microglia proliferation and migration, change in cell shape, alteration in gene profile. Such activation can devote to recover homeostasis of brain tissues. However, this behavior is considered counterproductive because activated microglia attempt to cease phagocytes of impaired cells, as the consequence, hamper the repair of epileptic tissue. However, at the same time, microglia can release anti-inflammation cytokines as well. In a nut shell, microglia play a double-sided role during epilepsy. Besides, microglias are also able to release cytokines such as interleukin-6, interleukin-1-beta and TNF-a, which can increase hyperexcitation of neurons and exert plethora oxidative pressure to brains.

2.3. Oligodendrocyte

Oligodendrocytes are glial cells who are responsible for myelination of neurons. This myelination is very crucial for normal function and signal transportation within axons. By forming sheathes wrapping axons of neurons, myelination can prevent electrical signals from leakage. Thus, guarantee stability of signal transportation. Besides, water channels along with potassium channels are expressed in oligodendrocytes, demonstrating their responsibility in regulating neuron metabolisms. Scientists have found astrocytes and oligodendrocytes together reside in panglial syncitiums. They are connected by gap junctions and assist siphoning of potassium ions into blood vessels. Apart from their metabolic responsibility, oligodendrocytes are demonstrated to participate glutamatergic transmission in CNS and express glutamine synthetase. Different from old perception, oligodendrocytes are now considered involved in epilepsy, as will be mentioned in later part.

3. lesion and dysfunction of glial cells in epilepsy

3.1. Cytokines

Epilepsy is known to be associated with inflammation [8]. Inflammation is able to induce epilepsy to healthy brains, so as other factors like seizure occurrence. A wide range of cytokines are released by both astrocytes and microglias after insults to brains like seizure occurrences. Such release of cytokines intends to initiate inflammation. However, the release of cytokines is double-sided in epileptogenesis, and, largely counterproductive. In epileptic tissue, activated microglia is one of the main sources of pro-inflammation cytokines such as TNFa, interleukins-1b, interleukin-6.

Via up-regulation of NMDA receptors at post-synaptic level, interleukin-1b can exacerbate epileptic condition in brains. Scientists have found the responsibility of interleukin-1b to neuronal dysfunction. Besides, interleukin-1b can decrease GABA mediated neurotransmmision, which impair inhibition and give rise to hyper-excitation [9].

Like the efficacy of interleukin-1b, TNFa also function as a type of inflammatory cytokines which can influence both inhibition and excitation in neurons. By acting on glutaminases and gap junctions, TNFa is able to increase glutamate release of microglia and inhibit glutamate uptake. Besides, TNFa is able to boost GABA receptor endocytosis [10]. The loss of GABA receptors and impairment of GABAergic transmission can lead to a decreased inhibition and give rise to hyper-excitation. The release of TNFa and interleukin-1b can together lead to the release of interleukin-6, which can exacerbate epileptic condition by boosting microgliosis and inhibiting neurogenesis in hippocampus. Because microglias are primarily responsible for the production of mentioned cytokines, microgenesis is observed to be detrimental. It is noticeable that microglias are also capable to release anti-inflammation cytokines like Arg-1; IL-4; IL-10.

Moreover, inflammation can lead to a series of alteration on many membrane proteins by changing their encoding genes [6]. Such effect is very significant because the alteration in gene expressions largely account for numbers of important abnormalities which will be discussed in later part such as redistribution of AQP4 and Kir4.1.

3.2. Water channels, potassium channels, cell swelling

In a majority of cases with TLE and MTS, loss of water channels and potassium channels are reported. These channels are expressed at end feet of astrocytes connecting blood vessels abundantly populated with neurons. During epilepsy, astrocytes go through a series of lesions which alter their gene sequences and functional structures. Among these lesions, disturbance of regulation of extracellular space is detrimental. The redistribution and loss of water channels and potassium channels (overwhelmingly majority of them are AQP4 and Kir4.1) can lead to damage of the homeostasis. The inability of completely implementing the transportation of potassium and water down the concentration out of cell bodies can lead to swelling of astrocytes. It still remains controversial whether the loss and reorganization of Kir4.1 and AQP4 is the consequence of seizures. For instance, Huntington disease also gives rise to such syndrome. The swelling of astrocytes can lead to the activation of volume-gated channel in astrocytes. This activation can give rise to release of glutamate into extracellular space. Glutamates are highly cytotoxic remained in neuronal clefts at high concentration, which can lead to epilepsy.

3.3. Glutamate metabolism

Down-regulation of glutamate transporters located on the surface of astrocytes, along with the down-regulation of glutamine synthetases are reported in number of cases such as patients with MTLE-HS [11]. This alteration will exacerbate the epileptic condition by impairing the removal of glutamate in neuronal clefts. At the same time, dysfunction of AQP4 channels can directly influence glutamate uptake due to disrupted equilibrium concentration near membrane, and, increased expression of glutamate receptors is reported in TLE models [12].

3.4. Gap junction

Gap junction are responsible for connection between astrocytes in Astro-syncitiums [13]. They can allow the transportation of kinds of molecules and second messengers like ATP; glutamate and calcium ions [14]. The very crucial redistribution of potassium and calcium ions are conducted by gap junctions among astrocytes. Nevertheless, gap junctions play a complicated and ambivalent role in epilepsy. Many studies have found the up-regulation of GJ mRNA in astrocytes. This alteration is assumed to partially account for the seizure generation and hyper-excitation of neuron networks. Scientist believe that the up-regulation of GJ and correlated proteins can facilitate the diffusion of messengers and signal molecules like ATP or glutamate in syncitiums and neuron networks [15]. At

the same time, some studies found loss of gap junctions after status seizure in animal models and patients. Besides, some experiments have demonstrated that the knockoff of rats' gene coding for gap junction along with Kir4.1 and AQP4 can lead to epilepsy.

3.5. Adenosine and adenosine kinase

Adenosine is a very important inhibitory neurotransmitter in humans' brains. They are resultants of hydrolyzed ATP released into extracellular space. Adenosines will be captured by nucleoside transporters in extracellular space and degraded by adenosine kinase in astrocyte cell bodies. Scientist have found up-regulation of adenosine kinase in epileptic models, which is considered to be responsible for the impairment of inhibition in brains. Adenosine is demonstrated to be anticonvulsant.

3.6. Adenosine triphosphate

The character and function of adenosine triphosphate in neuron networks is controversial and complicated. Adenosine triphosphate can act like a type of neurotransmitter. They can activate P2Y1 receptors and stimulate the release of calcium ions via gap junctions, which can further trigger the release of glutamate from astrocytes' cell body. However, in different extracellular concentration, targeting on different types of receptors, its function may be various. The release of adenosine triphosphate from pannexon-1 channels can contribute to epileptic activity in tissues acquired from epileptic zones of patients.

3.7. Microglia-neuron and microglia-astrocyte interaction in epilepsy

In KA-induced status epilepticus, scientists have found increasing interaction between neurons and microglias in CA1 region in hippocampus. Such interaction between microglia and neurons has been deeply investigated, however, scientist still know little about the mechanism under the condition that neurons are hyper-excited. Summarized from what scientists have observed, ATP and purinergic receptors is crucial in interaction between microglias and astrocytes. P2Y12 receptors on microglias can be activated by ATP released by neurons after status epilepsy, by which can increase microglia motility and boost interaction between microglias and neurons. Researchers have demonstrated that P2Y12 knock-off mice possess lower epileptic threshold that normal mice, indicating that P2Y12 receptors have helpful effect on curbing epilepsy.

Admittedly, the function and role of microglias is relatively complicated. Scientists have not figured out complete mechanisms revealing how microglias function. Partly this is because microglia play a double-sided role in epilepsy. Depending on the phase of lesion, region involved and different signals triggering them, they can exert both anti-epilepsy and pro-epilepsy effect to abnormal tissue. However, we have understood that neuron system is a highly cooperated and tightly-associated network, in which millions of microglias, astrocytes, neurons cooperate under very subtle mechanism. Their function and effect in epilepsy should not be considered separately, but in a view constructed on networks they shaped. Scientist have to put microglia into their networks and initiate further research, which can probably contribute to break through shedding light into darkness of contemporary knowledge.

3.8. Oligodendrocytes is complicated

Oligodendrocytes are basically responsible for myelination and wrap axons of neurons. In the past, scientists perceive them as only supportive and myelinating cells of neurons. However, more and more studies have revealed that oligodendrocytes participate in epilepsy, even though scientists primarily considered epilepsy as a disease only involved gray matters. Lesions in white matters have been observed and confirmed in patients with epilepsy in a recent neuroimaging study involving an immense group of test takers and standardized process.

Myelination is recently considered associated with epilepsy. Researchers studying in both focal and multi focal epileptic models have found abnormalities of myelination after electrical stimulation. New research using Wag/Rij rats and Scn8a+/mut mice found that activity-dependent myelination

resulting from absence seizures may contribute to epilepsy progression. Authors found increased oligodendrogenesis and myelination specifically within the seizure networks in the two models of generalized epilepsy with absence seizures, evident only after epilepsy onset.

Potassium homeostasis in white matters is maintained by oligodendrocytes, and such maintenance is associated with epilepsy. In mice whose Kir4.1 gene is knocked off, epilepsy is found. The damage to potassium buffering function of oligodendrocytes can lead to seizures. Such damage can impair the neurons' ability to remove potassium channel and decrease the efficiency of electrical signaling because recovery of axon concentration homeostasis is delayed. Lots of experiments have revealed new mechanism for epileptogenesis. This development in pathology paves the way for Appropriate diagnosis and prescription and possible drug designs targeting on refractory seizures.

What is more, scientist have located gap junctions in oligodendrocytes which can participate in glutamateric transmission. Oligodendrocytes are demonstrated to be associated with glutamate level in brains. They are showed to be able to regulate glutamate transportation apart from astrocytes. Loss of regulation of glutamate and subsequent hyper-excitation is identified as crucial cause of epilepsy. Removal of gap junctions in mice can contribute to decreased glutamate and glutamine levels. The role whose supportive function to glutamate regulation of oligodendrocytes is very appealing, searching on which can offer new thread and mechanism in treating epilepsy. More studies are acquired in molecular mechanism of this regulation.

4. Possible drug designs targeting on astrocytes abnormalities

4.1. Contemporary AED

Epilepsy researches mainly focus on how to inhibit abnormal electrical brain discharges, which lead to treatment options targeting neurons. Various anti-epileptic drugs enhancing inhibitory GABA or P1 adenosine transmission systems show their efficacy by modulating neuronal voltage-dependent sodium, calcium and potassium ion channels to suppress excessive neuronal activity.

Due to the limitation of contemporary science and devoid understanding to epilepsy, most of anti-epileptic drugs are designed to recover homeostasis within neurons. Number of AED has increased a lot in past decades but the underlying principle remained similar. They are highly useful in clinical treatment of epilepsy, but, bout 30 to 40 percents of patient react refractory to AEDs. This phenomenon is considered as the consequence of the interference of glial cells during epilepsy. More mechanisms and pathological principle related to glial cells which also go through lesions and abnormalities during epilepsy are found this decade. We hope to alleviate pain and recover tissue to their healthy condition. As the result, pharmaceutics and scientist insist on experimenting efficacy of AED targeting on glial lesions and discussing possible and viable medical plans.

4.2. Cytokines antagonists

Blocking interleukin-1b activity by means of antagonists, like interleukin-1b receptor antagonist, is efficacious to decrease seizure occurrence in MTLE models and in patients enrolled in a clinical study to treat febrile infection-related epilepsy. Same principle is considered to be efficient by blocking or neutralizing kinds of inflammatory cytokines.

4.3. Delivery of new channels

In Huntington disease, same problem of Kir4.1 and water channels are reported. It has been demonstrated that delivering Kir4.1 protein into astrocytes in order to promote expression of potassium channels is useful in alleviating Huntington disease. Having same problem in epilepsy, the loss of Kir4.1 channels and AQP4 channels can lead to astrocyte swelling and excessive glutamate release. Redistribution and loss of channel is substantial in epileptic models. As the consequence, it may be possible to recover normal channel systems and distribution by implantation of channel proteins, in order to recover homeostasis and concentration regulation.

4.4. Gap junction blockers

Plethora expression of mRNA coding for gap junctions is found in many epilepsy cases. This excessive expression will facilitate diffusion of signal molecule and ATP between astrocytes. Glutamate transportation are sped up by up-regulation of gap junction. Administration of gap junction blockers including carbenoxolone, mefloquine, quinine and quinidine are tested to be efficacious in curing severe seizures. It is noticeable that gap junctions also play double-sided role in epilepsy, as the consequence, researchers should be rigorous and meticulous testing drugs targeting gap junctions.

4.5. Glutamate regulation

In kinds of animal models of epilepsy, researchers have observed excessive glutamate release of astrocytes. And blocking astrocytic P2Y1 receptors are able to inhibit glutamate release. Besides, the down-regulation of glutamate transporters like EAAT1 can lead to hyper-excitation because it impairs neurons' ability to remove excitatory glutamate. An elegant study has showed that ceftriaxone is able to increase EAAT1 expression, thus, decrease glutamate level. This experiment indicated that targeting on glutamate transporters may have anticonvulsant effect, giving therapeutic suggestion to scientists.

4.6. Adenosine kinase antagonist and adenosine regualtion

Adenosine is a type of inhibitory neurotransmitter which is crucial for neuronal balance. They are captured by nucleoside transporters and degraded in astrocytes by their enzymes called adenosine kinase. Many studies have reported up-regulation of adenosine kinase in epileptic models and lead to insufficient adenosine remaining in neuron systems. As the consequence, scientist widely accept that adenosine is anticonvulsant. At the same time, adenosine kinase inhibitor is demonstrated to be also anticonvulsant. Targeting on the balance of adenosine and adenosine kinase, researchers have found a new pathway of recovering homeostasis.

Adenosine triphosphate, in another way, play very complex character in epilepsy. Interaction and kinds of phenomenon observed possess a high probability of cross-talking. An elegant study demonstrate that ATP as autocrine signal can activate P2Y1 receptors which can trigger calcium release and increase in glutamate release. As the consequence, P2Y1 antagonists become very intriguing for scientist testing their ability in epilepsy treatment.

4.7. Consider epilepsy curing in generalized viewpoint

What is noticeable is that causes of epilepsy are strikingly multiple. Just like cancer, external factor can be complicated, either chronic (bad habits or exposed to soot) or acute(radiation). In a final analysis, however, these external factors all lead to gene mutation, which further lead to irretrievable problems, like what happen to erroneous expression of channels and receptors.

Through decades of investigation, scientists believe that same mechanism is partially suitable for epilepsy. Abnormal discharge damage both tissues and genes, then lead to dysfunction such as down-regulation of mRNA of glutamate transporters. Besides, AQP4 and K+ channels are also expressed abnormally. Scientists believe future fields for epilepsy curing is genetic therapy. Only if we can restore cell’s gene, the dysfunction will be cured all for one time. Just like what we expect and experiment on cancers.

More and more clues have pointed to genes. Besides, to improve efficacy of current AEDs, designing new drug targeting on glial cells is necessary. Preceding part has demonstrated at a striking extent glial cells are responsible for epilepsy.

5. Summary

Decades’ effort of scientists has revealed major and important function of glial cells in brains. Abnormalities of tissues in epileptic brains deeply involve all types of glial cells. Kinds of factors, either chemical or physical, can lead to the abnormalities of glial cells. Some of these alterations are

morphological and some are genetic. These abnormalities will destroy balance between excitation and inhibition within brains and lead to hyper-excitation, and epilepsy is generated. Considering about limitations in epilepsy curing, two challenging and meaningful questions are offered: How to prevent epilepsy from happening? How to restore tissue's healthy condition and normal function? Epilepsy is different from cutting fingers. Direct relationship between a single cause and subsequent epilepsy is vague and correlation between various cause are found. Human's desire of curing epilepsy will no way be satisfied by just slowing down the process or alleviating the symptoms, instead of curing it for all. Firstly, in order to improve AEDs' efficacy and decrease their side-effects, AEDs need to be expanded and designed to solve glial problems. Such improvement and innovation have to base on what researchers have observed, closely related to abnormalities of glial cells we have demonstrated. Secondly but very crucial, human's view of glail cells has to be deep down into genetic level, which means, rectifying gene alterations which can generate epilepsy. Contemporary AEDs can only neutralized cell dysfunction. In the future, researchers will focus on genetic therapy in order to eliminate such disease. This idea is challenging but very promising considering about genetic therapies' breakthrough in other diseases.

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