

REVIEW

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The role of picornavirus infection in epileptogenesis



Runxuan Zhang¹, Jie Mu², Jing Chi³, Weijia Jiang⁴ and Xiaosa Chi^{5*}

Abstract

Picornaviridae are a family of small positive-strand RNA viruses, and transmitted via the respiratory or fecal-oral route. The neurotropic picornaviruses can induce acute or late recurrent seizures following central nervous system infection, by infecting the peripheral nerve, crossing the blood-brain barrier and migrating in the Trojan-horse method. Theiler's murine encephalomyelitis virus (TMEV), as a member of *Picornaviridae* family, can cause encephalitis, leading to chronic spontaneous seizures. TMEV-infected C57BL/6 mice have been used as an animal model for exploring the mechanism of epileptogenesis and assessing new antiepileptic drugs. Astrogliosis, neuronal death and microglial recruitment have been detected in the hippocampus following the picornaviruse-induced encephalitis. The macrophages, monocytes, neutrophils, as well as IL-6 and TNF- α released by them, play an important role in the epileptogenesis. In this review, we summarize the clinical characteristics of picornavirus infection, and the immunopathology involved in the TMEV-induced epilepsy.

Keywords: *Picornaviridae* infection, Theiler's murine encephalomyelitis virus, Seizure, Immune response

Background

Epilepsy is one of the most common neurological disorders that affects over 70 million people worldwide [1] and leads to 13 million disability adjusted life years each year. Epilepsy can also cause cognitive and psychosocial impairment [2]. According to the new classification of epilepsies by the International League Against Epilepsy in 2017, the etiology of epilepsy can be structural, genetic, infectious, metabolic, immune or unknown [3]. Emerging evidence has demonstrated that the viral infection plays a role in the epileptogenesis, especially in developing countries [4, 5]. The incidence of acute seizures in encephalitis patients following the infection of neurotropic viruses varies from 7 to 67%, depending on the type of virus [6]. Besides, the status epilepticus in the acute stage of viral encephalitis can be life-threatening [7]. Furthermore, patients who survived from viral encephalitis are 16 times more likely to develop late unprovoked seizures [8–10]. Currently, there is a lack of

sufficient evidence for the use of anticonvulsant prophylaxis for acute and late seizures in viral encephalitis [11]. Thus, intensive investigation of the mechanisms of seizure induced by viral infection may provide insights into the prevention of seizures following viral encephalitis.

To date, over 100 viruses have been reported to be associated with epileptogenesis, such as human herpes virus type 6, influenza A virus, rotavirus and picornaviruses [12]. As one of the largest viral families, *Picornaviridae* contains 54 species of small positive-strand RNA viruses, and is transmitted through the respiratory or fecal-oral route [13]. Some of the picornaviruses are neurotropic and can cause fatal encephalitis and meningoencephalitis concurrent with seizures [14, 15]. For animals, C57BL/6 mice infected by the Theiler's murine encephalomyelitis virus (TMEV) have been shown to suffer recurrent seizures following polioencephalitis, and can be used as an animal model to explore the underlying mechanisms of epileptogenesis [16–18]. In this review, we will summarize the clinical characteristics of seizures induced by picornaviruses and the mechanisms of epileptogenesis triggered by TMEV infection.

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Picornaviruses that induce seizures

Rhinoviruses, enteroviruses and parechovirus are picornaviruses commonly detected to induce encephalitis with seizures [19–22]. Neurotropic picornaviruses can infect the peripheral nerve, cross the blood-brain barrier (BBB) and migrate in the Trojan-horse manner, thereby infecting the central nervous system (CNS) [14, 23–25].

Human rhinovirus (HRV) is a common cause of respiratory infection. Seizures can occur in 22.7% of patients with HRV infection, which is higher than the other viruses in the respiratory tract [26]. Seizures mostly occur in patients with underlying neurological abnormalities or a history of seizure [26], although the mechanisms remain unknown. However, several causes for the seizures in the context of HRV infection have been proposed. For example, cytokines, such as interleukin-6 and interleukin-1, are related to the development of seizures [27]. The direct viral infection may also promote this process.

Human parechoviruses (HPEVs) belong to the *Parechovirus* genus of the *Picornaviridae* family [28]. HPEV infections are often associated with gastrointestinal and respiratory symptoms, but the encephalitis caused by HPEV3 with concomitant seizures have been reported in infants. In most patients, the development of seizure outbreak is followed by repeated seizures with an average interval of 9.5 h between the first and last seizures [29]. Central apnea and focal neurological signs have been described in some young infants with seizures [21]. The initial seizure symptom is often accompanied by multiple white matter lesions [30].

Coxsackievirus and other enteroviruses are the most possible cause of myocarditis. Epidemiological evidence has shown that infants with coxsackievirus infection present with high mortality, while young adults may have a self-limited disease. In an earlier report, a 14-month-old child infected by coxsackievirus B who was ultimately diagnosed as myocarditis presented with a tonic-clonic seizure as the prominent symptom [31]. In addition, the seizure occurred without fever, so it was identified not a febrile seizure. The cause of seizure in the patient may be related to transient hypoxia that resulted from supraventricular arrhythmia or heart block or cardiogenic embolism to the brain [32, 33]. However, the direct evidence of brain invasion by coxsackievirus was not found. However, this report suggested that seizure could be an initial presentation of myocarditis, which is important for the early diagnosis and treatment of myocarditis.

The infection with hepatitis A virus is a self-limited disease. However, in a 5-year-old patient infected with hepatitis A virus who complained the convulsions, RNA of hepatitis A virus was detected in the cerebrospinal fluid, which supported that the seizure activity resulted

from hepatitis A virus infection [34] via toxic metabolic product accumulation and direct effect of the virus.

TMEV-infected acute seizures or epilepsy

Description of the TMEV-induced model

TMEV is a member of the *Cardiovirus* genus in the *Picornaviridae* family. In C57BL/6(B6) mice, TMEV infection is considered not to cause demyelinating disease, and the virus will be cleared in the early stage of acute encephalitis [35], while the TMEV-infected SJL mice are susceptible to demyelination and are used as a model of multiple sclerosis [36]. The strains of TMEV can be divided into two subgroups based on their neurovirulence after intracerebral inoculation: the less neurovirulent Theiler's original (TO) group including the TO, Daniels (DA), BeAn 8386 (BeAn) and WW strains, and the more neurovirulent GDVII group including the GDVII and FA strains, which can induce fatal polioencephalomyelitis in short time in adult mice. In addition, a recent study characterized the geno- and phenotype of two naturally occurring variants of BeAn 8386 (BeAn-1 and BeAn-2) in the SJL/J and B6 mice, and found that the BeAn-1 substrain was more neurovirulent in SJL/J mice while BeAn-2 was more virulent in C57BL/6 mice [37]. These findings highlight that relatively minor variations in nucleotide sequence can lead to marked differences in neurovirulence.

A previous study showed that almost 51% of the C57BL/6 mice had transient afebrile seizures within 3 to 7 days [17]. Besides, TMEV infection also induced chronic seizures and altered seizure susceptibility [38]. The mice that develop seizures survived from the acute encephalitis and cleared the virus by 14 days after the infection with TMEV [39]. As to the frequency, the acute seizure lasted for 1 to 2 min during 2-h observation [17]. In addition, the percentage of C57BL/6 mice that developed seizures with DA strain infection is associated with the initial viral dose [39]. The TMEV-infected animals are likely to present with anxiety behaviors, poor performance in novel object exploration and impairment of episodic and spatial memory. Those psychoses have also been found in patients with epilepsy at a higher rate than the normal subjects [40]. Long-term video-EEG shows that a large proportion of TMEV-infected mice with epileptic episodes have experienced a distinct latent period in which no obvious seizures occur before the development of severe spontaneous epileptic seizures at 2, 4, and 7 months of age [41]. EEG recording further revealed that the frequency of EEG spikes and spike clusters are higher in the DA-infected C57BL/6 mice with chronic seizures than in the infected mice without seizures [42]. Moreover, the TMEV-induced mice have dramatic cell death and gliosis in CA1 and CA2 pyramidal regions, but not in CA3 [17, 38], which is similar with

the hippocampal sclerosis in patients with infection-induced temporal lobe epilepsy (TLE) [41]. These two prominent features are critical for the development of epilepsy and are considered to be a potential target for screening of patients for treatment [43]. Specifically, the gliosis includes astrogliosis and microgliosis [44].

The immune component involved in TMEV-induced seizures

Monocytes and granulocytes

In early studies, researchers noted that monocytes contributed to the development of epilepsy [35]. Peripheral circulating macrophages can infiltrate into the brains of the TMEV-infected mice at the onset of epilepsy, which is critical for epileptogenesis [45]. The similar situation has been observed in patients. The infiltration of monocytes has been found in the hippocampus of mesial TLE patients based on the biomarker CD45 [45]. The activated monocytes destroy the BBB, which increase the permeability of vessels to trigger the death of neurons and the generation of seizures [46]. A study monitored the kinetics of leukocyte infiltration during the first 48 h after TMEV infection, and found that the inflammatory monocytes appeared earlier than neutrophils [47]. Depletion of inflammatory monocytes and neutrophils resulted in the preservation of the hippocampus and maintenance of cognitive performance while depletion of neutrophils alone did not make any difference [48]. The administration of clodronate liposome that causes partly depletion of infiltrating macrophages by apoptosis in peripheral blood and the spleen decreases the rate of acute seizures in the TMEV-infected mice. But hippocampal damage seems not to be prevented. At the same time, the quantity of activated microglia in specific brain regions such as the hippocampus is found to increase as a response to the inhibition of macrophage infiltration. Indeed, microglia may have a protective function as they inhibit the development of seizures [49]. The different roles of infiltrating macrophages and microglia (resident cells) need to be explored deeply. The intrinsic relationship between infiltrating monocytes, neutrophils and macrophage is a critical element in the brain parenchyma injury. All of these cells are underlying points for the neuron protection and other comorbidities.

Therefore, the TMEV-induced mice are considered as an animal model that presents with many of the characteristics of encephalitis-induced human TLE, which can be used to investigate the relationship between inflammation and epilepsy. An obvious advantage of this model is that animals survive from the acute epilepsy, so the following research on chronic seizure can be carried out. In addition, neuronal degeneration in the CA1 pyramidal layer can be observed at 4 days post infection (dpi), while neurons were almost completely lost in the

layer at 14 dpi [17, 41]. In another research, caspase-associated apoptosis has been found in CA1 neurons at 1 to 2 dpi, which may result from the oxidative stress, and this event has proceeded to the end stage of apoptotic cascade by 4 dpi. However, the apoptosis may not be mediated in a cell-autonomous manner, but be pathologically caused by the disruption of hippocampal circuits [50]. Seizures are results from the decreased inhibitory neural CA3 networks during the acute period [51]. However, increased excitation occurs both during the early infection and at 2 months later, when spontaneous epilepsy occurs in the exciting CA3 circuits [52]. The two different mechanisms suggest application of diverse treatments in the virus-infected patients.

Cytokines

Oxidative and nitrosative damage caused by decreased GSH and an increase in 3NT level are pivotal factors that lead to cell death in the hippocampus. The increase in 3NT levels indicates that the reactive oxygen species/reactive nitrogen species-induced post-translational modification may promote the occurrence of epilepsy [53]. In fact, the alteration of oxidative status is influenced by the direct viral damage. In addition, the increased levels of cytokines, chemokines, complements and other inflammatory mediators can also cause damage to mitochondria, resulting in oxidative stress, especially IL-6 and TNF- α .

The mRNA and protein levels of TNF- α are increased during acute epilepsy in the TMEV-infected animal model. The protein expression ratio of TNF receptors (TNFR) (TNFR1:TNFR2) is augmented as well. TNF- α can exert completely opposite functions through different receptors, including TNFR1 and TNFR2. TNF- α binding to TNFR1 can activate caspase-3, inducing apoptosis. TNFR2 mediates cell protection from apoptosis, resulting in the expression of inflammatory mediators and anti-apoptotic proteins. The two receptors also have cross talks and cooperate to transmit signals [54]. TNF- α may strengthen excitatory synapses via TNFR1 to increase the excitability in the hippocampus, while TNFR2 may provide adverse effects during acute infection [55]. In addition, mice without TNFR1 show inhibited seizures in this model, consistent with that in the chemical-induced seizure model (kainic acid seizure model) [45, 56].

It has been reported that the TMEV-infected mice lacking IL-6 may have reduced seizures, different from that in the kainic acid-induced mice [57]. This discrepancy may be explained by the different agents used to induce seizure, the different roles inflammatory mediators play, and the different genetic backgrounds of mice. IL-6 functions in the development of acute epilepsy to decrease group-II metabotropic glutamate receptors

(mGluR2/3) and the AMPA receptor subunit 2 (GluA2) to increase glutamate release into the synapse, leading to strengthening of neuronal excitability [18]. Both resident CNS cells and infiltrating cells, which are recruited by chemokines, are important for the production of IL-6 in the brain and the development of seizures. Furthermore, macrophages are more likely to produce IL-6 standing for the infiltrating cells, while microglia and/or astrocytes are more likely to produce IL-6 standing for the resident CNS cells [58]. The main factors IL-6 and TNF- α are produced by both macrophages and microglia [59]. In particular, IL-6 mainly comes from infiltrating macrophages and microglia release TNF- α , inducing the onset of inflammation and then seizures. As mentioned above, the increased microglia can inhibit the macrophage infiltration, while the number of infiltrating macrophages does not decline.

Lymphocytes

The attack of T cells is also an important component of the immune system for viral clearance. However, CD8+ T cells are not the driving force to stop epilepsy by killing TMEV in OT-I mice (ovalbumin-specific CD8+ T cells) [45]. Above all, it is the innate immune response, rather than the adaptive immune response, that functions in the reduction of seizures.

Complement

The complement system, especially component 3 (C3), plays an important role in innate immune system. In addition, C3 can be released by many cells in the CNS, for example, astrocytes, microglia, neurons, and oligodendrocytes [60, 61]. After viral infection in the CNS, the expression of complement proteins is elevated [62]. Some researchers used C3-deficient C57BL/6 mice or depleted C3 in the periphery of C57BL/6 mic to evaluate whether C3 accelerates the process of seizure generation. No significance difference has been found between the C3-depleted mice and normal mice. The findings indicate that the activation promotes the development of seizures, which is not influenced by C3 in the periphery. The contribution of complement may be through the release of IL-6 and TNF- α [63].

Anti-inflammation treatment may slow down the process of epilepsy, or in other words, be disease-modifying. In contrast, drugs with direct antiseizure activity may reduce the presence of symptomatic seizures, without altering the disease at the initiation time [64].

As the drug resistance issue in the treatment of patients with epilepsy has been receiving more and more attention, a stable infection model such as the TMEV model is essential for the evaluation and modification of antiseizure agents. Many questions concerning chronic

spontaneous seizures, particularly the molecular mechanisms, remain unanswered.

Treatment assessment

Minocycline (MIN) and valproic acid (VPA) affect epilepsy through different nodes in anti-inflammation. MIN treatment reduces microglial activation, which alleviates the long-term epileptogenic process [65]. MIN also decreases the number of infiltrating macrophages by approximately 2-fold. TNF- α , which is mostly produced by microglia and IL-6, which mainly comes from infiltrating macrophages, are also decreased by administration of MIN. The prolonged treatment with VAP has a neuroprotection effect through inhibition of histone deacetylase (HDAC) activity, leading to the low expression of GAPDH. Thus, the nuclear translocation of GAPDH that is related to cell apoptosis is decreased [66]. VAP at therapeutic doses can mitigate the acute seizure burden [67]. However, low-dose VAP did not show an obvious influence on the chronic epilepsy after TMEV infection, suggesting that VAP does not participate in the development of seizures. However, the MIN-treated mice showed improvement in long-term behavior and decreased seizure threshold [64].

Carbamazepine (CBZ) is one of the traditional anti-seizure drugs. It is intriguing that the number of CBZ-treated mice with seizure presentation increased compared with the vehicle-treated mice. In another word, CBZ exacerbated the infection of TMEV, making animals more susceptible to the virus [67]. CBZ has been found to contribute to the immunological defects and induce lymphopenia [68]. CBZ has also been shown to provoke epilepsy after Herpes simplex encephalitis in clinical studies [69]. As to the long-term comorbidities, administration of CBZ during the acute infection period also lead to development of behavioral impairments, such as worse anxiety behavior and spatial memory deficits. Not all traditional antiseizure drugs can be used for infection-induced seizures. These studies indicate that anti-inflammatory agents may be a preventive strategy for future epilepsy. The TMEV-infected animal model provides a platform to study the mechanism of epileptogenesis and to evaluate the disease-modifying functions of compounds.

Wogonin isolated from *Scutellaria baicalensis* has been found as an antiepileptic reagent. Wogonin functions through enhancement of GABA binding with the γ subunit [70], and has less adverse effects than diazepam such as sedative and muscle relaxant effects [71]. In the TMEV-infected animal model, wogonin exerts an anti-inflammatory effect like MIN. Wogonin can decrease the number of mice with epileptic episodes by inhibiting the activated macrophages targeted by the IL-6-producing cells [67]. The relationship between

inflammation and GABA or other neurotransmitters like norepinephrine, dopamine, and serotonin remains to be investigated.

Not only infiltrating macrophages are important components in the development of seizures following TMEV infection, but inflammatory cytokines are also critical factors in TMEV-induced seizures. Increased metabotropic glutamate receptor 5 in the hippocampus has been found in resected brain tissues from TLE patients, consistent with that in the TMEV-induced mice from 3 dpi to 14 dpi [72, 73]. Administration of VU0360172, a selective positive allosteric modulator, can reduce the acute seizures 3 days post infection through the TNF- α pathway, suggesting that VU0360172 have a neuroprotective function. However, the long-term treatment (8 dpi) did not induce a significant reduction [73].

Conclusions

Seizure represents a serious burden for individuals, families and the society. The acquired seizures, especially the encephalitis-associated seizures, should be prevented, ameliorated, and inhibited in the early stage. But the mechanisms of epileptogenesis are illusive. Unfortunately, there are many patients resistant to antiepileptic drugs. The traditional drugs are facing a rigorous challenge, and discovery of more targets is needed.

TMEV, which has been successfully used to establish a TLE model in the C57BL/6 mice, belongs to the *Picornaviridae* family. This model can be used as a tool to investigate the detailed components that may influence the process of seizure generation and to evaluate antiepileptic drugs. Some viruses of the *Picornaviridae* family can cause seizures as a prominent or atypical symptom, which should receive more attention.

The induction of seizures by virus infection in both mice and humans is directly caused by the excessive inflammation, which could lead to irreversible tissue damage, forming a big strike for limited regeneration of organs. Therefore, therapeutic strategies should focus on the inhibition of immune response and the innate response, which are critical for the development of seizures.

Abbreviations

3NT: 3-nitrotyrosine; AMPA: α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid; BBB: Blood-brain barrier; CBZ: Carbamazepine; CNS: Central neurological system; DA: Daniels; dpi: Days post infection; EEG: Electroencephalogram; GABA: γ -aminobutyric acid; GAPDH: Glyceraldehyde-3-phosphate dehydrogenase; GluA2: Glutamate AMPA receptor subunit 2; GSH: Glutathione; HDAC: Histone deacetylase; HPEVs: Human parechoviruses; HRV: Human rhinovirus; IL-6: Interleukin-6; mGluR: Metabotropic glutamate receptors; MIN: Minocycline; OT-I: Ovalbumin-specific CD8⁺ T cells; TLE: Temporal lobe epilepsy; TMEV: Theiler's murine encephalomyelitis virus; TNF- α : Tumor necrosis factor- α ; TNFR: TNF receptors; TO: Theiler's original; VPA: Valproic acid

Acknowledgements

Not applicable.

Authors' contributions

XSC designed the review, and revised the manuscript. RXZ and JC conducted the systematic search and extracted the eligible studies. RXZ drafted the study. JM and WJJ revised the manuscript. All the authors read and approved the final manuscript.

Funding

This study was supported by the National Natural Science Foundation of Shandong, China (ZR2019PH040) and the National Natural Science Foundation of China (81901321).

Availability of data and materials

Not applicable.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

All authors gave consent to publication of this review.

Competing interests

The authors declare no conflicts of interest.

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Received: 12 August 2020 Accepted: 18 March 2021

Published online: 29 March 2021

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