Neurodegenerative Proteins in Epilepsy

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Lack of disease-modifying therapy against epileptogenesis reflects the complexity of the disease pathogenesis as well as the high demand to explore novel treatment strategies. In the pursuit of developing new therapeutic strategies against epileptogenesis, neurodegenerative proteins have recently gained increased attention. Owing to the fact that neurodegenerative disease and epileptogenesis possibly share a common underlying mechanism, targeting neurodegenerative proteins against epileptogenesis might represent a promising therapeutic approach.

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1. Introduction

Epileptogenesis refers to the gradual process by which the normal brain develops epilepsy. It involves an early brain-damaging insult, which prompts a cascade of molecular and cellular alterations that might ultimately lead to the occurrence of spontaneous seizures [1]. Epilepsy is a devastating brain disorder exhibited by an enduring susceptibility to induce epileptic seizures [2]. It is characterized by the occurrence (more than 24 h apart) of two unprovoked seizures, a single unprovoked seizure with a high risk of relapse, and the appearance of epileptic syndrome [3]. Epilepsy is caused by abnormal coordinated firing of neuronal cells mainly due to disparity among excitatory and inhibitory neurotransmission [4]. Epilepsy has emerged as a serious global health concern affection around 70 million individuals of the population worldwide [5]. There is an increased understanding that epilepsy does not merely exist alone, and it is always associated with other neurobehavioral comorbidities, including cognitive impairment, depression, anxiety, schizophrenia, autism, etc., possibly sharing a bidirectional relationship [6][7]. Epilepsy is a disease where people at risk can be identified but nothing can be done to halt or prevent the disease progression [8]. Despite the availability of around 30 United States Food and Drug Administration (USFDA) approved anti-epileptic drugs (AEDs) [9], these drugs only provide symptomatic relief rather than halting/terminating the disease progression. This clearly reflects the complex pathology of epilepsy, reflecting the further extensive need for pre-clinical and clinical research.

Though the precise cause of epilepsy is still elusive, seizures might be the consequence of any insult that disturbs the normal brain function. These insults comprise of acquired causes (stroke or traumatic brain injury), infectious (such as neurocysticercosis), and autoimmune diseases, as well as genetic mutations, etc. [2]. There is an increased understanding of the contribution of neuroinflammation, channelopathies, neurodegeneration, neurogenesis, neural reorganization, and plasticity in epilepsy [10][11]. In recent years, several findings have repeatedly reinforced the role of neuroinflammation in epilepsy [7][12][13], indicating that targeting brain inflammation

might be a possible therapeutic strategy against epilepsy. Similarly, traumatic brain injury (TBI) also leads to post traumatic epilepsy (PTE) [14][15]. However, the time duration that the TBI leads to PTE is not well understood, with different existing opinions regarding the percentage that develop epilepsy after TBI. Epilepsy also exhibits idiopathic "*genetic*" etiology or symptomatic "*acquired*" elements. Several susceptibility genes encoding ion channels, including voltage-gated sodium, potassium, and calcium channels, have been unraveled from genetic investigations [11]. Mutations in three alpha subunit genes (*SCN1A*, *SCN2A*, *SCN8A*) of the voltage-gated sodium channels (VGSCs) have been implicated in epilepsy [16]. Voltage-gated potassium (Kv) channels, calcium-activated potassium channels, inwardly rectifying (Kir) channels, and tandem pore domain (K2P) channels have also been implicated in epilepsy [17]. The high-voltage-activated (HVA) $Ca_{v2.1}$ (P/Q-type) channel, encoded by *CACNA1A*, has been associated with early onset epileptic encephalopathy [18].

Neurodegeneration taking place near the epileptogenic regions may induce neuroinflammatory response, network re-organization, and/or a series of molecular changes that may contribute to the transformation of the normal brain to an epileptic state, i.e., temporal lobe epilepsy (TLE) [19]. During epileptogenic phenomena, neurodegeneration mainly occurs in the hilus, cornu ammonis (CA)1, CA2 and CA3 pyramidal cell layer, and granule cells. Besides the hippocampus, neurodegeneration also occurs in the amygdala; the neighboring entorhinal, perirhinal, and para hippocampal cortices; the thalamus; and the cerebellum [20]. Neuroinflammation and excitotoxicity can result in neuronal loss [21], ultimately leading to changes in the hippocampal networks that account for epileptogenesis [22], further suggesting that the manipulation of neurodegenerative phenomena by inhibition of inflammation and excitotoxicity may limit the disruption of the hippocampal circuitry and the progression of epileptic seizures [23]. Moreover, there is evidence that neurodegenerative diseases and epileptogenesis after an acquired brain insult might share a common underlying mechanism [24].

2. Aβ-Mediated Neurodegeneration and Its Implication in Epilepsy

The β- and γ-secretase cleavage of amyloid precursor protein (APP) generates Aβ, which is the key component of senile plaques and, along with abnormal Aβ accumulation, represents the hallmark of Alzheimer's disease (AD). APP is a membrane-spanning protein exhibiting a large extracellular domain and a smaller intracellular domain. APP is acknowledged as the key source of the Aβ peptide observed in the neuritic plaques of AD patients and is a functionally crucial molecule in its full-length configuration, as well as being the source of several fragments with variable effects on neural function [25]. APP was shown to exert crucial physiological roles in the mammalian brain mainly by regulating the synaptic functions and neuronal survival, and even modulating GABA neurotransmission [26]. APP is extensively investigated against AD pathogenesis due to its role in the disease's pathogenesis through the generation of toxic Aβ aggregates, potentially initiating neurodegeneration [27].

Progressive neurodegeneration, with subsequent cognitive and behavioral impairments, characterizes AD pathogenesis. Aβ aggregation into oligomers and eventually into fibrils is established as the driving mechanism for neurotoxicity [28]. Brain Aβ oligomers, rather than amyloid plaques, are highly associated with neuronal loss [29]. Aβ exists in two different isoforms, with Aβ40 being more abundant, whereas Aβ42 is more susceptible to aggregation

and more relevant to the pathogenic process [30]. Intracerebroventricular (ICV) injection of $A\beta_{1-42}$ has been shown to mediate neurodegeneration and induce an AD-like phenotype in animals and non-human primates [31][32]. The underlying mechanisms behind $A\beta_{1-42}$-induced neurodegeneration includes mitochondrial disruption, oxidative stress, degeneration of cholinergic neurons, and increased $A\beta_{1-42}$ deposition, ultimately leading to cell death [33]. Furthermore, Aβ regulates the NMDA receptors (NMDARs) and disrupts the ionic balance between synaptic and extra synaptic NMDAR signaling [34][35]; however, the precise mechanism behind Aβ-mediated excitotoxicity stills remains obscure.

A plethora of data supports Aβ-mediated neurodegeneration in AD [36][37][38]. However, this neurodegenerative protein has also gained increased attention in epileptogenesis. Aβ has mainly been implicated in the pathology of acquired epilepsy, where increased amyloid production and deposition have been shown to contribute to acquired epilepsy [39]. In this case, spontaneous seizures are mainly initiated after injury to the normal brain as a result of brain trauma, stroke, infection, or SE [40]. Tg2576 mice expressing human APP with the Swedish mutation (*K670N/M671L*) guided by the hamster prion protein demonstrated electrically evoked seizures, as evident by the lower after-discharge threshold (ADT) current and increased vulnerability to kindling [39]. In accordance, Tg2576 mice exhibited spontaneous seizures, increased mortality, and lower thresholds to PTZ-induced seizures, suggesting that overexpression of APP might contribute to seizure activity in neurodegenerative disorders [41]. On the contrary, zebrafish larvae lacking APP are susceptible to PTZ-induced seizures. Moreover, it was unraveled that intact prion protein is required for the seizure susceptibility of APP mutants [42].

Investigating the role of Aβ in the context of epilepsy is of crucial importance based on several studies supporting a close association of AD and epileptic seizures, possibly sharing common underlying mechanisms [43][44][45]. In this respect, transgenic mice overexpressing mutant APP and producing excessive amounts of Aβ are crucial for understanding the mechanism of AD pathogenesis [46]. Familial AD (FAD) is the less prominent form of AD, with an earlier onset compared to sporadic AD (accounting for more than 90% of the AD cases). FAD has been associated with mutations in three major genes: *APP*, presenilin1 (*PS-1*), and presenilin 2 (*PS-2*), which ultimately induce an abnormal overproduction of Aβ [47]. *PS-1* is the catalytic subunit of γ-secretase that contributes to the production of Aβ, and gene mutations have a tendency to increase the produced Aβ42/Aβ40 ratio [48]. Moreover, *PS-1* mutations might also cause seizures independent of the APP processing [49]. In a study of *APdE9* mice (carrying mutant human *APPswe* and *PS1dE9* genes), a greater propensity of epileptic seizures was observed at the time of appearance of the first amyloid plaque compared to wild-type (WT) littermates. The Aβ-induced sustained depolarization was proposed as the cause of epileptic seizures in *APdE9* mice [46]. APP metabolites and mainly the APP intracellular domain (AICD) might modulate the neuronal networks as evident by the abnormal electroencephalogram (EEG) spiking events and a strong susceptibility to induced seizures by transgenic mice overexpressing AICD and its binding partner Fe65 [49].

There is further evidence that the neurodegenerative proteins associated with AD are dysregulated during epileptogenesis. In the experimental model of TLE induced by electrical stimulation at an intratrain pulse frequency of 50 Hz in female SD rats, dysregulation in the proteins associated with Aβ processing, deposition, plaque formation, and Aβ-associated pathology was observed from bioinformatics analysis [50].

Pro-epileptogenic effects of Aβ have been reported in the 4-aminopyridine (4AP)-induced seizure model of male Wistar rats. More specifically, a single injection of Aβ was shown to facilitate 4AP-induced seizure expression and decrease the latency for 4AP-induced seizures. It further surged the number of generalized seizures, impaired the time for full recovery, and favored seizure-induced death. These pro-epileptogenic effects of Aβ have been correlated with the disruption of normal hippocampal function by affecting the synaptic efficacy and its coordinated network activity [51].

Kainic acid (KA) is an extensively used epileptogenic, and is the neuroexcitotoxic agent that acts on kainate receptors (KARs) in the central nervous system (CNS) [52]. Systemic administration of KA leads to prolonged seizures, resulting in excitotoxic hippocampal neuronal injury mainly in the CA3 area [53]. In an experimental model of induced TLE in male SD rats by KA (12 mg/kg, I.P.), increased APP expression and its processing enzymes was observed. It is worth noting that APP levels were only increased significantly at 2 and 12 days but not at 12 h post-KA administration when compared to normal control rats. In fact, in the control hippocampus, APP immunoreactivity was mainly located in the CA1-CA3 pyramidal neurons and in granule cells of the DG but not in glial cells. On the contrary, after 12 days of KA administration, APP was localized mainly in the glial cells of the hippocampus. Immunoreactive APP was found to mainly be localized in a subset of glial fibrillary acidic protein (GFAP)-labelled reactive astrocytes. In addition, increased expression of beta-site APP cleaving enzyme 1 (BACE1) and several components of the γ-secretase complex such as presenilin 1 (PS-1), Nicastrin, presenilin enhancer 2 (PEN2), and anterior pharynx defective 1 (APH1), along with elevated expression of $A\beta_{1-40}$ and $A\beta_{1-42}$, was observed in the hippocampus of KA-treated rats compared to normal controls. In accordance, treatment of primary rat astrocytic cultures with KA resulted in increased Aβ production/secretion without compromising the cell viability [54]. This finding suggests that activated astrocytes demonstrate a crucial role in KA-induced neuronal degeneration by upregulating APP expression and increasing Aβ peptide production. Furthermore, it implies that lowering/inhibiting Aβ levels might exert beneficial effects in lessening the seizures and reducing neurodegeneration [54].

The relation between Aβ and epilepsy has also been explored in clinical studies of patients with refractory epilepsy (RE) who had undergone resection of the temporal lobe or hippocampal sections. An increased expression of Aβ precursor protein (β-*APP*) was detected when compared to the controls. Moreover, immunostaining confirmed the localization of β-*APP* mainly in the neuronal cytoplasm and the axons of patients with RE. This finding indicates that elevated β-*APP* expression levels might play a crucial role in the pathomechanism underlying RE [55]. In the hippocampus and temporal lobe cortex of drug-resistant TLE patients who underwent temporal lobe resection, several molecular alterations that resemble those seen in AD patients were observed, including an upregulation of full-length APP expression and enhanced APP amyloidogenic processing, evident by increased phosphorylated APP (pAPP), $A\beta_{42}$, and $A\beta_{56}$ expression [56].

Although there is existing strong evidence that Aβ possibly contributes to the generation of epileptic seizures, and given the availability of several treatment strategies targeting Aβ [57], there is a lack of clinical studies targeting Aβ in epilepsy and therefore the therapeutic value of this intervention remains unanswered.

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