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Review

Novel therapeutic targets for epilepsy intervention

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ABSTRACT

Epilepsy is a common neurological disorder involving recurrent seizures and affecting about 1% of the population worldwide. Despite several antiepileptic drugs and effective therapies available for epilepsy, about 25% of the patients show therapeutic failure. Thus there exists an unmet need for newer antiepileptic drugs targeting newer targets with different mechanisms of action. Current research in epilepsy generally focuses on mechanisms that control neuronal excitability. Recently attention has been focussed on novel targets, their various interactions, and signalling cascades relating to epilepsy. This review summarizes several experimental and clinical findings from literature and explores potential targets which may play crucial role in epilepsy.

1. Introduction

Epilepsy is an important neurological disorder which has been reported in literature since 3000 years. It has been found to affect about 1% of population worldwide and has profoundly affected many aspects of quality of life [1,2]. The incidences of epilepsy are currently seen more in the developing countries than the developed countries and it affects people of all races, ages and social groups [3]. Rural population of the developing countries is more affected than the urban population [3]. Epilepsy is primarily a disorder characterised by spontaneously occurring seizures that involves hyperexcitable neurons [1,4]. It is well-known that in epilepsy, there is an imbalance between GABA-mediated and glutamate mediated neurotransmission [1]. Epileptic seizures occur due to abnormal, excessive electrical discharges which may be localized or widely distributed. Several factors are responsible for occurrence of seizures which may include genetic predisposition, a physiological or chemical stimuli capable of precipitating seizure, an underlying central nervous lesion or a combination of these factors [5,6].

Despite of several antiepileptic drugs available for epilepsy, around 30% of epileptic patients i.e. about 15 million people in the world, show therapeutic failure [7,8]. Thus their exists an unmet need for newer antiepileptic drugs targeting newer targets with different mechanisms of action. Current research in epilepsy generally focuses on mechanisms that control neuronal excitability. Recently attention has been focussed on novel targets, their various interactions, and signalling cascades relating to epilepsy. [9,10].

This review summarizes several experimental and clinical findings from literature and explores potential targets which may play crucial role in epilepsy. From various experimental and clinical observations it is evident that brain inflammation is an important factor in epilepsy [11]. Thus several inflammatory targets like Interlukin-1β (IL-1β), Transforming Growth Factor β (TGF-β) and their role along with inhibition strategy are explained in this review. Since mammalian target of rapamycin (mTOR) plays a key role in multiple mechanisms of epileptogenesis [12] this target and its inhibition strategies are also mentioned in our review. Likewise several targets like P-glycoprotein (Pgp), mutations in voltage gated ion channels like Hyperpolarization-activated cyclic nucleotide-gated channels (HCN) and Kv7 or (M-) channels, Na-K-2Cl cotransporter (NKCC1) and their involvement in epilepsy is discussed.

2. Outline of mechanisms involved in pathogenesis of epilepsy

The primary mechanisms by which the currently available antiepileptic drugs eliminate seizures are gamma-aminobutyric

Abbreviations: IL-1B, interlukins 1-beta; LPS, lipopolysaccharide; ICE, IL-1β converting enzyme; TLE, temporal lobe epilepsy; BBB, blood brain barrier; NMDA, *N*-methyl-D-aspartate; IL-1R1, interlukin-1 receptor, type 1; TNF-alpha, tumor necrosis factor- alpha; PTZ, pentylenetetrazole; Pgp, P glycoprotein; COX-2, cyclooxygenase-2; HCN, hyperpolarization activated cyclic nucleotide gated ion channel; GABA, gamma-aminobutyric acid; Nfr2, nuclear factor -E2 related factor; NKCC1, Na-K-2Cl cotransporter; KCC2, K-Cl cotransporter; Trkb, tropomyosin-receptor-kinase B; BDNF, brain-derived neurotrophic factor; TGF-Beta, transforming growth factor beta; mTOR, mammalian target of rapamycin; TSC, tuberous sclerosis complex.

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acid (GABA), glutamate receptors and neuronal ion channels [13]. Recently, anti-inflammatory effects of antiepileptic drugs have gained attention [14]. For example, currently available antiepileptic drugs like carbamazepine and levetiracetam were found to exhibit anti-inflammatory effects, i.e. they reduced the expression of inflammatory mediators in glial cell cultures [14,15]. Levetiracetam was also able to normalize the resting membrane potential of astrocytes which was elevated by inflammatory mediators [14]. According to literature, it is also known that the disruption of blood-brain barrier (BBB) is responsible for increased abnormal neuronal firing [13]. Leukocyte invasion into brain as well as leakage of serum protein occurs due to the disruption of the BBB [13]. Seizure thresholds are lowered by these exogenous inflammatory mediators [16]. Thus, brain inflammation may promote epileptogenesis and hence we have discussed certain inflammatory mediators as potential targets for treatment of epilepsy.

Despite of several antiepileptic drugs available, the problem of pharmacoresistance still persists [17]. Thus there is a need to understand the pathomechanisms giving rise to pharmacoresistance [17]. Genetic mutations causing dysfunctioning of voltage gated ion channels contribute to different types of familial epilepsy [18]. Voltage gated channels control the excitability of normal cells by regulating their membrane potential, firing rate and synaptic transmission [19]. Functional changes occurring in these ion channels due to mutations causes hyperexcitability of neurons, leading to seizures [19].

Oxidative stress is involved in the progression of epilepsy and studies have shown that it is an underlying mechanism for progression of epilepsy, particularly induced by kainic acid and pilocarpine [20]. Mitochondrial superoxide radical mediated oxidative stress was suggested to play a role in excitotoxicity induced by kainic acid seizures and it was also suggested that antioxidants may prove beneficial in the treatment of seizures [21]. Two cation-chloride cotransporters have been discussed as potential targets in epilepsy as they can control the reverse potential of GABAA-receptor mediated current [22]. Similarly other targets like purinergic receptors which are ligand-gated ion channels are discussed as potential targets, as their activation by ATP contributes to glio- and neuro-transmission [23].

The potential targets for epilepsy based on the above mentioned mechanisms are discussed briefly as follows.

3. Targets related to inflammation

3.1. Interlukin-1β (IL-1β) role in epilepsy and its modulation to minimize seizures

Experimental seizures have led to induction of inflammatory processes in brain regions in which epileptic activity originates and spreads [13]. It has been observed that in rodent brain during seizures, synthesize and release IL-1β in astrocytes and microglia [24]. Within 30 min of seizure onset, astrocytes and microglia produce elevated cytokine levels. As a result of this, the wave of inflammation spreads to endothelial cells of BBB involving clusters of neurons in those areas in which seizures originate and spread [25]. In addition to elevation of IL-1β which occurs due to seizures, it can also modulate susceptibility to seizure inducing stimuli [26]. Thus activation of IL-1β receptor signalling in glia and neurons contributes to intrinsic brain inflammation [27]. Activation of this signalling further exacerbates seizures induced by kainic acid and bicuculine in rats and mice [26,28]. It is reported from previous studies that IL-1β converting enzyme (ICE, caspase 1) plays a key role in converting IL-1β in its active form and that the genetic deletion of ICE has prevented negative physiological responses to lipopolysaccharide (LPS) induced inflammation [29]. It has been reported from the previous studies that release of IL-1β is reduced due to inhibition of ICE/caspase-1 in organotypic hippocampal slices following exposure to proinflammatory stimuli [30]. Thus from above evidences it can be hypothesized that inhibitors of ICE/caspase-1 may prove beneficial in epilepsy and they can be investigated further. Previous studies have also reported a mechanistic link between proconvulsant effects of IL-1β and NMDA receptors [31]. It has been seen that enhanced Ca^{2+} influx is mediated by N-methyl-D-aspartate (NMDA) which occurs by Interlukin-1 receptor, type 1 (IL-1R1) dependent activation of Src kinases and neuronal sphingomyelinases which causes phosphorylation of NR2B subunit of NMDA receptors [31,32]. Also it has been seen that NMDA receptors having NR2B subunit are main targets for glutamate released from activated astrocytes, thus leading to induction of slow inward currents of neurons [31]. These slow inwards currents act as excitatory events. These currents are increased in animal models of epilepsy and can trigger action potentials in neurons due to their role in neuronal synchronization [33]. Thus these currents may act as an important molecular event by which IL-1β worsens seizures [34,35,36]. Also it has been reported from previous studies that IL-1β inhibits reuptake of glutamate from astrocytes and may lead to increased release of glutamate via tumor necrosis factor (TNF-α) from glia, ultimately promoting hyperexcitability [36,37]. The exact mechanism by which these proinflammatory cytokines like IL-1β and TNF-α inhibits reuptake of glutamate is unknown, but previous study reports from murine models and human fetal astrocyte cultures using nitric oxide synthase inhibitors have suggested that nitric oxide is involved in the suppression of glutamate uptake activity by IL-1β as IL-1β stimulated human astrocytes generate substantial amounts of nitric oxide [38,39,40]. Also studies carried out by Bezzi et al, [41] have suggested the involvement of TNF-α in releasing glutamate, where they had proposed a signaling cascade mechanism for glutamate exocytosis from astrocytes via TNF-α. From the results it was proposed that stromal cell-derived factor 1 (SDF-Iα) stimulates CXCR4-dependent signaling in astrocytes as well as microglia and contributes synergistically to release TNF-α with activation of tumor necrosis factor receptor 1 (TNFR1) in astrocytes and potentiate downstream signaling, causing glutamate release [41]. Thus inhibition of IL-1β may be beneficial strategy to minimize epilepsy.

3.2. Inhibition of IL-1β as an approach to treat epilepsy

Previous experimental studies by Maroso et al, [42] have reported the beneficial effect of VX-765 (a selective ICE/caspase-1 inhibitor) in epilepsy [42]. It was observed that in kainic acid induced seizures in C57BL-6 mice, VX-765 showed potent anticonvulsant effect by its inhibition of IL-1β via inhibition of ICE/caspase-1 and modulation of NMDA receptors [42]. Another recent experimental study by Carlos et al, [43] investigated the role of vinpocetine in pentylenetetrazole (PTZ) and 4-aminopyridine model of epilepsy. From the study it was proved that vinpocetine caused reduction of IL-1β expression in rat hippocampus. Based on this study, it was proposed that vinpocetine through its cerebral anti-inflammatory effect may also contribute to the anti-seizure action [43]. Thus targeting IL-1β inhibition by several approaches and signaling pathways like ICE/caspase-1 and NMDA receptor modulation discussed above may prove beneficial in epilepsy.

3.3. Modulators of transforming growth factor beta (TGF-β)

Recent studies have shown the involvement of TGF-β pathway in epilepsy. It has been demonstrated previously by Cachaeux et al. [44] that disruption of blood-brain barrier leads to the development of focal epileptiform activity and albumin is critical in this process of epileptogenesis [44]. Albumin interacts with TGF-β