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Neuroimmunomodulation in Epilepsy: A review

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Abstract
Epilepsy, also known as seizure disorder, is known to trigger lasting inflammatory reactions. Seizures are documented to cause brain inflammation through the stimulation of several neuronal and non-neuronal brain cells; It, in turn, aids in the structural and molecular alterations that take place during and after a seizure. When an inflammatory response begins, agents that promote inflammation, such as tumor necrosis factor (TNF) and interleukin (IL)-1, are released into the bloodstream. Aggravation has been demonstrated to be a significant figure in the advancement of epilepsy in both old and new examinations. Research into epileptogenesis's inflammatory pathways has uncovered potential new antiepileptic drugs' molecular targets. It is possible that molecules that target the key inflammatory pathways might be effective in preventing epilepsy. The present paper reviews and documents the correlation between neuroimmunomodulation and epilepsy and the potential role of related inflammatory molecules.

Introduction

The immune system acts as a homeostatic mechanism, which under physiological conditions maintains the constancy and integrity of body cells and tissues [1]. Research showed that the central nervous system (CNS) is connected to the immune system and the procedure is rather complicated which includes numerous neural, hormonal, and paracrine arrangements capable of emanating and receiving signals thereby altering the immune responses. This means that Aggravation has been demonstrated to be a significant figure in the advancement of epilepsy in both old and new examinations each other via neuroimmunomodulation [2].

A set of standard responses is produced in the CNS on any sort of stimulation of the immune system by pathogens [3]. Hypothalamic corticotropin-releasing factor (CRF) operates on the thoughtful sensory system and the Nerve center Pituitary-Adrenal hub (HPA hub), according to studies, mediating the behavioral, neurological, and neuroendocrine responses to stress. subsequently elevating the levels of immunosuppressive agents like some specific opiates, corticosteroids, and catecholamines [4].

Research also revealed that any sort of brain injury and trauma elicits an inflammatory response generally mediated by chemokines, cytokines, adhesion molecules, and complement activation, in injured portions [5]. Cytokines, which are produced by white blood corpuscles (WBC) of the immune system mediate the activity of CNS such as IL-Iβ which in turn activates the HPA axis. This causes increased secretion of glucocorticoids, which suppress the immune response via a negative feedback mechanism [6].

Toxicities, infections, inflammation, brain tumors, neurodegenerative disorders, brain injuries due to trauma and stroke, and some congenital defects are known to trigger secondary epilepsy [7]. Numerous research reported that antibodies can be epileptogenic and are related to some epileptic syndromes [8]. Epilepsy related to some other immunological sickness and childhood epilepsy proves the involvement of the immunological pathways [9]. Back in the 90s, a connection between the epileptogenic interaction and the safe framework was projected [10]. Subsequently, several studies provided pieces of evidence related to immunomodulation in epileptic cases. Studies recommend that the safe framework assumes a vital part in a few explicit types of epilepsy or seizure-related messes by showing the presence of autoantibodies to voltage-gated potassium channels and glutamic corrosive decarboxylase [11].

This review provides a comprehensive summary of the research that supports the possibility that the safe framework plays a part in the improvement of specific types of epilepsy.

A brief history

The concept of epileptic seizures has been established for ages since the time of human existence. There were many beliefs related to epilepsy before the understanding of the CNS. Several cultures have

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documented and recorded Epilepsy as per their understanding. The oldest record of an optionally summed-up tonic-clonic seizure was documented in Mesopotamia around 3000 years ago [12]. Records showed that Hippocrates penned down epilepsy almost 2500 years ago [13]. Epilepsy was thought to be caused by masturbation to an extreme during the 19th century. In this theory, the use of the first effective anticonvulsant—bromides—was recognized [14].

Experimental studies documenting epileptic episodes in the animal brain cortex by Fritsch, Hitzig, Ferrier, and Caton in the 1870s laid the groundwork for modern research into the causes of epilepsy [15]. The use of scalp electrodes to record electrical brain impulses from the human head was first introduced by Berger in 1929. This technique is now known as electroencephalography (EEG) and was first used to research and categorize epileptic convulsions [16]. Later, Gibbs, Lennox, Penfield, and Jasper improvised and developed the method recently used for the 2 major classes of epileptic seizures by correlating the convulsions with the ECG readings [17].

Epilepsy

The International League Against Epilepsy (ILAE) has put forward the following definition of epilepsy: a brain disease characterized by neurobiological, cognitive, psychologic, and social effects including epileptic seizures [18]. Typically, for epilepsy to be diagnosed, two or more unprovoked seizures must have occurred within 24 hours of one another. One spontaneous seizure occurring in the context of an interictal discharge is also enough for some professionals to diagnose epilepsy [19].

In those with epilepsy, aberrant neural discharges cause repeated seizures, which are the hallmarks of this neurological illness. The term epilepsy involves a range of syndromes and diseases with different etiopathogenesis [20].

Epilepsy is also known as seizure disorder. Seizures occur due to malfunctioning and unsynchronized uncontrollable firing from groups of neurons. These electrical impulses explode and spread to adjacent areas creating a storm of hypersynchronous electrical discharges [21]. The worldwide occurrence rate annually is 50 in 100,000 and 700 in 100,000, respectively [22].

Seizures may or may not be related to the precise site of the infarct, according to some research. When it comes to the clinical symptoms and pattern of seizures, some experts believe that the location of the epileptic discharges in the brain is vital. Based on this the patient might experience weird feelings and responses and even react strangely. They may also experience vigorous tremors or convulsions and even become unconscious. The condition is caused by a sudden change in electrical activity in the brain, which is presumed to develop due to excessive and abnormal neuronal discharges from a cluster of hyperexcitable neurons in the brain, causing a temporary communication problem between nerve cells [23]. Epileptic seizures are known to range from mild twitching in the extremities to loss of consciousness and uncontrollable convulsions. Changes such as distortion of awareness; sensory, motor, autonomic or mental events, complete or partial loss of consciousness, etc. arise from a group of excited neurons with a tendency of recurrent attacks [24].

The current improvement in surgical techniques and brain imaging helps to identify the structural abnormalities of the neuronal circuits, which aids in the control of seizures [20].

Neuropathological hallmarks

In humans and animals, a brain injury after a period may lead to spontaneous epileptic seizures that can continue throughout one's lifetime. The fundamental processes comprise multiple structural and functional neuronal modulations.

In studies with mice, researchers recognized the T-type Ca^{2+} channel $Ca_v3.2$ has a key role in epileptogenesis. Following status epilepticus, there is a brief and specific increase in the expression of the Cav3.2 subunit on both the mRNA and protein levels. This increase causes a transitory elevation of intrinsic burst firing and a rise in cellular T-type Ca2+ currents. Alternatively, animals deficient in Cav3.2 subunits do not exhibit similar functional alterations. In addition, the research found that Cav3.2−/-− mice didn't show any signs of neuropathological markers of persistent epilepsy, including mossy fiber sprouting and subfield-specific neuron loss in the hippocampus formation [25].

Studies detected mitochondrial dysfunction as a probable reason for epileptic seizures and treatment safe in serious types of epilepsy. Extensive mutations in mitochondria cause impairment of mitochondrial ATP synthesis. The crucial source of ATP for cellular Ca^{2+} homeostasis in neurons and mitochondria is mitochondrial oxidative phosphorylation, this influences neuronal volatility and synaptic transmission hence leading to the generation of seizures. Furthermore,

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mitochondrial dysfunction induces the death of neuronal cells, which is a trademark sign of treatment-safe worldly curve epilepsy [26].

Scientific investigations recognized the causes of focal epilepsy are local inflammatory lesions, like parasite cysts (such as neurocysticercosis and hydatid cysts), granulomas (a sign of TB), and brain abscesses) [27]. The results of different studies exhibited different disorders including degenerative hippocampus disease, tumors, ischemic lesions, chronic traumatic traumas, inflammatory lesions, malformative lesions neuropathological hallmarks [28].

Neuroinflammatory role

Studies established the neuroinflammatory role in Epilepsy and it's a complicated process. Besides triggering the local inflammatory responses, the inflammatory factors also disturb the electrical activity of the Glial cells and the neurons. Evidence suggests that epileptic seizures could in turn trigger neuro-inflammatory reactions, worsening the condition [29,30].

Clinical and experimental explanations revealed a profound relation between mind irritation and the etiopathogenesis of epilepsy. With different rodent models the role of various inflammatory molecules like the IL-1β system has been well documented and found to significantly aggravate seizure activity. These findings are believed to be a probable cause of epileptogenesis in humans [31].

Inflammation is a homeostatic mechanism commonly initiated after an infection or injury. This is known as a defensive mechanism for regenerating tissues and is responsible for pathogen clearance by producing inflammatory and anti-inflammatory molecules to prevent damaging consequences and consequently induces innate and adaptive immune responses. Under certain circumstances, inflammation has been studied to have pathologic outcomes on tissue that lead to cell damage, necrosis, and death [32].

Following this, researchers have also reported that the intracerebral application of a naturally occurring molecule like an inhibitor of interleukin 1 receptors (IL-1ra) blocks the impact of naturally occurring IL-1β and has been known to have powerful anticonvulsant activity [33]. Findings by Vezzani et al also suggested that IL-1β drags out seizures by expanding glutamatergic neurotransmission demonstrating the pro-convulsant effects [34]. The excitatory impact of IL-1β has likewise been accounted for in some other studies stating that this cytokine is capable of inhibiting glutamate uptake by astrocytes [35]. Besides, Additionally, it has been shown to decrease the maximum intensity of fluxes assisted by γ-aminobutyric acid (GABA) in cultured hippocampus neurons [36].

Furthermore, to explore the role of TNF-α on seizure, Vezzani in one of his research projects in 2004 projected that TNF-α lessens seizure movement by interfacing with TNF-α type II (p75) receptors in TNF-α knock out mice [37].

On the other hand, studies revealed that inhibitors of framework metalloproteinases and TNF-α-changing over compound decreased how much solvent TNF-α, which conceivably mitigated seizures and mind injury in a rodent model of bacterial meningitis [38]. So variations in receptor subtypes among experimental models or variations in TNF-α doses are the possible causes of the discrepancies seen in various investigations. In accordance with the different studies conducted related to the role of TNF-α, it can be concluded that lower levels are proconvulsive whereas higher concentrations of TNF-α are related to suppressive effects [39].

Experiments with transgenic mice with overexpressing IL-6 in the glia documented an upsurge in the sensitivity to glutamatergic (not cholinergic) agonists [40]. Again, research showed neuronal loss in the hippocampus particularly the deficiency of GABA-and parvalbumin-positive neurons of these mice. Another research acknowledged the neurodegenerative alterations with the development of conduct seizures, during a time-subordinate way, with overexpression of the cytokines in glia of TNF-α and IL-6 transgenic mice [41].

Hence, various studies demonstrated that neuroinflammatory reactions are capable of inducing epilepsy by altering neuronal structures and functions. Thus, by modulating the neuroinflammatory reaction the neuroinflammatory cascade can be controlled. Researchers projected that the astrocyte Cx43 mediated gap junction pathway is the fundamental pathway for controlling the epilepsy-induced neuroinflammatory cascade [42].

Interaction between the immune system and brain

The blood-cerebrum boundary goes about as a channel, keeping a few substances from entering the focal sensory system alongside blood; subsequently, the focal sensory system can be named as an 'invulnerability exclusion zone' [43]. However, scientists documented that though the immature T cells are unable to cross the

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blood-cerebrum obstruction; however, initiated Lymphocytes can cross the blood-mind hindrance by attaching themselves to the outer layer of the cerebral vascular endothelium and can initiate inflammatory reactions in the central nervous system [44].

The cells engaged with the cerebrum's fiery responses are the microglia, astrocytes, and endothelial cells. The microglia cells of the central nervous system are stimulated by injury, which consequently induces the inflammatory reaction, to maintain the homeostasis in CNS [45]. These microglia, during any sort of injury, damage, or infection to the CNS activate into macrophages to induce inflammatory reactions along with T cells and can cause neurotoxicity [46].

Thence, the brain is known to monitor immunity and observe peripheral inflammatory reactions mainly through two pathways: the neural and the humoral [47]. There is a neurological route that begins with the activation of vagal afferents, which provide signals to the brain regarding inflammation. Direct stimulation of the Vagus nerve's afferent sensory fibers occurs when vagal-associated immune cells, macrophages, and dendritic cells release cytokines; indirect stimulation occurs when chemoreceptive cells in vagal paraganglia release cytokines [48].

Researchers documented the crucial role played by the humoral components in safe-to-mind correspondence, explicitly in instances of foundational resistant tests [49,50]. Studies showed that at a very high plasma cytokine level, the blood-borne IL-1β and TNF cross the blood-mind deterrent by a saturable transporter interceded mechanism [51].

A neurohormonal mechanism, the HPA hub assumes a fundamental part in neuroimmunomodulation. Synthesis and secretion of glucocorticoids and catecholamines3 are increased during activation of the HPA pivot and the thoughtful sensory system (SNS). The PVMN, the foremost pituitary organ, and the adrenal cortex make up the HPA pivot, which is a pathway in the hypothalamus. A subset of PVN neurons code for corticotropin-releasing hormone (CRH), which stimulates the anterior pituitary to secrete adrenocorticotropin hormone (ACTH) via the pituitary portal blood circulation. The adrenal cortex produces immunosuppressive glucocorticoids, and ACTH is the primary hormone that stimulates their production and secretion. According to several studies, substances such as serotonin, acetylcholine (ACh), catecholamine, GABA, and hypothalamic-pituitary hormone seem to regulate the HPA axis.

IL-1 and IL-6 are also studied to influence the function of peripheral glucocorticoids modulating the function of corresponding glucocorticoid receptors [52]. The nuclear factor-κB is known to assume a critical part in cytokine synthesis, but this factor is suppressed by the immunosuppressive glucocorticoid [53].

Hence, glucocorticoids are known to suppress the production of cytokines that promote inflammation, including TNF, IL-1, IL-8, IL-11, IL-12, and interferon-γ, while simultaneously promoting the production of cytokines that inhibit inflammation, such as IL-4 and IL-10. Furthermore, glucocorticoids inhibit neutrophil, eosinophil, monocyte, and macrophage expression, adhesion, and infiltration [53]. Glucocorticoids are also studied to act as effective clinical anti-inflammatory agents [52].

Neuroimmunomodulation in epilepsy

Cooperation between the neuroendocrine and resistant frameworks is urgent to the host's defense mechanism. Stress harms one's health, it hinders the function of the immune system CRH primarily stimulates ACTH secretion and is also known to incorporate a series of reactions during the stress response. Over the last decades, research implied that CRH is the major stress-integrating peptide and is capable of modulating immune functions directly.

Current research data have established the role of CRH as a central immunosuppressant agent independent of circulating glucocorticoids. As mentioned earlier this effect of CRH is relatively mediated via stimulation of sympathetic outflow and at the periphery, CRH receptors are identified within the immune cells of the safe framework to intercede the effect. Therefore, the immunomodulatory effect of CRH indicates the correlation between the neuroendocrine and immune systems [53].

Again, it projected that oxidative pressure assumes a critical part as it increases the secretion of CRH and consequently, inactivates the macrophage. The increase in the emission of CRH animates the front pituitary, which thus modifies the creation of IL-1 [3].

Research has shown that any sort of brain injury like infection, seizure, trauma, or stroke may lead to brain inflammation [31]. Evidence suggests that inflammatory responses connected to the enactment of the natural safe framework play a part in the biochemical and structural changes that occur before, during, and after seizures. The production of pro-inflammatory mediators, including interleukin (IL)-1, adhesion molecules, tumor

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necrosis factor (TNF), vasoactive middle people, and receptive oxygen species, denotes the start of the incendiary process [54].

A crucial role in inducing a local inflammatory response is the rapid secretion of favorable to fiery cytokines by actuated macrophages. The more cytokines, such as IL-1β, TNF, and HMGB1, that are produced and secreted, the more harmful they are. This is because they cause tissue damage, low blood pressure, bleeding, and death [55].

Again, as mentioned earlier, in addition to their contribution to inflammation events, TNF and IL-1β are likewise referred to go about as sign particles for the acceptance of mind-determined neuroendocrine immunomodulatory reactions. The HPA pivot and the thoughtful division of the autonomic sensory system (SNS) go about as a mitigating adjusting instrument to control fiery responses [56].

According to 2018 research, a spike in CSF levels of supportive provocative cytokines in PE shows disruption to the blood-brain barrier. Once again, the same research found that less anti-inflammatory substances in blood and cerebrospinal fluid (CSF) are present when receptor antagonist IL-1 (RAIL-1) is not present. Thus, linking epilepsy with neuroimmunomodulatory alterations [57].

Conclusions

Researchers through the decades established a clear correlation between neuroimmunomodulation and epilepsy. Furthermore, signaling pathways play a crucial role in the neuroinflammatory response after epilepsy. They are the hallmarks for the occurrence of the event, diagnosis, and prediction of epilepsy. Currently, there are a plethora of studies are carried out to investigate and document the correlation between the different signaling pathways and the associated antibodies and their clinical applications.

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