EPİLEPSİ HASTALIĞINDA İL-1β VE İL-6'NIN ROLÜ

The Role of IL-1β and IL-6 in Epilepsy Disease

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ÖZET

Epilepsi yaygın bir kronik nörolojik bozukluktur ve patofizyolojisi pek çok şekilde anlaşılmamıştır. Sitokinler, periferal dokudaki iltihaplanma sırasında enflamatuar sistem hücreleri arasında iletişim kuran bir grup çözünür aracıdır. Her ne kadar sitokinlerin epilepsi etiyolojisindeki rolü hakkında bilgi sahibi olsak da, sitokinlerin epilepside temel fizyopatolojik mekanizmadaki rolü hakkında bilgi sınırlıdır. İnterlökinler (IL) akut ve kronik inflamasyon ile ilişkilidir ve bağışıklık yanıtında önemli bir rol oynar. Epilepside IL-1β ve IL-6'nın rollerini anlamak, epileptogenezi anlamak ve klinik tanı ve yeni tedavi seçenekleri geliştirmek için önemlidir. Bu nedenle, bu çalışmada, IL-1β ve IL-6 sitokinlerinin epilepside rollerini ve yerlerini derlemeye çalıştık.

Anahtar kelimeler: *Epilepsi; Sitokinler; IL-1β; IL-6*

ABSTRACT

Epilepsy is a common chronic neurological disorder and its pathophysiology has not been understood in many ways. Cytokines are a group of soluble mediators that communicate between inflammatory system cells during inflammation in the peripheral tissue. We have information about the role of cytokines in epilepsy etiology, but information on the role of cytokines in the basic physiopathological mechanism of epilepsy is limited. IL-1β and IL-6 are associated with acute and chronic inflammation and play an important role in immune response. Understanding the roles of IL-1β and IL-6 in epilepsy is important for understanding epileptogenesis and developing clinical diagnosis and new treatment options. Therefore, in this study, we tried to compile the roles and states of IL-1β and IL-6 cytokines in epilepsy.

Key Words: *Epilepsy; Cytokines; IL-1β; IL-6*

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INTRODUCTION

Epilepsy is a disorder caused by abnormal and excessive electrical discharge in neurons. It is a condition characterized by seizures triggered by a sudden, repetitive and unidentified event (1). An epileptic seizure is a temporary behavioral change in which the subjective symptoms such as objective symptoms, loss of consciousness, contraction and shivering, caused by abnormal excessive or synchronized neuronal activity in the brain, can be seen (2). Epilepsy is the third most common disease in the world among neurological disorders (3) and it is known that approximately 2% of the world's population suffers from epilepsy (4).

Cytokines are molecules that play an important role in the immune system regulation and inflammatory events of the organism. Cytokines control the reactions against foreign antigens and agents in the organism. It also plays an important role in local and systemic inflammatory responses by regulating intercellular relationships. Cytokines are very active substances and even small amounts can be effective. Since one of the related cytokines can cause the secretion of others, their effect mechanisms can be similar. Cytokines that play a critical role in immune regulation are soluble mediators of cell communication. In addition, these observations demonstrate the multi-directional nature of cytokine networks and the complex relationship between the immune system and epilepsy (5). Prolonged, recurrent seizures and brain injuries cause active immune responses to increase seizure sensitivity, strengthen neuronal arousal ability and induce destruction of the blood-brain barrier (BBB) (6). An important part of cytokines secreted from the immune system is interleukins (IL) and their main task is to stimulate immune system cells (7). ILs are proteins that regulate both the immune system and the central nervous system (CNS) (8). In addition, peripheral inflammation has been shown to synergistically strengthen seizures and increase seizure-induced proinflammatory cytokine production and microglial activation in febrile seizures (9). Among the different inflammatory cytokines studied, interleukin-6 (IL-6), interleukin-1 beta (IL-1β) and interleukin-1 receptor antagonist (IL-1Ra) were the most prominent in clinical trials (10). Studies in recent years have shown that epileptic seizures can induce cytokine production that affects the pathogenesis and course of epilepsy. In these studies, the focus is mostly on IL-1β and IL-6 (5). In this study, we aimed to review IL-6 and IL-1b changes triggered by epileptic seizures and their relationship with epilepsy type.

IL-1β

IL-1β is a member of the IL-1 family of 11 members. IL-1a, IL-1β and IL-1 receptor antagonist (IL1Ra) bind to the type 1 IL-1β receptor (IL1R1). IL-1β forms an inflammatory signal after binding to IL1R1 (11). IL-1 cytokine family is associated with neurological conditions such as stroke trauma and Alzheimer's disease. IL-1β provides neurological protection at low concentrations, but in pathological conditions; high IL-1β levels cause neurotoxic effects. Therefore, it is associated with seizure sensitivity and epileptogenesis (10). IL-1β conduces to neuronal degeneration observed in various neurological diseases and has recently been observed to cause neuronal injuries that may coexist with the epileptogenesis process. IL-1β induces Src kinase-mediated tyrosine phosphorylation of the N-Methyl-D-Aspartic Acid (NMDA) receptor subunit and as a result of this action, it increases NMDA receptor-mediated Ca+2 influx to neurons. This effect plays a role in increasing excitotoxicity and seizure formation (12). IL-1β can also inhibit the astrocytic reuptake of glutamate (13), thereby causing elevated extracellular glutamate levels (14). It is reported in the literature that astrocytic glutamate release may have a role in the occurrence of seizure-like events and a relationship with seizure power (15,16). In addition, IL-1β can increase neuronal glutamate release by activating excitable nitric oxide synthase in astrocytes (17). IL-1β can also inhibit GABA-mediated Cl currents, thereby reducing inhibitory transmission (18).

Through the immunohistochemical analysis of the temporal and cellular structures of inflammatory changes in the forebrains of epileptic rats (19,20), a rapid increase of IL-1β in active microglia and astrocytes was detected during acute seizures. During epileptogenesis and the observation of high expression of IL-1β in chronic epileptic tissue, IL-1β returned to basal expression level after seizure decreased. While

the increase in other cytokines remained connected to the ongoing epileptic activity, the increase in IL-1β surpassed the acute-inducing event. Chronic expression of IL-1β during epileptogenesis highlights the possibility that this cytokine may conduce to the mechanisms underlying the onset of seizures. In chronic epileptic tissues, microglia and astrocyte cells also express high levels of IL-1β (20). Recently, analysis of human brain samples from drug-resistant epileptic patients has shown that the IL-1β / IL-1R1 (Interleukin 1 receptor) system has strong activation in brain cells as well as in glia and neurons. Remarkably, in epilepsy associated with malformations of cortical development, a positive correlation was found between the percentage of cells with increased IL-1β expression and the frequency of seizures (19,20). In addition, the finding regarding that the ongoing inflammatory events occur during the epileptogenesis of experimental models shows that activation of the IL-1β system observed in human chronic epileptic tissue may precede the onset of epilepsy (21).

Recent data show that the natural immune system producing IL-1β plays a role in the onset of the seizures. In the later stages, the adaptive immune system can indirectly increase epileptogenesis by inducing neurodegeneration or by invading T lymphocytes and antibody complement activation. In addition, it is thought that disorders that occur in potassium homeostasis and cytotoxic glutamate buffering and caused by abnormal cytokine production induce seizures. This multi-factor seizure induction and the epileptogenesis inducement make it difficult to develop successful antiepileptogenic treatment strategies. For this reason, the use of IL-1β signaling inhibitors can be seen as a promising strategy (22).

IL-6

Interleukin-6 (IL-6) is a helical protein that binds to a specific IL-6 receptor on target cells and two molecules of mixed-signal transduction protein glycoprotein 130. As a result of the structure-function analysis, three molecular contact sites were defined between IL-6 and receptor subunits (23). It is known that the IL-6 receptor system consists of a ligand-binding chain and a signal transmitting molecule (24). It is an important cytokine group in the regulation of acute phase response against injury and infection (25). IL-6 primarily defined as a B cell differentiation factor, therefore one of the main functions of IL-6 is antibody induction (24). In addition, IL-6 can also act as an activation signal for other cytokines in the brain tissue. In the conducted researches, it was shown that IL-6 may increase the duration of the seizure and cause neurodegeneration. It was understood with the clinical trials that the increase in the IL-6 expression is associated with the spread and duration of the seizure (26). The irregularity of Type IL-6 cytokine signaling conduces to the onset of diseases such as rheumatoid arthritis, inflammatory bowel disease, osteoporosis, multiple sclerosis and various types of cancer (such as multiple myeloma and prostate cancer). Along with their functions in the inflammation and immune response, these cytokines also play an important role in hematopoiesis, liver and neuronal regeneration, embryonic development and fertility (25).

In a conducted research, it was shown that interleukin-6 deficiency increased neuronal damage in the brain tissue (27). In another study, an increase in the IL-6 levels was stated in patients with tonic-clonic seizures (28). In addition to this, cerebrospinal fluid (CSF) was taken and analyzed after epileptic seizures and increases in the inflammatory mediator (for example; cytokines such as IL-6 and IL-1 receptor antagonist) levels were observed. For example; CSF concentrations in some patients increased 24 hours after the tonic-clonic seizures (29). The effect of the duration and spread of the seizure on IL-6 levels has shown that patients with recurrent tonic-clonic seizures have the highest IL-6 concentrations. In single tonic-clonic seizures, prolonged partial seizures and similarly, increases in the IL-6 levels were recorded (26). High levels of IL-6 expression in the brains of transgenic rats have been found associated with the occurrence of age-related neurodegenerative changes and sporadic spontaneous seizures (30,31).

DISCUSSION

The effects of the IL-1β and IL-6 levels on brain tissue in epilepsy are known. In the conducted researches, a rapid increase of IL-1β in active microglia and

astrocytes was detected during acute seizures through the immunohistochemical analysis of the cellular structures of inflammatory changes in the forebrains of epileptic rats (19,20). Chronic expression of IL-1β during epileptogenesis highlights the possibility that this cytokine may conduce to the mechanisms underlying the onset of seizures. Remarkably, in epilepsy associated with malformations of cortical development, a positive correlation was found between the percentage of cells with increased IL-1β expression and the frequency of seizures (19). In a conducted research, it was shown that interleukin-6 deficiency increased neuronal damage in the brain tissue (27). In addition to this, cerebrospinal fluid (CSF) was taken and analyzed after epileptic seizures and increases in the inflammatory mediator (for example; cytokines such as IL-6 and IL-1 receptor antagonist) levels were observed. Particularly, the information stating that analyzed interleukins may increase the duration of the epileptic seizures and cause neurodegeneration is a highlighting situation regarding its effect on epilepsy. The fact that increased IL-1β and IL-6 levels are associated with the duration and frequency of the epileptic seizures and that these interleukins are among the most focused proinflammatory cytokines regarding both patients and experimental models of drug-resistant epilepsy (32) has turned it into a target for researches.

The one of the possible targets of anti-epilepsy strategies is the inflammatory response that occurs in the brain after the first epileptogenic damage. Evidence from experimental and clinical studies suggests that inflammatory mediators, in the brain, play an etiological role in epileptogenesis and neuropathology of epilepsy. Accordingly, strategies aimed at reducing levels of inflammatory cytokines can create a potential antiepileptogenic therapy. Considering the need to develop epileptogenesis treatment strategies, it has been investigated whether atorvastatin and pilocarpine develop short-term inflammatory response and behavioral changes after status epilepticus (SE). Therefore, the effect of atorvastatin on the key cytokine levels in the hippocampus and cerebral cortex, and the behaviour of mice is focused in the epileptogenic period. The analysis revealed an increase in the levels of IL-1β, IL-6, tumor necrosis factor alpha (TNF-α) and interferon-gamma (INF-γ) in the hippocampus and cerebral cortex of female and male mice exposed to SE. The treatment with atorvastatin reliably relieved the increase in epilepticus at IL-1β, IL-6, TNF-α and INF-γ levels. In another analysis, cytokine levels between women and men were compared. Interestingly, higher levels of proinflammatory cytokines (IL-1β, IL-6, TNF-α, INF-γ) were detected in females than in males. Thus, this study provides evidence that gender affects the type and severity of the central nervous system inflammatory response after epileptogenic brain insult. (33,34)

Retrospective studies have suggested that the IL-1 cytokine system may play an important role in the development of febrile status epilepticus (FSE) and mesial temporal lobe epilepsy (MTLE). It is known that IL-1β is the primary responsible cytokine for mediating febrile responses in humans and a powerful convulsant in epileptogenesis. Elevation of IL-1β causes a strong release of other proinflammatory cytokines, including IL-6 and IL-8, and an anticonvulsant such as the competitive antagonist IL-1Ra. Induction of IL-1Ra in response to IL-1β is an important component of anti-inflammatory autoregulation. The ratio of IL-1β and other proinflammatory cytokines to IL-1Ra is thought to play a key role in the development of febrile seizures and mediation of neuronal responses in the brain subsequent injury. (9,10,34).

CONCLUSION

We know that epileptic seizures cause substantial changes in the function of the autonomic nervous system (ANS). Therefore, epileptic seizures also affect the various organs and systems under the control of ANS. However, studies regarding the interleukins expressed in these tissues in epilepsy are insufficient. We offer the examination of these tissues in epilepsy which affects the ANS as a suggestion. Upon the literature review, it was observed that interleukin expressions examined in the blood and serum was significantly higher in the epileptic patients compared to the healthy control group (35). It is known that IL-6 expression is higher especially in the liver, gallbladder and lungs; and IL-1β expression is higher in the gastrointestinal system and lungs other than the brain

tissue. The role and effect of the IL-1β and IL-6 can be researched for the peripheral tissues in the lungs, liver and gastrointestinal system in chronic epilepsy. New information and new approaches for the epilepsy treatment can be provided to the literature in this regard.

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