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·Review·

IL-1β: an important cytokine associated with febrile seizures?

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Abstract: Febrile seizures (FSs) are the most common convulsions in childhood. Studies have demonstrated a significant relationship between a history of prolonged FSs during early childhood and temporal sclerosis, which is responsible for intractable mesial temporal lobe epilepsy. It has been shown that interleukin-1β (IL-1β) is intrinsically involved in the febrile response in children and in the generation of FSs. We summarize the gene polymorphisms, changes of IL-1β levels and the putative role of IL-1β in the generation of FSs. IL-1β could play a role either in enhancing or in reducing neural excitability. If the enhancing and reducing effects are balanced, an FS does not occur. When the enhancing effect plays the leading role, an FS is generated. A mild imbalance can cause simple FSs while a severe imbalance can cause complex FSs and febrile status epilepticus. Therefore, anti-IL-1β therapy may help to treat FSs.

Keywords: febrile seizures; IL-1β; cytokines; gene polymorphism

1 Introduction

Febrile seizures (FSs), associated with the rapid rise of body temperature, are the most common convulsions in childhood, occurring in 2%–5% of children before the age of 5 years[1]. While simple FSs (duration <15 min) are generally regarded as benign and have little influence on neurological activity, both complex FSs (duration 15–30 min) and febrile status epilepticus (SE, duration >30 min) are regarded as seizures that may predispose to later epilepsies including temporal lobe epilepsy (TLE)[2]. Thus, FSs are important and should be conquered. A family history of FSs is the most important risk factor, and the more relatives affected, the greater the risk[3]. Understanding the mechanisms that cause FSs may help to elucidate the relationship between interleukin-1β (IL-1β) and FSs, which can be further developed to find new anti-FS therapies.

Both clinical and experimental studies have revealed that the components of the immune response involved in FSs may play a role in their pathogenesis. The inflammatory cytokine IL-1 belongs to a cytokine family that modulates cellular proliferation, and has the capacity to induce other cytokines[4] as well as to act as an endogenous pyrogen[5]. It is intrinsically involved in the febrile response in children and in the generation of FSs in rodent models. The interleukin IL-1 family includes three genes: IL-1α, IL-1β, and their inhibitor, the IL-1β receptor antagonist IL-1Ra. IL-1β and IL-1α are pro-inflammatory cytokines while IL-1Ra works as an anti-inflammatory cytokine. In this short review, we focus on IL-1 gene polymorphisms, changes in IL-1 levels in FSs, and the putative role of IL-1β in the pathogenesis of FSs.

2 Gene polymorphisms

According to the morbidity statistics of FSs, monozygotic twins have a higher concordance rate than dizygotic twins[6], suggesting a genetic factor in the genesis of FSs.

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Polymorphisms of IL-1β, the IL-1β (-511) promoter gene, the IL-1β exon 5 gene and the IL-1Ra gene (IL-1RN) have been studied by many researchers, but the results seem to be contradictory. Different polymorphisms have been described in the IL-1β gene, and at least two influence protein production, one located in the promoter region at position -511 (IL-1β-511)[7] and the other in exon 5[8]. The IL-1β-511T single-nucleotide polymorphism (SNP) is associated with TLE[9,10] and susceptibility to FSs[11,12]. Peltola *et al.* also found that carriers of the promoter -511T allele and lacking the IL-1Ra allele 2 have an increased susceptibility to develop therapy-resistant epilepsy[13]. Also, the -511C/T polymorphism of the IL-1β gene is associated with the development of simple FSs of sporadic occurrence[14]. However, these findings have not been replicated by others[15-19], perhaps because of the sample sizes and experimental conditions (for a summary, see Table 1). In a population of individuals of European ancestry, the data revealed no association between IL-1β gene variation and TLE + hippocampal sclerosis (HS)[17]. The other gene polymorphism, IL-1β exon 5, is not significantly associated with susceptibility to FSs[20,21] (for a summary, see Table 2). So the IL-1β exon 5 gene is not useful in predicting such susceptibility. Only one report focused on the IL-1α gene polymorphisms, and the results were negative[22].

The IL-1Ra gene, IL-1Ra allele *I*, is associated with a higher susceptibility to FSs[20,21]. IL-1Ra intron 2 variable tandem repeat polymorphisms are significantly associated with resistance to FSs[23]. However, another study found no significant difference among the IL-1β-511, IL-1α-889, and IL-1Ra genotypes and alleles for FSs in Turkish children[22] (for a summary, see Table 3). These contradictory results

Table 1. IL-1β (-511) promoter gene polymorphisms and febrile seizures

References	Patients				Controls				Results	Country
	n	*1/1*	*1/2*	*2/2*	*n*	*1/1*	*1/2*	*2/2*		
Virta *et al*., 2002[11]	35	7	18	10	400	146	182	72	positive	Finland
Tilgen *et al*., 2002[18]	99	41	43	55	126	52	59	15	negative	Germany
Chou *et al*., 2003[16]	44	18	19	7	83	24	37	22	negative	China
Kira *et al*., 2005[14]	108	29	41	38	158	53	75	30	positive	Japan
Haspolat *et al*., 2005[22]	73	23	37	13	152	63	50	39	negative	Turkey
Matsuo *et al*., 2006[19]	27	13	8	6	18	5	8	5	negative	Japan
Serdaroğlu *et al*., 2009[23]	90	22	47	21	106	41	54	11	positive	Turkey
Kira *et al*., 2010[12]	249	70	116	63	225	76	106	43	negative	Japan
Chou *et al*., 2010[21]	103	30	47	26	143	48	63	32	negative	China

Single-nucleotide polymorphisms of IL-1β (-511) promoter: allele *1*, position -511C; allele *2*, position -511T. *1/1*: homozygote of allele *1*; *1/2*: allozygote of alleles *1* and *2*; *2/2*: homozygote of allele *2*.

Table 2. IL-1β exon 5 gene polymorphisms and febrile seizures

References	Patients				Controls				Results	Country
	n	*E1/E1*	*E1/E2*	*E2/E2*	*n*	*E1/E1*	*E1/E2*	*E2/E2*		
Tsai *et al*., 2002[20]	51	50	1	0	83	82	1	0	negative	China
Chou *et al*., 2010[21]	104	100	4	0	143	139	3	1	negative	China

Allelic size of IL-1β exon 5 after enzyme digestion: *E1*, 135 + 114 base pairs; *E2*, 249 base pairs. *E1/E1*, homozygote of allele *E1*; *E1/E2*, allozygote of alleles *E1* and *E2*; *E2/E2*, homozygote of allele *E2*.

Table 3. IL-1 receptor antagonist (IL-1RN) gene polymorphisms and febrile seizures

References	Patients				Controls				Results	Country
	n	*I/I*	*I/II*	*II/II*	*n*	*I/I*	*I/II*	*II/II*		
Tsai *et al.*, 2002[20]	51	49	2	0	83	69	14	0	positive	China
Haspolat *et al.*, 2005[22]	69	35	33	1	145	77	56	12	negative	Turkey
Matsuo *et al.*, 2006[19]	26	25	1	0	16	15	1	0	negative	Japan
Serdaroğlu *et al.*, 2009[23]	72[Δ]	40	21	10	106[Δ]	72	19	6	positive	Turkey
Chou *et al.*, 2010[21]	103	96	7	0	143	120	23	0	positive	China

Allelic size of IL-1RN: allele *I*, 410 base pairs; *II*, 240 base pairs. *I/I*: homozygote of allele *I*, *I/II*: allozygote of alleles *I* and *II*, *II/II*: homozygote of allele *II*.

[Δ]Genotypes of one patient and nine controls were identified as others, which were not listed here.

may be because of small sample sizes and inappropriate controls. Studies with more cases are needed to solve this sample size problem. Geographic and ethnic differences may also partly account for the contradictions in the results. When sampling, researchers should also consider the immigration effect. So, further replication in independent population studies will be of great value.

3 IL-1β levels in FSs

Helminen and Vesikari[24] were the first to show increased IL-1 production in peripheral blood mononuclear cells from FS patients after stimulation with lipopolysaccharide (LPS). Leukocytes from children with FSs have an exaggerated IL-1β response to stimulation with double-stranded RNA[19]. Also, in FS patients, the increased plasma IL-1β and cerebrospinal fluid (CSF) TNF-α levels during the acute phase of the FS decreased to normal three months later[25]. Animals with FSs receiving LPS and kainic acid showed increased IL-1β in the hypothalamus and hippocampus but not in the cortex compared with FS-free animals[26]. Conversely, another study reported no difference in serum or CSF IL-1β levels between FS and control children[27]. These contradictory results may be due to the sample size or experimental environment, i.e., different times of sampling or the short half-life and numerous interactions of the cytokines. Thus further work on IL-1β level variations in FSs is needed.

Tütüncüoğlu *et al.* found no significant difference in plasma IL-1α concentrations between FS and controls[25]. There is also no detectable difference in IL-1Ra in brain regions[26]. So, with the elevation of IL-1β and no change in IL-1Ra, the IL-1Ra/IL-1β ratio decreased[26]. Contradictorily, another study showed that the IL-1Ra/IL-1β ratio is significantly higher in FS patients than control children[28]. Since the production of IL-Ra is stimulated by IL-1β[29], the IL-Ra increase is much later than that of IL-1β, so these two different results may be due to the different convulsion phases in which the IL-Ra and IL-1β were assessed.

4 Potential role of IL-1β in FS

IL-1β affects the excitability of the central nervous system; it suppresses the induction of long-term potentiation (LTP) in the CA region and dentate gyrus of the rat hippocampus[30,31]. IL-1Ra[32] and a tripeptide inhibitor of IL-1β[33] inhibit the maintenance phase of LTP. When animals are given intracerebroventricular IL-1β, a dose-dependent increase of the proportion of animals that experience FSs is noted[26]. A study using IL-1 type 1 receptor (IL-1R1) knockout mice found that both the receptor and IL-1β play a role in the genesis of FSs[34]. Animals lacking IL-1R1 have a greater resistance to FSs, and exogenous IL-1β given to wild-type controls reduces the FS threshold[34]. Mice that overproduce IL-1Ra are considerably more resistant to experimental seizures[35] and epilepsy[26,36] than controls. However, IL-1β plays antiepileptic and neuroprotective roles in a rat amygdala kindling model[37].

IL-1β may change neural excitability by two concurrent means:

(1) Direct modulation of ion channels. IL-1β inhibits voltage-dependent Ca^{2+} channel (VDCC) activity in hippocampal CA1 neurons[38,39] and cortical neurons[40]. Zhou *et al*. showed that IL-1β decreases N-type Ca^{2+} channel (NCC) currents and significantly down-regulates the expression of NCC protein, but not the residual Ca^{2+} currents, except L-type Ca^{2+} channel currents[40], by activating protein kinase C in hippocampal neurons[4]. Also, IL-1β reduces the amplitudes of voltage-gated Na^+ currents and action potentials in cultured cortical neurons[41]. These studies showed a negative effect on excitatory neurotransmission. Contradictory results point out the positive effects on neuronal excitability. Qi showed that the half-activation voltage of Na^+ channels and the action potential threshold are positively affected by IL-1β[42], and IL-1β inhibits charybdotoxin-sensitive Ca^{2+}-activated K^+ channels activated by Ca^{2+} influx through voltage-gated Ca^{2+} channels[43,44]. This report also demonstrated that IL-1β increases neuronal excitability via the inhibition of Ca^{2+}-induced K^+ channels activated by Ca^{2+} influx through both NMDA receptors and voltage-gated Ca^{2+} channels in mechanically dissociated hippocampal CA1 neurons[43]. These contradictory results seem to show that IL-1β can both facilitate and reduce the excitability of neurons.

(2) Influence on both excitatory (AMPA, NMDA) and inhibitory (GABA) transmission. IL-1β down-regulates AMPA receptor expression and phosphorylation in a Ca^{2+}- and NMDA-dependent manner in hippocampal neurons[45]. It reduces the frequency of AMPA-dependent spontaneous excitatory postsynaptic currents and miniature excitatory postsynaptic currents[46] but enhances NMDA receptor-mediated currents[45,46]. Viviani *et al*. found that IL-1 increases NMDA receptor function by activating tyrosine kinases and subsequent NR2A/B subunit phosphorylation[47]. IL-1β increases the excitability of hippocampal CA1 neurons in the p38-dependent inhibition of the outward NMDA current[43]. These results showed that IL-1β facilitates excitatory neurotransmission. IL-1β can also depress the inhibitory system. It mediates the depression of GABA-induced current in cultured hippocampal neurons[48], which is dose-dependent and is blocked by IL-1Ra[48]. In addition, polymorphisms of the $GABA_A$ receptor gene and the IL-1Ra gene might be associated with susceptibility to FSs[49-51]. So these findings about the effects of IL-β on ion channels and transmitter receptors support the idea that IL-1β may affect the genesis of FSs; i.e., IL-1β enhances excitation and decreases inhibition, which in turn may cause an FS. Also, the effects of IL-1β on the excitability of neurons depend on many factors, such as the concentration of IL-1β, the functional state and the type of neuron, and the duration of time that the neuron is exposed to this cytokine. Therefore more research is necessary using different concentrations and exposure times of IL-1β and different types of neurons.

Moreover, IL-1Ra is structurally related to IL-1α and IL-1β and competes with these molecules to occupy IL-1β cell surface receptors. Thus IL-1Ra can play an anticonvulsant role in FS genesis. The production of IL-1β is accompanied by the synthesis of 100- to 1 000-fold excess of the endogenous IL-1Ra, which rapidly occludes the activation of this receptor[29], and the maximal increase after stimulation is several hours later than IL-1β[52]. This may explain why the FS is auto-restricted. Overall, these findings suggest that the balance between IL-1β and IL-1Ra during seizures plays a significant role in altering neuronal network excitability, thus affecting the maintenance and spread of seizures.

Another proinflammatory cytokine, TNF-α, also affects both the voltage-gated ion channels and the neurotransmitter receptors. L-type Ca^{2+}-currents in hippocampal neuronal cultures are enhanced by extended incubation with TNF-α[53]. TNF-α increases the cytosolic Ca^{2+} induced by AMPA and KCl in hippocampal neurons[54]. TNF-α stimulates microglia, slowly increasing the Ca^{2+} influx, and the Ca^{2+} concentration does not subsequently decline with removal of the cytokine[55]. The cytokine also causes the transient expression of a non-inactivating outward K^+ current in microglia[55]. In neurotransmitter receptors, TNF-α induces a rapid increase in the neuronal synaptic expression of AMPA receptors[56] and acts on these receptors to facilitate excitability[57,58]. TNF-α also induces the endocytosis of $GABA_A$ receptors, thus reducing inhibitory

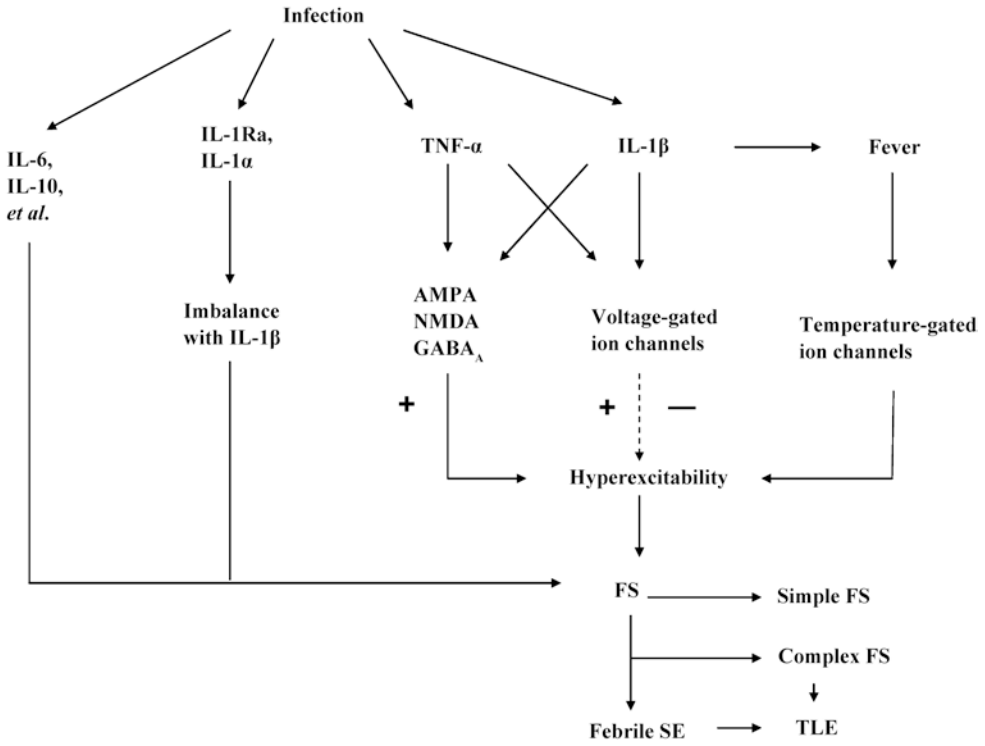

Fig. 1. Interleukin 1β (IL-1β) can change the excitability of the central nervous system by directly modulating ion channels and changing the effects of AMPA, NMDA and $GABA_A$ to cause high susceptibility to febrile seizures (FSs). If the enhancing and reducing effects are balanced, an FS does not occur. When the enhancing effect plays the leading role, an FS is generated. A mild imbalance can cause simple FSs while a severe imbalance can cause complex FSs and febrile status epilepticus (SE). Tumor necrosis factor α (TNF-α) can also induce neuronal hyperexcitability. During infection, the pro- and anti-inflammatory cytokines increase, and the imbalance of these cytokines may promote the genesis of FSs. IL-1 is an inducer of fever, and this facilitates excitability of the central nervous system by activating temperature-gated ion channels, which may also play a role in the genesis of FSs. IL-1Ra, interleukin-1 receptor antagonist; TLE, temporal lobe epilepsy.

synaptic strength[59]. Other inflammatory factors also participate in the genesis of FSs[60-62] (putative mechanisms summarized in Fig. 1).

5 Discussion

When children are infected, IL-1, which is well-known as the inducer of fever, increases[30]. In infections of the central nervous system, such as viral encephalitis and bacterial meningitis, the levels of IL-1 and TNF-α increase[63,64]. These cytokines are likely to be involved in synaptic plasticity, neural transmission, and Ca^{2+} signaling[65]. IL-1β directly modulates ion channels, enhancing NMDA and AMPA[45,46] and reducing the effectiveness of $GABA_A$[48], which can change the excitability of neurons and may promote FS generation. So in an integrative way, IL-1β can both enhance and reduce neural excitability (neurotoxic and neuroprotective effects)[66]. If the enhancing and reducing effects are balanced, an FS does not occur. Moreover, a mild imbalance could cause a simple FS while a severe imbalance could cause complex FSs and febrile SE, so anti-IL-1β therapy may help in the treatment of FSs. In addition, the interaction of IL-1β, IL-1Ra and the other inflammatory cytokines is also of great significance in the generation of FS.

In addition, many studies show that fever affects temperature-gated ion channels [such as transient receptor potential vanilloid subfamily member 1 (TRPV1) and hyperpolarization-activated cyclic nucleotide-gated chan-

nels] and changes neuronal excitability[67,68]. Furthermore, IL-1β application sensitizes TRPV1 currents[69]. These ion channels have been suspected to promote the genesis of epilepsy[70,71] and are probably involved in FSs.

In this review, we suggested that IL-1β plays an important role in the genesis of FSs, and this may help in both diagnosis and treatment: (1) Focusing on the treatment of those patients who have high genetic susceptibility may reduce the morbidity of FSs. (2) Reducing instead of enhancing the excitability effect of IL-1β may avoid the generation and the spread of FSs. (3) Increasing the level of IL-1Ra or applying exogenetic IL-1Ra when an FS has been generated may have an antagonistic effect on the FS. However, more research and clinical data are needed to support this point.

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