Published in final edited form as:

Brain Dev. 2009 May ; 31(5): 388–393. doi:10.1016/j.braindev.2008.11.013.

The role of interleukin-1 β in febrile seizures

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Abstract

Febrile seizures (FS) occur in children as a result of fever. Despite their prevalence, the pathophysiology of FS has remained unclear. Recent evidence from clinical and experimental studies has highlighted a potential role of immune generated products in the genesis of FS. Of particular interest are the pro-inflammatory cytokine, interleukin 1beta (IL-1 β) and its naturally occurring antagonist, interleukin 1 receptor antagonist (IL-1ra). Using a novel animal model of FS, involving the generation of physiological fever, we investigated the role of the IL-1 β /IL-1ra system in the genesis of FS. We found that animals with FS had increased hippocampal and hypothalamic IL-1 β compared to equally treated animals without FS, which was first evident at onset of FS in the hippocampus. There were no differences in IL-1ra levels. ICV IL-1 β increased the number of animals with FS while IL-1ra had an opposite anti-convulsant effect.

The data from these studies, in combination with recent results from other laboratories, have established a putative role for the IL-1 β /IL-1ra system in the genesis of FS.

Keywords

cytokines; seizures; rat; lipopolysaccharide

INTRODUCTION

Febrile seizures (FS) are caused by fever and are considered to be the most common form of seizure in humans [1]. They are exclusively limited to children, typically between the ages of 2 months and 5 years with both boys and girls being equally affected. In the United States 2 – 5% of children will experience a FS, while in certain other nations (notably Japan) the incidence

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is higher at 6 – 9%, suggesting a genetic link [1,2]. Febrile seizures can be subdivided into three different types based upon phenotype and duration of the seizure. Simple FS make up the first type; these are single seizures that occur during a febrile illness, are short in duration (< 15 min.), and have a generalized phenotype [3]. The second type of FS, complex febrile seizures, are longer in duration (15 – 30 min.), may have focal features, and can recur [4]. The third and final type of FS are termed febrile status epilepticus (febrile SE) and are seizures during a febrile illness that last greater than 30 min. While simple FS are generally regarded as benign, both complex FS and febrile SE are regarded as seizures that may produce neurological sequelae and/or predispose to later epilepsies including temporal lobe epilepsy (TLE) [5]. However, if and when sequelae occur is extremely difficult to predict. Although certain risk factors such as age, seizure duration, temperature at time of seizure, and family history can give some insight there is still no definitive predictor for which patients will develop future neurological problems [1,4,6]. An understanding of the mechanisms that bring about a FS may shed some light on the relationship of FS to later neurological sequelae.

The concern over the sequelae of FS is deeply rooted in the history of study into FS. Some of the seminal studies of FS conducted by Lennox in the 1940's showed FS to be a generally benign form of seizure with a rather good prognosis [7]. However, later on in the 1960's a few surgical series were published of patients undergoing temporal lobe resection for intractable TLE, and these showed that a large proportion of patients (50–70%) with intractable TLE had FS as children [8]. This revelation sparked much interest into the relation between childhood FS and adult TLE, which is still prevalent today. Although it is generally agreed upon that the vast majority of children that experience a FS will have no future afebrile seizures or FS beyond childhood, determining what occurs within the brains of the ones that do is extremely intriguing.

Despite the risk of sequelae after complex FS and febrile SE, there is little known about the pathophysiological mechanisms involved in these seizures. Although there have been identified genetic links in specialized cases of FS, namely generalized epilepsy with febrile seizures + and +2 (GEFS+ and GEFS+2), these mutations do not encompass the large majority of patients outside certain pedigrees [9–11]. Aside from a pure genetic source for FS, an alternative area of research has emerged that has examined the role of the immune system in the pathophysiology of FS, with particular focus on the neuro-immune response during FS and its contribution to the seizures and their sequelae.

Over the past two decades there has been emerging evidence from both clinical and experimental studies that components of the immune response involved in FS may play a role in their pathogenesis. In particular, studies have focused on the pro-inflammatory cytokines, which are released during fever (both peripherally and centrally), and their possible role in FS. Specifically several studies have focused on the pro-inflammatory cytokine interleukin-1 β (IL-1 β), although other studies have also examined additional cytokines such as tumour necrosis factor alpha (TNF α), interleukin-1 alpha (IL-1 α) and interleukin-6 (IL-6) [12]. In 1990, a study by Helminen and Vesikari was one of the first to suggest that an enhanced IL-1 β response in children with FS could play a role in the production of seizures [13]. They showed that peripheral mononuclear cells, extracted from children with FS, had a significantly exaggerated production of IL-1 β in response to the gram negative molecule, lipopolysaccharide (LPS), when compared to other children with bacterial infections that did not have seizures [13]. More recently a study by Matsuo *et al* showed that leukocytes from children with FS have exaggerated IL-1 β response to stimulation with double stranded RNA (a viral infection model) [14]. During the time between these studies several others have also examined the role of cytokines in human FS [15–17]. In addition to actual measurements of cytokines in children with FS, there was also the discovery that children with certain genetic alterations in the interleukin system were also more susceptible to FS. For example, a polymorphism found in

the IL-1 β gene cluster has been shown to increase production of IL-1 β in cultured monocytes treated with LPS [18]. This polymorphism has been associated with increased susceptibility to FS [19–21]. Although not all studies were in agreement, it is obvious that the role of immune generated products in FS is an area of great interest.

Since studies in humans have inherent difficulties (individual variability, recruitment, compliance, etc) animal models are often developed as a means to examine basic mechanisms involved in the pathogenesis of seizures [22]. In the case of FS we wanted to develop and characterize a model that employed an immune-generated fever as a mechanistic component of FS induction [23]. This in turn would allow us to examine the role of a neuro-immune response in the pathogenesis of FS.

DEVELOPMENT OF AN ANIMAL MODEL

The goal of our studies was to use immune-generated fever to lower seizure threshold as an animal model of FS. To accomplish this task we employed the LPS model of fever.

Lipopolysaccharide (LPS) is a component of the cell wall of gram-negative bacteria. It has been used to cause fever and the acute phase response in several species from mouse [24] to man [25]. LPS can work via several different pathways to signal the induction of fever. These pathways include signalling through vagal afferents, perivascular endothelial cells, and circumventricular organs [26]. This can occur by both direct action of LPS in these brain areas as well as by cytokines that are produced in the periphery in response to LPS [27–29]. Ultimately this results in the stimulation of the enzyme cyclooxygenase-2 (COX-2) which then catalyzes the conversion of arachidonic acid into prostaglandin E2 (PGE2) that then acts in the hypothalamus to raise the “set point” and produces the rise in body temperature that is fever [29,30]. In order to raise the “set point” several behavioural and physiologic processes become activated with the specific aim of raising body temperature.

Cytokines are produced in response to LPS not only by macrophages in the periphery, but also by microglia, astrocytes and some neurons in the CNS [26,31,32]. Some of the key pro-inflammatory cytokines that are produced in the response to LPS are TNF α , IL-1 α , IL-1 β , and IL-6 [17,24,31]. In addition to the pro-inflammatory cytokines, anti-inflammatory cytokines are also synthesized at the same time, and can include interleukin 1 receptor antagonist (IL-1ra), interleukin 10 (IL-10) and interleukin 18 (IL-18) [33]. Of particular importance in the immune response to LPS are the pro-inflammatory cytokines TNF α and IL-1 β [24,34]. Of the anti-inflammatory cytokines IL-1ra is probably the most widely studied of all. IL-1ra can block fever when given systemically or centrally (directly into the brain) [34]. This occurs by competitive inhibition at the interleukin 1 receptor type I (IL-1RI) that blocks IL-1 β signalling, and thus fever. The immune generated products (PGE2, TNF α , IL-1 β , and IL-1ra), produced by administration of systemic LPS, all play significant roles in the organism’s response to a pathogen, and thus the production of fever, so much so that these pathways are conserved across many species (for a summary of this pathway and its relation to FS see figure 1).

In order to use LPS in our model we first had to ensure that we could produce significant and replicable fevers in young animals. We used postnatal day 14 (P14) rats as subjects. Both the size and the appropriateness of the age of the animal [approximately reflecting human infants [36,37]] were critical factors in the selection. To measure fever we used implantable biotelemetric or datalogging devices that were surgically placed in the abdomen of each animal. In initial studies we tested a dose of 100 μ g/kg (injected i.p.) at normal ambient/room temperature (22°C), and found that animals developed prolonged hypothermia followed by a fever that was highly variable among individual animals [23]. In order to circumvent this issue we raised ambient temperature to 30°C, a temperature selected to be close to the both the thermal-neutral point for this age of animal [38] and the actual nest temperature (JGH

unpublished observations). By doing so we were able to elicit a monophasic LPS fever that had considerably less variability than those at normal room temperature [23]. We also explored dose effects and found that increasing the dose to 200 µg/kg further facilitated fever, and ultimately settled on the higher dose [23].

Since animals do not normally have seizures while febrile, we considered that some predisposition or abnormal excitability might be involved in susceptible animals. To mimic this situation, we paired the fever elicited by LPS with a subthreshold dose of a convulsant drug. In P14 rats we evaluated several candidate drugs at several dosages with differing mechanisms of action. Ultimately we found that both the GABA_A receptor antagonist pentylenetetrazol and the muscarinic cholinergic agonist pilocarpine produced significantly prolonged periods of hypothermia after administration, which would have mitigated the fever that we intended to pair it with. In the case of pilocarpine, its hypothermic effect persisted even when paired with an LPS fever [23]. We also tried the glutamate analog kainic acid (KA) and found that it did not cause hypothermia and actually produced a small but significant hyperthermic response. After having tested several doses for our model we arrived at a dose of 1.75 mg/kg, which in our studies only produced behavioural seizures in approximately 17% of naïve (ie non-febrile) animals [23].

To produce FS we first gave animals an injection of LPS (200 µg/kg, i.p.) and 2.5 hrs later during the rise of the LPS fever (peak is at 3 hrs), gave KA (1.75 mg/kg i.p.) and found that we could facilitate seizures. Ultimately it was found that the pairing of LPS and KA could produce FS in 50% of animals treated, while the other half of animals, despite the exact same treatment with LPS and KA, did not develop FS [23,39,40]. Thus, in our model all animals receive the same LPS/drug treatment but only some develop FS, allowing us to isolate changes associated with FS. In addition to producing FS we also carried out pathological studies to determine if these FS caused damage to the brain, particularly the hippocampus. Febrile seizures were produced in a cohort of animals that were then sacrificed at 72 hrs post seizure and processed for hematoxylin and eosin (H & E) staining. We found no evidence of any overt pathology in the hippocampi of animals with FS, those without FS, and several other control groups [23]. Thus the pairing of LPS and low dose KA was capable of producing FS in 50% of animals tested, FS occurred at clinically relevant temperatures, with a predictable onset of 60 min, duration of approximately 60 min (prolonged complex FS or febrile SE) and no overt histopathology evident with H&E. However, we still did not know the cause of these seizures.

LINKING CYTOKINES TO THE GENESIS OF FS

Some clinical studies over the years have attempted to treat FS by treating fever. For instance there have been some attempts to control FS with the use of antipyretics [41–43] reviewed in [44]. The main outcome of these studies was that the use of antipyretics was not effective in preventing FS recurrence. Since antipyretics block the action of COX-2 and thus the production of PGE2 (as shown in figure 1, path 1) the results of these studies indicate that the genesis of FS may involve alternate pathways outside the traditional febrogenic pathway involving COX-2 and PGE2. Thus the alternative was to examine the effect of cytokine induction and how this may factor into the production of seizures (figure 1, path 2).

As stated in the introduction, there is evidence from clinical literature that IL-1β may play a role in the genesis of FS. To further explore this we designed a series of experiments to determine: 1) whether levels of IL-1β and its naturally occurring antagonist IL-1ra are changed as a result of FS, 2) whether the onset of FS was associated with changes in IL-1β levels, and 3) if there was a causal link between changing levels of IL-1β and IL-1ra and the genesis of FS. First using our model we measured the amount of IL-1β and IL-1ra in several brain regions (hypothalamus, hippocampus and cortex) 3 hrs after KA treatment (2 hrs after seizure onset,

approximately 1 hr after seizure cessation) in animals treated with LPS and KA that had FS and those that did not have FS. Ultimately we found that there were increased amounts of IL-1 β found in the hypothalamus and the hippocampus but not the cortex of animals with FS compared to those without FS [39]. However, this was not accompanied by any changes in the levels of IL-1 α within the same brain regions. This suggests that there may be an imbalance of the ratio of IL-1 β :IL-1 α which may play a role in FS [39,45]. At this time point there were two likely sources of IL-1 β : 1) the LPS induced production of IL-1 β , and 2) seizure induced production of IL-1 β . In order to determine if IL-1 β was associated with the genesis of FS we used a separate group of animals and measured brain levels of IL-1 β at the onset of FS. We found that there was a significant increase of IL-1 β in the hippocampus of animals with FS compared to those equally treated, which did not have FS. However, levels of IL-1 β were unchanged in the hypothalamus and cortex [39]. This would suggest that a significant increase in hippocampal IL-1 β may be a factor in FS. Having established a clear association between altered levels of IL-1 β and the presence of a FS we wanted to test for a causal relation between the IL-1 β /IL-1 α system and FS. To do so we gave exogenous IL-1 β and IL-1 α intracerebroventricularly to animals 30 min after KA treatment. What we found was that IL-1 β dose dependently increased the number of animals that went on to develop FS, and that IL-1 α had the opposite effect [39]. This established a more causal role of the IL-1 β /IL-1 α system in the genesis of FS.

Another recent report has also found that IL-1 β may be of significant importance in the pathogenesis of FS. A study conducted by Dubé *et al* using IL-1RI knockout mice, in a different model of FS, found that both the receptor and IL-1 β played a role in the genesis of FS [46]. They showed that animals that lacked IL-1RI had a greater resistance to FS [46]. They also showed that exogenous IL-1 β given to wild type control animals reduced their FS threshold. In addition they were able to show that IL-1 β alone was capable of producing seizures [46]. Their results complement ours in clearly showing that the IL-1 β /IL-1RI signalling system is of significant importance in the genesis of FS. Thus the role of IL-1 β in the initial seizure is substantial and it may have a further role in any sequelae that occur as a result of a complex FS or febrile SE.

POTENTIAL MECHANISM OF IL-1 β IN FS

The mechanism by which IL-1 β influences FS may involve both excitatory (glutamatergic) and inhibitory (GABAergic) systems [23,39,46]. In terms of excitatory neurotransmission, IL-1 β has been shown to influence seizures through alterations in NMDA receptor phosphorylation. A study by Viviani *et al* showed that cultured hippocampal cells exposed to IL-1 β had increased Ca²⁺ influx when exposed to NMDA [47]. This study further showed that the increased influx of Ca²⁺ was due to phosphorylation of the NR2A/B subunit of the NMDA receptor, which was mediated by Src kinases [47]. This alteration in Ca²⁺ permeability could lead to increased excitability and thus could be a putative means by which IL-1 β can contribute to FS [39,46]. In addition there is also evidence that IL-1 β can influence GABAergic inhibition. A study by Wang *et al* showed that IL-1 β could decrease GABA_A receptor mediated currents in cultured hippocampal neurons [48]. The percent of GABA_A receptor mediated current inhibition was also dose dependant, and blocked by IL-1 α [48]. In addition there is also evidence that IL-1 β can reduce synaptic inhibition in hippocampal CA3 pyramidal cells *in-vitro* [49]. Taken in combination, the notion that IL-1 β may concurrently increase excitation and reduce inhibition provides a possible mechanism by which it may promote the genesis of FS. Of course, IL-1 β may have a number of other actions that cause increased excitability, including interactions with peptidergic systems in the brain [50,51].

CONCLUSIONS

The role of neuro-inflammation in seizures, epileptogenesis and neuro-degeneration is currently an area of considerable interest. There have been several studies recently that have provided insight into the mechanisms by which neuro-inflammation influences seizures and their outcome [52–54]. The role of cytokines (particularly IL-1 β) in these processes has received considerable attention in both humans and animal models. In such a specific case as FS, where we know that immune responses are integral, we find convincing data that IL-1 β plays a significant role in their pathogenesis [39,46]. The mechanisms by which IL-1 β promotes the genesis of FS may yet further apply to the ongoing molecular, cellular, and network reorganization that may follow other types of seizures and epilepsy.

Acknowledgments

Dr. S.L. Moshé is the recipient of the Martin A. and Emily L. Fisher Fellowship in Neurology and Pediatrics. Dr Q.J. Pittman is an Alberta Heritage Foundation for Medical Research Medical Scientist. This work was supported by the National Institutes of Health Research (S.L.M.), the Canadian Institutes of Health Research (Q.J.P) and the University of Calgary (J.G.H).

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FIGURE 1.

The peripheral and central response to LPS. Peripherally LPS stimulates macrophages to secrete pro- and anti-inflammatory cytokines. These can then act through perivascular endothelial cells circumventricular organs (CVOs) or vagal afferents to stimulate COX-2. COX-2 activation increases the production of prostaglandin E2 which then causes fever (path 1). At the same time pro- (TNF α , IL-1 β , and IL-6) and anti-inflammatory (IL-1ra) cytokines are generated in the brain (path 2). These cytokines have been shown to modulate neurotransmission and ultimately could contribute to the generation of seizures during fever.