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## Adaptive Immune Response in Epilepsy

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### 1. Introduction

Various brain injuries in humans such as neurotrauma, stroke, infection, febrile convulsions and status epilepticus are associated with the acute occurrence of seizures and an increased risk of developing epilepsy. Experimental studies in rodents have shown that these events induce a chronic decreased seizure threshold or the development of spontaneous seizures, supporting the notion, that central nervous system (CNS) injury can lead to lasting hyperexcitability. These injuries trigger inflammatory processes in the brain, which are rapidly ensuing and long-lasting, raising the possibility that inflammatory mediators may contribute to the development of epileptogenesis, and the consequent precipitation of spontaneous seizures.

On the other hand a pathogenic role of immunity in epilepsies has long been suggested based on observations of the efficacy of immune-modulating treatments and, more recently, by the finding of inflammation markers including autoantibodies in individuals with a number of epileptic disorders. Clinical and experimental data suggest that both innate and adaptive immunity may be involved in epilepsy. Innate immunity represents an immediate, nonspecific host response against pathogens via activation of resident brain immune cells and inflammatory mediators. These are thought to contribute to seizures and epileptogenesis. Adaptive immunity employs activation of antigen specific B and T lymphocytes or antibodies in the context of viral infections and autoimmune disorders.

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This review focused first on the description of the interaction between the immune system and CNS peculiar aspects and relevance for the pathogenesis of immune-mediated diseases of the CNS, second, we offer an overview of the experimental evidence in experimental models of seizures to discuss how inflammation modulates epilepsy, and whether inflammation is always detrimental to cell survival. Such research has also sought to determine how inflammatory mechanisms might be harnessed to develop therapies for epilepsy and third we describe causal clinical evidences of various forms of human epilepsy in which CNS inflammation and markers of adaptive immunity have been described, also we describe some of the treatments used in pharmacoresistant epilepsy with probable autoimmune origin.

## 2. Overview of the immune system

The natural defences presented by an individual to any external agent are included in the immune system; this is generally divided into innate and adaptive immunity. Innate immunity is the first response presented against insult, that is triggered by physical, chemical or bacteriological damage, the latter is the most familiar and easier to reproduce by introducing systemic lipopolysaccharide or LPS, which is the substance that covers the outer membrane of Gram (-) bacteria (Condie, 1955; Rivest, 2000). For its study, innate immunity is divided into the afferent arm, which identifies or perceives the insult, and the efferent arm, which is how the infection is eradicated (Tracey, 2009). Several studies have shown that depending on the agent causing the damage, pathway, organ and even insult cells triggers a series of molecules for defence of the individual and the communication between immune system cells can lead to it both by direct contact between cells or by the involvement of soluble factors known as cytokines. This will differentiate the humoral components of the afferent arm (LBP, CD14, collectins, properdin, C3b, pentraxins) and efferent (cytokines, antimicrobial peptides, lysozyme, BPI, complement, lactoferrin, acute phase reactants) and cellular components of the afferent arm (TLRs, dectin-1, CD14, formyl peptide receptor or FMLP, NOD1, NOD2) and efferent (antimicrobial peptides, proteases, lipases, glycosidases, cell adhesion molecules, H<sub>2</sub>O<sub>2</sub>, hydroxyl radical, oxygen halides, nitric oxide, peroxynitrite, etc.) (Beutler, 2004; Vezzani, 2005).

Until recently, adaptive immunity was considered a type of immune response independent of the innate immune response; now it is known that both responses are intertwined, so the participation of dendritic cells, monocytes, macrophages, B lymphocytes and T, specialized molecules of immune histocompatibility, complex class I and II (MHC I and II) that are present during the innate response, are the beginning of the adaptive response (Iwasaki, 2010). In this type of response antigen recognition is carried by the specific antigen-presenting cells (APCs) and antigen receptors. In the adaptive immune response; it is identified two ways: the conventional adaptive immunity in jawed vertebrates and unconventional characteristic of jawless vertebrates.

The first is mediated by immunoglobulins (Ig) and T cell receptors (TCRs) (Fig 1). Low-affinity IgM antibodies circulate in the blood prior to encountering pathogens, however, high-affinity IgG and IgA antibodies are required to inactivate toxins, neutralize viruses, and promote the clearance of microorganisms (Li, 2004). Prior to antigen exposure, the initial generation of a diverse antibody repertoire is achieved early in B-lymphocyte

development by the successful rearrangement of the V, D, and J gene. This recombination process depends on the recognition of recombination signal sequences (RSSs), which flank the segmental elements and create extensive variation in the receptor structure at junctional (joining) interfaces. V(D)J rearrangement form of somatic recombination occurs in the progenitors of B and T cells and is mediated by recombination-activating gene 1 (RAG1) and RAG2, which function in a lymphocyte- and site-specific recombinase complex and are supported by ubiquitous DNA repair factors (Fig 1A)(Gellert, 2002). The Immunoglobulins function first as membrane-bound receptors on B cells and their precursor cells, and they are selected for both antigen-binding specificity and affinity. A change in RNA splicing converts the membrane-bound receptor to a soluble product and is associated with the differentiation from receptor-expressing B cells to immunoglobulin-secreting plasma cells. A second wave of antibody diversification occurs through somatic hypermutation (SHM) (Fig. 1B) and/or gene conversion (GC) of the V region to generate high-affinity antigen binding sites (MacLennan, 1994). SHM is the predominant mechanism in mice and humans, whereas GC occurs in chickens and some other species (Weill and Reynaud 1996). In the same centroblast B cell, the heavy-chain V regions encoding the antigen binding sites are rearranged down the chromosome through class switch recombination (CSR) so that they can be expressed with one of the constant (C) region genes to carry out many different effector functions and be distributed throughout the body (Fig. 1C). Activation-induced cytidine deaminase (AID) mediates SHM, gene conversion and class-switch recombination (CSR).

The TCR is a clonotypic, membrane-bound receptor that binds peptide-MHC (pMHC). Similar to immunoglobulins, both classes of TCRs ( $\alpha\beta$  TCRs and  $\gamma\delta$  TCRs) are heterodimers in which a D segment is a rearranging component of one unit of the receptor heterodimer. The function of  $\alpha\beta$  TCRs relies on the polymorphic MHC class I and class II molecules expressed by antigen-presenting cells. By contrast,  $\gamma\delta$  TCRs function independently of MHC class I and class II molecules and it has been proposed that a forerunner of the rearranging antigen-binding receptors might have been a  $\gamma\delta$  TCR-like receptor (--12--). Genetically, TCRs are rearranged into  $\alpha$  and  $\beta$ -chains from a selection of 176 variable (V), diversity (D), joining (J), and constant (C) genes on chromosomes 7 and 14. Random recombination of these genes generates only 5–10% of the potential diversity within the TCR repertoire; exonucleolytic activity, random N nucleotide additions at the V(D)J junctions (Cabaniols, 2001) and  $\alpha\beta$  chain pairing contribute the remainder (Fig 1). Theoretical TCR diversity in humans has been placed in the region of  $10^{15}$  -  $10^{20}$  unique structures (Davis, 1988; Lieber 1991; Shortman, 1990), with direct *in vivo* estimates greater than  $2.5 \times 10^7$  unique structures (Arstila, 1999). Structurally, TCR  $\alpha$ - and  $\beta$ -chains fold to expose six highly flexible complementary determining region (CDR) loops that can contact the pMHC binding face. The germline-encoded CDR1 and CDR2 loops, from the TRAV and TRBV genes, participate heavily in MHC contacts and occasionally peptide contacts. The variable CDR3 loops, which span the V(D)J joints, are key to TCR diversity and participate heavily in peptide contacts. TCRs dock with pMHC complexes in a roughly diagonal fashion, such that the CDR3 $\alpha$  loops are placed over the peptide N-terminus and the CDR3 $\beta$  loops lie over the peptide C-terminus (Miles, 2010).

In unconventional adaptive immunity, the specific response to antigens of bacteria and blood cells is similar to cellular immunity and identified lymphocyte-like cells in organs

and tissues (Alder, 2005). On the other hand humoral mediators are somatically derived variants of leucine-rich repeats or LRRs, termed variable lymphocyte receptors (VLRs), which are as efficient as V (D) J process. The mechanism of VLRs assembly seems to be driven by a copy choice mechanism of recombination that is based on sequence similarities of individual LRR segments rather than by specific recombination elements (Han, 2008; Nagawa, 2007).

Although immunoglobulins, TCRs, and VLRs are structurally unrelated and somatic variations generated through unrelated mechanisms, these molecules develop clonal specificity through somatic recombination, show evidence of specific cell lineage compartmentalization in receptor expression and can share common features in the recipient's immune regulation (Litman, 2010).

### 3. Immunology of the nervous system

The CNS has developed strategies to limit the entry of immune elements as well as to limit the emergence of immune activation with the tissue itself. Immune privilege in the CNS is partially dependent on the blood-brain barrier (BBB), which is designed to limit the entry of solutes and ions into the CNS (Carson et al., 2006). Exclusion from, and selective entry of compounds into the CNS takes place in the capillary venules. In contrast, cell migration takes place at the post-capillary venules, where cell migration is controlled by adhesion molecules, cytokines and chemokines, and their receptors (Fig.2) (Owens et al., 2008). Not only the physical properties of the BBB, but also potentially damaging immune responses as such are regulated by the suppressive environment within the CNS. Both astrocytes and microglia play a major role in this regulation, while neurons are assumed to play a largely passive role being only the victims of immune responses. Microglia invade the brain early in development and take on a resting 'protective' role as sentinels, scattered uniformly throughout the CNS and forming a network of potential effector cells. In contrast to peripheral macrophages that are highly effective at inciting pro-inflammatory responses, microglia take on an opposing role, limiting inflammation. This role is extended also to astrocytes, the first cells that CNS-infiltrating immune cells encounter. Astrocytes suppress T helper 1 (Th1) and T helper 2 (Th2) cell activation, the proliferation and effector functions of activated T cells, and possess a wide variety of molecular mechanisms to induce apoptosis in activated T cells. Contrary to the idea that neurons only play a passive role, many of their products (i.e. neuropeptides and transmitters), as well as the neuronal membrane proteins CD22, CD47, CD200, CX3CL1 (fractalkine), intercellular adhesion molecule (ICAM), neural cell adhesion molecule (NCAM), semaphorins and C-type lectins all regulate inflammation (Tian, 2009). In addition, neurons express low levels of major histocompatibility complex (MHC) molecules and actively promote T-cell apoptosis via the Fas-Fas ligand pathway (CD95-CD95L). Neuronal expression of the cannabinoid (CB1) receptor is also implicated in suppressing inflammation. CB1 knockout mice more readily develop experimental autoimmune encephalomyelitis (EAE), the autoimmune model of multiple sclerosis (MS). Neurons also favour the differentiation of T-regulatory cells, by providing a local microenvironment dominated by transforming growth factor- $\beta$ 1 (TGF- $\beta$ 1). Damaged neurons, however, are less able to maintain this protective shield, allowing further insults.



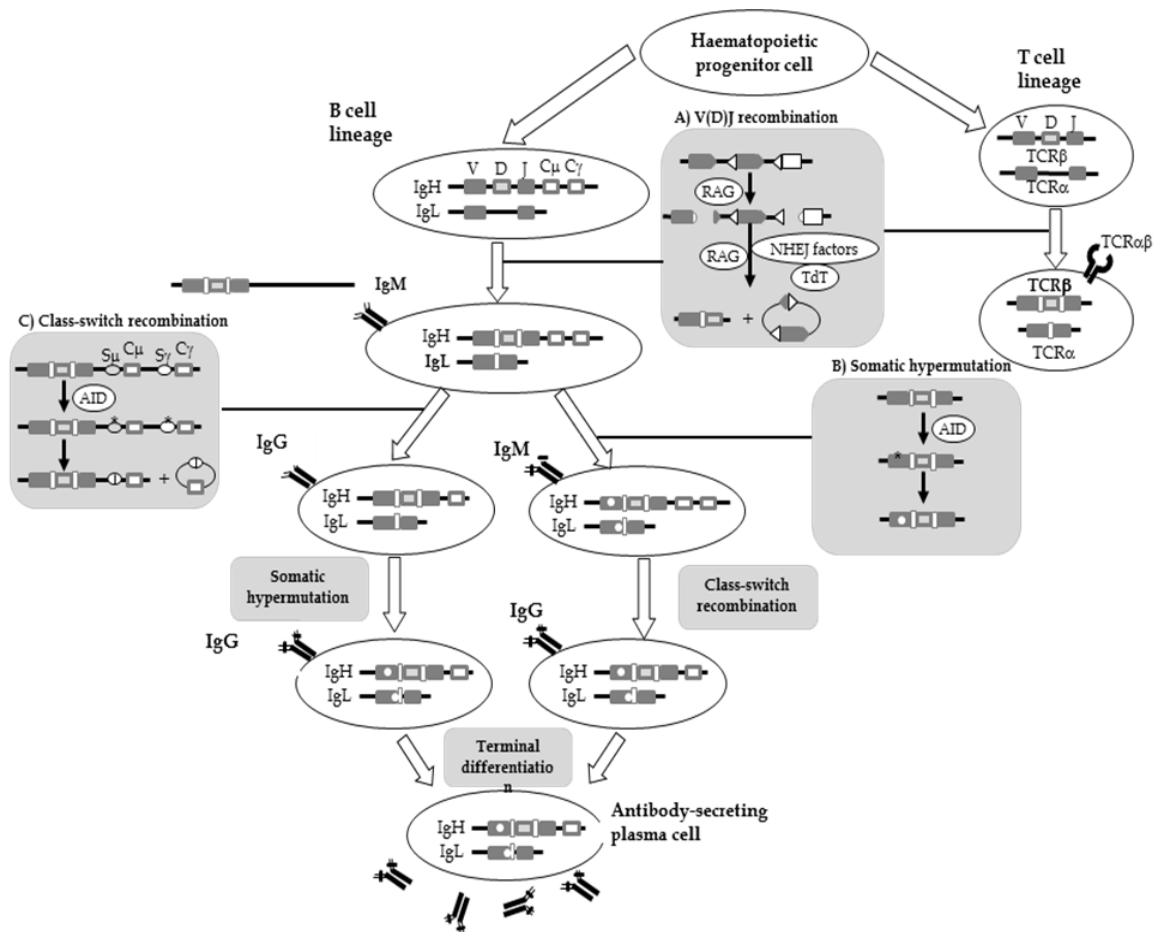


Fig 1. Conventional adaptive immune response in jawed vertebrates. A haematopoietic progenitor cell gives rise to distinct B and T cell lineages. During the development of Ig and TCR different recombination processes are involved. **A) V(D)J recombination.** In this process, RSSs (dark and white triangles) direct the RAG1–RAG2 recombinase complex to individual gene segments (dark and white boxes). The recombinase introduces two double-strand DNA breaks with blunt signal ends and hairpin-sealed coding ends. In the subsequent joining phase, TdT a template-independent DNA polymerase, adds random nucleotides to the junction of the gene elements, thereby increasing repertoire diversity dramatically; the RSSs are joined without further end processing and form excision circles. The key factors that facilitate each diversification step are NHEJ factors. Once functional DNA rearrangements occur, TCR sequences are unaltered. **B) Somatic hypermutation** is initiated by AID, which deaminates individual cytidines within the V(D)J exon of the immunoglobulin gene, leading to U:G mismatches (asterisk). Subsequent error-prone repair results in individual point mutations (white dot in the gene and white bar in the immunoglobulin molecules), and B cells with higher affinity for the original antigen are selected. **C) Class-switch recombination.** The AID creates U:G mismatches in the highly repetitive S regions (dark and white ovals) that are upstream of the exons encoding the constant regions of different isotypes. Error-prone repair leads to the generation of double-strand DNA breaks, excision of the intervening DNA (containing the Cμ exons) and joining of the remains of the S regions. The recombined, somatically mutated V(D)J region is then associated with Cγ, instead of Cμ. ( Modified from Litman, 2010). **B and T cell lineages.** Immunoglobulin heavy and light chain: IgH and IgL; T cell receptor α and β chain: TCRα and TCRβ. **A) V(D)J recombination.** Variable, diversity,

joining genes: V(D)J; Recombination signal sequences: RSSs; Recombination activating gene 1 and 2: RAG1 and RAG2; Terminal deoxynucleotidyl transferase: TdT; Non-homologous end-joining: NHEJ. **B) Somatic hypermutation.** Activation-induced cytidine deaminase: AID. **C) Class-switch recombination.** Switch (S); Constant region for the I $\mu$  isotype (C $\mu$ ) and a single representative downstream C $\gamma$  exon within the IgH locus.

#### 4. Innate and adaptive responses in epilepsy

Despite the immune-privileged environment, it is clear that both innate and adaptive inflammatory responses do occur in the CNS. Activation of the innate immune system is a crucial first line of defense, to opsonize and clear apoptotic cells. Furthermore, innate immune responses recruit cells of the adaptive immune system by secreting various cytokines and chemokines that induce adhesion molecules on the BBB, and by inducing the expression of costimulatory molecules on microglia. Through conserved pattern-recognition receptors (PRRs), local CNS cells may be triggered to develop innate responses. Among these receptors are Toll-like receptors (TLRs), which bind highly conserved structural motifs either from pathogens (pathogen-associated molecular patterns, or PAMPs) or from damaged or stressed tissues (danger-associated molecular patterns, or DAMPs). Thus, not only invading micro-organisms, but also endogenous signals can switch on innate responses in the CNS. Some DAMPs, including heat shock proteins, uric acid, chromatin, adenosine and ATP, high mobility group box chromosomal protein 1 (HMGB-1), galectins and thioredoxin have adjuvant and pro-inflammatory activity. TLRs can be widely up-regulated during neurological disorders in varying patterns on microglia, astrocytes, oligodendrocytes and neurons (Bsibsi, 2002). When activated, TLRs are generally assumed to promote the production of pro-inflammatory cytokines, evoking a damaging environment that may contribute to neuronal damage. *In vitro*, Ab activates microglia through TLRs (Jackson et al., 2006, Okun et al., 2009; Letiembre et al., 2009). TLRs also aid the uptake of Ab and other aggregated proteins, thereby promoting their clearance from the CNS. Although in this manner, TLRs may seem to play a beneficial role in epilepsy it is currently unclear whether cellular activation by TLRs in another way may also contribute to epileptogenesis (Ravizza et al., 2011). Therefore, rather than only playing a pathogenic role, several TLRs also play a role in repair during neurodegenerative disorders, under non-infectious conditions, suggesting that activation of at least some TLRs can also be used as a therapeutic strategy in CNS disorders (van Noort, 2007).

##### 4.1 Experimental evidence

Due to advances in both structural and functional neuroimaging, as well as opportunities to perform invasive investigations of the human brain in an epilepsy surgery setting, an increasing amount of research on focal epilepsy is now utilizing patients and tissue obtained from patients. Nevertheless, parallel studies on patients and well validated equivalent animal models remain indispensable to circumvent difficulties in clinical research resulting from ethical limitations, cost, inadequate sampling, and absence of appropriate controls. The reliability of animal models in analysing epileptogenic mechanisms and testing the efficacy of antiepileptic drugs (AEDs) depends on how faithfully the epileptic phenomenology mimics both the clinical and EEG features of human seizures. Moreover, since human epilepsies are defined as pathological conditions characterized by the recurrence of epileptic

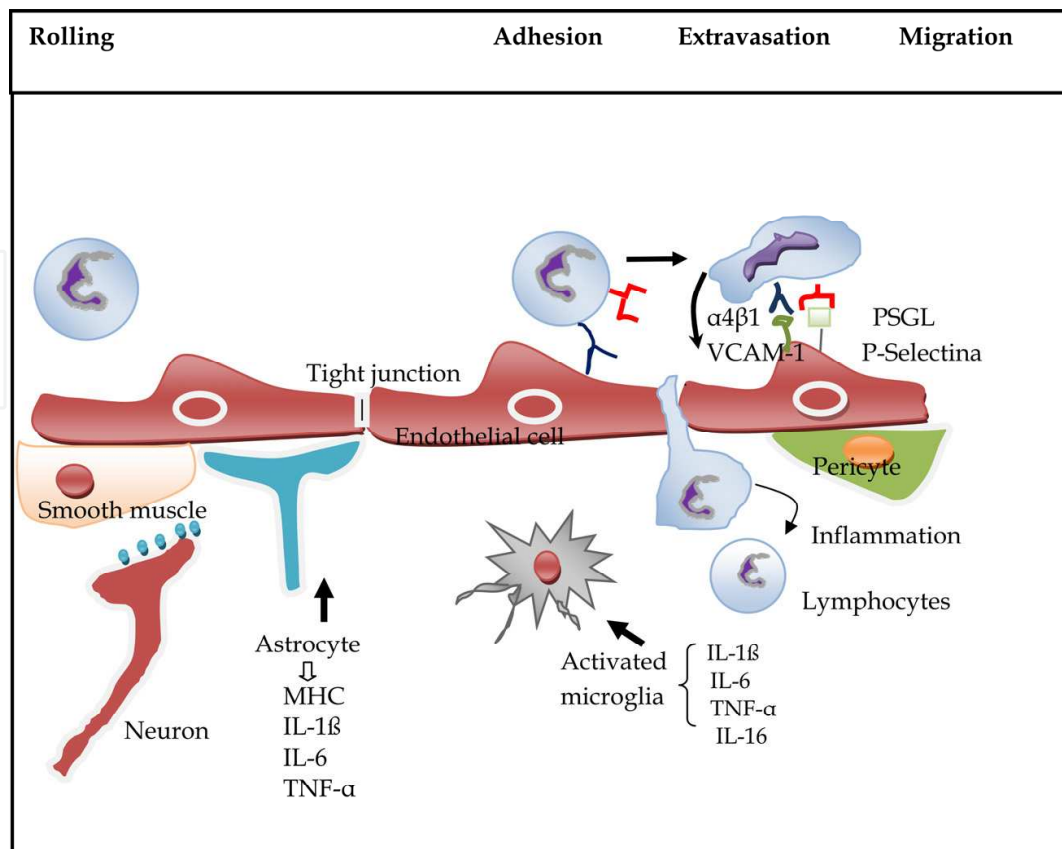


Fig. 2. T cell migration through the BBB in epilepsy. T-cell can enter the brain parenchyma by extravasation across the blood-brain barrier nonfenestrated endothelium and basal lamina. Antigen-presenting cells such as dendritic cells and macrophages are found in the subarachnoid space, in the perivascular space, and in the choroid plexus, whereas microglia are located in brain parenchyma; at these locations, these cells may encounter circulating CNS-borne antigens. The abnormal permeation across the barrier results in further, and perhaps distal, disruption of tight junctions, this time mediated by release of inflammatory mediators by both extravasated blood cells and activated microglia. Frank cellular immunoaggression occurs if and when histocompatibility mechanisms are activated and antibody-mediated reactions occur. IL, interleukin; TNF, tumor necrosis factor; IFN, interferon; CSF, colony-stimulating factor; MHC, major histocompatibility complex, modify by Mix et al (2007) and Oby and Janigro (2006).

seizures only animals presenting with recurrent seizures can be defined as animal models of epilepsy. The acute experimental procedures designed to induce seizures, such as the injection of convulsant drugs, maximal electroshock etc., should therefore be referred to as animal models of seizures and not epilepsies unless they also induce a permanent epileptogenic. In this way the models have been described as **acute experimental seizure models**, in which seizures are induced by electrical stimulation, topical convulsants that block inhibition (e.g., penicillin, bicuculline, picrotoxina, pentylenetetrazol, strychnine), or topical convulsants that enhance excitation (e.g., carbachol, kainic acid). **Chronic models** of focal epilepsy can be induced with freeze lesions, partially isolated cortical slabs, metals (e.g., alumina, cobalt, tungstic acid, ferric chloride), kindling, tetanus toxin, anti-GM1 ganglioside antibodies, hippocampal sclerosis (kainic acid, pilocarpine, self-



sustained status epilepticus), or focal dysplasia (neonatal freeze, prenatal radiation, MAM) (Engel, 2004).

Some of these epilepsy models in rodents trigger a prominent inflammatory response in brain regions recruited in the onset and propagation of epileptic activity; depending on the severity of the seizures, the inflammatory activity is affected in different ways (Minami, 1990;1991; Gahring, 1991;Jankowsky &Patterson, 2001; Kubera,2001; Oprica,2003; Turrin,2004). In models of temporal lobe epilepsy, the seizures produce changes in the function of the peripheral immune system. The thymus, for example, displays reduced weight, probably due to elevated corticosterone plasma levels during kainate-induced seizure; this steroid is induced during some kinds of stress or after a pathogenic infection. An increase in metabolic activity of splenocytes at the cellular level may be connected to enhanced phagocytic activity of macrophages (Kubera et al., 2001). The inflammatory response occurs during the 3 days following seizures. Although IL-1 $\beta$ , TNF- $\alpha$ , and IL-6 are expressed at very low levels in normal brain, their messenger RNA (mRNA) and protein levels are rapidly ( $\leq 30$  min) increased after the induction of seizures, declining to basal levels within 48-72 h from the onset of seizures. However, IL-1 $\beta$  is still up regulated in the brain 60 days after status epilepticus in rats with spontaneous seizures (Plata et al., 2000). The increase in interleukin (IL)-1 $\beta$ , IL-6 and TNF- $\alpha$  in microglia and astrocytes is followed by a cascade of downstream inflammatory events which may recruit cells of the adaptive immune system ( Vezzani and Granata, 2005).

The kindled model exhibited a significant up-regulation of IL-1  $\beta$ , IL-1RI, TNF- $\alpha$  and TGF- $\beta$ 1 mRNAs in several limbic brain regions. The overall profile of mRNA changes shows specificity of transcriptional modulation induced by amygdala kindling. The data support a role for cytokines and NPY in the adaptive mechanisms associated with generalized seizure activity (Gahring, 1997). Cytokine production is also induced in brain by audiogenic seizures(Lee, 2008). Production of proinflammatory molecules (a cytokine induced portfolio of genes that are established mediators of inflammation (Dinarello, 2000) is typically accompanied by the concomitant synthesis of anti-inflammatory mediators and binding proteins apt to modulate the inflammatory response, thus avoiding the occurrence of deleterious induction of genes that mediate inflammatory effects. In this respect, up regulation of IL-1-receptor antagonist (Ra), a naturally occurring antagonist of IL-1 $\beta$ , has been described after acute seizures, status epilepticus, and in kindling (Gasque ,1997; Gorter, 2006;Avignone ,2008). However, IL-1Ra and IL-1 $\beta$  are induced by seizures and IL-1Ra is produced with a delayed time course, differing from classic inflammatory reactions in which IL-1Ra is produced at 100- to 1,000-fold excess and concomitant with IL-1 $\beta$  production. Thus the brain is less effective than the periphery in inducing a crucial mechanism for rapidly terminating the actions of a sustained increase in endogenous IL-1 $\beta$ . Cytokine receptors in the CNS are expressed by neurons, microglia, and astrocytes. However, it is primarily microglia activation that has morphologic changes related to the seizures and inflammation; this is a complex process that includes changes in pharmacological and electrophysiological properties, migration, proliferation, and release of a variety of mediators. In the context of status epilepticus induced by kainate, microglia are activated within the same time course that is observed for neuronal degeneration (Hosokawa, 2003; Xiong,2003).

The immune response changes during all three phases of epileptogenesis. The genes related to immune response are induced during both acute and latent phases of epileptogenesis but

also during the chronic phase (in CA3). Although the immune response was greater one week after status epilepticus, the levels of secreted phosphoprotein 1 (Spp1 or osteopontin), a glycoprotein that promotes macrophage migration, Hg2a (or CD74; H-2 class II histocompatibility antigen), proteasomes (Psm9, macropain), toll-like receptor 4 (Tlr4), and tumor necrosis factor (Gorter,2006), also, the prostaglandin synthesis, illustrated by Cox-2 induction, was activated in the acute and chronic phases but not in the latent period, indicating that this process is related to the occurrence of seizure activity. Activation of prostaglandin receptors could increase intracellular calcium and subsequent glutamate release, which would increase excitability in the surrounding networks (Bezzi et al., 1998; Rozovsk et al.,1994)

An important component of the immune response is activation of the complement pathway. Although complement factors might invade the brain via a leaky BBB, part of the increased expression is likely to originate from activated glial cells (Ravizza et al., 2006;Vezzani, 2008). The complement system may be useful for eliminating aggregated and toxic proteins. However, overactivation of the complement system can also have damaging effects through the activation of microglia and proinflammatory cytokines. Interestingly, sequential infusion of individual proteins of the membrane attack pathway into the hippocampus of freely moving rats induces seizures as well as cytotoxicity (Ravizza et al., 2006).

The complement cascade is activated by three pathways: the classical, the alternative, and the lectin pathway; the lectin pathway leads to the formation of the C5b-C9 membrane attack protein complex (MAC). Complement activation in the CNS is increasingly recognized to be associated with exacerbation and progression of tissue injury in different degenerative and inflammatory diseases. Interestingly, sequential infusion of individual proteins of the membrane attack pathway (C5b6, C7, C8, and C9) into the hippocampus of awake, freely moving rats induces both behavioral and electrographic seizures as well as cytotoxicity, suggesting a role for the complement system in epileptogenesis. Rozowski and colleagues (1994) showed increased C1q and C4 mRNA in rat pyramidal neurons after systemic injection of convulsant doses of kainic acid in neuronal layers of limbic areas that are vulnerable to kainic acid-induced neurodegeneration (Vezzani, 2008); moreover, clusterin and C1q immunoreactivities were observed in both neurons and astrocytes, while increased immunoreactivities (as observed in vivo after seizures) were demonstrated following prolonged exposure of primary cultures of hippocampal neurons to glutamate. Additionally, with sequential infusion into the rat hippocampus the individual proteins of the MAC induced both behavioral and electrographic seizures as well as cytotoxicity (Ravizza et al, 2006).

In addition, there is prominent activation of the complement cascade during the epileptogenesis phase in the experimental model and in sclerotic hippocampi from a rat model of TLE and human TLE (Aronica et al., 2007). Interestingly, the expression of CD59, a complement inhibitor of the MAC, was increased in microglia, but only modestly in neurons, suggesting that in this cell population complement activation may be poorly controlled (Rozovsky et al., 1994). These findings are corroborated by clinical evidence showing that both IL-1 $\beta$  and IL-1 receptor type I (RI), NF $\kappa$ B and complex are overexpressed in lesional brain tissue of patients with diverse types of pharmacoresistant epilepsy (Sheng et al., 1994, Crespel et al., 2002)

## 4.2 Clinical evidence

From a clinical standpoint, a role of inflammation in the pathophysiology of human epilepsy is still hypothetical, although this possibility is supported by abundant evidence. The first insight into a role for inflammation in epilepsy originated from the demonstrated antiepileptic activity of select, powerful anti-inflammatory drugs, including steroids. Moreover, several reports showed increased markers of inflammation in serum, CSF, and brain resident cells in patients with epilepsy. For example, epileptic patients who have recently experienced tonic-clonic seizures display a proinflammatory profile of cytokines in plasma and CSF, consisting of higher IL-6 levels and a lower IL-1Ra-to-IL-1 $\alpha$  ratio. Because the IL-6 concentration is much higher in CSF than in plasma (Pacifci et al., 1995; Peltola et al., 1998) and the contribution of peripheral blood mononuclear cells (PBMCs) to increased plasma levels of cytokines is still unclear (Sheng et al., 1994), the most likely origin of CSF cytokines appears to be the brain. In the same way, Sinha et al. (2008) analyzed cytokine levels in patients with partial epilepsy, status epilepticus and some epilepsy syndromes. Compared to controls, the patient group showed detectable levels of the following cytokines in serum: IL-6, TNF- $\alpha$ , IL-2, IL-4, IFN- $\gamma$  and IL-1 $\beta$ . Serial analysis during the seizure-free period revealed a decrease in cytokine levels: TNF- $\alpha$  (25% to 12.5%), IFN- $\gamma$  (12.5% to 0%), IL-1 (25% to 0) and IL-2 (6.2% to 6.2%), IL-4 (18.8% to 0%) and IL-6 (18.8% to 6.2%). On the other hand, increased post-ictal serum cytokine levels were found in patients with several epilepsy syndromes. However, data collected using tissue of patients with TLE show that specific inflammatory pathways are chronically activated during epileptogenesis and that they persist in chronic epileptic tissue, suggesting that they may contribute to the etiopathogenesis of some types of epilepsy, such as TLE (Ravizza et al., 2008).

## 4.3 Temporal lobe epilepsy (TLE)

Temporal lobe epilepsy refers to both lesional and nonlesional epilepsies characterized by focal seizures arising from either the neocortex or the mesial temporal structures. One of these syndromes is TLE, associated with hippocampal sclerosis (HS), a histopathologic condition characterized by neuronal loss and gliosis, predominantly affecting the CA1 region and the dentate gyrus. Increased IL-1 $\alpha$  expression in microglia-like cells (Aronica et al., 2007), TLE with hippocampal sclerosis, and astroglial, microglial, and neuronal (5/8 cases) expression of C1q, C3c, and C3d were observed, particularly within regions where neuronal cell loss occurs (Crespel et al., 2002). Bauer et al (2009) showed that patients with well-characterized TLE led to immediate and long lasting postictal increase in systemic IL-6 levels; however this rise of IL-6 was lacking in patients with hippocampal sclerosis. The authors in accord with Meador et al.,(2004) suggest the cerebral lateralization of immune functions. On the other hand, there was expression of proinflammatory molecules in neurons and glia in brain tissue obtained from patients surgically treated for drug-resistant epilepsies (Crespel et al., 2002; Maldonado et al., 2003). In particular, the genes involved in the biological process of immunity and host defense are highly overrepresented in HS TLE patients; the functional gene classes most affected are chemokines and neuropeptides (De Simoni et al., 2000; van Gassen et al., 2008). Evaluation of immunological parameters applied to different groups of epileptogenic focus localization has shown that the increase of CD8+ lymphocytes is limited to temporal and lateralized patients. Patients with extratemporal localization of focus, as well as psychogenic cases, show normal levels of immunological lymphocyte markers (Lorigados-Pedre., 2004). Thus, upregulation of these chemokines in

the human TLE hippocampus may contribute not only to neuropathology, but also to epileptogenesis. Early up regulation of chemokines, for instance, after viral infection, may represent a common pathway linking the various predisposing factors in the etiology of TLE, such as trauma, febrile seizures, meningitis, encephalitis, and tumors.) These data show that specific inflammatory pathways are chronically activated during epileptogenesis and that they persist in chronic epileptic tissue, suggesting that they may contribute to the etiopathogenesis of TLE (van Gassen et al, 2008)

#### 4.4 Rasmussen's encephalitis

Rasmussen's encephalitis serves as a prototype of inflammatory epilepsy. The autoimmune nature of this condition was suspected after the discovery of autoantibodies against the glutamate receptor GluR3, one of the AMPA ( $\alpha$ -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid) subunits. Subsequently, anti-GluR3 antibodies were detected in other epilepsy syndromes, including early-onset noninflammatory focal epilepsy and catastrophic infantile epilepsy (Mantegazza et al., 2002). There is no effective medical treatment for Rasmussen's encephalitis, except perhaps steroids, which can be useful when given early in the course of the disease (Robitaille, 1991). Functional hemispherectomy has been the main procedure used to stop progression of the disease; in this way, the tissue could be examined and the progression of an inflammatory process confirmed. Pardo et al. (2004) describe the effect of disease duration on the burden of pathology. The greatest intensity of inflammation and microglial proliferation with nodule formation are generally seen in early states (Fig.3), followed by a decrease in the later stages. The intensity of inflammation, as represented by accumulation of T cells and microglial proliferation (Fig.3), has been reported to bear an inverse correlation with disease duration (Bauer et al., 2002; 2007). Different stages of inflammation may coexist in the same patient with a multifocal distribution, which is consistent with an ongoing and progressive immune-mediated process (Gahring et al., 2001; Neumann et al., 2002). CD8<sup>+</sup> T cells are located in close opposition to degenerating neurons and may contribute to neuronal cell death via secretion of granzyme B, a strong activator of caspase-mediated apoptosis (He et al., 1998; Bien et al., 2002; 2005). Activated CD4<sup>+</sup> T cells may also prime B cells to produce autoantibodies. The resulting autoantibodies may destroy neurons, either directly by excessive stimulation of receptor-mediated ion channels or indirectly by binding complement factors and leading to the formation of the MAC (Bien et al., 2002; 2007) which can induce neuronal loss and seizures (Xiong et al., 2003). Epileptic activity may induce inflammatory mediators in microglia, astrocytes, neurons, and endothelial cells and may alter the properties and permeability of the BBB, thus facilitating the entry of components of the adaptive immune system and molecules usually excluded from the brain parenchyma. These phenomena may consolidate and perpetuate inflammatory reactions in the brain of an affected individual and exacerbate brain damage, thus contributing to brain atrophy. It is still unknown which mechanism ultimately leads to the autoimmune process: viral infection (Xiong et al., 2003), head trauma, or even seizures per se; knowledge of the factors that precipitate the disease can enable prevention of the future development of chronic epilepsy. These recent findings recall attention to the possibility that a viral antigen may act as the initiating event in the complex pathogenetic mechanism leading to brain damage in RE. A cytotoxic T-cell response is in fact compatible with a viral infection, and a viral infection could explain the peculiar hemispheric distribution with centrifugal expansion observed in RE. Previous



studies failed to conclusively link a specific virus to RE, but this of course does not rule out the possible role of an unknown virus.

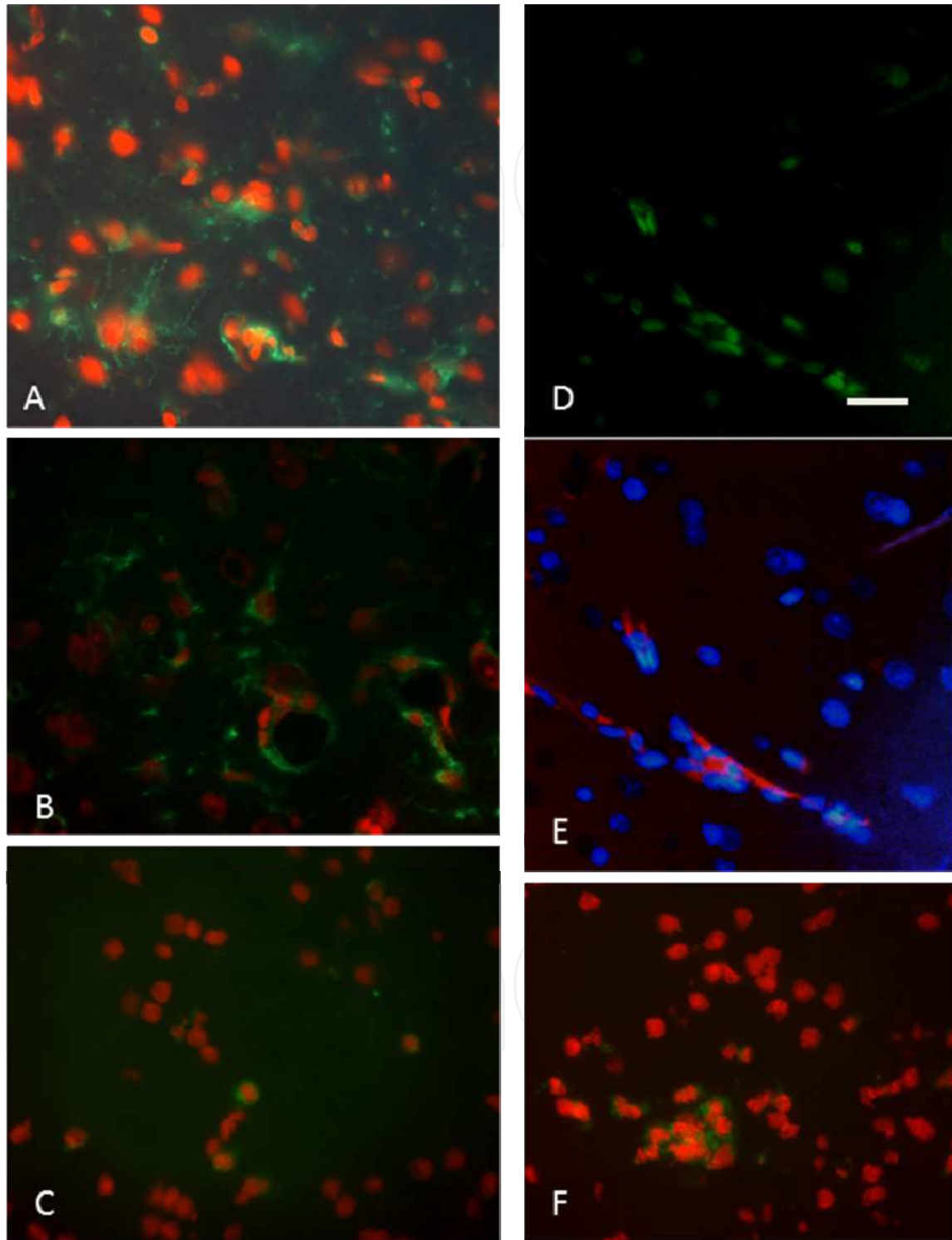


Fig. 3. Photomicrographs of activated microglia (HLA-Dr positive cells, green), A) nodules of microglia in Rasmussen syndrome, B) cortical dysplasia. Cytotoxic T lymphocytes (CD8 +, green) in dysplasia and TLE in (F). Coexpression in capillary of P-glycoprotein (green) and Cox-2 (red) in D and E in Rasmussen syndrome. (scale bar 20  $\mu$ m D-F)



#### 4.5 West syndrome (WS)

WS is an age-related epileptic encephalopathy with onset in the first year of life, featuring clustered spasms and hypsarrhythmia. It may occur in previously healthy children (cryptogenic WS) but more frequently is a symptom of different congenital or acquired diseases (symptomatic WS). Regardless of the etiology, WS patients benefit most from steroid treatment. Steroid efficacy, together with the possibility of spasm disappearance after viral infections (Hattori, 2001), has long been considered an index for an inflammatory or immune-mediated pathogenesis. A recent report (You et al., 2009), of increased serum levels of IL-2, TNF- $\alpha$ , and IFN- $\alpha$  in both cryptogenic and symptomatic WS reinforce this hypothesis. These cytokines are produced by monocytes and lymphocytes, and TNF- $\alpha$  is also produced by brain glial cells; all three have effects that may contribute to seizures and neuronal cell damage (Brunson et al., 1991). The presence of proinflammatory molecules in both cryptogenic and symptomatic WS patients suggests that cytokine changes are likely to be related to epilepsy rather than to the underlying etiology. However, symptomatic patients displayed a greater elevation of IL-2 levels, which varied depending on the underlying disorder (Prasad et al., 1996). If the extent of the inflammatory reaction depends also on the underlying disease, this could partly explain the different efficacies of steroid treatment in selected etiologic subgroups of symptomatic WS patients. For example, treatment with steroids and adrenocorticotrophic hormone ACTH prevents patients with SW from developing Lenox-Gastau (Klein & Livingston, 1950). However, the mechanism underlying the anticonvulsant action of corticosteroids or ACTH remains elusive. Observations from animal models suggest that ACTH acts to repress infantile spasms by suppressing the level of endogenous corticotrophin releasing hormone (CRH) because stress receptors are located in areas of the brain known to be involved in seizure generation (Klein, 1950). It is postulated that the stimulation of synthesis of glucocorticoids that interact with CNS steroid receptors, which then influence voltage-dependent calcium channels, stimulates neurosteroid synthesis in glia and neurons that modulate GABA<sub>A</sub> receptors, down-regulating CRH, which has pro-convulsant activity in the immature brain, and immunomodulation (Joels, 1991)

#### 4.6 Febrile seizures (FS)

FS are the most common cause of seizures in children, affecting 2 to 5% of children. The threshold to febrile seizures is dependent on body temperature, but the threshold varies with individuals and according to age and maturation (Millichap, 1959). A genetic susceptibility to inflammation may influence the threshold convulsive temperature. Seventeen to 30% of febrile seizure patients have a family history of febrile seizures (Millichap, 1959). A biallelic polymorphism in the promoter region of IL-1 at  $\beta$  the -511 position that can increase IL-1  $\beta$  production occurs more frequently in patients with prolonged febrile convulsions (Virta et al., 2002; Kanemoto et al., 2003). In experimental animals, intraventricular injection of IL-1  $\beta$  reduce the seizure threshold in 14-day old mice subjected to hyperthermia, while IL-1receptor knock-out mice have higher seizure thresholds, supporting the role of proinflammatory cytokines in triggering febrile seizures (Dubé et al., 2005)

Viruses are being increasingly implicated as causative agents of febrile seizures. Neurotropic viruses, such as the herpesviruses and influenza A, are commonly associated

with febrile seizures in the United States and Asia (Hall et al., 1994; Chiu et al., 2001). Fever induced by viral infection is regulated by components of the immune response, particularly proinflammatory cytokines. Proinflammatory cytokines are higher in influenza-associated febrile seizures, further suggesting a causative role for cytokines in the pathogenesis of febrile seizures.

## 5. Anti-inflammatory treatments in epilepsy

Nearly 30% of epilepsy patients are refractory to conventional anti-epileptic drugs, and many alternative treatments have been tried to control epilepsy.(Prasad et al 1996). Immunotherapy, such as corticosteroids and ACTH, has been used to treat epilepsy since ACTH was first reported to have beneficial effects in the treatment of infantile spasms in 1950 (Klein, 1950 & Livingston,1950). For example there is no effective medical treatment for Rasmussen's encephalitis, except perhaps steroids,which can be useful when given early in the course of the disease(Bahi-Buisson et al., 2007), A long term follow-up of 11 Rasmussen's encephalitis patients who received steroids showed that 45% of patients had significant improvement of motor function and reduction of seizure frequency with disappearance of epilepsia partialis continua, while 55% patients had no benefit from steroid therapy and ultimately underwent hemispherotomy. Two initial responders to steroid treatment experienced progressive recurrence of seizures one to four years after the discontinuation of steroids and received a hemispherotomy. ACTH is a well-known effective treatment for infantile spasms that not only results in seizure control, but also improves both behavior and background EEG (Low, 1958). Meta-analysis reveals that ACTH is probably effective for short-term treatment of infantile spasms and leads to resolution of hypsarrhythmia (Mackay et al., 2004). Time to response is usually two weeks. Oral steroids can render 30 to 40% of patients seizure-free (Baram et al., 1996; Hrachovy et al., 1983). Further, early use of steroids is more effective; patients treated within one month of spasm onset had a better outcome than those treated after more than one month (Lombroso et al., 1983). The mechanism behind the anticonvulsant action of corticosteroids or ACTH remains elusive. Possibilities include (1) stimulation of glucocorticoid synthesis that interacts with CNS steroid receptors, which then influences voltage-dependent calcium channels; (2) stimulation of neurosteroid synthesis in glia and neurons that modulate GABAA receptors; (3) down-regulation of corticotrophin releasing hormone (CRH) that has proconvulsant activity in the immature brain; or (4) immunomodulation (Hrachovy et al.,1994; Baram et al., 1998; Reddy et al., 2000; Joëls, 2001).

On the other hand, various classes of specific anti-inflammatory drugs have been studied using models of status epilepticus or in kindling. The outcome measures were affected differently by inhibition of specific inflammatory pathways depending on the experimental model and the treatment schedule. For example non steroidal anti-inflammatory drugs (NSAIDs) NSAIDs act as inhibitors of constitutive COX-1 and inducible COX-2 enzymes. COX-2 selective inhibitors, such as celecoxib, parecoxib and SC58236, have been used to interfere with status epilepticus-induced epileptogenesis that was provoked either by electrical stimulation or systemic injection of pilocarpine in rats. These effects were observed under celecoxib treatment, thus a direct anticonvulsant action of this drug cannot be excluded.

Clinical phase	Drug/treatment	Animal models or Seizure type	Mechanism	References
Experimental (I)	Methanolic extract of <i>Asparagus pubescens</i>	PTZ-induced seizures	Inhibits inflammation and seizures	Nwafor et al., 2003
Experimental(I)	Aqueous and ethanolic extract of <i>Solanum nigrum</i>	Picrotoxin, pentylenetetrazole, and electroshocks induced seizures	Immunomodulatory activity	Jain et al, 2011., Ravi et al., 2009
Experimental(I)	Pralnacasan or VX-765	Kainic acid induced seizures	Interleukina converting enzyme/caspase 1 inhibitors and IL-1beta receptor antagonists	Vezzani et al., 2010
Experimental(I)	Naringin	kainic acid-induced status epilepticus in rats	Attenuated the TNF- $\alpha$ and malondialdehyde levels.	Golechha et al, 2011
Experimental(I)	Dexamethasone	Lithium and pilocarpine induced status epilepticus	IL-1 type 1 receptor antagonist and reduction in the number of circulating T-cells (CD3+)	Marchi et al, 2009
Experimental(I)	Naringin, a bioflavanoid	kainic acid (KA)-induced seizures	Antioxidant and anti-inflammatory activity.	Golechha et al., 2011
Experimental(I)	SC-58236, Celecoxib	electrically induced SE, Rat model of pharmacoresistant epilepsy	Selective inhibition of cyclooxygenase-2	Holtman et al., 2010, Schlichtiger et al, 2010
Experimental(I)	Minozac	Electroconvulsive shock	Suppression of proinflammatory cytokine	Somera-Molina et al., 2009; Chrzaszcz et al., 2010
Phase II/III	VX-765	Resistant partial epilepsy	ICE/caspase-1 blockade	Clinical trials gov.
In use	ACTH, prednisolone, and prednisone	Several epileptic syndromes	Antiinflammatory effects	Özkara Ç and Vigevano, 2011
In use	Dexamethasone, methylprednisolone and hydrocortisone	West, Landau-Kleffner or Lennox-Gastaut syndromes and Rasmussen encephalitis	Antiinflammatory effects and improvement of BBB integrity	Marchi et al., 2011
In use	Vigabatrin /and ACTH	Infantile spasms	Interfere with the cellular immune response	Ibrahim et al., 2010

Table 1. Immunotherapy treatments in epilepsy

Daily celecoxib treatment, starting 24 h post-status epilepticus for 42 days, resulted in reduction in the number and frequency of video-monitored spontaneous seizures (Jung, 2006). Other COX-2 inhibitors including nimesulide and rofecoxib, nonselective COX inhibitors such as paracetamol, naproxen, ibuprofen, mefenamic acid and indomethacin, and one selective COX-1 inhibitor SC560, have been tested in the kindling model of epileptogenesis, induced either by repetitive PTZ injections or by electrical stimulation. A significant delay in stage 5 seizure acquisition (i.e. delay in kindling development) was shown in NSAIDs-treated animals, with the exception of ibuprofen, which was found to be ineffective (Tanaka et al., 2009).

Three classical immunosuppressant agents have been used, namely cyclosporine A, FK-506 also known as Tacrolimus, and rapamycin. Their mechanisms of action include inhibition of T lymphocyte activation, although rapamycin alters multiple cellular functions by inhibiting mTOR kinase. Daily systemic injection of cyclosporine A or FK-506 during electrical amygdala kindling prevented the acquisition of stage 5 seizures in rats (Moia et al., 1994). Similar effects of FK-506 were shown in PTZ mkindling in mice (Singh, 2003). However, after drug withdrawal, stimulated animals showed stage 5 seizures, indicating that the treatments failed to inhibit epileptogenesis while providing anticonvulsant effects (Moia et al., 1994). Opposite effects were reported by Suzuki et al. (2001), showing acceleration of PTZ kindling in rats treated with FK-506. The pretreatment with VID-82925<sup>o</sup> kinase inhibitor molecule in 4-AP induced seizures model which revealed antiepileptogenic effect and it significantly suppressed the manifestation of epileptiform activity and was also effective against ictogenesis during the stable phase of focus (Gajda et al., 2011). Overall, these data indicate that the efficacy of immunosuppressant in kindling epileptogenesis is still controversial and requires further investigation, possibly using similar treatment protocols in the same kindling models. More consistent data are obtained in models of status epilepticus-induced epileptogenesis where T-cells do not appear to play a major role. Future studies are needed to target specific molecules involved in some of the pathways of the inflammatory process and to reduce adverse effects.

## 6. Concluding remarks

Accumulating evidence suggests that inflammatory and immune reactions may play an important role in promoting increased neuronal excitability, decreasing seizure threshold and is likely to be involved in the molecular, structural and synaptic changes characterizing epileptogenesis. Also, brain inflammation may contribute to the intractability of seizures and comorbidity in chronic epilepsy patients. Histologic analysis of the human brain from individuals with epilepsy of various etiologies strongly suggests the existence of a chronic inflammatory state in the brain almost invariably associated with neuronal loss, reactive gliosis, and activation of microglia. This observation, together with reports that anti-inflammatory drugs have anticonvulsant efficacy in some cases of drug-refractory epilepsies, suggests the possibility that chronic inflammation in the brain may be implicated in the etiopathogenesis of seizures and the associated long-term events. This hypothesis is supported by functional studies in experimental models of seizures, showing that some proinflammatory molecules exacerbate seizures, decrease the threshold for inducing convulsions, or cause seizures, per se.

Anti-inflammatory therapy may be particularly helpful when given during the latency period shortly after the initial neurologic insult, but prior to the onset of epilepsy, before permanent changes can occur in the neuronal aggregates that promote hyperexcitability and seizure spread. It is necessary to confirm with laboratory tests in serum and blood-cerebrospinal fluid to know the immune response of the epilepsy patient to give pharmacological therapy when the immune response is exacerbated. The causative role of inflammation in the pathogenesis of chronic intractable epilepsy needs to be established and requires further investigation from both the clinical and basic sciences. Pharmacological experiments in animal models suggest that antiepileptogenic effects might be achieved by interfering with specific pro-inflammatory pathways post-injury, although further studies are required to characterize the best targets and protocols for successful pharmacological intervention with limited side-effects.

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## **Recent Advances in Immunology to Target Cancer, Inflammation and Infections**

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Immunology is the branch of biomedical sciences to study of the immune system physiology both in healthy and diseased states. Some aspects of autoimmunity draws our attention to the fact that it is not always associated with pathology. For instance, autoimmune reactions are highly useful in clearing off the excess, unwanted or aged tissues from the body. Also, generation of autoimmunity occurs after the exposure to the non-self antigen that is structurally similar to the self, aided by the stimulatory molecules like the cytokines. Thus, a narrow margin differentiates immunity from auto-immunity as already discussed. Hence, finding answers for how the physiologic immunity turns to pathologic autoimmunity always remains a question of intense interest. However, this margin could be cut down only if the physiology of the immune system is better understood. The individual chapters included in this book will cover all the possible aspects of immunology and pathologies associated with it. The authors have taken strenuous effort in elaborating the concepts that are lucid and will be of reader's interest.

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