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Temporal Lobe Epilepsy: Cell Death and Molecular Targets

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1. Introduction

According to data from the World Health Organization (WHO), epilepsy is a common chronic brain disorder affecting approximately 50 million people worldwide. The hallmark of epilepsy is the recurrence of seizures, which on a cellular level is characterized by synchronized discharges of large groups of neurons that interrupt normal function. TLE is the most frequent type of human epilepsy (Engel, 2001; Willianson et al., 1993). In about 40% of patients, the seizures are refractory to medical therapy (De Lanerolle & Lee, 2005). The majority of these patients suffer from symptomatic focal epilepsies, which are frequently a consequence of brain trauma, complicated febrile convulsions, prolonged seizures (status epilepticus; SE), ischemic lesions and brain tumors (French et al., 1993; Mathern et al., 1995). Neuroimaging and cognitive testing of patients with refractory epilepsy also suggest detrimental effects as a result of repeated seizures over time, including volume reduction within the involved brain structures. TLE syndrome is characterized by partial seizures that may or may not be secondarily generalized. The common symptoms include abdominal sensations and fear in patients with mesial temporal sclerosis (Devinski, 2004).

Neuropathological studies indicate that TLE is frequently associated with hippocampal sclerosis that is routinely detected by imaging studies during the presurgical evaluation of patients with an intractable TLE (Mathern et al., 1995). In a review, de Lenarolle and Lee (2005) cited that about 70% of hippocampi removed surgically from patients with TLE showed hippocampal sclerosis, and 30% did not show sclerosis, known as paradoxical TLE. The etiology and the pathogenesis of this type of medial temporal lobe damage are not known. Several studies have shown a correlation between severe childhood illness (infection, febrile convulsions, prolonged seizure and hippocampal atrophy in TLE (Cavanagh & Meyer 1956; Mathern et al., 1995). However, not all TLE patients exhibiting hippocampal damage have a history of an initial insult. Some experimental and human data suggest that recurrent seizures may cause progressive damage to the hippocampus (Sloviter, 1983; Mathern et al., 1995). Until recently, it was unknown whether the damage found in the hippocampus was the cause or the consequence of TLE. However, the surgical

removal of the sclerotic hippocampus results in the best seizure-free outcome (De Lanerolle & Lee, 2005).

2. Neuropathological findings in temporal lobe epilepsy

The hippocampus or Ammon's horn is one of the most vulnerable areas in the temporal lobe to develop cell loss following seizures. The histological pattern of hippocampal sclerosis in TLE patients is characterized by the loss of pyramidal cells in the prosubiculum and the CA1 of the hippocampus (Mathern et al., 1995). These findings also include neuronal loss in the hilus of the dentate gyrus and the adjacent CA3 region of the hippocampus (Mouritzen, 1982; Babb & Lieb 1984). In many cases, the hippocampal damage in TLE was accompanied by aberrant mossy fiber reorganization. Mossy fibers from the dentate granule cells, which normally innervate the hilar mossy cells and the CA3 pyramidal cells and interneurons, reorganize and project into the inner third of the molecular layer of the dentate gyrus (Sutula et al., 1989; Babb et al., 1991; Szabadics & Soltesz, 2009). The term "mesial temporal sclerosis" has been introduced to describe cellular damage in the hippocampus, amygdala and entorhinal cortex (De Lanerolle & Lee, 2005).

3. Epileptogenesis

The development of an epileptic disorder involves a cascade of events that become activated by an initial insult to the brain. Based on studies using animal models (Turski et al., 1983; Leite et al., 1990) or human patients, there is a period so that events triggered by an initial insult (trauma or SE) can generate an active epileptic focus. It is believed that this latency period (weeks in animal models or years in patients) reflects a reaction mechanism resulting from cellular loss and is required for the synaptic reorganization to occur, which leads to an increased excitability and to changes in synchronization that establishes the chronic epileptic disorder. Figure 1 is a schematic diagram showing the events activated at different time points following an insult in human and in animal epilepsy models, which could be involved with the development of spontaneous seizures.

Thus, epilepsy can be considered an active process that results in both ictal phenomena and permanent interictal functional and structural changes in the brain (Mathern et al., 1995). Patients who develop TLE demonstrate a progression in both the number of seizures and in the neurological symptoms related to the seizure, such as cognitive and behavioral disorders (Engel et al., 1991, French et al., 2004). The long latency before the usual complex partial seizures form in TLE offers a potential time window for therapeutic interventions, which may be a good alternative to prevent the appearance of seizures.

4. Experimental animal models of TLE

The experimental animal models provide a useful approach to assess the mechanisms involved in the epileptogenesis. The damage precedes the appearance of spontaneous seizures in several animal models of partial epilepsies. *SE* induced by systemic injection of pilocarpine or kainic acid caused structural brain damage in rats. Cell loss was observed in the hilus and the CA3 region of the hippocampus as well as in the amygdala, entorhinal cortex, thalamus and cerebral cortex (Turski et al., 1983). Moreover, prominent mossy fiber sprouting occurred (Mello et al., 1993). According to Olney et al. (1974), kainic acid and
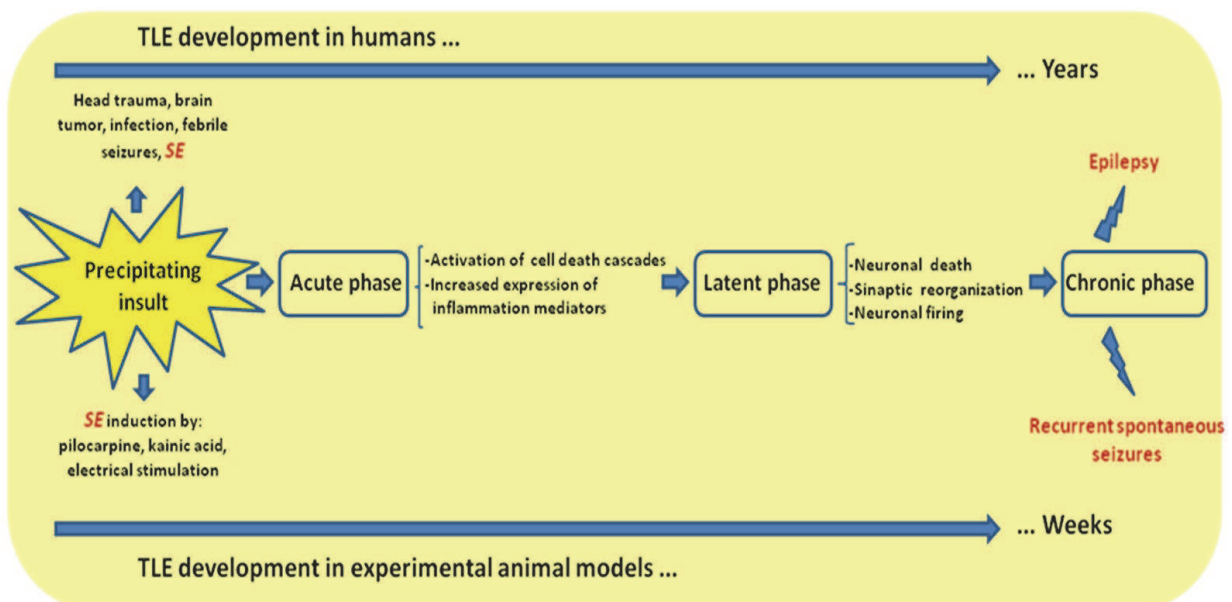
Fig. 1. A schematic diagram of epileptogenesis in patients and an experimental model of TLE. An initial precipitant insult can cause lesioning or functional changes. During a latent period, which can take years (5-10 years) in patients or weeks (2-3 weeks) in animal models, the insult initiates the reorganization of the brain and becomes prone to generate spontaneous motor seizures. Epileptogenesis includes changes that involve cell death, inflammation, neurogenesis, gliosis, sprouting, dendritic plasticity, and blood-brain barrier damage (Pitkanen & Lukasiuk, 2011). The short time frame for the development of the main features of the pathogenesis of TLE in animals encourages use in this study.

other glutamate analogues are toxic because they activate glutamate receptors on neuronal membranes, resulting in prolonged depolarization, neuronal swelling and death. By activating M1 muscarinic receptors, pilocarpine activates phospholipase C, which in turn produces diacylglycerol (DG) and inositol triphosphate (IP3), which results in alterations in calcium and potassium concentrations that lead to enhanced excitability (Raza et al., 2004; Smolders et al., 1997, Smolders et al., 1996).

The increased excitability in the hippocampus resulted in the decreased activity of ATPases that were unable to repolarize the membrane or promote calcium extrusion (Fernandes et al., 1996; Funke et al., 1998). High intracellular calcium can promote glutamate release, which by activating glutamate receptors allows the influx of additional calcium to induce *SE*, excitotoxicity and cell death (Smolders et al., 1997; Fernandes et al., 1996). In these experimental models, the recurrent spontaneous seizures occurred after a latent period, which is reminiscent of the human TLE (Mello et al., 1993). Inflammatory mediators have been described in the hippocampus of rats treated with pilocarpine, and molecules, such as kinins and prostaglandins, and also participate in the pathophysiology of TLE (Naffah-Mazzacoratti et al., 1995; Argañaraz et al., 2003; Perosa et al., 2007).

Kindling is an animal model of TLE where increasingly stronger seizures are induced by electrically stimulating brain areas (Goddard et al., 1969). Repeated seizures induce progressive cellular alterations, not only in the hippocampus, but also in the amygdala and the entorhinal cortex (Cavazos et al., 1994). Furthermore, studies have demonstrated that the neuronal loss is accompanied by aberrant mossy fiber axonal growth of the dentate granule cells in the hippocampus (Cavazos et al., 1991).

5. Molecular changes in epileptogenesis

Significant cell death and reorganization occurs in the CA1 region, and studies have shown an intense synaptic reorganization of calbindin and parvalbumin-positive neurons, which are presumably GABAergic neurons, that results in the inhibition of inhibitory neurons leading to abnormal synchrony and seizure activity (Wittner et al., 2002). This suggests that hyperexcitability is not due to the loss of γ-aminobutyric acid (GABA) but involves other mechanisms that are related to increased excitatory neurotransmission. In addition, there is evidence that mossy cells in the hilus and pyramidal neurons in the CA3 region show increased expression of GluR1 that promotes the excitation of granule cells (Eid et al., 2002).

To date, studies have focused on the increased astrogliosis in this region, which could also contribute to the hyperexcitability. There is evidence that astrocytes contribute to the high levels of glutamate in hippocampal areas where neurons are sparse (De Lanerolle & Lee, 2005). Some changes in astrocytes, such as high sodium channels expression, reduced inward rectifying potassium channels, elevated expression of GluR1 and downregulation of glutamine synthetase, an enzyme responsible for the conversion of glutamate to glutamine, represent potential mechanisms by which astrocytes can release glutamate (O'Connor et al., 1998; Schroder et al., 2000; Eid et al., 2004, van der Hel et al., 2005).

Astrocytes can modulate the inflammatory reactions through the expression of the transcription factor nuclear factor kB (NF-kB) and activation of prostaglandin E2 (PGE2) in response to interleukin-1β (IL-1β) (Dong & Benveniste, 2001). PGE2 increases calcium levels within astrocytes and contributes to glutamate release (Bezzi et al., 1998).

In addition to IL-1β, astrocytes can also produce other immunological agents, such as interleukins (IL-1, IL10 and IL-6), interferon-alpha and beta (IFN-α and β), tumor necrosis factor-alpha (TNF-α) and transforming growth factor-beta (TGF-β) (Dong & Benveniste, 2001; John et al., 2005). Studies have shown that IL-1β is upregulated in the sclerotic hippocampus from patients with TLE and can exacerbate seizures through glutamate release (John et al., 2005). The genes regulated by IL-1β are upregulated in sclerotic hippocampi from TLE patients (John et al., 2005).

Growing evidence indicates that purines are widely involved in the molecular mechanisms underlying the various functions of astrocytes, either by modulating intracellular molecules involved in energy metabolism and nucleic acid synthesis or by activating a variety of membrane receptors (Neary et al., 1996; Abbrachio & Burnstock, 1998). By activating P2 receptors, purines can also modulate calcium influx, and there is substantial evidence that cellular cascades initiated by calcium influx and perturbed intracellular calcium homeostasis are involved in the status epilepticus-induced excitotoxic cell death. Other studies have indicated that large amounts of ATP released from dying cells after the insult might induce reactive astrogliosis, microglia proliferation and act as a powerful chemoattractant at the site of injury (Davalos et al., 2005). Both astrocytes and activated microglia are able to induce the release of cytokines, such as IL-1β, TNF-α, and IL-6, which could influence the neuroinflammatory processes during neurodegeneration (Sanz & Di Virgilio, 2000). The activation of microglial P2X7 receptors by ATP induces TNF-α release, and this effect is regulated by extracellular signal-regulated kinase (ERK) and p38 mitogen-activated protein (MAP) kinase (Suzuki et al., 2004).

It is not known whether microglia protect or damage neurons or whether TNF is beneficial or toxic. However, recent studies have demonstrated that P2X7 receptors were able to modulate the immune response of glial cells, and the expression of P2X7 receptors was

increased in the rat hippocampus following pilocarpine-induced SE (Dona et al., 2009; Fernandes et al., 2010). Several authors have reported that the neuroinflammation is an injury-induced glial activation that can contribute to the pathology of epilepsy (Naffah-Mazzacoratti et al., 1995; Rappold et al., 2006; Vezzani & Granata, 2005).

6. Cell death secondary to seizures

The mechanism by which seizures cause neuronal death is understood based on studies that examined glutamatergic neurotransmission. The glutamatergic neurotransmission induced by excitotoxicity leads to the over-activation of glutamate receptors, which causes an excessive influx of Na^+ and Ca^{2+} that induces osmolytic stress, cell swelling/rupturing, free radical production, which damages DNA, and protease activation leading to the proteolysis of cell and organelle membranes. This ultimately culminates with cell necrosis (Fujikawa, 2005, 2006). The glutamate-mediated excitotoxicity and necrosis are primary contributing factors, but seizures also activate programmed cell death pathways, such as apoptosis (Henshall 2007, 2008).

7. Apoptosis

Apoptosis is the physiological process of programmed cell death (Strasser et al., 2000). Apoptotic signals through a highly ordered molecular cascade that is energy-dependent and may involve new gene transcription. Several studies have identified key genes in the nematode worm, *Caenorhabditis elegans*, that promoted (ced-3, ced-4) or inhibited (ced-9) apoptosis (Ellis and Horvitz, 1986; Hengartner et al., 1992). Further, the mammalian homologues of these genes allowed for the characterization of two classes of proteins involved in apoptosis: caspases and Bcl-2 (Hengartner and Horvitz, 1994; Yuan et al., 1993).

8. Caspases and Bcl-2

Caspases are aspartate-specific cysteine proteases present in cells as zymogens. A proteolytic cleavage is required for the enzymes to become active. In mammals, fourteen types of caspases have been identified and were divided into the inflammatory/cytokine-processing caspases that include -1, -4, -5, -11, and -12. The apoptosis-regulatory caspases were divided into initiators of apoptosis that include -8, -9, and -10, and the apoptotic executioners are caspases -3, -6, and -7 (Thornberry and Lazebnik, 1998; Henshall & Simon, 2005). The activation of cell death signaling is initiated by a caspase, which will then activate specific executioner caspases. The executioner caspases will cleave key structural and functional proteins within the cell, such as actin and the inhibitor of caspase-activated DNase (ICAD), as well as providing feedback loops for further processing of caspases (Mashima et al., 1997; Sakahira et al., 1998; Thornberry and Lazebnik, 1998; Henshall and Simon, 2005).

The Bcl-2 gene family is comprised of more than 20 different members that regulate apoptosis positively, pro-apoptotic, or negatively, anti-apoptotic, primarily by affecting the mitochondria (Henshall and Simon, 2005; Kroemer et al., 2007). Many efforts have been made to elucidate the role of Bcl-2 proteins in apoptosis (Henshall & Simon, 2005; Kim et al., 2006). The pro-apoptotic Bcl2 family protein, Bax, becomes active by binding to tBid and can trigger the formation of pores in the mitochondrial membrane, which allows the

release of the apoptogenic factor, cytochrome c. The Bcl-2 pro-apoptotic proteins, Bim and Puma, neutralize the anti-apoptotic protein Bcl2. The proteins Bcl-2 and Bcl-xl confer protection by promoting oligomerization with pro-apoptotic members, by maintaining the integrity of the mitochondria, by mobilizing calcium and by acting as an antioxidant (Henshall & Simon, 2005).

The high level of intracellular calcium (Ca^{2+}) that results from the activation of glutamate can trigger mitochondrial dysfunction directly or activate calcium phosphatases (e.g., PP2B and calcineurin) or regulatory molecules responsible for the release of Bad from the anti-apoptotic protein, 14-3-3 (for details see Henshall & Simon, 2005). The transcription factor, Fox-O, is involved as a second regulatory step, is activated by dephosphorylation and upregulates Bim, whereas p53 upregulates Puma. These BH3-only proteins may promote Bax/Bak by inactivating the anti-apoptotic Bcl-2, Bcl-xl, Bcl-w or by directly activating Bax/Bak. Cytochrome *c* is released from Apaf-1, which then triggers caspase-9 activation, blocks various heat shock protein (HSP) activity and the X-linked inhibitor of apoptosis protein (XIAP). The extrinsic and intrinsic pathways converge on the activation of the executioner caspases, -3 and -7 that can then cleave key substrates (e.g., ICAD).

The endoplasmic reticulum (ER) is an organelle that acts as a key trigger in the induction of the intrinsic pathway of apoptosis (Xu et al., 2005). Protein misfolding that arises from an increased intracellular calcium level can act as a potential ER stressor. Under persistent stress, apoptosis is triggered by a mitochondrial-mediated pathway (Smith & Deshmukh, 2007), and this process requires Bax for the initiation of the pathway and Apaf-1 for cell death execution (Smith & Deshmukh, 2007).

9. Intrinsic and extrinsic pathways of apoptosis

Apoptosis can be initiated by two different routes known as extrinsic death receptor pathway, and intrinsic mitochondrial pathway (see Henshall and Simon, 2005).

In the extrinsic pathway, a cell death-promoting stimulus activates an initiator caspase via a recruitment scaffold. Activation of the cell surface-expressed death receptors, such as the TNF superfamily (TNFR1; TNF receptor 1) or Fas, causes the death effector domains (DED) within the prodomain to bind to homologous regions on the death receptor (DR) adaptor proteins, such as Fas-associated death domain (FADD), which forms an intracellular complex known as the DISC (death-inducing signaling complex), leading to caspase-8 activation (Henshall, 2005, Thornberry and Lazebnik, 1998).

The caspase cascade is initiated by caspase-8 and culminates with the activation of executioner caspases, such as caspase-3, which cleave intracellular structural and survival proteins and activate enzymes responsible for DNA fragmentation (Henshall and Simon, 2005, Thornberry and Lazebnik, 1998).

The intrinsic pathway is triggered following the disruption of intracellular organelle homoeostasis or DNA damage (Verhagen et al., 2000). This pathway is characterized by mitochondrial dysfunction that causes the release of apoptogenic factors, such as cytochrome *c*, which activates Apaf-1 (apoptotic protease-activating factor 1) and caspase-9 and is followed by downstream executioner caspase activation and cell death (Figure 3). Smac/DIABLO is released following mitochondrial damage and blocks active caspase inhibitors (Verhagen et al., 2000).

The cross-talk between the two apoptotic pathways can occur through the cleavage of Bid by activated caspase-8. Cleavage of Bid leads to truncated Bid (tBid) formation, which

translocates into the mitochondria and induces the release of cytochrome c and Smac/DIABLO (Figure 3) (Madesh et al., 2002).

10. Seizures activate apoptosis

Several studies have indicated that seizures can activate the intrinsic and extrinsic apoptotic pathways in the brain (Henshall, 2007). The release of cytochrome *c*, Apaf-1, activated caspase-9 and -3 and subsequent DNA fragmentation in the rat hippocampus after a short *SE* duration indicate activation of the intrinsic pathway (Turski et al., 1983; Leite et al., 1990). Further, the intrinsic pathway can be activated by calcium. Pro-apoptotic Bcl-2 proteins (Bad, Bid and Bim) can be activated via calcium-dependent mechanisms, and each protein was found to be activated by seizures *in vivo* (Weiss et al., 1986; Mello et al., 1993).

The importance of the Bcl-2 family in human epilepsy has been studied extensively. Elevated Bcl-w, reduced Bim and normal levels of Bcl-xl, Bax, Bad and Bid have been reported in the hippocampus obtained from patients with intractable seizures (Murphy et al., 2007; Shinoda et al., 2004, Yamamoto et al., 2006a). Serum analysis has also provided indirect evidence for the modulation of Bcl-2 in patients with epilepsy (El-Hodhod et al., 2006). These Bcl-2 expression patterns may reflect the repertoire of genes that regulate cell death that may lower the vulnerability of the brain to further neuronal loss (El-Hodhod et al., 2006). Indeed, repeated electroshock seizures in rats and mice, a protocol used to evoke a damage-refractory state, adjust the balance of pro- and anti-apoptotic Bim and Bcl-w levels and demonstrate a similar pattern to those observed in patients (Murphy et al., 2007; Shinoda et al., 2004).

The secondary role of the extrinsic pathway in cell death during seizures was demonstrated by the presence of caspase-8 cleavage in the early stages following the seizures (Henshall et al., 2001). The cleavage of a select group of caspases (-3, -7, -8 and -9) was detected in the hippocampus of rats after repeated electroshock seizures, indicating that the progression of apoptosis signaling may occur (Yamamoto et al., 2006b, Schindler et al., 2006, Yamamoto et al., 2006c).

In addition, activated TNFR1 and DISC were detected in a seizure-damaged hippocampus from rats (Henshall et al., 2003; Shinoda et al., 2003), and patients with TLE (Yamamoto et al., 2006).

Currently, it is not known whether TNF is beneficial or toxic to neurons. TNF may enhance injury induced by ischemia and trauma (Barone et al., 1997; Meistrel et al., 1997) as well as provide neuroprotection by inducing the expression of anti-apoptotic and antioxidative proteins (Yang et al., 2002). The dual effect of TNF is mediated by different TNF receptors, with the p55 TNFR1 mediating the neurotoxic effect and p75 TNF receptor 2 (TNFR2) eliciting the neuroprotection (Yang et al., 2002). By blocking protein synthesis, TNFR1 can trigger apoptosis and cause stress to the ER in the hippocampus of a patient during seizures (Yamamoto et al., 2006; Shinoda et al., 2003). These data suggest that glutamate excitotoxicity is not the only mechanism resulting in cell death after seizures. Efforts have been made to determine the temporal order of intrinsic and extrinsic pathway activation to clarify the relevance of these signaling pathways in neuronal death that is secondary to seizures.

In summary, apoptosis signaling pathways contribute to the neurodegenerative mechanism elicited by seizures and may be involved in epileptogenesis. Several apoptotic regulatory proteins have homeostatic functions in the cells involved with seizure or epilepsy

susceptibility, such as Bcl-2 members, Bax and Bak, which regulate intracellular calcium at the ER membrane (White et al., 2005). In this vein, altered levels of Bcl-2 proteins in the TLE patient's brain may influence a spectrum of intracellular responses, including excitability. It has been reported that caspases can have other functions in addition to apoptotic signaling. The importance of activated caspases in normal cells during development and signaling has recently been extended to the CNS where these proteases have been shown to contribute to axon guidance, synaptic plasticity and neuroprotection (McLaughlin, 2004; Lamkanfi et al., 2007). Finally, efforts have been made to elucidate the physiological and pathological role of Bcl-2 proteins and caspases in the brain.

11. Caspase activity in temporal lobe epilepsy

Several reports have shown that seizures can occur after the activation of caspase-1 (Eriksson et al., 1999), caspase-3 (Becker et al., 1999; Kondratyev and Gale 2000; Weise et al., 2005), caspase-8 (Tan et al., 2002) or caspases-2 and -9 (Henshall et al., 2001).

Henshall et al. (2001) and Li et al. (2006) reported that caspase-8 and -9 are activated in the hippocampus 40 min after focal SE was induced by kainic acid. The different location of caspase expression after SE suggests different functions in the brain. Weise et al. (2005) reported the expression of activated caspase-3 in hippocampal neurons after pilocarpine-induced SE while other authors (Narkilahti et al., 2003; Ferrer et al., 2000) have detected active caspase-3 primarily in astrocytes and, to a lesser degree, in neurons. These data suggest that caspase-3 could exert an important role in the astrocytic death following SE and may have other unknown functions.

Using biochemical and immunohistochemistry assays, we have demonstrated that inflammatory caspase-1 and the apoptotic executioner caspase-3 are activated in the hippocampus of rats at 90 min after the seizure onset and at 7 days after SE (latent period) (in preparation). Interestingly, the most intense caspase activity was observed in the latent period where the highest amount of neuronal death occurs. The neuronal damage is necessary to generate spontaneous seizures in this model (Turski et al., 1983).

The activation of caspase-1 by SE induced by pilocarpine is involved in inflammatory mediator generation. Fantuzzi et al. (1999) demonstrated that caspase-1 is specifically required for processing pro-IL-1β and pro-IL-18 to their active forms. IL-1β can modulate the hyperexcitability by increasing glutamate release (Kamikawa et al., 1998), inhibiting glutamate reuptake by glial cells (Ye and Sontheimer, 1996) and increasing the calcium influx mediated by NMDAR through activation of Src family kinases (Viviani et al., 2003). There are a growing number of studies showing the role of inflammation in the injury process caused by seizures (Ravizza et al., 2006; Vezzani et al., 1999; 2000). Thus, caspase-1 inhibition may be a promising anticonvulsant and neuroprotective therapy.

12. Caspase inhibition as neuroprotective strategy in temporal lobe epilepsy

Because caspases are differentially activated during epileptogenesis as demonstrated by Gorter et al. (2007) using microarray assays, caspase selective inhibitors are considered potential targets for novel neuroprotective and anticonvulsant agents for epilepsy (Kondratyev and Gale, 2000; Henshall et al., 2001; Ravizza et al., 2006). Inhibition of caspase-1 reduced seizures in rats, whereas the deletion of the caspase-1 gene delayed acute seizure onset (Ravizza et al., 2006). Inhibition of caspase-3 and -9 provides neuroprotection after *SE*

was induced by kainate (Henshall et al., 2001), and the inhibition of caspase-8 may attenuate neuronal death by decreasing cleaved Bid, caspase-9, and the release of cytochrome *c* from mitochondria (Li et al., 2006).

The caspase inhibition was also used as a neuroprotective strategy against injury caused by *SE* induced by pilocarpine (Persike et al., 2008).

Several studies determined that tellurium compounds, as the non-toxic AS-101, ammonium trichloro(dioxoethylene-O,O') tellurate, exert anti-apoptotic, anti-inflammatory, and immunomodulatory effects (Okun et al., 2007a; Sredni et al., 2007). These effects are primarily caused by the unique tellurium-thiol chemistry, which enables the interaction between the tellurium compound with the reactive cysteine residues of the inflammatory and apoptotic caspases leading to caspase inhibition (Albeck et al., 1998; Okun et al., 2007b). AS-101 not only interacts with catalytic thiols from cysteine proteases but also interacts with non-catalytic thiols (Okun et al., 2007b). It has been demonstrated that AS-101 can upregulate the anti-apoptotic proteins Bcl-2, p21Ras, PI3 kinase and the glial cell line derived neurotrophic factor (GDNF), and AS-101 can inhibit IL-1β and caspase-1 and -3 (Makarovsky et al., 2003; Okun et al., 2006a,b; Sredni et al., 2007). AS-101 is currently being tested in Phase II clinical trials in cancer patients (Sredni et al., 1995, 1996, Frei et al., 2008) and was recently suggested as a promising agent for treatment of Parkinson's disease (Sredni et al., 2007).

A compound of tellurium(IV), the organotelluroxetane RF-07 (see Figure 2), is an analogue of AS-101 (Persike et al., 2008). The administration of RF-07 prior to pilocarpine significantly blocked the behavioral and electrographic symptoms of SE in rats (Figure 3). To evaluate if this activity could be related to caspase inhibition, RF-07 was used in an "*in vitro*" assay to test recombinant caspases -3 and -8. RF-07 showed a potent inhibitory effect on both caspase -3 and -8 (Persike et al., 2008). The RF-07 was also tested in hippocampal homogenates from rats euthanized 90 min after pilocarpine-induced *SE*. RF-07 was the most potent inhibitor of caspase-like activity compared with commercial caspase inhibitors (Persike et al., 2008). Based on the results of this study, RF-07 inhibits not only caspases but other proteases that were activated during seizures, such as cathepsins, matrix metalloproteinases and plasminogen activators (see Figure 4).
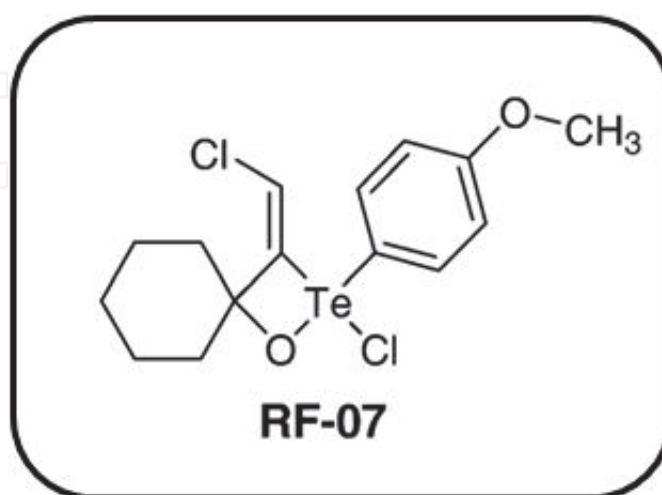

Fig. 2. The molecular structure of the neuroprotector tellurium(IV) compound, (4-{2-Chloro-3-[chloromethylidene]-1-oxa-2l4-telluraspiro[3.5]non-2-yl}phenyl Methyl Ether).

Taken together, these data show that RF-07 represents a promising anti-epileptic and/or agent for epilepsy. Further investigations are ongoing to elucidate the mechanisms by which RF-07 inhibits pilocarpine-induced seizures. Studies using proteomic analysis may help to clarify these mechanisms.
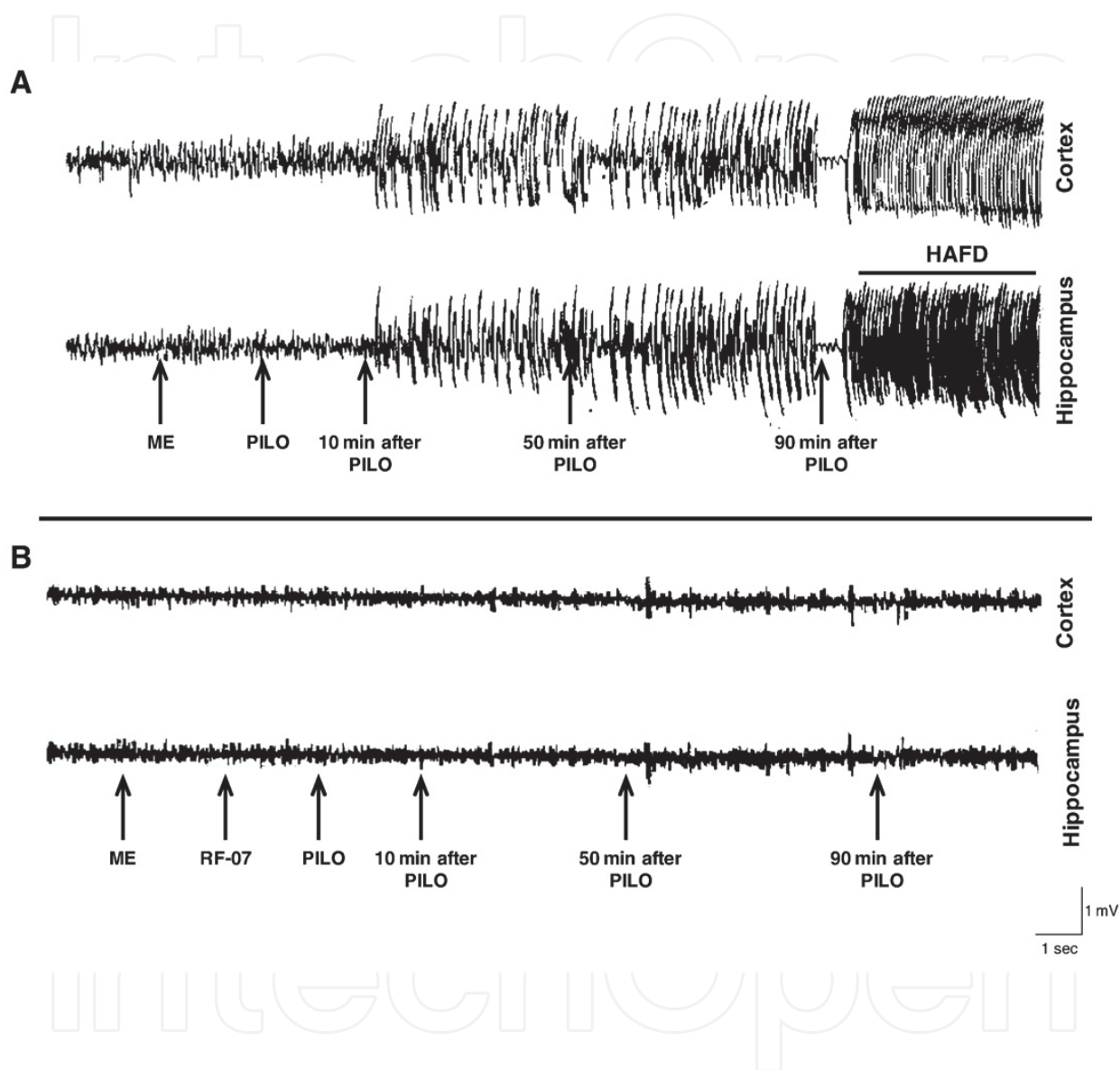

Fig. 3. Electroencephalographic recording showing the blockade of the brain high amplitude and frequency discharges (HAFD) following RF-07 injected prior to pilocarpine in rats. (**A**) N-methyl-scopolamine did not change the control recordings. N-methyl-scopolamine was used to prevent the peripheral effects of pilocarpine. The electrographic seizure started 10 min after pilocarpine administration and was highly synchronized in the hippocampus and cortex. (**B**) The rats were pre-treated systemically with RF-07 15 min prior to pilocarpine. As shown, rats did not develop seizures, which exhibited electrographic activity in the hippocampus and cortex similar to the pre-pilocarpine pattern (Persike et al., 2008).
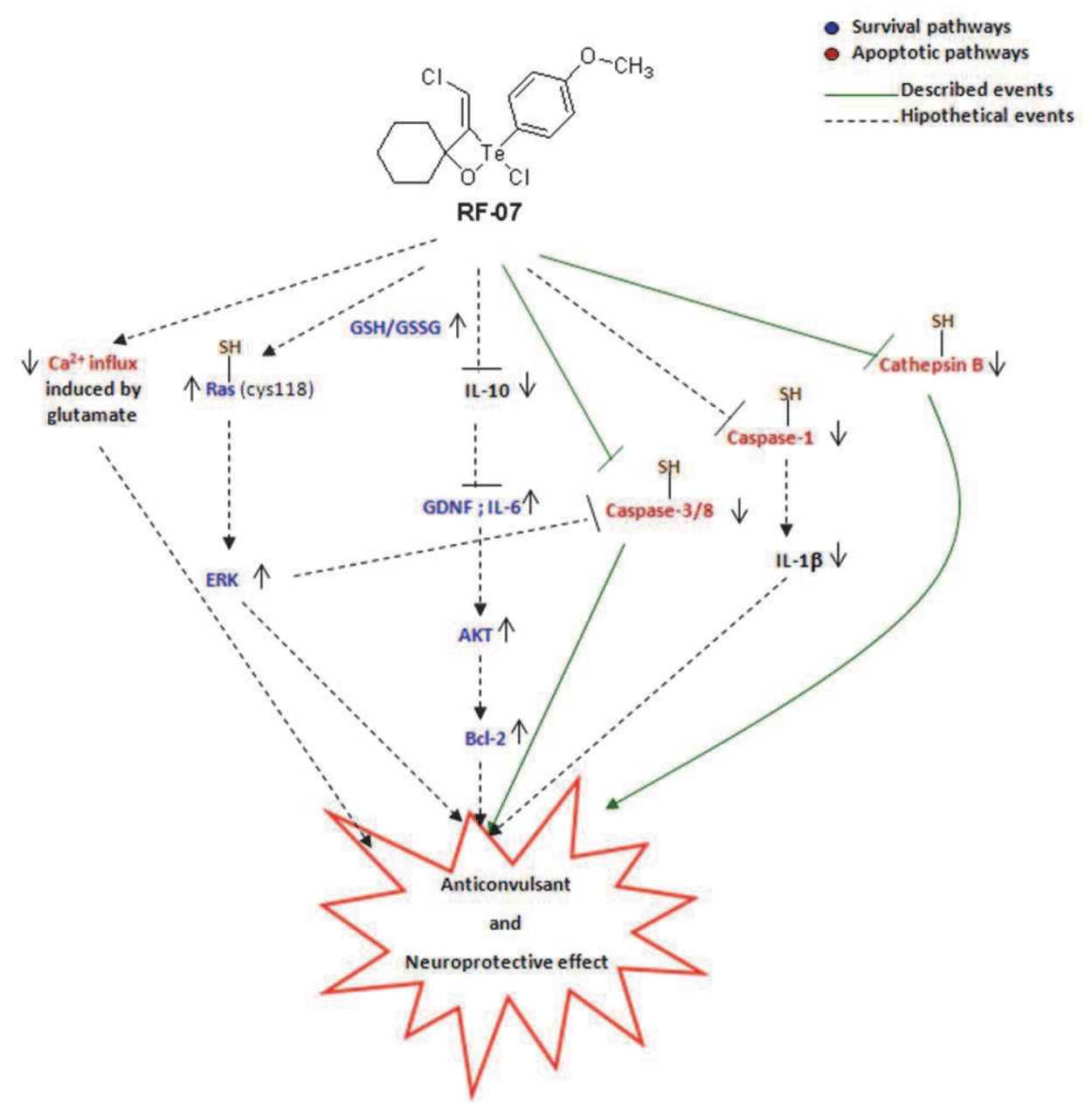
Fig. 4. A hypothetical diagram showing the signaling pathways modulated by RF-07. As previously described for AS-101, the RF-07 can bind to the cysteine residues of several proteins, such as Ras, cathepsins and caspases-1, -3 and -8. By binding to Ras, RF-07 increased the enzymatic activity, but upon binding to caspases, inhibited its activity. Ras activates ERKs, which then induces the expression of Bcl-2 to protect neurons from oxidative stress and mitochondrial disruption. The inhibition of caspases -1, -3 and -8 can prevent apoptosis and reduce the production of the pro-inflammatory cytokine IL-1β. In parallel, RF-07 could inhibit IL-10 production in addition to an increase in the ratio of GSH/GSSG. This inhibition would result in GDNF/IL-6 upregulation. By inhibiting cathepsin, RF-07 reduced the degradation of extracellular matrix components (Based on Sredni et al., 2007; Cunha et al., 2005 and Gorter et al., 2007).

13. Conclusion

Temporal lobe epilepsy is a progressive epileptic syndrome in which most of patients exhibit hippocampal sclerosis characterized by pyramidal cell degeneration, astrogliosis and aberrant mossy fiber sprouting in the inner molecular layer of the dentate gyrus. We have demonstrated that the caspase-mediated inflammatory process has been reported as a possible mechanism involved with the pathogenesis of TLE, and caspase inhibitors could be a promising therapeutic strategy. The knowledge about the physiological role of caspases in the CNS could improve our understanding about the balance between mediators of survival and cell death in the epileptogenesis.

14. Acknowledgements

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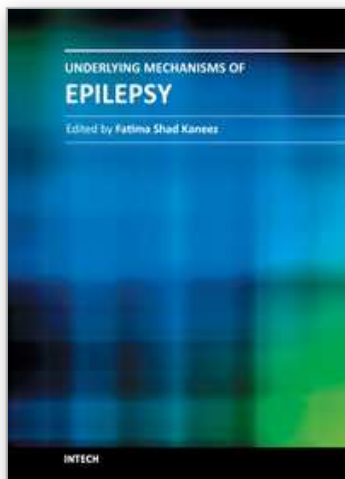
Underlying Mechanisms of Epilepsy

Edited by Prof. Fatima Shad Kaneez

This book is a very provocative and interesting addition to the literature on Epilepsy. It offers a lot of appealing and stimulating work to offer food of thought to the readers from different disciplines. Around 5% of the total world population have seizures but only 0.9% is diagnosed with epilepsy, so it is very important to understand the differences between seizures and epilepsy, and also to identify the factors responsible for its etiology so as to have more effective therapeutic regime. In this book we have twenty chapters ranging from causes and underlying mechanisms to the treatment and side effects of epilepsy. This book contains a variety of chapters which will stimulate the readers to think about the complex interplay of epigenetics and epilepsy.

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