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Modulating neuroinflammation and oxidative stress to prevent epilepsy and improve outcomes after traumatic brain injury

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Abstract

Traumatic brain injury (TBI) is a leading cause of death and disability in young adults worldwide. TBI survival is associated with persistent neuropsychiatric and neurological impairments, including posttraumatic epilepsy (PTE). To date, no pharmaceutical treatment has been found to prevent PTE or ameliorate neurological/neuropsychiatric deficits after TBI. Brain trauma results in immediate mechanical damage to brain cells and blood vessels that may never be fully restored given the limited regenerative capacity of brain tissue. This primary insult unleashes cascades of events, prominently including neuroinflammation and massive oxidative stress that evolve over time, expanding the brain injury, but also clearing cellular debris and establishing homeostasis in the region of damage. Accumulating evidence suggests that oxidative stress and neuroinflammatory sequelae of TBI contribute to posttraumatic epileptogenesis. This review will focus on possible roles of reactive oxygen species (ROS), their interactions with neuroinflammation in posttraumatic epileptogenesis, and emerging therapeutic strategies after TBI. We propose that inhibitors of the professional ROS-generating enzymes, the NADPH oxygenases and myeloperoxidase alone, or combined with selective inhibition of cyclooxygenase mediated signaling may have promise for the treatment or prevention of PTE and other sequelae of TBI.

Keywords

Posttraumatic epilepsy; Oxidative-stress; Neuroinflammation; Redox-signaling; NADPH oxidase; Myeloperoxidase and Traumatic Brain Injury

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1. Introduction

Traumatic brain injury (TBI) is a major cause of death and disability among young adults in the United States. Each year an estimated 1.7 million Americans sustain a TBI: 52,000 die, 275,000 are hospitalized and survive (Leo and McCrea, 2016), and about 124,000 develop long-term disability (Selassie et al., 2008). Depending upon the type, severity and location of the injury and the age, general health and genetic constitution of the individual, TBI may result in wide range of disabilities with potentially devastating impact on quality of life. These may include sensory, motor and cognitive impairments, affective disturbances (Stocchetti & Zanier, 2016), as well as posttraumatic epilepsy (PTE), which will be the focus of this review.

PTE is defined as recurring spontaneous seizures occurring more than 7 days after injury. PTE complicates 3–5% of moderate TBI and as many as 50% of severe TBI. TBI is the leading cause of epilepsy with onset in young adulthood (Annegers, 1996; Annegers et al., 1998). While the specific mechanisms of human posttraumatic epileptogenesis are not known, the formation of a posttraumatic epileptic focus must involve some subset of the pathophysiological cascades unleashed by brain trauma.

There is presently no means to prevent or cure any of the functional impairments induced by TBI, including PTE. Pharmacological treatment for PTE and other epilepsies is symptomatic – drugs must be taken regularly to suppress seizures. Over 2 dozen drugs are now available for treatment of epilepsy, but the proportion of patients with adequate seizure control did not grow appreciably as new drugs were introduced, and about 1/3 of epilepsy patients suffer seizures that cannot be controlled with antiseizure drugs (Loscher and Schmidt, 2011).

Because the physiological basis of the propensity to spontaneously generate paroxysms of abnormal hypersynchronous neuronal activity (seizures) in clinical epilepsy is unknown, current antiseizure drugs have been developed to suppress seizures by altering the balance of neural excitation and inhibition (White et al., 2007; Loscher et al., 2013). Epilepsy drug development has largely been guided using evoked seizure models (Loscher and Schmidt, 2011; Loscher et al., 2013), and the discovered drugs overwhelmingly target neuronal and synaptic mechanisms (Kaminsky et al., 2014). While the sheer number of drugs available for the treatment of epilepsy attests to the success of this drug development strategy, the lack of disease-preventing or disease-modifying drugs and the sizable proportion of unresponsive patients suggests that clinically important pathogenic mechanisms may have been overlooked.

While many factors may have contributed to the failure of clinical trials to identify effective treatments, growing attention to the complexity of TBI and new insights into the mechanisms mediating epileptogenesis after brain injury point to new strategies and avenues of intervention. In particular, two recent advances provide a likely path to the development of novel drugs to control currently refractory seizures and to prevent the development of epilepsy after epileptogenic brain insults (e.g. Infection, stroke and trauma). First, a body of research that has grown exponentially since the 1990s has elaborated a wide variety of non-neuronal and non-synaptic mechanisms that may contribute to epileptogenesis. These

include astroglial (Aronica et al., 2012; Robel, 2017) and microglial (Eyo et al., 2017; Hiragi et al. 2018) mechanisms, blood-brain barrier disruption (Heinemann et al., 2012; van Vliet et al., 2015), inflammation (Vezzani and Granata, 2005; Vezzani et al., 2013; de Vries et al., 2016), generation of reactive oxygen species (ROS) and oxidative stress (Shin et al., 2011; Pearson-Smith and Patel, 2017. The second advance is the development of etiologically realistic syndrome specific models of acquired epilepsies that feature the development of chronic spontaneous recurrent seizures (Kelly et al., 2001; D'Ambrosio et al., 2004; 2005; Dube et al., 2006; Stewart et al. 2010; Rakhade et al., 2011; Reid et al., 2016; Ping and Jin, 2016), and are highly likely to incorporate epileptogenic mechanisms that operate in the corresponding human epilepsies (Curia et al., 2016). Together, these advances should pave the way for discovery of novel treatments to address the needs of patients whose seizures are inadequately controlled by available anti-seizure drugs and to prevent epilepsy after brain injury. This review will focus on the roles of ROS, professional ROS-generating enzymes and neuroinflammation, and on strategies targeting them, either alone or in combination with cyclooxygenase-related inflammatory mechanisms, to treat or prevent epilepsy.

2. Reactive Oxygen Species, Redox Signaling & Oxidative Stress

ROS – superoxide ($O_2^{\bullet -}$), hydrogen peroxide (H_2O_2) and the hydroxyl radical ($^{\bullet}OH$) – are the reactive products of sequential 1-electron reduction of molecular oxygen. They are generated by mitochondria, and by other cellular enzymes often as side products of oxidative metabolism. ROS, particularly the highly reactive radical species, $O_2^{\bullet -}$ and $^{\bullet}OH$, can oxidize lipids, nucleic acids and proteins to damage membranes and DNA, and inactivate enzymes, receptors and ion channels (Pisoschi and Pop, 2015). They can also react spontaneously or via enzyme catalyzed reactions to generate further damaging species. In the presence of iron, superoxide and H_2O_2 are converted to the much more reactive $^{\bullet}OH$. Moreover, superoxide will react with nitric oxide to generate peroxynitrite (ONOO-). Myeloperoxidase (MPO) produces hypochlorous acid ($HOCl^-$) and inducible nitric oxide synthase (iNOS) produces nitric oxide ($NO^{\bullet}$). Cyclooxygenases (COX-1 and COX-2) produce prostaglandin intermediates from arachidonic acid, via peroxidase activity first to PGG_2 then to PGH_2. A family of NADPH oxidase (NOX) enzymes catalyze the production of $O_2^{\bullet -}$ and H_2O_2 from molecular oxygen. These are the key players in the cellular generation of ROS and induction of neuroinflammation (Fig 1).

When the cells are in homeostasis, there is a balance between ROS generation by mitochondria and ROS producing pro-oxidant enzymes (e.g. NOX, iNOS, MPO and COX) and ROS scavenging by antioxidant enzymes (e.g. catalase, superoxide dismutase and glutathione reductase), and endogenous antioxidant molecules such as glutathione, ascorbic acid and tocopherols (Valko et al., 2007; Circu and Aw, 2010). Outside of the microbicidal oxidative burst of phagocytic cells, ROS have conventionally been regarded as unavoidable toxic byproducts of oxidative metabolism that are kept in check by cellular antioxidant defenses. However, in homeostatic conditions, ROS also participate in redox signaling (Jiang et al., 2011; Lambeth and Neish, 2014, Scheiber and Chandel, 2014). Contained, localized generation of ROS, particularly H_2O_2, can reversibly oxidize vulnerable protein cysteine residues to modulate the activities of a wide range of enzymes, ion channels and transporters (Valko et al., 2007; Jiang et al., 2011). Oxidative stress arises when the balance between

ROS levels and antioxidant environment is upset, leading to deleterious effects (Hole et al., 2011). Excess ROS can cause irreversible oxidative damage to cells, proteins, lipids, and DNA leading to cellular necrosis or apoptosis and consequent cellular or tissue injury (Chaudhari et al., 2014; Lambeth and Neish, 2014). Moreover, superoxide can inactivate antioxidant enzymes. Therefore, oxidative stress is implicated in a variety of acute and chronic diseases (Keyer et al., 1995; Maraldi, 2013). Two possible therapeutic approaches can be utilized to reduce the ROS in the body: i) scavenge ROS by administering antioxidants or enhancing the activities of endogenous antioxidant enzymes, ii) prevent or diminish ROS generation by inhibiting the various pro-oxidant enzymes.

3. NADPH-Oxidases

NOXs and dual oxidases (DUOXs) comprise a family of seven enzymes that together constitute the primary source of regulated physiological ROS production (Sirokmany et al., 2016). Each produces ROS as the principal product of its catalytic activity. NOX1, NOX2, NOX3 and NOX5 generate superoxide while NOX4, DUOX1 and DUOX2, predominantly produce hydrogen peroxide (Bedard and Krause, 2007; Nisimoto et al., 2014; Ma et al., 2017). These ROS-producing enzymes are differentially expressed in a variety of tissues and cell types throughout the body, where they play key roles in redox signaling (Lambeth and Neish, 2014; Scheiber and Chandel, 2014; Nordzeike and Medrano-Fernandez, 2018) and other specialized functions. For instance, the well-studied prototypic NOX, NOX2, was first found in phagocytic cells (neutrophils and macrophages), where it is highly enriched. It fuels the cytotoxic respiratory burst in these cells and has long been recognized for its role in innate immunity (Rada, 2008) and inflammatory diseases (Segal, 1996; Biemond et al., 1986; Weiss and Reddy, 1989).

While all NOX isoforms have been detected (mRNA or protein) in brain tissue, the regional distribution of NOX isoforms in the brain has not yet been extensively mapped. NOX2 and NOX4 appear to be the main isoforms expressed in the brain under physiological conditions, and NOX2 is quantitatively the most important (Sorce et al., 2017; Sorce and Krause, 2009). Both have been demonstrated in tissue samples from a variety of brain regions including neocortex, hippocampus and cerebellum (Sorce and Krause, 2009; Ma et al., 2017). NOX2 is predominantly expressed in microglia, consistent with these cells' role as the principal resident immune cells in the brain with the potential for phagocytic activity. NOX1, NOX2 and NOX4 expression has been reported in primary cultures of neurons, astrocytes and microglia from various species. NOX enzymes are inducible and upregulation of 1 or more NOX isoforms, almost invariably including NOX2, has been reported after experimental brain insults and in brain tissue from patients suffering from brain injuries and from a variety of neurological/neurodegenerative disorders (Ma et al., 2017). NOX expression has been reported to be elevated in human brain after TBI, and in patients suffering from Alzheimer's disease, amyotrophic lateral sclerosis and multiple sclerosis (Ma et al., 2017;2018). Experimental brain insults that result in increased NOX expression include controlled cortical impact (mechanical brain injury), ischemia/re-perfusion, and status epilepticus induced by electrical stimulation, the muscarinic agonist, pilocarpine and the excitotoxin, kainic acid (Patel et al., 2005; Pestana et al., 2010; Zhang et al., 2012; Cooney et al., 2013;Williams et al., 2015).

Thus, excessive induction and activity of NOX isoforms is associated with brain tissue injury and dysfunction in a variety of pathological conditions and experimental brain insults (Lambeth, 2007; Sorce and Krause, 2009). Conversely, NOX inhibition or genetic deletion of specific NOX isoforms is often reported to improve outcomes after experimental insults that typically induce elevated NOX expression. For example, pharmacological inhibition of NOX activity significantly diminished neurodegeneration after electrically or pilocarpine-induced status epilepticus in rats (Pestana et al., 2010; Williams et al., 2015). Genetic deletion of NOX2 and NOX4 have both been reported to reduce infarct volume in rodent stroke models (Chen et al. 2011, Klienschnitz et al., 2010). In rodent TBI models, inhibition of NOX2 has been reported to attenuate injury-induced increases of markers of astroglial and microglial activation, decrease neuronal loss in neocortex and hippocampus, and improve functional recovery (Zhang et al., 2012; Feng et al., 2017). In NOX2 knockout mice, microglial activation was attenuated and neurogenesis enhanced after TBI compared to wild type (Dohi et al., 2010; Wang et al., 2018b).

NOXs are increasingly recognized as major sources ROS contributing to the pathophysiology of a wide range of clinical conditions and attractive targets for the development of new drugs (Bedard and Krause, 2007; Kahles and Brandes, 2013; Lambeth and Neish, 2014; Diebold et al., 2015; Sorce et al., 2017). NOX-generated ROS may contribute to pathology in two ways. First, elevated ROS production may lead to pathological dysregulation of redox-regulated processes. Also, excessive ROS generation may lead to oxidative damage to cells and tissues. Superoxide is the product of the most abundant NOX in brain and it the most common free radical generated following traumatic brain injury (Kontos and Povlishock, 1986; Kontos and Wei, 1986). Under the acidic conditions characteristic of TBI, superoxide converts to hydroperoxyl radical ($HO2\bullet$), a more lipid soluble and powerful oxidant than the superoxide itself. This results in greater lipid peroxidation and additional brain tissue damage and mitochondrial disfunction (Mustafa et al., 2010; Singh et al., 2013). It has also been shown that peroxynitrite (ONOO-) exacerbates pathophysiology post TBI, demonstrated by treatment with iNOS inhibitor or peroxynitrite scavenger, which resulted in beneficial effects in TBI injured mice and rats (Deng-Bryant et al., 2008; Mesenge et al., 1998; Wada et al., 1998). These data indicate a mainly deleterious role of ROS in TBI and support the idea that inhibition of NOX activity after TBI will have therapeutic benefit.

4. Myeloperoxidase (MPO)

Myeloperoxidase is actively synthesized by promyelocytes and promyelomonocytes in bone marrow during the differentiation. MPO accounts for up to 2–5% of the cellular protein in neutrophils (Bos et al., 1978). Phagosomes of neutrophils discharge the cocktail of antimicrobial systems to destroy the microorganisms in the body (Klebanoff, 2005). The cocktail includes MPO, hydrogen peroxide and halide (mainly chloride) ion (Hampton et al., 1998). The potent and primary antimicrobial oxidant produced by MPO is hypochlorous acid (HOCl or OCl^-) (Fig 1), other reactive agents and radicals synthesized by MPO are $OSCN^-$, $NO_2\bullet$ and $Thr\bullet$. While the HOCl acts as microbial killing and is useful for protection against invading microorganisms, in pathological conditions, all these reactive species and radicals will react with lipids, proteins, and DNA and other biomolecules

leading to various pathologies, including cardiac dysfunction, atherosclerosis, diabetes; and CNS diseases such as ischemia/reperfusion and Parkinson's disease (Malle et al., 2006; Malle et al., 1997). It is yet to be determined whether myeloperoxidase will play a direct role in TBI pathophysiology, however, when the blood brain barrier (BBB) is compromised during severe and penetrating traumatic brain injuries, neutrophils are infiltrated into the brain. It has been shown that infiltrated neutrophils are involved in inflammation and neurodegeneration, via exacerbating oxidative-stress environment and working with other innate immunity cells (Ryu et al., 2007).

5. Cyclooxygenase-1 and Cycloxygenase-2

Both COX-1 and COX-2 catalyze the conversion of arachidonic acid to prostaglandin-G_2 and then to prostaglandin-H_2, which will be converted to a five different prostanoids, prostaglandin-E_2 (PGE_2), prostaglandin-D_2 (PGD_2) prostaglandin-F_2 (PGF_2), prostacyclin (PGI_2) and thromboxane (TXA_2) by cell specific synthase enzymes depending on the need of environment (Fig 1). These prostanoid ligands will activate eleven receptors (including splice variants). PGE_2 activates EP1, EP2, EP3 and EP4; PGD_2 activates DP1 and DP2; PGF_2 activates FPα and FPβ; PGI_2 activates IP and TXA_2 activates TPα and TPβ receptors. Functionally, EP2, EP4, DP1 and IP receptors mediate smooth muscle relaxation via intracellular cAMP signaling, whereas EP1, FP and TP mediate smooth muscle contraction by intracellular calcium signaling, and DP2 and EP3 inhibit the cAMP signaling (Rojas et al., 2019). Although some of these receptors share a common endogenous ligand for activation (e.g. EP1-EP4 share PGE_2; DP1 and DP2 share PGD_2), their downstream signaling mechanisms differ, suggesting the value of prostaglandins in various physiological and pathological functions. So far studies point to a proinflammatory role for EP2, EP4 and DP1, whereas the IP receptor acts as a cardioprotective receptor whose function must not be disrupted with any therapeutic agents (Egan et al., 2004). In view of the COX-2 inhibitor drug, Vioxx, experience (Grosser et al., 2010), future anti-inflammatory agents should target selectively the proinflammatory receptors, such as the EP2 receptor (Ganesh, 2014), rather than blocking the entire COX-2 cascade, to bypass the adverse effects on humans.

TBI in humans induced a sustained inflammation, including the activation of microglia and ongoing white matter degeneration for many years after single TBI (Johnson et al., 2013). Mice with TBI induced by a single episode of controlled cortical impact also exhibited persistent microglial activation in the injured cortex throughout 1 year after injury, and it was associated with progressive lesion expansion, hippocampal neurodegeneration, and loss of myelin (Loane et al., 2014). The prevailing hypothesis is that the cytokines, chemokines and COX-2, rapidly released by astrocytes and dying neurons, will trigger the inflammatory environment in the brain, leading to microglial activation. Once activated, the microglia further induce additional cytokines and chemokines, COX-2 and ROS. Animal models of TBI also present this neuroinflammatory environment (Bergold, 2016; Chiu et al., 2016; Simon et al., 2017). For example, Strauss et al. (2000), showed that COX-2 (mRNA and protein) peaks from around 6 h until 3 days post injury and returns to sham levels by 7 days in the ipsilateral cerebral cortex and in the ipsilateral and contralateral hippocampus in the cortical contusion and lateral fluid percussion injury models of TBI. Shojo et al. (2017), reported time-dependent increases in COX-1 and COX-2 in the cortex starting at 3h in a TBI

model of lateral fluid percussion injury; and, COX-1 was specifically induced in degenerating neurons, whereas COX-2 was expressed in macrophages. Kunz et al. (2002), found that COX-2 mRNA was upregulated in cortex and dentate gyrus regions starting at 3h until 72 h in a another fluid percussion injury rat model of TBI.

The above data suggest that COX-2 will be a therapeutic target, and preclinical data underscore that the COX-2 inhibitors will have beneficial functional outcome in various models of TBI. Although it is not clear why the COX-2 selective drugs were not tested in clinical trials, it may be due to the fatal adverse cardiotoxic effects found with chronic use of COX-2 drugs in patients with other diseases (Egan et al., 2004; Funk and FitzGerald, 2007; Grosser et al., 2010).

A key question is how to intervene in the cross talk among the players of neuroinflammation (cytokines, chemokines, COX-2, gliosis) and oxidative burst and oxidative stress enzymes (NOX and INOS). It has been shown that conditional deletion of COX-2 in neurons blunted 34 out of 38 inflammatory cytokines and chemokines and gliosis in a status epilepticus brain injury model (Serrano et al., 2011). Moreover, it has been shown that a specific prostanoid receptor EP2 activation and inhibition will have an effect on expression levels of inflammatory mediators, ROS producing enzymes in vitro microglia cultures suggesting a cross-talk between prostanoid signaling and inflammatory mediators (Quan et al., 2013).

6. ROS, Inflammation and the Pathophysiology of TBI

Mechanical trauma to the brain produces a limited primary injury (e.g. disruption of cell membranes, blood vessels and blood-brain barrier, resulting in the immediate demise of neurons, glia and epithelial cells), and unleashes secondary injury processes that progress over time, expanding the volume of injured tissue to account for much of the injury-induced disability. Only the secondary injury, which is mediated by processes unleashed by the primary injury and may progress for weeks, months or even years before homeostasis is reestablished, can be effectively targeted by therapeutic measures.

TBI is a complex injury to a complex organ, and its pathophysiology has been the subject of many excellent reviews (Ray et al., 2002; Werner and Engelhard, 2007; Borgens and Liu-Snyder, 2012; Prins et al., 2013; Quillinan et al., 2016; Morganti-Kossmann et al., 2019). Here, some important pathophysiological pathways will be outlined, emphasizing those that are likely contributors to posttraumatic epileptogenesis. Membrane disruption induced by the mechanical injury results in widespread neuronal depolarization and massive release of glutamate, extravasation of blood components through a disrupted blood-brain barrier (BBB) into the brain parenchyma and release of damage associated molecular patterns (DAMPs; e.g. ATP, RNA, high-mobility group box-1) from damaged cells (Hirsiger et al., 2012). Glutamate release induces further depolarization of still-viable neurons, Ca^{++} influx, mitochondrial damage and associated energy deficits, increased generation of toxic ROS by damaged mitochondria, and neuronal excitotoxicity. ROS deplete cellular antioxidants, react with nucleotides and proteins and initiate peroxidation of cellular membranes, further damaging cells and organelles. DAMPs released from dead and damaged cells initiate cytokine signaling cascades that orchestrate the inflammatory response that results in the

destruction and clearance of damaged cells and the eventual establishment of a new tissue homeostasis. The cellular inflammatory response involves further ROS generation due to the respiratory bursts of neutrophils, macrophages and activated microglia attracted to the site of injury. Thus the physiological processes required to reestablish homeostasis in the damaged brain also contribute to the widening of the injury and a progressive loss of function, and inflammation and ROS generation are thought to be the most important secondary injury processes operating after the acute period after injury.

Although we lack a detailed understanding of its role in the pathogenesis of TBI, inflammation is well accepted as an important pathway of secondary injury and inflammatory mechanisms and inflammation-related therapeutic targets have been recently reviewed (Ruppel et al., 2002; Cornelius et al., 2013 Rodriguez-Rodrigues et al., 2014; Hall et al., 2015; Toklu et al., 2015; Frati et al., 2017). Elevated expression of key pro-inflammmatory cytokines is consistently observed in human and animal brain tissue following TBI (Ott et al., 1994; Holmin and Hojeberg, 2004; Ziebell and Morganti-Kossmann, 2010; Helmy et al., 2011). In experimental models, injury-related endpoints are often improved by pharmacological inhibition of pro-inflammatory cytokine synthesis, knock-out or knock-down of pro-inflammatory cytokine expression or by inhibition of receptor binding (Fogal and Hewett, 2008). Conversely, overexpression or application of exogenous pro-inflammatory cytokines is frequently reported to exacerbate brain injury (Toulmond and Rothwell, 1995; Lloyd et al., 2008; Ziebell and Morganti-Kossmann, 2010; Helmy et al., 2011; Gyoneva and Ransohoff, 2015). While research in this area has been extensive, the roles of TNF-α, IL-1β and IL-6, and associated signaling pathways (particularly NFkB) have been particularly well studied, and the roles of high mobility group box 1 (HMGB1) and Toll-like receptor-4 (Laird et al., 2014; Parker et al., 2017; Paudel et al., 2018) in secondary injury have commanded considerable attention, recently.

ROS also have long been postulated to contribute importantly to the secondary injury following brain trauma. Trauma-induced hypoxia/ischemia and calcium fluxes both promote ROS generation from mitochondria, and mitochondrial ROS generation is stimulated by ROS (Zorov et al., 2014). While most ROS are short-lived and difficult to demonstrate directly, the products of their reactions with lipids, proteins and nucleic acids, are consistently elevated after experimental TBI (Inci et al., 1998; Tyurin et al., 2000; Mendez et al., 2004; Ansari et al., 2008) and in blood and postmortem tissue from TBI victims (Cristofori et al., 2001; Varma et al., 2003; Yen et al., 2015; Schiavone et al., 2017). In experimental TBI models, a wide range of antioxidant treatments have been reported to reduce injury-induced neurodegeneration and improve functional recovery (Slemmer et al., 2008). While early studies focused on treatments with small-molecule and catalytic antioxidants that metabolize or scavenge ROS, many recent investigations have focused on ROS generated by NOX. NOX expression is increased after experimental TBI (Dohi et al., 2010; Cooney et al., 2013) and in surgical specimens from contused human brain (Li et al., 2015). Many studies have shown that knockdown, knock-out or inhibition of NOX2 can reduce oxidative stress markers, cortical lesion volume, BBB disruption, neurodegeneration, and a range of neurological deficits in several different TBI models (Choi et al., 2012; Ferreira et al, 2013; Loane et al., 2013; Luo et al., 2013; Song et al., 2013; Lu et al., 2014).

Thus NOX-derived ROS play a significant role in the secondary expansion of injury after brain trauma.

7. ROS and Inflammation in Epilepsy and Epileptogenesis

Over the past 25 years, a burgeoning literature has demonstrated neuroinflammation and ROS generation to have deleterious roles in epilepsy and epileptogenesis (Vezzani and Granata, 2005; Choi and Koh, 2008; Waldbaum and Patel, 2010; Aronica and Crino, 2011; Vezzani et al., 2011; Cardenas-Rodriguez et al., 2013; Devinsky et al., 2013; Rowley and Patel, 2013; Gorter et al., 2015; Vezzani et al., 2016; de Vries et al., 2016; Aronica et al., 2017; Pearson-Smith and Patel, 2017; Webster et al., 2017; Hiragi et al., 2018; Paudel et al., 2019), suggesting a broad overlap between the pathophysiological cascades unleashed by TBI and the inflammatory and oxidative processes that promote spontaneous seizures. Neuroinflammation, as indicated by glial reaction and increased expression of proinflammatory cytokines and other mediators, is a consistent feature of the epileptic brain regardless of etiology. Seizures induce inflammation and several inflammatory cytokines have been demonstrated exacerbate seizures. IL-1β, TNF-α and IL-6 have all been demonstrated to modulate neuronal excitability either directly or indirectly (Vezzani and Viviani, 2015; Iori et al., 2016). Studies have implicated many cytokines in epilepsy and epileptogenesis

Like inflammation, elevated ROS generation and oxidative stress appear to be consistent features of experimental epileptogenic insults (Liang et al., 2000; Waldbaum and Patel, 2010; Bhuyan et al., 2015) and of post-mortem tissue from TBI victims (Buritica et al., 2009) and surgical specimens from chronic epilepsy patients (Lopez et al., 2007; Rumia et al., 2013). Also similar to inflammation, increased ROS appear to be both a cause and consequence of seizures (Patel, 2004). In fact, inflammation and ROS generation appear to be inextricably linked. Inflammatory pathways modulate ROS generation and ROS, in turn, modulate inflammatory pathways (van der Vliet et al., 2014; Harijith et al., 2014; Singel and Segal, 2016; Forrester et al., 2018). Deleterious levels of ROS could be generated in critical compartments by a variety of sources including mitochondria, NOX enzymes and other enzymes that generate ROS as side-products, and contributing sources may change over time after an epileptogenic insult (Kovac et al., 2017). Historically, mitochondria have been considered to be the most important source of ROS both constitutively and in pathological conditions, and ROS regarded as intrinsically destructive. However, following the discoveries of enzymes, receptors, transport proteins and ion channels that are reversibly modulated by ROS (Valko et al., 2007; Lambeth and Neish, 2014; Scheiber and Chandel, 2014; Nordzieke and Medrano, 2018)), and the NOX family of enzymes whose sole activity is to generate ROS at the expense of biological reducing equivalents (Bedard and Krause, 2007; Nayernia et al., 2014), it is now apparent that ROS can modulate a wide range of physiological processes, and that NOX enzymes are an important source of ROS in many pathological conditions.

Cytotoxicity is the best known effect of ROS generation. While the necessity of neurodegeneration for acquired epileptogenesis has not been firmly established, most epileptogenic insults are associated with significant loss of neurons, and abnormal network

activity is a plausible consequence of widespread loss of neurons. Thus, neuroprotection is widely expected to oppose epileptogenesis. The particular vulnerability of neurons to ROS is well-known (Cobley et al., 2018), and antioxidant treatments (MacGregor et al., 1996; Marklund et al., 2001; Deng-Bryant et al., 2008; dos Santos et al., 2011; Zhang et al., 2012; Ambrogini et al., 2014; Pandya et al., 2014) and treatments that reduce NOX activity (Dohi et al., 2010; Ferriera et al., 2013; Pestana et al., 2010; Choi et al., 2012; Kim et al., 2013) are almost invariably reported to be neuroprotective after experimental TBI and other experimental insults that can result in epilepsy, including electrically or chemoconvulsant-induced status epilepticus. Pretreatment of animals with antioxidants has been reported to reduce or retard seizure activity after administration of convulsants such as kainate, pentylenetetrazole and pilocarpine (Devi et al., 2008; Shin et al., 2011). Such anticonvulsant effects are accompanied by decreases in indicators of oxidative stress, but it is not clear that protection from oxidative damage to cells is responsible. For instance, among the strongest anticonvulsant effects reported was that induced by α-lipoic acid pretreatment on pilocarpine induced seizures (de Freitas, 2010): the latency to first seizure was more than three times longer in α-lipoic acid-treated rats and only 25% of α-lipoic acid-treated rats developed seizures as compared to 100% of rats treated with pilocarpine alone. Pilocarpine is well known to induce ROS generation resulting in oxidative stress, and de Freitas (2010) measured a 50% depletion of reduced glutathione in brains of pilocarpine-treated animals that was reversed by the α-lipoic acid treatment, which also increased glutathione peroxidase activity. While oxidative stress was doubtless reduced by α-lipoic acid treatment, the treatment also reduced the activity of the sodium-potassium pump, which would likely promote neuronal hyperexcitability.

Although the neuroprotective effects of a variety of antioxidant treatments following TBI and electrically and chemoconvulsant-induced status epilepticus (SE), protocols that form the basis of most chronic epilepsy models, have been demonstrated, the effects of antioxidants on the development of spontaneous seizures have rarely been assessed in chronic epilepsy models. One group found melatonin treatment to decrease the frequency of spontaneous seizures in the chronic phase after kainate-induced SE in spontaneously hypertensive rats (Petkova et al., 2014) but not rats of the Wistar strain (Tchekalarova et al., 2013), and resveratrol, a natural compound with antioxidant and anti-inflammatory properties was found to decrease the incidence of spontaneous seizures in a kainate model (Wu et al., 2009). In contrast, a catalytic antioxidant failed to affect spontaneous seizures in the pilocarpine model (Pearson et al., 2015). More recently, Pauletti et al. (2017) showed that a transient treatment that increased brain glutathione levels markedly decreased the frequency of the spontaneous seizures that developed after electrically induced SE. These investigators also showed that treatment maintained HMGB1, a DAMP that is thought to promote epileptogenesis (Ravizza et al., 2018; Paudel et al., 2018; 2019).

In principle, ROS could contribute to epileptogenesis by exacerbating neuroinflammation, by disrupting the activities of redox-regulated cellular processes, or via their cytotoxic effects on neurons and other brain cells. Toxic or disruptive levels of ROS could be generated by a variety of sources including mitochondria, NOX enzymes and other enzymes that generate ROS as side-products, and contributing sources may change over time after an epileptogenic insult (Kovac et al., 2017).

8. NOX, Redox Regulation and Posttraumatic Epileptogenesis

While the details remain poorly delineated, roles for inflammation in ictogenesis and epileptogenesis are now well established, and the interaction of ROS with inflammation provide multiple avenues for ROS modulation of epileptogenesis. For example, signaling through interleukin-1 β (IL-1β), tumor necrosis factor-α (TNF-α) and HMGB1 – all under active investigation for their contributions to epilepsy and epileptogenesis (van Vliet et al., 2018; Webster et al., 2017; Ravizza et al., 2018; Paudel et al., 2018; 2019) – is subject to redox modulation. HMGB1 is a DAMP with chemokine-like and cytokine-like activities that depend on the redox state of 2 cysteine residues. HMGB1 exhibits leukocyte chemoattractant properties when these are in their reduced states, and promotes proinflammatory cytokine (including IL-1β and TNF-α) secretion when these cysteine residues are oxidized (Venereau et al., 2012; Yang et al., 2013; Paudel et al., 2019). ROS also promote activation of nuclear factor-)κB (NFκB; Kaur et al., 2015), a transcription factor required for maximal transcription of many pro-inflammatory mediators, including TNF-α and IL-1β (Christman et al., 2000), both of which signal, in part, via NFkB activation (Allan et al., 2005; Schutze et al., 1995). As a result, ROS can influence both the magnitude of expression of these important inflammatory mediators and downstream effects of IL-1β and TNF-α receptor ligation, and NOX-derived ROS are frequently implicated. For example, NOX inhibition has been found to attenuate TNF-α-evoked BBB dysfunction (Abdullah and Bayraktutan, 2014) and IL-1-induced astrocyte migration (Yang et al., 2015). NOX activity is also a potent modulator of the cellular component of inflammation. NOX activity generates the cytotoxic respiratory burst of activated microglia and macrophages (Haslund-Vinding et al., 2017), and NOX derived ROS promote both microglial proliferation (Mander et al., 2006) and their pro-inflammatory M1-like polarization (Kumar et al., 2016; Wang et al 2017). Thus, ROS generated by NOX and other sources potently modulate a number of the postulated inflammatory substrates of epilepsy and epileptogenesis.

Redox regulation is not restricted to inflammatory pathways, and quite a number of proteins with epilepsy-relevant functions are known to be directly or indirectly modulated by ROS. These include various ion channels (Annunziato et al., 2002), transporters (Sorg et al., 1997) and neurotransmitter receptors (Peterson and Weir, 2002). The effects of ROS on N-methyl-D- aspartate (NMDA) receptors and the sodium-potassium pump are of particular interest in the context of epilepsy. NOX is the predominant source NMDA-receptor mediated ROS generation (Brennan et al., 2009) and NOX activation, in tandem with phosphorylation of extracellular signal-related kinases 1 and 2, induce upregulation of NR1 and NR2B subunits and enhanced neuronal excitability after pilocarpine-induced status epilepticus (Di Miao et al., 2011;2013). In addition, a recent study has provided evidence that NMDA receptor induced ROS generation by NOX is required for seizure initiation in several models (Malkov et al., 2019). The sodium-potassium pump, which is critical to the maintenance of cellular membrane potential, is also well-known to be subject to redox modulation (Bogdonova et al., 2016). Accordingly, the activity of the sodium-potassium pump was reported to be diminished after experimental TBI in parallel with increased oxidative stress markers (Lima et al., 2008), and NOX inhibition prevented reductions in sodium-potassium pump activity

induced by both TBI (Ferreira et al., 2013) and pilocarpine-induced status epilepticus (de Freitas et al., 2010).

The most compelling evidence implicating NOX-derived ROS in posttraumatic epileptogenesis involves the role of NOX in the death of parvalbumin expressing γ-aminobutyric acid (GABA)ergic inhibitory interneurons (PVINs). In rodents, PVINs account for 40–50% of GABAergic interneurons in the neocortex and up to 30% in the hippocampus (Jiang et al., 2016). These cells make abundant synapses on the somas and proximal dendrites of pyramidal cells and typically emit high frequency spike trains upon depolarization, providing potent inhibition (Jiang et al., 2016). They have thus been of great interest to epilepsy research, and hypofunction of these interneurons due to loss of excitatory drive formed the basis of the “dormant basket cell” hypothesis of acquired temporal lobe epilepsy (Sloviter, 1991). A progressive loss of PVINs in rodents after experimental brain trauma or status epilepticus has been reported by many groups (Toth et al., 1997; Dinocourt et al., 2003; Pavlov et al., 2011; Marx et al. 2013; van der Hel et al., 2014; Wang et al. 2018a), and PVINS appear to be depleted with respect to reference tissue in surgical specimens from epileptic patients and postmortem brain tissue from TBI victims (Leifer et al., 1991; Zhu et al., 1997; Andrioli et al., 2007; Buritica et al., 2009). Recently diverse studies have bolstered the case for a causal link between the loss or disfunction of PVINs and epileptic activity. Drexel and colleagues (2017) used genetic and DREADD (designer receptors exclusively activated by designer drugs) techniques to permanently or transiently silence PVINs in the subiculum of adult mice to demonstrate that prolonged silencing of subicular PVINs results in the development of clustered spike and wave discharges and spontaneous recurrent seizures. Two groups have demonstrated amelioration of pro-epileptic effects of brain injuries by using either focal administration of a partial tropomyosin receptor kinase B (TrkB) agonist (Gu et al., 2018) or a pharmacogenetic approach (Wang et al., 2018b) to activate PVINS after injury. In the cortical undercut model of TBI, treatment with a partial TrkB receptor agonist increased immunoreactivity for parvalbumin and a GABAergic marker, decreased the frequency of spontaneous and evoked epileptoform discharges in vitro and increased the frequency of pyramidal cell miniature inhibitory postsynaptic currents. In vivo, the treatment reduced the incidence of pentylenetetrazole-induced electrographic seizures. Targeted pharmacogenetic activation of PVINs increased the latency to seizure and shortened the duration of the first generalized seizure after kainate administration and, when administered during the chronic phase after kainate-induced status epilepticus, reduced the frequency and duration of spontaneous seizures. A third group used paired pulse transcranial magnetic stimulation to noninvasively monitor GABA-mediated neocortical inhibition after experimental TBI in rats (Hsieh et al. 2017). This demonstrated a progressive loss of paired-pulse inhibition, indicative of a loss GABAergic inhibitory activity over the course of 6 weeks after injury. Immunohistochemical studies revealed a parallel decrease in parvalbumin-positive interneurons and a marker for their associated perineuronal nets in the perilesional neocortex over the same time period. Further, elevated levels of oxidative stress markers in that study implicate ROS in the loss of PVINs.

PVINs are vulnerable to a wide range of stresses besides epileptogenic insults, and in many instances the loss or phenotypic alteration of PVINs has been shown to be mediated by NOX-derived ROS. In rodents IL-6, ketamine exposure, intermittent hypoxia and sepsis all

induce loss of PVINs (Behrens et al., 2007; 2008; Ji et al., 2015; Yuan et al. 2015; Liang et al. 2016, Zhang et al., 2016a), and PVIN loss is also observed in models of post-operative cognitive decline, posttraumatic stress disorder and social stress (Schiavone et al., 2009; Liu et al., 2016; Qiu et al., 2016; Sun et al., 2016). In all of these studies, the loss of PVIN phenotype was prevented by treatment with the NOX inhibitor apocyanin. A study comparing postmortem brain tissue from human subjects who died from blunt force TBI and spontaneous intracerebral hemorrhage (Schiavone et al., 2017) found that both oxidative stress markers and NOX2 immunoreactivity were elevated in TBI sections compared to reference specimens and that NOX2 mainly colocalized with immunoreactivity for parvalbumin and GAD67, markers for PVINs. Based on their data these investigators conclude that NOX2 is a crucial and specific molecular agent mediating the trauma-induced loss of PVINs. Thus, there is a substantial body of evidence indicating that NOX-derived ROS mediate the trauma-induced death or dysfunction of a specific subpopulation of neocortical and hippocampal neurons whose loss or impaired function has been linked to the development of spontaneous seizures.

There is also limited evidence pointing to a role for myeloperoxidase in epileptogenesis. Zhang et al. (2016b) demonstrated MPO immunostaining throughout the resected temporal lobe of a refractory epilepsy patient but not in the temporal lobe of a non-epileptic patient, and found increased numbers of MPO-positive cells in the hippocampi of mice during pilocarpine-induced epileptogenesis. Selectively inhibiting MPO delayed the appearance of spontaneous seizures and reduced their frequency. These data are in accord with a previous report that the frequency of spontaneous seizures in the chronic phase after pilocarpine-induced SE was reduced in neutrophil-depleted mice (Fabene et al., 2008). Interestingly MPO has been detected in cells other than neutrophils in several neurodegenerative disorders (Gellhaar et al., 2017), and Zhang et al. (2016b) found that the MPO immunoreactivity detected in mouse hippocampus after pilocarpine treatment colocalized with both neutrophil and microglia/macrophage markers.

9. Conclusions

The main lines of evidence supporting inhibition of NOX-mediated ROS generation for the treatment of posttraumatic epilepsy are summarized in Table 1. The roles of ROS, COX, and inflammation, and their interactions, offer opportunities to develop novel treatments for acute TBI and to prevent or modify posttraumatic epileptogenesis. TBI and posttraumatic epileptogenesis are complex disease processes involving multiple pathways and multi-targeted combination therapies have recently been promoted for both (Loscher et al., 2013; White and Loscher, 2014; Kline et al., 2016; Somayaji et al., 2018). NOX and COX inhibitors are likely to affect both inflammation and epileptogenesis after head injury, and, together may act synergistically to improve outcomes after head injury. Because the pathophysiology of head injury evolves over time, and drug targets may be exposed and disappear as secondary injury and repair progress (Somayaji et al., 2018; Mohamadpour et al., 2019), it cannot be assumed that the highest tolerated doses administered as early as possible and for as long as possible will be most effective. NOX and COX inhibitors and their therapeutic time windows should be systematically investigated with etiologically realistic models of PTE and head injury.

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Highlights

- Reactive oxygen species (ROS) and neuroinflammation have been identified as important contributors to both epileptogenesis and the evolving secondary injury after traumatic brain injury (TBI).
- After TBI, ROS may contribute to secondary injury and epileptogenesis via both their well-known cytotoxic properties and their effects on a wide range of redox-regulated processes, enzymes and pathways.
- Inflammation and oxidative stress/ROS generation are highly interdependent and mutually reinforcing after TBI. Thus, inhibitors targeting either pathway are likely to affect both, and, combination therapies targeting elements of both pathways may exhibit synergistic effects on posttraumatic epileptogenesis and other sequelae of TBI.
- The multi-prong approach to target inflammation with prostanoid receptor antagonists and oxidative stress/ROS generation with inhibitors of NADPH oxidase enzymes and myeloperoxidase is a promising strategy to prevent epileptogenesis and reduce secondary injury after TBI.

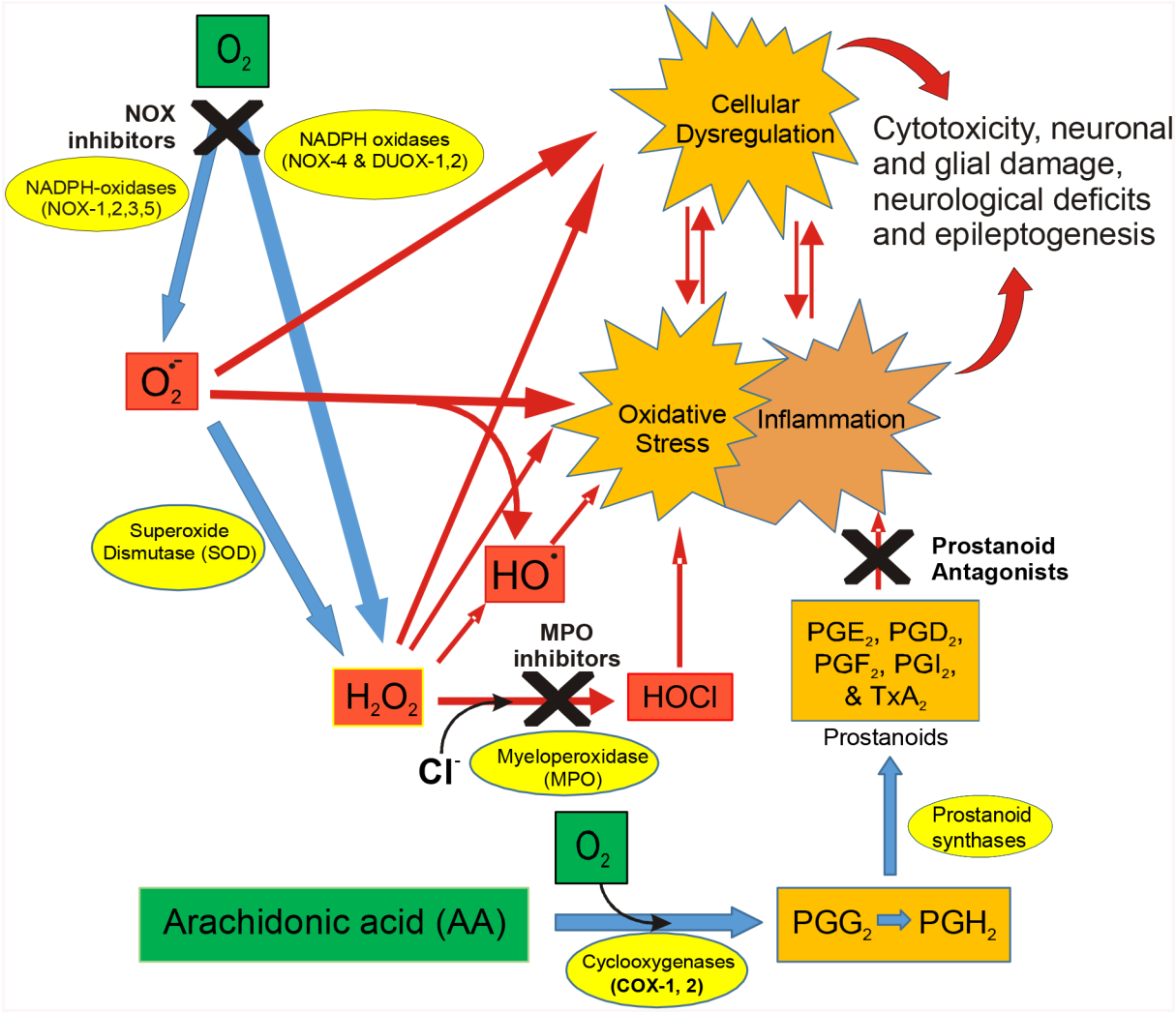

Figure 1:

TBI results in inflammation and increased ROS generation, which are closely linked and self-reinforcing. Pathological ROS production can both alter the activities of redox regulated enzymes and pathways and directly induce cytotoxic oxidative stress, initiating or exacerbating inflammation. Both ROS and inflammatory mediators can alter and impair the function of neurons, glia and other brain cells, resulting in increased production of inflammatory mediators and increased neuronal excitability. The figure illustrates how inhibitors of ROS-generating enzymes and of proinflammatory prostanoid receptors can be deployed either together or separately to alter the vicious cycles of inflammation, oxidative stress and cellular dysregulation that drive secondary injury after TBI.

Table 1.

Lines of evidence supporting the development of NOX inhibitors to prevent or modify PTE.

Summary of evidence indicating potential benefit of NOX inhibition for PTE	References
NOX expression and oxidative stress are both increased after experimental TBI.	Inci et al., 1998; Tyurin et al., 2000; Mendez et al., 2004; Ansari et al., 2008
Elevated NOX expression and oxidative stress are observed in surgical specimens and post-mortem brain tissue from human TBI victims and chronic epilepsy patients.	Cristofori et al., 2001; Varma et al., 2003; Yen et al., 2015; Li et al., 2015; Schiavone et al., 2017
Antioxidant treatments often reduce neurodegeneration and improve functional recovery after experimental TBI	Slemmer et al., 2008
Knock-out, knock-down or pharmacological inhibition of NOX reduces oxidative stress markers, cortical lesion volume, BBB disruption, neurodegeneration, and a range of neurological deficits in diverse TBI models	Choi et al., 2012; Ferreira et al, 2013; Loane et al., 2013; Luo et al., 2013; Song et al., 2013; Lu et al., 2014
ROS generation and oxidative stress are increased after experimental epileptogenic brain insults	Liang et al., 2000; Waldbaum and Patel, 2010; Bhuyan et al., 2015
ROS generation, oxidative stress and NOX are increased in brain tissue from chronic epileptic patients.	Lopez et al., 2007; Rumia et al., 2013; Pecorelli et al.,2015
NOX activation participates in pro-epileptogenic upregulation of NMDA receptor NR1 and NR2B subunits after pilocarpine induced status epilepticus – a model epileptogenic injury.	DiMaio et al., 2011; 2013
Many ion channels/transporters, including the neuronal Na^+/K^+ pump, are redox modulated. Experimental TBI- and pilocarpine-induced decreases in Na^+/K^+ pump activity are diminished by NOK inhibition	Bogdonova et al., 2016; Lima et al., 2008; Ferreira et al., 2013;de Freitas et al., 2010
NOX activity both modulates inflammatory signaling that is thought to contribute to epileptogenesis and is modulated by inflammatory mediators.	van der Vliet et al., 2014; Singel and Segal, 2016; Forrester et al., 2018
NOX-derived ROS stimulate microglial activation and promote a proepileptogenic M1-like activation state	Mander et al., 2006; Kumar et al., 2016; Wang et al., 2017
NOX-derived ROS have been implicated in the death or dysfunction of PVINs - a subpopulation of GABAergic interneurons long postulated to play a role in epileptogenesis - after a variety of - epileptogenic experimental brain insults.	Behrens et al., 2007; Ji et al., 2015; Yuan et al. 2015; Liang et al. 2016, Zhang et al., 2016a Schiavone et al., 2009; Liu et al., 2016; Qiu et al., 2016
NOX2 and oxidative stress markers elevated in brain section from human subjects who died from blunt force TBI, and NOX2 immunoreactivity mainly colocalized with PVIN markers.	Schiavone et al., 2017