Clinical and experimental data suggest that stress contributes to the pathology of epilepsy. We review mechanisms by which stress, primarily via stress hormones, may exacerbate epilepsy, focusing on the intersection between stress-induced pathways and the progression of pathological events that occur before, during, and after the onset of epileptogenesis. In addition to this temporal nuance, we discuss other complexities in stress-epilepsy interactions, including the role of blood-brain barrier dysfunction, neuron-glia interactions, and inflammatory/cytokine pathways that may be protective or damaging depending on context. We advocate the use of global analytical tools, such as microarray, in support of a shift away from a narrow focus on seizures and towards profiling the complex, early process of epileptogenesis, in which multiple pathways may interact to dictate the ultimate onset of chronic, recurring seizures.
vulnerability has not been frequently applied to epilepsy, despite evidence that many persistent changes induced by stress are likely to affect mechanisms of epilepsy. Perhaps most importantly, early life stress can cause long-lasting alterations in the regulation of the hypothalamic-pituitary adrenal (HPA) axis [7], which controls the release of stress hormones (glucocorticoids; GCs). These alterations, which are effected by cognitive mechanisms (neural plasticity in reinforcing stress-responsive networks [8, 9]) and genetic transcriptional mechanisms (classical and epigenetic regulation of genes controlling the HPA axis [10, 11]), lead to adult animals that have an impaired stress response to aversive stimuli, including increase in stress hormone release and impairment of HPA negative feedback [12]. Thus, all aspects of the stress response that may directly exacerbate epilepsy (described in subsequent sections) are likely to be particularly potent in individuals that have experienced early life stress. For example, early life stress affects adult induction of immune and inflammatory pathways [13, 14], which have been implicated in neural damage in epilepsy. Similarly, early life stress decreases the expression of brain-derived neurotrophic factor (BDNF) in the adult brain [15–17], which is a critical mediator of neuroprotection across epilepsy models.

Early life stress may also have a profound impact on the development of white matter in the brain. Preliminary work in our lab and others indicates that stress may increase or decrease myelination, depending on developmental stage and other unknown factors (unpublished data and [18]). These paradoxical findings are echoed by the literature showing that GCs induce in vitro oligodendrocyte precursor cells (OPCs) to differentiate into mature oligodendrocytes [19–21] and promote oligodendrocyte survival [22], yet total removal of GCs by adrenalectomy results in hypomyelination [23] while prenatal GC treatment delays myelination in sheep [24]. If early life stress does result in delayed and/or hypomyelination, it would constitute a startling and underappreciated similarity to a variety of seizure syndromes. Delayed myelination is a hallmark of infantile spasms [25] and other seizure disorders [26], and several genetic hypomyelination disorders or manipulations include severe seizure symptoms [27, 28]. In these models, treatment is associated with white matter recovery: amino acid supplement of patients with a serine biosynthesis disorder resulted in restoration of white matter and major seizure reduction [29, 30]. Pharmacologically (L-alillyglycine, bicuculline, and kainic acid) or electrically induced seizures also cause demyelination [31, 32], and alterations of white matter have been associated with both symptomatic and idiopathic epilepsy [33–35] and with hippocampal sclerosis [36]. Indeed, while glia have received a surge of recent interest for causal roles in epilepsy, this attention has focused almost exclusively on astrocytes. Possible roles for oligodendrocytes remain largely uninvestigated.

Direct investigation of early life stress on subsequent epilepsy is sparse, but there have been at least a few studies in rodents. One study subjected pups to maternal separation (MS) or normal rearing and then induced status epilepticus (SE) by lithium-pilocarpine at P16 and assessed subsequent advent of behavioral seizures in adulthood. Only one normally reared rat showed adult spontaneous recurrent seizures (SRS), whereas all 8 rats from the MS group developed SRS [37], though it is not clear if this difference can be attributed to a persistent “vulnerability” created by MS or to a more immediate effect of the MS stress on severity of induced SE. Another group subjected rats to MS or mild handling and assessed seizure induction by amygdala kindling subsequently in adulthood. MS rats required significantly less stimulation for seizure induction [38]. Gendered analysis indicates that this effect may only hold true for female rats [39]—an interesting finding given the well-known effects of sex hormones both on stress response and on epilepsy [9, 40–42]. A similar study showed that chronic GC supplement in adult adrenalectomized rats also accelerated the rate of amygdala kindling [43], indicating that interactions between GCs and seizure threshold may be generalized outside of the early life period.

The limited available direct evidence, as well as general observations of persistent changes mediated by early life stress, indicates that it could cause a life-long vulnerability for subsequent epilepsy. Given that the factors that govern whether or not epileptogenesis occurs after traumatic injury are poorly understood, the role of early life stress vulnerability deserves more in-depth study.

3. Mechanisms by Which Stress May Exacerbate Etiological Incidents

The most common form of symptomatic epilepsy involves a precipitating traumatic incident—an initial prolonged seizure (SE), stroke, traumatic brain injury, or infection/fever—that is followed by onset of epilepsy after a delay of months to years. A wealth of evidence indicates that damage suffered during such incidents and possibly also the induction of repair mechanisms constitute the first steps of epileptogenesis. Can activation of stress pathways during etiological incidents exacerbate damage or otherwise contribute to the proximate steps of epileptogenesis?

One of the common occurrences across different types of precipitating incidents is immediate neurological injury and cell death. GCs exacerbate such neural injury. For example, viral vector blockade of glucocorticoid receptors (GR) during kainic acid (KA) treatment (used to induce SE and associated excitotoxic cell death) significantly reduced the size of the ensuing hippocampal lesion and also significantly reduced cell death in KA-treated neural cell culture cotreated with GCs [44]. The damaging effects of GCs appear to be at least partially dependent on their downregulation of BDNF, as exogenous BDNF also attenuates the in vitro cell death. GC induction of proinflammatory pathways (discussed in Section 4) also plays a major role by leading to excitotoxic cell death [45]. Similarly, stress treatment prior to stroke (via the middle cerebral artery occlusion model) increases levels of pro-inflammatory TNF-α and IL-1β, causing more extensive cell death in the infarct [46, 47].

Breakdown of the blood-brain barrier (BBB) is also common across etiological incidents. Research in our lab and in our collaborator’s has shown that BBB disruption
allows serum albumin to enter the brain and activate the
transforming growth factor beta receptor (TGF-βR) signal-
ing pathway in astrocytes, ultimately inducing epileptiform
activity and spontaneous seizures. Blockade of the TGF-βR
prevents albumin-induced signaling, epileptiform activity,
and reduces seizures detected by EEG monitoring ([48–50]
and unpublished data). Interestingly, stress also disrupts the
BBB [51–53] and thus may directly contribute to postinjury
BBB leakiness, likely through induction of pro-inflammatory
pathways [54].

4. Mechanisms by Which Stress May Contribute
to Epileptogenesis

Beyond the proximate precipitating incident, the process of
epileptogenesis occurs over a period of weeks to years and is
marked by a somewhat stereotypical progression of restruc-
turing events that precede the onset of chronic spontaneous
seizures [55, 56]. The role of astrocytes in this process has
come to be one of the most studied frontiers in epilepsy
research, due to the effects of activated astrocytes and
gliosis on regulating excitability via extracellular ions and
neurotransmitters, and to the association of glial scars with
hippocampal sclerosis [57, 58]. Pro-inflammatory cytokine
pathways are common mediators of astrocyte activation
and epileptogenesis across epilepsy models. For example,
albumin activation of the TGF-β pathway in astrocytes leads
to the induction of pro-inflammatory and cytokine pathways
including NF-κB [48]. Similarly, pilocarpine-induced SE
causes an increase in leukocyte adhesion molecules and
local leukocyte recruitment, a critical first step in the
induction of the pro-inflammatory immune response [59].
In both cases, blockade of this initial pro-inflammatory event
prevents subsequent onset of epileptic activity. While GCs are
generally thought of as anti-inflammatory, and indeed often
used as therapeutic peripheral anti-inflammatory agents,
they actually have pro-inflammatory roles within brain [60].
Indeed, stress increases the expression or activity of a number
of mediators of inflammation in the brain, including NF-κB,
TNF-α, IL-1α, IL-1β, prostaglandins, and free radicals such
as NO [45, 61–63] via both catecholamines and GCs [60, 64].
Thus, stress would be expected to enhance pro-inflammatory
pathways that are major aspects of epileptogenesis.

Aberrant neurogenesis in the hippocampus is also a
hallmark of epileptogenesis [65, 66], including the ectopic
migration of new neurons into the hilus. Stress and GCs
influence the proliferation, differentiation, and survival of
neural stem cells in the hippocampus [67–69]. Generally,
stress decreases neurogenesis at both proliferation and
survival stages [69], but also decreases the percentage of pre-
cursor cells that adopt a neural cell fate (unpublished data).
It is unknown how or if stress effects on neurogenesis may
interact with aberrant neurogenesis during epileptogenesis.

5. Mechanisms by Which Stress May Exacerbate
the Frequency or Severity of Seizures

After the progression of epileptogenesis and the onset of
epilepsy, patients experience spontaneous recurrent seizures
that vary in frequency and severity. As mentioned in
the introduction of this paper, stress is the major self-
reported precipitant affecting seizure frequency. In support
of these clinical studies, stress pathways have been shown
to promote neural activity in a variety of ways, suggesting
that stress may directly contribute to the hyperexcitability
that causes spontaneous seizures. Corticotropin-releasing
hormone (CRH)—which is released in the brain as the first
step of the stress hormone response—causes an increase in
neural discharge and modulates glutamatergic transmission
[70–72]. While CRH acts directly on a variety of neural
receptors [71, 73], it also ultimately induces release of GCs
from the adrenal glands. GCs themselves increase the release
of excitatory glutamate [74], while stress paradigms similarly
induce an increase in extracellular glutamate and aspartate
[75]. Excitatory actions of GCs can be mediated by fast-
acting protein mechanisms [76–78] as well as the classical
delayed (transcriptional) effects of GR, which have been
shown to modulate calcium currents in particular [79, 80].

6. Complexity in Epileptogenic Pathways and
Experimental Implications

We see from the above that stress pathways converge with a
variety of other signaling pathways associated with epilepsy,
including regulators of excitotoxic cell death, myelination,
inflammation, astrocitic activation, and neurogenesis. The
nature of this interaction depends on the timing of stress
relative to the progression of epilepsy. However, a variety
of other variable factors make these pathway interactions
quite complex. Firstly, it should be noted that many
events associated with epileptogenesis, such as inflammation,
gliosis, and neurogenesis, are frequently assumed to be
pathological. Equally plausible in many cases is that these
pathways may represent (failed) attempts of neuroprotection
and recovery. Stress itself is often conceptualized as having
an “inverted U-shaped” effect on a given task or output, with
extremely low or high amounts of GCs being “detrimental”
but moderate amounts being “beneficial.” Furthermore, it
is widely recognized that the effects of stress may vary
depending on task or context. For example, early life stress
is detrimental by many metrics, but may also lead to a
blunting of inflammatory response that is protective in
terms of epilepsy vulnerability [60]. This type of nuanced
analysis must be applied when considering the effect of stress
on epilepsy (protective and detrimental effects of stress on
epilepsy are reviewed in depth by [81]); it would also be well
applied to epileptic pathways in themselves. Inflammation,
reactive astrocytes, and neurogenesis in particular have
been alternately described as protective or pathological.
The specific effects of these mechanisms may vary depending
on severity of injury (i.e., protective after mild precipitating
brain trauma, but overexpressed and damaging after severe
brain injury) or on the specific stage of epileptogenesis.

Similarly, it is important to consider that most of
these mechanisms are investigated in the context of “strong
inference” type experimentation, wherein a specific pathway
is genetically or pharmacologically manipulated, and specific
Figure 1: Transcriptional analysis of GC-responsive genes that are modulated by albumin treatment. Arrays from three animals that were sacrificed 24 hours after albumin treatment [48] were reanalyzed to identify genes that are modulated by both stress and the model of albumin-induced epileptogenesis. *Genes mentioned in text.
outputs such as cell death or seizure onset are interpreted as markers of pathology. In taking a step back to a more global view of epilepsy, we emphasize that a large number of molecular mechanisms are in play at any given moment, interacting in complex ways. What is the net output, for example, when pathways known to be neuroprotective, and others known to cause neural damage, are induced at the same time?

To address such complexity in epileptogenic mechanisms, we advocate the use of global analytical tools such as microarrays. While microarrays are frequently used as a discovery tool, they may also be used in a much more targeted fashion to characterize global events surrounding a specific mechanism. For example, we used microarrays to characterize the transcriptional profile that follows albumin binding to TGF-β1, including a number of pro-inflammatory outputs [48]. Such transcriptional profiles are being gathered for a variety of epilepsy models by the Consortium for Epilepsy Microarray (Raymond Dingledine, personal communication), and used to define the common set of genes that are modulated across different models of epilepsy, as well as clarify interacting mechanisms and beneficial/detrimental effects. To demonstrate the utility of this approach, we reanalyzed our previous array data from rats treated with albumin, focusing on a subset of genes identified as “core GC responsive genes” by the Microarray Consortium (Figure 1). This allowed us to delineate the numerous transcriptional intersections between stress and our epilepsy model. Of particular note, in context of the mechanisms discussed in this paper, is synergistic modulation of pro-inflammatory cytokine pathways by both albumin treatment and GCs, including chemokine (C-C motif) ligand 2 (Ccl2), interleukin-6 (Il6), tumor necrosis factor (Tnf), and interleukin-1 beta (Il1b). We look forward to future use of these microarray resources, which will elucidate the common pathways in various types of epileptogenesis and allow for nuanced analysis of exacerbating risk factors, such as stress.

7. Conclusions

Stress may create vulnerability to epilepsy prior to etiological incidents, as well as exacerbate epileptogenesis following traumatic injury. While potential effects of stress on neural injury are well understood, the ways in which early life stress may create vulnerability for epilepsy, particularly in regard to possible roles for white matter, represent an unknown frontier for future research. While seizures continue to be the defining aspect of epilepsy, nuanced and global analysis of the complex events that occur during epileptogenesis may offer greater insight into the progression of, and possible therapeutic interventions against, epilepsy.

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