Biomarkers of Epileptogenesis: Psychiatric Comorbidities (?)

Andres M. Kanner · Andrey Mazarati · Matthias Koepp

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Abstract The last decade has witnessed a significant shift on our understanding of the relationship between psychiatric disorders and epilepsy. While traditionally psychiatric disorders were considered as a complication of the underlying seizure disorder, new epidemiologic data, supported by clinical and experimental research, have suggested the existence of a bidirectional relation between the two types of conditions: not only are patients with epilepsy at greater risk of experiencing a psychiatric disorder, but patients with primary psychiatric disorders are at greater risk of developing epilepsy. Do these data suggest that some of the pathogenic mechanisms operant in psychiatric comorbidities play a role in epileptogenesis? The aim of this article is to review the epidemiologic data that demonstrate that primary psychiatric disorders are more frequent in people who develop epilepsy, before the onset of the seizure disorder than among controls. The next question looks at the available data of pathogenic mechanisms of primary mood disorders and their potential for facilitating the development and/or exacerbation in the

severity of epileptic seizures. Finally, we review data derived from experimental studies in animal models of depression and epilepsy that support a potential role of pathogenic mechanisms of mood disorders in the development of epileptic seizures and epileptogenesis. The data presented in this article do not yet establish conclusive evidence of a pathogenic role of psychiatric comorbidities in epileptogenesis, but raise important research questions that need to be investigated in experimental, clinical, and population-based epidemiologic research studies.

Key Words Major depressive disorder · Serotonin · Opioids · Selective serotonin-reuptake inhibitors · Hypothalamic–pituitary–adrenal axis · Glutamate · GABA

Introduction

For a long-time, the search for biomarkers of epileptogenesis has focused on “epilepsy”- or “seizure”-related variables, such as excitatory (e.g., glutamate) and inhibitory [e.g., gamma amino-butyric acid (GABA)] neurotransmitters. Yet, in people with epilepsy (PWE), data from epidemiologic studies have shown a higher prevalence of primary psychiatric disorders *preceding* the onset of the seizure disorder than in the general population [1–6]. In addition, in animal models of depression, rapid amygdala kindling was achieved more rapidly when the animal was subjected to conditions of great stress [7]. These observations have raised the question of whether psychiatric comorbidities can be “a risk” for the development of epilepsy and, if so, could we identify a biomarker for epileptogenesis among their pathogenic mechanisms. The aim of this article is to try to address this question.

A. M. Kanner (✉)

Department of Neurology, University of Miami, Miller School of Medicine, 1120 NW, 14th Street, Room 1324, Miami, FL 33136, USA
e-mail: a.kanner@med.miami.edu

A. Mazarati

Department of Pediatrics, D. Geffen School of Medicine at UCLA, Los Angeles, CA, USA

A. Mazarati

Children’s Discovery and Innovation Institute, D. Geffen School of Medicine at UCLA, Los Angeles, CA, USA

M. Koepp

Department of Clinical and Experimental Epilepsy, UCL Institute of Neurology, Queen Square, London, UK

Epidemiologic Data

Traditionally, psychiatric comorbidities in epilepsy have been considered to be a “complication” of the seizure disorder. Yet, population-based studies of primary psychiatric disorders have established that not only are PWE more likely to develop these comorbid conditions than the general population, but have also suggested that patients with “primary” psychiatric disorders are at higher risk of developing epilepsy [1–7]. For example, in the first study, conducted in Sweden, depressive disorders were seven times more common among patients with new-onset epilepsy, *preceding the seizure disorder*, than among age- and sex-matched controls [1]. A second study from Omstead County, Minnesota, USA, included all adults aged 55 years and older at the time of the onset of their epilepsy; a diagnosis of depression *proceeding the time of their first seizure* was 3.7 times more frequent among patients than among controls, after adjusting for medical therapies for depression [2]. In both studies, the increased risk was greater among patients with focal-onset seizures. A third population-based study, conducted in Iceland, included adults and 324 children aged 10 years and older with a first unprovoked seizure or newly diagnosed epilepsy, and 647 controls [3]. A major depressive episode (MDE), according to *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* criteria, was associated with a 1.7-fold increased risk for developing epilepsy, while a history of attempted suicide before the onset of epilepsy was 5.1-fold more common among patients than among controls. In the population, children with an attention deficit disorder of the inattentive type were 3.5-fold more likely to develop epileptic seizures or epilepsy than controls [4]. In a population-based study conducted in the UK, a history of depressive and anxiety disorders, suicidality, and psychosis was identified to be 2–4-fold more frequently during the 3 years preceding the onset of epilepsy in patients than in controls [5]. These data were supported by the findings of a Swedish population-based study, in which investigators compared the risk of developing unprovoked seizures or epilepsy among patients who had been hospitalized for a psychiatric disorder with a group of controls, matched for gender and year of diagnosis, and randomly selected from the register of the Stockholm County population [6]. The age-adjusted odds ratio (OR) for the development of unprovoked seizures was significantly higher for all psychiatric disorders [2.7, 95 % confidence interval (CI) 2.0–3.6]; the OR for major depressive disorders (MDD) was 2.5 (95 % CI 1.7–3.7), for bipolar disorder it was 2.7 (95 % CI 1.4–5.3), for anxiety disorder it was 2.7 (95 % CI 1.6–4.8), and for suicide attempt it was 2.6 (95 % CI 1.7–4.1), independent of the psychiatric disorder. Of note, the OR among depressed patients was higher for idiopathic or cryptogenic seizure disorders (3.9, 95 % CI 2.4–6.1) than for symptomatic seizures (1.5, 95 % CI 0.8–2.6). Likewise, in a

population based-study conducted in Taiwan, patients with schizophrenia had a 6-fold higher risk of developing epilepsy than controls [7].

Yet, is it possible that this phenomenon may be the expression of an iatrogenic process, mediated by the psychiatric patients’ exposure to psychotropic drugs, many of which are considered to have “proconvulsant properties”? Data from one study appear to dispel this concern with respect to the antidepressant drugs. Indeed, Alper et al. [8] looked at the incidence of seizures experienced by patients with primary MDD randomized to an antidepressant or placebo in the course of multicenter, randomized, placebo-controlled trials of selective serotonin reuptake inhibitors (SSRIs) and serotonin norepinephrine reuptake inhibitors submitted to the Food and Drug Administration for regulatory purposes. They found that a higher incidence of epileptic seizures was identified among depressed patients randomized to placebo than to the antidepressant drug (standardized incidence ratio=0.48; 95 % CI 0.36–0.61). Furthermore, the incidence of seizures in these patients was 19-fold higher than the rates published for the general population. In addition, an antiepileptic effect of the SSRIs fluoxetine and citalopram has been suggested in various animal models of epilepsy (see below) and in open trials in PWE [9–11]. In fact, a review of the literature has suggested that seizures associated with antidepressant drugs are likely to occur in the setting of overdoses. This observation seems to be supported by data from an experimental study done in rats in which seizures were induced with pilocarpine [12]. Seizure prevention was observed when intrahippocampal perfusion of serotonin yielded extracellular concentrations ranging between 80 % and 350 % of baseline levels, while worsening of seizures occurred at concentrations >900 % of baseline.

However, an iatrogenic process cannot be completely discounted in patients with psychotic disorders, as a higher incidence of seizures was identified among patients randomized to clozapine, followed by olanzapine and to a lesser degree, quetiapine than to placebo in the same study [8]. A predisposition to the development of seizures mediated by the psychotic process coupled with an iatrogenic effect of antipsychotic drugs may also be a possibility.

Can Pathogenic Mechanisms of Primary Psychiatric Disorders Facilitate the Occurrence of Seizures?

If psychiatric disorders exert an intrinsic effect on the development of epilepsy, some of their operant neurobiologic pathogenic mechanisms should be able to facilitate the development of epileptic seizures and of, or possibly, influencing the epileptogenic process. To address this question, we will focus our discussion on a review of some of the pathogenic mechanisms operant in primary mood disorders. These will include i) disturbances of neurotransmitters in the central nervous system (CNS); ii) a hyperactive hypothalamic–pituitary–

adrenal axis (HPA-A), resulting in high serum cortisol levels and associated with widespread structural changes; iii) disturbances of CNS opioid secretion and; iv) inflammatory mechanisms.

Human Data

Disturbance of Neurotransmitters

Serotonin

Abnormal serotonergic activity has long been identified as one of the pivotal pathogenic mechanisms of primary mood and anxiety disorders. The serotonin- $1A$ (5-HT $_{1A}$) receptor family is the most abundant in the CNS, and is located predominantly in limbic structures. In recent studies, decreased serotonergic activity has been postulated as a potential pathogenic mechanism of seizure disorders. For example, studies with positron emission tomography (PET) have used [^{18}F]FCWAY and [^{18}F]MPPF to investigate 5-HT $_{1A}$ receptor binding in the CNS. These studies revealed similar functional abnormalities in primary MDD and temporal lobe epilepsy (TLE) (without depression), which consisted of decreased 5-HT $_{1A}$ receptor binding in the hippocampus, amygdala, cingulate gyrus, insula, and raphe nucleus [13–16]. In one study of patients with TLE and normal hippocampus volume, the decrease in 5-HT $_{1A}$ binding was restricted to the temporal pole [17], and was more pronounced in the seizure-onset zone and in regions where the discharge propagated than in regions where only interictal paroxysms or no epileptic activity was recorded [18].

5-HT-transporter activity was lower in the insula and fusiform gyrus on the epileptogenic side, more so in depressed than euthymic patients with TLE. In the insular cortex there was a correlation between 5-HT-transporter and 5-HT $_{1A}$ asymmetry for patients with TLE, but not for healthy controls, suggesting greater loss of 5-HT $_{1A}$ receptors to compensate for reduced transport, such that higher synaptic 5-HT levels can be expected to be maintained at the sites that have fewer 5-HT $_{1A}$ receptors [19].

The reduction in 5-HT $_{1A}$ receptor binding in patients with mesial TLE may be explained, on the one hand, by a decrease in receptor density due to downregulation caused by hyperexcitability, or, on the other hand, by an increase in endogenous 5-HT as a reactive process to modulate hyperexcitability. Lothe et al. [20] confirmed an association of depressive symptoms in TLE patients with changes of the central serotonergic pathways, in particular within raphe nuclei, insula, cingulate gyrus, and epileptogenic hippocampus. These changes are likely to reflect lower extracellular 5-HT concentration in more depressed patients, with an upregulation of receptors a less likely alternative.

Glutamate

Increased glutamatergic activity is typically associated with the development of epileptic seizures and epileptogenesis, *per se*. Yet, high concentrations of glutamate in the brain have been identified in patients with primary mood disorders. The evidence is derived from the following observations: i) high glutamate concentrations in cerebrospinal fluid, which correlated with suicidal ideation, and decreased (with lower glutamine) after treatment [21]; ii) a potential antidepressant effect of *N*-methyl-D-aspartate (NMDA) antagonist drugs [22, 23]; iii) increased cortical glutamate concentrations identified with magnetic resonance spectroscopy (1H -MRS) in frontal and occipital lobes [24]. A recent MRS study reported an elevated ratio of glucose/creatine in the right hippocampus in PWE with moderate depressive symptoms with the ratio of glucose/creatine in the right hippocampus correlating with the severity of depressive symptoms [25]. Of note, glutamatergic and monoaminergic systems are closely interconnected, as evidenced by the projection of glutamatergic neurons from the cortex to the locus coeruleus, raphe nucleus, and substantia nigra. Likewise, serotonergic and noradrenergic agents can interfere with the neurotransmission of glutamate. For example, chronic treatment with the SSRI fluoxetine, the serotonin norepinephrine reuptake inhibitor reboxetine, and the norepinephrine reuptake inhibitor desipramine cause a reduction of depolarization-evoked release of glutamate [26].

GABA

Decreased GABAergic activity has been identified as one of the pivotal pathogenic mechanisms of the epilepsies. Likewise, decreased GABA has been reported in the cerebrospinal fluid of patients with MDD [27], and studies with 1H -MRS in unmedicated adults with MDD have revealed decreased GABA levels in dorsomedial, dorsal anterolateral prefrontal and ventromedial prefrontal regions, and occipital regions [28]. A study of the GABA-synthesizing enzyme, glutamic acid decarboxylase (GAD) and its two isoforms GAD $_{65}$ and GAD $_{67}$, found a decrease of the density of GAD $_{65}$ and GAD $_{67}$ messenger RNA (mRNA)-positive neurons by 45 % and 43 %, respectively, in the hippocampus, and of GAD $_{65}$ in the cingulate and prefrontal cortices of patients with bipolar disorder [29]. One study found decreased GABA synthesis in depressed patients before pharmacotherapy [30], while others showed a normalization of cortical GABA concentrations after treatment with the SSRI citalopram [31] or electroshock therapy [32].

The role of GABA receptors has been investigated in studies using transcranial magnetic stimulation, a treatment modality for treatment-resistant MDD. It is based on the activation of cortical neurons with pulsatile magnetic fields and relies on GABAergic inhibition measured with two

variables: short-interval cortical inhibition (SICI) and the cortical silent period (CSP). The SICI is assessed with the delivery to the motor cortex of an initial subthreshold conditioning stimulus followed by a suprathreshold test stimulus. Inhibitory GABAergic interneurons are activated when the interval between the two stimuli is between 1 and 5 ms, which is an expression of GABAA-mediated inhibitory activity [33], while CSP reflects GABAB activity [34]. A decreased GABAergic tone in MDD has been suggested by shorter SICI and CSP [35]. For example, decreased cortical inhibition has been illustrated in one study of 35 patients with MDD and 35 healthy controls; shorter SICIs and CSPs were found in the left hemisphere of psychiatric patients [36]. Data from a separate study suggest that loss of GABAA inhibitory effect is more likely to occur in patients with treatment-resistant MDD, as suggested by a study of 85 patients, 25 with treatment-resistant MDD, 16 with MDD on no medication for at least 1 month, 19 fully recovered from a MDE on psychotropic drug, and 25 healthy controls. Compared with healthy controls, the 3 patient groups had impaired CSP measures, but abnormal SICI were only found in patients with treatment-resistant MDD [37].

Hyperactive HPA-A

High cortisol secondary to a hyperactive HPA-A is the first biologic marker of MDD, which reflects a failure of the adrenal gland to suppress the secretion of cortisol to a dose of dexamethasone (DEX; also known as the DEX suppression test). An abnormal DEX suppression test has been identified in about 50 % of patients with MDD [38], and has been also reported in patients with TLE [39]. Furthermore, as 5-HT_{1A} receptor binding and its mRNA expression are under tonic inhibition by glucocorticoid receptor stimulation, reduction in 5-HT_{1A} receptor binding and its mRNA expression in depression may be caused by cortisol hypersecretion [40]. This observation may explain the decreased 5-HT_{1A} receptor binding identified on PET studies of humans with depressive disorders and epilepsy cited above.

Neuropathologic consequences attributed to excessive cortisol have included i) decreased glial density and neuronal size in the cingulate gyrus; ii) decreased neuronal sizes and neuronal density in layers II, III, and IV in the rostral orbito-frontal cortex, resulting in a decrease of cortical thickness; iii) decrease of glial density in cortical layers V and VI associated with decreases in neuronal sizes in the caudal orbito-frontal cortex; and iiiii) a decrease of neuronal and glial density and size in all cortical layers of the dorsolateral prefrontal cortex [41–46]. Finally, elevated levels of glucocorticoids have been associated with reduced astrocytic activity and interference with their function. In this manner they may undermine neuronal and cortical function in MDD by causing the accumulation of excessive synaptic glutamate [47].

Structural Changes

Neuroimaging studies have found significant hippocampal atrophy, ranging from 8 % to 19 %, in depressed patients compared with nondepressed controls [48–50]. For example, in comparing hippocampal volumes of 20 patients with treatment-resistant depression with 20 patients that had recovered from depression and 20 healthy controls, Shah et al. [51] found that patients with treatment-resistant depression were more likely to have hippocampal atrophy [51]. Moreover, an inverse relationship between duration of depression and total hippocampal volume has been demonstrated [52]. Similarly, hippocampal atrophy is also the most frequently identified abnormality in patients with TLE and primary depression [53].

Structural imaging studies report increased depressive morbidity, in pathologically heterogeneous TLE patients, with enlarged amygdalar volume [54, 55], or preserved T₂ relaxometry in the contralateral amygdala of TLE-positive hippocampal sclerosis patients [56]. Mesial TLE (mTLE) has also been implicated [57, 58], but this is not a consistent finding [53, 59, 60]. Left-sided mTLE was considered a risk factor [58], but this has not been confirmed by others [53, 57, 61–63]. Reduced hippocampal volume has been variably associated with greater depressive symptomatology. An early study by Quiske et al. [57] assessed 60 TLE patients and reported that patients with mTLE had higher Beck-Depression-Inventory (BDI) scores (e.g., more severe symptoms of depression) than neocortical TLE patients, independent of the lateralization of the lesion [57]. These two latter studies suggest that the neuroanatomical link(s) between depression and TLE reside within the limbic system, rather than the temporal lobe per se. This finding has been replicated, although the atrophy was specific to the hippocampus *contralateral* to the seizure onset [53, 61]. A subsequent study using three-dimensional surface mapping, also found significantly increased contralateral hippocampal atrophy in depressed (BDI ≥ 14) mTLE patients [62]. Others have not found an association between depression and hippocampal atrophy using hippocampal volumetry studies [55, 56, 59].

Mesio-temporal structures are not the only limbic regions involved in depression, both in primary mood disorders and in PWE [55, 56, 64], as extratemporal abnormalities have been identified in both clinical populations [65, 66], suggesting dysfunction of a distributed neural network. Indeed, there is a large body of evidence of structural and functional abnormalities in primary depression, implicating orbital and medial prefrontal cortices, and anatomically related structures within the limbic, striatal, thalamic, and basal forebrain structures [65–67]. There have been meta-analytic reports in the primary affective disorder literature of reduced gray matter volume in orbito-frontal cortex, cingulate gyrus [67–69], and thalamus [67] compared with healthy controls. These studies confirm the validity of the neuropathologic findings in the primary mood disorders cited above.

In patients with TLE of mesio-temporal lobe origin, Lin et al. 70 [70] have identified decreased cortical thickness in temporal lateral and extratemporal cortex using voxel-based morphometric analyses of brain magnetic resonance imaging (MRI) studies. Furthermore, in a study of 48 adults with treatment-resistant TLE, 24 with and 24 without a depressive disorder and 96 healthy controls, Salgado et al. [58], using voxel-based morphometric analysis, found that patients with TLE with depression had a greater number of areas of gray matter volume loss than those with without depression in temporal and frontal lobe regions bilaterally and in the left thalamus. Of note, in a separate study of 165 patients with TLE, the same group of investigators found that gray matter atrophy in patients with treatment-resistant and remitting-relapsing epilepsy was more widespread than in seizure-free patients [71]. Significant differences included cortical atrophy of bilateral periorbital cortex, cingulate gyrus, and temporal lobes.

Functional neuroimaging studies have also supported the role of temporal and extratemporal structures in depressive disorders of patients with TLE. For example, in a study of patients with TLE and comorbid depression, 18-fludeoxyglucose (FDG)-PET demonstrated bilateral frontal and ipsilateral orbitofrontal hypometabolism [72, 73]. In a study of 31 patients with focal epilepsy, Schmitz et al. [74] used interictal single-photon emission computed tomography and found an inverse relationship between the total score of the BDI and contralateral temporal and bilateral frontal perfusion in left-sided focal patients. In a pilot study, Gilliam et al. [75] investigated the association between depressive symptoms, clinical variables, and 18FDG-PET in 62 patients with refractory focal epilepsy. Age, seizure rate, number of current antiepileptic medications and scores on the adverse events profile were similar between 55 patients with an abnormal PET compared with 7 patients with a normal PET. However, depression scores were, in contrast, significantly higher in the group of patients with an abnormal PET scan, the majority of which showed temporal lobe abnormalities. In a separate study, Gilliam et al. [76] performed a ^1H -magnetic resonance spectroscopy imaging study of 31 patients with TLE and demonstrated a significant correlation between the severity of depressive symptoms and the extent of hippocampal dysfunction. The extent of hippocampal dysfunction explained 57 % of the variance in mood state. In interpreting these data, however, we must keep in mind the one major drawback in clinical imaging in PWE: that of specificity. Indeed, MRI, functional MRI and FDG-PET show both cause and consequence of seizure activity, in the focus and projection area of the seizure onset. Furthermore, multiple lesions are often detected, and the significance of these changes is unclear. In summary, while there are more articles in the literature on the association between TLE and depression, its prevalence appears to be relatively high in frontal lobe and idiopathic

generalized epilepsy, though additional research is necessary to establish its frequency in the latter two types of epilepsy.

Disturbances of CNS Opiate Function

Opioid receptors mediate the analgesic, rewarding, addictive, and mood regulatory effects of opioid agonists through their three main receptor classes: δ -(DOR), κ -(KOR) and μ -(MOR). There is an increasing body of evidence implicating opioid neurotransmission in mood disorders [77], as evidenced by the blunted euphoric response to opioids in depression [78] and large increases in μ -receptors in postmortem suicide studies [79]. Mayberg et al. [80] reported increased *in vivo* binding of ^{11}C -Carfentanil in unipolar depressed patients, which colocalized with metabolic abnormalities in the anterior cingulate cortex, and dorsal and ventral prefrontal and subcallosal orbitofrontal cortex [81].

The role of endogenous opioid release in mood states in healthy human volunteers and depressed patients has been demonstrated via mood induction studies [82, 83]. Zubieta et al. [82] observed increased amygdala binding of [^{11}C] diprenorphine (DPN), a nonspecific opioid receptor antagonist, during mood elation, which could be interpreted as a decrease in constitutive activation. This has also been found for the MOR system in paired PET studies of induced sadness [82] in several regions, including perigenual anterior cingulate gyrus and amygdala [84]. Opposing effects on MOR availability were shown for healthy women compared with women with a mood disorder [85].

Sixty percent of the very high concentration of opioid receptor binding in the amygdala derives from KOR binding [86]. Therefore, it is likely that KORs are at least involved in the mediation of the acute effects on mood in this structure [83]. KOR antagonists given systemically to rats led to antidepressant-like effects similar to 3 antidepressant drugs [87], consistent with the generally dysphoric effect of KOR agonists [84].

Similarly, there is evidence that agonists at DORs are important mediators of the mood-lifting and antidepressant actions of opioids [88], with the caveat that DORs are generally less prominent in the human compared with rodent brains. In humans, cortical DORs only contribute about 20–40 % of total cortical opioid receptor concentration [86] and there is little DOR binding in the medial temporal lobe, including the amygdala.

In TLE, there is evidence for a dynamic relationship between opioid peptide receptor availability and seizures. Studies suggest increased MOR and KOR availability in the ipsilateral temporal lobe during the interictal period in TLE [89]. Decreased [^{18}F] carfentanil (CFX) binding in the presumed epileptogenic zone was observed accidentally during a fortuitous ictal scan (Dr W. Theodore, NIH, personal communication).

In TLE, postictal opioid peptide receptor binding is increased in the ipsilateral temporal lobe [90]. The finding of

changes in opioid receptor availability over a time course of hours following spontaneous seizures suggests an important role of the endogenous opioid receptor-mediated neurotransmission in temporal lobe seizures

The *in vivo* demonstration in humans of selective regional alterations of MOR and KOR binding in TLE supports the hypothesis derived from animal studies (see below) that endogenous ligand binding to these receptor subtypes plays a role in the tonic anticonvulsive mechanism that limits the spread of seizure activity from the epileptogenic focus.

Inflammatory Disturbances

The connection between depression and chronic inflammation is widely accepted. Markers of inflammation (e.g., inflammatory cytokines and chemokines), including proinflammatory cytokines, interleukin (IL)-1 β , IL-2, and IL-6, interferon- γ , and tumor necrosis factor- α are present in the blood of patients with MDD [91–93]. The prevalence of depression is significantly higher among patients with identified chronic inflammatory diseases (e.g., rheumatoid arthritis) than in the general population [94]. Symptoms of depression represent a common side effect of chemokine immunotherapy [95]. Recent studies have reported the association between the polymorphism of IL1- β promoter and MDD [96], and implicated IL- β gene polymorphism (specifically, its rs16944 variant, which results in the increased IL1- β levels) in the SSRI-resistant forms of major depressive disorder [97].

Among the various cytokines, IL-1 β has been found to display proconvulsant properties (see below). Furthermore, IL-1 β and its receptor type 1 (IL-1R1) have been found to be overexpressed in human brains of patients with TLE, cortical dysplasias, and tuberous sclerosis [98–101]. The mechanisms responsible for IL-1 β proconvulsant properties involve a reduction in glutamate uptake by glial cells or an enhanced release of glutamate from these cells, mediated by tumor necrosis factor- α [102, 103].

PET with α -[^{11}C]-methyl-L-tryptophan (AMT) was originally thought to reflect 5-HT synthesis. AMT hotspots correlated with the duration of seizure intractability in tuberous sclerosis: the longer the duration of seizure intractability, the greater the number of AMT hotspots, regardless of Tuberous sclerosis complex (TSC) mutation [104]. Subsequent studies in PWE suggested that AMT may accumulate in epileptic cortex and in epileptogenic lesions as a result of increased metabolism via the inflammatory kynurenine pathway. A recent AMT–PET study in a patient with new-onset refractory status epilepticus showed inflammatory changes overlapping with the epileptogenic cortex mapped by chronic intracranial electroencephalographic monitoring [105]. Resection of the epileptic focus resulted in long-term seizure freedom, and the nonresected portion of the PET-documented abnormality normalized. Histopathology

showed reactive gliosis and inflammatory markers in the AMT–PET-positive cortex.

Animal Data

Do animal models of depression and epilepsy support the clinical data cited above? To address this question, studies of animal models of depression and epilepsy focusing on 5-HT, a hyperactive HPA, opioid disturbances, and inflammatory processes will be reviewed.

Experimental setting may be particularly useful for disentangling complex relationships between epilepsy and coexisting psychiatric disorders. Transgenic animals, as well as models of acquired epilepsy and of depression represent relatively clean reproducible systems where either epilepsy or depression constitute an unequivocal and on-demand primary pathology. Furthermore, the natural evolution of epilepsy and associated depression can be examined without interference from antiepileptic and antidepressant therapeutic interventions.

Mechanisms of depression and epilepsy are manifold, and involve virtually all classical neurotransmitters, as well as every known neuromodulatory mechanism (e.g., bioactive neuropeptides, endocannabinoids, innate and adaptive immunity, etc.).

Dysregulation of the HPA-A

The dysregulation of the HPA-A represents a neuroendocrine substrate of chronic stress. HPA-A dysregulation involves a failure of autoinhibitory mechanisms via which circulating cortisol (or corticosterone in rodents) inhibits the release of corticotropin releasing hormone (CRH) from the hypothalamus and of adrenocorticotrophic hormone (ACTH) from anterior pituitary. In turn, unabated production of CRH and ACTH lead to high sustained levels of circulating cortisol [106–108]. Consequently, the function of the HPA-A switches from adaptive (i.e., to effectively cope with stressful stimuli) to maladaptive. Ramifications of HPA-A dysregulation are manifold and, among others, include depression and epilepsy.

Experimental evidence that the hyperactivity of the HPA-A leads to depressive behavior is overwhelming [107–112]. Thus, chronic stress induced in rodents by maternal separation, prolonged physical restraint, cold stress, and sleep deprivation results in the HPA-A hyperactivity [112–115]; the latter is evident by the elevated plasma corticosterone level and/or positive DEX or DEX/CRH tests [116]. Concurrently, animals develop depressive behaviors, such as increased immobility in the forced swimming test (FST) in rats and in the tail suspension test in mice (which serve as indicators of hopelessness/despair), as well as the loss of saccharin or sucrose consumption preference (which suggests the presence of anhedonia) [117, 118]. Similarly, an exogenous administration of

corticosterone is sufficient to produce the aforementioned depressive behaviors in rodents [119, 120]. Finally, mice that are selectively bred to present with the depressive phenotype have chronically elevated plasma corticosterone levels [121].

At the same time, hyperactive HPA-A resulting from either stress of exogenously applied corticosterone, primes the brain for epilepsy. Thus, repeated physical restraint in rats accelerates the rate of amygdala kindling (i.e., reduces the number of electrical stimuli needed to reach fully kindled state) and increases the duration of secondary generalized complex partial seizures [122]. Repeated separation of neonatal rat pups from dams also accelerates the rate of amygdala kindling [123], increases the sensitivity to pentylenetetrazole-induced convulsions in adulthood [124], and exacerbates the increase of plasma corticosterone levels under conditions of pilocarpine status epilepticus [124]. Similarly, exogenous administration of corticosterone promotes kindling epileptogenesis [125–127], enhances the sensitivity to convulsive effects of intrahippocampally injected kainic acid in rats [128], and increases the frequency of interictal epileptiform events in the kainic acid model of chronic epilepsy in mice [129].

While there is compelling evidence that pre-existing stress facilitates epileptogenesis upon the introduction of a secondary epileptogenic insult, the question whether stress in itself may be epileptogenic, or whether a second hit [e.g., traumatic brain injury (TBI) or status epilepticus] is required to produce epileptic disorder remains, by and large, unanswered. In this regard, experiments reporting the presence of spontaneous seizures in adolescent, and even in some adult, rats that have been subjected to stress using simulated poverty paradigm (i.e., limiting maternal nesting) during neonatal age, but in the absence of a secondary epileptogenic procedure, suggest that stressful stimuli not only enhance susceptibility to epilepsy, but may also be epileptogenic in their own rights [130].

Conversely, animals subjected to primary epileptogenic events develop both HPA axis dysfunction and behavioral depressive impairments. Early studies established that the activation of glutamate receptors by both kainic acid and NMDA in rats increase plasma corticosterone and ACTH levels [130–132]. Later, HPA axis dysfunction under conditions of chronic epilepsy was reported. Thus, rats in which chronic epilepsy is induced by lithium chloride and pilocarpine status epilepticus exhibit chronically elevated plasma corticosterone levels, as well as a positive DEX/CRH test (i.e., failure of exogenously administered DEX to suppress plasma corticosterone, and exacerbated and prolonged increase of plasma corticosterone upon systemic injection of CRH) [133, 134]. The extent of the HPA-A dysfunction positively correlates with the severity of depressive behavior assessed by the FST [133, 134]. TBI in rats is well known to lead to chronic epilepsy [135, 136]. At the same time, TBI induces HPA-A hyperactivity [137] along with depressive behavioral abnormalities [138–140].

These data show that epilepsy in itself may play a role of a stressful stimulus and may lead to depression. Therefore, it is possible to imagine an involvement of a vicious circle, whereby epileptogenic stimuli trigger the HPA-A dysfunction (and consequently lead to depression), and the HPA dysregulation, in turn, would further exacerbate the severity of epilepsy. Conversely, the observation that status epilepticus-induced increase of plasma corticosterone level in rats is amplified by the exposure to stress earlier in life [124] suggests an opposite sequence of events, when pre-existing stress combined with a subsequent epileptogenic insult worsens depression secondary to seizures. From this standpoint, it seems worth exploring the therapeutic effects of drugs that would normalize the function of the HPA-A (such as glucocorticoid receptor blockers, or cortisol synthesis inhibitors [111]) in conjunction with standard anticonvulsant and antidepressant treatments of patients with concurrent epilepsy and depression, as this would presumably disrupt the discussed vicious circles and improve treatment outcomes.

Dysfunction of Serotonergic Transmission

The raphe nuclei are the main source of serotonergic innervation in the brain. Raphe serotonergic afferents in prefrontal cortex and the hippocampus are involved in the regulation of mood, and neurotransmission in these afferents is compromised in depression. Diminished serotonergic tone in raphe-forebrain projections may stem from a dysfunction of mechanisms that regulate 5-HT release. One such mechanism is a short-feedback autoinhibitory loop involving 5-HT_{1A} autoreceptors. Activation of these receptors by 5-HT released from raphe neurons hyperpolarizes the latter, thus inhibiting their own firing [141, 142]. Under normal conditions, 5-HT_{1A} receptor-mediated autoinhibition of 5-HT release acts as a sensor providing for the adequate functioning of ascending 5-HT pathways and related mood responses. At the same time, excessive function of these receptors (e.g., due to the 5-HT_{1A} receptor gene polymorphism, or their acquired upregulation) would shift the balance in favor of autoinhibition, effectively diminishing 5-HT release, with depression being a major consequence. Indeed, mice with genetically enhanced levels of 5-HT_{1A} autoreceptors exhibit increased vulnerability to depression [143], whereas inbred mice with high vulnerability to depression have exacerbated physiological responses to the stimulation of raphe 5-HT_{1A} receptors (including hyperthermia and inhibition of raphe neuronal firing). In contrast, pharmacological blockade of raphe 5-HT_{1A} receptors produces an antidepressant effect in the FST [144]. At the same time, depression may stem from a deficiency of postsynaptic (i.e., forebrain) 5-HT_{1A} receptors, the latter representing a target for 5-HT released from raphe. Indeed, selective pharmacological stimulation of postsynaptic 5-HT_{1A} receptors exerts beneficial effects in animal models of depression [145–147].

The involvement of 5-HT transmission in epilepsy has been documented in several animal models. Fluoxetine, an SSRI, alleviated kindled seizures in rats [148], reduced frequency of spontaneous recurrent seizures [149], and normalized interictal neuronal hyperexcitability [150] in the pilocarpine model of TLE. Another SSRI, citalopram, exerts anti-convulsant effects in the kainic acid model of chronic epilepsy [151]. Activation of raphe neuropeptide galanin type 2 receptors attenuates the severity of electrically induced status epilepticus via stimulation of serotonergic transmission in the raphe–hippocampal pathway, while activation of galanin type 1 receptors increases seizure severity by inhibiting 5-HT release [152]. Pharmacological stimulation of postsynaptic 5-HT_{1A} receptors has been proven to be anticonvulsant in several studies involving *in vitro* models of epileptiform activity [153–156], as well as *in vivo*, under conditions of kainic acid model of limbic seizures [157, 158]. Mice lacking 5-HT_{1A} receptors in the hippocampus, exhibit enhanced vulnerability to, and higher mortality from, seizures induced by kainic acid [159]. Genetic epilepsy-prone rats, which are characterized by hypersensitivity to audiogenic seizures, show widespread dysfunction of serotonergic transmission, including reduced 5-HT concentration and decreased 5-HT_{1A} receptor binding [160–162].

The role of ascending 5-HT pathways in epilepsy-associated depression has been directly addressed in studies involving chronic epilepsy following lithium chloride and pilocarpine status epilepticus. These animals present with depressive behaviors in the FST, and in saccharin preference tests. The severity of depressive behavior positively correlates with the diminished serotonergic tone in the raphe–forebrain projection. Compromised 5-HT transmission appears to be a result of the upregulation of 5-HT_{1A} autoreceptors; indeed, the function of 5-HT_{1A} autoreceptors measured by autoradiography is significantly increased in chronic epileptic rats, while selective pharmacological blockade of these receptors reverses depressive behavior [163]. At the same time, postsynaptic 5-HT_{1A} receptors are downregulated in rats with pilocarpine epilepsy, whereas pharmacological stimulation of these receptors exerts antidepressant effects [163]. Thus, under conditions of chronic epilepsy, serotonergic transmission may be compromised on presynaptic (i.e., via the upregulation of autoreceptors and subsequently diminished 5-HT output), as well as postsynaptic (i.e., via the downregulation of postsynaptic receptors and subsequently reduced effectiveness of the transmitter reaching the target) levels; this exemplifies a notion that epilepsy-associated depression has multifaceted mechanisms, even when it comes to one transmitter and one pharmacological receptor type.

While it appears clear that genetic defects in serotonergic transmission represent a conceivable explanation for the epilepsy–depression connection, mechanisms underlying acquired serotonergic deficiency are less understood. In the light

of this review, a reported connection between the HPA-A and serotonergic transmission is intriguing, as it may bridge the two mechanisms implicated in both disorders. Indeed, several reports suggest that excessively high levels of glucocorticoids (as it occurs in stress) upregulate 5-HT_{1A} autoreceptors [164, 165], an obvious consequence being diminished serotonergic tone in raphe afferents. Indeed, in rats with chronic epilepsy and concurrent depression, local pharmacological blockade of raphe glucocorticoid receptors normalizes 5-HT output from raphe into the forebrain and mitigates the severity of depressive behavior [163]. This observation suggests that the already discussed hyperactivity of the HPA-A, among other mechanisms, may cause secondary serotonergic dysfunction in depression associated with epilepsy. Such a possibility outlines yet another positive feedback scenario, under which epileptogenic insult or recurrent seizures act as stressful stimuli, which result in HPA-A dysregulation. The latter would lead to depression via several mechanisms, including compromised serotonergic transmission. In turn, the diminished serotonergic tone would further exacerbate the severity of both depression and of epilepsy.

Disturbances of Opioid Neurotransmission

Opioid receptor availability reflects endogenous opioid concentrations. Exogenously applied opioids have predominantly inhibitory actions on neuronal activity and transmitter release throughout the CNS. However, in the hippocampus different opioids activate different mechanisms in different cell types resulting in opposing functional effects. MOR- or DOR agonists (enkephalin) inhibit GABA release on inhibitory interneurons, resulting in excitation of pyramidal neurons ("disinhibition") [166]. KOR opioid agonists (dynorphine) act presynaptically at the perforant path–granule cell synapse to inhibit excitatory glutamate release in the dentate molecular layer [167].

It is possible that the two systems regulate different subsets of synapses, finetuning hippocampal excitability at many levels. While studies of the effect of administered opioids in different models have given conflicting results, with anticonvulsant action [168] and exacerbation of kindled seizures [169], there is consensus that endogenous opioids are released following induced partial or generalized seizures, and contribute to a raised seizure threshold [170].

Changes in the levels of opioids in the hippocampus have been reported following induced seizures using various experimental animal models [171]:

- hippocampal seizure activity caused release of enkephalins
- proenkephalin mRNA content was transiently upregulated, leading to a rebound peptide rise that exceeds control levels
- amygdaloid kindling resulted in a selective decrease of μ -receptor binding density in the CA1 and CA2 region,

apparent 24 h after the last seizure, and which normalized by 7 days.

Stimuli known to release endogenous opioids, such as electroconvulsive seizures, the animal equivalent of ECT, reduced the severity of seizures, and the anticonvulsant effect was partially blocked by naloxone. Electroconvulsive seizures led to increases of endogenous opioids and compensatory decreases of both MOR and DOR binding sites, lasting approximately 1 week, in the ventral tectal area and nucleus accumbens [172]. There is a large, sophisticated, and at times controversial body of animal data showing that endogenous opioid release may occur following induced and spontaneous seizures. However, the human relevance of these studies can only, at best, be inferential. They require confirmation of direct measurements made in humans.

Brain Inflammation

In the laboratory, Gram-negative infection mimicked in rodents by lipopolysaccharide produces sickness behavior, which, among other symptoms, is characterized by the increased immobility in the FST (i.e., state of despair/hopelessness) and by the lack of saccharin/sucrose preference (i.e., anhedonia) [173]. Furthermore, even depressive impairments not primarily associated with inflammatory stimuli (e.g., depression induced by stress) are readily improved by anti-inflammatory medications [174, 175]. Among various components of innate immunity, the inflammatory cytokine IL-1 β has been particularly strongly implicated in inflammation-induced depression [176–179]. For example, central administration of IL-1 β is sufficient to produce behavioral [176] and neuroendocrine (i.e., elevated plasma corticosterone levels [180]) signs of depression in rodents. Furthermore, IL-1 β may directly impair serotonergic transmission, as it has been shown to suppress the firing of raphe serotonin neurons *in vitro* [181, 182].

At the same time, brain inflammation (including both innate and adaptive immune responses) plays a detrimental role in epilepsy. Various models of chronic epilepsy and acute seizures are consistently associated with the activation of astro- and microglia, disruption of the blood–brain barrier, and leukocyte extravasation in the brain parenchyma [183, 184]. Among innate immune mechanisms, the activation of several inflammatory cytokines and their receptors has been mechanistically connected to both epileptogenesis and ictogenesis. Among these cytokines, IL-1 β appears to play a critical and best-defined role. Both IL-1 β and its receptor (IL-1RI) are overexpressed in the hippocampus in models of TLE in rodents [185, 186]. Pharmacological inhibition of either IL-1 β (e.g., by inhibiting the IL-1 β -synthesizing enzyme, caspase-1 [187]) or its receptor (e.g., by means of IL-1RI antagonist, IL-1-ra [188]) exert potent anticonvulsant effects

in kindling and kainic acid models of TLE, as well as in *in vitro* seizure models [184]. Knockout mice lacking IL-1RI have increased resistance to seizures induced by hyperthermia [188]. As stated above, the proconvulsant action of IL-1 β occurs through facilitating glutamatergic transmission, particularly through the phosphorylation of the NR2B subunit of the NMDA receptor [189].

Considering the involvement of IL-1 β in depression, on the one hand, and in epilepsy, on the other, it is not surprising that this cytokine also plays a critical role in epilepsy-associated depression. Indeed, protracted pharmacological blockade of hippocampal IL-1RI by means of IL-1RA significantly alleviates depressive behavior in rats with chronic epilepsy resulting from status epilepticus [144]. Furthermore, IL-1RI blockade normalizes the activity of the HPA-A, downregulates 5-HT_{1A} autoreceptors, and ultimately stimulates 5-HT release in raphe–forebrain pathways [144, 163]. These results provide direct evidence that the interaction between immune, neuroendocrine and neurotransmitter systems underlies epilepsy-associated depression. In particular, seizure-induced chronic overexpression of hippocampal IL-1 β and/or its receptor subsequently activate the HPA-A, which, in turn, upregulates 5-HT_{1A} receptors and diminishes central serotonergic tone.

The enhanced IL-1 β signaling in the epileptic brain may also play a role in the SSRI resistance of epilepsy-associated depression. SSRI resistance represents a significant challenge in the management of major depressive disorder, as between 30 % and 50 % of depression patients do not respond, or respond poorly, to this class of antidepressants [190, 191]. Along these lines, depression in chronic epileptic rats is not amenable to fluoxetine monotherapy [150]. It has been suggested that SSRI resistance is due to the polymorphism of 5-HT_{1A} receptor gene, which is responsible for the upregulation of 5-HT_{1A} autoreceptors [192]. However, as has been discussed, 5-HT_{1A} upregulation may be acquired, rather than inherited, as it may stem from the ongoing IL-1 β –HPA-A stimulatory drive. Thus, it is conceivable that the disruption of IL-1 β signaling in the epileptic brain and subsequent normalization of 5-HT_{1A} autoreceptor function would restore the effectiveness of SSRI. This suggestion has been confirmed directly, whereby adjunctive therapy with a low, ineffective on its own, dose of IL-1RA renders fluoxetine therapeutically effective in animals with epilepsy-associated depression [193].

Conclusion

In summary, the experimental data reviewed may support the notion that pre-existing dysfunction of the HPA-A (i.e., chronic stress), opioid disturbances, serotonergic transmission (e.g., due to genetic abnormalities), or innate immunity (e.g., chronic inflammation) may each contribute to the development of

depression and epilepsy alike. Furthermore, close interactions exist between neuroendocrine, neurotransmitter, and inflammatory mechanisms; these interactions may result in multiple vicious circles, in 3 of the 4 discussed systems (Fig. 1). Yet, the existence of such vicious circles certainly complicates discerning between primary and secondary conditions in the epilepsy–depression connection. It is also possible that instead of one disorder being a consequence of the other, epilepsy and depression develop concurrently and independently as a result of the same pathological event (e.g., status epilepticus, brain trauma, stress, or an inflammatory disease). At the same time, given that not all patients with epilepsy present with symptoms of depression, and not all patients with MDD have epilepsy, it is obvious that a “perfect storm” is required for the comorbidity to develop. Thus, it is conceivable that more than one of the discussed components (and likely other components not discussed here) should be present at the same time. For example while 5-HT_{1A} receptor gene polymorphism alone may be insufficient for the evolvement of either depression or epilepsy, an otherwise inconsequential event (e.g., mild stress, brain

trauma, or an inflammatory disease) would trigger both depression and epilepsy, with ensuing self-perpetuating and mutually amplifying pathophysiological events leading to further exacerbation of both conditions.

Thus, can pathogenic mechanisms operant in mood disorders be considered as potential biomarkers of epileptogenesis? Not yet. Significant experimental and clinical research studies are yet to be performed to find the answers. For example, experimental studies can test whether a depressive disorder can facilitate the development of post-traumatic epilepsy by comparing whether rats subjected to a paradigm leading to equivalent states of depression (by using various animal model of depression) are more prone to developing epileptic seizures after being subjected to head trauma (using a post-traumatic epilepsy animal model) than control rats. In humans, important data can be derived from multicenter studies in which the above cited neurochemical, inflammatory, and neuroimaging variables are clearly identified in cohorts of patients with a first primary MDE, who are then followed prospectively for several years, at the end of which the presence of those

Fig. 1 Interactions between neuroendocrine, neurotransmitter, and inflammatory mechanisms. HPA = hypothalamic–pituitary–adrenal; 5-HT = serotonin; AEDs = antiepileptic drugs; SE = status epilepticus; TBI = traumatic brain injury

variables is compared between patients who go on to develop epileptic seizures and those who do not. Furthermore, these variables can be compared between those who develop a treatment-resistant epilepsy and those who respond to pharmacotherapy. While such studies are expensive, they are feasible and not unlike the prospective studies that are being conducted today in the identification of pathogenic mechanisms in Alzheimer's disease. For now, the data reviewed in this article have opened many avenues of investigation that could eventually confirm the hypothesis or rule it out.

Required Author Forms Disclosure forms provided by the authors are available with the online version of this article.

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