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Review

Neurobiologic properties of mood disorders may have an impact on epilepsy: Should this motivate neurologists to screen for this psychiatric comorbidity in these patients?

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ABSTRACT

Epilepsy and psychiatric comorbidities have a complex relation, which can be manifested by their relatively high comorbid occurrence and the existence of a bidirectional relation, whereby not only are people with epilepsy (PWE) at greater risk of developing psychiatric disorders, but patients with primary psychiatric disorders are at higher risk of developing epilepsy. The existence of common pathogenic mechanisms operant in primary psychiatric disorders and epilepsy has been postulated as one of the leading hypothesis to explain their close and very complex relation. The neurobiologic characteristics of mood disorders can be used as a model to test this hypothesis. In this manuscript, we highlight data that suggest how several neurobiologic aspects of mood disorders can facilitate the epileptogenic process in animal models and explain the increased risk of patients with primary mood disorders to develop epilepsy in general and treatment-resistant epilepsy in particular. It is our hope that the inclusion of these data in this Special Issue will motivate neurologists to screen common psychiatric comorbidities in PWE.

This article is part of the Special Issue "Obstacles of Treatment of Psychiatric Comorbidities in Epilepsy".

1. Introduction

Mood, anxiety, attention-deficit, and psychotic disorders have higher prevalence rates in people with epilepsy (PWE) than in people with other chronic medical disorders and the general population [1]. Population-based studies demonstrate that one of every three PWE will have experienced a psychiatric disorder in the course of their life, with mood and anxiety disorders been the most frequently recognized comorbidities in adults and children and attention-deficit disorders with hyperactivity (ADHD) in pediatric populations. Contrary to the assumption that psychiatric comorbidities are a consequence of the seizure disorder, as suggested by the latest definition of epilepsy ("*Epilepsy is a disorder of the brain characterized by an enduring predisposition to generate epileptic seizures, and by the neurobiologic, cognitive, **psychological**, and social **consequences of this condition***") [2], psychiatric comorbidities often precede the onset of the seizure disorder. In addition, several population-based studies conducted in the USA, Canada, Europe, Iceland, and Asia have demonstrated that all of these psychiatric comorbidities are associated not only with an increased risk of developing epilepsy [3–6] but also of having treatment-resistant epilepsy [6–8].

The causes of this very complex relation between epilepsy and psychiatric comorbidities are multifactorial. Yet, the existence of common pathogenic mechanisms operant in epilepsy and these psychiatric disorders has been proposed as a likely explanation for their relatively high comorbid prevalence rates, the bidirectional relation between epilepsy and the psychiatric comorbidities, and the associated increased risk of treatment-resistant epilepsy [9,10].

Recognition of the very close and complex relations between psychiatric comorbidities and epilepsy should motivate neurologists to investigate the presence of psychiatric comorbidities early in the evaluation process of a seizure disorder in the same manner as they screen for comorbid diabetes, hypertension, and cardiovascular disease in patients with stroke. This article summarizes some of the available experimental and clinical data on the potential impact of several neurobiologic aspects of primary mood disorders on the increased risk of developing not only epilepsy but also treatment-resistant epilepsy [3–5,8–10].

1.1. Can psychiatric comorbidities be identified in animal models of epilepsy?

The equivalent of depressive and anxiety symptomatology in rats has been identified in several animal models of epilepsy. For example, the Genetic Absence Epilepsy Rats from Strasbourg illustrates the existence of the equivalent symptoms of depression (demonstrated with

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the sucrose preference test) and of anxiety (established with the Elevated Plus Maze and the Open Field Arena) in a rat model of generalized epilepsy [11]. These symptoms *preceded* and *followed* the onset of the epileptic seizures. Equivalent symptoms of depression were demonstrated with the sucrose preference test and the forced swimming test in the two strains of the genetically epilepsy-prone rat (GEPR) [12]. In this animal model of epilepsy, inborn defects of the arborization of noradrenergic and serotonergic neurons arising from the locus coeruleus and the raphe nuclei led to pre- and postsynaptic deficient transmission of serotonin (5-HT) and norepinephrine (NE) [13]. Furthermore, worsening of seizures in these rats was facilitated by the interference in the synthesis and/or release of NE and/or 5-HT while protection of seizures was associated with noradrenergic (desipramine) and serotonergic drugs (fluoxetine and sertraline). Similar findings have been reported in other animal models, including nongenetic animal models in the rat, rabbit, cat, and monkey [14–17].

Early life stress has also been shown to facilitate the process of epileptogenesis in rodents. For example, in three studies that investigated the impact of early postnatal life stress in rats triggered by maternal separation, fewer electrical stimulations in the amygdala were needed to reach a fully kindled state in animals subjected to early separation compared with controls [18–20]. High concentrations of serum corticosterone (CORT) were found to play a pivotal pathogenic role [21–25]. This point is discussed in detail below. Clearly, these data demonstrate the existence of the equivalent of psychiatric comorbidities in animal models of epilepsy.

1.2. Can neurobiologic properties of mood disorders have an impact on the seizure disorder?

As stated above, several population studies established that not only are PWE at an increased risk of developing psychiatric disorders but patients with *primary* psychiatric disorders are also at increased risk of developing epilepsy [3–5,8–10]. Furthermore, patients with psychiatric disorders, preceding the onset of epilepsy, have been found to be at increased risk of developing treatment-resistant epilepsy. The first study to suggest this phenomenon included 780 consecutive patients with new-onset epilepsy [7]. A psychiatric history preceding the onset of the seizure disorder and in particular a history of depression was associated with a greater than twofold higher risk of developing treatment-resistant epilepsy. A more recent study conducted in Canada confirmed these findings [6]. Furthermore, in a prospective study of 138 consecutive patients with new-onset epilepsy, those who endorsed symptoms of depression and anxiety before the start of pharmacotherapy with antiepileptic drugs (AEDs) were significantly less likely to be seizure-free after 12 months of therapy [8]. In an observational study conducted in Brazil, treatment-resistant focal epilepsy was associated with a history of mood + anxiety disorders [26]. In addition, psychiatric comorbidities, presenting as personality disorders with and without mood, anxiety, and psychotic disorders in patients with treatment-resistant temporal lobe epilepsy (TLE) identified at the presurgical evaluation was associated with a worse postsurgical seizure outcome [27]. A review of the literature suggests that several neurobiologic pathogenic mechanisms operant in primary mood disorders may increase cortical hyperexcitability. These pathogenic mechanisms are summarized below.

1.2.1. Hyperactive hypothalamic–pituitary–adrenal axis (HPAA)

A hyperactive HPAA yielding high cortisol blood levels is the first biomarker identified for major depressive disorders [28]. Nonsuppression to a dexamethasone suppression test is suggestive of a hyperactive HPAA and can be found in up to 50% of patients with primary major depressive disorders. By the same token, high cortisol levels have been associated with the process of epileptogenesis in several animal models of epilepsy. For example, in studies conducted in rats, CORT was found to facilitate the kindling process; this effect was reversed with CORT antagonists [21–25]. Neuropathologic examinations of hippocampi in these animals revealed a decrease in the total number of Corpus Ammonum-3 (CA3) pyramidal cells, a finding also reported in animal models of chronic TLE [25] and of depression, as high CORT inhibits neurogenesis in the dentate gyrus.

In patients with primary major depressive disorders, high serum cortisol levels have also been associated with a decreased glial cell density in frontal lobes at the level of the cingulate, orbitofrontal, and dorsolateral prefrontal cortices [29–32]. Since recapturing of synaptic glutamate is one of the functions of glial cells, a decrease in these cells' counts can result in excessive glutamate, one of the neurotransmitters with excitatory properties that play a pivotal role in the generation of epileptic seizures and the process of epileptogenesis.

1.2.2. Neurotransmitter disturbances

Glutamate. Studies conducted in patients with primary major depressive disorders revealed high plasma and cerebrospinal fluid concentrations of glutamate [33,34], which have correlated with the severity of the depressive disorder [35]. Furthermore, high glutamate concentrations were identified in the frontal lobe cortex in a postmortem study of patients with primary major depression [36] while an increase in glutamate signal in occipital and frontal lobe cortices was found with magnetic resonance imaging (H1-MRS) [37,38].

As alluded above, high cortisol secretion and the resulting decrease in glial cells may explain the high glutamate concentrations in the brain of these patients. Other suggested mechanisms include dysfunction of glutamate transporter proteins, whose function is to maintain low extracellular glutamate concentrations through a regulation of its packaging in presynaptic vesicles before its release to the synaptic cleft and through a reuptake mechanism into glial and neuronal cells [39].

The use of N-Methyl-D-aspartate (NMDA) antagonists to treat pharmacoresistant primary major depression has been suggested as another possible evidence of the pathogenic role of glutamate in this condition [40–42]. Indeed, an antidepressant effect of ketamine, an NMDA receptor antagonists, has been reported in two double-blind placebo-controlled trials [40,41] of patients with treatment-resistant major depressive disorder and in one double-blind controlled trial with the NR2B subunit selective N-methyl-D-aspartate receptor antagonist CP-101,606 (Traxoprodil) [42].

GABA is one of the typical neurotransmitters with inhibitory properties of epileptiform activity, and which has been the target of pharmacotherapy of epilepsy since the development of AEDs. In patients with primary major depression, low GABAergic activity in the central nervous system has been identified, as evidence by low concentrations in cerebrospinal fluid (CSF) [43] and in the cortex (identified with magnetic resonance spectroscopy (1-MRS)) [44–46] as well as a decreased cortical GABAergic activity in left frontal lobes identified with transcranial magnetic stimulation [47]. Of note, a normalization of GABAergic cortical concentrations has been achieved after the treatment with selective-serotonin-reuptake inhibitors (SSRIs) [38] and electroshock therapy (ECT) [48].

Monoaminergic neurotransmitters (5HT, NE, and dopamine [DA]) play dominant pathogenic roles in mood and anxiety disorders and are the targets of their pharmacotherapy while DA and NE are the neurotransmitters targeted in the pharmacologic treatment of ADHD. Animal models of epilepsy have suggested a potential pathogenic role of 5HT and NE in epilepsy manifested by decreased serotonergic and noradrenergic activity, as illustrated in the GEPR cited above [12,13,49–56]. Furthermore, decreased 5HT secretion in the raphe–hippocampal serotonergic pathway, lower concentrations and turnover in the hippocampus, and a decreased release from the hippocampus following raphe stimulation have been demonstrated in the pilocarpine–lithium animal model of status epilepticus [50]. In addition, the SSRI fluoxetine reversed the cortical hyperexcitability that followed the development of status epilepticus [50].

Anticonvulsant effects of SSRIs and tricyclic antidepressant drugs have been investigated in animal models. In a review of the literature of 51

studies, two-thirds of studies suggested an antiseizure effect while a proconvulsant effect or no effect was reported in the remaining [57]. An "inverted u-shaped" concentration–response antiepileptic effect of 5HT was suggested in an animal model of epilepsy using pilocarpine-induced seizures [51]. Hippocampal perfusion of 5HT was carried-out, and extracellular concentrations were correlated with seizure occurrence and frequency. When extracellular concentrations ranged between 80 and 350% of baseline levels, rats were protected from seizures while concentrations >900% of baseline worsened seizures. Of note, the same authors demonstrated a similar concentration–response antiepileptic effect of DA in the same animal model. Of note, the high extracellular 5-HT concentrations were associated with significant increases in extracellular glutamate. The findings of this study mimic observations in clinical practice, whereby most seizures attributed to antidepressants in humans have been associated with overdoses.

1.2.3. Neuroinflammatory mechanisms

Proinflammatory cytokines (interleukin-1β (IL-1β), IL-2, IL-6, interferon-γ, and tumor necrosis factor-α) are common pathogenic mechanisms operant in mood disorders and epilepsy [58]. In experimental studies performed in rodents, administration of IL-1β resulted in an elevation of plasma CORT levels [59–61] and the development of clinical phenomena equivalent to symptoms of depression [60]. Of note, IL-1β was also found to suppress the firing of raphe 5HT neurons in vitro and thus, interfering with serotonergic transmission [61]. Conversely, IL-1β displayed proconvulsant properties in rats, which were blocked by its naturally occurring antagonist (IL-1RA) [62–64]. The mechanisms responsible for IL-1β proconvulsant properties involve a reduction in glutamate uptake by glial cells or an enhanced release of glutamate from these cells mediated by TNF-α [62]. Furthermore, IL-1β and its receptor (IL-1RI) have been found to be overexpressed in the hippocampus of patients with mesial temporal sclerosis in TLE [64], in cortical tubers and giant cell tumors of tuberous sclerosis complex [65], and in malformations of cortical development [66].

2. Concluding remarks

The data summarized above suggest the existence of common pathogenic mechanisms operant in depressive and probably also anxiety disorders and epilepsy and may explain their relatively high comorbid occurrence, their bidirectional relation, and the worse course of the seizure disorder associated with a prior history of depression. The data summarized here are, however, a representation of the peak of the iceberg, and the research in these areas is just beginning. Furthermore, other factors have to play a role in the increased risk of epilepsy in people with mood disorders, as most of them do not develop epilepsy. Nonetheless, the impetus to include this article in this special issue was to remind neurologists that mood disorders are a neurologic disorder with psychological symptoms, and as such, they should be motivated to incorporate the investigation of this comorbidity in all patients with epilepsy.

Conflict of interest

None of the authors has any conflict of interest to disclose.

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