Epilepsy & Behavior 38 (2014) 3–7

Contents lists available at ScienceDirect

Epilepsy & Behavior

journal homepage: www.elsevier.com/locate/yebeh

Review

Is depression associated with an increased risk of treatment-resistant epilepsy? Research strategies to investigate this question

Andres M. Kanner *

Department of Neurology, University of Miami, Miller School of Medicine, USA

ARTICLE INFO

Article history:
Accepted 24 June 2014
Available online 26 September 2014

Keywords:
Major depressive disorder
Glutamate
Serotonin
Hypothalamic–pituitary–adrenal hyperactivity
1β-Interleukin
Hippocampal atrophy
Gamma-aminobutyric acid

ABSTRACT

Persons with epilepsy (PWE) have a higher risk of developing depressive disorders (DDs), and people with primary DD have an increased risk of developing epilepsy. Furthermore, a lifetime history of DD has been associated with a worse response of the seizure disorder to pharmacotherapy and epilepsy surgery. The first part of this article reviews the literature of this problem with the intention of highlighting the neurobiologic pathogenic mechanisms operant in DD with a potential to facilitate the epileptogenic process and/or cortical hyperexcitability in humans and experimental animal studies of depression. They include the following: (i) a hyperactive hypothalamic–pituitary–adrenal axis and the associated structural and functional abnormalities of limbic structures, (ii) increased glutamatergic activity and decreased GABAergic and serotonergic activity, and (iii) immunologic disturbances. In the second part of this article, we suggest research strategies to test the hypothesis of whether depression worsens the course of epilepsy and identify the pathogenic mechanisms operant in this process.

This article is part of a Special Issue entitled "NEWroscience 2013".

1. Introduction

Depressive disorders (DDs) are the most common psychiatric comorbidity in persons with epilepsy (PWE), with lifetime prevalence rates ranging between 30 and 35% in population-based studies [1]. The negative impact of comorbid DD on the quality of life of PWE has been recognized for a long time [2–6]. Recent studies have also shown that DDs worsen the tolerance of patients to antiepileptic drugs (AEDs) [7,8]. In addition, the negative impact of DD appears to include the patient's worse response to pharmacologic [9,10] and surgical treatment of the seizure disorder [11–13]. In fact, an ongoing prospective study of the variables associated with response to pharmacologic treatment in patients with newly diagnosed epilepsy has identified a past psychiatric history and a current psychiatric history of depression as potential variables associated with persistent seizures. For a long time, the occurrence of epileptic seizures in patients with primary DD has been attributed to "proconvulsant effects" of antidepressant drugs and poor compliance with AEDs. Yet, in a study published in 2007 [14], antidepressant drugs of the class of selective serotonin reuptake inhibitors (SSRIs) and serotonin–norepinephrine reuptake inhibitors (SNRIs) were found to be associated with a *lower* incidence of seizures than placebo in patients with primary DD. Indeed, that study investigated the incidence of seizures experienced by patients with primary major depressive disorder (MDD) in the course of randomized placebo-controlled trials of SSRIs and the SNRI, venlafaxine; a significantly higher incidence of epileptic seizures was identified among depressed patients randomized to placebo than to antidepressant drugs (standardized incidence ratio = 0.48; 95% CI = 0.36 to −0.61). Furthermore, this incidence was 19-fold higher than the rates published for the general population. These data must be coupled with those of several population-based studies of patients with newly diagnosed epilepsy which have demonstrated a complex relation between DD and epilepsy, whereby not only PWE are at greater risk of developing DD [1] but also patients with primary DD are at greater risk of developing epilepsy [15–19]. In this manuscript, we review the question of whether DD can negatively affect the pharmacologic response to AEDs and/or surgical treatment of epileptic seizure disorders and suggest research strategies to study these questions.

2. The evidence of the negative impact of DD on the seizure disorder

2.1. Depressive disorders are associated with a worse response of the seizure disorder to pharmacologic treatment

In a retrospective study of 780 consecutive patients with new-onset epilepsy carried out to identify predictors of treatment resistance to AEDs, a psychiatric history, and, in particular, a history of depression

* Department of Neurology, Comprehensive Epilepsy Center, 1120 NW, 14th Street, Room #1324, Miami, FL 33136, USA. Tel.: +1 305 243 4015; fax: +1 305 243 8108.
E-mail address: a.kanner@med.miami.edu.

http://dx.doi.org/10.1016/j.yebeh.2014.06.027
1525-5050/

was associated with a greater than two-fold higher risk of developing intractable epilepsy [9]. Likewise, in a prospective study of 138 consecutive patients with new-onset epilepsy, a screening for symptoms of depression and anxiety was undertaken before the start of pharmacotherapy in all patients; those who endorsed these symptoms were significantly less likely to be seizure-free after 12 months of therapy [10].

2.2. A lifetime history of DD is associated with a worse postsurgical seizure outcome following an anterotemporal lobectomy

In a study of 100 consecutive patients who underwent an anterotemporal lobectomy for the treatment of refractory temporal lobe epilepsy (TLE), a lifetime history of depression was identified in 12% of patients free of auras and disabling seizures, in 67% of patients with only auras, and in close to 80% of patients with persistent seizures [11]. In two other studies that included 280 and 115 patients with TLE secondary to mesial temporal sclerosis, a preoperative psychiatric diagnosis was associated with a significantly lower likelihood of a postsurgical seizure-free state [12,13]. A fourth study of 72 patients with MTS only, however, failed to show the same findings [14]. The latter study differed from the others by having a shorter postsurgical follow-up period, which may account for the differences.

Thus, if iatrogenic effects of antidepressant drugs cannot account for the bidirectional relation and/or worse course of epileptic seizures, these phenomena could result from a proconvulsant effect of pathogenic mechanisms operant in primary DD. The primary putative mechanisms include the following: (i) endocrine disturbances such as a hyperactive hypothalamic–pituitary–adrenal axis yielding structural, functional, and neuropathologic changes; (ii) neurotransmitter disturbances in the central nervous including serotonin (5-HT), norepinephrine (NE), glutamate, and gamma-aminobutyric acid (GABA); and (iii) immunologic disturbances. A review of the available literature appears to lend support to this hypothesis. Below are some of the relevant data.

2.2.1. Endocrine disturbances

A hyperactive hypothalamic–pituitary–adrenal axis (HPAA) yielding high cortisol blood levels was among the first neurobiologic markers of MDD identified and is found in up to 50% of patients examined using the dexamethasone suppression test (DST) [20]. Some investigators have demonstrated normalization of the DST with treatment with antidepressant medication, though other investigators have found the abnormal response to DST to be a trait of MDD as it fails to normalize following remission of psychiatric symptoms. Of note, patients with TLE were found to have a hyperactive HPAA with the DST, which is of comparable magnitude to that of patients with primary MDD [21].

The potential proconvulsant effect of high cortisol serum concentration was suggested by data from several experimental studies done with rats in which corticosterone (CORT) was found to facilitate the kindling process [22–27], an effect that was reversed with CORT antagonists. Additionally, application of exogenous CORT mimics chronic stress and induces a persistent increase in interictal EEG epileptiform activity in pilocarpine-induced limbic seizures [28]. These studies are summarized in another publication [29], but two studies deserve special mention. In the first study, acceleration of the kindling process was facilitated by early postnatal maternal separation of rats from their dams [22]. This effect was particularly seen in female rats, which exhibited enhanced CORT responses during and after kindling, with a similar trend seen in males. Of note, neuropathologic changes were identified consisting of a reduction in the total number of CA3 pyramidal cells. The second study investigated the long-term effect of isolation of rats at birth on the HPAA and on the development and course of seizures following status epilepticus at postnatal day 10 with the lithium–pilocarpine model of SE [23]. The isolated rats exhibited higher CORT plasma levels following SE than nonisolated rats, while the rats subjected to both isolation and SE displayed a decreased seizure threshold at adult age (postnatal day 100) compared with controls and rats which underwent isolation only or SE only. Furthermore, in animal models of depression, a reduction in the total number of CA3 pyramidal cells and interference with neurogenesis of granule cells in the adult hippocampal dentate gyrus have been reported [23,29–31], two changes that are typically seen in animal models of chronic TLE and that have been associated with persistence of spontaneous seizures [32].

In studies conducted in humans with mood disorders, high cortisol serum concentrations have also been associated with structural, functional, and neuropathologic abnormalities in temporal and frontal lobe structures. For example, in patients with primary MDD, a 10 to 20% bilateral decrement in the hippocampal volume has been reported by several investigators [33–35], the magnitude of which has been correlated with the duration of the depressed state [34]. Likewise, high cortisol plasma levels have been associated with decreased cortical thickness in the frontal lobe of patients with primary MDD, which has been attributed to a decrease of glial and/or neuronal cell density and size in the cingulate gyrus; in layers II, III, and IV of the rostral orbitofrontal cortex; and in cortical layers V and VI of the caudal orbitofrontal cortex; and in all cortical layers of the dorsolateral prefrontal cortex [36–40].

Data from one study may provide a potential mechanism by which these neuropathologic changes may contribute to the worsening of seizure control of PWE with a DD. This study used voxel-based morphometric analyses in brain MRIs of 48 adults with treatment-resistant TLE, 24 with and 24 without MDE, and 96 healthy controls [41]. Patients with TLE and a MDE had a greater number of areas with gray matter volume loss than those without depression in the temporal and frontal lobe regions bilaterally and in the left thalamus. Of note, the association between decreased cortical thickness and worse seizure control was suggested by data from another study which used the same methodology to measure gray matter volume and cortical thickness in the MRI of 165 patients with TLE secondary to mesial temporal sclerosis [42]. Bilateral cortical gray matter atrophy involving the orbital cortex, cingulate gyrus, and temporal–lateral neocortex was significantly more frequent among patients with treatment-resistant epilepsy than among seizure-free patients. It will be important to characterize any analogous frontal cortex atrophy in animal models of epilepsy where hyperactivity of the HPAA has been described such as the Wistar Audiogenic Rat strain [43].

Furthermore, high cortisol levels can impact cortical hyperexcitability through their effects on activity of neurotransmitters, including 5-HT, glutamate, and GABA. For example, a decrease in glial cells' density and function associated with high cortisol levels can result in an excess of synaptic concentrations of the excitatory neurotransmitter glutamate (see also below). Likewise, cortisol decreases serotonergic activity, which in animal models of epilepsy has been found to have anticonvulsant effects (see also below). Of note, high CORT levels in rats were found to cause lower mRNA expression of 5HT1A and decreased receptor binding in the hippocampus, which was blocked with pretreatment with the tricyclic antidepressants (TCAs) imipramine and desipramine [44]. In the same publication, the authors included an analysis of mRNA expression of 5HT1A in the brains of suicidal victims that suffered from depression; they identified the same findings as seen in the brains of rats.

2.2.2. Neurotransmitter disturbances

Depressive disorders have been found to be associated with disturbances of multiple neurotransmitters, particularly 5-HT, NE, dopamine, glutamate, and GABA. In this review, we focus on 5-HT, glutamate, and GABA and the potential mechanisms by which these neurotransmitters can play a pathogenic role in epileptic seizures.

2.2.2.1. Serotonin. The role of 5-HT can be identified in animal models of epilepsy as well as in studies done in patients with TLE. Several detailed reviews have been published highlighting the pathogenic role of 5-HT in animal models of depression and epilepsy [29,44–53]. For example,