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Review

Managing epilepsy-associated depression: Serotonin enhancers or serotonin producers?

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ABSTRACT

Depression is one of the major psychiatric comorbidities having a major impact on the quality of life in people with epilepsy (PWE). Selective serotonin reuptake inhibitors (SSRIs) are considered as safest therapy for the treatment of depression in PWE. Although administration of SSRIs increases the synaptic serotonin levels, it decreases the overall serotonin synthesis in the brain. Long-term therapy with SSRIs has been reported to decrease serotonin synthesis, which may be the possible reason for lessening of their antidepressant effect over time as well as elevated seizure outcomes observed in PWE. Thus the present scenario warrants streamlined studies to explore the safety and efficacy of SSRIs as well as approaches beyond SSRIs for treatment of depression in epilepsy. In this review, we outline the approaches which may restore serotonin levels rather than a pseudo enhancement of serotonin with SSRIs. The potential of various anti-inflammatory approaches such as selective cyclooxygenase-2 inhibitors, inflammatory cytokine inhibitors, and indoleamine 2,3-dioxygenase inhibitors pertaining to their serotonin restoring effects is discussed as possible therapy for treatment of depression in epilepsy.

1. Introduction

Epilepsy is a neurological disorder characterized by an enduring predisposition to generate epileptic seizures, affecting nearly 65 million people worldwide [1]. The abnormal neuronal discharges leading to neuroplastic changes further associate this disorder with cognitive, psychiatric as well as somatosensory comorbidities having a debilitating effect on a patient's quality of life [2]. Out of the various psychiatric comorbidities, depression has been found to be the major psychiatric comorbidity associated with epilepsy [3]. As per the Diagnostic and Statistical Manual of Mental Disorders IV (DSM-IV) and the International Classification of Diseases (ICD), prevalence of major depressive disorder (MDD) in epilepsy is 17.4% (10.0–24.9) which is significantly more than the 10.7% (10.2–11.2) prevalence of depression in a healthy population [3]. Further, apart from epilepsy itself, treatment with some antiepileptic drugs (AEDs) further worsens the associated depression [4]. Moreover, pertaining to the purported ictogenic potential of antidepressants (ADs), treatment of depression in people with epilepsy (PWE) often remains neglected.

2. Serotonergic hypothesis of depression and current status of selective serotonin reuptake inhibitors (SSRIs) for treatment of depression in epilepsy

The serotonin deficiency theory of depression was conceptualizes in the 1950s and was strengthened by subsequent clinical and preclinical observations [5]. The raphe nucleus serotonergic projections from brain stem to the hippocampus and prefrontal cortex comprise the important neurocircuitry modulating the mood [6,7]. The release of serotonin from the raphe nucleus is regulated by a number of intrinsic and external mechanisms. The most efficient mechanism consists of short feedback autoinhibitory loop that involves somato-dendritic 5-HT1A receptors (autoreceptors). The upregulation of raphe 5-HT1A autoreceptors may result in compromised raphe-hippocampus as well as raphe-prefrontal cortex serotonergic transmission [6,8]. This enhanced autoinhibition of serotonin release in raphe nucleus has been reported to be associated with depression [8–10]. Elevated levels of proinflammatory cytokines such as IL-1β have been reported to upregulate 5-HT1A autoreceptors in raphe nucleus, which may explain the neuroimmunological mechanisms of depression [8,11]. The long-term administration of SSRIs such as escitalopram has been reported to desensitize the 5-HT1A autoreceptors, thus restoring the serotonergic neurotransmission in the raphe nucleus [6].

Beside 5-HT1A, various post-synaptic serotonin receptors such as 5-HT2A/2C, 5-HT3, and 5-HT4 have also been implicated in regulating the serotonin levels in the raphe nucleus. The stimulation of GABAergic

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interneurons via 5-HT2A/2C and 5-HT3 receptors connected to pyramidal neurons in prefrontal cortex [12,13], or stimulation of pyramidal neurons (via 5-HT2A receptors) connected to GABAergic interneurons in the raphe nucleus [14], lead to inhibition of raphe nucleus serotonin neurons [15,16]. 5-HT4 receptor agonism in prefrontal cortex has also been reported to increase the firing rate of serotonergic neurons in the dorsal raphe nucleus [17]. Thus, inhibiting 5-HT2A/C, 5-HT3, and activating 5-HT4 receptors in the prefrontal cortex may restore serotonin firing in raphe nucleus. These neural adaptations in the raphe nucleus may mediate the clinical effects of antidepressants and favor the serotonergic hypothesis of depression [18]. This approach has been extended to treat depression associated with epilepsy, but reports regarding their safety are inconclusive.

The meta-analysis of clinical trials did not find any evidence of increased seizure risk with SSRIs but their safety in PWE has not been fully confirmed [19]. In PWE, long-term treatment with SSRIs (1 month to approximately 15 months) did not worsen of seizure outcomes [20–23]; rather, some studies even concluded improvement in seizure outcome [24,25]. In contradiction to this, some studies suggest exacerbation of seizure frequency [26–28]. A recent clinical report by McKean et al. has also reported breakthrough seizures while dispensing vilazodone for the treatment of depression in a patient with a history of epilepsy [29].

Similarly, preclinical studies also demonstrate both proconvulsant or anticonvulsant effects of SSRIs in chronic epileptic animals. The exploration of efficacy and safety of SSRIs in acute models of epilepsy does not appeal as much as it may not mimic the actual clinical situations. However, as per present literature reports, only three studies have been reported employing a chronic model of epilepsy. Hernandez et al. found that 5-days fluoxetine treatment inhibited spontaneous recurrent seizures following pilocarpine-induced status epilepticus [30], while in the same model, Mazarati et al. found no differences in spontaneous recurrent seizures following 10 days of fluoxetine treatment [31]. In the post-kainic acid-induced status epilepticus model, Vermoesen et al. reported reduced seizure frequency and increased seizure duration after 4 days of citalopram treatment, without affecting seizure severity [32]. Thus, both reports of a beneficial as well as deleterious effects for SSRIs exist and this lack of consensus hinders the confidence of physicians with regard to the prescription of SSRIs for treatment of depression in PWE.

Although mechanistic reasons for these discrepancies are still elusive, the hypothesis that may explain the doubtful efficacy and safety of SSRIs for treating depression in epilepsy is discussed as follows. In chronic animal models of epilepsy, serotonin levels have been reported to be significantly decreased [33–37]. This condition may further be deteriorated with SSRI administration, as long-term administration of SSRIs has been reported to decrease serotonin synthesis by 60%, although synaptic serotonin levels were elevated. It is the endogenous mechanism that leads to reduced synthesis of serotonin when its uptake is blocked [38]. As treatment of depression requires long-term administration, administering ADs such as SSRIs may further decrease overall serotonin levels, which may lead to a proconvulsant effect with prolonged therapy. The sustained elevated serotonin levels in the synapse may lead serotonin receptors to get internalized or downregulated. Thus, overall decreased serotonin levels and downregulation of serotonin receptors may lead to diminishing of antidepressant as well as anticonvulsant effects of elevated serotonin levels with SSRIs. These effects may explain the non-effectiveness of SSRIs in countering the depression associated with epilepsy and proconvulsant effects after prolonged therapy in chronic epilepsy [31,39]. Furthermore, the abrupt cessation of SSRIs after prolonged therapy may lead to lowering of the seizure threshold and other discontinuation syndromes [40] (Fig. 1).

Thus, we may conclude that the existing evidence on the efficacy and safety of different ADs for the treatment of depression in PWE is very limited. We have no high-quality evidence to inform the choice as well as comparative data of AD drugs or class of drugs to treat depression in PWE. There is a lack of evidence and comparative data for the safety of SSRIs with regard to seizurogenic potential. As per present literature reports, most of the clinical studies were small, open-labeled, and contained short periods of treatment and seizure analysis on highly selected patient populations. To be conclusive regarding the efficacy as well as safety, the comparative, double blind, randomized controlled studies with long longitudinal follow-up are required in large populations to better inform the ADs or class of ADs for treatment of depression in epilepsy. These inconclusive results also warrant better protocol designs for exploration of SSRIs as well as drives us to think beyond SSRIs for safe and effective management of depression associated with epilepsy.

3. Altered tryptophan metabolism: possible relation to depression in epilepsy

Tryptophan is an essential amino acid that is biotransformed in the body following two different pathways to serve different physiological needs. The first pathway involves hydroxylation of tryptophan by tryptophan hydroxylase leading to synthesis of serotonin whereas the second pathway involves the action of dioxygenase enzymes to convert tryptophan into kynurenine. Availability of tryptophan as a substrate is rate-limiting for both enzymes. Less than 5% of tryptophan undergoes hydroxylation by tryptophan hydroxylase leading to synthesis of serotonin. Deficient production of serotonin contributes to depressed mood, and disturbances of sleep and circadian rhythms. About 95% of tryptophan is metabolized via the kynurenine pathway and it represents the major source of the coenzyme NAD+. It plays a critical role in many fundamental biological processes, including redox reactions required for mitochondrial function [41]. The kynurenine pathway is mainly regulated by two key enzymes: indoleamine 2,3-dioxygenase (IDO) and tryptophan 2,3-dioxygenase (TDO), which differ in their tissue localization and regulation [42]. Both IDO and TDO are widely expressed in all tissues and their expression is regulated by pro-inflammatory cytokines and the CNS immune response [43–46]. TDO is predominantly expressed in the liver [47], responsible for metabolism of tryptophan, and is primarily activated by glucocorticoids (corticosterone in rodents and cortisol in humans).

Proinflammatory cytokines, such as interleukin-6 (IL-6), interleukin-1β (IL-1β), tumor necrosis factor- α (TNF-α), upregulated in epilepsy have been reported to elevate IDO activity in the brain [48,49]. Elevated activity of IDO leads to enhanced kynurenine/tryptophan ratio as well as decreases serotonin/tryptophan ratio. In the brain, the tryptophan hydroxylase, which converts tryptophan into serotonin, is only 50% saturated with its substrate, making tryptophan availability a rate-limiting factor. Therefore, depletion of tryptophan pertaining to enhanced IDO activity has an immediate impact on the brain serotonin levels [50].

IDO is expressed in the central nervous system (CNS) in endothelial cells, macrophages/microglia, and astrocytes [51]. The kynurenine generated from tryptophan is metabolized to either kynurenic acid [pertaining to the action of kynurenine aminotransferase (KAT) enzyme] or quinolinic acid [pertaining to the action of kynurenine 3-monooxygenase (KMO) and kynureninase (KYNU) enzyme]. Kynurenic acid has potent neuroprotective action while quinolinic acid acts on *N*-methyl-D-aspartate (NMDA) type glutamate receptors to produce oxidative stress and depression-like phenotypes [52,53]. All the major enzymes in the kynurenine pathway viz. IDO, KMO, and KYNU have been reported to be upregulated in epilepsy leading to abnormal production of kynurenine and quinolinic acid. In the CNS, macrophages and microglia represent the main sources of quinolinic acid, which contributes to excitotoxic neuronal damage largely via overactivation of NMDA receptors [49]. Astrocytes appear to lack the functional KMO enzyme; therefore, these cells favor the formation of kynurenic acid rather than the toxic metabolites.