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Review

Should antidepressant drugs of the selective serotonin reuptake inhibitor family be tested as antiepileptic drugs?

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ABSTRACT

For a long time, there has been a misconception that all antidepressant drugs have proconvulsant effects. Yet, antidepressants of the selective serotonin reuptake inhibitor (SSRI) family not only have been shown to be safe when used in patients with epilepsy (PWE) but also have been found to possess antiepileptic properties in animal models of epilepsy. In humans randomized to SSRIs vs. placebo for the treatment of major depressive episodes, the incidence of epileptic seizures was significantly lower among those treated with the antidepressants. These data raise the question of whether there is enough evidence that would support a randomized placebo-controlled trial to test antiepileptic effect of SSRIs in PWE. This article reviews the preclinical and clinical data to address this question.

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1. Introduction

Depression is a relatively frequent psychiatric comorbidity in patients with epilepsy (PWE), with lifetime prevalence rates of 30 to 35% [1]. Yet, despite its high prevalence, it goes often untreated, in part due to a long-held concern that antidepressant drugs may have proconvulsant properties. If that is the case, how can antidepressant drugs of the selective serotonin reuptake inhibitor (SSRI) family be considered as having antiepileptic properties? The fact is that antidepressant drugs do not lower the seizure threshold unless taken at very high doses (e.g., in the case of overdoses) [2] with the exception of four antidepressant drugs (chlorimipramine, maprotiline, amoxapine, and bupropion) that are known to be associated with the occurrence of epileptic seizures at therapeutic doses [2,3]. By the same token, several population-based studies have demonstrated that a history of depression may increase the risk of epileptic seizures by threefold to sevenfold [4–8]. Thus, the occurrence of epileptic seizures in patients with major depressive episodes (MDE) may have been the expression of the natural course of the mood disorder and not related to the treatment with antidepressant medication. In fact, Alper et al. explored the incidence of seizures across randomized control trials (RCTs) of SSRIs in primary depressive disorders [8]. Two particularly interesting findings emerged. First, as calculated by person-years exposed to drug, these investigators demonstrated that subjects randomized to antidepressants were 52% less likely (69% less likely when excluding bupropion immediate-release formulation) to develop seizures compared with those randomized to placebo. Second, patients randomized to placebo across the RCTs were 19 times more likely to experience a seizure compared with the expected incidence in the general population [8]. Do the data from this study suggest that SSRIs have a "protective effect" against spontaneous seizures, and are there sufficient data to support that SSRIs should be tested as antiepileptic agents? The purpose of this article is to review the preclinical and clinical data to answer this question.

2. Preclinical studies

The synaptic increase of serotonin (5HT) is the primary effect of SSRIs. Animal models have provided ample evidence that 5-HT plays a role in neural excitability, epileptogenesis, and seizure propagation. As reviewed elsewhere [9–11], agents that increase extracellular 5-HT, such as 5-hydroxytryptophan and SSRIs, inhibit focal and generalized seizures in several animal models of generalized epilepsy and focal epilepsy. As reviewed by Bagdy et al. [10], at least fourteen 5HT receptor subtypes have been identified, and the 5HT1A, 5HT2C, 5HT3, and 5HT7 subtypes have been shown to play a role in seizure generation.

For example, two animal models of generalized epilepsy in which generalized tonic-clonic seizures are induced with audiogenic stimuli include the genetically epilepsy-prone rat (GEPRs) [12] and the DBA/2J mouse [13]. In the GEPR model, abnormal serotonergic axon arborization has been identified in the brain coupled with

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deficient postsynaptic $5HT_{1A}$ receptor density in the hippocampus. Incremental increases in 5HT levels with the SSRI sertraline resulted in a dose-dependent seizure-frequency reduction, which correlated with the extracellular serotonergic thalamic concentration [14,15]. In addition, the 5-HT precursor 5-HTP has been shown to have anticonvulsant effects in GEPRs when combined with a monoamino-oxidase inhibitor (MAOI) [16].

The pathogenic role of 5HT has been demonstrated in focal epilepsy models such as electrical stimulation of hippocampus in cats, bicuculline injection in deep pre-piriform cortex of rats [17], and the lithium–pilocarpine model of status epilepticus in Wistar rats [18]. For example, Mazaratti et al. used a status epilepticus (SE) model [a common animal model of temporal lobe epilepsy (TLE)] in male Wistar rats to demonstrate the decrease of 5-HT concentration and turnover in the hippocampus as well as 5-HT release from the hippocampus in response to raphe nuclei stimulation. Fluoxetine has also been shown to prevent seizures when pre-administered in the bicuculline model of focal epilepsy in rats [19].

Lopez Meraz et al. studied the impact of two $5HT_{1A}$ receptor agonists, 8-OH-DPAT and indorenate, in three animal models of epileptic seizures (tonic-clonic seizures induced by pentylenetetrazol [PTZ], status epilepticus of limbic seizures induced by kainic acid [KA], and tonic-clonic seizures induced by amygdala kindling) in Wistar rats [20]. They found that 8-OH-DPAT lowered the incidence of seizures and the mortality induced by PTZ, increased the latency and reduced the frequency of wet-dog shakes and generalized seizures induced by KA, and at high doses diminished the occurrence and delayed the establishment of status epilepticus. Indorenate increased the latency to the PTZ-induced seizures and decreased the percentage of rats that showed tonic extension and death, augmented the latency to wet-dog shakes and generalized seizures, and diminished the number of generalized seizures. Likewise, increased audiogenic seizures are seen in 5-HT_{2c} receptor knockout mice [21]. Conversely, depletion of 5-HT through pharmacologic or genetic manipulation has been shown to result in lowering of seizure threshold. For example, 5-HT antagonists reverse the 5-HT mediated anticonvulsant effects of SSRIs such as fluoxetine, as they lower the seizure threshold, and were found to increase seizure severity in the WAG/Rij rat model of absence seizures and in the bicuculline-induced focal seizure model [22].

3. Impact of 5HT on the antiepileptic effect of AEDs

Increased extracellular 5-HT, as measured by microdialysis in GEPR, contributes to the anticonvulsant effects of many AEDs including phenytoin, carbamazepine, valproate, lamotrigine, oxcarbazepine, and zonisamide [23–32]. For example, after establishing an anticonvulsant effect of carbamazepine in the GEPR, Yan et al. showed that the addition of 5HT depleting drugs results in a blockage of this anticonvulsant protection [26]. Likewise, Clinckers et al. investigated the impact of oxcarbazepine (OXC) infusion on the extracellular hippocampal concentration of 5HT and DA in the focal pilocarpine model for limbic seizures [27]. When oxcarbazepine was administered together with verapamil or probenecid (to ensure its passage through the blood-brain barrier), complete seizure remission was obtained associated with an increase in 5HT and DA extracellular concentrations [28]. Furthermore, SSRIs such as fluoxetine enhance anticonvulsant effects of phenytoin, carbamazepine, phenobarbital, and valproate in the maximal electroshock seizure model in mice [33].

Of note, the serotonergic anticonvulsant effect appears to have an "inverted u-shaped" concentration–response effect, as suggested by a study of pilocarpine-induced seizures in rats in which hippocampal perfusion of 5HT up to extracellular concentrations ranging between 80% and 350% of baseline levels protected these rats from seizures, while concentrations > 900% of baseline worsened seizures [34]. It should be noted that the high extracellular 5-HT concentrations were associated with significant increases in extracellular glutamate.

4. Potential mechanisms of action

The antiepileptic effect of $5HT_{1A}$ receptors has been associated with a membrane hyperpolarizing response associated with increased potassium conductance in hippocampal kindled seizures in cats and in intrahippocampal KA-induced seizures in freely moving rats [35,36].

The pharmacologic effect of SSRIs is not limited to 5HT; indeed, they influence other neurotransmitter systems involved in epileptogenesis and seizure propagation. The $5HT_{1A}$ receptor is found on cholinergic neurons in the septum and glutamatergic neurons in the hippocampus and forebrain regions, where 5HT agonists stimulate acetylcholine and inhibit glutamate release, respectively [37]. The $5HT_{1A}$ receptor serves as an auto-inhibitor, and stimulation decreases 5HT release post-synaptically. Stimulation of $5HT_{1A}$ receptors in the thalamic relay neurons results in an increase in GABA release and, consequently, decrease in excitatory activity necessary for spike wave discharges in absence models [38]. The $5HT_{2C}$ subtype receptor not only is mostly expressed in the choroid plexus but also is present in the cortex, including limbic structures and basal ganglia. While stimulation of $5HT_{2C}$ receptors results in inhibition of noradrenergic and dopamine release and stimulation of GABA and glutamate release, $5HT_{2C}$ agonists prevent seizures, and $5HT_{2C}$ antagonists lower seizure threshold respectively in both focal and generalized models of epilepsy [39]. Furthermore, genetic mutations of $5HT_{2C}$ lead to audiogenic seizures [13]. The highest densities of the $5HT3_3$ receptors are found in the brainstem, specifically in the dorsal vagal nuclei, spinal trigeminal nuclei, and area postrema and less so in the hippocampus, amygdala, and cortex [39,40].

The antiepileptic effect of 5HT families of receptors is not uniform, however. For example, although activation of $5HT_3$ receptors results in decreased acetylcholine release and increased GABA and dopamine release, it also results in increased seizure duration in animal models [38]. Blockade of $5HT_3$ results in increased audiogenic seizure latency and decreased severity of seizures in the DBA/2J mouse model [41]; (see also Table 1).

Conversely, glutamate, the primary excitatory neurotransmitter of the brain, may have direct effects on 5-HT mediated antidepressant and anticonvulsant properties [42]. Tract tracing techniques in rodent models have shown that neurons containing transporters of glutamate filled synaptic vesicles differentially project from cortical and subcortical structures into the dorsal raphe nucleus (DRN), where they may modulate 5-HT transmission [43]. For instance, vesicular glutamate transporters VGLUT1 are present in axons from prefrontal cortex, and VGLUT2 is present in axons from hypothalamic regions and the lateral habenula to the DRN, respectively. Stress and negative stimuli activate the lateral habenula [44] while a lesion of the region reverses depressogenic effects by modulating DRN 5HT levels [45]. The VGLUT1-3 and excitatory amino acid transporters (EAAT-1, EEAT-2, EEAT-3, and EEAT-4) are critical in metabolizing extracellular glutamate and, therefore, preventing neurotoxicity. As reviewed by Sanacora et al. [46], chronic psychosocial stress leads to increased presynaptic glutamate release, impaired glutamate clearance, and altered glutamate/glutamine cycling. Several glutamate antagonists have shown potential to serve as potent antidepressants in both preclinical and preliminary human trials [46].

In addition to the direct interactions between 5HT and glutamate circuits, both systems are influenced by pro-inflammatory cytokines that lead to neurotoxicity [47]. Interleukin-2, interferon, and tumor necrosis factor-alpha may induce indoleamine 2,5 deoxygenase (IDO) which metabolizes tryptophan (the precursor to 5HT) into kynurenine (KYN) quinolinic acid (QUIN). Kynurenine independently has depressogenic effects, and QUIN serves as an NMDA agonist, stimulating glutamate release [48]. Furthermore, QUIN causes changes in astrocytes, leading to a further decrease in extracellular glutamate metabolism [49]. Selective serotonin reuptake inhibitors have been shown to suppress inflammatory cytokines by inhibiting interferon