Does Serotonin Play a Role in Epilepsy?

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Studies in experimental models have suggested a potential role for serotonergic transmission in epilepsy, and interest in this research has been increased by the development of positron emission tomography (PET) ligands that can be used to study 5-hydroxytryptamine (5-HT) receptors and transporters. The serotonergic system is very complex. At least 13 distinct G protein–coupled 5-HT receptors and one ligand-gated ion channel receptor (5-HT$_3$) are divided into seven distinct classes (5-HT$_1$ to 5-HT$_7$) (1). The receptors vary widely in their distribution and effects, innervating vascular structures and gut smooth muscle as well as neuronal tissue. Several receptor subtypes may be relevant to epilepsy.

Effects of 5-HT$_{1A}$–Receptor Activation

Central 5-HT$_{1A}$ receptors function both as somatodendritic presynaptic autoreceptors in the raphe nuclei and as postsynaptic receptors in terminal field areas, such as the hippocampus, and may have different functional and regulatory characteristics, depending on the structures innervated (2,3). In the raphe nuclei, activation of 5-HT$_{1A}$ autoreceptors produces inhibition of serotonergic neurons and decreases 5-HT release and neurotransmission. In contrast, postsynaptic 5-HT$_{1A}$–receptor activation in the hippocampus increases 5-HT neurotransmission (4). The 5-HT$_{1A}$ somatodendritic autoreceptors and postsynaptic receptors may differ in their adaptive response to prolonged stimulation during long-term treatment with selective serotonin reuptake inhibitors (SSRIs), such as fluoxetine, which has antiseizure effects in several models (5). The fluoxetine effect is not dependent on γ-aminobutyric acid (GABA) receptors, may be mediated by multiple receptor subtypes, and shows regional variation (6). For example, rats treated over the long term with fluoxetine showed desensitization of 5-HT$_{1A}$ somatodendritic autoreceptors in the dorsal raphe nucleus but not of postsynaptic 5-HT$_{1A}$ receptors in the hippocampus (7).

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5-HT$_{1A}$ receptor activation elicits a membrane hyperpolarizing response related to increased potassium conductance (8,9) and has an anticonvulsant effect in various experimental in vivo as well as in vitro seizure models, including hippocampal kindled seizures in cats; intrahippocampal kainic acid–induced seizures in freely moving rats; and picrotoxin-, bicuculline-, and kainic acid–induced seizures in rat hippocampal slice preparations (10–15). The anticonvulsant effects of 5-HT$_{1A}$–receptor activation differ from region to region and from model to model. For instance, 5-HT inhibits low Mg^{2+}–induced epileptiform activity, by reduction of *N*-methyl-D-aspartate (NMDA) receptor–mediated excitatory postsynaptic potentials, in the subiculum and entorhinal cortex but not in areas CA3 and CA1 of the hippocampus (16,17).

One model, the genetically epilepsy-prone rat (GEPR), illustrates 5-HT effects on seizure susceptibility. GEPRs have decreased 5-HT$_{1A}$–receptor density in the hippocampus compared with that in nonepileptic control rats (18). In addition, the SSRI sertraline produces a dose-dependent reduction in the intensity of audiogenic seizures in GEPRs, correlating with increased extracellular thalamic 5-HT concentrations (19). However, the model is complex, and other neurotransmitters may play a role, as 5-HT–receptor activation increases release of catecholamines (20). For example, 5-HT$_{1B}$–receptor activation can inhibit rat ventral tegmental GABA release, and 5-HT$_{1B/1D}$ activation increases nucleus accumbens dopamine release (21,22). Similarly, one study reported that the anticonvulsant effects of fluoxetine in GEPRs are mediated through an increase in extracellular 5-HT, but are enhanced by a 5-HT$_{1A}$ antagonist rather than an agonist (23). In contrast to the GEPR model, intracerebroventricular injection of the 5-HT$_{1A}$ agonist, 8-hydroxy-2-(di-*n*-propylamine)tetralin (8-OH-DPAT), in the WAG/RIJ rat absence model, caused an increase in spike–wave discharges, whereas the NMDA-receptor antagonist, MK-801, resulted in a decreased spike–wave discharges and blocking of the 8-OH-DPAT effect (24).

Other receptor subtypes have received less attention. One study suggested an excitatory role for 5-HT$_3$ receptors in a rat-kindling model (25). In a male Wistar rat model, blockade of a number of receptors (5-HT$_3$ as well as 5-HT$_{2A/C}$ and 5-HT$_{1A}$) did not alter the reduction in seizure severity and increase in threshold produced by fluoxetine (26).

Several knockout mouse models suggest a relation between 5-HT, hippocampal dysfunction, and epilepsy. 5-HT$_{1A}$ knockout mice display lower seizure thresholds and higher lethality in response to kainic acid administration. Furthermore, 5-HT$_{1A}$

knockout mice demonstrate impaired hippocampal-dependent learning and enhanced anxiety-related behaviors—interactions between serotonergic and other neurotransmitters may contribute to the behavioral phenotype (27,28). However, the mice also exhibit increases in dopamine content and turnover as well as increases in norepinephrine concentration in locus ceruleus projection regions, complicating interpretation of the phenotype (29).

5-HT_{2C}–receptor knockout mice show a combination of obesity- and sound-induced seizures; other receptor types are not altered in this model, suggesting that the clinical effects are receptor subtype specific (30–32). In contrast, activation of 5-HT_{2C} receptors potentiates cocaine-induced seizures (33). Interestingly, treatment-induced [^{3}H]5-HT releases were all significantly less pronounced in rat pups with prenatal exposure to cocaine (34).

Serotonin may play a role in the mechanism of action of some antiepileptic drugs (AEDs). Studies in GEPRs suggest that carbamazepine (CBZ) and valproate (VPA) release 5-HT as part of their mechanism of action, whereas lamotrigine (LTG) inhibits 5-HT uptake (35–37). CBZ administration causes large increases in extracellular serotonin concentration and dose-related anticonvulsant effects in GEPRs. Further research must be performed to determine whether these mechanisms make a significant contribution to AED efficacy in humans.

Human PET Imaging Studies

Several PET ligands have been developed for imaging serotonergic neurotransmission (38,39). WAY100635, a potent, highly selective, silent 5-HT_{1A} antagonist, labeled with either [^{11}C] or [^{18}F], has been used to image 5-HT_{1A} receptors in human brain (38). The evidence suggests that WAY-100635 PET activity in the hippocampus and cerebral cortex reflects mainly postsynaptic 5-HT_{1A} receptor binding, not sensitive to endogenous 5-HT, and assuming binding kinetics are not altered, is a reliable indicator of receptor number (40). A study using [^{18}F]*trans*-4-fluoro-*N*-2-[4-(2-methoxyphenyl)piperazin-1-yl]ethyl-*N*-(2-pyridyl) cyclohexanecarboxamide ([^{18}F]FCWAY) and PET, found decreased 5-HT_{1A} volume of distribution ipsilateral to the epileptic focus in mesial temporal regions, including hippocampus, entorhinal cortex, and parahippocampal gyrus, of patients with temporal lobe epilepsy (41). After partial volume correction, the 5-HT_{1A} volume reductions were significant compared both with contralateral regions in patients and with corresponding regions in normal volunteers. Reduced [^{18}F]FCWAY activity was found in patients both with and without hippocampal atrophy on magnetic resonance imaging (MRI). [^{18}F]FCWAY binding potential showed trends toward reduction in brainstem raphe and ipsilateral thalamus as well.

[^{11}C]α-methyl-L-tryptophan (AMT) is a tracer developed to measure serotonin synthesis. Several studies have shown an association between AMT uptake and spiking in tubers in patients with tuberous sclerosis; interictal spike frequency was significantly correlated with AMT uptake (42–44). Patients with neocortical epilepsy showed increased AMT uptake in the region of the epileptic focus, as defined by scalp ictal EEG, even when MRI was normal (45). The sensitivity of AMT PET for seizure onset was lower, but the specificity was higher than that of [^{18}F]fluorodeoxyglucose (FDG)-PET in children with neocortical epileptic foci (46). Regions of increased AMT uptake were smaller than corresponding FDG-PET hypometabolic areas. Cortical developmental malformations, in particular, were associated with increased AMT uptake. These PET data are supported by an autoradiographic study of tissue resected from two patients with focal cortical dysplasia, showing serotonergic hyperinnervation (47).

The mechanism for increased AMT uptake has not been determined, although several theories have been proposed. Some researchers have suggested that increased AMT uptake in seizure foci may reflect its diversion from 5-HT synthesis to production of excitatory quinolinic or kynurenic acid, via the kynurenine pathway in epileptic foci (42). However, in a human brain tissue study, no differences were found in the concentrations of quinolinic acid between focus and nonfocus regions, and cerebral spinal fluid concentrations of quinolinic acid were significantly lower in patients than in controls (48). Alternately, increased hippocampal AMT uptake could indicate greater serotonergic innervation (49). Augmented neurogenesis in patients exhibiting increased AMT uptake may account for the report of increased hippocampal AMT PET uptake in temporal lobe epilepsy patients with normal hippocampal volumes but not with hippocampal atrophy (50). Studies demonstrating that increasing synaptic serotonin levels result in decreased receptor binding to both 5-HT_2 and 5-HT_{1A} support the potential mechanism of agonist-mediated downregulation of 5-HT_{1A} receptors as an explanation for reduced hippocampal activity on FCWAY PET (51,52). However, seizures themselves, as well as neuronal loss, may affect 5-HT receptors. The 5-HT_{1A} ligand [^{18}F]-MPPF [4-(2′-methoxyphenyl)-1-[2′-[N-(2″-pyridinyl)-*p*-fluorobenzamido]ethyl]piperazine] in rats with kainic acid–induced seizures showed initial decreased binding from day 1 to day 6 after injection, although it was followed by a relative increase between days 6 and 30, whether or not hippocampal neuronal loss was present (52). Reduced 5-HT_{1A} binding, without significant neuronal loss, could be due to depressed expression of 5-HT_{1A} receptors related to kainic acid–induced seizures in animal models (53). So far, however, data are too limited to confirm a relation of seizure frequency to reduced 5-HT_{1A} binding in temporal lobe foci on human FCWAY PET.

Clinical Implications

The preliminary imaging studies suggest that FCWAY and AMT PET may be of potential clinical value. However, only limited data have been collected. Methodologic factors to be considered in evaluating the results of the imaging studies include test sensitivity and the possibility that differences in 5-HT ligand binding of less than 15% to 20% between patients and controls might be missed (54). Furthermore, variations may exist between men and women in 5-HT precursor uptake or synthesis that could affect outcome but have not been identified because of the small patient groups studied (55–57). Age-related declines in 5-HT_{1A}, 5-HT_{2A}, and transporter activity also have been reported—although some 5-HT_{1A} studies did not show this effect (58–61).

Altered serotonergic neurotransmission may be a feature common to patients with depression and epilepsy. Fewer 5-HT–imaging studies have been performed in patients with seizures than in subjects with depression, and the studies have not included ligands for other receptor groups, such as 5-HT_2 or 5-HT transporters. The role of serotonin in the pathophysiology of depression is well established, and selective serotonin reuptake blockers are an important therapeutic modality (62). In patients with depression, PET studies have shown consistent reductions in 5-HT_{1A} receptor binding—although widespread, the greatest reduction may be in raphe and mesial temporal cortex (63). In contrast, 5-HT_2 and transporter PET studies have shown mixed results, with reports of decreased, increased, and unchanged binding (64). It will be interesting to see whether patients with depression, in addition to epilepsy, have regional alterations in 5-HT_{1A} and other receptor-subtype binding potential not found in patients with epilepsy alone, suggesting a physiological link between the two conditions.

Although confirmation of altered 5-HT binding potentially could lead to pharmacologic intervention, numerous methodologic obstacles would have to be overcome. Low-dose fluoxetine may have antiseizure potential, although clinical effects, reported in open, uncontrolled trials, have been weak and inconsistent (65,66). Increased seizures, or seizures in patients who never had them before, reported occasionally in patients taking SSRIs, appear be related to drug doses or levels that exceed the usual therapeutic range (67). SSRIs are less likely to cause seizures than are other antidepressants (68).

SSRIs affect serotonergic transmission over a wide range of both pre- and postsynaptic receptor subtypes that have a spectrum of binding potentials and dissociation constants, explaining variable (pro- or antiepileptic, for example) dose-related effects. In addition, increased 5-HT release or receptor activation is likely to affect other neurotransmitters, producing additional indirect effects from SSRI administration.

To test the therapeutic potential of 5-HT–mediated agents, it would be necessary to use a 5-HT_{1A} agonist that could potentially overcome the problem of nonspecific SSRI action. However, a specific agonist might still exert opposite effects on serotonergic transmission by binding to presynaptic autoreceptors, as well as to postsynaptic receptors. The overall therapeutic effect would depend on a subtle balance between opposing actions on neuronal excitability.

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