Epilepsy and Depression: Imaging Potential Common Factors

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ABSTRACT

Patients with seizure disorders have an increased incidence of depression. This may be due in part to psychosocial factors, or side effects of antiepileptic drugs. However, there may be underlying physiologic mechanisms for the relationship. Neuroimaging studies, including structural magnetic resonance imaging, positron emission tomography measurements of cerebral glucose metabolism, and, more recently, imaging of serotonin 1A receptors, may provide additional data to explain overlapping clinical manifestations of epilepsy and depression.

INTRODUCTION

Several potential explanations have been proposed for the increased incidence of depression observed in patients with seizure disorders. Psychosocial factors, such as reduced social, educational and professional opportunities, the stress of never knowing when a seizure may occur, and the persistent stigma against people with epilepsy, which remains strong even in "developed" countries such as the USA, may play an important role.[1-3] Some antiepileptic drugs (AEDs), particularly barbiturates, themselves can be associated with depression, although others appear to have antidepressant effects.[4] However, depression is thought to be more common in patients with complex partial seizures (CPS) and temporal lobe foci, and particularly mesial-temporal sclerosis (MTS), suggesting that underlying biological factors may be important as well.[5-7] Some studies have found sex and laterality effects, as well as evidence for increased frontal dysfunction in depressed CPS patients, but the evidence is less compelling.[4-5] Moreover, there are differences between results of studies in epilepsy clinics and community surveys, which find a lower incidence of depression, particularly in well-controlled or seizure-free patients.[8] However, evidence that depression can precede the onset of epilepsy reinforces the idea of a biological association.[9]

Indirect evidence of a link between depression and epilepsy comes from therapeutic studies showing antidepressant effects of AEDs, as well as newer treatments such as vagal nerve stimulation and transcranial magnetic stimulation.[1-2,10-14] However, the lack of a clear understanding of the mechanisms of action of these approaches precludes drawing any pathophysiologic conclusions from their observed effects. Moreover, in some cases, large enough adequate-blinded, randomized, controlled trials have not been published.[14-15]

IMAGING EPILEPSY AND DEPRESSION

Neuroimaging has provided another approach to studying the common physiology of epilepsy and depression. Structural imaging has shown that patients with mesial-temporal sclerosis (MTS) have significantly higher depression scores than patients with neocortical temporal foci.[7] Reduced N-acetyl aspartate (NAA) on temporal lobe magnetic resonance spectroscopy (MRS) correlated significantly with depression in patients with temporal lobe epilepsy (TLE).[16] Moreover, an association between MTS and depression has been found in patients with psychogenic nonepileptic seizures as well, suggesting that the pathology itself, or its location, rather than the presence of a seizure disorder, may be a significant factor.[17] In contrast, studies of the amygdala in patients with epilepsy found that those with recurrent interictal aggression were not more likely to have amygdalar sclerosis, and less likely to have hippocampal sclerosis, than patients with epilepsy but no interictal aggression.[18] Moreover, the same investigators reported that patients with "dysthymia" had significantly larger bilateral amygdala volumes than those without "dysthymia" or normal controls.[19]

Some of the differences in outcome between these studies may have been due to differences in case definitions, or the severity of the depressive symptoms, as well as seizure-related factors, such as disease duration, seizure

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frequency, and etiology. Neuropathological studies, as well as those based on the use of earlier imaging techniques, such as pneumoencephalography and computed tomography, tended to show similar dichotomous findings.[20]

GLUCOSE METABOLISM, DEPRESSION AND EPILEPSY

Patients with bipolar depression have been reported to have decreased cerebral metabolic rate for glucose (CMRglc), which, at least in some studies, increased when state changed from depressed to manic.[21] The decreased metabolism has been most prominent in frontotemporal regions, as well as insula and basal ganglia.[22-24] Although hippocampal atrophy has been reported in patients with depression, other investigators have shown that CMRglc reduction is not due to cerebral volume loss.[25,26] Some symptoms may be associated with relative regional increases as well as decreases in CMRglc.[27] Baseline cerebral blood flow (CBF) and CMRglc may be increased in some regions in patients with depression.[28-30] Regional differences in CMRglc may reflect functional heterogeneity.[31] The abnormalities of regional (CBF) and glucose metabolism are in multiple prefrontal cortical and limbic structures that have been implicated in emotional processing. Decreased hippocampal metabolism may predict depression severity.[31] Interestingly, a correlation between treatment response and CMRglc has been described for several therapeutic modalities; the interaction is region and trait specific.[32-36] Some regions may show increases and others decreases in CMRglc, correlating with therapeutic effects. For example, successful paroxetine therapy increased glucose metabolism in dorsolateral, ventrolateral, and medial prefrontal cortex, parietal cortex, and dorsal anterior cingulate, while left anterior and posterior insular regions as well as right hippocampal and parahippocampal regions decreased.[37]

In patients with epilepsy, several positron emission tomography (PET) studies have shown that depression is associated with hypometabolism. Bromfield et al[38] used the Beck depression inventory and 18-F-deoxyglucose PET to study patients with CPS. Bilateral inferior frontal metabolism was significantly lower in depressed patients, and distinguished those with high scores on the Beck scale from age and sex-matched controls. Victoroff et al[39] reported that the combination of left temporal lobe hypometabolism and high-degree hypometabolism was strongly associated with a history of major depressive events.

A study using single photon emission computed tomography (SPECT) showed that for patients with left-sided epilepsy, higher scores on the Beck depression inventory were associated with lower contralateral temporal and bilateral frontal perfusion, and higher occipital perfusion.[40] Another SPECT study showed no regions of relatively decreased activity in depressed compared with non-depressed epilepsy patients. Depressed patients showed relative hyperactivity in the left hemisphere, particularly dorsolateral prefrontal cortex, striatum, thalamus and temporo-parietal regions. Comparison of these data with normal population data revealed that in the depressed epilepsy group regional activities were within the normal range, while corresponding results from the non-depressed group were below normal range.[41] Children with epilepsy and aggressive behavior showed bilateral prefrontal and temporal neocortical hypometabolism, suggesting a widespread dysfunction of cortical regions, which normally exert an inhibitory effect on subcortical aggressive impulses.[42]

Several tentative conclusions can be drawn from these studies. The frontal cortex, and perhaps the left temporal cortex, appears to play a role in modulating mood in patients with depression, as well as the combination of epilepsy and depression. Barbiturates, the drugs that cause the greatest (global) depression of CMRglc, are also the ones most likely to be associated with depression in patients with seizures. However, they show a wide range of results, differing in the severity of the depression in the patients scanned, as well as in epilepsy syndrome and other factors that have potential effects on PET results. Moreover, CBF and CMRglc are relatively nonspecific measures, influenced by a wide range of factors, such as the effect of antiepileptic drugs. In addition to leading to mood alterations, and thus affecting blood flow and metabolism indirectly, these can have direct effects, reducing CMRglc or CBF.[43] Drug treatment does not appear to have been controlled adequately in the studies that have been performed.

PET can be used, however, to image the distribution of neurotransmitters that may play more specific functional roles in neurologic and psychiatric syndromes. One family of neurotransmitters of particular interest, with clear pathophysiologic relevance for depression, and possible implications for epilepsy, is serotonin (5-hydoxytryptamine, 5-HT).

SEROTONIN IMAGING IN EPILEPSY AND DEPRESSION

Several PET ligands have been developed for imaging serotonin receptors. WAY100635, a potent, highly selective, silent 5-HT_{1A} antagonist, labeled with either [11C] or [18F], has been used to image 5-HT_{1A} receptors in human brain.[44-49] Ligands for 5-HT_2 receptors and serotonin transporters have been developed as well.[50-51]

There are at least 13 distinct G-protein-coupled 5-HT receptors and one ligand-gated ion channel receptor (5-HT_3), divided into 7 distinct classes (5-HT_1 to 5-HT_7).[52] The 5-HT_{1A} receptors that have been studied both in patients with depression and seizures are distributed throughout the CNS. Their cell bodies are in the raphe nuclei, where autoreceptors inhibit cell firing; postsynaptic 5-HT_{1A} receptors are present in a number of limbic structures, particularly the hippocampus, as well as temporal neocortex.[44,52-55]

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.[54,55] In the raphe nuclei, activation of the 5-HT_{1A} autoreceptors produces inhibition of serotonergic neurons and decreased 5-HT release and neurotransmission, whereas activation of the postsynaptic 5-HT_{1A} receptors, for example in the hippocampus, increases 5-HT neurotransmission.[56] The 5-HT_{1A} somatodendritic autoreceptors and postsynaptic receptors may also differ in their adaptive response to chronic stimulation by 5-HT due to long-term treatment with selective 5-HT reuptake inhibitors such as fluoxetine. Rats chronically treated with fluoxetine showed desensitization of 5-HT_{1A} somatodenritic autoreceptors in the dorsal raphe nucleus but not the postsynaptic 5-HT_{1A} receptors in the hippocampus.[57] The evidence suggests that WAY-100635 PET activity in the hippocampus and cerebral cortex mainly reflects postsynaptic 5-HT_{1A} receptor binding, not sensitive to endogenous 5-HT.[58]

DEPRESSION

The role of serotonin in the pathophysiology of depression is well-established, and selective serotonin reuptake blockers are an important therapeutic modality.[59] PET studies have shown consistent reductions in 5-HT_{1A} receptor binding in patients with depression. Although widespread, the greatest reduction may be in raphe and mesial temporal cortex.[60] Reduced 5-HT_{1A} receptor binding was not changed by selective serotonin reuptake inhibitor treatment.[61] In contrast, 5-HT_2 PET studies have shown mixed results, with reports of decreased, increase, and unchanged binding.[62-66] Some studies found an increase and others a decrease after drug treatment; various agents were used.[67-69] Among patients who had recently attempted suicide, reduction was greater among deliberate self-injury than deliberate self-poisoning patients.[70] Studies of serotonin transporters found increased activity in thalamus, hypothalamic/midbrain area.[71-72] Other investigators reported reduced activity.[73-74]

EPILEPSY

Animal Models

5-HT has anticonvulsant effects mediated by the 5-HT_{1A} receptor, which elicits a membrane hyperpolarizing response due to increased potassium conductance.[75-76] The 5-HT_{1A} receptor activation exerts an anticonvulsant effect in various experimental seizure models, including hippocampal kindled seizures in cats, in vitro picrotoxin-induced, bicuculline-induced and kainic acid-induced seizures in rat hippocampal slice preparations, and intrahippocampal kainic acid induced seizures in freely-moving rats.[77-82]

Genetically epilepsy-prone rats (GEPR-9) have decreased 5-HT_{1A} receptor density in the hippocampus compared to nonepileptic control rats.[83] In addition, 5-HT concentration, activity of the synthetic enzyme tryptophan hydozylase, and possibly second messenger responsiveness, are reduced as well.[84] Sertraline produced a dose-dependent reduction in the intensity of the audiogenic seizures correlating with extracellular thalamic 5-HT concentration; other receptor subtypes in addition to 5-HT_{1A} may play a role.[85]

Moreover, the model is complex, and other neurotransmitters, including norepinephrine, are effective in a manner similar to 5-HT: enhancement of noradrenergic transmission in the superior colliculus has an anticonvulsant effect.[86] The 5-HT_{1A} knockout (KO) mice display lower seizure threshold and higher lethality in response to kainic acid administration as well as impaired hippocampal-dependent learning.[87] They also show enhanced anxiety-related behaviors.[88]

The 5-HT_{2C} receptor knockout shows a combination of obesity and sound induced seizures; other receptor types are not altered in this model.[89-91] In contrast, activation of 5-HT_{2C} receptors potentiates cocaine-induced seizures.[92] Interestingly, treatment-induced [3H] 5-HT releases were all significantly less pronounced in the pups prenatally exposed to cocaine.[93] However, it is important to remember that the enhanced response to epileptogenic agents in knockouts may be multifactorial.

Interactions between serotonergic and other neurotransmitter systems further complicate the picutre. In an absence model, intracerebroventricular injection of the 5-HT_{1A} agonist 8-OH-DPAT caused an increase in spike-wave discharges, and the NMDA antagonist MK-801 a decrease, also blocking the 8-OH-DPAT effect.[94] The 5-HT_{1B} receptor activation can inhibit rat ventral tegmental GABA release, and 5-$HT_{1B/1D}$ activation increases nucleus accumbens dopamine release.[95-96] Serotonin may play a role in the mechanism of action of some antiepileptic drugs. Carbamazepine and valproate may release 5-HT as part of their mechanism of action, while lamotrigine may inhibit 5-HT uptake.[97-99] However, these drugs have multiple mechanisms of action, including regulation of active ion channels, and there is little data to suggest which is the most important for epilepsy therapy.

Human PET studies

Using [18F]FCWAY PET, decreased 5-HT_{1A} volume of distribution was found ipsilateral to the epileptic focus in hippocampus and other mesial temporal regions of patients with temporal lobe epilepsy. There was reduction in the midbrain raphe and ipsilateral thalamus as well, suggesting a global as well as local process.[100] The reduced blinding in the epileptic focus persisted after MRI-based partial volume correction, and reduced binding was found in patients with and without hippocampal atrophy on MRI. Thus, the finding is not due solely to reduced neuronal number. However, it is possible that 5-HT_{1A} receptor loss could be early, nonspecific evidence of neuronal dysfunction. This would make [18F]FCWAY PET a very valuable tool for studying patients with epilepsy, even though 5-HT_{1A} receptors did not play a central pathophysiologic role.

The [11C] alpha-methyl-L-tryptophan (AMT) is a tracer developed to measure serotonin synthesis. Several studies

have shown a correlation between AMT uptake and spiking in tubers in patients with tuberous sclerosis (TS).[101-102] There was a significant correlation between AMT uptake and the frequency of interictal spikes.[103]

In patients with neocortical epilepsy, there was increased AMT uptake in the region of the epileptic focus as defined by scalp ictal EEG, even when MRI was normal.[104] The sensitivity of AMT PET for seizure onset was lower, but its specificity higher than FDG PET.[105] AMT PET abnormalities were smaller than corresponding FDG PET hypometabolic regions. Cortical developmental malformations were associated with increased AMT uptake. In patients with temporal lobe epilepsy, AMT-PET showed increased hippocampal uptake in patients with normal volume but not atrophy.[106]

Chugani and Chugani[107] have suggested that increased hippocampal AMT uptake may represent increased serotonergic innervation. Increased neurogenesis in patients with increased AMT uptake may account for the normal hippocampal volume in these subjects. This could also lead to agonist-mediated down-regulation of 5-HT_{1A} receptors. Increasing synaptic serontonin levels decreased receptor binding to both 5-HT_2 and 5-HT_{1A}, supporting this potential mechanism.[108-109] However, a study using the 5-HT_{1A} ligand MPPF in rats with kainic acid induced seizures and hippocampal damage showed initial decreased binding from day 1 to day 6 post injection followed by a relative increase between day 6 and day 30, in rats with and without hippocampal neuronal loss.[110] The existence of rats showing MPPF decrease without significant neuronal loss suggested that decreased MPPF binding could follow depressed expression of 5-HT_{1A} receptors as part of a stress reaction induced by kynurenic acid (KA) induced status epilepticus.[110]

It has been suggested that AMT uptake may reflect its diversion from 5-HT synthesis to production of excitatory quinolinic or kynurenic acid via the kynurenine pathway in epileptic foci.[101] In a human brain tissue study, no differences were found in the concentrations of quinolinic acid between focus and nonfocus regions, and CSF concentrations were significantly lower in patients than controls.[111] Thus, this hypothesis is unproven.

CONCLUSION: PROSPECTS AND PROBLEMS

Additional methodologic factors that need to be considered in evaluating the results of these imaging studies include test sensitivity, and the possibility that differences of less than 15-20% between patients and controls might be missed.[112] There may be variations between men and women in 5-HT precursor uptake or synthesis that could affect outcome between the generally small patient groups that are studied.[113-115] Age-related declines in 5-HT_{1A}, 5-HT_{2A}, and transporter activity have been reported; some 5-HT_{1A} studies did not show this effect.[116-119]

Altered serotonergic neurotransmission may be a common feature in patients with depression and epilepsy. Reduced 5-HT_{1A} receptor binding seems better established for depressive disorders, and possibly for temporal lobe epilepsy, while increased 5-HT precursor uptake has been found in several epileptic syndromes. Other receptor subtypes, and serotonin transporters, have not been studied in patients with seizures. Moreover, additional data needs to be collected on the relation of altered 5-HT uptake and receptor binding to neuronal loss in epileptic foci, as well as interaction with other neurotransmitter systems. One very interesting potential research direction, the role of serotonergic neurotransmission in the depression often associated with epilepsy, has not yet been explored, but patients with epilepsy and depression do respond well to selective serotonin reuptake inhibitors.

Given the complexity of the serotonergic system, it might be very difficult to design therapeutic approaches to epilepsy based on the imaging data. Even administration of a specific 5-HT_{1A} receptor ligand might have erratic and unpredictable effects, given the existence of pre-, post-, and somatodentritic receptors in several anatomic locations of potential importance for seizure onset and regulation.

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