Mood disorder and epilepsy: a neurobiologic perspective of their relationship

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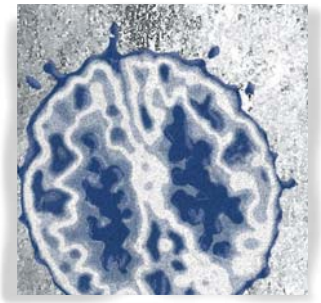

Mood disorders are the most frequent psychiatric comorbidity in patients with epilepsy.[1] For example, in a population-based study carried out in Canada, Tellez-Zenteno et al found a 17.4% lifetime prevalence of major depressive disorders in these patients (95%CI: 10.0-24.9) compared with 10.7% (95%CI: 10.2-11.2) in the general population.[2] Furthermore, patients with epilepsy had a 24.4% (95%CI: 16.0-32.8) lifetime prevalence for any type of mood disorder vs 13.2% (95%CI: 12.7-13.7) among the general population. In addition, the lifetime prevalence of suicidal ideation was twice as high in patients with epilepsy (25%; 95%CI: 17.4-32.5) compared with that of the general population (13.3%; 95%CI 12.8-13.8). Among the different types of epilepsy, temporal lobe epilepsy (TLE) and frontal lobe epilepsy (FLE) have been associated most frequently with the occurrence of mood disorders.[1] The high association between

Mood disorders are the most frequent psychiatric comorbidity in epilepsy, and in particular in temporal lobe epilepsy. For a long time, depressive disorders were considered to be the expression of a reactive process to the obstacles of a life with epilepsy. Data obtained in the last two decades, however, have demonstrated biochemical, neuropathological, and neurophysiologic changes mediating the development of mood disorders, which in fact can be tested in animal models. Furthermore, there is also evidence that mood disorders and epilepsy have a complex relationship which is bidirectional; that is, not only are patients with epilepsy at greater risk of developing depression, but patients with depression have a higher risk of developing epilepsy. Such a relationship can only be explained by the existence of common pathogenic mechanisms that are operant in both conditions. These include changes in neurotransmitters, such as serotonin, norepinephrine, glutamate, and γ-aminobutyric acid. Such a bidirectional relationship also appears to have important clinical consequences. Indeed, patients with a history of mood disorders are twice as likely to develop pharmacoresistant epilepsy as those without such a history. These data are reviewed in this article.

Dialogues Clin Neurosci. 2008;10:39-45.

Keywords: *serotonin; norepinephrine; hippocampal atrophy; major depressive disorder; genetically epilepsy-prone rat*

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Selected abbreviations and acronyms

5-HT	*serotonin*
DA	*dopamine*
GABA	*γ-aminobutyric acid*
GEPR	*genetic epilepsy-prone rat*
NE	*norepinephrine*
TLE	*temporal lobe epilepsy*

TLE and FLE on the one hand and mood disorders on the other is not surprising, given the evidence that these conditions may share common pathogenic mechanisms. The purpose of this article is to review such evidence.

Animal models

How does epileptic activity facilitate the development of symptoms of depression?

In a recent study, Mazarati et al investigated whether chronic increase in seizure susceptibility induced by kindling results in the development of behavior suggestive of "symptoms of depression" in rats.[3] To that end, 3-week-old Wistar rats underwent a rapid kindling with 84 subconvulsant electrical stimulations to the ventral hippocampus every 5 minutes. Two to 4 weeks later, the investigators subjected the rats to two tests, the forced swim test (FST) and the test of taste preference for calorie-free saccharin or sucrose solutions. These tests are widely used in the investigation of the equivalent symptoms of depression in animal models. In the FST, the rat is placed in a situation of despair, which allows for the assessment of its ability to adopt active strategies in an inescapable stressful situation. Failure to do so, as evidenced by increased immobility time during the FST, is interpreted as being equivalent to a depression-like state. The second test tries to replicate the loss of the animal's ability to experience pleasure. In rats, such symptoms can be assessed by the loss of taste preference; although normal animals prefer sweetened to regular water, animals with suspected depression do not exhibit such a preference.

Mazarati et al found that kindled animals exhibited a sustained increase in immobility time in the FST and the loss of taste preference toward calorie-free saccharin, as compared with controls. They concluded that that "the neuronal plastic changes associated with the kindling state are accompanied by the development of depressive behavior."

Neurotransmitter changes in animal models of epilepsy: what do they have in common with mood disorders?

The pathogenic role played by neurotransmitters such as serotonin (5-HT), norepinephrine (NE), and dopamine (DA) in the pathophysiology of mood disorders has been recognized for four decades.[4] More recently, however, γ-aminobutyric acid (GABA) and glutamate have been identified as having a significant pathogenic role as well. The pivotal pathogenic role of GABA and glutamate in epilepsy has been demonstrated in multiple experimental studies with animals and humans. The role of 5-HT and NE is less recognized, but well substantiated in animal and human studies. This section will focus on the common pathogenic mechanisms mediated by NE and 5-HT in mood disorders and epilepsy.

The genetic epilepsy-prone rat (GEPR) with its two strains (GEPR-3 and GEPR-9) provides an animal model of both epilepsy and depression.[5] Both strains are characterized by genetically determined predisposition to sound-induced generalized tonic/clonic seizures (GTCS) as well as marked kindling acceleration, with the most rapid rate exhibited by GEPR-9.[5,6] In addition, GEPRs display similar endocrine abnormalities to those identified in patients with major depressive disorder, such as increased corticosterone serum levels, deficient secretion of growth hormone, and hypothyroidism.[5]

Both strains of rats have innate noradrenergic and serotonergic pre and postsynaptic transmission deficits. Of note, GEPR-9 rats have a more pronounced NE transmission deficit and, in turn, exhibit more severe seizures than GEPR-3 rats.[5] Deficient arborization of neurons arising from the locus coeruleus, coupled with excessive presynaptic suppression of stimulated NE release in the terminal fields and lack of postsynaptic compensatory upregulation, mediate the noradrenergic deficiencies.[5-8] There is also evidence of deficits in serotonergic arborization in the GEPR's brain coupled with deficient postsynaptic serotonin$_{1A}$ (5-HT$_{1A}$)receptor density in the hippocampus.[5,9-11] Increments of either NE and/or 5-HT transmission can prevent seizure occurrence, while reduction will have the opposite effect.[5] Thus, the selective serotonin reuptake inhibitor (SSRI) sertraline resulted in a dose-dependent seizure-frequency reduction in the GEPR which correlates with the extracellular thalamic serotonergic thalamic concentration.[10,11]In addition, the 5-HT precursor 5-HTP has been shown to have anticon-

vulsant effects in GEPRs when combined with a monoamine-oxidase inhibitor (MAOI), while SSRIs and MAOIs have been found to exert anticonvulsant effects in genetically prone epilepsy mice and baboons, as well as in non-genetically-prone cats, rabbits, and rhesus monkeys.[12-15]

The antiepileptic effect mediated at the 5-HT_{1A} receptors has been related to a membrane hyperpolarizing response associated with increased potassium conductance in hippocampal kindled seizures in cats, and in intrahippocampal kainic acid-induced seizures in freely moving rats.[16] In fact, antiepileptic drugs (AEDs) with established psychotropic effects such as carbamazepine, valproic acid, and lamotrigine have been found to cause an increase in 5-HT.[17] Furthermore, the anticonvulsant protection of carbamazepine can be blocked with 5-HT-depleting drugs in GEPRs.[18]

An anticonvulsant effect of serotonergic activity has been reported in other animal models of epilepsy. Lopez Meraz et al studied the impact of two 5-HT_{1A} receptor agonists, 8-OH-DPAT and indorenate, in three animal models of epileptic seizures (clonic-tonic 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.[19] 8-OH-DPAT lowered the incidence of seizures and the mortality induced by PTZ, increased the latency and reduced the frequency of wet-dog shake 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 shake and generalized seizures, and diminished the number of generalized seizures.

Clinckers et al investigated the impact of oxcarbazepine (OXC) infusion on the extracellular hippocampal concentration of 5-HT and DA in the focal pilocarpine model for limbic seizures.[20] When OXC was administered together with verapamil or probenecid (so as to ensure its passage through the blood-brain barrier), complete seizure remission was obtained, associated with an increase in 5-HT and DA extracellular concentrations.[21]

In addition, it has been suggested that the anticonvulsant effect of vagus nerve stimulation (VNS) in the rat could be mediated by activation of the locus coeruleus.[22] Deletion of noradrenergic and serotonergic neurons in the rat prevents or reduces significantly the anticonvulsant effect of VNS against electroshock or pentylenetetrazol-induced seizures.[23] Of note, deletion of NE neurons resulted in a significant immobility time in the FST.

Human studies

An abnormal serotonergic transmission has been found in the brain of depressed patients through the measurement of 5-HT_{1A} receptors.[24-27] Using positron-emission tomography (PET) imaging, a decrease in 5-HT_{1A} receptor binding has been also identified in patients with TLE.[28-30] Deficits in 5-HT transmission in human depression is thought to be partially related to a paucity of serotonergic innervation of its terminal areas suggested by a scarcity of 5-HT levels in brain tissue, plasma, and platelets, and with a deficit in serotonin transporter binding sites in postmortem human brain.[31-35] Serotonin stores and transporter protein are important components of serotonin terminals, so that a combined deficit is a plausible indicator of reduced axonal branching and synapse formation.

With respect to abnormal serotonergic activity in functional neuroimaging studies of patients with primary major depression, Sargent et al demonstrated reduced 5-HT_{1A} receptor binding potential of values in frontal, temporal, and limbic cortex with PET studies using [11C]WAY-100635 in both unmedicated and medicated depressed patients compared with healthy volunteers.[24] Of note, binding potential values in medicated patients were similar to those in unmedicated patients. Drevets et al, using the same radioligand, reported a decreased binding potential of 5-HT_{1A} receptors in mesial-temporal cortex and in the raphe in 12 patients with familial recurrent major depressive episodes, compared with controls.[25] A deficit in the density or affinity of postsynaptic 5-HT_{1A} receptors has been identified in the hippocampus and amygdala of untreated depressed patients who committed suicide.[26] In addition, impaired serotonergic transmission has been associated with defects in the dorsal raphe nuclei of suicide victims with major depressive disorder, consisting of an excessive density of serotonergic somatodendritic impulse-suppressing 5-HT_{1A} autoreceptors.[27]

Similar abnormalities in 5-HT_{1A} receptor binding have been identified in patients with TLE. For example, in a PET study of patients with TLE using the 5-HT_{1A} receptor antagonist ([18F] trans-4-fluro-N-2-[4-(2-methoxyphenyl) piperazin-1-yl]ethyl-N-(2-pyridyl) cyclohexanecarboxam-

ide), reduced 5-HT_{1A} binding was found in mesial temporal structures ipsilateral to the seizure focus, in patients with and without hippocampal atrophy.[28] In addition, a 20% binding reduction was found in the raphe and a 34% lower binding in the ipsilateral thalamic region to the seizure focus. In a separate PET study aimed at quantifying 5-HT_{1A} receptor binding in 14 patients with TLE, decreased binding was identified in the epileptogenic hippocampus, amygdala, anterior cingulate, and lateral temporal neocortex ipsilateral to the seizure focus, as well as in the contralateral hippocampi, but to a lesser degree, and in the raphe nuclei.[29]

Other investigators using the 5-HT_{1A} tracer, 4,2-(methoxyphenyl)-1-α[2-(*N*-2-pyridinyl)-*p*-fluorobenzamido]ethylpiperazine ([^{18}F]MPPF), found that the decrease in binding of 5-HT_{1A} was significantly greater in the areas of seizure onset and propagation identified with intracranial electrode recordings. As in the other studies, reduction in 5-HT_{1A} binding was present, even when quantitative and qualitative MRI were normal.[30]

Reduction in 5-HT_{1A} receptor binding is not restricted to patients with TLE. PET studies with the 5-HT_{1A} receptor antagonist carbonyl-carbon 11-WAY-100635 ([11c]WAY-100635) found a decreased binding potential in the dorsolateral prefrontal cortex, raphe nuclei, and hippocampus of 11 patients with juvenile myoclonic epilepsy compared with 11 controls.[36]

In a recently published study, Hasler et al compared 5-HT_{1A} receptor binding between 37 TLE patients with and without major depressive disorder (MDD) with interictal PET using the 5-HT_{1A} antagonist [(18)F]FCWAY.[37] The MDD was diagnosed by clinical and structured psychiatric interviews. They found that, in addition to a decrease in 5-HT_{1A} receptor binding in the epileptic focus, patients with TLE and MDD exhibited a significantly more pronounced reduction in 5-HT_{1A} receptor binding, extending into nonlesional limbic brain areas outside the epileptic focus. The side of the ictal focus and the presence of mesial temporal sclerosis were not associated with the presence of comorbid depression. In a second study in 45 patients with TLE, Theodore et al demonstrated an inverse correlation between increased severity of symptoms of depression identified on the Beck Depression Inventory and 5-HT_{1A} receptor binding at the ipsilateral hippocampus to the seizure focus and to a lesser degree at the contralateral hippocampus and midbrain raphe.[38] Likewise, Gilliam et al correlated the severity of symptoms of depression using the BDI-II in 31 patients with TLE with the magnitude of hippocampal abnormalities identified with ^{1}H magnetic resonance spectroscopic imaging (^{1}H-MRSI) technique at 4.1 Tesla using creatine/*N*-acetylaspartate ratio maps.[39]

Clinical implications

The existence of common pathogenic mechanisms between mood disorders and epilepsy may explain the higher incidence of mood disorders in patients with epilepsy. In theory, however, patients with mood disorders should be at greater risk of suffering from epilepsy *following* the development of the depressive disorder. Data from three population-based studies appear to confirm this hypothesis. Indeed, while, depression in patients with epilepsy is typically conceptualized as a "complication" of the seizure disorder, such a "unidirectional relationship" between the two disorders was called into question in the last 15 years, first in a Swedish population-based-case control study in which depression was found to be seven times more common among patients with *new-onset* epilepsy, *preceding the seizure disorder*, than among age- and sex-matched controls.[40] When analyses were restricted to cases with a "localized-onset" seizure, depression was 17 times more common among cases than among controls. Next, in a population-based study that included all adults aged 55 years and older at the time of the onset of their epilepsy, living in Olmstead County, Minnesota (USA),[41] the investigators found that a diagnosis of depression *preceding the time of their first seizure* was 3.7 times more frequent among cases than among controls after adjusting for medical therapies for depression. As in the Swedish study,[40] this increased risk was greater among cases with partial-onset seizures. An interesting finding of this study was that, among people with epileptic seizures, an episode of major depression had taken place closer to the time of the first seizure than for controls. Another population-based study carried out in Iceland investigated the role of specific symptoms of depression in predicting the development of unprovoked seizures or epilepsy in 324 children and adults, aged 10 years and older with a first unprovoked seizure or newly diagnosed epilepsy and 647 controls.[42] Major depression was associated with a 1.7-fold increased risk for developing epilepsy while a history of attempted suicide was 5.1-fold more common among cases than among controls.

Jones et al studied the cognitive and psychiatric profile of 103 children aged 8 to 18 years, 53 with recent onset epilepsy (<1 year in duration) of *idiopathic* etiology and

50 healthy children matched for age.[43] Each child underwent a structured psychiatric diagnostic interview to characterize the spectrum of lifetime-to-date history of comorbid psychiatric disorder. Compared with the control group, children with epilepsy exhibited an elevated rate of lifetime-to-date *Diagnostic and Statistical Manual of Mental Disorders*, 4th edition *(DSM-IV)*[44] Axis I disorders, including significantly higher rates of depressive disorders (22.6 vs 4%), anxiety disorders (35.8 vs 22%), and attention-deficit-hyperactivity disorder (ADHD, 26.4 vs 10%). Of note, 45% of children with epilepsy exhibited *DSM-IV* Axis I disorders *before the first recognized seizure*.

Data from another study suggested that psychiatric pathology could be a risk factor for the development of unprovoked nonfebrile seizures and epilepsy in children. For example, McAfee et al conducted a retrospective cohort study in 133 440 pediatric patients (age 6 to 17 years) without history of seizures or prior use of anticonvulsant medications.[45] The data source for this study was a research database containing pharmacy and medical claims for members of a large US-based managed care organization. The incidence rate of seizures among children without psychiatric diagnoses was 149 per 100 000 person-years (95% CI 122-180), while that among children with psychiatric diagnoses other than ADHD was 513 per 100 000 person-years (95% CI 273-878).

The impact of a history of depression preceding the onset of epilepsy on the course of the seizure disorder

The existence of common pathogenic mechanisms appears to have an impact on the response to treatment of epileptic seizures. For example, in a study in 780 patients with newly diagnosed epilepsy that were followed over a 20-year period, Hitiris et al found that seizures had been controlled in 462 patients, while in 318 patients epilepsy remained refractory to AED therapy.[46] Univariate and multivariate logistic regression analyses demonstrated that pharmacoresistance was associated with prior or current psychiatric comorbidity, particularly depression and intermittent recreational drug use.

The negative impact of psychiatric history on seizure control has not been restricted to pharmacotherapy, but has been identified in studies that investigated postsurgical seizure outcome following an anterotemporal lobectomy (ATL). The first study by Anhoury et al reported that a presurgical psychiatric history was associated with a worse postsurgical seizure outcome following an ATL in 126 patients.[47] In a recent study, Kanner et al demonstrated that a lifetime history of depression was a predictor of failure to reach a postsurgical seizure outcome free of auras and disabling seizures following an ATL in 100 consecutive patients followed for a mean period of 8.3±3.3 years.[48] (Kanner et al, unpublished material).

Conclusion

The data presented in this article are clearly indicative of a complex relationship between mood disorders and epilepsy, which is based on the sharing of common pathogenic mechanisms. This review was restricted to the role of NE and 5-HT. Yet, the potential pathogenic mechanisms include DA, GABA, and glutamate, as well as abnormalities of common neuroanatomical structures that are part of the limbic circuit, including amygdala, hippocampus, orbitofrontal and mesial frontal cortex, nucleus accumbens, basal ganglia and thalamic nuclei, and the raphe nuclei and locus coeruleus.[49] The implications for neurologists are not merely theoretical, but bear great significance with respect to the negative impact of mood disorders on the response to pharmacologic and surgical treatments of seizures. ❑

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Trastorno afectivo y epilepsia: una perspectiva neurobiológica de su relación

Los trastornos afectivos constituyen la comorbilidad más frecuente en la epilepsia, particularmente en la epilepsia del lóbulo temporal. Por largo tiempo los trastornos depresivos fueron considerados expresión de un proceso reactivo a los obstáculos de una vida con epilepsia. Sin embargo, datos obtenidos en las últimas dos décadas han demostrado cambios bioquímicos, neuropatológicos y neurofisiológicos que median el desarrollo de los trastornos del ánimo, los que de hecho pueden ser probados en modelos animales. También existe evidencia que los trastornos afectivos y la epilepsia tienen una compleja relación que es bidireccional; esto significa que no sólo los pacientes con epilepsia tienen mayor riesgo de desarrollar depresión, sino que los pacientes con depresión tienen mayor riesgo de desarrollar epilepsia. Tal relación sólo puede ser explicada por la existencia de mecanismos patogénicos comunes que operan en ambas direcciones. Estos incluyen cambios en neurotransmisores como serotonina, noradrenalina, glutamato y ácido gama-aminobutírico. Esta relación bidireccional también parece tener importantes consecuencias clínicas. De hecho, pacientes con historia de trastornos afectivos duplican la probabilidad de desarrollar epilepsia resistente a fármacos en relación con aquellos que no tienen ese antecedente. Estos datos son revisados en este artículo.

Troubles de l'humeur et épilepsie : perspective neurobiologique de leur interaction

Le trouble de l'humeur est la comorbidité la plus fréquente au cours de l'épilepsie, et en particulier de l'épilepsie du lobe temporal. Les troubles dépressifs de l'épileptique ont pendant longtemps été considérés comme l'expression d'une réaction aux obstacles rencontrés au cours de la vie. Les données obtenues ces 10 dernières années ont néanmoins mis en évidence des changements biochimiques, neuropathologiques et neurophysiologiques facilitant l'émergence des troubles de l'humeur, et pouvant en fait être testés sur des modèles animaux. De plus, il existe également des arguments en faveur d'une relation complexe, bidirectionnelle, entre les troubles de l'humeur et l'épilepsie; non seulement les patients épileptiques ont plus de risque de développer une dépression, mais les patients dépressifs ont quant à eux un risque plus élevé de développer une comitialité. Une telle relation ne peut s'expliquer que par l'existence de mécanismes pathogéniques communs intervenant dans les deux affections. Des modifications au niveau des neurotransmetteurs, comme la sérotonine, la norépinéphrine, le glutamate et l'acide γ-aminobutyrique en font partie. Ces relations bidirectionnelles entraînent des conséquences cliniques importantes. En effet, les patients ayant des antécédents de troubles de l'humeur ont deux fois plus de risque de développer une épilepsie pharmacorésistante que ceux qui en sont indemnes. Ces données sont examinées dans notre article.

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