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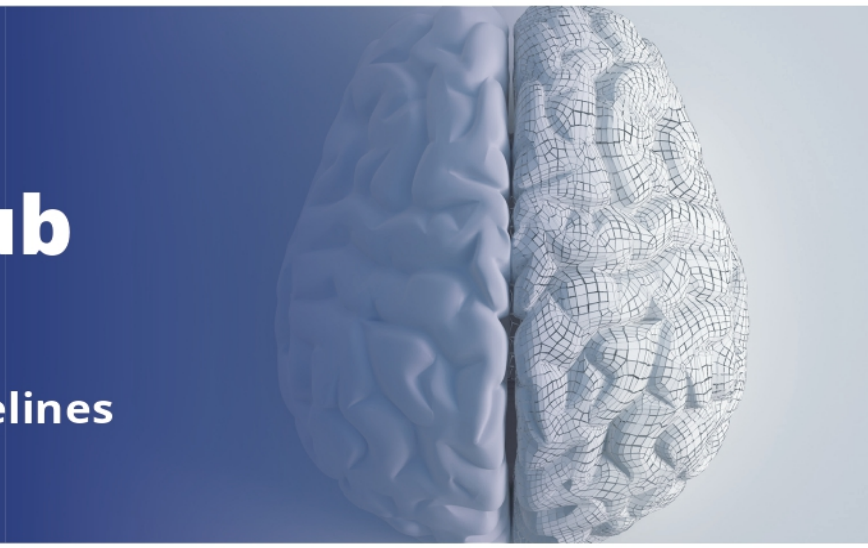

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EPILEPSY SPECTRUM DISORDER

Depression and epilepsy: A bidirectional relation?

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Summary

A bidirectional relation between depressive disorders and epilepsy has been suggested by several population-based studies and is supported by experimental studies. This article reviews the potential pathogenic mechanisms operant in both disorders that may explain such a relation. These mechanisms include a hyperactive hypothalamic–pituitary–adrenal (HPA) axis and its neuroanatomic and neuropathologic complications, as well as disturbances in serotonergic, noradrenergic, γ-aminobutyric acid (GABA)ergic and glutamatergic neurotransmitter systems, all of which may be interrelated.

KEY WORDS: Serotonin, Norepinephrine, Glutamate, Depression, Attention deficit hyperactivity disorder, Temporal lobe epilepsy.

Psychiatric comorbidities in epilepsy have been considered to reflect a "consequence or complication" of the seizure disorder. Yet, in recent years, a bidirectional relationship between depressive disorders (DDs) and epilepsy has been demonstrated, as not only are people with epilepsy (PWE) at greater risk of developing a DD, but patients with DD have a three- to seven-fold higher risk of developing epilepsy (Forsgren & Nystrom, 1999; Hesdorffer et al., 2000, 2006). These data may be explained by the existence of common pathogenic mechanisms operant in both conditions (Kanner, 2009). The purpose of this article is to examine the available data in experimental studies with animals and studies done in humans supporting this hypothesis, and to propose other common potential pathogenic mechanisms operant in epilepsy and DDs.

Animal Models of Epilepsy and Psychiatric Comorbidities

The Genetic Absence Epilepsy Rats from Strasbourg (GAERS) illustrate the existence of epilepsy and psychiatric comorbidities in an animal model of generalized epilepsy (Jones et al., 2008). One study of 47 GAERS and 73 nonepileptic control rats (NEC) were subjected to behavioral measures of depression [the Sucrose-Preference Test (SPT)] and anxiety [the Elevated Plus Maze (EPM), and the Open Field Arena (OFA)] at 7 and 13 weeks of age, ages prior to and after seizure onset. The GAERS exhibited significantly greater levels of behaviors equivalent to symptoms of depression and anxiety on these measures, including reduced consumption of sucrose solution in the SPT (equivalent to anhedonia in humans), lower percentage of time in the open arms of the EPM, and reduced exploratory activity and less time spent in the inner area of the OFA (equivalent to anxiety symptoms). These differences were evident *preceding* and *following* the onset of epilepsy. Clearly, increased anxiety- and depressive-like behaviors in GAERS were not a consequence of seizures, but rather an expression of comorbid neurologic and psychiatric-like conditions.

The genetically epilepsy-prone rat (GEPR) with its two strains, GEPR3 and GEPR9, is another animal model of epilepsy with comorbid behaviors equivalent to depressive symptomatology manifested by decreased sucrose consumption in the SCT and increased immobility time in the forced swimming test (FST) (Jobe, 2006). The GEPR harbors inborn defects in pre- and postsynaptic transmission of both serotonin (5HT) and norepinephrine (NE) resulting from deficient arborization of noradrenergic and serotonergic neurons arising from the locus ceruleus and raphe nuclei (Jobe et al., 1994). The pathogenic role of 5HT and NE was demonstrated by the worsening of

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seizures with substances that interfere with the synthesis or release of NE (reserpine and tetrabenazine, which inactivate NE storage vesicles; α-methyl-m-tyrosine, a false NE transmitter; α-methyl-ρ-tyrosine, an NE synthesis inhibitor) or 5HT (ρ-chlorophenylalanine, a 5HT synthesis inhibitor). Conversely, treatment with noradrenergic (desipramine) and serotonergic drugs [selective-serotonin reuptake inhibitors (SSRIs), fluoxetine and sertraline] has been shown to block seizures. Similar anticonvulsants effects of serotonergic and noradrenergic drugs have been demonstrated in other animal models, including nongenetic animal models in the rat, rabbit, cat, and monkey (Piette et al., 1963; Polc et al., 1979; Yanagita et al., 1980; Meldrum et al., 1982).

In humans, functional neuroimaging studies with positron emission tomography (PET) targeting the $5HT_{1A}$ receptor have suggested a potential common pathogenic role of 5HT in epilepsy and DDs, as several studies have demonstrated a decreased binding of $5HT_{1A}$ in common mesial-temporal structures, cingulate gyrus and raphe nuclei, in both disorders (Sargent et al., 2000; Toczek et al., 2003; Theodore et al., 2006; Hasler et al., 2007). Furthermore, the report of a significant drop in seizure frequency in three open trials with SSRIs in patients with treatment-resistant epilepsy supports the pathogenic role of 5HT (Favale et al., 1995, 2003; Specchio et al., 2004).

Serotonin's anticonvulsant effect may be also mediated through direct and indirect mechanisms, the latter including inhibition of voltage-gated ion channels, and effect on inhibitory neurotransmitter receptors [γ-amino butyric acid (GABA), excitatory receptors (e.g., glutamate)] and neurosteroid synthesis (Robinson et al., 2003; Ye et al., 2008). Of note, the serotonergic anticonvulsant effect appears to have an ''inverted u-shaped'' concentration–response effect, as suggested by a study in pilocarpine-induced seizures in which hippocampal perfusion of 5HT up to extracellular concentrations ranging between 80% and 350% of baseline levels protected these rats from seizures, whereas concentrations >900% of baseline worsened seizures (Clinckers et al., 2004). Of note, the high extracellular 5HT concentrations were associated with significant increases in extracellular glutamate.

Can a Bidirectional Relation between Epilepsy and Psychiatric Disturbances Be Demonstrated in Animal Models?

Epilepsy causes psychiatric disturbances

Mazarati et al. (2008) used an animal model of lithium- and pilocarpine-induced status epilepticus (SE) [a common animal model of temporal lobe epilepsy (TLE)] with male Wistar rats. Post-SE animals exhibited increase in immobility time in the FST and decrease consumption of saccharin in the SCT. Furthermore, investigators demonstrated a decrease of 5HT concentration and turnover in the hippocampus and of 5HT release from the hippocampus in response to raphe nuclei stimulation.

Psychiatric disturbances facilitate the development of epileptic activity

Three studies have suggested that early postnatal life stress, consisting of maternal separation (MS), can accelerate the kindling process in rats. In two studies, male and female nonepileptic rats were exposed to MS on postnatal days 2–14 for 180 min/day or early handling (EH) and brief separation (15 min/day). At 7 weeks of age, rats of both genders exposed to MS displayed significantly increased anxiety, as evidenced by reduced time spent in the open arms of the elevated plus maze compared with EH rats. In female rats, but not in male rats, fewer stimulations were required following MS than EH to reach the fully kindled state (39.6 ± 6.4 vs. 67.1 ± 9.4; $p < 0.0001$) (Salzberg et al., 2007; Jones et al., 2009). Likewise, the third study used cross-fostering as a model for early life stress in seizure-prone (FAST) and seizure resistant (SLOW) rats, which underwent amygdala kindling until six class V seizures were recorded. An increased kindling rate was observed among all cross-fostered rats compared to nonfostered rats (Gilby et al., 2009). Clearly, the data from these studies suggest that early life stress in rodents can facilitate the process of epileptogenesis.

Other Putative Pathogenic Mechanisms

A hyperactive hypothalamic–pituitary–adrenal axis

An abnormal dexamethasone suppression test was the first biologic marker of major depressive disorders (MDDs) in humans and has been recently demonstrated in patients with TLE (Zobel et al., 2004) as well as in animal models of epilepsy (Mazarati et al., 2009). Using the lithium and pilocarpine–induced SE model cited earlier, Mazaratti et al. demonstrated an increase of corticosteroid (CS) serum concentrations during the interictal period, which also correlated with the severity of equivalent symptoms of depression. Likewise, Kumar et al. (2007) demonstrated that CS administration accelerated electrical amygdala kindling in female nonepileptic Wistar rats 10–13 weeks of age. Compared to a control group infused with water, CS-treated rats required a significantly lower number of stimulations to reach a full kindled state (45.2 vs. 86.5, $p < 0.01$). The addition of mineralocorticoid and glucocorticoid CS antagonists resulted in inhibition of the kindling acceleration.

The impact of increased CS on CNS 5HT has been demonstrated by López et al. (1998), who found a significant elevation of basal plasma CS in rats subjected to chronic

unpredictable stress compared to nonstressed rats and a decrease in $5HT_{1A}$ mRNA and binding in the hippocampus. Furthermore, pretreatment with the tricyclic antidepressant drugs imipramine or desipramine prevented the decreases in $5HT_{1A}$ mRNA and binding. Because $5HT_{1A}$ receptor binding and its mRNA expression are under tonic inhibition by glucocorticoid receptor stimulation, reduction in $5HT_{1A}$ receptor binding and its mRNA expression in depression may be caused by cortisol hypersecretion. This observation may explain the decreased $5HT_{1A}$ receptor binding identified on PET studies of humans with DDs and epilepsy cited earlier.

In experimental studies with rats and monkeys, CS have been found to be neurotoxic at high concentrations, causing (1) damage of hippocampal neurons, particularly CA3 pyramidal neurons, mediated by reduction of dendritic branching and loss of dendritic spines that are included in glutamatergic synaptic inputs; (2) decreased levels of brain-derived neurotrophic factor (BDNF) reversed by long-term administration of antidepressants; and (3) interference with neurogenesis of granule cells in the adult hippocampal dentate gyrus (Sapolsky, 2000a,b; Shirayama et al., 2002). All of these effects result in structural changes in the dentate gyrus, pyramidal cell layer of hippocampus, amygdala, and temporal neocortex (Sapolsky, 2000a,b; Bowley et al., 2002; Shirayama et al., 2002). In the frontal lobes, high CS secretion has been associated with a decrease in glial cell numbers in subgenual, cingulated, and dorsolateral sections of the prefrontal cortex (Öngür et al., 1998; Rajkowska et al., 1999; Rajkowska, 2001; Cotter et al., 2001a,b, 2002).

As stated earlier a hyperactive hypothalamic–pituitary–adrenal (HPA) axis was identified in humans with TLE without DDs, of comparable magnitude to that of patients with MDDs (Zobel et al., 2004). In humans with primary MDD, a hyperactive HPA has been postulated as one of the operant pathogenic mechanisms mediating the atrophy of hippocampi, and frontal lobes, including cingulate gyrus and orbitofrontal and dorsolateral cortex demonstrated by multiple investigators (Coffey, 1994; Bremner et al., 2000, 2002; Sheline, 2006). In fact, neuropathologic consequences attributed to excessive cortisol have included: (1) decreased glial densities and neuronal size in the cingulate gyrus; (2) decreased neuronal sizes and neuronal densities in layers II, III, and IV in the rostral orbitofrontal cortex resulting in a decrease of cortical thickness; (3) a significant decrease of glial densities in cortical layers V and VI associated with decreases in neuronal sizes in the caudal orbitofrontal cortex; and (4) a decrease of neuronal and glial density and size in all cortical layers of the dorsolateral prefrontal cortex (Öngür et al., 1998; Rajkowska et al., 1999; Cotter et al., 2001a,b, 2002). Finally, elevated levels of glucocorticoids reduce the activity of astrocytes and interfere with their function. In this manner they may undermine neuronal and cortical function in MDDs by causing the accumulation of excessive synaptic glutamate (see subsequent text) (Crossin et al., 1997).

Disturbances of glutamate and GABA

In epilepsy, the pathogenic role of the excitatory and inhibitory neurotransmitters glutamate and GABA has been established for a long time. In DDs, the pathogenic mechanisms of these neurotransmitters are now being recognized in studies of experimental models of depression and in pharmacologic, neuropathologic, and neuroimaging studies in humans. The available data are suggestive of a dysfunction in the regulation of glutamate and GABA neurotransmission, but the actual mechanisms operant are complex and are yet to be elucidated (Kugaya & Sanacora, 2005; Machado-Vieira et al., 2009). Glutamatergic and monoaminergic systems are closely interconnected as evidenced by the projection of glutamatergic neurons from the cortex to the locus coeruleus, raphe nucleus, and substantia nigra. Likewise, serotonergic and noradrenergic agents can interfere with the neurotransmission of glutamate. For example, chronic treatment with the SSRI fluoxetine, the serotonin-norepinephrine reuptake inhibitor (SNRI) reboxetine, and the norepinephrine reuptake inhibitor desipramine causes a reduction of depolarization-evoked release of glutamate (Robinson et al., 2003; Bonanno et al., 2005).

Three lines of evidence support a pathogenic role of glutamate and GABA in DDs: (1) dysfunction of glutamate transporter proteins; (2) abnormal concentrations of cortical glutamate and GABA identified with functional neuroimaging studies using proton magnetic resonance spectroscopy (H1-MRS) and neuropathologic studies; and (3) antidepressant effects of glutamate receptor antagonists (Brambilla et al., 2003; Kugaya & Sanacora, 2005).

Dysfunction of glutamate transporter proteins

In animal models of depression, glutamatergic dysfunction has been suggested by disturbance of glutamate transporters (vGluT1 and excitatory amino acid transporters EAAT-1, EEAT-2 (found primarily in glial cells), EEAT-3 (localized principally in neurons), and EEAT-4 (localized in the cerebellum) (Kugaya & Sanacora, 2005; Zink et al., 2010). Glutamate transporters play pivotal roles in the maintenance of glutamate's low extracellular concentrations, a mechanism through which they protect neurons from excitotoxic damage and they limit the amplitude and duration of excitatory postsynaptic currents in glutamatergic synapses. Because there is no process by which glutamate is metabolized, its synaptic concentrations depend on re-uptake of these transporter proteins localized on glia and neurons (Zarate et al., 2002). Using an animal model of depression with Sprague Dawley rats, Zeng et al. (2010) showed a significantly suppressed expression of

the glial glutamate transporter EAAT2 in hippocampus and cerebral cortex compared to littermates with low failure rate and not symptomatic animals. Likewise, elevated extracellular glutamate levels, neuronal death, and epilepsy were related to decreased expression and function of glial glutamate transporters in a mouse model of tuberous sclerosis complex (Tsc1(GFAP)CKO mice), involving inactivation of the *Tsc1* gene in glial cells (Zeng et al., 2010). In this study, early treatment with ceftriaxone prior to the onset of epilepsy increased expression of glial glutamate transporters, decreased extracellular glutamate levels, neuronal death, and seizure frequency, and improved survival in Tsc1(GFAP)CKO mice. However, treatment with this drug had no impact on seizures after the start of epilepsy.

In humans, reduced expression of EAAT1, EAAT2, and glutamine synthetase has been found in the frontal brain regions in postmortem brain tissue from individuals with MDDs, as well as decreases in EAAT3 and EAAT4 mRNA expression in the striatum of individuals with mood disorders resulting in elevated synaptic glutamate concentrations (Choudary et al., 2005). In a study done in 12 patients with pharmacoresistant TLE, decreased expression of EAAT-1 and EAAT-2 was found to be associated with a decreased extracellular clearance of glutamate in CA1 of the hippocampus by approximately 40% and 25%, respectively. Whether the downregulation of these glutamate transporters reflected an adaptive response to neuronal death or the cause of neuronal death has yet to be established (McCullumsmith & Meador-Woodruff, 2002).

Abnormal concentrations of cortical glutamate and GABA

Most 1H-MRS studies in humans with major depressive and bipolar disorders used the combined measure Glx, which reflects the sum of intracellular and extracellular pools of glutamate, glutamine, and GABA, due to their overlapping concentration peaks, but are an overwhelming expression of intracellular pools in neurons and glia (Capizzano et al., 2007; Walter et al., 2009). It has been suggested that the abnormal Glx measured by H1-MRS in MDDs is related to the decrease of glial cell counts and density cited above (Yildiz-Yesiloglu & Ankerst, 2006). Studies carried out in adults with MDDs revealed reductions in Glx levels in the anterior cingulate gyrus, dorsolateral prefrontal brain regions, and amygdala/anterior hippocampus. One study has also revealed elevated glutamate concentrations in the occipital cortex (Kugaya & Sanacora, 2005). These findings have not been uniform, as one study of bipolar depressed children and one of unmedicated adult patients revealed elevated levels of Glx in the frontal lobe and basal ganglia (Rosenberg et al., 2004) and in the cingulate gyrus, respectively (Dager et al., 2004). Likewise, studies done in unmedicated adults with MDDs revealed decreased GABA levels in dorsomedial, dorsal anterolateral prefrontal, and ventromedial prefrontal regions and occipital regions (Walter et al., 2009).

Study of the GABA–synthesizing enzyme, glutamic acid decarboxylase (GAD) and its two isoforms, GAD_{65} and GAD_{67}, found a decrease of the density of GAD_{65} and GAD_{67} mRNA–positive neurons by 45% and 43%, respectively, in the hippocampus and of the GAD_{65} in the cingulate and prefrontal cortices of patients with bipolar disorder (Heckers et al., 2002). Furthermore, Mason et al. (2001) found a decreased GABA synthesis in depressed subjects using carbon13C-MRS, while Sanacora et al. (2002) showed a normalization of GABA concentrations with the SSRI citalopram.

Antidepressant effects of glutamate receptor antagonists

There is a growing evidence suggesting that antidepressant effects of various *N*-methyl-D-aspartate (NMDA) and metabotropic antagonists (including MK-801, ketamine, mGluR5 antagonist 2-methyl-6-(phenylethynyl)-pyridine (MPEP), and the mGluR2/3 antagonists LY341495 and MGS0039) in animal models of depression including the FST, the tail suspension–induced immobility tests, and in learned helplessness models of depression (Kugaya & Sanacora, 2005; Machado-Vieira et al., 2009).

The NMDA antagonist ketamine has shown antidepressant effects in two double-blind placebo-controlled studies carried out in patients with pharmacoresistant depression. The first study included seven patients with MDDs in whom the efficacy of a single dose of 0.5 mg/kg was assessed in a double-blind placebo-controlled paradigm. Subjects with depression evidenced significant improvement in depressive symptoms within 72 h after ketamine but not placebo infusion (Berman et al., 2000). The second study included 18 patients with treatment-resistant MDDs and followed the response to treatment for 2 weeks; the NMDA antagonist ketamine demonstrated antidepressant effects within 2 h of a single administration of an intravenous subanesthetic dose in a double-blind placebo cross-over study; the antidepressant effect persisted for 1–2 weeks (Zarate et al., 2006); 50% of patients met response criteria within 2 h and 71% by 24 h.

Riluzole (2-amino-6-(trifluoromethoxy) benzothiazole) is a drug with an indication for the treatment of amyotrophic lateral sclerosis. Its mechanism of action consists of the inhibition of glutamate but it also has effects on α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid (AMPA) receptor trafficking and glutamate reuptake. Repeated doses of riluzole have been found to elevate significantly brain-derived growth factor (BDNF) in hippocampus, an effect that has been associated with antidepressant effects of antidepressant drugs (Katoh-Semba et al., 2002).

The antidepressant effects of this drug were suggested in open trials, particularly a 6-week open-label monotherapy trial carried out in 19 patients with treatment-resistant

MDD (Zarate et al., 2004). Riluzole has been tested in open trials as add-on therapy; in one study of eight patients with bipolar depression, combination with lithium for 8 weeks significantly improved depressive symptoms (Zarate et al., 2005). Another trial of 10 patients with treatment-resistant MDD with Riluzole as add-on therapy to antidepressant drugs therapy resulted in a significant improvement in depressive symptoms after 6–12 weeks of treatment (Sanacora et al., 2007). The findings of these trials must be replicated in double-blind placebo-controlled studies. Yet, today, these data have led psychopharmacologists to develop a comprehensive program to develop psychotropic drugs that target glutamatergic neurotransmission for the treatment of treatment-resistant MDDs.

In contrast to the antidepressant effect identified in drugs that modulate glutamate transmission, no antidepressant effect has been found in GABAergic agents. In fact, AEDs with GABAergic effects such as barbiturates, vigabatrin, and tiagabine have been associated with significant psychiatric adverse events, including depressive episodes. The inhibition of 5HT secretion by GABAergic mechanisms has been postulated as one of the potential mechanisms responsible for this phenomenon; however, no clear-cut answer exists as of yet.

Clinical Implications

The data reviewed in the previous pages provides a possible explanation for the bidirectional relation between depression and epilepsy. Clearly, structural, neuropathologic, and neurotransmitter disturbances associated with primary MDDs may potentially facilitate the development of a seizure disorder either spontaneously or in the presence of an insult to the central nervous system. In addition, these changes may explain the finding that patients with a history of depression preceding the onset of epilepsy are twice as likely to develop a treatment-resistant epilepsy (Hitiris et al., 2007). Furthermore, patients with a history of treatment-resistant TLE who have a lifetime history of depression are significantly less likely to achieve complete seizure-freedom after a temporal lobectomy (Kanner et al., 2009).

On the bases of the data presented herein, it is reasonable to consider the hypothesis of whether antidepressants of the SSRI or SNRI families may yield antiepileptic efficacy, just as antiglutamatergic agents are being tested today for the treatment of treatment-resistant depression.

Clearly, the data presented in this review represent do not represent all the potential pathogenic mechanisms under consideration today. It should be also emphasized that data observed in several animal models of depression and epilepsy may not necessarily apply to humans. Therefore, these hypotheses need to be tested in additional experimental studies and later on in humans.

Disclosure

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