Can neurobiological pathogenic mechanisms of depression facilitate the development of seizure disorders?

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People with epilepsy have a high risk of developing depressive disorders, and people with primary depressive disorders have a high risk of developing epilepsy. Furthermore, a lifetime history of depressive disorders has been associated with a poor response of the seizure disorder to pharmacotherapy and epilepsy surgery. The aim of this Review is to identify the principal neurobiological pathogenic mechanisms of depressive disorders with the potential to facilitate the epileptogenic process or cortical hyperexcitability in experimental animal studies or those that can aggravate known pathogenic mechanisms of epilepsy in human beings. These mechanisms include (1) a hyperactive hypothalamic–pituitary–adrenal axis; (2) structural and functional abnormalities of cortical structures; (3) increased glutamatergic and decreased GABAergic and serotonergic activity; and (4) immunological abnormalities. The data presented in this Review provide experimental evidence that might begin to explain the bidirectional relation between depressive disorders and epilepsy and that can be regarded as a source for future research.

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Introduction

Depressive disorders are the most common psychiatric comorbidity in patients with epilepsy, with lifetime prevalence rates of around 35% in population-based studies.[1] Not only are people with epilepsy at high risk of developing depressive disorders, but people with primary depressive disorders have a high risk of developing epilepsy.[2–4] Furthermore, a lifetime history of depressive disorders is associated with a poor response of the seizure disorder to pharmacological and surgical treatments.[5–8] The occurrence of epileptic seizures in depressed patients is typically attributed by clinicians to the long-held belief that antidepressant drugs have a proconvulsant effect, whereas the worse course of the seizure disorder is blamed on the association between a depressed state and poor compliance of antiepileptic drugs (AEDs). However, proconvulsant effects of antidepressants have only been associated with overdoses or high serum concentrations resulting from slow metabolism. Yet, four antidepressants (clomipramine, amoxapine, maprotiline, and bupropion) can cause seizures at therapeutic doses.[9,10]

Thus, if depressive disorders play a part in the development or course of seizure disorders, their neurobiological pathogenic mechanisms would be expected to facilitate the epileptogenic process in some way. In this Review, we describe the available published work on several pivotal neurobiological pathogenic mechanisms of depressive disorders identified in animal models of depression and in clinical studies of patients with a primary major depressive disorder (MDD) and bipolar disorders that had an influence on cortical excitability or facilitation of seizure occurrence, or both.

Epidemiology and prevalence

Epidemiological and prevalence data of depressive disorders in people with epilepsy are derived from studies that use structured psychiatric interviews and clinical psychiatric assessments to calculate point or lifetime prevalence rates of well-defined mood disorders (according to a predetermined set of diagnostic criteria, such as the diagnostic and statistical manual of mental disorders, fourth edition [DSM-IV][11]) or studies that use screening instruments (eg, the Center for Epidemiological Studies depression scale) to identify symptoms of depression over the previous 2–4 weeks. For the purpose of this Review, only population-based studies that included data on lifetime incidence of depressive disorders were selected, because these studies are more likely to be representative of the general population of people with epilepsy and to report more accurately the actual prevalence of depressive disorders, which can recur in more than 50% of patients over time.[12,13]

The largest and most methodologically sound data are derived from a Canadian population-based study,[1] which showed the association between epilepsy and psychiatric comorbidities, in particular mood disorders. This study yielded a lifetime prevalence of mood disorders of 24·4% in patients with epilepsy (95% CI 16·0–32·8) compared with 13·2% (12·7–13·7) in control individuals; 17·4% (10·0–24·9) of patients with epilepsy had a lifetime prevalence of MDD compared with 10·7% (10·2–11·2) of control individuals. The lifetime prevalence of any mood disorder (including MDD, bipolar disorder, dysthymia, or cyclothymia) was 34·2% (25·0–43·3) in people with epilepsy compared with 19·6% (19·0–20·2) in those without epilepsy. Other epidemiological studies provide data that specifically suggest a bidirectional relation between epilepsy and psychiatric disorders. Not only are people with epilepsy at high risk of developing depressive disorders, but people with primary depressive disorders are at high risk of developing epilepsy, as shown in several population-based studies.[2–4,14–16] In a study from Sweden, depressive disorder was seven times more common among patients with new-onset epilepsy, preceding the seizure disorder, than among age-matched and sex-matched control invidivuals.[2] A second study undertaken in Olmstead County (MN, USA) included all adults aged 55 years and over at the time of onset of

epilepsy;[3] a diagnosis of depression preceding their first seizure was 3·7 times more frequent among cases than among control individuals, after adjusting for medical treatments for depression. In both studies, the increased risk was greater among patients with partial-onset seizures than among patients with generalised epilepsy. A third population-based study done in Iceland included 324 patients aged 10 years and older with a first unprovoked seizure or newly diagnosed epilepsy and 647 control individuals.[4] A major depressive episode, according to DSM-IV criteria, was associated with a 1·7-times increased risk for developing epilepsy, whereas a history of attempted suicide was 5·1 times more common among cases than among control individuals. In a recent Swedish population-based study,[14] investigators assessed the risk of developing unprovoked seizures or epilepsy among patients who had been admitted to hospital for a psychiatric disorder (n=1885) compared with control individuals who were matched for sex and year of diagnosis and who were selected randomly from the register of the Stockholm County population. The age-adjusted odds ratio (OR) for development of unprovoked seizures was significantly higher for patients with any psychiatric disorder than for control individuals (2·7, 95% CI 2·0–3·6); the OR was 2·5 (1·7–3·7) for MDD, 2·7 (1·4–5·3) for bipolar disorder, 2·7 (1·6–4·8) for anxiety disorder, and 2·6 (1·7–4·1) for suicide attempt independent of a psychiatric disorder. The OR among depressed patients was higher for those who developed idiopathic or cryptogenic seizure disorders (3·9, 2·4–6·1) than for those who developed symptomatic seizures (1·5, 0·8–2·6). The association was highest when the depressive disorder was diagnosed less than 2 years before the seizure occurrence (6·3, 2·8–14·6). Similar findings were reported in a retrospective cohort study of 133 440 paediatric patients (age 6–17 years) without a history of seizures or previous use of AEDs.[15] The incidence of seizures among children with a history of psychiatric diagnoses was more than three times higher (513 per 100 000 person-years, 95% CI 273–878) than among children free of any psychiatric diagnosis other than attention deficit hyperactivity disorder (ADHD; 149 per 100 000 person-years, 122–180). Similarly, in a study of the incidence of seizures experienced by patients with a primary MDD during randomised, placebo-controlled trials of selective serotonin-reuptake inhibitors (SSRIs) and serotonin-norepinephrine-reuptake inhibitors (SNRIs), a higher incidence of epileptic seizures was identified among depressed patients randomly assigned to placebo than among those assigned to antidepressant drugs (standardised incidence ratio 0·48, 95% CI 0·36–0·61);[16] furthermore, this incidence was 19 times higher than the rates published for the general population. Clearly, all of these population-based studies confirm the high risk of developing epileptic seizures or epilepsy in patients with a history of depressive disorders.

The effect of depression on the course of seizure disorders

A lifetime history of depression has been associated with a poor course of seizure disorders. For example, in a study of 780 consecutive patients with new-onset epilepsy,[5] a psychiatric history and a history of depression were associated with amore than double the risk of developing treatment-resistant epilepsy compared with those with no lifetime psychiatric history. Likewise, in a study of 138 consecutive patients with new-onset epilepsy who were started on AEDs,[6] those who were identified as having symptoms of depression and anxiety in the A-B neuropsychological assessment schedule completed before the start of treatment were significantly less likely to be seizure free after 12 months of treatment than those who did not have any psychiatric history. Furthermore, in a study of 100 consecutive patients who underwent an anterior temporal lobectomy for the treatment of refractory temporal lobe epilepsy,[7] a lifetime history of depression was associated with worse post-surgical seizure control than those who had no lifetime history of depression. Similar data have been published by others.[8]

These findings suggest that pathogenic mechanisms of depressive disorders might help mediate the high risk of developing epilepsy or the poor course of the seizure disorder, or both, in people with epilepsy. The next section examines this notion.

Pathogenic mechanisms of depression that might facilitate the epileptogenic process

There are several neurobiological pathogenic mechanisms of primary depressive disorders.[17] Among these are four categories of mechanisms that have an effect on cortical hyperexcitability and the epileptogenic process: (1) endocrine abnormalities; (2) structural and functional abnormalities of cortical and subcortical structures; (3) neurotransmitter abnormalities; and (4) immunological abnormalities.

Endocrine abnormalities

A hyperactive hypothalamic–pituitary–adrenal axis (HPAA) resulting in high blood cortisol concentrations was among the first neurobiological abnormalities identified in up to 50% of patients with a primary MDD by use of the dexamethasone suppression test.[17] This abnormality is a trait of depressive disorders because it fails to normalise after remission of the depressive episode. Likewise, in experimental studies in rats, corticosterone facilitated the kindling process, one of the principal models of epileptogenesis.[18–24] For example, in one study,[18] male rats randomly assigned to corticosterone-releasing pellets given before amygdala kindling displayed accelerated behavioural signs of epilepsy and severe tonic-clonic seizures compared with those assigned to placebo. In another study,[19] Wistar rats pretreated with low-dose corticosterone achieved a fully

kindled state in the electrical amygdala kindling rat model with fewer stimulations than rats pretreated with saline (32 *vs* 81), and fewer stimulations were needed to reach the first class V seizure (14 *vs* 57). The same group of investigators showed that this effect could be blocked with the use of corticosterone antagonists acting on mineralocorticoid and glucocorticoid receptors.[20]

Separation of newly born pups from their dam has been used as an animal model of depression and anxiety, as well as to study its effect on HPAA function. An acceleration of the kindling process after early postnatal maternal separation has been reported in three studies.[21–23] In particular, one of these studies compared seizure-induced serum corticosterone concentrations and CA3 pyramidal cell count in rats that underwent maternal separation with early handling.[23] Female rats separated from their dams exhibited enhanced corticosterone responses during and after kindling. A similar pattern occurred in male rats, and there was a reduction in the total number of CA3 pyramidal cells in both sexes. Another study in rats investigated the effect of isolation at birth on the HPAA and on the development and course of seizures after status epilepticus at postnatal day 10 (P10) by use of the lithium-pilocarpine protocol.[24] The group of isolated rats had higher corticosterone plasma concentrations after status epilepticus than non-isolated rats, whereas the rats subjected to both isolation and status epilepticus had a decreased seizure threshold at P100 compared with control individuals and rats that underwent only isolation or only status epilepticus.

High cortisol concentrations can affect cortical hyperexcitability through effects on neurotransmitters, including glutamate, serotonin, and GABA. For example, the decrease in glial cell density and function associated with high cortisol concentrations can result in an excess of synaptic glutamate.[25] Primary depressive disorders have been associated with excessive glutamate activity (see below). Likewise, cortisol decreases the activity of serotonin, which has anticonvulsant effects in animal models of epilepsy (table 1).[26–31]

Clearly, these studies show an association between high corticosterone concentrations and facilitation of the kindling process. In people with temporal lobe epilepsy, a hyperactive HPAA was noted, with the dexamethasone suppression test, that was of comparable magnitude to that in patients with a primary MDD.[32] However, anti-seizure activity has also been associated with sex hormones, including progesterone and testosterone, through the effects of their respective metabolites on $GABA_A$ receptors.[33]

In animal models of depression and in studies done in patients with mood disorders, high serum cortisol concentrations have also been associated with structural, functional, and neuropathological abnormalities in temporal and frontal lobe structures, which are reviewed in the following section.

Structural and functional abnormalities of cortical and subcortical structures

In animal models of depression, a reduction in the total number of CA3 neuronal cells and interference with neurogenesis of granule cells in the adult hippocampal dentate gyrus have been reported[23,34–36]—changes that are typically noted in animal models of chronic temporal lobe epilepsy and that have been associated with persistence of spontaneous seizures.[37] Furthermore, in patients with a primary MDD, a 10–20% bilateral decrease in hippocampal volume has been reported by several investigators,[38–40] the magnitude of which was associated with the duration of the depressed state.[39]

Likewise, high plasma cortisol concentrations have been associated with decreased cortical thickness in the frontal lobe of patients with a primary MDD, which has been attributed to a decrease in glial or neuronal cell density and size in the cingulate gyrus, in layers II, III, and IV of the rostral orbitofrontal cortex, in cortical layers V and VI of the caudal orbitofrontal cortex, and also resulting from a decrease in neuronal and glial density and size in all cortical layers of the dorsolateral prefrontal cortex.[41–45] The next question to address is whether these neuropathological changes play a part in the worse seizure control of people with epilepsy with depressive disorders. Data from two studies seem to support this hypothesis. One study used voxel-based morphometric analyses in brain MRI scans of 48 adults with treatment-resistant temporal lobe epilepsy (24 with and 24 without a major depressive episode) and 96 healthy control individuals.[46] Patients with temporal lobe epilepsy and a major depressive episode had a greater number of areas with bilateral grey matter volume loss in temporal and frontal lobe regions and in the left thalamus than those with only temporal lobe epilepsy. Using the same methodology, a second study measured the cortical thickness in MRI scans of 165 patients with temporal lobe epilepsy secondary to mesial temporal sclerosis.[47] Bilateral cortical grey matter atrophy involving the orbital cortex, cingulate gyrus, and temporal-lateral neocortex was significantly more frequent among patients with treatment-resistant epilepsy than among seizure-free patients.

Studies with PET that target the $5\text{-}HT_{1A}$ receptor with the ligand ^{18}F-trans-4-fluoro-N-2-[4-(2-methoxy-phenyl)piperazin-1-yl]ethyl-N-(2-pyridyl) cyclohexane-carboxamide revealed functional abnormalities in patients with a primary MDD[48–51] that were identical to those seen in patients with temporal lobe epilepsy who did not have depression. These abnormalities consisted of decreased binding of the ligand to the $5\text{-}HT_{1A}$ receptor in the hippocampus, amygdala, cingulate gyrus, insula, and the raphe nucleus.[48–51] High cortisol concentrations might play a part in this process, because high corticosterone concentrations in rats caused lower mRNA expression of $5\text{-}HT_{1A}$ receptors and decreased binding of serotonin to the receptor in the hippocampus,

which was not noted after pretreatment with the tricyclic antidepressants imipramine and desipramine.[52] The investigators analysed mRNA expression of 5-HT_{1A} receptors in the brains of suicide victims who had depression and identified the same findings as those noted in the brains of rats.

Neurotransmitter abnormalities

The involvement of neurotransmitters as common pathogenic mechanisms in depression and epilepsy has been proposed for at least two decades. However, most of the attention has been focused on abnormalities of the monoaminergic neurotransmitters, particularly serotonin and norepinephrine.[26–31,53–59] For example, in the pilocarpine-lithium animal model of status epilepticus, Mazarati and colleagues[53] reported abnormal serotonin secretion in the raphe-hippocampal serotonergic pathway, lower serotonin concentrations and turnover in the hippocampus, and decreased serotonin release from the hippocampus after raphe stimulation. Additionally, administration of fluoxetine, a SSRI, reversed cortical hyperexcitability after status epilepticus. Several detailed reviews have been published on the pathogenic role of these two neurotransmitters in depression and their effect in epilepsy.[26–31,54–59] Furthermore, an anticonvulsant effect of serotonin has been reported in several animal models of epilepsy.[26–31,56–59] In an animal model of epilepsy in which seizures were induced in conscious rats with pilocarpine, a hippocampal perfusion of serotonin prevented limbic seizures when its extracellular concentrations ranged between 80% and 350% of baseline levels, whereas concentrations above 900% of baseline worsened seizures.[31] These findings suggest an inverted U-shaped antiepileptic effect of serotonin, which is in accordance with the clinical findings that antidepressant-induced seizures (with SSRIs, SNRIs, and tricyclic antidepressants) are typically associated with overdoses (tables 1 and 2).

Glutamate and GABA are neurotransmitters with pivotal but opposing pathogenic roles in epilepsy: glutamate has excitatory properties, whereas GABA has widespread inhibitory effects. Thus, high glutamatergic and low GABAergic activity in depressive disorders could facilitate a hyperexcitable state. Data supporting the existence of such abnormalities have been identified in animal models of depression as well as in people with major depressive and bipolar disorders and are summarised below.

Glutamate

Excessive glutamate activity plays an important pathogenic part in major depressive and bipolar disorders. High plasma and CSF concentrations of glutamate were first reported in the 1980s in patients with MDD and have been confirmed by several investigators.[60,61] Furthermore, an association between plasma glutamate concentrations and the severity of the depressive disorder has been also

	Serotonergic abnormalities or experimental procedure	Effects on epileptic activity
GEPR-3, 9[26,27]	Abnormal serotonergic arborisation in the brain in general and deficient postsynaptic 5-HT_{1A}-receptor density in the hippocampus	Predisposition to sound-induced generalised tonic-clonic seizures; marked acceleration of kindling; inhibition of serotonin synthesis with diet-free tryptophan worsens seizure severity; and the serotonin precursor 5-hydroxy-L-tryptophan has anticonvulsant effects when combined with the selective serotonin-reuptake inhibitor fluoxetine
Genetically prone mice and baboons and non-genetically prone cats, rabbits, and rhesus monkeys[28–31]	Administration of selective serotonin-reuptake inhibitors and monoamine oxidase inhibitors	Prevention of seizures

GEPR=genetically epilepsy-prone rat. 5-HT=5-hydroxytryptamine (serotonin).

***Table 1*: Serotonergic abnormalities in animal models of epilepsy**

	Noradrenergic abnormalities or experimental procedure	Effects on epileptic activity
GEPR-9>3[26,56,57]	Deficient arborisation of neurons arising from the locus coeruleus, and excessive presynaptic suppression of norepinephrine release in the terminal fields and absence of postsynaptic compensatory upregulation	Predisposition to sound-induced generalised tonic-clonic seizures; marked acceleration of kindling; and inhibition of norepinephrine synthesis worsens seizure severity, which is blocked by pretreatment with the noradrenergic tricyclic antidepressant desipramine
GEPR-9>3[26]	Administration of norepinephrine false transmitter α-methyl-m-tyrosine, the norepinephrine synthesis inhibitor α-methyl-Δ-tyrosine, and the serotonin synthesis inhibitor Δ-chlorophenylalanine	Facilitation of epileptic seizures
Rat[58,59]	Destruction of noradrenergic neurons in the locus coeruleus in rats subjected to electroshock or pentetrazol-induced seizures in which VNS had been implanted	VNS prevented seizures before destruction of norepinephrine cells, and destruction of the locus coeruleus prevented or significantly reduced the anticonvulsant effect of VNS

GEPR-9>3 means that these abnormalities were more severe in the GEPR-9 strain than the GEPR-3 strain. GEPR=genetically epilepsy-prone rat. VNS=vagus nerve stimulation.

***Table 2*: Noradrenergic abnormalities in animal models of epilepsy**

suggested.[62] Although an association between plasma and CSF concentrations is yet to be established, the high CSF glutamate concentration is suggestive of the abnormal glial-neuronal glutamine-glutamate cycle associated with NMDA receptor systems in the brains of patients with depression.[62]

Glutamate transporter proteins are one of the systems that maintain low extracellular concentrations of glutamate, through regulation of its packaging in presynaptic vesicles before release to the synaptic cleft and through regulation of the reuptake mechanisms into glial and neuronal cells.[63] These transporters include the vesicular glutamate transporters (vGluT1, vGluT2, and vGluT3) and the excitatory aminoacid transporters (EAAT-1, EAAT-2, EAAT-3, and EAAT-4); EAAT-1 and EAAT-2 are found primarily in glial cells, EAAT-3 principally in neurons, and EAAT-4 in the cerebellum. Abnormalities in the glutamate transporter system have been identified in animal models of depression and in people with depressive disorders;[64,65] these can result in neuronal hyperexcitability and death, as shown by the findings from several studies. Using the learned helplessness animal model of depression, mRNA expression of glial glutamate transporters EAAT-2 and vGluT1 was measured in the hippocampus and cerebral cortex of Sprague Dawley rats and compared with expression in control rats or rats with mild symptoms of helplessness;[65] there was a significantly reduced expression of both glutamate transporters in rats displaying overt symptoms of helplessness. Likewise, in human beings, reduced expression of EAAT-1, EAAT-2, and glutamine synthetase were noted in the frontal cortex at post mortem in brain tissue from individuals with MDD, as were decreases in EAAT-3 and EAAT-4 mRNA expression in the striatum of individuals with mood disorders, which resulted in raised synaptic glutamate concentrations.[66] In a separate study, substantial downregulation of two key members of the glutamate/neutral aminoacid transporter protein family solute carrier 1 (SLC1), SLC1A2 and SLC1A3, were found in the brains of patients with MDD.[67] Furthermore, raised extracellular glutamate concentrations, the development of epilepsy, and neuronal death were associated with decreased expression and function of glial glutamate transporters in a mouse model of tuberous sclerosis (*Tsc1*^{GFAP}CKO mice), which involved inactivation of the *Tsc1* gene in glial cells.[68]

High concentrations of glutamate in the frontal lobe were reported in a study of the brains of patients with MDD at post mortem.[69] Likewise, using proton magnetic resonance spectroscopy, Sanacora and colleagues[70] reported a significant increase in occipital lobe glutamate signal in patients with MDD compared with healthy control individuals.

The forced swim test is an animal model of depression, which is typically used to identify compounds with potential antidepressant properties. This test is based on the innate ability of rodents to react actively in stressful situations from which they see no escape, such as their placement in containers of water, which causes them to start swimming. Acquiring an immobile posture is indicative of a reaction to despair, which has been associated with depression.[53] Trials with NMDA and metabotropic antagonists (including dizocilpine maleate, ketamine, the metabotropic glutamate receptor 5 [mGluR5] antagonist 2-methyl-6-(phenylethynyl)-pyridine [MPEP], and the mGluR2/3 antagonists LY341495 and MGS0039) have shown antidepressant effects, as evidenced by dose-dependent reductions in immobility time.[64,71] The mechanism of action on glutamate receptors is complex: although it is achieved by blocking NMDA receptors, these drugs also enhance the presence of glutamate at AMPA receptors. A possible explanation lies in the role that NMDA receptors play in directly exciting interneurons. By blocking these NMDA receptors, a decreased excitability of interneurons can result, leading to disinhibition of primary glutamatergic synapses. In fact, pretreatment with the AMPA receptor antagonist NBQX diminished the antidepressant effect.[72] This effect was also identified with other NMDA antagonists such as dizocilpine maleate and Ro25-6981.

An antidepressant effect of NMDA receptor antagonists has been reported in patients with a treatment-resistant MDD, including in three double-blind, placebo-controlled trials, two with ketamine[73,74] and one with the NR2B subunit-selective NMDA receptor antagonist CP-101,606.[75] Findings from two open-label trials with riluzole[76,77] also suggested an antidepressant effect, but these findings must still be replicated in double-blind, placebo-controlled studies. Of note, antidepressants of the tricyclic, SSRI, and SNRI families downregulate glutamatergic receptors of the NMDA family and potentiate glutamatergic receptors of the AMPA family.[65,78]

GABA

Evidence of decreased GABAergic activity in patients with MDD is derived from the following data. A decrease in the CSF concentration of GABA was reported over 30 years ago and has since been confirmed by others.[79] GABA is synthesised by the enzyme glutamic acid decarboxylase (GAD) and its two isoforms, GAD_{65} and GAD_{67}. A study of the brains of patients with bipolar disorder at post mortem revealed a decrease in the density of GAD_{65} and GAD_{67} mRNA-positive neurons in the hippocampus by 45% and 43%, respectively.[80] Findings from a separate study showed decreased GAD_{65} mRNA expression in the cingulate gyrus, ranging from 27% to 37%.[81] In another study of 14 patients with MDD (nine of whom died by suicide) and nine control individuals who were assessed at post mortem, Rajkowska and colleagues[82] noted a significant decrease in GABAergic interneurons in the dorsolateral prefrontal cortex of the brains of the patients with MDD. Likewise, findings from a study of the brains of suicide victims compared with the brains of control individuals

revealed a decrease in mRNA expression of GAD subunits α1, α3, α4, and δ in the frontal lobe.[83]

The first study to investigate intra-cortical GABA concentrations was limited to occipital regions, because of technical reasons, and revealed lower GABA concentrations in patients with MDD compared with control individuals.[84] These data were replicated in a larger study of 33 patients with MDD and 38 control individuals.[85] Although low occipital GABA concentrations were suggested as a trait abnormality in a study of 31 patients with a recurrent mood disorder (15 with MDD and 16 with bipolar disorder),[86] other findings have shown normalisation of GABA concentrations with antidepressant[70] and electroshock[87] therapy.

Decreased GABA concentrations have also been reported in frontal lobe structures, including in the dorsomedial and dorsal anterolateral prefrontal regions,[88] which are the cortical areas where decreased glial cell density was reported in the brains of patients with MDD at post mortem (see earlier).[41–45] Similar findings were reported in a study that included two groups of depressed patients, one with treatment-resistant MDD and one with MDD that did not meet the criteria of being resistant to treatment, and a control group of healthy individuals. The lowest GABA concentrations were identified in patients with treatment-resistant MDD.[89]

Transcranial magnetic stimulation has become a treatment modality for treatment-resistant MDD. It is based on the activation of cortical neurons with pulsatile magnetic fields and relies on GABAergic inhibition measured with two variables: short-interval cortical inhibition (SICI) and the cortical silent period (CSP). SICI is assessed by delivery to the motor cortex of an initial subthreshold conditioning stimulus followed by a suprathreshold test stimulus. Inhibitory GABAergic interneurons are activated when the interval between the two stimuli is between 1 and 5 ms, which is an expression of $GABA_A$-mediated inhibitory activity,[90] whereas the CSP measures $GABA_B$ activity.[91]

Findings from several studies have suggested that GABAergic activity is decreased in MDD, evidenced by shorter SICI and CSP.[92–94] Decreased cortical inhibition was reported in one study of 35 patients with MDD and 35 healthy control individuals; shorter SICI and CSP were found in the left hemisphere of psychiatric patients than in the left hemisphere of control individuals.[93] Data from another study suggested that loss of $GABA_A$ inhibitory effect is more likely to occur in patients with treatment-resistant MDD.[94] This study included 85 participants: 25 with treatment-resistant MDD, 16 with MDD but who had not been on drug treatment for at least 1 month, 19 who had fully recovered from a major depressive episode on psychotropic drugs, and 25 healthy control individuals. Compared with healthy control individuals, the three patient groups had lower CSP measurement, but abnormal SICI was only found in patients with treatment-resistant MDD.[94]

Immunological abnormalities

Proinflammatory cytokines, in particular interleukin-1β (IL-1β), IL-2 IL-6, interferon-γ, and tumour necrosis factor-α (TNFα), have been identified as pathogenic mechanisms in animal models of depression and in clinical studies in patients with mood disorders.[95] Among these, IL-1β, has proconvulsant properties. For example, seizures triggered in rats with kainic acid and bicuculline are exacerbated with intracerebral injection of IL-1β,[96] while administration of its naturally occurring antagonist (IL-1RA) has anticonvulsant activity.[97] Furthermore, IL-1β, its receptor type 1 (IL-1R1), and IL-IRA were upregulated in the brains of rats that underwent electrically and chemically induced seizures,[98] and all three were over-expressed in the brains of patients with temporal lobe epilepsy, cortical dysplasias, and tuberous sclerosis.[99–101]

The mechanisms responsible for IL-1β proconvulsant properties involve a reduction in glutamate uptake by glial cells or an enhanced release of glutamate from these cells, mediated by TNFα.[102,103] Other suggested mechanisms are thought to be mediated through IL-1R1 activation of neuronal sphingomyelinase and Scr kinases, which also result in increased glutamatergic activation.[104]

Other potential mechanisms

Do antidepressants have antiepileptic properties?

The therapeutic pharmacodynamic effects of antidepressant drugs are based on an increase in CNS serotonergic, norepinephrinergic, or dopaminergic activity, or a combination thereof. By the same token, drugs that increase extracellular serotonin and norepinephrine, such as 5-hydroxytryptophan, SSRIs, and tricyclic antidepressants, have inhibited focal and generalised seizures in animal models of epilepsy.[105–107] For example, in two strains (3 and 9) of the genetically epilepsy-prone rat (GEPR), compounds that interfere with the synthesis or release of norepinephrine (eg, reserpine and tetrabenazine, which inactivate norepinephrine storage vesicles; α-methyl-m-tyrosine, a false norepinephrine transmitter; and α-methyl-□-tyrosine, a norepinephrine synthesis inhibitor) or serotonin (□-chlorophenylalanine, a serotonin synthesis inhibitor) cause a worsening of seizures in both strains.[26,27,56] Conversely, treatment with norepinephrinergic (desipramine) and serotonergic drugs (SSRIs, such as fluoxetine, citalopram, and sertraline) blocked seizures.[26] Furthermore, increase of extracellular serotonin in the GEPR (measured by microdialysis) contributes to the anticonvulsant effects of AEDs including phenytoin, carbamazepine, valproate, lamotrigine, and zonisamide.[108–110] Similar anticonvulsant effects of serotonergic and norepinephrinergic drugs have been reported in other animal models, including non-genetic animal models in the rat, rabbit, cat, and monkey.[29,30,111,112] Findings from open-label trials with SSRIs have shown an improvement in seizure frequency in patients with treatment-resistant epilepsy,[113–115] but these data need to be replicated in double-blind randomised placebo-controlled trials.

Alternative psychiatric episodes or forced normalisation

This phenomenon is another example of the close and complex relation between psychiatric disorders and epilepsy and consists of an inverse relation between seizure remission, after a long history of poorly controlled epilepsy, and the development shortly after of de-novo psychopathology.[116,117] It was first reported in 1953 by Landoldt,[18] who described the development of de-novo psychotic episodes in patients with intractable epilepsy whose seizures suddenly remitted and whose electroencephalogram recordings normalised; hence the term forced normalisation. Forced normalisation is rare, with a prevalence of less than 1% reported in a study of 611 consecutive patients,[118] and has been identified in patients with focal and generalised epilepsy. Although most reports have focused on the development of psychotic episodes, forced normalisation can present as non-psychotic episodes, including depressive, manic, and anxiety, and conversive episodes, which accounted for about half of the cases in one study of 44 occurrences of forced normalisation in 36 patients.[119] However, the actual prevalence of non-psychotic episodes remains unknown, because more often than not they are not recognised. The pathogenic mechanisms that are operant in forced normalisation remain unknown. Forced normalisation has been associated with seizure remission resulting from various AEDs, including ethosuximide, topiramate, vigabatrin, and levetiracetam, as well as epilepsy surgery and vagal nerve stimulation.[120]

Conclusion

In this Review, we present data that establish an association between a lifetime history of psychiatric disorders (and in particular mood disorders) and an increased risk of epilepsy. Furthermore, psychiatric comorbidities have been associated with a worse response to treatment. The neurobiological pathogenic mechanisms of depressive disorders reviewed here seem to enhance cortical hyperexcitability or facilitate the epileptogenic process, or both, in experimental studies. Although data from clinical studies done in patients with mood disorders are supportive of the validity of animal data, no studies have been undertaken to prove that these are the actual pathogenic mechanisms mediating the increased risk of epileptic seizures or treatment-resistant epilepsy in depressed patients. Conversely, these data provide proof of principle to undertake experimental and prospective clinical research studies to identify which of and how these pathogenic mechanisms contribute to the bidirectional relation between epilepsy and depressive disorders. However, one can never exclude the possibility of an unrecognised partial seizure disorder, presenting with simple or complex partial seizures, or both, which can lead to the development of a mood disorder that is recognised before the first identified epileptic seizure. Over time, the untreated seizure disorder might facilitate the development of treatment-resistant epilepsy.

Search strategy and selection criteria

We did a search for original research and review articles in English, French, and Spanish through computerised searches of Medline, Embase, and Web of Science, with no date limits set. We identified epidemiological studies of comorbid psychiatric disorders in epilepsy. Next, we searched for studies of animal models of depression, with a special focus on pathogenic mechanisms that are known to occur in the epileptogenic process (eg, kindling) or that have been identified as playing a pivotal part in animal models of epilepsy or in epilepsy in human beings.

The effect of psychiatric variables on seizure disorders is limited, because most patients with a lifetime history of a psychiatric disorder do not develop epilepsy. One important question is whether the neuropathological and neurochemical abnormalities caused by the psychiatric disorder make several neuroanatomical structures more vulnerable to endogenous or exogenous insults, which in turn might facilitate the development of the seizure disorder. This hypothesis can be tested, for example, in prospective studies of patients with new-onset epilepsy in whom some or all of the following independent variables can be obtained before the start of AED treatment: (1) a lifetime psychiatric history and a family psychiatric history (which is a significant risk factor for psychopathology); (2) a dexamethasone suppression test; (3) measurement of IL-1β, 1IL-R1, and IL-1RA; (4) high-resolution brain MRI with volumetric measurements of mesial temporal and frontal lobe structures and voxel based morphometric analyses; and (5) magnetic resonance spectroscopy studies of the brain with measurement of cortical glutamate and GABA signals. Seizure-freedom versus treatment-resistant epilepsy would be the dependent variables.

Space limitations precluded inclusion of all the known neurobiological pathogenic mechanisms of depressive disorders that have proconvulsant potential (eg, corticotropin releasing factor, dopamine, and galanin). However, this Review does highlight the role of two potential common pathogenic mechanisms, glutamate and GABA, in depressive disorders.

The data presented in this Review emphasise the need for early recognition and treatment of comorbid psychiatric disorders by any clinician treating people with epilepsy. However, whether early and successful treatment of a first major depressive episode prevents an increased risk of developing epilepsy has not been investigated. Future research will hopefully provide answers to this complex problem.

Conflicts of interest

I declare that I have no conflicts of interest.

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