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ARTICLE

Pathophysiology of mood disorders in temporal lobe epilepsy

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Abstract
Objective: There is accumulating evidence that the limbic system is pathologically involved in cases of psychiatric comorbidities in temporal lobe epilepsy (TLE) patients. Our objective was to develop a conceptual framework describing how neuropathological, neurochemical and electrophysiological aspects might contribute to the development of psychiatric symptoms in TLE and the putative neurobiological mechanisms that cause mood disorders in this patient subgroup. *Methods:* In this review, clinical, experimental and neuropathological findings, as well as neurochemical features of the limbic system were examined together to enhance our understanding of the association between TLE and psychiatric comorbidities. Finally, the value of animal models in epilepsy and mood disorders was discussed. *Conclusions:* TLE and psychiatric symptoms coexist more frequently than chance would predict. Alterations and neurotransmission disturbance among critical anatomical networks, and impaired or aberrant plastic changes might predispose patients with TLE to mood disorders. Clinical and experimental studies of the effects of seizures on behavior and electrophysiological patterns may offer a model of how limbic seizures increase the vulnerability of TLE patients to precipitants of psychiatric symptoms.

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Early observations and clinical aspects

Association between epilepsy and depression has been observed for over 2,400 years. As reviewed by Kanner,[1] Hippocrates stated that "*Melancholics ordinarily become epileptics, and epileptics, melancholics: what determines the preference is the direction the malady takes; if it bears upon the body, epilepsy, if upon the intelligence, melancholy*". Studies published during the second half of the XIX century also recognized that patients with epilepsy often presented with depressed mood, languidness, misanthropy and suicidal tendency.[2] Depression is generally defined by the presence of certain behaviors and thought patterns. Some of the major symptoms include low mood, reduced interest or pleasure in all activities, appetite changes, insomnia or hypersomnia, psychomotor agitation or retardation, fatigue or loss of energy, worthlessness or excessive guilt, reduced ability to think or concentrate and frequent morbid thought of death or suicidal ideation.[3] Depressive symptoms are often poorly recognized, and inadequate treatment might lead to a significantly impaired quality of life.[4]

In present numbers, the prevalence of depression in patients with recurrent seizures ranges from 20% to 80%.[5,6] The phenomenology of depression in epilepsy is a matter of debate. The most frequent symptoms include feelings of anhedonia, guilt and suicidal ideation. Other authors also report high anxiety, neuroticism, hostility, feelings of depersonalization, and rare manic and depressive-psychotic manifestations.[2] Presentation of depressive symptoms in epilepsy is often milder than in major depression,[7,8] but they are source of significant disruption in patients' daily activities, social relations, quality of life and require pharmacologic therapy to remit.[5] Depressive symptoms in epilepsy can be classified in 3 categories: (I) major depressive disorder, meeting Diagnostic and Statistical Manual, 4th edition (DSM-IV) diagnostic criteria; (II) atypical depression or dysthymia; or (III) a dysthymic-like disorder with intermittent symptoms that can be milder than those of major depression.[6] According to their temporal relationship with seizures, depressive symptoms can be ictal, peri-ictal or interictal, the latest being the most frequent.[5]

Until mid-XX century, depression in epilepsy was thought to be mostly of the "reactive" type,[9-11] in which depressive symptoms may be a reaction to stresses in life, including the effect of any underlying conditions. Indeed, as emphasized by Robertson and Trimble,[2] influential events such as "(...) repeated distressing episodes of loss of consciousness leading to morbidity, loss of self-esteem, and, often, personal embarrassment. The difficulty of getting a job, the social stigmatization, and the recurrent loss of dignity that the epileptic patient faces must be important provoking factors for the ensuing depression". However, studies from the last two decades have demonstrated biochemical, neuropathological and neurophysiologic changes mediating the development of mood disorders,[10] meaning that it is more usual for depression in epilepsy to be of the "endogenous" type.[12,13] As noted by Kanner *et al.*,[14] depression in epilepsy is often a combination of intrinsic and extrinsic processes that act synergistically.

In the late 1970's, Rodin *et al.* reported that patients with temporal lobe epilepsy (TLE) showed higher depression scores than patients with other types of epilepsy.[15] A few years later, a similar study suggested that patients with complex partial seizures that secondarily generalized had worse scores when compared with those with primarily generalized convulsive seizures.[16] Regarding seizure type, other studies have shown that depression is more frequent in patients with non-epileptic seizures than in those with epileptic seizures.[17] In pediatric patients, depression is also more frequent in cases with focal complex partial seizures than in patients with primarily generalized seizures.[18] Although seizure frequency or intractability[19] might not be related to the severity of depression, it is known that seizure type,[8,18] duration of epilepsy and antiepileptic drugs[8] are related to different levels of depressive symptomatology. By the same token, it has been recently found that the presence of secondarily generalized seizures is more frequent in adult mesial TLE patients with psychiatric comorbidities than in mesial TLE patients without psychiatric symptoms.[20] In fact, patients with mesial TLE seem particularly prone to comorbid depression.[21]

Atypical features may affect 20%[22] to 70%[23] of patients with depressive symptoms. In 1923, Kraepelin described a pleomorphic affective disorder in epilepsy, coined by Blumer et al.[24] "interictal dysphoric disorder", characterized by labile depressive symptoms (depressive mood, lack of energy, pain, insomnia), labile affective symptoms (fear, anxiety), and the presence of irritability and outbursts of aggressive/euphoric behavior as key symptoms. The prevalence of interictal dysphoria in TLE is about 17%.[25] Dysphoria is considered a psychopathological entity closer related to bipolar rather than unipolar mood disorders. In fact, one of the most famous historic figures presenting six of the seven cardinal symptoms of interictal dysphoric disorder was Vincent van Gogh,[26] who also exhibited signs of interictal personality.[27] Dysphoric symptoms may also occur in patients with chronic diseases other than TLE - such as migraine and different focal epilepsies[25,28] - as well as in premenstrual dysphoria.[29] Despite the high frequency of interictal dysphoria in epilepsy cases, classic bipolar disorder (type I) is rare,[8] ranging up to 1.4%.[30] Bipolar symptoms tend to be milder in patients with epilepsy than in pure bipolar patients, which often present fluctuating mood disturbances, rapid cycling of mood episodes and more frequent hallucinations.[31]

In addition to mood disorders, personality disorders other than the commonest interictal type[27] are also frequent in patients with epilepsy. In a series of TLE patients with hippocampal sclerosis from our epilepsy surgery center, 41.4% presented at least one Axis I diagnosis, according to DSM-IV criteria.[32] The majority (19.4%) had depression, 10.7% psychosis, 5.9% interictal dysphoric disorder, and 5.4% anxiety disorders. Personality disorders (Axis II) occurred in 12.4% of the patients, and, in some cases, overlapped with Axis I diagnosis. Most frequent traits were borderline, histrionic, epileptic personality disorder, antisocial, narcissistic, schizoid, and passive-aggressive personality.[32] Predominance of DSM-IV cluster A (paranoid, schizotypal, schizoid) and B (borderline, histrionic, antisocial, narcissistic), over cluster C personality disorders (avoidant, dependent, obsessive-compulsive) may indicate presence of non-epileptic seizures.[33] Other authors also reported high incidence of dependent-childish behavior[31] and deficits in social cognition.[34] Considering the type of epilepsy, patients with juvenile myoclonic epilepsy are more impulsive than

non-epileptic controls,[35] and adult patients with epileptic seizures present higher scores of schizoid, antisocial, histrionic, avoidant, dependent, passive aggressive and depressive traits compared to controls.[36] Also, a higher proportion of patients with epileptic seizures and personality disorders fits within DSM-IV cluster C when compared to patients with non-epileptic seizures.[33] Interestingly, schizoid, obsessive-compulsive and avoidance traits are correlated with epilepsy duration, but not with anxiety or depression presence.[36] Depersonalization and derealization traits are more frequent in patients with non-epileptic seizures than on those with epileptic seizures.[37] Several data suggest that epilepsy is not a primary pathophysiologic mechanism for developing dissociative symptoms[38,39] and that the presence of anxiety and depression is an important factor.[40] On the other hand, several data since Hughlings Jackson's in the late XIX century have found similarities between the so-called dreamy states or experiential phenomena[41] and behaviors redolent of depersonalization.[42]

Suicide is more common in people with epilepsy than in the general population, and the mortality ratio is further raised in those with TLE and those treated surgically.[43] Risk factors for suicide include: presence of mood disorders (depression and bipolar disorder) and other psychiatric disorders (for example schizophrenia-like psychosis), personality disorders (specially borderline personality disorder), substance abuse, self-destructive behavior, previous suicide attempts, chronic illness, stigmatization of epilepsy, periictal suicidal impulses and pharmacological treatment.[44] In a large study of more than ten thousand patients with epilepsy, five suicides were registered during a 12-year period and all occurred in patients with long-standing complex partial seizures and dysphoric disorder a short time after achieving full control of seizures.[45] In electroconvulsive treatment (ECT), controlled seizures can be elicited by a bifronto-temporal stimulus above the threshold for a generalized tonic-clonic seizure. Furthermore, most patients with endogenous depression who receive ECT recover completely or improve considerably.[46] Could chronic seizures also have a protective effect in comorbid endogenous depression cases, similar to what is seen in forced normalization? Landolt's early observations included dysphoric disorders on normalization of the electroencephalogram,[47] and the emergence or worsening of psychopathology on suppression of seizure activity has been widely reported.[45] As summarized by Blumer *et al.*,[45] when seizures are decreased or controlled, dysphoric symptoms, depressive mood and psychosis tend to be exacerbated, but the precise nature of the seizure-suppressing mechanisms is insufficiently understood.

Comorbidity does not necessarily imply causality; quoting Gabb et al.,[48] "(...) epilepsy begets depression, but does depression beget epilepsy?" Supporting the idea, a history of depression preceding the onset of epilepsy is up to six times more frequent in patients than in controls.[49,50] Such cases would fit within the endogenous depression type, and suggest the possibility of common pathogenic mechanisms operant in both disorders.[14] Possible neuropathological, neurochemical and electrophysiological mechanisms will be explored in the next sections.

Neuropathological aspects

In a series of one hundred patients with temporal lobe lesions (tumors, atrophy or cryptogenic), ninety-five had paroxysmal psychiatric manifestations such as hallucinations, perceptual illusions, disturbances of emotion or mood, personality disorders (mostly schizoid traits) and automatisms.[11] The predominant mood disorders were depression and anxiety, the latter resembling dysphoric features. Indeed, presence of mesial temporal sclerosis has been considered a predisposing factor for the development of mood disorders in focal epilepsy.[21] Although temporal lobe involvement seems unequivocal in depression manifestation,[51] paralimbic structures such as temporal and prefrontal cortex are also compromised.[52,53] Focal hypometabolism in ipsilateral orbitofrontal cortex is usually found in TLE patients with depression when compared with TLE patients without depression; after epilepsy surgery, patients in whom depression developed only postoperatively also show hypometabolism in the ipsilateral orbitofrontal region.[52] Interestingly, Rajkowska et al.[54] have previously demonstrated significant decrease in cortical thickness, neuronal sizes and neuronal and glial densities within the orbitofrontal cortex of pure depressed patients.

Monoaminergic neurotransmission is classically related with major depression, mostly because the mechanism of action of antidepressant drugs that augments these neurotransmitters in the synapses.[55] Positron-emission tomography (PET) imaging studies have shown reduced binding of serotonin (5-HT) receptor 1A in frontal, temporal and limbic cortex[56] and in the raphe[57] in depressive patients when compared with controls. A deficit in the density of postsynaptic serotonergic receptors also has been identified in the hippocampus and amygdala of patients who committed suicide.[58] Furthermore, impaired serotonin transmission, consisting of an excessive density of serotonergic somatodendritic 5-HT_{1A} autoreceptors in the dorsal raphe has been found in suicide victims with major depression.[59] Similar 5-HT alterations are found in TLE patients. A PET study using a 5-HT_{1A} receptor antagonist showed reduced affinity in mesial temporal structures ipsilateral to the seizure focus in TLE patients with and without hippocampal atrophy.[60] Reduction in 5-HT_{1A} binding was also found in the raphe nucleus and in ipsilateral thalamic regions.[60] Another study investigating TLE patients found decreased affinity of 5-HT_{1A} in the epileptogenic hippocampus, amygdala, anterior cingulate, and lateral temporal neocortex ipsilateral to the seizure focus, as well as in the contralateral hippocampus.[61] Studies conducted in TLE patients with comorbid depression also indicate abnormalities in serotonergic neurotransmission. 5-HT_{1A} receptor binding in TLE patients with major depression show decreased signal when compared with TLE patients without depression, independent of the side of the lesion and the degree of hippocampal sclerosis.[62] Another PET study found an inverse correlation between the severity of depressive symptoms and the affinity of 5-HT_{1A} binding in the ipsilateral hippocampus, and a positive correlation between the severity of depressive symptoms and the magnitude of hippocampal abnormalities.[63]

Brain regions involved in both TLE and depression include the temporal lobes with hippocampus, amygdala, entorhinal and temporal cortex, the frontal lobes, subcortical structures such as basal ganglia and thalamus, and the connecting pathways.[64] Neuropathological data on TLE and comorbid

depression are scant. Recent data suggest that there is a structural basis for psychiatric symptoms in patients with TLE. There is evidence of N-Methyl-D-aspartate (NMDA) receptor subunit NR1 up-regulation in the dentate gyrus molecular layer in unmedicated TLE patients with depressed mood when compared to TLE patients without psychiatric comorbidities.[65] In addition to that, in our series of hippocampi from mesial TLE patients with depression we found CA4 neuronal density as high as in non-epileptic controls, and increased mossy fiber sprouting when compared with mesial TLE patients without psychiatric history.[20] Although antidepressant treatment does not cause mossy fiber sprouting, chronic administration of fluoxetine causes robust changes in the serotonergic modulation of the mossy fiber synaptic transmission in mice.[66] Serotonin is able to potentiate the mossy fiber synaptic transmission, and chronic fluoxetine reduces the synaptic potentiation induced by higher concentrations of serotonin; meanwhile, low concentrations of serotonin might enhance synaptic potentiation, which represent the stabilization of the serotonergic modulation.[67] In mesial TLE with depression, enhanced mossy fiber sprouting might act as a protection against depressive symptoms, or conversely, the increased sprouting could represent an insufficient compensatory response to the chronic or subsequent stress provoked by depressive episodes.[20] Further cellular physiological studies in animal models would be important in order to clarify the involvement of the dentate gyrus and mossy fibers in psychiatric disorders, since the clinical significance of sprouting remains to be elucidated.[67]

In the last two decades, several neuropathological studies have been done with *post-mortem* brain samples from patients with major depression, especially in fronto-limbic regions. Gross morphological changes such as focal lesions are not present in depression (as usually found in TLE – for review see [68]), but cytomorphological differences between depressed and control subjects can be demonstrated at the microscopic level.[69] Reduced glial density in depressive disorder is found in prefrontal cortex,[54] entorhinal cortex and amygdale.[70] In fact, amygdalar glial reduction seems pathognomonic, and mostly related to astrocytes[71] or oligodendrocytes.[72] The cortical regions where neuronal pathology has been detected include the hippocampus, orbitofrontal, prefrontal and cingulate cortex, without clear definition whether a true loss of cells underlies reductions in cell density and size.[69] Other evidences of neuronal pathology comprise reductions in the precursor form of brain-derived neurotrophic factor (BDNF) in the hippocampus of specimens with major depression,[73] although treatment with antidepressants may increase hippocampal BDNF protein expression.[74] In the prefrontal cortex, reduced glutamic acid decarboxylase (GAD) expression is seen in unmedicated patients with major depression, but not in antidepressant medicated patients.[75] There is similar gamma-aminobutyric acid (GABA) depletion assessed through calcium-binding proteins staining in prefrontal interneurons,[76] and possible diminished local serotonin release in subjects with major depression.[59] In agreement with those findings, the use of GABA agonists and antagonists is able to modulate depressive symptoms, and chronic administration of antidepressant drugs induce marked changes in GABAergic function.[77] Furthermore, several anticonvulsant and GABA-mimetic agents possess mood stabilizing and antidepressant properties.[77,78] Patients with TLE show decreased expression of glutamate transporters in the dentate gyrus,[79] as well as patients with major depressive disorder in the frontal brain regions, striatum and hippocampus, leading to increased glutamatergic neurotransmission.[80,81] Hasler et al. showed that levels of glutamate/glutamine and GABA were decreased in prefrontal dorsomedial and ventromedial regions of patients with major depression.[82] Imaging studies have also shown a decrease in glutamate in the anterior cingulate cortex of adults[83] and children[84] with depression. In unmedicated adults with depressive disorder, decreased GABA levels and synthesis in dorsomedial, dorsalanterolateral prefrontal, and ventromedial prefrontal regions and occipital regions were found.[78,85] In addition, treatment with the NMDA antagonist ketamine has shown improvement of depressive symptoms in patients with major depression, and in patients with treatment-resistant major depression.[86,87]

Imaging studies in bipolar disorder have shown increased amygdala, hippocampus and temporal lobe volume in bipolar patients when compared to schizophrenics, and the amygdala in bipolar cases is actually larger than in normal subjects.[88] Such increase in volume is controversial, since no changes in neuronal or glial densities are seen in amygdala specimens of patients with bipolar disorder.[71] In the hippocampus, nonpyramidal neuronal density is significantly decreased in CA2 of bipolar patients compared to control subjects, with no other differences in the pyramidal or nonpyramidal neurons throughout the Ammon's horn between any groups.[89] In the entorhinal cortex, decreased vesicular glutamate transporter 1 mRNA expression is found, but not in the hippocampus or temporal cortex.[90] Other studies have also reported decreased neuronal and glial density in the prefrontal cortex of bipolar specimens, as well as enlargement of layer III interneuronal neuropil.[91] In interictal dysphoric disorder, normal magnetic resonance imaging and normal electroencephalogram is found in the majority of cases.[28] Based on what is known about bipolar cases and on TLE with psychiatric comorbidities, it would be expected neuropathological changes underlying interictal dysphoria, whereas no answer to this hypothesis is available up to now.

Evidences from animal models

One of the first described TLE models was electrical kindling, which is characterized by the sustained increase in seizure susceptibility and the absence or minimal extent of neuronal injury, as well as the absence of spontaneous recurrent seizures when the number of kindled seizures is low.[92,93] However, spontaneous motor seizures may appear after sufficient electrical stimulation (*e.g.* ranging from 88 to 293 stimuli in amygdala kindling).[94,95] Systemic[96] or intracerebral[97] administration of pilocarpine or kainate in rodents leads to a pattern of repetitive limbic seizures and *status epilepticus* (SE), which can last for several hours.[98] Neuropathological changes - such as neuron loss - in several hippocampal subfields and reorganization of mossy fibers into the molecular layer of the fascia dentata are observed in both models and are similar to hippocampi from patients with hippocampal sclerosis.[98]

One of the challenges associated with understanding mechanisms of depression in epilepsy has been the lack of validated animal models of this condition.[99] So far, studies

that attempted to develop valuable animal models of comorbidity between epilepsy and depression focused on behavioral alterations in animal models of epilepsy classically linked to depression. As already mentioned, two of the major symptoms in depression are despair and anhedonia. In rodents, the behavioral equivalents to these emotional states are accessed by two classical tests: the forced swim test and the saccharin or sucrose taste preference test. The forced swim test relies in the adaptive behavior of rodents when confronting a stressful situation. Basically, rodents exhibit two patterns of behavior: active escaping and/or exploring behavior or immobility, when their movements are limited to those necessary to keep their heads above the water. An increase in immobility time is regarded and related to the degree of despair. The taste preference evaluates the hedonic state measuring rodent's natural preference for sweets: when given access to tap water and sweet solution they strongly prefer the latter. However, animals submitted to experimental stress have a decrease in consumption of the sweet solution, indicating an alteration of underlying reward mechanisms.[100]

Several studies have shown that rats submitted to SE induced by lithium-pilocarpine, kainate or electrical kindling spent a significantly longer time immobile in the forced swim test and exhibited loss of preference for saccharin solution when compared to non-epileptic animals,[101-105] indicating that rats submitted to seizures show an increase in depressive behavior. Although immobility time is increased in post-SE rats, severity of behavioral, endocrine and biochemical hallmarks of depression seem independent of seizure frequency,[105] similarly to what occurs in humans.[19] However, there is a positive correlation between severity of depression and hippocampal hyperexcitability, suggesting that depressive symptoms may be a net result of limbic dysfunction.[106]

Nevertheless, other studies using pharmacological models of epilepsy were unable to replicate these data. Recent experimental studies have shown that mice submitted to SE induced by pilocarpine, lithium-pilocarpine, focal kainate administration or kindling showed decrease in depression-like behavior.[107-110] Results from our laboratory also indicate that rats submitted to SE induced by lithium-pilocarpine do not present depressive behavior in the forced swim test and in the learned helplessness paradigm during the silent phase of epileptogenesis (unpublished results). These discrepancies can be the result of differences in the protocol used, mainly, (1) rodent's age at the time of the SE induction; (2) time after SE and frequency of recurrent spontaneous seizures; (3) used species and gender.

Although there are still controversies if animal models of epilepsy can present with behavioral alterations related to depressive symptoms, there is evidence about shared mechanisms. The genetic absence of epilepsy in rats from Strasbourg (GAERS) show depressive and anxiety-like behavior before the onset of seizures, indicating that common biological alterations could be underlying the two neurological conditions.[111] Ferrero et al.[112] showed that chronic treatment with fluoxetine enhances seizure threshold and the basal glutamate release. Interestingly, when rats are submitted to the learned helplessness paradigm, there is no effect of fluoxetine in seizure threshold or glutamate release.[112] In fact, rats bred for susceptibility to depression-like phenotypes present higher mortality than non-depressive rats after SE induction by kainate.[113] Also, rats that spent more time immobile in the forced swim test show faster and more intense hippocampal kindling.[114] Evidences also link stress with seizure susceptibility. Rats treated with corticosterone supplementation are more sensitive to epileptogenesis in the amygdala kindling model of TLE.[115] Also, the genetic model of epilepsy Wistar audiogenic rats (WAR)[116] has increased adrenal gland hyperplasia associated with enhanced pituitary and adrenal responsiveness after hypothalamic-pituitary-adrenal (HPA) axis stimulation.[117] Besides HPA hyperactivity, WARs also display hypertension, tachycardia and increased sympathetic tone[118] as well as a pattern of endogenous anxiety revealed by decreased exploration in both the open arms of the elevated plus maze and in the open field.[119] Thus, the WARs are currently being explored as a genetically developed strain with epilepsy and a variety of neuropsychiatric comorbidities.

Neurotransmitter systems altered in epilepsy and mood disorders

Several experimental cues from the common neurobiological alterations between epilepsy and comorbid depression came from the genetic epilepsy prone rat (GEPR). GRPR-3 and GEPR-9 strains have predisposition to sound-induced generalized seizures and marked kindling acceleration. They also present depressive behavior manifested by decreased sucrose consumption and increased immobility time in the forced swim test.[120] Moreover, GEPR exhibit endocrine alterations - such as increased corticosterone serum levels, deficient secretion of growth hormone, and hypothyroidism[121] - in accordance to what is found in depressive patients, such as elevated concentrations of circulating cortisol and corticotrophin.[122] In addition to that, GRPR-3 and GEPR-9 strains are marked by noradrenaline and 5-HT neurotransmission deficits, resulting from impaired arborization of noradrenergic and serotonergic neurons arising in the locus coeruleus and raphe nuclei.[123] Likewise, substances that interfere with synthesis or release of noradrenaline or 5-HT have been found to accentuate seizures,[121] and an increase in noradrenergic or serotonergic neurotransmission might prevent seizures.[124-128]

Disturbances in glutamate and GABA

The excitatory and inhibitory misbalance in epilepsy is known for a long time.[64] However, only recently the involvement of GABA and glutamate was recognized in depressive disorders.[129] There is evident relation between glutamatergic and monoaminergic neurotransmission. Glutamatergic neurons projects from the cortex to monoaminergic subcortical nuclei like locus coeruleus, raphe nucleus, and substantia nigra.[129] Also, drugs that augment noradrenaline and 5-HT usually decreases glutamate response.[130,131]

In a recent review, Kanner proposes three lines of evidence that support a pathogenic role of glutamate and GABA in depression: (1) dysfunction of glutamate transporter proteins; (2) abnormal concentrations of cortical glutamate and GABA; and (3) antidepressant effects of glutamate receptor antagonists.[129] Glutamate transporters are important to maintain low excitatory extracellular glutamate's levels and consequently regulate the synaptic concentration. Experimental studies have shown reduced expression of

glutamate transporters excitatory amino acid transporters in animal models of depression.[132,133] Also, decreased function of glutamate transporters are related to elevated extracellular glutamate levels, neuronal death, and epilepsy.[134]

The role of the excitatory/inhibitory neurotransmission in mood disorders is strengthened by the antidepressant effects of several glutamate antagonists. NMDA and metabotropic glutamate receptor antagonists (including MK-801, ketamine, mGluR5 antagonist 2-methyl-6-(phenylethynyl)-pyridine (MPEP), and the mGluR2/3 antagonists LY341495 and MGS0039) have antidepressant activity in the forced swim test, tail suspension test and learned helplessness models of depression.[132,135]

Deregulation of Hypothalamus-Pituitary-Adrenal (HPA)

Deregulation of the HPA system is a central feature of depressive disorders. Briefly, hypothalamus secretion of corticotropin-releasing factor (CRF) stimulates synthesis and release of pituitary gland adrenocorticotropin. In turn, the latter stimulates adrenal cortex to secrete glucocorticoids. These hormones are central to successfully coping with a major physical stressor, as they mobilize stored energy, increase cardiovascular tone, and suppress costly anabolism. HPA deregulation occurs when failures in the negative-feedback that controls the level of circulating glucocorticoid are present.[136] Several brain structures regulate this activity, including the hippocampus, which has inhibitory influence on hypothalamic CRF-containing neurons, while the amygdala exert excitatory control.[137] A neurotoxic role for augmented glucocorticoids has been extensively described in experimental data. High levels of glucocorticoids leads to injury of synapses,[138,139] particularly involving CA3 pyramidal neurons, reduction of dendritic branching and spines that are part of glutamatergic synaptic inputs,[136] decrease in BDNF levels, and interference with neurogenesis of granule cells in the adult hippocampal dentate gyrus.[140] All of these effects result in structural changes in the dentate gyrus, pyramidal cell layer of hippocampus, amygdala, and temporal neocortex.[70,140,141] In the frontal lobes, high corticosteroid secretion has been associated with a decrease in glial cell numbers in subgenual, cingulated, and dorsolateral sections of the prefrontal cortex.[54,142-146]

Neuronal alterations are also associated with the development of mood and anxiety disorders.[147] Patients with major depressive disorder exhibit alterations that are linked with hyperactive HPA such as atrophy of hippocampi, and frontal lobes, including cingulate gyrus and orbitofrontal and dorsolateral cortex demonstrated by multiple investigators.[148-150] In fact, neuropathologic consequences attributed to excessive cortisol include: (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.[54,142-146]

Furthermore, enhanced glucocorticoids levels can be involved in the disruption of raphe-hippocampal serotonergic transmission found in depressive patients. It's proposed that a mechanism involved in the regulation of 5-HT neurotransmission from raphe, involves somatodendritic 5-HT_{1A} autoreceptors.[99] The activation of raphe 5-HT_{1A} autoreceptors by locally released serotonin inhibits firing of serotonergic neurons and further neurotransmitter release.[151] Clinical and experimental data have suggested that glucocorticoids can cause an up-regulation of 5-HT_{1A} in raphe, therefore, leading to an enhanced autoinhibition of 5-HT.[59,152] So in chronic stress conditions like depression or after SE it is possible that the elevated corticosteroid levels could lead to reduced 5-HT neurotransmission.[99]

Recently, abnormal functioning of HPA comparable to those found in depressive patients has been demonstrated in humans with TLE without depressive disorders[149] as well as in animal models of epilepsy.[104] Again, using the lithium-pilocarpine model, Mazaratti group showed an increase in corticosteroid serum levels in SE rats that is correlated with depressive-like behavior and raphe-hippocampal serotonergic deficit. Furthermore, local raphe treatment with glucocorticoid receptor blocker reversed both enhanced immobility time in the forced swim test and raphe-hippocampal serotonin deficit hallmarks of depression.[104] As cited before, corticosteroid treatment can accelerate amygdala kindling and this process is inhibited by corticosteroid antagonists.[111,153] This mechanism may also be involved in depression associated with epilepsy: in TLE patients with concurrent depression, binding affinity of raphe 5-HT_{1A} receptors is increased, and positively correlated with the severity of clinical symptoms of depression.[154]

Exacerbated HPA function promoted by chronic stress is related with decrease in 5-HT_{1A} mRNA expression and binding in the hippocampus, an effect prevented by tricyclic antidepressants.[155] 5HT_{1A} receptor binding and its mRNA expression are under tonic inhibition by glucocorticoid receptor stimulation. Accordingly, high levels of corticosteroid could underlie the reduced 5-HT_{1A} receptor binding seen in patients with depression.[129]

Furthermore, increased corticosteroid concentrations are associated with decreased levels of BDNF. BDNF is related with plasticity and survival of adult neurons and glia;[156] and reduced BDNF levels might contribute to hippocampal injury. This deficiency is ameliorated by antidepressant treatment and is related to treatment efficacy. Administration of antidepressant drugs increases BDNF expression in several brain structures.[74,157,158] Also, BDNF administration produces anti-depressant effects in rats.[141,159] However, TLE patients have an increased BDNF expression that might either act as a neuroprotector factor promoting cell survival or contribute to modifications in neuronal circuitries related to epileptogenesis.[160]

Hippocampal neuroinflammation is another possible common pathological mechanism in TLE and depression. Interleukin-1 beta (IL-1ß) signaling could be underlying these alterations.[99] Clinical and experimental studies have linked increased IL-1ß and its receptor activation as a feature of TLE.[161] Also, IL-1ß can induce activation of HPA axis and facilitate depressive symptoms.[162] In fact, 2-week intrahippocampal administration of an IL-1ß antagonist reduced the biochemical, endocrine and behavioral features of depression

but had no effect in frequency of spontaneous seizures in lithium-pilocarpine SE model.[106]

Synaptic plasticity

Neural plasticity is a key feature in a mammal's brain that could sustain changes in organization and functional dynamics of nervous tissue allowing adaptive behavior to different ecological demands.[163] In accordance, experience can modify brain activity including maladaptive plasticity in response to brain injury. A number of studies have connected neural plasticity with the pathophysiology of mental disorders like epilepsy, mood disorders and schizophrenia. Current theories hypothesize that neuroplastic alterations during development may contribute to structural and functional changes in important circuits, which can have long-lasting effects on adult brain function.[164]

A decrease in plasticity is related to an increase of the threshold for adaptation[165] making the individual more vulnerable to negative input[166]. Reduced spine and synapse density have been shown in *post-mortem* studies of depressed patients[167] and in animal models;[168] also, such features may be restored with antidepressant treatment.[169] In addition to morphological rearrangement, activity-dependent changes in synaptic efficacy (*i.e.* synaptic plasticity) are also affected in depression.[170] This kind of plasticity affects neurotransmission efficiency and might regulate information flow and behavior.[163] Reduction of long-term potentiation (LTP) and enhancement of CA1 long-term depression (LTD) is observed in animal models of depression.[171,172] Illustrating the severity of these plastic modifications caused by stress events, Ryan et al.[173] showed that acute inescapable foot-shock stress - used to study learned helplessness - inhibited LTP in the dorsal hippocampus for at least 4 weeks.

Also, antidepressant drugs as well as electroconvulsive therapy (ECT) effectively modulate synaptic plasticity in the hippocampus and other brain structures.[169,174-176] For example, escitalopram restored CA1-LTP and monoamine levels in neonatal clomipramine-exposed rats.[177] Additionally, tianeptine, a selective serotonin reuptake enhancer, counteracted the negative effects of acute stress on synaptic plasticity.[178] Lithium, a well-known drug used in bipolar disorder related to cell survival and neurogenesis, enhances LTP induction in the hippocampus' dentate gyrus.[179,180]

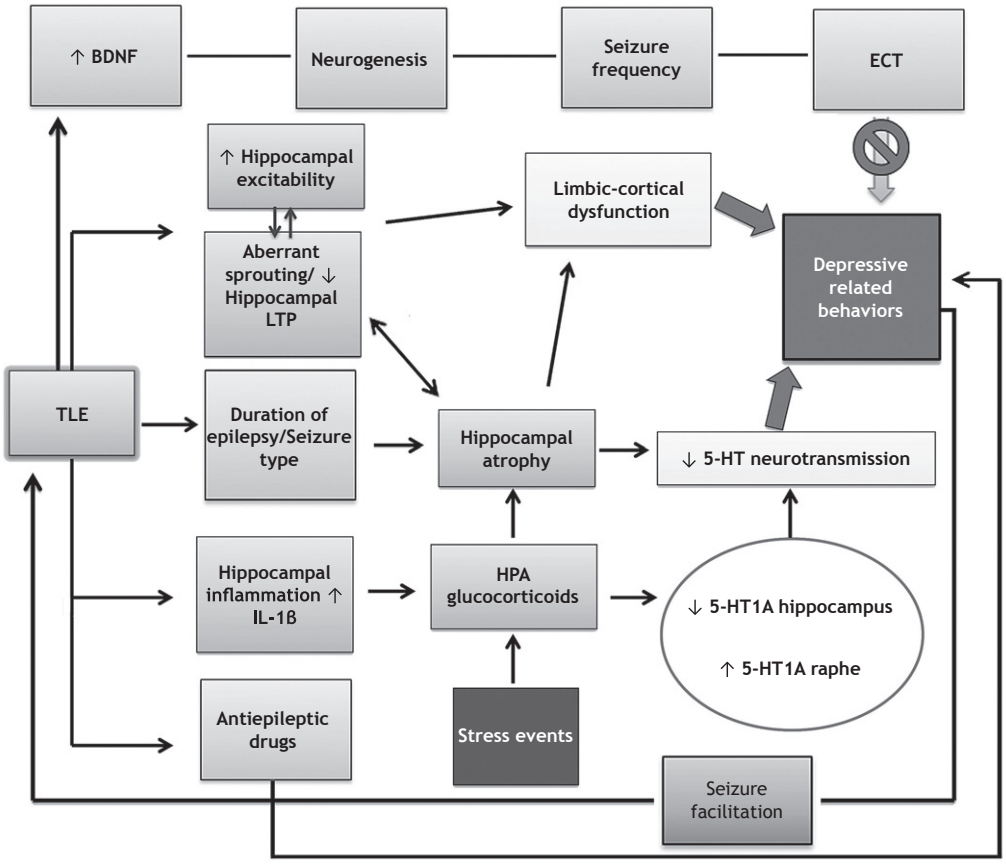
The existence of a continuum between plasticity and pathology is an appealing hypothesis sustained by some authors.[181] Synaptic efficiency is constantly regulated on a dynamic equilibrium, maintaining the balance between excitation and inhibition. In a pathological situation this normal process could be deregulated, which might result in an increase in excitation and a decrease in inhibition. This unbalanced condition could lead to an epileptic focus and subsequent seizure activity. The mechanisms underlying these types of changes would presumably be very long-lasting forms of plasticity resistant to reversal and/or LTD.[181,182] In addition, morphological changes independent of LTP could be responsible for the development of pathology.[183] However, LTP itself is associated with morphological changes similar to those seen as a result of kindling.[184] In fact, LTP and kindling share similar mechanisms such as the requirement of high-frequency stimulation, glutamatergic transmission and an increase in the intracellular calcium. Moreover, LTP and kindling involve changes in gene expression, protein synthesis, morphology and the activity of metabotropic glutamate receptors.[181,182]

It is proposed that seizure activity causes an indiscriminate and widespread induction of long-term potentiation, consuming and thereby reducing overall hippocampal plasticity available for information processing. In fact, repeated seizures reduce the ability to induce LTP and impair spatial learning in animals.[185] The amount of learning deficits seen in animals is similar in time course as the transitory cognitive impairment seen following ECT in humans treated for severe affective disorder.[185] Further, the effects of ECT in humans or electroconvulsive seizures in animal models on LTP can be blocked by the NMDA antagonist ketamine.[185] This suggests that seizures "saturate" the synapses with long-term facilitation that decreases the capacity for plasticity including LTP and memory. Kindling also suppresses LTP,[186] and lithium-pilocarpine induced SE promotes a severe reduction of LTP in the hippocampus, which is related to impaired fear memory formation.[187] Neonatal seizures in animals can induce long-term loss of LTP, impair spatial learning, and alter NMDA protein expression.[188] Also, LTP is markedly reduced in the epileptogenic hippocampus of humans with TLE, but LTP is quite normal in the hippocampus, which is not the primary seizure focus.[189]

Most of the works have investigated changes in synaptic plasticity in the pathological hippocampus. Studies that investigate changes in more expanded circuitry including thalamus, prefrontal cortex and amygdala, for instance, are of great importance to better understand the pathophysiology of the disease and the genesis of a comorbid condition. For example, a recent work by Sloan and Bertram[190] shows that epileptic rats present a significant reduction in the thalamically-induced responses in the prefrontal cortex, reducing thalamo-cortical communication. Importantly, some studies have shown that the effects of depression on LTP impairment and cognitive deficits may be mediated via profound alterations in neural information flow in the thalamus-cortical pathway.[191] In addition, thalamocortical dysrhythmia is found in a series of pathological conditions such as neurogenic pain, tinnitus, Parkinson's disease and depression.[192]

Conclusions

As summarized in the Flowchart, emerging results from a variety of clinical and experimental paradigms suggest that epilepsy and mood disorders have shared and also antagonistic mechanisms. Cytoarchitectural and neuropil disarray are seen in these conditions, and such changes are indicative of robust circuitry dysfunction. Both mood disorders and epilepsy present marked changes in hippocampal synaptic plasticity. The most evident is a reduction in the ability of LTP induction, which is reflected in the cognitive deficits shown in both conditions, since LTP represents a cellular mechanism underlying memory and learning. Defining whether these plastic changes are possible causes or simply a consequence is still a matter of debate. Studies conducted in TLE experimental models such as amygdala kindling, SE (pilocarpine, kainate), as well as research with genetically developed strains (GAERS, GEPRs, WARs) indicate that changes in the dynamics of information processing caused by genetic



Flowchart Some of the cooperative and antagonistic mechanisms that underlie the close association between TLE and depressive symptoms. Not shown in the scheme are genetic features such as those present in familiar epilepsies and mood disorders, and those modeled in the genetically developed strains. They are obvious components of the complexity of these comorbidities.

susceptibility and the experience of repeated seizures can produce behavioral alterations related to depressive states. However, to better understand these complex interactions, it will be necessary to investigate possible changes in synaptic plasticity (electrophysiology, gene and protein expression) in models of TLE and comorbid depression.

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** Modest*
*** Significant*
**** Significant. Amounts given to the author's institution or to a colleague for research in which the author has participation, not directly to the author.*

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ARTIGO

Fisiopatologia dos transtornos de humor na epilepsia do lobo temporal

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DESCRITORES
Epilepsia do lobo temporal;
Depressão maior;
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Comorbidades psiquiátricas;
Neuropatologia;
Plasticidade sináptica;
Modelos animais.

Resumo
Objetivo: Há evidências crescentes do envolvimento do sistema límbico nas comorbidades psiquiátricas associadas à epilepsia do lobo temporal (ELT). Nosso objetivo foi descrever o panorama atual das alterações neuropatológicas, neuroquímicas e eletrofisiológicas que podem contribuir para o desenvolvimento de sintomas psiquiátricos na ELT e explorar possíveis mecanismos neurobiológicos que podem levar ao aparecimento das desordens de humor nesse subgrupo de pacientes. *Métodos:* Achados clínicos, de modelos experimentais e neuropatológicos foram revistos, assim como características neuroquímicas do sistema límbico foram examinadas em conjunto para auxiliar nossa compreensão sobre a associação entre ELT e transtornos de humor. *Conclusões:* A ELT e os sintomas psiquiátricos coexistem numa frequência muito maior do que o acaso poderia sugerir. Alterações e desregulação de redes anatômicas essenciais, além de mudanças plásticas aberrantes ou deficientes, podem predispor o cérebro de pacientes com ELT a transtornos de humor. Estudos experimentais e clínicos sobre o efeito das crises no comportamento e nos padrões eletrofisiológicos podem oferecer um modelo de como as crises límbicas aumentam a vulnerabilidade a sintomas psiquiátricos em pacientes com ELT.

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Primeiras observações e aspectos clínicos

Há mais de 2.400 anos se observa a associação entre a epilepsia e a depressão. Conforme revisto por Kanner,[1] Hipócrates mencionou que "melancólicos geralmente se tornam epiléticos, e epiléticos, melancólicos: o que determina a preferência é a direção que a doença toma; se está relacionada ao corpo, epilepsia, se à inteligência, melancolia". Estudos publicados durante a segunda metade do século XIX também reconheceram que pacientes com epilepsia normalmente apresentavam humor depressivo, prostração, misantropia e tendência suicida.[2] Em geral, define-se a depressão pela presença de certos comportamentos e padrões de pensamento. Alguns dos principais sintomas incluem o humor deprimido, a redução do interesse ou prazer em todas as atividades, mudança de apetite, insônia ou hipersonia, agitação ou retardamento psicomotor, fadiga ou perda de energia, sentimento de inutilidade ou de culpa excessiva, capacidade reduzida de pensar ou se concentrar e frequente pensamento mórbido de morte e ideação suicida.[3] Normalmente, há dificuldades de se reconhecer sintomas depressivos e o tratamento inadequado pode levar a uma qualidade de vida bastante comprometida.[4]

De acordo com números atuais, a prevalência da depressão em pacientes com crises recorrentes varia de 20% a 80%.[5,6] A fenomenologia da depressão na epilepsia é assunto para debate. Os sintomas mais frequentes incluem sentimentos de anedonia, culpa e ideação suicida. Outros autores também relatam alto grau de ansiedade, neuroticismo, hostilidade, sentimentos de despersonalização e raras manifestações com mania e sintomas psicóticos relacionados à depressão.[2] A manifestação de sintomas depressivos na epilepsia é normalmente mais branda do que na depressão maior,[7,8] mas os sintomas podem ocasionar a interrupção significativa das atividades diárias dos pacientes, das relações sociais e da qualidade de vida e requerem terapia farmacológica para remissão.[5] Sintomas depressivos na epilepsia podem ser classificados em três categorias: (I) transtorno depressivo maior, de acordo com os critérios diagnósticos do *Diagnostic and Statistical Manual*, 4ª ed. (DSM-IV); (II) depressão atípica ou distimia; ou (III) transtorno similar à distimia com sintomas intermitentes que podem ser mais brandos do que aqueles da depressão maior.[6] De acordo com a relação temporal com as crises, os sintomas depressivos podem ser ictais, periictais ou interictais, sendo os últimos os mais frequentes.[5]

Até meados do século XX se acreditava que a depressão na epilepsia era, na maioria das vezes, do tipo "reativa",[9-11] em que sintomas depressivos podem ser uma reação aos estresses da vida, incluindo o efeito de quaisquer doenças subjacentes. De fato, conforme enfatizado por Robertson *et al.*,[2] acontecimentos importantes como "(...) repetidos episódios angustiantes de perda de consciência levando à morbidade, à perda de autoestima e, geralmente, à vergonha. A dificuldade de se conseguir um emprego, a estigmatização e a recorrente perda da dignidade enfrentadas pelo paciente epilético podem ser importantes fatores provocadores da depressão". No entanto, nas últimas duas décadas, estudos mostraram transformações bioquímicas, neuropatológicas e neuropsicológicas mediando o desenvolvimento dos transtornos de humor,[10] o que significa que é mais comum a depressão ser do tipo "endógena" na epilepsia.[12,13] Conforme observado por Kanner *et al.*,[14] a depressão na epilepsia é normalmente uma combinação de processos intrínsecos e extrínsecos que agem sinergicamente.

No fim da década de 1970 Rodin *et al.*[15] relataram que pacientes com epilepsia do lobo temporal (ELT) mostraram escores de depressão mais altos do que pacientes com outros tipos de epilepsia.[15] Alguns anos depois, um estudo similar sugeriu que pacientes com crises parciais complexas secundariamente generalizadas tiveram escores piores quando comparados àqueles com crises convulsivas primariamente generalizadas.[16] Em relação ao tipo de crise, outros estudos mostraram que a depressão é mais frequente em pacientes com crises não epiléticas do que em pacientes com crises epiléticas.[17] Em pacientes pediátricos, a depressão também é mais frequente em casos com crises parciais complexas focais do que em pacientes com crises primariamente generalizadas.[18] Embora a frequência da crise ou a intratabilidade[19] possa não estar relacionada à gravidade da depressão, sabe-se que o tipo de crise,[8,18] a duração da epilepsia e as drogas antiepiléticas[8] estão relacionados a diferentes níveis de sintomatologia depressiva. Por essa mesma razão, em descoberta recente, observamos que a presença de crises secundariamente generalizadas é mais frequente em pacientes adultos com ELT mesial com comorbidades psiquiátricas do que em pacientes adultos com ELT mesial sem sintomas psiquiátricos.[20] Na verdade, pacientes com ELT medial parecem particularmente propensos à depressão comórbida.[21]

Características atípicas podem afetar 20%[22] a 70%[23] dos pacientes com sintomas depressivos. Em 1923 Kraepelin descreveu um distúrbio afetivo pleomórfico em epilepsia, designada por Blumer *et al.*[24] como "transtorno disfórico interictal", caracterizado por sintomas depressivos lábeis (humor depressivo, falta de energia, dor, insônia), sintomas afetivos lábeis (medo, ansiedade) e pela presença de irritabilidade e rompantes de comportamento agressivo/eufórico como sintomas principais. A prevalência de disforia interictal em ELT é de cerca de 17%.[25] A disforia é considerada uma entidade psicopatológica com relação mais próxima ao transtorno bipolar do que transtornos de humor unipolares. De fato, uma das figuras históricas mais famosas que apresentou seis dos sete sintomas cardinais do transtorno disfórico interictal foi Vincent van Gogh,[26] que também mostrou sinais de personalidade interictal.[27] Sintomas disfóricos também podem ocorrer em pacientes com doenças crônicas além da ELT – como enxaqueca e diferentes epilepsias focais[25,28] –, bem como disforia pré-menstrual.[29] Apesar da alta frequência da disforia interictal em casos de epilepsia, o transtorno bipolar clássico (tipo I) é raro,[8] variando até 1,4%.[30] Sintomas bipolares tendem a ser mais brandos em pacientes com epilepsia do que em pacientes bipolares puros, que geralmente apresentam distúrbios de humor flutuantes, ciclo rápido de episódios de humor e alucinações mais frequentes.[31]

Além dos distúrbios de humor, os transtornos de personalidade além do tipo interictal mais comum[27] são frequentes em pacientes com epilepsia. Dentre os pacientes com ELT com esclerose do hipocampo que passaram pelo nosso centro cirúrgico de epilepsia, 41,4% apresentaram ao menos um diagnóstico do Eixo I, de acordo com os critérios de DSM-IV.[32] A maioria apresentou depressão (19,4%), 10,7% psicose, 5,9% transtorno disfórico interictal e 5,4% transtornos de ansiedade. Transtornos de personalidade (Eixo II) ocorreram em 12,4% dos pacientes e, em alguns casos, se sobrepuseram ao

diagnóstico do Eixo I. Os traços mais frequentes eram transtorno de personalidade epilética, borderline, histrônica, antissocial, narcisística, esquizoide e passivo-agressiva.[32] A predominância dos transtornos de personalidade dos grupos A (paranoide, esquizotipal e esquizoide) e B (*borderline*, histriônico, antissocial, narcisística) do DSM-IV pode indicar a presença de crises não epilépticas.[33] Outros autores também relataram alta incidência de comportamento infantil dependente[31] e déficit de cognição social.[34] Considerando o tipo de epilepsia, os pacientes com epilepsia mioclônica juvenil são mais impulsivos do que os controles não epiléticos[35] e os pacientes adultos com crises epiléticas apresentam índices elevados de traços esquizoide, antissocial, histrônico, de evitação, dependente, passivo-agressivo e depressivo em comparação aos controles.[36] Ainda, uma proporção maior de pacientes com crises epiléticas e transtornos de personalidade se encaixa dentro do Grupo C, se comparada a pacientes com crises não epiléticas.[33] É interessante que os traços esquizoide, obsessivo-compulsivo e de evitação correlacionam-se à duração da epilepsia, mas não à ansiedade ou à presença da depressão.[36] Os traços de despersonalização ou desrealização são mais frequentes em pacientes com crises não epiléticas do que nos que manifestam crises epiléticas.[37] Diversos dados sugerem que a epilepsia não é um mecanismo fisiopatológico primário para o desenvolvimento de sintomas dissociativos[38,39] e que a presença da ansiedade e depressão é um fator importante.[40] Por outro lado, vários dados mostrados desde a época de Hughlings Jackson no fim do século XIX evidenciaram semelhanças entre os chamados estados oníricos ou fenômenos experiênciais[41] e os comportamentos sugestivos de despersonalização.[42]

O suicídio é mais comum em pessoas com epilepsia do que na população em geral e a taxa de mortalidade é mais alta naqueles com ELT e que passaram por tratamento cirúrgico.[43] Os fatores de risco para o suicídio incluem a presença de transtornos de humor (depressão e transtorno bipolar) e outros transtornos psiquiátricos (por exemplo, psicose do tipo esquizofrênica), transtornos de personalidade (especialmente transtornos de personalidade *borderline*), dependência de drogas, comportamento autodestrutivo, tentativas anteriores de suicídio, doenças crônicas, estigmatização da epilepsia, impulsos peri-interictais de suicídio e tratamentos farmacológicos.[44] Em um amplo estudo com mais de 10 mil pacientes com epilepsia, cinco suicídios foram registrados durante um período de 12 anos e todos ocorreram em pacientes com longas crises parciais complexas e com transtornos disfóricos logo depois de se alcançar o controle total das crises.[45] Na terapia eletroconvulsiva (TEC), as crises controladas podem ser evocadas pelo estímulo bifrontotemporal acima do limiar para uma crise tônico-clônica generalizada. Ademais, a maioria dos pacientes com depressão endógena que faz TEC se recupera por completo ou melhora consideravelmente.[46] Poderiam as crises crônicas também ter um efeito de proteção em casos de depressão endógena comórbida, semelhantes ao que se veem na normalização forçada? As primeiras observações de Landolt incluíram transtornos disfóricos na normalização do eletroencefalograma[47] e a emergência ou a piora da psicopatologia por causa da supressão da atividade de crise foi amplamente relatada.[45] Conforme resumido por Blumer *et al.*,[45] quando se diminuem ou se controlam as crises, os sintomas disfóricos, o humor depressivo e a psicose tendem a ser exacerbados, mas a natureza precisa dos mecanismos de supressão das crises ainda não é compreendida por completo.

A comorbidade não implica necessariamente em causalidade. Como levantado por Gabb *et al.*,[48] "(...) a epilepsia causa depressão, mas será que a depressão provoca a epilepsia?" Apoiando essa ideia, há um histórico de depressão precedendo o início da epilepsia, que é até seis vezes mais frequente em pacientes do que em controles.[49,50] Tais casos se encaixariam no tipo de depressão endógena e sugerem a possibilidade de mecanismos patogênicos comuns operantes em ambos os transtornos.[14] Possíveis mecanismos neuropatológicos, neuroquímicos e eletrofisiológicos serão explorados nas próximas seções.

Aspectos neuropatológicos

Em uma série de 100 pacientes com lesões no lobo temporal (tumores, atrofia ou criptogênicas), 95 apresentaram manifestações psiquiátricas paroxísticas, tais como alucinações, ilusões perceptuais, distúrbios de emoção ou humor, transtornos de personalidade (na maioria traços esquizoides) e automatismos.[11] Os transtornos de humor predominantes foram depressão e ansiedade, tendo o último características disfóricas. Na verdade, a presença de esclerose temporal mesial é considerada um fator de predisposição para o desenvolvimento de transtornos de humor em epilepsia focal.[21] Embora o envolvimento do lobo temporal pareça inequívoco na manifestação da depressão,[51] estruturas paralímbicas, tais como o córtex temporal e pré-frontal, também estão prejudicadas.[52,53] O hipometabolismo focal no córtex orbitofrontal ipsilateral é normalmente encontrado em pacientes com ELT e depressão, quando comparado a pacientes com ELT, sem depressão; após a cirurgia de epilepsia, os pacientes que desenvolveram depressão apenas no pós-operatório também mostram hipometabolismo na região orbitofrontal ipsilateral.[52] É interessante ressaltar que Rajkowska *et al.*[54] demonstraram anteriormente uma diminuição significativa da espessura cortical, dos tamanhos neuronais e das densidades neuronal e glial dentro do córtex orbitofrontal de pacientes deprimidos puros.

A neurotransmissão monoaminérgica está classicamente relacionada à depressão maior, na maioria das vezes, por causa do mecanismo de ação de drogas antidepressivas que aumenta esses neurotransmissores na sinapse.[55] Os estudos de aquisição de imagem por tomografia por emissão de pósitrons (PET) mostraram ligação reduzida do receptor de serotonina (5-HT) 1 A no córtex frontal, temporal e límbico[56] e na rafe[57] em pacientes depressivos quando comparados aos controles. Um déficit na densidade dos receptores serotonérgicos pós-sinápticos também foi identificado no hipocampo e na amídala de pacientes que cometeram suicídio.[58] Além disso, a transmissão comprometida de serotonina, que consiste de uma densidade excessiva de autorreceptores somatodentríticos serotonérgicos 5-HT_{1A} na rafe dorsal, foi encontrada em vítimas de suicídio com depressão maior.[59] Alterações semelhantes de 5-HT foram encontradas em pacientes com ELT. Um estudo com PET usando um antagonista do receptor 5-HT_{1A} mostrou uma afinidade reduzida nas estruturas temporais mesiais ipsilaterais ao foco da crise em pacientes com ELT

com ou sem atrofia do hipocampo.[60] A redução na ligação de 5-HT_{1A} também foi encontrada no núcleo da rafe e nas regiões talâmicas ipsilaterais.[60] Outro estudo que investiga pacientes com ELT encontrou afinidade de 5-HT_{1A} no hipocampo epileptogênico, na amídala, no giro do cíngulo anterior e no neocórtex temporal lateral, ipsilateral ao foco da crise, bem como no hipocampo contralateral.[61] Estudos conduzidos em pacientes com ELT e depressão comórbida também indicam anormalidades na neurotransmissão serotonérgica. A ligação do receptor 5-HT_{1A} em pacientes com ELT com depressão maior mostra a diminuição do sinal quando comparada a pacientes com ELT sem depressão, independentemente do lado da lesão e do grau da esclerose do hipocampo.[62] Outro estudo com PET encontrou uma correlação inversa entre a severidade dos sintomas depressivos e a afinidade da ligação de 5-HT_{1A} no hipocampo ipsilateral e uma correlação positiva entre a gravidade de sintomas depressivos e a magnitude das anormalidades do hipocampo.[63]

As regiões cerebrais envolvidas tanto em ELT quanto na depressão incluem os lobos temporais com o hipocampo, a amídala, o córtex entorrinal e temporal, os lobos frontais, as estruturas subcorticais, tais como os gânglios da base e o tálamo, e as vias de conexão.[64] Dados neuropatológicos sobre ELT e depressão comórbida são escassos. Dados recentes sugerem que há uma base estrutural para sintomas psiquiátricos em pacientes com ELT. Há indícios de *up-regulation* da subunidade NR1 do receptor N-*Methyl*-D-*aspartate* (NMDA) na camada molecular do giro denteado em pacientes com ELT não medicados com humor depressivo se comparados a pacientes com ELT sem comorbidades psiquiátricas.[65] Além disso, em nossa série de hipocampos de pacientes com ELT mesial com depressão, encontramos a densidade neuronal CA4 tão alta quanto em controles não epiléticos e um aumento de brotamento de fibras musgosas quando comparados a pacientes com ELT mesial sem histórico psiquiátrico.[20] Embora o tratamento antidepressivo não cause brotamento de fibras musgosas, a administração crônica de fluoxetina causa mudanças expressivas na modulação serotonérgica da transmissão sináptica de fibras musgosas em ratos.[66] A serotonina é capaz de potencializar a transmissão sináptica de fibras musgosas e a fluoxetina reduz a potenciação sináptica induzida por concentrações maiores de serotonina; entretanto, baixas concentrações de serotonina podem aumentar a potenciação sináptica, o que representa a estabilização da modulação serotonérgica.[67] Na ELT mesial com depressão, o aumento do brotamento de fibras musgosas pode agir como uma proteção contra sintomas depressivos ou, de modo inverso, o maior brotamento poderia representar uma resposta compensatória insuficiente ao estresse crônico ou subsequente provocado por episódios depressivos.[20] Mais estudos fisiológicos celulares em modelos animais seriam importantes para esclarecer o envolvimento do giro denteado e das fibras musgosas em transtornos psiquiátricos, uma vez que o significado clínico de brotamento ainda deve ser elucidado.[67]

Nas últimas duas décadas, alguns estudos neuropatológicos foram feitos com amostras cerebrais *post-mortem* de pacientes com depressão maior, especialmente nas regiões frontolímbicas. Alterações morfológicas macroscopicamente evidentes, como as lesões focais, não estão presentes na depressão (conforme normalmente encontrado em ELT[68]), mas diferenças citomorfológicas entre sujeitos deprimidos e controles podem ser demonstradas ao nível microscópico.[69] A densidade glial reduzida no transtorno depressivo é encontrada no córtex pré-frontal,[54] no córtex entorrinal e na amídala.[70] Na verdade, a redução glial da amídala parece patognomônica e, na maior parte das vezes, relacionada aos astrócitos[71] ou oligodendrócitos.[72] As regiões corticais onde a patologia neuronal foi detectada incluem o hipocampo e os córtex orbitofrontal, pré-frontal e cingulado, sem uma definição clara se há verdadeira perda celular subjacente à redução da densidade e do tamanho do célula.[69] Outros indícios de patologia neuronal compreendem reduções na forma precursora do fator neurotrófico derivado do cérebro (BDNF) no hipocampo da amostra com depressão maior,[73] embora o tratamento com antidepressivos possa aumentar a expressão da proteína do BDNF no hipocampo.[74] No córtex pré-frontal, a expressão reduzida da descarboxilase do ácido glutâmico é observada em pacientes sem medicamentos e com depressão maior, mas não em pacientes medicados com antidepressivos.[75] Há uma depleção semelhante do ácido gama-aminobutírico (GABA) avaliada por meio da coloração dos interneurônios pré-frontais para proteínas de ligação do cálcio,[76] e possível diminuição da liberação local de serotonina em indivíduos portadores de depressão maior.[59] Em concordância com aquelas descobertas, o uso de agonistas e antagonistas do GABA é capaz de modular sintomas depressivos e a administração crônica de antidepressivos induz mudanças marcantes na função GABAérgica.[77] Além disso algumas drogas anticonvulsivantes e GABA-miméticas têm propriedades estabilizadoras do humor e antidepressivas.[77,78] Pacientes com ELT mostram diminuição da expressão dos transportadores de glutamato no giro denteado,[79] bem como os pacientes com transtorno depressivo maior nas regiões frontais do cérebro, corpo estriado e hipocampo, o que leva ao aumento da neurotransmissão glutamatérgica.[80,81] Hasler *et al*.[82] mostraram que os níveis de glutamato/glutamina e de GABA diminuíram nas regiões pré-frontais dorsomedial e ventromedial com depressão maior.[82] Estudos de aquisição de imagens também mostraram uma diminuição do glutamato no córtex cingulado anterior de adultos[83] e crianças[84] com depressão. Em adultos não medicados com transtorno depressivo foi encontrada a diminuição dos níveis e da síntese de GABA nas regiões dorsomedial, pré-frontal dorsal-anterolateral, ventromedial e occipital.[78,85] Além disso, o tratamento com o antagonista de NMDA, a ketamina, mostrou melhora dos sintomas depressivos em pacientes com depressão maior e em pacientes com depressão maior resistente ao tratamento.[86,87]

Estudos de aquisição de imagens do transtorno bipolar mostraram o aumento de volume da amídala, do hipocampo e do lobo temporal. De fato, foi encontrado um aumento da amígdala em casos de transtorno bipolar comparados a sujeitos normais.[88] Tal aumento de volume é controverso, uma vez que nenhuma alteração das densidades neuronal ou glial é vista nas amostras da amídala de pacientes com transtorno bipolar.[71] No hipocampo, a densidade neuronal não piramidal diminui significativamente em CA2 de pacientes bipolares, se comparada à de sujeitos controle, sem nenhuma outra diferença nos neurônios piramidais e não piramidais por todo o corno de Ammon entre quaisquer grupos.[89] No córtex entorrinal encontra-se uma diminuição da expressão

do RNAm do transportador vesicular 1, mas não no hipocampo ou no córtex temporal.[90] Outros estudos também relataram uma diminuição das densidades glial e neuronal no córtex pré-frontal das amostras bipolares, bem como o alargamento do nerópilo interneuronal da camada III.[91] No transtorno disfórico interictal, imagens por ressonância magnética e eletroencefalograma normais são encontrados na maioria dos casos.[28] Com base no que se sabe sobre o transtorno bipolar e a ELT com comorbidades psiquiátricas, esperaria-se encontrar alterações neuropatológicas subjacentes `a disforia interictal, no entanto nenhuma resposta a essa hipótese foi encontrada até agora.

Evidências a partir de modelos animais

Um dos primeiros modelos de ELT descritos foi o modelo de *kindling* elétrico, caracterizado pelo aumento controlado da susceptibilidade a crises e pela ausência ou extensão mínima do dano neuronal, bem como pela ausência de crises recorrentes espontâneas quando o número de crises *kindling* é baixo.[92,93] No entanto, crises motoras espontâneas podem aparecer após estimulação elétrica suficiente (*e.g.* variando de 88 a 293 estímulos no *kindling* da amídala).[94,95] A administração sistêmica[96] ou intracerebral[97] da pilocarpina ou do cainato em roedores leva a um padrão de crises límbicas repetitivas e ao *status epilepticus* (SE), que pode durar por algumas horas.[98] As alterações neuropatológicas – tais como a perda neuronal – em algumas subáreas do hipocampo e a reorganização de fibras musgosas na camada molecular da fáscia denteada são observadas em ambos os modelos e são semelhantes aos hipocampos dos pacientes com esclerose hipocampal.[98]

Um dos desafios associados com o entendimento dos mecanismos de depressão em pacientes epilépticos tem sido a falta de modelos animais validados nessa condição.[99] Até agora, estudos que tentaram desenvolver modelos animais válidos de comorbidade entre epilepsia e depressão focaram-se nas alterações de comportamento classicamente relacionadas à depressão em modelos animais de epilepsia. Conforme já mencionado, dois dos maiores sintomas de depressão são desamparo e anedonia. Nos roedores, os equivalentes comportamentais a esses estados emocionais são acessados por dois testes clássicos: o teste do nado forçado e o teste de preferência de paladar pela sacarina ou sacarose. O teste do nado forçado se baseia no comportamento adaptativo de roedores quando confrontados a situações estressantes. Basicamente, os roedores exibem dois padrões de comportamento: de esquiva ativa e/ou exploração ou imobilidade, quando os movimentos estão limitados àqueles necessários para manter a cabeça acima da água. O aumento do tempo de imobilidade está relacionado ao grau de desamparo. O teste de preferência de paladar avalia o estado hedônico medindo a preferência natural por doces: quando têm acesso à água da pia e a uma solução doce, os ratos demonstram uma forte preferência pela última. No entanto, animais submetidos ao estresse experimental apresentam uma diminuição do consumo de solução doce, o que indica uma alteração dos mecanismos de recompensa.[100]

Diversos estudos mostraram que ratos submetidos ao SE induzido pelo lítio-pilocarpina, cainato ou *kindling* elétrico ficaram imobilizados durante um tempo muito maior no teste de nado forçado e exibiram perda de preferência pela solução de sacarina quando comparados a animais não epiléticos,[101-105] o que indica que ratos submetidos às crises mostram um aumento do comportamento depressivo. Embora o tempo de imobilidade seja maior em ratos com pós-SE, a gravidade dos marcos comportamentais, endócrinos e bioquímicos da depressão parecem independentes da frequência da crise,[105] de maneira semelhante ao que ocorre em humanos.[19] No entanto, há uma correlação positiva entre a gravidade da depressão e a hiperexcitabilidade hipocampal, o que sugere que os sintomas depressivos possam ser o resultado da disfunção límbica como um todo.[106]

Todavia, outros estudos usando modelos farmacológicos de epilepsia foram incapazes de reproduzir esses dados. Estudos experimentais recentes mostraram que os ratos submetidos ao SE induzido pela pilocarpina, pelo lítio-pilocarpina, pela administração do cainato focal ou pelo *kindling* mostraram uma diminuição do comportamento semelhante à depressão.[107-110] Os resultados do nosso laboratório indicam que ratos submetidos ao SE induzido pelo lítio-pilocarpina não apresentam comportamento depressivo no teste do nado forçado e no paradigma do desamparo aprendido durante a fase silenciosa da epileptogênese (resultados não publicados). Essas discrepâncias podem ser o resultado de diferenças no protocolo usado, principalmente quanto (1) à idade dos roedores no momento da indução de SE; (2) ao tempo após SE e à frequência de crises espontâneas recorrentes; e (3) às espécies usadas.

Embora ainda haja controvérsias acerca da possibilidade de os modelos animais de epilepsia apresentarem alterações comportamentais relacionadas aos sintomas depressivos, há indícios sobre mecanismos compartilhados. A ausência genética de epilepsia em ratos de Estrasburgo mostra comportamentos depressivos e ansiosos antes do início das crises, indicando que alterações biológicas comuns podem ser subjacentes a ambas as condições.[111] Ferrero *et al*.[112] mostraram que o tratamento crônico com fluoxetina eleva o limiar da crise e a liberação basal de glutamato. É interessante observar que quando ratos estão submetidos ao paradigma do desamparo aprendido, não há efeito da fluoxetina no limiar da crise ou na liberação de glutamato.[112] De fato, ratos criados para serem suscetíveis a fenótipos semelhantes à depressão apresentam maior mortalidade do que ratos não depressivos após a indução do SE pelo canaito.[113] Ainda, ratos que passaram mais tempo imóveis no teste do nado forçado mostraram *kindling* hipocampal mais rápido e intenso.[114] Evidências também mostram ligação entre o estresse com suscetibilidade à crise. Ratos tratados com suplementação de corticosterona são mais sensíveis à eliptogênese no modelo de *kindling* da amídala em ELT.[115] Além disso, o modelo de epilepsia de ratos audiogênicos Wistar (WAR)[116] apresenta hiperplasia da glândula adrenal associada ao aumento da capacidade de resposta pituitária e adrenal após a estimulação do eixo hipotalâmico-pituiário-adrenal (HPA).[117] Além da hiperatividade de HPA, WARs também apresentam depressão, taquicardia e maior tônus simpático[118], bem como um padrão de ansiedade endógena revelado pela diminuição da exploração tanto nos braços abertos do labirinto em cruz elevado quanto no campo aberto.[119] Assim, os WARs estão sendo explorados como uma cepa desenvolvida geneticamente com epilepsia e uma variedade de comorbidades neuropsiquiátricas.

Sistemas de neurotransmissores alterados nos transtornos de epilepsia e humor

Algumas sugestões experimentais acerca das alterações neurobiológicas comuns entre epilepsia e depressão comórbida são advindas do rato geneticamente propenso à epilepsia (GEPR). As cepas GRPR-3 e GEPR-9 têm predisposição a crises generalizadas induzidas por som e evidente aceleração do *kindling*. Também apresentam comportamento depressivo manifestado pela diminuição do consumo de sacarose e pelo aumento do tempo de imobilidade no teste do nado forçado.[120] Além disso, GEPR exibe alterações endócrinas – tais como níveis séricos elevados de corticosterona, secreção deficiente do hormônio de crescimento e hipotiroidismo[121] – de acordo com o que foi encontrado em pacientes depressivos, como concentrações elevadas de cortisol e corticotrofina circulantes.[122] Ademais, as cepas GRPR-3 e GEPR-9 são marcadas pelos déficits de neurotransmissão de noradrenalina e 5-HT, resultado da arborização comprometida de neurônios noradrenérgicos e serotonérgicos que surgem no lócus cerúleo e nos núcleos da rafe.[123] Igualmente, descobriu-se que substâncias que interferem na síntese ou liberação de noradrenalina ou 5-HT acentuam as crises[121] e um aumento na neurotransmissão noradrenérgica ou serotonérgica pode preveni-las.[124-128]

Distúrbios no glutamato e GABA

A falta de equilíbrio entre a excitação e a inibição na epilepsia já é conhecida há bastante tempo.[64] No entanto, apenas recentemente o envolvimento do GABA e do glutamato foi reconhecido nos transtornos depressivos.[129] Há relação evidente entre a neurotransmissão glutamatérgica e a monoaminérgica. Os neurônios glutamatérgicos projetam do córtex até os núcleos subcorticais monoaminérgicos, como o lócus cerúleo, os núcleos da rafe e a substância negra.[129] Também, as drogas que aumentam a noradrenalina e 5-HT geralmente diminui a resposta ao glutamato.[130,131]

Em uma revisão recente, Kanner propõe três linhas de evidência que apoiam o papel patogênico do glutamato e do GABA na depressão: (1) a disfunção das proteínas do transportador de glutamato; (2) as concentrações anormais do glutamato cortical e do GABA; e (3) os efeitos antidepressivos dos antagonistas do receptor de glutamato.[129] Os transportadores de glutamato são importantes para manter baixos níveis extracelulares excitatórios do glutamato e, consequentemente, regulam a concentração sináptica. Estudos experimentais mostraram expressão reduzida de transportadores do glutamato ou transportadores de aminoácidos excitatórios em modelos animais de depressão.[132,133] Ainda, a diminuição da função dos transportadores de aminoácido está relacionada aos elevados níveis de glutamato extracelular, à morte neuronal e à epilepsia.[134]

O papel da neurotransmissão excitatória/inibitória em transtornos de humor é fortalecido pelos efeitos antidepressivos de alguns antagonistas do glutamato. Antagonistas de NMDA e de receptores metabotrópicos do glutamato (incluindo MK-801, cetamina, antagonista mGluR5 2-*methyl*-6-(*phenylethynyl*)-*pyridine* [MPEP] e os antagonistas mGluR2/3 LY341495 e MGS0039) têm atividade antidepressiva no teste de nado forçado, no teste de suspensão pela cauda e nos modelos de desamparo aprendido.[132,135]

Desregulação do eixo hipotálamo-pituitário-adrenal (HPA)

A desregulação do sistema HPA é uma característica central dos transtornos depressivos. De maneira sucinta, a secreção pelo hipotálamo do fator de liberação de corticotropina (CRF) estimula a síntese e a liberação de adrenocorticotropina pela glândula pituitária. Como consequência, o último estimula o córtex adrenal a secretar glicocorticoides. Esses hormônios são fundamentais para preparar o organismo no enfrentamento de um evento estressor importante, já que mobilizam energia armazenada, aumentam o tônus cardiovascular e suprimem o anabolismo. A desregulação do eixo HPA ocorre quando há falhas no *feedback* negativo que controla o nível de glicocorticoide circulante.[136] Algumas estruturas cerebrais regulam essa atividade, incluindo o hipocampo, que tem uma influência inibitória nos neurônios CRF hipotalâmicos, enquanto que a amídala exerce controle excitatório.[137] Nos dados experimentais, descreve-se extensivamente o papel neurotóxico dos glicocorticoides aumentados. Altos níveis de glicocorticoides levam ao dano das sinapses,[138,139] particularmente envolvendo neurônios piramidais de CA3, a redução do neurônio piramidal, da ramificação dendrítica e espinhos que fazem parte dos *inputs* sinápticos glutamatérgicos,[136] a diminuição dos níveis de BDNF e a interferência com as células granulares no giro denteado hipocampal de adultos.[140] Todos esses efeitos resultam em mudanças estruturais no giro denteado, na camada de células piramidais do hipocampo, na amídala e no neocórtex temporal.[70,140,141] Nos lobos frontais, a alta secreção de corticosteroides já foi associada à diminuição do número de células gliais nas seções subgenual, cingulada e dorsolateral do córtex pré-frontal.[54,142-146]

As alterações neuronais também estão associadas ao desenvolvimento dos transtornos de humor e ansiedade.[147] Os pacientes com transtorno depressivo maior exibem alterações relacionadas à hiperatividade de HPA, tal como a atrofia do hipocampo e dos lobos frontais, incluindo o giro cingulado e o córtex orbifrontal e dorsolateral demonstrados por múltiplos investigadores.[148-150] De fato, as consequências neuropatológicas atribuídas aos cortisol excessivo incluem: (1) a diminuição das densidades gliais e do tamanho neuronal no giro cingulado; (2) a diminuição dos tamanhos neuronais e das densidades neuronais nas camadas II, III e IV no córtex orbitofrontal rostral, o que resulta na diminuição da espessura do córtex; (3) diminuição significativa das densidades gliais nas camadas V e VI do córtex associada à diminuição significativa dos tamanhos neuronais no córtex orbitofrontal caudal; e (4) a diminuição das densidades neuronal e glial e do tamanho em camadas corticais do córtex pré-frontal dorsolateral.[54,142-146]

Além disso, níveis aumentados de glicocorticoides podem estar envolvidos na interrupção da transmissão serotonérgica rafe-hipocampo encontrada em pacientes depressivos. Propõe-se que um mecanismo envolvido na regulação da neurotransmissão de 5-HT da rafe envolve autorreceptores 5-HT_{1A} somatodentríticos.[99] A ativação dos autorreceptores 5-HT_{1A} da rafe pela serotonina liberada localmente inibe a descarga de neurônios serotonérgicos e a liberação adicional de neurotransmissores.[151] Dados clínicos e experimentais sugerem que os glucocorticoides podem causar uma suprarregulação de 5-HT_{1A} na rafe, o que leva, portanto, à

autoinibição de 5-HT.[59,152] Dessa maneira, em condições de estresse crônico, como a depressão, ou após o SE, é possível que os níveis elevados de corticosteroides possam levar à neurotransmissão reduzida de 5-HT.[99]

Recentemente, o funcionamento anormal de HPA comparável àquele encontrado em pacientes depressivos foi demonstrado em seres humanos com ELT sem transtornos depressivos,[149] bem como em modelos animais de epilepsia.[104] Mais uma vez, usando o modelo lítio-pilocarpina, o grupo de Mazaratti mostrou um aumento dos níveis séricos de corticoide em ratos SE que está relacionado ao comportamento semelhante ao depressivo e ao déficit serotonérgico da rafe-hipocampo. Além disso, o tratamento local da rafe com o bloqueador do receptor glicocorticoide reverteu o tempo maior de imobilidade nos marcos de depressão do teste do nado forçado e o déficit de serotonina na rafe-hipocampo.[104] Conforme citado anteriormente, o tratamento com corticosteroide pode acelerar o *kindling* da amídala e esse processo é inibido pelos antagonistas do corticosteroide.[111,153] Esse mecanismo também pode estar envolvido na depressão associada à epilepsia: em pacientes com ELT com depressão simultânea, a afinidade de ligação dos receptores 5-HT_{1A} da rafe é aumentada e positivamente correlacionada à gravidade dos sintomas clínicos de depressão.[154]

A função exacerbada do HPA promovida pelo estresse crônico está relacionada à diminuição da expressão e ligação do RNAm de 5-HT_{1A} no hipocampo, um efeito evitado pelos antidepressivos tricíclicos.[155] A ligação do receptor de 5HT_{1A} e a expressão de seu RNAm estão sob inibição tônica pela estimulação de receptores de glucocorticoide. Sendo assim, níveis elevados de corticosteroide poderiam estar relacionados à redução da ligação do receptor 5-HT_{1A} observado em pacientes com depressão.[129]

Além disso, maiores concentrações de corticosteroides estão associadas a níveis menores de BDNF. O BDNF relaciona-se à plasticidade e à sobrevivência dos neurônios adultos e da glia[156] e níveis reduzidos do BDNF podem contribuir para o dano do hipocampo. Essa deficiência é melhorada pelo tratamento com antidepressivos e se relaciona com a eficácia do tratamento. A administração de antidepressivos aumenta a expressão do BDNF em diversas estruturas cerebrais.[74,157,158] Ainda, a administração do BDNF gera efeitos antidepressivos em ratos.[141,159] No entanto, pacientes com ELT apresentam uma expressão maior do BDNF que pode tanto agir como um fator de neuroproteção quanto promover a sobrevivência das células ou contribuir para modificações em circuitos neuronais relacionados à epileptogênese.[160]

A neuroinflamação do hipocampo é outro possível mecanismo patológico comum entre ELT e depressão. A sinalização *Interleukin*-1 *beta* (IL-1ß) poderia estar por trás dessas alterações.[99] Os estudos clínicos e experimentais têm considerado o aumento de IL-1ß e a ativação de seu receptor como uma característica de ELT.[161] Ainda, IL-1ß pode induzir a ativação do eixo HPA e facilitar sintomas depressivos.[162] De fato, durante duas semanas, a administração intra-hipocampal de um antagonista de IL-1ß reduziu as características comportamentais, endócrinas e bioquímicas da depressão, mas não teve efeito na frequência de crises espontâneas no modelo SE do lítio-pilocarpina.[106]

PLASTICIDADE SINÁPTICA

A plasticidade neural é uma característica fundamental no cérebro de mamíferos que pode sustentar mudanças na organização e dinâmica funcional do tecido nervoso, o que permitiria comportamento adaptativo a demandas ecológicas diferentes.[163] A experiência pode modificar a atividade cerebral incluindo a plasticidade não adaptativa como resposta aos danos cerebrais. Uma série de estudos relacionou a plasticidade neural à fisiopatologia dos transtornos mentais como a epilepsia, os transtornos de humor e a esquizofrenia. As teorias atuais levantam a hipótese de que as alterações neuroplásticas durante o desenvolvimento podem contribuir para as mudanças estruturais e funcionais em circuitos importantes, que podem ter efeitos duradouros no funcionamento do cérebro de adultos.[164]

Uma diminuição da plasticidade está relacionada ao aumento do limiar para adaptação[165], o que torna o indivíduo mais vulnerável ao *input* negativo.[166] Redução nas espinhas dendríticas e na densidade sináptica foram mostradas em estudos *post-mortem* de pacientes deprimidos[167] e em modelos animais;[168] ainda, tais características podem ser recuperadas com tratamento antidepressivo.[169] Além da reorganização morfológica, mudanças na eficácia sináptica dependente de atividade (*i.e.* plasticidade sináptica) também são afetadas na depressão.[170] Esse tipo de plasticidade afeta a eficiência da neurotransmissão e pode regular o fluxo de informação e o comportamento.[163] Observa-se a redução da potenciação de longa duração (LTP) e o aumento da depressão de longa duração (LTD) de CA1 em modelos animais de depressão.[171,172] Para ilustrar a intensidade dessas modificações plásticas causadas pelos eventos de estresse, Ryan *et al*.[173] mostraram que o estresse agudo induzido por choque inescapável nas patas – usado para estudar o desamparo aprendido – inibiu LTP no hipocampo dorsal por pelo menos quatro semanas.

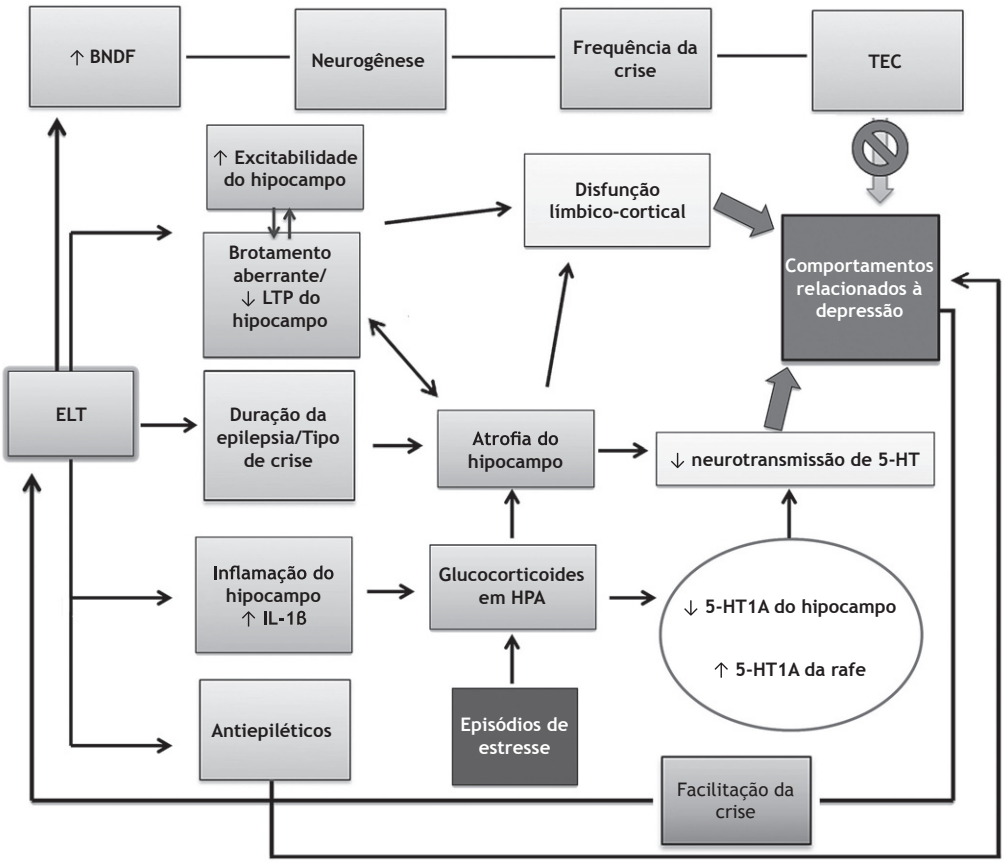
Ainda, antidepressivos, bem como a terapia eletroconvulsiva (TEC), modulam efetivamente a plasticidade sináptica no hipocampo e outras estruturas no cérebro.[169,174-176] Por exemplo, o escitalopram reestabeleceu os níveis de LTP em CA1 e de monoaminas em ratos neonatos expostos à clomipramina.[177] Além disso, a tianeptina, um acentuador da recaptação seletiva de serotonina, neutralizou os efeitos negativos do estresse agudo na plasticidade sináptica.[178] O lítio, uma droga amplamente no transtorno bipolar, relacionada à sobrevivência e à neurogênese, aumenta a indução de LTP no giro denteado do hipocampo.[179,180]

A existência de um continuum entre a plasticidade e a patologia é uma hipótese atraente sustentada por alguns autores.[181] A eficiência sináptica é constantemente regulada de acordo com um equilíbrio dinâmico, o que mantém a distribuição balanceada entre a excitação e a inibição. Em uma situação patológica, esse processo normal poderia estar desregulado, o que resultaria no aumento da excitação e na diminuição da inibição. Essa condição de desequilíbrio poderia levar a um foco epilético e à subsequente crise. Os mecanismos subjacentes a esses tipos de mudança seriam presumivelmente formas de plasticidade de longa duração resistentes à reversão e/ou LTD.[181,182] Além disso, mudanças morfológicas independentes de LTP poderiam ser responsáveis pelo desenvolvimento da patologia.[183] No entanto, a LTP está associado às mudanças morfológicas semelhantes

àquelas vistas como consequência do *kindling*.[184] Na verdade, LTP e *kindling* compartilham mecanismos semelhantes, tais como a exigência da estimulação de alta-frequência, a transmissão glutamatérgica e um aumento do cálcio intracelular. Ademais, LTP e *kindling* envolvem mudanças na expressão do gene, na síntese de proteínas, na morfologia e na atividade dos receptores de metabotrópicos de glutamato.[181,182]

É proposto que a crise ocasiona uma indução ampla e indiscriminada da potenciação de longa duração, o que consome e, portanto, reduz a plasticidade geral do hipocampo disponível para o processamento de informação. De fato, crises repetidas reduzem a habilidade de indução de LTP e prejudicam a aprendizagem espacial de animais.[185] Quanto ao tempo, o valor do déficit observado em animais é semelhante ao prejuízo cognitivo transitório observado, seguindo a TEC em humanos em tratamento para transtornos afetivos.[185] Além disso, os efeitos de TEC em humanos ou crises eletroconvulsivas em modelos animais em LTP podem ser bloqueados pelo antagonista NMDA, a ketamina.[185] Isso sugere que as crises "saturam" as sinapses com facilitação de longa duração que diminui a capacidade da plasticidade, incluindo LTP e memória. O *kindling* também suprime LTP[186] e SE induzido pelo lítio-pilocarpina promove uma drástica redução de LTP no hipocampo, que está relacionada a prejuízo na formação de memória aversiva.[187] As crises neonatais em animais podem induzir a perda a longo prazo da LTP, prejudicar a aprendizagem espacial e alterar a expressão da proteína NMDA.[188] Ainda, a LTP é bastante reduzida no hipocampo epileptogênico de humanos com ELT, mas LTP é razoavelmente normal no hipocampo, quando este não é o foco primário de crise.[189]

A maioria dos trabalhos tem investigado mudanças quanto à plasticidade sináptica no hipocampo patológico. Estudos que investigam mudanças em um circuito mais amplo, que inclui o tálamo, o córtex pré-frontal e a amídala, por exemplo, são de grande importância para compreender melhor a fisiopatologia da doença e a gênese da condição comórbida. Um estudo recente de Sloan e Bertram[190] mostra que ratos epiléticos apresentam uma redução significativa das respostas induzidas pelo tálamo no córtex pré-frontal, o que reduz a comunicação tálamo-córtex. É importante ressaltar que alguns estudos têm demonstrado que os efeitos da depressão no comprometimento da LTP e nos déficits cognitivos podem ser mediados através de profundas alterações no fluxo da informação neural na via tálamo-córtex.[191] Além disso, a disritmia talamocortical é encontrada em uma série de condições patológicas, tais como dor neurogênica, zumbido, doença de Parkinson e depressão.[192]



Fluxograma Alguns dos mecanismos cooperativos e antagonísticos subjacentes à associação próxima entre ELT e os sintomas depressivos. As características genéticas, tais como as presentes nas epilepsias familiares e nos transtornos de humor e as modeladas nas cepas geneticamente desenvolvidas, não aparecem no esquema. São componentes óbvios da complexidade dessas comorbidades.

Conclusões

Conforme resumido no Fluxograma, os resultados observados a partir de uma variedade de paradigmas clínicos e experimentais sugerem que a epilepsia e os transtornos de humor têm mecanismos em comum e também antagonistas. Observa-se um desarranjo citoarquitetural do neurópilo nessas condições e tais mudanças são indicativas de uma robusta disfunção do circuito. Tanto os transtornos de humor quanto a epilepsia apresentam mudanças importantes na plasticidade sináptica do hipocampo. A mais evidente é a redução da habilidade da indução de LTP, que se reflete nos déficits cognitivos mostrados em ambas as condições, uma vez que LTP representa um mecanismo celular subjacente à memória e ao aprendizado. Definir se essas mudanças plásticas são possíveis causas ou simplesmente uma consequência é ainda uma questão a ser debatida. Estudos conduzidos em modelos experimentais de ELT, tais como o *kindling* da amídala, SE (policarpina e cainato), bem como pesquisas com cepas geneticamente desenvolvidas (GAERS, GEPRs, WARs), indicam que mudanças quanto à dinâmica do processamento de informação causadas por suscetibilidade genética e a experiência de crises repetidas podem provocar alterações comportamentais relacionadas aos estados depressivos. No entanto, para compreender melhor essas complexas interações, será necessário investigar possíveis mudanças quanto à plasticidade sináptica (eletrofisiologia, gene e expressão da proteína) em modelos de ELT e depressão comórbidas.

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** Modesta*
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