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Rhythm and blues: animal models of epilepsy and depression comorbidity

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Abstract

Clinical evidence shows a strong, bidirectional comorbidity between depression and epilepsy that is associated with decreased quality of life and responsivity to pharmacotherapies. At present, the neurobiological underpinnings of this comorbidity remain hazy. To complicate matters, anticonvulsant drugs can cause mood disturbances, while antidepressant drugs can lower seizure threshold, making it difficult to treat patients suffering from both depression and epilepsy. Animal models have been created to untangle the mechanisms behind the relationship between these disorders and to serve as screening tools for new therapies targeted to treat both simultaneously. These animal models are based on chemical interventions (e.g. pentylenetetrazol, kainic acid, pilocarpine), electrical stimulations (e.g. kindling, electroshock), and genetic/selective breeding paradigms (e.g. Genetically Epilepsy-Prone Rats (GEPRs), Genetic Absence Epilepsy Rat from Strasbourg (GAERS), WAG/Rij rats, Swim Lo-Active rats (SwLo)). Studies on these animal models point to some potential mechanisms that could explain epilepsy and depression comorbidity, such as various components of the dopaminergic, noradrenergic, serotonergic, and GABAergic systems, as well as key brain regions, like the amygdala and hippocampus. These models have also been used to screen possible therapies. The purpose of the present review is to highlight the importance of animal models in research on comorbid epilepsy and depression and to explore the contributions of these models to our understanding of the mechanisms and potential treatments for these disorders.

Keywords

Epilepsy; Depression; Animal Model; Comorbidity

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1. Introduction

As early as 400 B.C., Hippocrates noted that “Melancholics ordinarily become epileptics, and epileptics, melancholics.” Clearly, the ancients were aware of a bidirectional comorbidity between epilepsy and unipolar depression [1], which has since been confirmed. Epileptics are 3–5 times more likely to develop unipolar depression than people without epilepsy. Given the higher incidence of depression in individuals with many serious diseases, this may not seem surprising; however, patients with active or past depression, or a family history of depression, are also at elevated risk of developing epilepsy, a risk that goes up several fold if there is also a history of suicide attempts [2]. Thus, this bidirectional relationship cannot be explained away as a psychosocial phenomenon and suggests a shared neurobiological substrate. The comorbidity between epilepsy and unipolar depression is associated with worsened prognosis, negative impact on quality of life, and treatment resistance. Furthermore, several anticonvulsant medications can cause depressed mood, among them gabapentin, lamotrigine, oxcarbazepine, tiagabine, and valproate, whereas some antidepressants increase the risk of seizure, particularly in overdose situations, emphasizing the challenge of treating these patients [3, 4]. Recent epidemiological studies have indicated an increased suicidality risk in patients on antiepileptic medications, particularly levetiracetam, lamotrigine, and topiramate [5–11]. Although some of these studies have been limited to retrospective assessments with low statistical power, have failed to account for the possible contribution of co-morbid psychiatric disorders, or did not distinguish between patients using antiepileptic drugs for epilepsy versus off-label uses, the potential for elevated suicide risk with antiepileptic medications is a serious concern that requires further investigation and improvements to current treatment of epilepsy in patients with comorbid epilepsy and depression. Indeed, the FDA has requested that a “black box” warning be placed on these drugs [3, 12]. While there have been many advances in our understanding of epilepsy and depression since the days of Hippocrates, it is still unclear what mechanisms underlie this comorbidity, which systems should be targeted to treat the disorders, and how best to test promising therapies for efficacy and safety.

Animal models are an important tool for studying and treating many complex disorders, and such models of epilepsy and unipolar depression comorbidity are now being developed. Here we provide a compilation of the current knowledge in the field and discuss potential mechanisms and therapeutic targets. Table 1 provides a summary of existing animal models of epilepsy and unipolar depression comorbidity. In the following sections, we offer a framework for understanding how each model reflects aspects of the diseases and discuss paradigms used to create the models, potential underlying neurochemical and neuroanatomical mechanisms, and directions for future studies.

2. Existing animal models of depression and epilepsy comorbidity

2.1 Paradigms

Several different types of epilepsy have been clinically associated with depression, including both partial and generalized epilepsies. Partial epilepsies have a defined, focal region of seizure onset, though generalization to other brain regions may occur secondarily. There is a particularly high correlation between depression and complex partial seizures, which feature

impaired consciousness and may often be characterized by motor automatisms. Temporal lobe epilepsy (TLE), a complex partial epilepsy affecting the temporal lobe region of the brain, is strongly associated with depression. Pilocarpine, kainic acid, and kindling paradigms serve as good animal models of TLE because their use impacts temporal lobe structures and produces similar motor automatisms.

Generalized epilepsy involves multiple brain regions and is characterized by either tonic/clonic motor convulsions or brief losses of consciousness (absence seizures). While several studies suggest that depression is less common in patients with generalized epilepsies than partial epilepsies, a link between generalized convulsive or absence epilepsies and depression does exist [13].

Animal models of depression and epilepsy comorbidity exhibit a wide range of epilepsy-and depression-related phenotypes. Several models evaluate differences in seizure susceptibility by measuring the latency to seizure onset following a single dose of chemical convulsant or the threshold of electrical stimulation required to initiate seizure onset. While these models are useful in the study of acute seizure behaviors characteristic of epilepsy, they cannot be used to study epilepsy development (i.e. epileptogenesis). We therefore need animal models of epilepsy that also help us understand epileptogenesis and the underlying neural changes that may occur during this progression. Such models currently include paradigms that elicit spontaneous seizures several weeks after chemical convulsant-induced status epilepticus (SE, a defined period of continuous motor seizing) and kindling paradigms, which apply doses of chemical convulsant or electrical shock that are initially subthreshold, but eventually provoke behavioral seizures following repeated administration.

As with epilepsy, several different aspects of depression can be modeled using animal paradigms. In the forced swim test (FST), a rat or mouse is placed in a container of water, and the duration of struggling (active movement of all 4 paws, forepaws breaking surface of water) and floating (complete immobility, no limb movement) are measured. Because antidepressants increase struggling behavior, immobility is considered a depressive-like phenotype. The tail suspension test (TST), in which a mouse is suspended from a rod by its tail and assessed for immobility, is also commonly used and shows predictive validity.

Anhedonia, or a loss of pleasure in previously enjoyed activities, is another key characteristic of clinical depression that is modeled in rodents by testing for sucrose or saccharin preference compared to water in a 2-bottle choice paradigm. A lack of preference or decreased consumption of sucrose is considered an anhedonic-like phenotype associated with depression.

2.2 Chemical convulsant-induced seizures

2.2.1 Pentylenetetrazol—Several animal models of epilepsy and associated depression have been created by assessing depression-related behaviors following administration of chemical convulsants. Pentylenetetrazol (PTZ), a GABA-A receptor antagonist, induces generalized tonic-clonic seizures and can be administered as either one large dose or a series of subconvulsive doses (i.e. kindling). PTZ-kindled rats spent significantly more time immobile in the FST [14]; however, another study reported no difference in FST immobility

in PTZ-kindled mice [15]. This discrepancy may be due to differences in dosage, time course, and/or species, which could be clarified by further studies of depression-related phenotypes, such as anhedonia, following PTZ.

2.2.2 Kainic acid—Kainic acid (KA) is an ionotropic glutamate (kainate) receptor agonist that induces primary limbic seizures with secondary generalization. Following acute KA-induced seizures, rats exhibited increased immobility in the FST, as well as increased immobility in the FST and decreased sucrose preference after repeated KA-induced seizures that persisted for months [16, 17]. We showed that rats selectively bred for high immobility in the FST (the SwLo rat, discussed in detail in section 2.4.4) exhibited increased mortality following KA-induced seizures [18]. However, other studies have reported decreases in FST immobility following intrahippocampal infusion of KA in female mice [19], suggesting future studies on the role of sex, species, and route of administration in this model are warranted.

2.2.3 Pilocarpine—Pilocarpine, a muscarinic acetylcholine receptor agonist that induces primary limbic seizures with secondary generalization, is the most commonly used chemical convulsant for studies of epilepsy and depression comorbidity. Following pilocarpine administration, we can measure latency to onset of acute limbic motor seizures, which often progress to SE. After a predetermined period in SE, seizures can be terminated using an anticonvulsant, such as diazepam or phenytoin, and the development of spontaneous seizures can be assessed following a several-week latency period. A number of studies reported more immobility in the FST several weeks after pilocarpine-induced SE in rats [20–26]; researchers also saw a decrease in saccharin preference (when assessed), a further indication of a depression-and anhedonic-like phenotype in these epileptic rats. SwLo rats also demonstrated increased susceptibility to both acute pilocarpine-induced seizures and the appearance of spontaneous seizures 5 weeks following pilocarpine-induced SE [27].

Despite these results, several other studies failed to find a depression-like phenotype in pilocarpine-treated animals despite the appearance of spontaneous seizures following SE, and in fact noted decreased immobility in the FST and TST [28–30]. Interestingly, while the studies that found an association between pilocarpine-induced seizures and immobility in the FST used male animals, all but one of the negative studies used female mice, pointing to the possibility of sex or species differences. Additional studies that include animals of both genders and different species, as well as studies assessing other measures of depression, such as sucrose preference or intracranial self-stimulation, could clarify this issue.

2.3 Electrically induced seizures

2.3.1 Electrical kindling—In the kindling paradigm, electrical stimulation is applied via intracranial (depth) electrode to a specific brain region of interest, with some of these regions implicated in both depression and epilepsy (e.g. the amygdala and hippocampus). Initially, a “subthreshold” current is applied that induces an electrographic seizure, but not a behavioral seizure. Repeated stimulations at this current eventually produce behavioral seizures and serve as a model for the epileptogenic process. Stimulations are typically administered once or twice a day over multiple days, and an animal is considered “fully

kindled" after the expression of one or more seizures characterized by rearing and/or falling behaviors (a stage 4 or 5 on the Racine scale) following 2 or more consecutive stimulations. There are also "rapid kindling" paradigms now that require many stimulations per day and greatly accelerate the kindling process.

Studies of depression-related behaviors following kindling have yielded mixed results. Standard amygdala or hippocampal kindling did not produce differences in immobility in the FST or preference for sucrose in rats [31, 32]. FAST rats, which were selectively bred for accelerated amygdala kindling and showed a variety of anxiety-related phenotypes, actually had increased sucrose preference versus their SLOW kindling counterparts [33]. However, rapid kindling of the ventral hippocampus increased immobility in the FST and decreased saccharin preference, suggestive of a depressive-like phenotype [34]. While we did not see any differences in the rate of amygdala or hippocampal kindling in the SwLo model of depression, these rats did show a profound increase in wet dog shake seizure behaviors during kindling [27]. Combined, these findings suggest that the timing of stimulations, as well as the behavioral endpoint, are important modulators of depression-related behaviors and kindling. It is possible that the delayed time course of classical kindling experiments, which occur on the scale of weeks to months, may allow for the development of compensatory mechanisms that protect against depressive phenotypes, while the rapid kindling paradigm does not permit such compensation.

2.3.2 Other electrically induced seizure paradigms—Other electrically induced seizure models have also been developed. These paradigms include maximal electroshock (MES, a generalized tonic-clonic model involving stimulation through earclip or corneal electrodes), the 6 Hertz model (6 Hz, a model of treatment-resistant epilepsy through corneal electrode stimulation), and the increasing current electroshock model (ICES, a model of treatment-resistant limbic seizures induced via a train of electrical pulses of linearly increasing intensity). Although depression-related phenotypes have not been investigated in these models, they have been used to assess the efficacy and mechanism of action of various antidepressants at reducing seizure behaviors, as discussed further in sections 3.2 and 3.3.

2.4 Genetic/selective breeding models

Several inbred or selectively bred rat lines have been studied as models of comorbid epilepsy and depression, including the Wistar Albino Glaxo/from Rijswijk (Wag/Rij) rats, the Genetic Absence Epilepsy Rats from Strasbourg (GAERS), the Genetically Epilepsy-Prone Rats (GEPR), and the Swim Lo-Active (SwLo) rats. All of these rat lines were generated based on an epilepsy-like phenotype, and then tested for behaviors relevant to depression, with the exception of the SwLo rats, which were selectively bred for immobility in the FST and then tested for seizure susceptibility and epileptogenesis. Also of interest is the dopamine β-hydroxylase knockout (Dbh −/−) mouse, which shows enhanced seizure susceptibility, but decreased responsivity to antidepressants.

2.4.1 Wistar Albino Glaxo/from Rijswijk (Wag/Rij) rats—The Wag/Rij rats are an inbred line displaying spontaneous slow wave discharges (SWD) in cortical EEGs. They are a well-established model of absence epilepsy and respond to absence pharmacotherapies

[35]. Numerous studies of these rats have revealed depression-like phenotypes. Wag/Rij rats exhibited elevated FST immobility compared to outbred Wistar rats, which was reversed by chronic, but not acute, treatment with the antidepressant imipramine. The Wag/Rij rats also showed decreased sucrose consumption, suggestive of anhedonia [36].

2.4.2 Genetic Absence Epilepsy Rats from Strasbourg (GAERS)—The GAERS are another absence model selectively bred for SWD in the EEG from a subset of outbred Wistar rats [37]. Similar to the Wag/Rij rats, GAERS were also found to consume significantly less sucrose [38]. While this points to an anhedonic phenotype, it is difficult to draw conclusions from a single test.

2.4.3 Genetically Epilepsy-Prone Rats (GEPRs)—The GEPRs were selectively bred for susceptibility to audiogenic, generalized tonic-clonic seizures. This model has been subdivided further into the GEPR-3 and GEPR-9 lines, with the GEPR-9s having more severe seizures. Hyperthermia and general handling procedures are often sufficient to induce seizures in these rats, and they are also more susceptible than normal rats to seizures induced by several electrical and chemical seizure-inducing paradigms. Importantly, electrographic, behavioral, and pharmacological characteristics seen in both types of GEPRs are reminiscent of human tonic-clonic epilepsies [39]. The GEPRs also display depression-and anhedonic-like phenotypes. GEPR-3s exhibited increased immobility in the FST, decreased saccharin consumption, and disturbances in the sleep-wake cycle similar to those seen in human depression, supporting the validity of the GEPR-3s as a genetic model of generalized epilepsy and depression comorbidity [40].

2.4.4 Swim Lo-Active (SwLo) rats—So far, all the cases discussed have begun with a model of epilepsy or seizure susceptibility, and then assessed potential depressive-like behaviors. To our knowledge, the SwLo rats are the only model that represents the opposite approach. Originating from outbred Sprague-Dawley rats, the SwLo rat line has been selectively bred for nearly 60 generations for increased immobility in the FST. This phenotype can be reversed by chronic, but not acute, antidepressant treatment, strengthening the validity of these animals as a rodent model of depression and antidepressant drug efficacy [41, 42]. Their counterparts, the SwHi rats, have been selectively bred for increased activity in the FST and represent a model of depression resilience. Although the SwLo rats were selectively bred using the FST, they demonstrate other depression and anhedonic-like phenotypes, including decreased response to dopaminergic drugs and increased intracranial self-stimulation threshold [43–45] (C. West, personal communication).

To determine whether SwLo rats might be a useful model of comorbidity launched from the depression side of the equation, we tested them for seizure susceptibility and epileptogenesis using a battery of paradigms. In our first set of studies, we found that SwLo rats showed no difference in their response to flurothyl, which induces cortical, generalized seizures, but they had increased mortality following kainic acid-induced limbic seizures, potentially via enhanced generalization to brainstem areas [18]. These initial results suggested that SwLo rats might best model temporal lobe epilepsy and depression comorbidity. We recently confirmed this by showing that SwLo rats exhibited decreased latency to pilocarpine-induced seizures, as well as increased spontaneous seizures, following pilocarpine-induced

SE. When assessed in electrical seizure-induction paradigms, the SwLo rats had a decreased threshold to ICES-induced seizures and differences in certain parameters of the kindling paradigm [27]. Interestingly, the amygdala and hippocampal kindling rates were not altered in SwLo rats, but they had a decreased stimulation threshold and displayed more wet dog shake seizure behavior during kindling. These findings argue that SwLo rats will make a useful rodent model of depression-related TLE comorbidity, the only such model of its kind to date.

2.4.5 Dopamine β-hydroxylase knockout mice (Dbh −/−)—Dopamine β-hydroxylase (DBH) converts dopamine to norepinephrine in noradrenergic neurons, and DBH knockout (Dbh −/−) mice lack NE completely [46]. Dbh −/− mice demonstrated enhanced seizure susceptibility and/or severity in a variety of paradigms, including flurothyl, PTZ, kainic acid, and auditory stimulation [47]; they were also resistant to the anticonvulsant effects of valproic acid and the ketogenic diet [48, 49]. Interestingly, while FST performance is normal in Dbh −/− mice, they showed a marked resistance to antidepressants (see section 3.1.5) [50]. Thus, Dbh −/− mice may serve as a model for studying anticonvulsant/antidepressant treatment resistance.

2.5 Limitations of animal models

While animal models are useful and necessary for enhancing our understanding of clinical conditions, they are not without their limitations. For example, the FST is considered the “gold standard” for screening novel therapeutic approaches for treating depression. However, despite its high predictive validity, the FST differs from clinical treatment of depression in several ways. Antidepressant treatment typically increases struggling in the FST or TST within 30–60 minutes, while chronic treatment of at least 2–4 weeks is required for improvement of depression symptoms in clinical populations. The SwLo rats were created in an attempt to address this limitation, and in fact only respond to antidepressant treatment following chronic administration [42]. Despite this improvement, animal models of depression have thus far not proven especially useful for identifying the mechanistic underpinnings of the disorder. Part of the problem likely stems from difficulties attributing “depressive-like symptomology” to changes in motor behavior in rodents. Much of what is currently known about the causes of depression has been determined by identifying the pharmacological targets of medications that offer clinical efficacy. However, numerous studies specifically targeting these same mechanisms often fail to show antidepressant effects, and drugs targeting novel molecules that improve depressive-like symptoms in animal models have failed to exhibit clinical benefit, emphasizing the need for caution in generalizing the findings from animal models to the clinical condition.

Although the face and construct validity of animal models of seizure susceptiblilty and epilepsy tend to be better than those for depression, they are still plagued by limitations. While these models have been used to identify several therapeutic strategies to reduce seizure susceptibility, none of the therapies to date have been able to prevent epileptogenesis, or the development of epilepsy. Similarly, models such as the electrical kindling paradigm are useful for observing the progression of seizure severity, but do not typically elicit the spontaneous, unprovoked seizures necessary for a clinical diagnosis of

epilepsy. Thus, despite the great promise demonstrated by these models and their utility as screening tools for novel therapeutics, further development of animal models of co-morbid epilepsy and depression is essential to addressing these shortcomings and improving the translational impact of these models.

3. Potential mechanisms and therapeutic targets

3.1 Neurotransmitters of interest

A variety of neurotransmitters have been implicated in epilepsy and depression individually, including acetylcholine, dopamine, GABA, glutamate, norepinephrine, and serotonin. Because this information has been reviewed extensively elsewhere, this review will focus only on their roles in animal models of epilepsy and depression comorbidity. Likewise, many of these neurotransmitters have been implicated in clinical studies of epilepsy and depression. This information has also been reviewed elsewhere and is beyond the scope of this commentary [51–55].

3.1.1 Acetylcholine—Because pilocarpine is a muscarinic receptor agonist known to produce both epilepsy and depression-like phenotypes, acetylcholine is a logical candidate to mediate comorbidity. Indeed, acetylcholine levels were elevated in the cortex and hippocampus following pilocarpine-induced SE [56]. Similarly, acetylcholine levels were also increased in the thalamus and striatum of GEPRs [57]. However, administration of carbachol, another muscarinic agonist, decreased the number and duration of SWD in Wag/Rij rats [58], indicating acetylcholine may play opposing roles in absence and partial epilepsies. Interestingly, carbachol can also be used to kindle motor seizures, and the wet dog shaking behavior associated with carbachol kindling may have muscarinic mechanisms [59]. In the SwLo rat, wet dog shaking was elevated during both hippocampal and amygdala kindling, pointing to possible muscarinic dysfunction in this model [27]. Combined, these findings suggest that muscarinic dysfunction in general may have opposing effects in partial and absence comorbidity models. A role for acetylcholine in the depression-like behaviors of these models has not been investigated yet and should be explored in the future.

3.1.2 Dopamine—Dopamine is known for its key role in mediating reward in the mesocorticolimbic system, and impairment of this pathway is believed to contribute to the anhedonic symptomatology of depression. Dopamine exerted complex effects on seizure generation: stimulation of D1 receptors was proconvulsant, whereas stimulation of D2 receptors was anticonvulsant [60]. Using a variety of monoamine reuptake blockers and glutamatergic drugs, Smolders et al reported that compounds that significantly increased dopamine levels in the hippocampus acted as anticonvulsants in the pilocarpine model of limbic seizures and as antidepressants in both the FST and TST [26]. Moreover, KA administration that elicited seizures and depressive behaviors significantly lowered dopamine levels in the hippocampus [17]. SwLo rats are also known to have decreased tissue dopamine levels and dopamine release in the prefrontal cortex, and reduced locomotor response following infusion of dopaminergic drugs into the nucleus accumbens [43, 45]. Interestingly, infusion of amphetamine into the nucleus accumbens decreased immobility in

the FST [44]. Further studies to assess the contribution of dopamine to seizure susceptibility in the SwLo rat would be helpful.

Dopamine has also been implicated in rodent models of absence epilepsy and depression comorbidity. Wag/Rij rats exhibited elevated levels of cFos immediate early gene activation in multiple terminal regions for the dopaminergic system, including the frontal cortex, nucleus accumbens, and striatum [36]. Furthermore, administration of a D2/D3 agonist showed antidepressant activity in the Wag/Rij rats, whereas a D2/D3 antagonist exacerbated depressive phenotypes in the FST [61]. These compounds produced very little effect in Wistar control rats, indicating the dopaminergic system plays a key role in the Wag/Rij phenotypes; however, additional studies in the Wag/Rij rats did not implicate dopaminergic system dysfunction as a cause for SWD [62]. These findings suggest that dopaminergic alterations in Wag/Rij rats are more strongly related to depression-like phenotypes than seizure-related SWD, meaning dopaminergic abnormalities may only underlie certain aspects of the comorbidity.

Collectively, the current results support alterations in the dopaminergic systems of rodent models of partial and absence epilepsy, and these alterations could be behind certain components of the depression and epilepsy comorbidity phenotypes. Furthermore, pharmacological elevation of dopaminergic function may have both antidepressant and anticonvulsant efficacy, as well.

3.1.3 GABA—$GABA_A$ receptors are ligand-gated Cl channels that hyperpolarize the cell, whereas $GABA_B$ receptors are metabotropic, G protein-coupled receptors that activate a signaling cascade that opens a K^+ channel, allowing for a slower but more prolonged hyperpolarization of the cell. Decreases in GABA transmission have been implicated in the excess excitation that is characteristic of epilepsy. Accordingly, some models of generalized convulsive seizures and depression comorbidity were associated with decreases in GABA, and increases in GABA levels can be therapeutic. For example, androstenol, which is thought to potentiate $GABA_A$ receptor function [63], decreased immobility in the FST and protected against 6 Hz and PTZ-induced seizures in a dose-dependent fashion in mice. Although $GABA_B$ receptors have been implicated in seizure susceptibility and depression individually, little is known about the role of these receptors in convulsive comorbidity models.

In animal models of absence epilepsy and depression comorbidity, GABA has complex effects that depend on the particular receptor subtype and brain region involved. Wag/Rij rats have decreased cortical $GABA_B$ receptor function [64], and antagonism of $GABA_A$ receptors by bicuculline administration in the ventrobasal thalamic complex increased the magnitude of SWD and was alleviated by co-administration of a $GABA_B$ antagonist. However, administration of the $GABA_B$ antagonist alone had no effect on SWDs, suggesting $GABA_B$ receptors serve primarily as modulators of $GABA_A$ function [65]. Vigabatrin and ethosuximide, two anticonvulsants that increase GABA levels, were found to exhibit both anticonvulsant and antidepressant effects in Wag/Rij rats, supporting a role for GABA in this comorbidity model [66, 67]. In GAERS, $GABA_A$ inhibitory postsynaptic currents in the nucleus reticularis thalami had an increased amplitude and slower decay, as

well as decreased paired-pulse depression, reminiscent of human epilepsy and computer-generated models of absence epilepsy [68]. Because these changes were present prior to the onset of seizures, they are unlikely to represent a compensatory response to absence epilepsy. Collectively, these results imply that subtle, region-specific alterations in GABAergic function may underlie the absence seizure phenotype, and perhaps the depressive phenotype of these animals, with alterations in $GABA_A$ in some brain regions potentially increasing seizure susceptibility, and alterations in $GABA_B$ playing a modulatory role in neural excitation [68]. Further research on the role of GABA in depression-related behaviors of these models is needed.

3.1.4 Glutamate—As the primary excitatory neurotransmitter in the brain, changes in the levels and function of glutamate are often a component of epilepsy. Ionotropic glutamate receptors, consisting of NMDA, AMPA, and kainate subtypes, are ligand-gated cation channels that depolarize the cell. Metabotropic glutamate receptors, or mGluRs, are G protein-coupled receptors that signal via second messenger pathways and allow for slower, more prolonged actions.

Ionotropic glutamate receptors are clearly implicated in epilepsy and depression separately, but have rarely been evaluated for simultaneous seizure and depression-like phenotypes in comorbidity models. For example, in the kainic acid model of comorbid epilepsy and depression, kainate induced seizures by activating kainate receptors. Antagonism of NMDA or AMPA receptors had a therapeutic effect on the progression of amygdala kindling [69] and self-sustaining SE induced by electrical stimulation of the perforant pathway [70]. NMDA antagonists such as ketamine decreased immobility in the FST and protected against stress-induced depression phenotypes in the sucrose preference test [71]. In regards to metabotropic glutamate receptors, administration of AIDA, an mGluR1 antagonist, decreased seizure severity following pilocarpine administration and decreased immobility in the TST (but not the FST) [26].

In the GAERS absence seizure model, cortical NMDA responses were much more widely distributed and of longer duration, perhaps contributing to their hyperexcitable synchronicity [72]. Additionally, ionotropic glutamatergic receptors were found to interact in the Wag/Rij model. Administration of NMDA increased the frequency of SWD, but this increase could be blocked by co-administration of an AMPA antagonist. Similarly, administration of AMPA alone increased the frequency of SWD [73], but co-administration of an NMDA receptor-antagonist was sufficient to block this increase. In GEPRs, inhibition of glutamate synthesis, NMDA, or AMPA receptors attenuated seizure severity [74]. Contrary to the pilocarpine-SE model, where decreases in mGluR 2/3 activation increased with seizure sensitivity, mGluR 2/3 antagonists decreased seizure frequency in Wag/Rij rats [75].

Combined, these observations hint at a role for both ionotropic and metabotropic glutamate receptors in comorbid epilepsy and depression and point to a therapeutic role for antagonists of these receptors. However, determining the contribution of various glutamate receptors and their therapeutic potential in seizure and depression phenotypes simultaneously will require more research.

3.1.5 Norepinephrine (NE)—As part of the monoamine hypothesis of depression, noradrenergic dysfunction has been implicated in the etiology and treatment of that disorder, and NE has less well known but potent anticonvulsant properties [76], as well, meaning alterations in this system may both underlie comorbidity and serve as a novel therapeutic target.

NE function has been studied in some animal models of depression and epilepsy comorbidity. Perhaps the best characterized of these is the GEPR model, which has profound and widespread deficits in NE transmission in both GEPR-3s and GEPR-9s, including impairments in the telencephalon, thalamus/hypothalamus, midbrain, pons/medulla, and cerebellum [77]. 6-OHDA lesions of the noradrenergic system in the GEPR model exacerbated seizure severity, whereas increasing NE signaling using NE reuptake inhibitors or α1, β1, or β2 agonists dose-dependently relieved seizures [78, 79]. SwLo rats have a specific decrease in NE in the hippocampus [45], and chronic, but not acute, treatment with NE reuptake inhibitors rescued the depression-like phenotype of these rats in the FST [42]. It would be interesting to see whether noradrenergic drugs are also antidepressant in GEPR rats and anticonvulsant in SwLo rats.

Mice that lack norepinephrine (Dbh −/−) showed decreased seizure thresholds, enhanced seizure severity, and increased mortality in response to flurothyl-, PTZ-, kainic acid-and sound-induced seizures, and seizure susceptibility is rescued by restoring NE transmission [47, 80, 81]. Somewhat surprisingly, Dbh −/− mice had no baseline immobility differences in the FST or TST; however, they were resistant to the effects of multiple classes of antidepressant drugs. Restoration of NE levels with L-threo-3,4-dihydroxyphenylserine (DOPS) reinstated the antidepressant effect of desipramine in FST, demonstrating the importance of NE transmission for antidepressant efficacy [50].

Norepinephrine transporter (NET) knockout (NET −/−) mice have increased basal extracellular NE levels and show decreased immobility in the FST and TST and decreased PTZ and kainic acid seizure threshold [82, 83]. These results indicate that NET −/− mice may be a model of comorbidity resilience, although other studies have seen a proconvulsant phenotype under some conditions [84].

Additional support for the role of NE in epilepsy and depression comorbidity comes from rats kindled with PTZ; they exhibited decreased immobility in the FST and TST following treatment with NET inhibitors [15]. NE transporter abundance was significantly increased in the perirhinal cortex following PTZ kindling, which would presumably decrease extracellular NE levels, suggesting that the noradrenergic dysfunction may be directly involved in this model of the comorbidity [15]. Finally, NE depletion attenuated the anticonvulsant activity of the ketogenic diet, vagus nerve stimulation, and valproic acid [49, 85, 86]. Taken as a whole, these findings argue strongly that NE plays a role in epilepsy and depression comorbidity, as well as treatment efficacy.

3.1.6 Serotonin—Serotonin, the other monoamine implicated in depression, also modulates seizure susceptibility and may be involved in at least some aspects of depression and epilepsy comorbidity in a variety of models.

The pilocarpine-induced SE paradigm, which produced spontaneous seizures and increased immobility in the FST, decreased hippocampal serotonin concentration, turnover, and release [20, 24]. Furthermore, several compounds that produce anticonvulsant and antidepressant effects in the pilocarpine model, such as citalopram, imipramine, MK-801, and MPEP, also increased hippocampal serotonin release [26].

Several studies have assessed the role of various serotonergic subtypes. Specifically, a number of studies have revealed increases in the function of the presynaptic serotonin 1A autoreceptor and expression of the serotonin 2C receptor following pilocarpine-induced seizures [23, 25]. The depression-like phenotypes associated with these models were reversed by the 5-HT1A agonist 8-OH-DPAT, and b. monnieri, an herbal remedy which increases hippocampal serotonin levels. Expression of the 5-HT5b gene and hippocampal 5-HT levels were reduced following KA-induced seizures and were associated with increased immobility in the FST and decreased sucrose preference [16, 17].

GEPR-9s exhibited deficits in serotonergic transmission, including impaired tryptophan hydroxylase activity, widespread decreases in concentration and uptake of 5-HT, and alterations in 5-HT receptor abundance [87, 88]. Carbamazepine, which increases serotonin levels, also decreased seizure severity in a dose-dependent fashion in both GEPR-3s and GEPR-9s [89]. Coadministration of a 5-HT 1A receptor antagonist (pindolol or LY 206130) with fluoxetine made fluoxetine more effective at reducing seizures in GEPR-9s [90]. Thus, studies with KA and the GEPRs point to the involvement of deficits in serotonergic tone in multiple animal models of comorbid epilepsy and depression and reveal candidate targets for treatment.

3.2 Other mechanisms of interest

Beyond the classical neurotransmitters, there are several other classes of molecules and systems that are worthy of discussion. Although some of these have been implicated in epilepsy or depression individually, they deserve consideration for future investigation in the context of comorbidity.

3.2.1 Ion channels—Many different ion channels have been implicated in epilepsy, including voltage-gated Na^+, Ca^{2+}, and K^+ channels. Rare mutations in ion channels cause familial epilepsy, and mood disorders are included in the phenotypic spectrum of some epilepsy-associated ion channel mutations [91], which means that ion channel dysfunction may also contribute to comorbidity.

Amiloride, which blocks epithelial Na^+ channels, was an effective antidepressant in the FST and anticonvulsant in the PTZ and ICES paradigms [92]. JPZ-4, a dual Na^+ and Ca^{2+} channel blocker, also decreased immobility in the FST and increased seizure thresholds in the 6 Hz, MES, and PTZ models [93]. However, another Na^+ channel blocker, lamotrigine, has been associated with increased risk of suicidality in the clinical population [6–11]. These results highlight the necessity of improvements in our understanding of the role of Na^+ activity in these phenotypes and their treatment.

Ca^{2+} channels are also implicated in rodent models of comorbid epilepsy and depression, and Ca^{2+} channel blockers have been put forward as effective treatment strategies. In the GEPR model, Ca^{2+} channel current and subunit abundance were increased in the inferior colliculus [94], and a variety of Ca^{2+} channel antagonists had anticonvulsant properties [95]. Additionally, in Wag/Rij rats, expression of Cav2.1 channels in the reticular thalamic nucleus increased along with the appearance of SWD [96]. Treatment with ethosuximide, which likely acts by blocking Ca^{2+} channels, decreased both SWD and FST immobility. Na^{+} channel blockers, such as zonisamide or carbamazepine, did not impact FST performance, suggesting that Ca^{2+} channel activity may be more relevant for the comorbidity in this model, with more therapeutic potential [67]. Interestingly, an increase in suicidality has been suggested following treatment with levetiracetam [5, 7, 10, 11], which may act through inhibition of Ca^{2+} channels [97]. Additional studies are therefore clearly warranted to elucidate the role of Ca^{2+} channels in epilepsy, depression, and/or suicidality.

Entry of K^{+} helps the neuron return to its resting potential, thereby terminating the action potential, and K^{+} channel dysfunction can cause neuronal hyperexcitability. Several K^{+} channel subunits and channel function were reduced in the hippocampus and cortex of GEPR rats [98]; similar changes in K+ channel subunits could be blocked by treatment with ethosuximide in Wag/Rij rats [99]. Additionally, certain K^{+} channel knockout mice demonstrated depression-like phenotypes. Knockout of the Kv4.2 K^{+} channel produced fluoxetine-resistant FST immobility in mice [100]. TASK3 knockout mice, which lack expression of the Kcnk9 K^{+} channel, also displayed increased immobility in both the FST and TST [101]. Importantly for the comorbidity of depression with epilepsy, mutations in the *TASK3* gene have also been identified in the GAERS model of absence epilepsy [102]. Interestingly, the deletion of other Trek-1 (Kcnk2) K^{+} channels was associated with depression resistance [103]. Together, these findings hint at an intriguing role for K^{+} channel dysfunction in both depression and epilepsy, but determining whether K^{+} channels are a viable therapeutic target for comorbidity awaits further studies targeting these phenotypes simultaneously.

3.2.2 Hypothalamic-Pituitary-Adrenal Axis—Stress plays a major role in the development of depression and is also a common trigger for seizures in epileptic patients. Stress exerts many of its effects on the brain and body via regulation of the hypothalamic-pituitary-adrenal axis (HPA). Stress triggers the release of corticotrophin releasing hormone (CRH) from the hypothalamus, which stimulates the release of adrenocorticotropic hormone (ACTH) from the anterior pituitary, which in turn elicits the release of glucocorticoids (cortisol in humans, corticosterone in rodents; CORT) from the adrenal cortex. A negative feedback loop decreases the activity of this pathway when glucocorticoid levels are high by acting at the level of the pituitary and hypothalamus.

In general, the HPA axis is overactive in several animal models of depression and epilepsy comorbidity. For example, exposure to early life stress increased CORT levels and lowered the number of stimulations required to achieve amygdala kindling in Wistar rats [104]. Rats exposed to pilocarpine-induced SE showed an elevation of CORT levels that was not suppressed with dexamethasone administration, and a positive correlation was seen between the degree of CORT elevation and immobility in the FST [22]. In this model, administration

of CRH increased CORT levels and immobility in the FST. Blocking glucocorticoid receptors with intra-raphe (but not intra-hippocampal) mifepristone improved FST scores only in the most severely depressed rats [23].

HPA axis activation has also been linked to the severity of seizure phenotypes in models of absence epilepsy. Wag/Rij rats exhibited an elevation in foot shock stress-induced CORT levels. Interestingly, SWD were significantly decreased in the first 15 minutes following foot shock, while CORT levels were still elevated, and then SWD were increased after CORT levels return to baseline, suggesting that the period of HPA hyperactivity may worsen seizure frequency [105]. While the connections between HPA axis activity and comorbid epilepsy and depression are still unclear, there does appear to be a relationship that merits further investigation.

3.2.3 Neuroinflammation—Neuroinflammatory responses are frequently linked with depression and epilepsy clinically and have also been assessed in rodent models of their comorbidity. In the pilocarpine-induced SE model, intrahippocampal delivery of an interleukin-1 receptor antagonist (IL-1ra) decreased FST immobility and increased preference for saccharin solution. Basal CORT levels were normalized, and serotonin release and response to dexamethasone were both partially restored following IL-1ra; however, there were no effects on seizure frequency [21]. Coadministration of fluoxetine and IL-1ra, but not fluoxetine alone, was also effective at improving the depression-like phenotypes, but again had no effect on seizure frequency [24]. Other studies using animal models of comorbid epilepsy and depression have found varying effects of IL-1 alterations on seizure frequency. For example, IL-1B activation was elevated in GAERS, and blockade of IL-1β synthesis decreased SWD duration and number [106]. In contrast, IL-1β administration was anticonvulsant in an amygdala kindling paradigm [107]. These studies indicate that neuroinflammatory molecules like IL-1β may contribute to some aspects of comorbid epilepsy and depression, but the precise nature of these effects remains a mystery for now.

3.2.4 Neurotrophins—Neurotrophins, particularly brain derived neurotrophic factor (BDNF) and its receptor, TrkB, likely contribute to depression and epilepsy and mediate therapeutic efficacy. Indeed, decreases in BDNF are seen in adults with epilepsy [108] and depression, and these abnormalities can be reversed following antidepressant treatment [109]. TrkB and BDNF have also been implicated in animal models of epilepsy and depression. For example, overexpression of hippocampal BDNF decreased the severity of spontaneous seizures following pilocarpine-induced SE, pointing to an anticonvulsant effect of BDNF signaling [110]. By contrast, in a kainic acid-induced SE paradigm, transgenic mice with increased TrkB expression showed accelerated development of spontaneous seizures, while mice expressing a dominant negative form of TrkB showed delayed development of spontaneous seizures, indicating TrkB signaling has a proconvulsant effect [111]. Likewise, deletion of TrkB in the hippocampus inhibited amygdala and hippocampal kindling epileptogenesis, suggesting a proconvulsant effect of TrkB activation [112]. Interestingly, this effect of TrkB knockout was not phenocopied by BDNF knockout, implicating another TrkB ligand.

BDNF and TrkB have also been assessed in rodent models of depression. Exercise, which has antidepressant and anticonvulsant properties, causes an increase in BDNF expression [113] (discussed further in section 3.4.2). Mice expressing a Val66Met mutation that leads to decreased BDNF exhibited decreased sucrose preference and increased FST immobility following restraint stress [114], implying BDNF may serve as a protective mechanism against the harmful effects of stress on depression phenotypes. Similarly, blockade of TrkB with K252a prevented lamotrigine from exerting antidepressant effects in a variety of tests, suggesting that TrkB is also important for antidepressant drug efficacy [115]. Despite these studies on the role of neurotrophic factors in depression and epilepsy separately, more work is needed to uncover the role of BDNF and TrkB in the comorbidity of these disorders, especially in terms of the seemingly contradictory findings concerning seizure susceptibility. Moreover, the dual antidepressant and proconvulsant effects of BDNF/TrkB signaling highlight the difficulties of finding treatment strategies that are not contraindicated.

3.3 Brain regions of interest

Several regions of the brain have been implicated in animal models of comorbid epilepsy and depression. Because the hippocampus and amygdala show structural and metabolic abnormalities in patients with depression and epilepsy, can be electrically kindled, and experience profound neuronal loss following pilocarpine-or KA-induced SE, these regions are of interest for TLE models [19, 29]. The vast majority of animal models of comorbid limbic epilepsy and depression are associated with changes in structure, neurotransmitters, ion channels, and other mechanisms discussed above that lead to dysfunction of the hippocampus and/or amygdala.

Other neuroanatomical substrates are also implicated in depression and epilepsy comorbidity. A large body of evidence has demonstrated a role for the inferior colliculus and other midbrain regions in the comorbid phenotype of the GEPRs [94, 116]. In Wag/Rij rats, the frontocortical regions, striatum, and nucleus accumbens appear to be important for the seizure and depression-related phenotypes [61]. Of these regions, the prefrontal cortex and nucleus accumbens are also implicated in the SwLo rat phenotypes [44, 45], while the thalamus appears to be a key region in GAERS and GEPRs [68, 77].

Each of these brain regions has been discussed in depth in the individual sections on mechanisms underlying co-morbid epilepsy and depression (for further detail, see sections 3.1 and 3.2). Though not reiterated here, it is important to note that a contribution of these same regions in multiple paradigms is suggestive of a causal role or potential therapeutic target for depression and epilepsy co-morbidity.

3.4 Non-pharmacological therapies

Difficulties with safe and efficacious treatment are a major clinical problem in depression and epilepsy comorbidity; patients are often refractory to treatment, and many anticonvulsants have depressant effects, while several antidepressants have proconvulsant effects [3, 4], meaning non-pharmacological therapies may be especially useful for this clinical population. Three such therapies, vagus nerve stimulation, exercise, and the ketogenic diet, have demonstrated both anticonvulsant and antidepressant properties in

animal models. Because these therapies appear to have the potential for clinical efficacy while simultaneously lacking adverse effects on one disease or the other, they may represent the best therapeutic strategies to explore in the future for the treatment of epilepsy and depression comorbidity.

3.4.1 Vagus nerve stimulation—Vagus nerve stimulation (VNS) is used clinically to treat otherwise refractory depression and epilepsy as separate conditions. Stimulation of the vagus nerve decreased immobility in the FST in mice in a 5-HT-dependent manner [117], while it also reduced PTZ-induced cortical electrographic spiking in rats [118]. Consistent with the antidepressant and anticonvulsant properties of NE discussed in section 3.1.5, multiple effects of VNS were dependent upon an intact locus coeruleus [86], suggesting the augmentation of noradrenergic function underlies its therapeutic efficacy. Despite these promising results, little is known about the effects of VNS on comorbid epilepsy and depression symptoms, which should be explored for their therapeutic potential.

3.4.2 Aerobic exercise—Aerobic exercise has both anticonvulsant and antidepressant effects clinically and in animals. Rats exposed to 3 weeks of voluntary wheel running showed decreased KA-induced seizure severity associated with increased expression of galanin mRNA in the locus coeruleus, and the anticonvulsant effects were blocked by pretreatment with a galanin receptor antagonist [119]. Additionally, 28 days of voluntary wheel running increased hippocampal BDNF levels and decreased immobility in the FST and TST in mice [113]. While research in this area is just taking off, exercise nevertheless shows great promise as a non-pharmacological therapy for comorbid epilepsy and depression.

3.4.3 Ketogenic diet—The ketogenic diet (KD) is a high-fat, low-carbohydrate, low-protein diet used for nearly 100 years to control refractory epilepsy. Interestingly, rats fed a ketogenic diet displayed decreased immobility in the FST, indicating the diet may also have antidepressant properties [120]. The anticonvulsant effects of the KD may be mediated at least in part by NE, as demonstrated by loss of efficacy in Dbh −/− mice [85]. Whether the ketogenic diet can alleviate both depression-and seizure-related phenotypes in an animal model of comorbidity has yet to be determined.

4. Conclusion

The bidirectional comorbidity between depression and epilepsy has become recognized as a serious clinical problem due to its negative impact on patients' quality of life and challenges to successful treatment and prognosis. The high incidence and impact of depression in epilepsy has raised enough alarm that an expert panel of neurologists and psychiatrists from the Epilepsy Foundation's Mood Disorders Initiative wrote and published a "Consensus Statement" to improve the recognition and treatment of depressive disorders in patients with epilepsy [121]. The establishment of several chemical, electrical, and genetic animal models of this comorbidity is a crucial step toward a better understanding of the underlying neurobiological substrates and potential therapeutics.

Though these animal models have revealed some useful information, this field is still in its infancy, with many issues that need to be addressed. Despite the wealth of animal models of epilepsy that also show depression-related phenotypes, there is currently only one model of depression that also shows enhanced seizure susceptibility and epileptogenesis: the SwLo rat. More models addressing this direction of the comorbidity are needed for a better understanding of the similarities and differences in causes, mechanisms, and treatment strategies for this half of the comorbidity equation. Additionally, many of the current models focus on seizure susceptibility rather than true epilepsy (i.e. the development of unprovoked, spontaneous seizures). Because the clinical comorbidity is between depression and epilepsy, rather than depression and seizure susceptibility per se, a stronger emphasis on animal models of epileptogenesis may be more clinically relevant.

Future studies on the genetic underpinnings of this comorbidity are also needed. Since both diseases are known to have a large genetic component, it seems likely that genetic risk factors also contribute to comorbidity [122]. Genetic/selective breeding models of comorbidity represent valuable resources for the identification of susceptibility genes. Quantitative trait loci (QTL) and linkage mapping studies, microarrays, and/or analysis of protein expression could all be used to uncover candidates for predictive screening or targets for novel therapeutics. Targeting these candidates with site-specific genetic manipulations and/or viral vectors and assessing the effect on the phenotypes of interest would also contribute a great deal to both our understanding of and ability to treat epilepsy and depression comorbidity.

In conclusion, further investigation of current animal models and the development of entirely new animal models are critical for the discovery of neurobiological substrates underlying epilepsy and depression comorbidity, for identifying novel therapeutic targets, and as a screening tool for testing the safety and efficacy of such new treatments.

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References

1. Kanner AM. Depression in epilepsy: a neurobiologic perspective. Epilepsy Currents. 2005; 5:21–27. [PubMed: 16059450]
2. Hesdorffer DC, Hauser WA, Olafsson E, Ludvigsson P, Kjartansson O. Depression and suicide attempt as risk factors for incident unprovoked seizures. Annals of Neurology. 2006; 59:35–41. [PubMed: 16217743]
3. Hesdorffer DC, Kanner AM. The FDA alert on suicidality and antiepileptic drugs: Fire or false alarm? Epilepsia. 2009; 50:978–986. [PubMed: 19496806]
4. Judge BS, Rentmeester LL. Antidepressant overdose-induced seizures. Neurologic Clinics. 2011; 29:565–580. [PubMed: 21803210]
5. Andersohn F, Schade R, Willich SN, Garbe E. Use of antiepileptic drugs in epilepsy and the risk of self-harm or suicidal behavior. Neurology. 2010; 75:335–340. [PubMed: 20660863]
6. Bagary M. Epilepsy, antiepileptic drugs and suicidality. Current Opinion in Neurology. 2011; 24:177–182. [PubMed: 21293270]

7. Fountoulakis KN, Gonda X, Samara M, Siapera M, Karavelas V, Ristic DI, et al. Antiepileptic drugs and suicidality. Journal of Psychopharmacology. 2012
8. Machado RA, Espinosa AG, Melendrez D, Gonzalez YR, Garcia VF, Rodriguez YQ. Suicidal risk and suicide attempts in people treated with antiepileptic drugs for epilepsy. Seizure. 2011; 20:280–284. [PubMed: 21269844]
9. Olesen JB, Hansen PR, Erdal J, Abildstrom SZ, Weeke P, Fosbol EL, et al. Antiepileptic drugs and risk of suicide: a nationwide study. Pharmacoepidemiology and Drug Safety. 2010; 19:518–524. [PubMed: 20235081]
10. Patorno E, Bohn RL, Wahl PM, Avorn J, Patrick AR, Liu J, et al. Anticonvulsant medications and the risk of suicide, attempted suicide, or violent death. JAMA. 2010; 303:1401–1409.
11. VanCott AC, Cramer JA, Copeland LA, Zeber JE, Steinman MA, Dersh JJ, et al. Suicide-related behaviors in older patients with new anti-epileptic drug use: data from the VA hospital system. BMC Medicine. 2010; 8:4. [PubMed: 20064226]
12. Mula M, Hesdorffer DC. Suicidal behavior and antiepileptic drugs in epilepsy: analysis of the emerging evidence. Drug, Healthcare and Patient Safety. 2011; 3:15–20.
13. Shehata GA, Bateh Ael A. Cognitive function, mood, behavioral aspects, and personality traits of adult males with idiopathic epilepsy. Epilepsy & Behavior. 2009; 14:121–124. [PubMed: 18801461]
14. Mortazavi F, Ericson M, Story D, Hulce VD, Dunbar GL. Spatial learning deficits and emotional impairments in pentylenetetrazole-kindled rats. Epilepsy & Behavior. 2005; 7:629–638. [PubMed: 16246633]
15. Takechi K, Suemaru K, Kawasaki H, Araki H. Regulatory role of the dopamine and norepinephrine transporters in pentylenetetrazol-kindled mice: association with effect of antidepressants. European Journal of Pharmacology. 2011; 673:33–39. [PubMed: 22044920]
16. Koh S, Magid R, Chung H, Stine CD, Wilson DN. Depressive behavior and selective down-regulation of serotonin receptor expression after early-life seizures: reversal by environmental enrichment. Epilepsy & Behavior. 2007; 10:26–31. [PubMed: 17196883]
17. Tchekalarova J, Pechlivanova D, Atanasova T, Markova P, Lozanov V, Stoynev A. Diurnal variations in depression-like behavior of Wistar and spontaneously hypertensive rats in the kainate model of temporal lobe epilepsy. Epilepsy & Behavior. 2011; 20:277–285. [PubMed: 21277833]
18. Tabb K, Boss-Williams KA, Weiss JM, Weinshenker D. Rats bred for susceptibility to depression-like phenotypes have higher kainic acid-induced seizure mortality than their depression-resistant counterparts. Epilepsy research. 2007; 74:140–146. [PubMed: 17400428]
19. Groticke I, Hoffmann K, Loscher W. Behavioral alterations in a mouse model of temporal lobe epilepsy induced by intrahippocampal injection of kainate. Experimental Neurology. 2008; 213:71–83. [PubMed: 18585709]
20. Mazarati A, Siddarth P, Baldwin RA, Shin D, Caplan R, Sankar R. Depression after status epilepticus: behavioural and biochemical deficits and effects of fluoxetine. Brain. 2008; 131:2071–2083. [PubMed: 18559371]
21. Mazarati AM, Pineda E, Shin D, Tio D, Taylor AN, Sankar R. Comorbidity between epilepsy and depression: role of hippocampal interleukin-1beta. Neurobiology of Disease. 2010; 37:461–467. [PubMed: 19900553]
22. Mazarati AM, Shin D, Kwon YS, Bragin A, Pineda E, Tio D, et al. Elevated plasma corticosterone level and depressive behavior in experimental temporal lobe epilepsy. Neurobiology of Disease. 2009; 34:457–461. [PubMed: 19285131]
23. Pineda EA, Hensler JG, Sankar R, Shin D, Burke TF, Mazarati AM. Plasticity of presynaptic and postsynaptic serotonin 1A receptors in an animal model of epilepsy-associated depression. Neuropsychopharmacology. 2011; 36:1305–1316. [PubMed: 21346733]
24. Pineda EA, Hensler JG, Sankar R, Shin D, Burke TF, Mazarati AM. Interleukin-1beta causes fluoxetine resistance in an animal model of epilepsy-associated depression. Neurotherapeutics. 2012; 9:477–485. [PubMed: 22427156]
25. Krishnakumar A, Nandhu MS, Paulose CS. Upregulation of 5-HT2C receptors in hippocampus of pilocarpine-induced epileptic rats: antagonism by Bacopa monnieri. Epilepsy & Behavior. 2009; 16:225–230. [PubMed: 19700373]

26. Smolders I, Clinckers R, Meurs A, De Bundel D, Portelli J, Ebinger G, et al. Direct enhancement of hippocampal dopamine or serotonin levels as a pharmacodynamic measure of combined antidepressant-anticonvulsant action. Neuropharmacology. 2008; 54:1017–1028. [PubMed: 18378264]
27. Epps SA, Tabb KD, Lin SJ, Kahn AB, Javors MA, Boss-Williams KA, et al. Seizure Susceptibility and Epileptogenesis in a Rat Model of Epilepsy and Depression Co-Morbidity. Neuropsychopharmacology. 2012 In press.
28. Dos Santos JG Jr. Longo BM, Blanco MM, Menezes de Oliveira MG, Mello LE. Behavioral changes resulting from the administration of cycloheximide in the pilocarpine model of epilepsy. Brain Research. 2005; 1066:37–48. [PubMed: 16343452]
29. Groticke I, Hoffmann K, Loscher W. Behavioral alterations in the pilocarpine model of temporal lobe epilepsy in mice. Experimental Neurology. 2007; 207:329–349. [PubMed: 17714705]
30. Muller CJ, Groticke I, Bankstahl M, Loscher W. Behavioral and cognitive alterations, spontaneous seizures, and neuropathology developing after a pilocarpine-induced status epilepticus in C57BL/6 mice. Experimental Neurology. 2009; 219:284–297. [PubMed: 19500573]
31. Helfer V, Deransart C, Marescaux C, Depaulis A. Amygdala kindling in the rat: anxiogenic-like consequences. Neuroscience. 1996; 73:971–978. [PubMed: 8809816]
32. Ma J, Leung LS. Schizophrenia-like behavioral changes after partial hippocampal kindling. Brain Research. 2004; 997:111–118. [PubMed: 14715156]
33. Runke D, McIntyre DC, St-Onge V, Gilby KL. Relation between startle reactivity and sucrose avidity in two rat strains bred for differential seizure susceptibility. Experimental Neurology. 2011; 229:259–263. [PubMed: 21324316]
34. Mazarati A, Shin D, Auvin S, Caplan R, Sankar R. Kindling epileptogenesis in immature rats leads to persistent depressive behavior. Epilepsy & Behavior. 2007; 10:377–383. [PubMed: 17368107]
35. Sarkisova K, van Luijtelaar G. The WAG/Rij strain: a genetic animal model of absence epilepsy with comorbidity of depression Progress. Neuropsychopharmacology & Biological Psychiatry. 2011; 35:854–876.
36. Sarkisova KY, Midzianovskaia IS, Kulikov MA. Depressive-like behavioral alterations and c-fos expression in the dopaminergic brain regions in WAG/Rij rats with genetic absence epilepsy. Behavioural Brain Research. 2003; 144:211–226. [PubMed: 12946611]
37. Danober L, Deransart C, Depaulis A, Vergnes M, Marescaux C. Pathophysiological mechanisms of genetic absence epilepsy in the rat. Progress in Neurobiology. 1998; 55:27–57. [PubMed: 9602499]
38. Jones NC, Salzberg MR, Kumar G, Couper A, Morris MJ, O'Brien TJ. Elevated anxiety and depressive-like behavior in a rat model of genetic generalized epilepsy suggesting common causation. Experimental Neurology. 2008; 209:254–260. [PubMed: 18022621]
39. Jobe PC, Dailey JW, Wernicke JF. A noradrenergic and serotonergic hypothesis of the linkage between epilepsy and affective disorders. Critical Reviews in Neurobiology. 1999; 13:317–356. [PubMed: 11028680]
40. Jobe, PC.; Weber, RJ. Co-morbidity of neurological and affective disorders: the model of the genetically epilepsy-prone rat. In: Gilliam, FG.; Kanner, AM.; Sheline, YI., editors. Depression and Brain Dysfunction. Abingdon, Oxon, UK: Taylor & Francis; 2006. p. xxiip. 298
41. Weiss JM, Cierpial MA, West CH. Selective breeding of rats for high and low motor activity in a swim test: toward a new animal model of depression. Pharmacology, Biochemistry, and Behavior. 1998; 61:49–66.
42. West CH, Weiss JM. Effects of antidepressant drugs on rats bred for low activity in the swim test. Pharmacology, Biochemistry, and Behavior. 1998; 61:67–79.
43. West CH, Bonsall RW, Emery MS, Weiss JM. Rats selectively bred for high and low swim-test activity show differential responses to dopaminergic drugs. Psychopharmacology. 1999; 146:241–251. [PubMed: 10541723]
44. West CH, Boss-Williams KA, Weiss JM. Motor activation by amphetamine infusion into nucleus accumbens core and shell subregions of rats differentially sensitive to dopaminergic drugs. Behavioural Brain Research. 1999; 98:155–165. [PubMed: 10210531]

45. Weiss JM, West CH, Emery MS, Bonsall RW, Moore JP, Boss-Williams KA. Rats selectively-bred for behavior related to affective disorders: proclivity for intake of alcohol and drugs of abuse, and measures of brain monoamines. Biochem Pharmacol. 2008; 75:134–159. [PubMed: 18053966]
46. Thomas SA, Marck BT, Palmiter RD, Matsumoto AM. Restoration of norepinephrine and reversal of phenotypes in mice lacking dopamine beta-hydroxylase. Journal of Neurochemistry. 1998; 70:2468–2476. [PubMed: 9603211]
47. Szot P, Weinshenker D, White SS, Robbins CA, Rust NC, Schwartzkroin PA, et al. Norepinephrine-deficient mice have increased susceptibility to seizureinducing stimuli. The Journal of Neuroscience. 1999; 19:10985–10992. [PubMed: 10594079]
48. Szot P, Weinshenker D, Rho JM, Storey TW, Schwartzkroin PA. Norepinephrine is required for the anticonvulsant effect of the ketogenic diet. Brain Research Developmental Brain Research. 2001; 129:211–214. [PubMed: 11506865]
49. Schank JR, Liles LC, Weinshenker D. Reduced anticonvulsant efficacy of valproic acid in dopamine beta-hydroxylase knockout mice. Epilepsy Research. 2005; 65:23–31. [PubMed: 15955669]
50. Cryan JF, Dalvi A, Jin SH, Hirsch BR, Lucki I, Thomas SA. Use of dopaminebeta-hydroxylase-deficient mice to determine the role of norepinephrine in the mechanism of action of antidepressant drugs. The Journal of Pharmacology and Experimental Therapeutics. 2001; 298:651–657. [PubMed: 11454927]
51. Krishnan V, Nestler EJ. The molecular neurobiology of depression. Nature. 2008; 455:894–902. [PubMed: 18923511]
52. Werner FM, Covenas R. Classical neurotransmitters and neuropeptides involved in major depression: a review. The International Journal of Neuroscience. 2010; 120:455–470. [PubMed: 20583898]
53. Kanner AM. Mood disorder and epilepsy: a neurobiologic perspective of their relationship. Dialogues in Clinical Neuroscience. 2008; 10:39–45. [PubMed: 18472483]
54. Noebels JL. The biology of epilepsy genes. Annual Review of Neuroscience. 2003; 26:599–625.
55. Kanner AM. Depression and epilepsy: do glucocorticoids and glutamate explain their relationship? Current Neurology and Neuroscience Reports. 2009; 9:307–312. [PubMed: 19515283]
56. Jope RS, Simonato M, Lally K. Acetylcholine content in rat brain is elevated by status epilepticus induced by lithium and pilocarpine. Journal of Neurochemistry. 1987; 49:944–951. [PubMed: 3612132]
57. Laird HE 2nd, Hadjiconstantinou M, Neff NH. Abnormalities in the central cholinergic transmitter system of the genetically epilepsy-prone rat. Life Sciences. 1986; 39:783–787. [PubMed: 3018414]
58. Berdiev RK, van Luijtelaar G. Cholinergic stimulation of the nucleus basalis of Meynert and reticular thalamic nucleus affects spike-and-wave discharges in WAG/Rij rats. Neuroscience Letters. 2009; 463:249–253. [PubMed: 19638297]
59. Turski WA, Czuczwar SJ, Turski L, Sieklucka-Dziuba M, Kleinrok Z. Studies on the mechanism of wet dog shakes produced by carbachol in rats. Pharmacology. 1984; 28:112–120. [PubMed: 6200891]
60. Starr MS. The role of dopamine in epilepsy. Synapse. 1996; 22:159–194. [PubMed: 8787131]
61. Sarkisova KY, Kulikov MA, Midzyanovskaya IS, Folomkina AA. Dopamine-dependent nature of depression-like behavior in WAG/Rij rats with genetic absence epilepsy. Neuroscience and Behavioral Physiology. 2008; 38:119–128. [PubMed: 18197376]
62. Willoughby JO, Mackenzie L, Hiscock JJ, Sagar S. Non convulsive spike-wave discharges do not induce Fos in cerebro-cortical neurons. Brain Research Molecular Brain Research. 1993; 18:178–180. [PubMed: 8479286]
63. Kaminski RM, Marini H, Ortinski PI, Vicini S, Rogawski MA. The pheromone androstenol (5 alpha-androst-16-en-3 alpha-ol) is a neurosteroid positive modulator of GABAA receptors. The Journal of Pharmacology and Experimental Therapeutics. 2006; 317:694–703. [PubMed: 16415088]

64. Inaba Y, D'Antuono M, Bertazzoni G, Biagini G, Avoli M. Diminished presynaptic GABA(B) receptor function in the neocortex of a genetic model of absence epilepsy. Neuro-Signals. 2009; 17:121–131. [PubMed: 19176980]
65. Staak R, Pape HC. Contribution of GABA(A) and GABA(B) receptors to thalamic neuronal activity during spontaneous absence seizures in rats. The Journal of Neuroscience. 2001; 21:1378–1384. [PubMed: 11160409]
66. Russo E, Citraro R, Scicchitano F, Urzino A, Marra R, Rispoli V, et al. Vigabatrin has antiepileptogenic and antidepressant effects in an animal model of epilepsy and depression comorbidity. Behavioural Brain Research. 2011; 225:373–376. [PubMed: 21807031]
67. Sarkisova KY, Kuznetsova GD, Kulikov MA, van Luijtelaar G. Spike-wave discharges are necessary for the expression of behavioral depression-like symptoms. Epilepsia. 2010; 51:146–160. [PubMed: 19674046]
68. Bessaih T, Bourgeais L, Badiu CI, Carter DA, Toth TI, Ruano D, et al. Nucleus-specific abnormalities of GABAergic synaptic transmission in a genetic model of absence seizures. Journal of Neurophysiology. 2006; 96:3074–3081. [PubMed: 16971676]
69. Gilbert ME. The NMDA-receptor antagonist, MK-801, suppresses limbic kindling and kindled seizures. Brain Research. 1988; 463:90–99. [PubMed: 2848609]
70. Mazarati AM, Wasterlain CG. N-methyl-D-asparate receptor antagonists abolish the maintenance phase of self-sustaining status epilepticus in rat. Neuroscience Letters. 1999; 265:187–190. [PubMed: 10327162]
71. Autry AE, Adachi M, Nosyreva E, Na ES, Los MF, Cheng PF, et al. NMDA receptor blockade at rest triggers rapid behavioural antidepressant responses. Nature. 2011; 475:91–95. [PubMed: 21677641]
72. Pumain R, Louvel J, Gastard M, Kurcewicz I, Vergnes M. Responses to Nmethyl-D-aspartate are enhanced in rats with petit mal-like seizures. Journal of Neural Transmission Supplementum. 1992; 35:97–108. [PubMed: 1512597]
73. Peeters BW, Ramakers GM, Ellenbroek BA, Vossen JM, Coenen AM. Interactions between NMDA and nonNMDA receptors in nonconvulsive epilepsy in the WAG/Rij inbred strain. Brain Research Bulletin. 1994; 33:715–718. [PubMed: 7514947]
74. Faingold CL, Naritoku DK, Copley CA, Randall ME, Riaz A, Anderson CA, et al. Glutamate in the inferior colliculus plays a critical role in audiogenic seizure initiation. Epilepsy Research. 1992; 13:95–105. [PubMed: 1361165]
75. Ngomba RT, Biagioni F, Casciato S, Willems-van Bree E, Battaglia G, Bruno V, et al. The preferential mGlu2/3 receptor antagonist, LY341495, reduces the frequency of spike-wave discharges in the WAG/Rij rat model of absence epilepsy. Neuropharmacology. 2005; 49(Suppl 1):89–103. [PubMed: 16043198]
76. Weinshenker D, Szot P. The role of catecholamines in seizure susceptibility: new results using genetically engineered mice. Pharmacology & Therapeutics. 2002; 94:213–233. [PubMed: 12113799]
77. Jobe PC, Laird HE 2nd, Ko KH, Ray T, Dailey JW. Abnormalities in monoamine levels in the central nervous system of the genetically epilepsy-prone rat. Epilepsia. 1982; 23:359–366. [PubMed: 6284498]
78. Ko KH, Dailey JW, Jobe PC. Evaluation of monoaminergic receptors in the genetically epilepsy prone rat. Experientia. 1984; 40:70–73. [PubMed: 6692893]
79. Wang C, Mishra PK, Dailey JW, Jobe PC, Browning RA. Noradrenergic terminal fields as determinants of seizure predisposition in GEPR-3s: a neuroanatomic assessment with intracerebral microinjections of 6-hydroxydopamine. Epilepsy Research. 1994; 18:1–9. [PubMed: 8088252]
80. Weinshenker D, Szot P, Miller NS, Palmiter RD. Alpha(1) and beta(2) adrenoreceptor agonists inhibit pentylenetetrazole-induced seizures in mice lacking norepinephrine. The Journal of Pharmacology and Experimental Therapeutics. 2001; 298:1042–1048. [PubMed: 11504801]
81. Szot P, Lester M, Laughlin ML, Palmiter RD, Liles LC, Weinshenker D. The anticonvulsant and proconvulsant effects of alpha2-adrenoreceptor agonists are mediated by distinct populations of alpha2A-adrenoreceptors. Neuroscience. 2004; 126:795–803. [PubMed: 15183527]

82. Xu F, Gainetdinov RR, Wetsel WC, Jones SR, Bohn LM, Miller GW, et al. Mice lacking the norepinephrine transporter are supersensitive to psychostimulants. Nature Neuroscience. 2000; 3:465–471.
83. Kaminski RM, Shippenberg TS, Witkin JM, Rocha BA. Genetic deletion of the norepinephrine transporter decreases vulnerability to seizures. Neuroscience Letters. 2005; 382:51–55. [PubMed: 15911120]
84. Ahern TH, Javors MA, Eagles DA, Martillotti J, Mitchell HA, Liles LC, et al. The effects of chronic norepinephrine transporter inactivation on seizure susceptibility in mice. Neuropsychopharmacology. 2006; 31:730–738. [PubMed: 16052243]
85. Weinshenker D. The contribution of norepinephrine and orexigenic neuropeptides to the anticonvulsant effect of the ketogenic diet. Epilepsia. 2008; 49(Suppl 8):104–107. [PubMed: 19049603]
86. Fornai F, Ruffoli R, Giorgi FS, Paparelli A. The role of locus coeruleus in the antiepileptic activity induced by vagus nerve stimulation. The European Journal of Neuroscience. 2011; 33:2169–2178. [PubMed: 21535457]
87. Statnick MA, Dailey JW, Jobe PC, Browning RA. Abnormalities in brain serotonin concentration, high-affinity uptake, and tryptophan hydroxylase activity in severe-seizure genetically epilepsy-prone rats. Epilepsia. 1996; 37:311–321. [PubMed: 8603634]
88. Statnick MA, Dailey JW, Jobe PC, Browning RA. Abnormalities in 5-HT1A and 5-HT1B receptor binding in severe-seizure genetically epilepsy-prone rats (GEPR-9s). Neuropharmacology. 1996; 35:111–118. [PubMed: 8684590]
89. Dailey JW, Reith ME, Yan QS, Li MY, Jobe PC. Anticonvulsant doses of carbamazepine increase hippocampal extracellular serotonin in genetically epilepsy-prone rats: dose response relationships. Neuroscience Letters. 1997; 227:13–16. [PubMed: 9178847]
90. Browning RA, Wood AV, Merrill MA, Dailey JW, Jobe PC. Enhancement of the anticonvulsant effect of fluoxetine following blockade of 5-HT1A receptors. European Journal of Pharmacology. 1997; 336:1–6. [PubMed: 9384247]
91. Mahoney K, Moore SJ, Buckley D, Alam M, Parfrey P, Penney S, et al. Variable neurologic phenotype in a GEFS+ family with a novel mutation in SCN1A. Seizure. 2009; 18:492–497. [PubMed: 19464195]
92. Ali A, Ahmad FJ, Pillai KK, Vohora D. Evidence of the antiepileptic potential of amiloride with neuropharmacological benefits in rodent models of epilepsy and behavior. Epilepsy & Behavior. 2004; 5:322–328. [PubMed: 15145301]
93. Foreman MM, Hanania T, Stratton SC, Wilcox KS, White HS, Stables JP, et al. In vivo pharmacological effects of JZP-4, a novel anticonvulsant, in models for anticonvulsant, antimania and antidepressant activity. Pharmacology, Biochemistry, and Behavior. 2008; 89:523–534.
94. N'Gouemo P, Faingold CL, Morad M. Calcium channel dysfunction in inferior colliculus neurons of the genetically epilepsy-prone rat. Neuropharmacology. 2009; 56:665–675. [PubMed: 19084544]
95. De Sarro G, De Sarro A, Federico F, Meldrum BS. Anticonvulsant properties of some calcium antagonists on sound-induced seizures in genetically epilepsy prone rats. General Pharmacology. 1990; 21:769–778. [PubMed: 2276595]
96. van de Bovenkamp-Janssen MC, Scheenen WJ, Kuijpers-Kwant FJ, Kozicz T, Veening JG, van Luijtelaar EL, et al. Differential expression of high voltage-activated Ca2+ channel types in the rostral reticular thalamic nucleus of the absence epileptic WAG/Rij rat. Journal of Neurobiology. 2004; 58:467–478. [PubMed: 14978724]
97. Vogl C, Mochida S, Wolff C, Whalley BJ, Stephens GJ. The Synaptic Vesicle Glycoprotein 2A Ligand Levetiracetam Inhibits Presynaptic Ca2+ Channels through an Intracellular Pathway. Molecular pharmacology. 2012; 82:199–208. [PubMed: 22554805]
98. Verma-Ahuja S, Evans MS, Pencek TL. Evidence for decreased calcium dependent potassium conductance in hippocampal CA3 neurons of genetically epilepsy-prone rats. Epilepsy Research. 1995; 22:137–144. [PubMed: 8777900]

99. Blumenfeld H, Klein JP, Schridde U, Vestal M, Rice T, Khera DS, et al. Early treatment suppresses the development of spike-wave epilepsy in a rat model. Epilepsia. 2008; 49:400–409. [PubMed: 18070091]
100. Lockridge A, Su J, Yuan LL. Abnormal 5-HT modulation of stress behaviors in the Kv4.2 knockout mouse. Neuroscience. 2010; 170:1086–1097. [PubMed: 20801198]
101. Gotter AL, Santarelli VP, Doran SM, Tannenbaum PL, Kraus RL, Rosahl TW, et al. TASK-3 as a potential antidepressant target. Brain Research. 2011; 1416:69–79. [PubMed: 21885038]
102. Holter J, Carter D, Leresche N, Crunelli V, Vincent P. A TASK3 channel (KCNK9) mutation in a genetic model of absence epilepsy. Journal of Molecular Neuroscience. 2005; 25:37–51. [PubMed: 15781965]
103. Heurteaux C, Lucas G, Guy N, El Yacoubi M, Thummler S, Peng XD, et al. Deletion of the background potassium channel TREK-1 results in a depression-resistant phenotype. Nature Neuroscience. 2006; 9:1134–1141.
104. Kumar G, Jones NC, Morris MJ, Rees S, O'Brien TJ, Salzberg MR. Early life stress enhancement of limbic epileptogenesis in adult rats: mechanistic insights. PLoS ONE. 2011; 6:e24033. [PubMed: 21957442]
105. Tolmacheva EA, Oitzl MS, van Luijtelaar G. Stress, glucocorticoids and absences in a genetic epilepsy model. Hormones and Behavior. 2012; 61:706–710. [PubMed: 22465594]
106. Akin D, Ravizza T, Maroso M, Carcak N, Eryigit T, Vanzulli I, et al. IL-1beta is induced in reactive astrocytes in the somatosensory cortex of rats with genetic absence epilepsy at the onset of spike-and-wave discharges, and contributes to their occurrence. Neurobiology of Disease. 2011; 44:259–269. [PubMed: 21645619]
107. Sayyah M, Beheshti S, Shokrgozar MA, Eslami-far A, Deljoo Z, Khabiri AR, et al. Antiepileptogenic and anticonvulsant activity of interleukin-1 beta in amygdala-kindled rats. Experimental Neurology. 2005; 191:145–153. [PubMed: 15589521]
108. LaFrance WC Jr. Leaver K, Stopa EG, Papandonatos GD. Blum ASCINNM, author reply P. Decreased serum BDNF levels in patients with epileptic and psychogenic nonepileptic seizures. Neurology. 2010; 75:1285–1291. [PubMed: 20921514]
109. Kozisek ME, Middlemas D, Bylund DB. Brain-derived neurotrophic factor and its receptor tropomyosin-related kinase B in the mechanism of action of antidepressant therapies. Pharmacology & Therapeutics. 2008; 117:30–51. [PubMed: 17949819]
110. Paradiso B, Zucchini S, Su T, Bovolenta R, Berto E, Marconi P, et al. Localized overexpression of FGF-2 and BDNF in hippocampus reduces mossy fiber sprouting and spontaneous seizures up to 4 weeks after pilocarpine-induced status epilepticus. Epilepsia. 2011; 52:572–578. [PubMed: 21269288]
111. Heinrich C, Lahteinen S, Suzuki F, Anne-Marie L, Huber S, Haussler U, et al. Increase in BDNF-mediated TrkB signaling promotes epileptogenesis in a mouse model of mesial temporal lobe epilepsy. Neurobiology of Disease. 2011; 42:35–47. [PubMed: 21220014]
112. Kotloski R, McNamara JO. Reduction of TrkB expression de novo in the adult mouse impairs epileptogenesis in the kindling model. Hippocampus. 2010; 20:713–723. [PubMed: 19603519]
113. Sartori CR, Vieira AS, Ferrari EM, Langone F, Tongiorgi E, Parada CA. The antidepressive effect of the physical exercise correlates with increased levels of mature BDNF, and proBDNF proteolytic cleavage-related genes, p11 and tPA. Neuroscience. 2011; 180:9–18. [PubMed: 21371535]
114. Yu H, Wang DD, Wang Y, Liu T, Lee FS, Chen ZY. Variant brain-derived neurotrophic factor Val66Met polymorphism alters vulnerability to stress and response to antidepressants. The Journal of Neuroscience. 2012; 32:4092–4101. [PubMed: 22442074]
115. Li N, He X, Zhang Y, Qi X, Li H, Zhu X, et al. Brain-derived neurotrophic factor signalling mediates antidepressant effects of lamotrigine. The International Journal of Neuropsychopharmacology. 2011; 14:1091–1098. [PubMed: 20846461]
116. N'Gouemo P, Yasuda R, Faingold CL. Seizure susceptibility is associated with altered protein expression of voltage-gated calcium channel subunits in inferior colliculus neurons of the genetically epilepsy-prone rat. Brain Research. 2010; 1308:153–157. [PubMed: 19836362]

117. Furmaga H, Shah A, Frazer A. Serotonergic and noradrenergic pathways are required for the anxiolytic-like and antidepressant-like behavioral effects of repeated vagal nerve stimulation in rats. Biological Psychiatry. 2011; 70:937–945. [PubMed: 21907323]

118. Zhang JL, Zhang SP, Zhang HQ. Antiepileptic effects of electroacupuncture vs vagus nerve stimulation on cortical epileptiform activities. Journal of the Neurological Sciences. 2008; 270:114–121. [PubMed: 18394652]

119. Reiss JI, Dishman RK, Boyd HE, Robinson JK, Holmes PV. Chronic activity wheel running reduces the severity of kainic acid-induced seizures in the rat: possible role of galanin. Brain Research. 2009; 1266:54–63. [PubMed: 19248773]

120. Murphy P, Likhodii S, Nylen K, Burnham WM. The antidepressant properties of the ketogenic diet. Biological Psychiatry. 2004; 56:981–983. [PubMed: 15601609]

121. Barry JJ, Ettinger AB, Friel P, Gilliam FG, Harden CL, Hermann B, et al. Consensus statement: the evaluation and treatment of people with epilepsy and affective disorders. Epilepsy & Behavior. 2008; 13(Suppl 1):S1–S29. [PubMed: 18502183]

122. Kanner AM, Nieto JC. Depressive disorders in epilepsy. Neurology. 1999; 53:S26–S32. [PubMed: 10496231]

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Table 1

Animal Models of Epilepsy and Depression Comorbidity

Model	Seizure Phenotype	Depression Phenotype	Comments	Reference
Partial Epilepsy				
Kainic Acid (Acute and SE)	Primary limbic seizures with secondary generalization	↑ FST immobility ↓ Sucrose preference	↓ Hippocampal DA ↓ 5-HT and *Htr5b* gene expression are proconvulsant and/or prodepressant ↑ TrkB signaling is proconvulsant; ↓ TrkB signaling is anticonvulsant	[9] [8, 9] [98]
Pilocarpine (Acute and SE)	Primary limbic seizures with secondary generalization	Mixed results on FST ↓ Sucrose preference Sex & species may be important	↑ ACh in cortex & hippocampus following seizure ↑ Hippocampal DA is anticonvulsant & antidepressant ↓ mGluR 1 activation is anticonvulsant & antidepressant ↓ 5-HT hippocampal concentration, turnover, release, evoked cortical release ↑ 5-HT is anticonvulsant & antidepressant ↑ 5-HT 1A function & 5-HT 2C levels following seizures ↑ CORT, CRH administration are proconvulsant ↓ Glucocorticoid receptor activation is antidepressant ↓ IL-1 activation is antidepressant but has no effect on seizures ↑ BDNF expression is anticonvulsant	[43] [18] [18] [12, 74] [17, 18] [17, 74] [14] [15] [13, 16] [97]
Electrical Kindling	Primary limbic seizures with secondary generalization	Mixed results on FST & sucrose preference Time course may be important	↓ NMDA/AMPA activation is anticonvulsant ↑ CORT is proconvulsant ↑ IL-1B is anticonvulsant ↓ TrkB expression is anticonvulsant	[56] [91] [94] [99]
SwLo	Enhanced susceptibility to primarily limbic seizures; exacerbated spontaneous seizures following pilocarpine-induced SE	Selectively bred based on ↑ immobility in FST	↓ Prefrontal DA levels & release ↑ DA is antidepressant ↓ Hippocampal NE ↑ NE is antidepressant	[37] [35] [37] [34]
Generalized Convulsive Epilepsy				
Pentylenetetrazol (PTZ)	Generalized tonic-clonic seizures	Mixed results on FST	↑ $GABA_A$ potentiation (Androstenol) is anticonvulsant & antidepressant ↑ NET in perirhinal cortex; antidepressant effect of NE & DA reuptake inhibition ↓ Na^+ channel activation is anticonvulsant & antidepressant	[50] [7] [80, 81]

Model	Seizure Phenotype	Depression Phenotype	Comments	Reference
GEPRS	Selectively bred based on susceptibility to audiogenic seizures; generalized tonic-clonic seizures	↑ FST immobility ↓ Saccharin consumption Altered diurnal motor activity	↑ ACh in thalamus and striatum ↓ Glutamate synthesis, ↓ Activation of NMDA/AMPA are anticonvulsant ↓ NE throughout the brain ↑ Activation of α1, β1, β2 receptors is anticonvulsant ↓ NE via 6-OHDA lesion of the locus coeruleus, A1, or noradrenergic dorsal bundle is proconvulsant ↓ 5-HT concentration, uptake, tryptophan hydroxylase, 5-HT 1A receptors (in hippocampus) ↑ 5-HT (carbamazepine) is anticonvulsant ↓ 5-HT 1A receptor activation is anticonvulsant when coadministered with fluoxetine ↑ 5-HT 1B receptors in hippocampus ↑ Ca^{2+} current & subunit abundance in inferior colliculus ↓ Ca^{2+} activation is anticonvulsant ↓ K^+ subunit levels & function in hippocampus & cortex	[44] [61] [64] [65] [66] [76] [77] [78] [76] [82, 103] [83] [85]
Dbh -/-	↑ seizure susceptibility	↓ antidepressant responsivity	↓ NE is proconvulsant & confers resistance to antidepressants ↑ NE restores antidepressant effect of desipramine; ↑ NE or adrenergic receptor activation is anticonvulsant against flurothyl-and PTZ-induced seizures	[39–42, 67, 68]
Generalized Absence Epilepsy				
Wag/Rij	Inbred line with spontaneous SWD in cortical EEG	↑ FST immobility ↓ Sucrose consumption	↑ ACh via carbachol is anticonvulsant ↑ cFos activation in DA terminals; not related to SWD ↑ D2/D3 activation (parlodel) is antidepressant ↓ D2/D3 activation (raclopride) is prodepressant ↓ $GABA_A$ activation (bicuculline) is proconvulsant; attenuated by coadministration of $GABA_B$ antagonist ↓ $GABA_B$ function in neocortex ↑ GABA (vigabatrin, ethosuximide) is anticonvulsant & antidepressant ↑ Activation of NMDA/AMPA is anticonvulsant; blocked by ↓ activation of AMPA/NMDA, respectively ↓ mGluR 2/3 activation is anticonvulsant ↓ Na^+ channel activation had no effect on depression ↑ Cav2.1 Ca^{2+} channel expression with SWD ↓ Ca^{2+} channel activation is anticonvulsant & antidepressant ↓ K^+ subunit levels & function in hippocampus & cortex; reversed by Ca^{2+} channel blockade ↑ CORT following stress associated with ↓ in SWD	[45] [28, 49] [48] [48] [52] [51] [53, 54] [60] [62] [54] [84] [54] [86] [92]
GAERS	Selectively bred for spontaneous SWD	↓ sucrose consumption	↑ $GABA_A$ postsynaptic current amplitude ↑ NMDAR distribution, longer duration Mutation in *TASK3* (TWIK-related acid-sensitive K^+ channel 3) gene ↑ IL-1B activation; ↓ IL-1B synthesis is anticonvulsant	[55] [59] [89] [93]

Abbreviations: 5-HT, serotonin; ACh, acetylcholine; AMPA, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid; BDNF, brain-derived neurotrophic factor; CORT, corticosterone; CRH, corticotropin-releasing hormone; DA, dopamine; Dbh, Dopamine beta-hydroxylase; EEG, electroencephalography; FST, forced swim test; GABA, γ-aminobutyric acid; GAERS, Genetic Absence Epilepsy Rats from

Strasbourg; GEPRs, Genetically Epilepsy-Prone Rats; IL, interleukin; mGluR, metabotropic glutamate receptor; NE, norepinephrine; NET, norepinephrine transporter; NMDA, N-methyl-D-aspartate; SE, status epilepticus; SWD, slow wave discharge; SwLo, Swim Lo-Active; TrkB, Tyrosine-related kinase B; Wag/Rij, Wistar Albino Glaxo/from Rijswijk; WDS, wet dog shake