Depression in Epilepsy: A Neurobiologic Perspective

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Depression is the most frequent psychiatric comorbidity in patients with epilepsy. By the same token, patients with depression are at higher risk of developing epilepsy than are controls. Such bidirectional relations raise the question of whether both disorders share common pathogenic mechanisms, presenting with common neurotransmitter abnormalities and involvement of the same neuroanatomic structures. In this article, some of the available data in support of this hypothesis are reviewed.

Around 400 B.C., Hippocrates wrote, "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" (1). Hippocrates' supposition that "epileptics become melancholics" reflects current thinking of a unidirectional relation between depression and epilepsy, because depression is the most frequent psychiatric comorbidity in epilepsy (2–6). In contrast, Hippocrates' suggestion that patients with depression are at increased risk of developing epilepsy comes as a surprise to most clinicians, investigators, and patients alike. However, the premise is supported by two studies published in the last decade.

In a population-based, case control study carried out in patients with newly diagnosed epilepsy, Fosgren and Nystrom (7) found that a history of depression (preceding the onset of epilepsy) was seven times more frequent among patients than among age- and sex-matched controls. Similarly, in a population-based, case–control study of the incidence of new-onset epilepsy among adults aged 55 and older, Hesdorffer et al. (8) found that patients were 3.7 more likely to have a history of depression preceding their initial seizure than were controls. In this study, the authors also controlled for medical therapies of depression. Whereas data of these two studies suggest a bidirectional relation between depression and epilepsy,

they cannot be interpreted as an indication of a causal relation. However, the high comorbidity prevalence rates of these two disorders suggest that depression and epilepsy may share pathogenic mechanisms. The purpose of this review is to examine some of the available data on their common pathogenic mechanisms.

Neurotransmitter Abnormalities in Epilepsy and Depression

It is reasonable to assume that neurotransmitter abnormalities in epilepsy and depression account for the antiepileptic and psychotropic properties of several antiepileptic drugs (AEDs), such as carbamazepine (CBZ), oxcarbazepine, valproic acid (VPA), and lamotrigine (LTG). Ample evidence exists that serotonin (i.e., 5-hydroxytryptamine [5-HT]), norepinephrine (NE), dopamine, γ-aminobutyric acid, and glutamate are operant in the pathogenesis of both disorders (9–14). This review focuses on common abnormalities of serotonergic and noradrenergic transmission—both of which are pivotal pathogenic mechanisms of mood disorders and the bases for development of antidepressant pharmacologic treatment (9). Likewise, decreased serotonergic and noradrenergic activity facilitates the kindling process of seizure foci, exacerbates seizure severity, and intensifies seizure predisposition in some animal models of epilepsy (10).

Are Abnormal Serotonergic and Noradrenergic Transmission Common Pathogenic Mechanisms to Epilepsy and Depression?

Experimental Data

In animal models of epilepsy, compelling experimental data on the pathogenic role played by 5-HT and NE in seizure predisposition are illustrated in studies of two strains of genetic epilepsy-prone rats (GEPR), GEPR-3 and GEPR-9, which are characterized by predisposition to sound-induced generalized tonic–clonic seizures (15–17) and, particularly in GEPR-9s, a marked acceleration of kindling (10). Both strains of rats have innate serotonergic and noradrenergic pre- and postsynaptic transmission deficits. Noradrenergic deficiencies in GEPRs appear to result from deficient arborization of neurons arising from the locus coeruleus (18,19), coupled with excessive presynaptic suppression of NE release in the terminal fields and lack of postsynaptic compensatory upregulation (10,20). GEPR-9 rats have a more pronounced NE transmission deficit and, in turn, exhibit more severe seizures than do GEPR-3 rats (21). Evidence also

exists of deficits in serotonergic arborization in the GEPR brain as well as deficient postsynaptic serotonin$_{1A}$-receptor density in the hippocampus (22). Of note, patients with major depressive disorder (MDD) display endocrine abnormalities similar to those identified in GEPRs, including increased corticosterone serum levels, deficient secretion of growth hormone, and hypothyroidism (23).

Increments of either NE or 5-HT transmission can prevent seizure occurrence, whereas reduction will have the opposite effect (10,24). For example, drugs that interfere with the release or synthesis of NE or 5-HT exacerbate seizures in the GEPRs, including NE storage vesicle inactivators; reserpine or tetrabenazine; the NE false transmitter, α-methyl-m-tryosine; the NE synthesis inhibitor, α-methyl-p-tyrosine; and the 5-HT synthesis inhibitor, p-chlorophenylalanine. Conversely, drugs that enhance serotonergic transmission, such as the selective serotonin reuptake inhibitor (SSRI) sertraline, resulted in a dose-dependent seizure frequency reduction in the GEPR that correlates to the extracellular thalamic serotonergic concentration (25). The 5-HT precursor 5-hydroxy-L-tryptophan (5-HTP) has anticonvulsant effects in GEPRs when combined with the SSRI, fluoxetine (26). SSRIs and monoamine oxidase inhibitors (MAOIs) can exert anticonvulsant effects in experimental animals, such as mice and baboons, which are genetically prone to epilepsy (24,27), as well as nongenetically prone cats (28), rabbits (29), and rhesus monkeys (30). In addition, an antiepileptic effect of 5-HT$_{1A}$ receptors has been correlated to a membrane-hyperpolarizing response, which is associated with increased potassium conductance in hippocampal-kindled seizures in cats and in intrahippocampal kainic-acid–induced seizures in freely moving rats (31,32).

As mentioned, AEDs with established psychotropic effects (CBZ, VPA, and LTG) can cause an increase in 5-HT (33–38). In GEPRs, the anticonvulsant protection of CBZ can be blocked with 5-HT–depleting drugs (34). In addition, the anticonvulsant effect of the vagal nerve stimulator (VNS) in the rat may be mediated by activation of the locus coeruleus (39). Deletion of noradrenergic and serotonergic neurons in the rat prevents or significantly reduces the anticonvulsant effect of VNS against electroshock or pentylenetetrazol-induced seizures (40). Furthermore, the effect of VNS on the locus coeruleus may be responsible for its antidepressant effects identified in humans.

Clinical Data

Deficits in 5-HT transmission in human depression may, in part, be related to a paucity of serotonergic innervation in terminal areas, which is suggested by a scarcity of 5-HT levels in brain tissue, plasma, and platelets, as well as by a deficit in serotonin transporter–binding sites in postmortem human brain (41–55). A deficit in the density or affinity of postsynaptic 5-HT$_{1A}$ receptors has been identified in the hippocampus and amygdala of untreated depressed patients who committed suicide (56). Furthermore, in suicide victims with MDD, impaired serotonergic transmission is associated with defects in the dorsal raphe nuclei that result from suppression of 5-HT$_{1A}$ autoreceptors caused by excessively dense serotonergic somatodendritic impulses (57).

In a positron emission tomography (PET) study, using the 5-HT$_{1A}$ receptor antagonist [^{18}F]$trans$-4-fluoro-N-2-[4-(2-methoxyphenyl)piperazin-1-yl]ethyl-N-(2-pyridyl) cyclohexanecarboxamide ([^{18}F]FCWAY), reduced 5-HT$_{1A}$ binding was found in mesial temporal structures ipsilateral to the seizure focus in patients with temporal lobe epilepsy (TLE), with and without hippocampal atrophy (58). In addition, a 20% binding reduction was found in the raphe and a 34% lower binding in the thalamic region ipsilateral to the seizure focus (these differences yielded a statistical trend). In a separate PET study aimed at quantifying 5-HT$_{1A}$–receptor binding in 14 patients with TLE, a binding reduction was identified in the raphe nuclei; in the epileptogenic hippocampus, amygdala, anterior cingulate, and lateral temporal neocortex ipsilateral to the seizure focus; and in the contralateral hippocampi, but to a lesser degree (59).

In contrast to animal studies, research on the impact of pharmacologic augmentation or reduction in 5-HT and NE transmission on seizures in humans has been rather sparse and based mostly on uncontrolled data. For example, depletion of monoamines from use of reserpine is associated with an increase in frequency and severity of seizures in patients with epilepsy (60,61), whereas the use of reserpine at doses of 2–10 mg/day was found to reduce the electroshock seizure threshold and the severity of the resulting seizures in patients with schizophrenia (62–64). The tricyclic antidepressant imipramine, with reuptake inhibitory effects of NE and 5-HT, was reported to suppress absence and myoclonic seizures in the only double-blind, placebo-controlled studies carried out so far (65–67). Open trials with the tricyclic antidepressant, doxepin, and the SSRIs, fluoxetine and citalopram, yielded an improvement in seizure frequency, but no controlled studies with SSRIs have been performed (68–71).

Are Common Neuroanatomic Structures Involved in Depression and Epilepsy?

A review of the literature reveals structural and functional abnormalities of the same neuroanatomic regions in primary depression and in epileptic seizure disorders that are frequently associated with comorbid depression (72,73). In epilepsy, relevant areas include mesial and orbitofrontal regions as well as mesial temporal and subcortical structures, such as thalamic nuclei. In primary MDD, Sheline (73) described the existence of morphologic and volumetric changes in various neuroanatomic structures that form a "limbic–cortical–striatal–pallidal–thalamic tract." The tract consists of two branches: (1)

a limbic–thalamic–cortical branch that includes the amygdala, hippocampus, and medial-dorsal nucleus of the thalamus as well as the mesial and ventrolateral prefrontal cortex; and (2) a branch running in parallel and linking the caudate, putamen, and globus pallidus with limbic and cortical regions. It is not surprising to find prevalence rates of depression ranging from 19% to 65% among patients with epilepsy of mesial temporal or frontal lobe origin (72). Evidence of common structural involvement will next be reviewed in greater detail.

Temporal Lobe Abnormalities

Hippocampal atrophy is among the most frequently identified abnormality in patients with epilepsy and primary depression. Furthermore, neuroimaging studies performed in patients with epilepsy and comorbid depression have identified a correlation between the severity of depression and severity of mesial temporal structural abnormalities, as identified in studies using magnetic resonance imaging (MRI), single-photon emission computed tomography (SPECT) scans with the tracer [^{99m}Tc]-hexamethylene propylene amine (^{99m}Tc-HMPAO), and proton magnetic resonance spectroscopy (^{1}H-MRS) (74–76).

In two separate studies of patients with a history of primary MDD in remission, Sheline et al. (77,78) reported bilateral, smaller hippocampal volumes than those of age, sex, and height-matched normal controls. They also identified large hippocampal low-signal foci ($\geq$4.5 mm in diameter), and their number correlated with the total number of days depressed. A significant inverse correlation between the duration of depression and left hippocampal volume also was demonstrated. More recently, in a study of 38 female patients with a history of MDD, Sheline and colleagues (79) established that hippocampal atrophy was prevented with antidepressant drug therapy. They found a significant correlation between reduction in hippocampal volume and the duration of untreated depression, whereas no correlation was found between hippocampal volume loss and length of depression for patients taking antidepressant medication.

Both the neuropathologic findings and the magnitude of hippocampal volume reductions differ significantly between the two disorders, with reductions in TLE being significantly greater than those in MDD. In mesial temporal sclerosis, neuropathologic findings consist of neuronal cell loss and astrocytosis in hippocampal formation, amygdala, entorhinal cortex, and occasionally in parahippocampal gyrus. In hippocampus, neuronal cell loss is prominent in areas CA1 and CA4, the dentate gyrus, and the subiculum (82). Unfortunately, few neuropathologic studies of the human hippocampal formation in patients with primary MDD are available. However, Lucassen et al. (83) compared 15 hippocampi of patients with a history of MDD with 16 matched controls and nine steroid-treated patients (high steroids are associated with hippocampal atrophy). In 11 of 15 depressed patients, three steroid-treated patients,

and one control, rare but convincing apoptosis was identified in entorhinal cortex, subiculum, dentate gyrus, CA1 and CA4.

Hippocampal atrophy in primary MDD has been attributed to two potential pathogenic mechanisms: (a) an alteration in brain-derived neurotrophic factors (BDNF), resulting from the mood disorder; and (b) high glucocorticoid exposure. It has been suggested that a decrease in BDNF levels in the dentate gyrus and pyramidal cell layer of hippocampus, amygdala, and neocortex is mediated by glucocorticoids and can be reversed with antidepressant therapy (84,85). Antidepressant drugs increased hippocampal BDNF levels in humans (86). High glucocorticoid exposure stems from excessive activation of the hypothalamic–pituitary–adrenal axis, with almost half of all individuals with depression having impaired dexamethasone suppression of adrenocorticotropic hormone (ACTH) and cortisol. These changes are also reversible to treatment with antidepressants (87). In animal studies with rats and monkeys, deleterious effects of prolonged glucocorticoid exposure were associated with damage to hippocampal neurons; impeded granule cell development in the adult hippocampal dentate gyrus; transient and reversible atrophy of the CA3 dendritic tree; and finally, results in cell death in extreme and prolonged conditions (88–91). In a neuropathologic study of amygdala and entorhinal cortex of seven patients with MDD, 10 with bipolar disorder (BPD), and 12 controls the specimens of MDD patients and those of patients with BPD had a significant reduction of glial cells and of the glial/neurons ratio in left amygdala and to a lesser degree in left entorhinal cortex (81).

Therefore are the neuropathologic changes of TLE magnified in the presence of a chronic, untreated depressive disorder? Whereas no answer to this question is available, some data suggest a negative impact of a psychiatric history on seizure outcome after pharmacologic (92) and surgical treatment (93,94). In a study of 90 patients who underwent an anterotemporal lobectomy for the management of a refractory TLE, a lifetime history of depression (identified at the time of the presurgical evaluation) was a predictor of a worse seizure outcome (94). Thus could these data suggest that depression may be a biologic marker for more severe epilepsy?

Frontal Lobe Abnormalities

Functional disturbances of frontal lobe structures have been recognized in TLE, particularly among patients with comorbid depression, and correlate to bilateral reduction in inferofrontal metabolism (95–98). Additionally, neuropsychological testing with the Wisconsin Card Sorting Test, which is highly sensitive to frontal-lobe–mediated executive dysfunction, has revealed poor performance in patients with TLE and comorbid depression (99).

Involvement of frontal lobes in primary depression has been demonstrated with functional neuroimaging (e.g., PET,

SPECT) and neuropsychological studies (100,101). Executive abnormalities consistently are found in studies on depressive disorders, with stronger results apparent with more severe pathology. These neuropsychological disturbances correlated to reduced blood flow in mesial prefrontal cortex (102,103). Furthermore, in tests demanding executive function, cingulate cortex and striatum could not be activated in patients with MDD (104).

Likewise, structural changes have been identified in the cingulate gyrus and white matter of the orbitofrontal and prefrontal cortex, including smaller orbitofrontal cortex volumes in young adults (105,106) and in geriatric patients with MDD (107,108). Of note, the magnitude of prefrontal volume changes was related to the severity of the depression, as elderly patients with minor depression had lesser changes than did those with MDD (109).

Neuropathologic studies have documented structural cortical changes in frontal lobes of depressed patients. Rajkowska et al. (110) found decreases in cortical thickness, neuronal sizes, and neuronal densities in layers II, III, and IV of the rostral orbitofrontal region in the brains of depressed patients. In the caudal orbitofrontal cortex, significant reductions in glial densities in cortical layers V and VI associated with decreases in neuronal sizes were identified. Finally, in all cortical layers of the dorsolateral prefrontal cortex, the authors demonstrated a decrease in density and size of neuronal and glial cells.

Conclusions

Clearly, these data appear to suggest the involvement of common neuroanatomic structures and neurotransmitters in depression and epilepsy, which may explain the bidirectional relation between the two disorders and their frequent comorbid occurrence. This review only begins to examine the very complex interplay between neurobiologic aspects of mood disorders and epilepsy. Importantly, the review illustrates that depression in epilepsy is much more than a "psychosocial" complication!

References

1. Lewis A. Melancholia: a historical review. J Mental Sci 1934;80:1–42.
2. Hermann BP, Seidenberg M, Bell B. Psychiatric comorbidity in chronic epilepsy: identification, consequences, and treatment of major depression. Epilepsia 2000;41(suppl 2): S31–S41.
3. Wiegartz P, Seidenberg M, Woodard A, Gidal B, Hermann B. Co-morbid psychiatric disorder in chronic epilepsy: recognition and etiology of depression. Neurology 1999;53(suppl 2):S3–S8.
4. Jacoby A, Baker GA, Steen N, Potts P, Chadwick DW. The clinical course of epilepsy and its psychosocial correlates: findings from a U.K. Community study. Epilepsia 1996;37:148–161.
5. O'Donoghue MF, Goodridge DM, Redhead K, Sanders JW, Duncan JS. Assessing the psychosocial consequences of epilepsy: a community-based study. Br J Gen Pract 1999;49:211–214.
6. Edeh J, Toone B. Relationship between interictal psychopathology and the type of epilepsy: results of a survey in general practice. Br J Psychiatry 1987;151:95–101.
7. Forsgren L, Nystrom L. An incident case referent study of epileptic seizures in adults. Epilepsy Res 1990;6:66–81.
8. Hesdorffer DC, Hauser WA, Annegers JF, et al. Major depression is a risk factor for seizures in older adults. Ann Neurol 2000;47:246–249.
9. Nemeroff CB, Owens MJ. Treatment of mood disorders. Nat Neurosci 2002;5(suppl):1068–1070.
10. Jobe PC, Dailey JW, Wernicke JF. A noradrenergic and serotonergic hypothesis of the linkage between epilepsy and affective disorders. Crit Rev Neurobiol 1999;13:317–356.
11. Nestler E J, et al. Neurobiology of depression. Neuron 2002;34:13–25.
12. Ressler KJ, Nemeroff CB. Role of serotonergic and noradrenergic systems in the pathophysiology of depression and anxiety disorders. Depress Anxiety 2000;12(suppl 1):2–19.
13. Hoyer D, Martin G. 5-HT receptor classification and nomenclature: towards a harmonization with the human genome. Neuropharmacology 1997;36:419–428.
14. Van Praag HM, de Kloet R, Van Os J. Monoamines and depression. In: Stress, the brain and depression. Cambridge University Press, 2004:91–117.
15. Jobe PC, Dailey JW. Genetically epilepsy-prone rats (GEPRs) in drug research. CNS Drug Rev 2000;6:241–260.
16. Coffey LL, Reith MEA, Chen NH, Jobe PC, Mishra PK. Amygdala kindling of forebrain seizures and the occurrence of brainstem seizures in genetically epilepsy-prone rats. Epilepsia 1996;37:188–197.
17. Jobe PC, Mishra PK, Dailey JW, Ko KH, Reith MEA. Genetic predisposition to partial (focal) seizures and to generalized tonic/clonic seizures: interactions between seizure circuitry of the forebrain and brainstem. In: Berkovic SF, Genton P, Hirsch E, Picard F, eds. Genetics of focal epilepsies. Avignon, France: John Libbey, 1999:251.
18. Clough RW, Peterson BR, Steenbergen JL, Jobe PC, Fells JB, Browning RA, Mishra PK. Neurite extension of developing noradrenergic neurons is impaired in genetically epilepsy-prone rats (GEPR-3s): an in vitro study on locus coeruleus. Epilepsy Res 1998;29:135–146.
19. Ryu JR, Jobe PC, Milbrandt JC, Mishra PK, Clough RW, Browning RA, Dailey JW, Seo DO, Ko KH. Morphological deficits in noradrenergic neurons in GEPR-9s stem from abnormalities in both the locus coeruleus and its target tissues. Exp Neurol 1999;156:84–91.
20. Yan QS, Jobe PC, Dailey JW. Thalamic deficiency in norepinephrine release detected via intracerebral microdialysis: a synaptic determinant of seizure predisposition in the genetically epilepsy-prone rat. Epilepsy Res 1993;14:229–236.
21. Jobe PC, Mishra PK, Adams-Curtis LE, Deoskar VU, Ko KH, Browning RA, Dailey JW. The genetically epilepsy-prone rat (GEPR). Ital J Neurol Sci 1995;16:91.
22. Dailey JW, Mishra PK, Ko KH, Penny JE, Jobe PC. Serotonergic abnormalities in the central nervous system of seizure-naive genetically epilepsy-prone rats. Life Sci 1992;50:319–326.
23. Jobe PC, Weber RH. Affective disorder and epilepsy comorbidity in the genetically epilepsy prone-rat (GEPR). In: Gilliam F, Heline YI, Kanner AM, eds. Neurologic dysfunction in depression. Parthenon Publishing (in press).

24. Meldrum BS, Anlezark GM, Adam HK, Greenwod DT. Anticonvulsant and proconvulsant properties of viloxazine hydrohloride: pharmacological and pharmacokinetic studies in rodents and epileptic baboon. Psychopharmacology (Berlin) 1982;76:212.

25. Yan QS, Jobe PC, Dailey JW. Further evidence of anticonvulsant role for 5-hydroxytryptamine in genetically epilepsy prone rats. Br J Pharmacol 1995;115:1314–1318.

26. Yan QS, Jobe PC, Dailey JW. Evidence that a serotonergic mechanism is involved in the anticonvulsant effect of fluoxetine in genetically epilepsy-prone rats. Eur J Pharmacol 1993;252:105–112.

27. Lehmann A. Audiogenic seizures data in mice supporting new theories of biogenic amines mechanisms in the central nervous system. Life Sci 1967;6:1423.

28. Polc P, Schneeberger J, Haefely W. Effects of several centrally active drugs on the sleep wakefulness cycle of cats. Neuropharmacology 1979;18:259.

29. Piette Y, Delaunois AL, De Shaepdryver AF, Heymans C. Imipramine and electroshock threshold. Arch Int Pharmacodyn Ther 1963;144:293.

30. Yanagita T, Wakasa Y, Kiyohara H. Drug-dependence potential of viloxazine hydrochloride tested in rhesus monkeys. Pharmacol Biochem Behav 1980;12:155.

31. Beck SG, Choi KC. 5-Hydroxytryptamine hyperpolarizes CA3 hippocampal pyramidal cells through an increase in potassium conductance. Neurosci Lett 1991;133:93–96.

32. Okuhara DY, Beck SG. 5-HT1A receptor linked to inward-rectifying potassium current in hippocampal CA pyramidal cells. J Neurophysiol 1994;71:2161–2167.

33. Yan QS, Mishra PK, Burger RL, Bettendorf AF, Jobe PC, Dailey JW. Evidence that carbamazepine and antiepilepsirine may produce a component of their anticonvulsant effects by activating serotonergic neurons in genetically epilepsy-prone rats. J Pharmacol Exp Ther 1992;261:652–659.

34. Dailey JW, Reith MEA, Yan QS, Li MY, Jobe PC. Anticonvulsant doses of carbamazepine increase hippocampal extracellular serotonin in genetically epilepsy-prone rats: dose response relationships. Neurosci Lett 1997;227:13–16.

35. Dailey JW, Reith ME, Steidley KR, Milbrandt JC, Jobe PC. Carbamazepine-induced release of serotonin from rat hippocampus in vitro. Epilepsia 1998;39:1054–1063.

36. Dailey JW, Reith ME, Yan QS, Li MY, Jobe PC. Carbamazepine increases extracellular serotonin concentration: lack of antagonism by tetrodotoxin or zero Ca2+. Eur J Pharmacol 1997;328:153–162.

37. Southam E, Kirkby D, Higgins GA, Hagan RM. Lamotrigine inhibits monoamine uptake in vitro and modulates 5-hydroxytryptamine uptake in rats. Eur J Pharmacol 1998;358:19–24.

38. Whitton PS, Fowler LJ. The effect of valproic acid on 5-hydroxytryptamine and 5- hydroxyindoleacetic acid concentration in hippocampal dialysates in vivo. Eur J Pharmacol 1991;200:167–169.

39. Naritokku DK, Terry WJ, Helfert RH. Regional induction of fos immunoreactivity in the brain by anticonvulsant stimulation of the vagus nerve. Epilepsy Res 1995;22:53.

40. Browning RA, Clark KB, Naritoku, DK, Smith DC, Jensen RA. Loss of anticonvulsant effect of vagus nerve stimulation in the pentylenetetrazol seizure model following treatment with 6-hydroxydopamine or 5,7-dihydroxy-tryptamine. Soc Neurosci 1997;23:2424.

41. Asberg M, Traskman L, Thoren P. 5-HIAA in the cerebrospinal fluid: a biochemical suicide predictor? Arch Gen Psychiatry 1976;33:1193–1197.

42. Brown GL, Ebert MH, Goyer PF, et al. Aggression, suicide, and serotonin: relationships to CSF amine metabolites. Am J Psychiatry 1982;139:741–746.

43. Brown GL, Linnoila MI. CSF serotonin metabolite (5-HIAA) studies in depression, impulsivity, and violence. J Clin Psychiatry 1990;51(suppl):31–41.

44. Roy A, De Jong J, Linnoila M. Cerebrospinal fluid monoamine metabolites and suicidal behavior in depressed patients: a 5-year follow-up study. Arch Gen Psychiatry 1989;46:609–612.

45. Langer SZ, Galzin AM. Studies on the serotonin transporter in platelets. Experientia 1988;44:127–130.

46. Nemeroff CB, Knight DL, Krishnan RR, et al. Marked reduction in the number of platelet-tritiated imipramine binding sites in geriatric depression. Arch Gen Psychiatry 1988;45:919–923.

47. Malison RT, Price LH, Berman R, et al. Reduced brain serotonin transporter availability in major depression as measured by [^{123}I]-2 beta-carbomethoxy-3 beta-(4-iodophenyl)tropane and single photon emission computed tomography. Biol Psychiatry 1998;44:1090–1098.

48. Ogilvie AD, Harmar AJ. Association between the serotonin transporter gene and affective disorder: the evidence so far. Mol Med 1997;3:90–93.

49. Ogilvie AD, Battersby S, Bubb VJ, Fink G, Hammar AJ, Goodwim GM, Smith CA. Polymorphism in serotonin transporter gene associated with susceptibility to major depression. Lancet 1996;347:731–733.

50. Cheetham SC, Crompton MR, Czudek C, Horton RW, Katona CL, Reynolds GP. Serotonin concentrations and turnover in brains of depressed suicides. Brain Res 1989;502:332–340.

51. Stanley M, Virgilio J, Gershon S. Tritiated imipramine binding sites are decreased in the frontal cortex of suicides. Science 1982;216:1337–1339.

52. Perry EK, Marshall EF, Blessed G, Tomlinson BE, Perry RH. Decreased imipramine binding in the brains of patients with depressive illness. Br J Psychiatry 1983;142:188–192.

53. Leake A, Fairbairn AF, McKeith IG, Ferrier IN. Studies on the serotonin uptake binding site in major depressive disorder and control post-mortem brain: neurochemical and clinical correlates. Psychiatry Res 1991;39:155–165.

54. Briley MS, Langer SZ, Raisman R, Sechter D, Zarifian E. Tritiated imipramine binding sites are decreased in platelets of untreated depressed patients. Science 1980;209:303–305.

55. Langer SZ, Zarifian E, Briley M, Raisman R, Sechter D. High-affinity binding of 3H-imipramine in brain and platelets and its relevance to the biochemistry of affective disorders. Life Sci 1981;29:211–220.

56. Cheetham SC, Crompton MR, Katona CL, Horton RW. Brain 5-HT1 binding sites in depressed suicides. Psychopharmacology 1990;102:544–548.

57. Stockmeier CA, Shapiro LA, Dilley GE, Kolli TN, Friedman L, Rajkowska G. Increase in serotonin-1A autoreceptors in the midbrain of suicide victims with major depression-postmortem evidence for decreased serotonin activity. J Neurosci 1998;18:7394–7401.

58. Toczek MT, Carson RE, Lang L, Ma Y, Spanaki MV, Der MG, et al. PET imaging of 5-HT1A receptor binding in patients with temporal lobe epilepsy. Neurology 2003;60:749–756.

59. Savic I, Lindstrom P, Gulyas B, Halldin C, Andree B, Farde L. Limbic reductions of 5-HT1A receptor binding in human temporal lobe epilepsy. Neurology 2004;62:1343–1351.

60. Lewis JJ. Rauwolfia derivates. In:Root WS, Hofmann FG, eds. Physiological pharmacology. New York: Academic Press,1974:79.

61. Maynert EW, Marczynski TJ, Browining RA. The role of the neurotransmitters in the epilepsies. In: Friedlander WJ, ed. Advance in neurology. New York, Raven Press, 1975;79.

62. Naidoo D. The effects of reserpine (Serpasil) on the chronic disturbed schizophrenic: a comparative study of rauwolfia alkaloids and electroconvulsive therapy. J Nerv Ment Disord 1956;123:1–13.

63. Noce RH, Williams DB, Rapaport W. Reserpine (Serpasil) in management of the mentally ill. JAMA 1955;158:11.

64. Tasher DC, Chermak MW. The use of reserpine in shock-reversible patients and shock-resistant patients. Ann N Y Acad Sci 1955;61:108.

65. Fromm GH, Rosen JA, Amores CY. Clinical and experimental investigation of the effect of imipramine on epilepsy. Epilepsia 1971;12:282.

66. Fromm GH, Wessel HB, Glass JD, Alvin JD, VanHorn G. Imipramine in absence and myoclonic-astatic seizures. Neurology 1978;28:953.

67. Fromm GH, Amores CY, Thies W. Imipramine in epilepsy. Arch Neurol 1972;27:198.

68. Ojemann LM, Friel PN, Trejo WJ, Dudley DL. Effect of doxepin on seizure frequency in depressed epileptic patients. Neurology 1983;33:66.

69. Favale E, RubinoV, Mainardi P, Lunardi G, Albano C. The anticonvulsant effect of fluoxetine in humans. Neurology 1995;45:1926.

70. Specchio LM, Iudice A, Specchio N, La Neve A, Spinelli A, Galli R, Rocchi R, Ulivelli M, de Tommaso M, Pizzanelli C, Murri L. Citalopram as treatment of depression in patients with epilepsy. Clin Neuropharmacol 2004;27:133–136.

71. Hovorka J, Herman E, Nemcova II. Treatment of interictal depression with citalopram in patients with epilepsy. Epilepsy Behav 2000;1:444–447.

72. Kanner AM, Balabanov A. Depression in epilepsy: how closely related are these two disorders? Neurology 2002;58(suppl 5):S27–S39.

73. Sheline YI. Neuroimaging studies of mood disorder effects on the brain. Biol Psychiatry 2003;54:338–352.

74. Gilliam F, Maton B, Martin RC, et al. Extent of 1H spectroscopy abnormalities independently predicts mood status and quality of life in temporal lobe epilepsy. Epilepsia 2000;41(suppl):54.

75. Quiske A, Helmstaedter C, Lux S, et al. Depression in patients with temporal lobe epilepsy is related to mesial temporal sclerosis. Epilepsy Res 2000;39:121–125.

76. Schmitz EB, Moriarty J, Costa JC, Ring HA, Ell PJ, Trimble MR. Psychiatric profiles and patterns of cerebral blood flow in focal epilepsy: interactions between depression, obsessionality, and perfusion related to the laterality of the epilepsy. J Neurol Neurosurg Psychiatry 1997;62:458–463.

77. Sheline YI, Wang PW, Gado MH, Sernansky JG, Vannier MW. Hippocampal atrophy in recurrent major depression. Proc Natl Acad Sci U S A 1996.93:3908–3913.

78. Sheline YI, Sanghavi M, Mintun MA, et al. Depression duration but not age predicts hippocampal volume loss in medically healthy women with recurrent major depression. J Neurosci 1999;19:5034–5043.

79. Sheline YI, Gado MH, Kraemer HC. Untreated depression and hippocampal volume loss. Am J Psychiatry 2003;160:1516–1518.

80. Sheline YI, Gado MH, Price JL. Amygdala core nuclei volumes are decreased in recurrent major depression. Neuroreport 1998;9:2023–2028.

81. Bowley MP, Drevets WC, Ongur D, Price JL. Low glial numbers in the amygdala in major depressive disorder. Biol Psychiatry 2002;52:404–412.

82. Mathern GW, Babb TL, Armstrong DL. Hippocampal sclerosis. In: Engel J, Pedley TA, eds. Epilepsy: a comprehensive textbook. Philadelphia: Lippincott-Raven, 1997:133–155.

83. Lucassen PJ, Muller MB, Holsboer F, Bauer J, Holtrop A, Wouda J, Hoogendijk WJG, DeKloet ER, Swaab DF. Hippocampal apoptosis in major depression is a minor event and absent from subareas at risk for glucocorticoid overexposure. Am J Pathol 2001;158:453–468.

84. Smith MA, Makino S, Kvetnansky R, Post RM. Effects of stress on neurotrophic factor expression in the rat brain. Ann N Y Acad Sci 1995;771:234–239.

85. Nibuya M, Morinobu S, Duman RS. Regulation of BDNF and trkB mRNA in rat brain by chronic electroconvulsive seizure and antidepressant drug treatments. J Neurosci 1995;15:7539–7647.

86. Chen B, Dowlatshahi D, MacQueen GM, Wang JF, Young LT. Increased hippocampal BDNF immunoreactivity in subjects treated with antidepressant medication. Biol Psychiatry 2001;50:260–265.

87. Holsboer F. Stress, hypercortisolism and corticosteroid receptors in depression: implications for therapy. J Affect Disord 2001;62:77–91.

88. Holsboer F. Corticotropin-releasing hormone modulators and depression. Curr Opin Invest Drugs 2003;4:46–50.

89. Reul JM, Holsboer F. Corticotropin-releasing factor receptors 1 and 2 in anxiety and depression. Curr Opin Pharmacol 2002;2:23–33.

90. Sapolsky RM. Glucocorticoids and hippocampal atrophy in neuropsychiatric disorders. Arch Gen Psychiatry 2000;57:925–935.

91. Fuchs E, Gould E. Mini-review: in vivo neurogenesis in the adult brain: regulation and functional implications. Eur J Neurosci 2000;12:2211–2214.

92. Mohanraj R, Brodie MJ. Predicting outcomes in newly diagnosed epilepsy [Abstract]. Epilepsia 2003;44(suppl 9):15.

93. Anhoury S, Brown RJ, Krishnamoorthy ES, Trimble MR. Psychiatric outcome after temporal lobectomy: a predictive study. Epilepsia 2000;41:1608–1615.

94. Kanner AM, Tilwalli S, Smith MC, Bergen D, Palac S, Balabanov AJ, Byrne RA Presurgical history of depression is associated with a worse postsurgical seizure outcome following a temporal lobectomy [Abstract]. Neurology 2003;62(suppl 5):A389.

95. Bromfield E, Altshuler L, Leiderman D. Cerebral metabolism and depression in patients with complex partial seizures. Epilepsia 1990;31:625.

96. Horner MD, Flashman LA, Freides D, Epstein CM, Bakay RA. Temporal lobe epilepsy and performance on the Wisconsin card sorting test. J Clin Exp Neuropsychol 1996;18:310–113.

97. Hempel A, Risse GL, Mercer K, Gates J. Neuropsychological evidence of frontal lobe dysfunction in patients with temporal lobe epilepsy. Epilepsia 1996;37(suppl 5):119.

98. Jokeit H, Seitz RJ, Markowitsch HJ, Neumann N, Witte OW, Ebner A. Prefrontal asymmetric interictal glucose hypometabolism and cognitive impairment in patients with temporal lobe epilepsy. Brain 1997;12:2283–2294.

99. Hermann BP, Wyler AR, Richey ET. Wisconsin card sorting test performance in patients with complex partial seizures of temporal-lobe origin. J Clin Exp Neuropsychol 1988;10:467–476.

100. Baxter LR, Schawrtz JM, Phelps ME, Mazziotta JC, Guze BH, Selin CE, Gerner RH, Sunida RM. Reduction of the prefrontal cortex glucose metabolism common to three types of depression. Arch Gen Psychiatry 1989;46:243–250.

101. Starkstein SE, Robinson RG. Depression and frontal lobe disorders. In: Miller BL, Cummings JL, eds. The human frontal lobes, functions and disorders. New York: The Gilford Press, 1998:3–26, 537–546.

102. Bench CJ, Friston KJ. Regional cerebral blood flow in depression measured by positron emission tomography: the relationship with clinical dimensions. Psychol Med 1993;23:579–590.

103. Dolan RJ, Bench CJ. Neuropsychological dysfunction in depression: the relationship to cerebral blood flow. Psychol Med 1994;24:849–857.

104. Elliott R, Baker SC. Prefrontal dysfunction in depressed patients performing a complex planning task: a study using positron emission tomography. Psychol Med 1997;27:931–942.

105. Bremner JD, Vithilingham M, Vermetten E, Nazeer A, Adil J, Khan S, Staib LB, Charney DS. Reduced volume of orbitofrontal cortex in major depression. Biol Psychiatry 2002;51:273–279.

106. Coffey CE, Wilkinson WE, Weiner RD, et al. Quantitative cerebral anatomy in depression: a controlled magnetic resonance imaging study. Arch Gen Psychiatry 1993;50:7–16.

107. Lai T, Payne ME, Byrum CE, Steffens DC, Krishnan Kr. Reduction of orbital frontal cortex volume in geriatric depression. Biol Psychiatry 2000;48:971–975.

108. Taylor WD, Steffens DC, McQuoid DR, Payne ME, Lee SH, Lai TJ, Krishnan KR. Smaller orbital frontal cortex volumes associated with functional disability in depressed elders. Biol Psychiatry 2003;53:144–149.

109. Kumar A, Zhisong J, Warren B, Jayaram U, Gottlieb G. Late-onset minor and major depression: early evidence for common neuroanatomical substrates detected by using MRI. Proc Natl Acad Sci U S A 1998;95:7654–7658.

110. Rajkowska G, Miguel-Hidalgo JJ, Wei J, Dilley G, Pittman SD, Meltzer HY, Overholser JC, Roth BL, Stockmeier CA. Morphometric evidence for neuronal and glial prefrontal cell pathology in major depression. Biol Psychiatry 1999;45:1085–1098.