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REVIEW

Malfunction in GABA and Glutamate as Pathways to Depression: A Review of the Evidence

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Abstract: With nearly one fifth of the population experiencing depression sometime during their lives, plus the recent finding that depression rivals smoking in its association with mortality, the search for effective pharmacological treatments for depression remains urgent. However, despite this heavy disease burden upon society, the various waves of antidepressants developed in the last 40 years have shown significant side effects and little specific efficacy over placebo. One potential treatment may be via re-establishment of glutamate and GABA neurotransmitter systems that have been shown to malfunction in depressed patients. The literature describing possible causal links between GABA and/or glutamate malfunction and depression is reviewed, plus those studies which provide experimental data to confirm this hypothesis. While there is plausible support for the links between malfunction of these neurotransmitters and depression, few data exist yet regarding development of effective antidepressant medications based upon these findings.

Keywords: glutamate, GABA, depression

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Clinical and subsyndromal depression (including bipolar depression) adversely effect physical health, relationships and cognitive performance.[1–4] In fact, some recent data suggest that depression poses a similar risk as does smoking for mortality from all causes, even when related health factors such as blood pressure, alcohol intake, cholesterol and social status are taken into account.[5] With between 13% (Europe) and 17% (USA) of people having a major depressive episode at some time in their lives,[6–8] depression has been described as the principal contributor to the total disease burden,[9] and has also been predicted to become the second leading cause of mental illness by 2020.[10,11]

Although depression is often defined as a number of related disorders,[12] one distinction which has been supported by factor analytic studies is that between melancholic and non-melancholic depression.[13] Melancholic depression is marked by anhedonia, psychomotor difficulties, excessive guilt or hopelessness, suicidal features and disturbances of appetite or weight, which distinguish patients suffering from this subtype of depression from those who exhibit general distress.[13–15] Melancholic patients have distinct biological and psychological features, the former including dysfunction of: (i) the hypothalamic-pituitary-adrenal (HPA) axis[16–19] which is related to emotional and sympathetic nervous system problems such as excessive guilt and hopelessness; (ii) the thyroid axis (related to psychomotor abnormalities, weight loss and sleep disturbances);[20] (iii) REM[21] which may also reflect changed circadian rhythms that are found in melancholic patients; and (iv) left dorsolateral prefrontal cortex activity,[22] which is associated with mood problems. Thus, melancholic depression may be conceptualized as having a significant biological structure, and may be likely to be vulnerable to biologically-based (i.e. pharmacological) treatments, including a range of antidepressants.

Since the serendipitous discovery of the antidepressant effects of monoamine oxidase inhibitors in the mid-1960's,[23,24] the "Monoamine" hypothesis of depression has dominated the development of pharmacological treatments and research.[25] Under that hypothesis, deficiencies in the principal neurotransmitters serotonin (5-HT), noradrenaline and dopamine contribute to the development of depression by reducing effective synaptic transmission.[25] Because these monoamines are taken up post-synatically via monoamine oxidases, medications which inhibit that uptake process have been the mainstream of antidepressant treatments by increasing the levels of these neurotransmitters available at the synapse. These original monoamine oxidase inhibitors have been supplemented by tricyclics and selective serotonin uptake inhibitors, noradrenaline uptake inhibitors, or combinations of both[26] but all with significant side effects, even including increased risk of suicide.[27] In addition, none of these agents has been shown to be more than marginally superior to placebo in their effects, with a mean difference of only 1.7 points on the 52-point Hamilton Depression Scale, described as "clinically negligible".[28,29]

This limited efficacy of existing antidepressants suggests further investigation of alternative antidepressant medications. Several promising avenues for development of antidepressants based upon different neurochemical pathways, including modification of excessive glucocorticoid activity within the HPA axis;[30–35] brain-derived neurotrophic factor;[36,37] selective 5-HT receptors;[38] cytokines;[39] the anti-epileptic Pregabalin;[40] and a concentration upon neuronal plasticity rather than neurogenesis.[41] One other pathway between neurotransmitter status and depression which has recently received attention is malfunction of the glutamate and GABA neurotransmitter systems, both of which have been shown to be significantly associated with depression.[42,43] This paper presents an introduction to GABA and glutamate and reviews the literature to date regarding their association with depression and the effects of treatments designed to remedy malfunctions in their production.

Glutamate: An Excitatory Amino Acid

Glutamate is one of the small molecule neurotransmitters which act very quickly as exciters, allowing very fast nervous system responses, including transmission of signals from the senses to the brain and motor signals back to muscles.[44] Glutamate is derived from glucose by the actions of glutamic dehydrogenase, which comes from NADP-Isocitrate dehydrogenase, Isocytrate, Citrate and Acetyl-CoA, within the tricarboxylic acid cycle, all of which are products of glycolysis.[45,46] Glutamate (which is metabolized to GABA in GABAergic neurons) is secreted by the cytosol of the presynaptic terminals in sensory

pathways and the cerebral cortex and is stored in transmitter vesicles in the presynaptic terminal. Those vesicles release glutamate into the synaptic gap whenever an action potential reaches the presynaptic terminal. Glutamate has three ligand-gated ion channel receptors: NMDA, AMPA and kainite,[45] all of which are also receptors to other excitatory amino acids but most sensitive to glutamate.[46]

GABA: An Inhibitory Amino Acid

Derived from glutamate by the enzyme glutamic acid decarboxylase,[47] gamma-aminobutyric acid (GABA) is also a small, fast-acting molecule that is secreted in the terminals of the spinal cord, cerebellum, basal ganglia and cortex. With glycine, GABA is one of the two major inhibitory neurotransmitters of the CNS,[45] although GABA is more concentrated in the telencephalon (cerebral cortex, basal telencephalon) and diencephalon (thalamus and hypothalamus)[46] and has been described as the major source of synaptic inhibition in the nervous system.[45] After GABA has interacted with receptors at the post synapse, it is taken up by glial cells or the presynaptic terminal.[46] GABA acts via two receptors: $GABA_A$ (a postsynaptic, ligand-gated chloride channel) and $GABA_B$ (a presynaptic receptor which modulates neurotransmitter release).[45,46] GABA is also important for synaptic plasticity and neurogenesis.[48]

Possible Causal Links between Glutamate and GABA Malfunction and Depression

Because GABA and glutamate are inextricably linked, many of the possible pathways between glutamate or GABA and depression may be common. These pathways are briefly described below.

Loss of cognitive ability

Burt[46] referred to glutamate and GABA as the primary neurotransmitters for most of the neurons intrinsic to the cerebral cortex. The cortical excitation-inhibition processes which underlie cognitive functions are dependant upon these two neurotransmitters.[45] Because the cerebral cortex has large association areas, giving us our intelligence, reasoning, planning, "ingenuity and resourcefulness, individual personalities and ability to make decisions"[46] (p. 465), the negative impact of inadequate glutamate and GABA supply and/or functioning upon the ability of the individual to think and reason is plausible.[49–51] This has been documented by Zahr, Mayer, Pfefferbaum and Sullivan[52] in the cognitive decline of aged persons.

Cell apoptosis

Deficits in glutamate transporters in depressed patients[53] may lead to accumulations of extracellular glutamate and cytotoxic damage to neurons and glia.[54] These elevated extracellular glutamate concentrations may hyperactivate glutamate receptors outside the synapse, increasing intracellular Ca^+ and leading to cell apoptosis,[55] perhaps associated with impaired cognitive ability.

Dysregulation of growth factors in the brain

Evans, et al[56] noted that fibroblast growth factor system transcripts in the frontal cortical regions of brains from depressed patients showed glutamate-influenced dysregulation, which may also contribute to cell apoptosis.

Dopamine firing and downstream signalling mechanisms may be impaired via deterioration in the links between glutamate receptors, G-protein receptors and second messenger systems[53] and contribute to impaired cognition. Jones, Kilpatrick and Phillipson[57] and Benes, Vincent and Molloy[58] showed that GABA malfunction led to decreased firing of dopaminergic neurons in mammals.

Decreased serotonin and noradrenaline expression

Elevated glutamate correlates with lowered serotonin, also implicated in depression.[59] Similar findings have been reported for depleted GABA[60] in rats' brains.

Research Findings on Glutamate, GABA and Depression

Earlier studies showed that GABA was reduced in the plasma and CSF of depressed patients[61] but those data do not easily generalize to the brain[62] and therefore the remainder of the literature reviewed below will be confined to glutamate and GABA concentrations in the human brain. Animal studies[63] are not included here but show data consistent with those from depressed humans.

Table 1 presents a limited summary of published literature on brain studies of glutamate and GABA in depressed vs. non-depressed individuals, as identified from PubMed, Google Scholar, Science Direct and hand-searching from reference lists of articles in April, 2009. Of the six studies which reported on glutamate, three showed lowered levels in depressed patients compared to healthy controls;[64–66] one[53] found dysregulation of genes coding for glutamatergic transmitter systems (which would decrease glutamate); one noted higher glutamate in recovered depressed patients;[62] and one reported higher glutamate in depressed than in non-depressed patients,[67] commenting that the increased glutamate and decreased GABA was consistent with a single shared pathway controlling these excitatory and inhibitory systems.

Fourteen studies measured GABA, and four of those reported reduced levels in MDD patients compared to nondepressed persons;[66–69] one reported that GABA increased after ECT,[70] although Jinno and Kosaka[71] noted that this was most likely due to alterations in glutamic acid decarboxylase expression rather than increases in cell numbers) and another after SSRI therapy;[72] one showed dysregulation of GABAergic transmitter systems which would reduce GABA;[53] two found that unipolar depressed patients had lower GABA but bipolar patients did not;[65,73] two reported reduced presence of GABA-synthesising enzymes;[74,75] one reported that GABAergic interneurons were of lower density and size in depressed vs. non-depressed patients;[76] one found that MDD treatment-resistance patients had lower GABA than MDD patients who were not treatment-resistant or healthy control patients;[77] and one study found that GABA was lower in unipolar and bipolar depressed patients.[62]

However, there are some limitations in the generalisability of the data shown in Table 1. Although most (8) studies were of the occipital cortex, five others examined the prefrontal cortex and the anterior cingulate areas, which Hassler et al[66] argued are most involved with depression and where glial cell abnormalities have been reported in depressed patients, therefore being more relevant to studies of depression than the occipital area. However, this argument has been challenged by recent data from Gaillard, et al[78] who found that occipital activation caused prefrontal activity. In addition, whereas GABA concentrations reflect only local GABAergic neurons, glutamate is accessed from the entire brain pool, which may mask local levels,[79] leaving some of the findings on glutamate open to question.

Some methodological limitations present in these studies are: (i) diagnosed MDD patients are compared with those who are bipolar, "unipolar depressed", MDD treatment-resistant, "recovered depressed" and "recovered bipolar", whereas DSM-IV-TR[12] separates these into different depressive disorders; and (ii) different diagnostic criteria are applied across studies. Eleven used the DSM-IV Structured Clinical Interview for Major Depressive Disorder (SCID) or the ICD equivalent, both of which have accepted validity, but four studies did not report how they diagnosed their patients. Brambilla, Perez, Barale, Schettine and Soares[80] commented that "low GABAergic cortical function may probably be a feature of a subset of disorders", and so the variability in diagnoses and diagnostic criteria limit generalizability of the findings shown in Table 1 to depression *per se*.

Taking these potential limitations into account, three of those 15 studies examined prefrontal and related brain areas (where mood disorders occur in patients with SCID-diagnosed MDD).[66,76,77] One study reported lower glutamate in MDD patients than in healthy controls, and three studies found reduced GABA to be associated with MDD. On the basis of Gaillard et al's[78] finding that occipital activity causes prefrontal activity, it may be that the data from occipital studies (including the apparently contradictory findings reported by Sanacora et al,[67] deserve further consideration.

Other Disorders

Reduced GABA has also been shown in panic disorder[81] and schizophrenia,[74] suggesting a common aetiology underlying some of these mental disorders.[80] It is of interest to note that Gos, et al[48] reported increased levels of GAD-ir, neuropil, a precursor for GABA synthesis, in the brains of suicidal patients who had been depressed. However, panic disorder, schizophrenia and suicide are not mood disorders[12,82] and there is some evidence of variations in serotonin and noradrenalin receptors and transporters in the brains of suicide victims compared to non-suicide depressed patients.[83]

Table 1. Studies of glutamate and GABA across depressed vs. nondepressed participants.

Author	Year	Target Ss, *n*	How identified	Control Ss, *n*	Area studied	Methodology	Glutamate	GABA
Sanacora, et al	1999	MDD, 14	DSM-IV SCID	Non-depressed, 18	Occipital cortex	MRI		Reduced in MDD pts.
Auer, et al	2000	MDD, depressed, bipolar, 19	ICD-10, Hamilton Rating Scales	Non-depressed, 18	Anterior cingulate	MRI	Sig. lower in depressed vs. Control Ss.	
Mason, et al	2000	Unipolar MDD, 13; Bipolar, 5	Not reported	Non-depressed, 17	Cortex	MRI		Lower in Unipolar than controls; ns diffs bipolar vs. controls.
Sanacora, et al	2000	MDD, 13	DSM-IV SCID	Non-depressed, 17	Occipital cortex	MRI		Reduced GABA in MDD Ss.
Mason, et al	2001	Unipolar, 24; bipolar, 12	Not reported	Non-depressed, 36	Occipital cortex	MRI	Lower in unipolar than controls	Lower GABA in unipolar than controls, not bipolar vs. Controls.
Sanacora, et al	2002	MDD, 11	DSM-IV SCID	NA	Occipital cortex	MRI		GABA increased after SSRIs
Sanacora, et al	2003	MDD Pts pre- post-ECT, 10	DSM-IV SCID	NA	Occipital cortex	Magnetic resonance spectroscopy		GABA increased after ECT
Sanacora, et al	2004	MDD, 33	DSM-IV SCID	Non-MDD, 38	Occipital cortex	Magnetic resonance spectroscopy	MDD had sig. higher than Controls	MDD had sig. lower than Controls.
Choudary, et al	2005	MDD, 9; BPD, 6	Not reported	Non depressed, 7	Anterior cingulate cortex, left dorsolateral prefrontal cortex	RNA from deceased Ss' brain tissue to examine gene expression	Dysregulation of genes for glutamatergic transmitter systems	Dysregulation of genes for GABAergic transmitter systems.
Hassler, et al	2007	MDD pts, 20	DSM-IV SCID	Non-MDD age and sex matched, 20	Prefrontal areas with glial cell abnormalities in MDD	Magnetic resonance spectroscopy	MDD had sig. lower than Controls	MDD had sig. lower than Controls.
Bhagwagar, et al	2007	Recovered depressed,15; Recovered bipolar, 16	DSM-IV SCID	Non-depressed, 18	Occipital cortex	Magnetic resonance spectroscopy	Higher in recovered depressed and recovered bipolar than Controls	Lower in recovered depressed and recovered bipolar than Controls.
Rajkowska, et al	2007	MDD, 14	DSM-IV SCID to next of kin, Medical records	Non-depressed, 11	Prefrontal cortex	Immunostaining		MDD sig. lower density and size of GABAergic interneurons.

(*Continued*)

Table 1. (*Continued*)

Author	Year	Target Ss, *n*	How identified	Control Ss, *n*	Area studied	Methodology	Glutamate	GABA
Thompson, et al	2009	MDD, 15; Bipolar, 15	DSM-IV diagnosis (From Torrey, et al, 2000, pp. 152)	Non-depressed, 15	GAD_{67} mRNA	RNA from deceased Ss' brain		Lower GAD_{67} (Enzyme for GABA synthesis).
Unschuld, et al	2009	Unipolar depression, 541	Not reported	Non-depressed, 541	GAD-2 gene region	Examined for polymorphisms		Lower GAD-2 (Activates enzyme to convert glutamate to GABA).
Price, et al	2009	MDD-treatment-resistant, 15; MDD, nontreatment-resistant, 18	DSM-IV SCID	Non-depressed, 24	Occipital cortex, anterior cingulate cortex	Magnetic resonance spectroscopy		Both occipital and anterior cingulate cortices showed reduced GABA in MDD-treatment-resistant Ss vs. nontreatment-resistant Ss and healthy control Ss.

Abbreviations: MDD, major depressive disorder; DSM-IV SCID, diagnostic and statistical manual (4th rev) structured clinical interview for depression; ICD-10, international classification of diseases (10th rev); MRI, magnetic resolution imaging; SSRIs, selective serotonin reuptake inhibitors; ECT, electroconvulsive therapy; NA, not available; BPD, bipolar disorder.

Treatments Based on Glutamate, GABA

Changes in neurotransmitter concentrations such as those reported above from studies of GABA and glutamate malfunction may reflect dysfunction that is associated with melancholic (rather than non-melancholic) depressed individuals. If (as noted above) melancholic patients have a biologically-based inability to experience pleasure, then it may be difficult to motivate them to undertake the homework activities required by many psychological therapies because they cannot receive appropriate reinforcement from engagement in pleasure-instigating activities (e.g. in behavior therapy models).[84] Similarly, cognitive techniques require the patient to examine their negative thoughts while experiencing negative mood[85] but melancholic patients may not be able to experience such negative emotions, instead remaining apathetic.[13] These limitations for the application of non-pharmacological treatments, plus the side effects noted for monoamine-based antidepressants and their limited efficacy compared to placebo argue strongly in favor of further investigation of the potential efficacy of medications based upon reinstatement of glutamate and GABA functions in depressed individuals.

Several attempts have been made to develop antidepressants based upon GABA.[42] For example, the GABA-mimetic agents progabide and fengabine have been shown to be as effective as tricyclics in reducing depressive symptoms[86] but have not been persevered with to the clinical development stage. Tiagabine, which is a selective GABA reuptake inhibitor has reduced MDD.[87] Focus upon the glutamate receptor NMDA with blocking agents has produced some initial support for this avenue.[42,88]

Conclusion

Glutamate and GABA have wide-ranging effects on neurological function and there is sufficient evidence connecting them with potential pathways to depression to justify investigation of epidemiological data which link malfunctions in these systems and the presence of depression. However, data reviewed herein suggest that, although there is some evidence to support a role for pharmacological interventions for depression that are based upon alleviation of the glutamate/GABA malfunction observed in depressed patients, those data are currently insufficient to draw

conclusions at this stage regarding the potential efficacy of those interventions.

Disclosure

The author reports no conflicts of interest.

References

1. Druss BG, Rosenheck RA. Patterns of health care costs associated with depression and substance abuse in a national sample. *Psychiatric Services*. 1999;50:214–8.
2. Judd LL, Paulus MP, Wells KB, Rapaport MH. Socioeconomic burden of sunsyndromal and major depression in a sample of the general population. *The American Journal of Psychiatry*. 1996;153:1411–7.
3. Lyness JM, Heo M, Datta CJ, et al. Outcomes of minor and subsyndromal depression among elderly patients in primary care settings. *Annals of Internal Medicine*. 2006;144:496–504.
4. Nutt D. Anxiety and depression: Individual entities or two sides of the same coin? *International Journal of Psychiatry in Clinical Practice*. 2004;8:19–24.
5. Mykletun A, Bjerkeset O, Overland S, Prince M, Dewey M, Stewart R. Levels of anxiety and depression are predictors of mortality: The HUNT study. *British Journal of Psychiatry*. 2009;195:118–25.
6. Alonso J, Angermeyer MC, Bernert S, et al. Prevalence of mental disorders in Europe: Results from the European Study of Epidemiology of Mental Disorders (ESEMeD) project. *Acta Psychiatrica Scandinavia*. 2004;109(Suppl):21–7.
7. Kessler RC, McGonagle KA, Shanyang Z, et al. Lifetime and 12-month prevalence of DSM-III-R psychiatric disorders in the United States: Results from the National Comorbidity Survey. *Archives of General Psychiatry*. 1994;51:8–19.
8. Kessler RC, Berglund P, Borges G, Nock M, Wang PS. Trends in suicide ideation, plans, gestures, and attempts in the United States. *The Journal of the American Medical Association*. 2005;293:2488–95.
9. Ustun TB, Ayuso-Mateos JL, Chatterji S, Mathers C, Murray CJL. Global burden of depressive disorders in the year 2000. *British Journal of Psychiatry*. 2004;184:386–92.
10. Murray CJ, Lopez AD. Alternative projections of mortality and disability by cause 1990–2020: Global burden of disease study. *Lancet*. 1997;349:1498–504.
11. WHO. *Cross-national comparisons of the prevalences and correlates of mental disorders*. WHO International Consortium in Psychiatric Epidemiology. *Bulletin of the World Health Organisation*. 2001;78: 413–26.
12. APA. *Diagnostic and Statistical Manual of Mental Disorders* (4th ed, Text Revision). Washington, DC: American Psychiatric Association; 2000.
13. Leventhal AM, Rehm LP. The empirical status of melancholia: Implications for psychology. *Clinical Psychology Review*. 2005;25:25–44.
14. Clark LA, Watson D. Tripartite model of anxiety and depression: Psychometric evidence and taxonomic implications. *Journal of Abnormal Psychology*. 1991;100:316–35.
15. Marcos T, Salamero M. Factor study of the Hamilton Ratings Scale for Depression and the Beck Melancholic Scale. *Acta Psychiatrica Scandinavia*. 1990;82:178–81.
16. Du J, Wang Y, Hunter R, Wei Y, et al. Dynamic regulation of mitochondrial function by glucorticoids. *Proceedings of the National Academy of Sciences*. 2009;106:3543–8.
17. Fiocco AJ, Wan N, Weekes N, Pim H, Lupien SJ. Diurnal cycle of salivary cortisol in older adult men and women with subjective complaints of memory deficits and/or depressive symptoms: Relation to cognitive functioning. *Stress*. 2006;9:143–52.
18. Gillespie CF, Nemeroff CB. Hypercortisolemia and depression. *Psychosomatic Medicine*. 2005;67(Suppl 1):S26–8.
19. Segerstrom SC, Miller GE. Psychological stress and the human immune system: A meta-analytic study of 30 years of inquiry. *Psychological Bulletin*. 2004;130:601–30.
20. Thase ME, Howland RH. Biological processes in depression: An updated review and integration. In: Beckham EE, and Leber WR, (Eds.). *Handbook of depression*. NY: Guilford; 1995.
21. Rush AJ, Giles DE, Schlesser MA, et al. Dexamethasone response, thyrotropin-releasing hormone stimulation, rapid eye movement latency, and subtypes of depression. *Biological Psychiatry*.1997;41:915–28.
22. Galynker II, Cai J, Ongsengg F, Finsetone H, Dutta E, Serseni D. Hypofrontality and negative symptoms in major depressive disorder. *Journal of Nuclear Medicine*. 1998;39:608–12.
23. Coppen A. The biochemistry of affective disorders. *British Journal of Psychiatry*. 1967;113:1237–64.
24. Schildkraut JJ. The catecholamine hypothesis of affective disorders: A review of supporting evidence. *American Journal of Psychiatry*. 1965;122: 509–22.
25. Rang HP, Dale MM, Ritter JM, Flower RJ. *Pharmacology* (6th ed.). Philadelphia: Elsevier; 2007.
26. Potter WZ, Padich RA, Rudorfer MV, Krishnan KRR. *Tricyclics, Tetracyclics, and Monoamine Oxidase inhibitors*. In: Stein DK, Kupfer DJ, Schatzberg AF, (Eds.). The textbook of mood disorders. Washington, DC: American Psychiatric Publishing Inc; 2006:251–61.
27. Gunnell D, Saperia J, Ashby D. Selective serotonin reuptake inhibitors (SSRIs) and suicide in adults: Meta-analysis of drug company data from placebo controlled, randomised controlled trials submitted to the MHRA's safety review. *British Medical Journal*. 2005;330:385–8.
28. Kirsch I, Moore TJ, Scoboria A, Nichols SS. The Emperor's new drugs: An analysis of antidepressant medication data submitted to the U.S. Food and Drug Administration. *Prevention and Treatment*. 2002; 5:1–11.
29. Moncrieff J, Kirsch I. Efficacy of antidepressants in adults. *British Medical Journal*. 2005;331:155–7.
30. Brown ES, Bobadilla L, Rush AJ. Ketoconazole in bipolar patients with depressive symptoms: A case series and literature review. *Bipolar Disorders*. 2001;3:23–9.
31. Ising M, Zimmerman US, Kunzel HE, et al. High-affinity CRF1 receptor antagonist NB1-34041: Preclinical and clinical data suggest safety and efficacy in attenuating elevated stress response. *Neuropsychopharmacology*. 2007;32:1941–9.
32. Murphy BE. Antiglucocorticoid therapies in major depression: A review. *Psychoneuroendocrinology*. 1997;22(Suppl):S125–32.
33. Seidman SN. *Targeting peptide and hormonal systems*. In: Stein DK, Kupfer DJ, Schatzberg AF, (Eds.). The textbook of mood disorders. Washington, DC: American Psychiatric Publishing Inc; 2006:305–16.
34. Surget A, Saxe M, Leman S, et al. Drug-dependent requirement of hippocampal neurogenesis in a model of depression and of antidepressant reversal. *Biological Psychiatry*. 2008;64:293–301.
35. Thakore JH, Dinan TG. Cortisol synthesis inhibition: A new treatment strategy for the clinical and endocrine manifestations of depression. *Biological Psychiatry*. 1995;37:364–8.
36. Groves JO. Is it time to reassess the BDNF hypothesis of depression? *Molecular Psychiatry*. 2007;12:1–10.
37. Sen S, Duman R, Sanacora G. Serum brain-derived neurotrophic factor, depression, and antidepressant medications: Meta-analyses and implications. *Biological Psychiatry*. 2008;64:527–32.
38. Svenningson P, Tzavara ET, Qi H, et al. Biochemical and behavioral evidence for antidepressant-like effects of 5-HT6 receptor stimulation. *Journal of Neuroscience*. 2007;27:4201–9.
39. Raison CL, Borisov AS, Majer M, et al. Activation of central nervous system inflammatory pathways by Interferon-Alpha: Relationship to monoamines and depression. *Biological Psychiatry*. 2009;65:296–303.
40. Showraki M. Pregabalin in the treatment of depression. *Journal of Psychopharmacology*. 2007;21:883–4.
41. Bessa JM, Ferreira D, Melo I, et al. The mood-improving actions of antidepressants do not depend on neurogenesis but are associated with neuronal remodeling. *Molecular Psychiatry*. 2009;14:764–73.
42. Sanacora G, Saricicek A. GABAergic contributions to the pathophysiology of depression and the mechanisms of antidepressant action. *CNS and Neurological Disorders-Drug Targets*. 2007;6:127–40.

43. Sanacora G, Zarate CA, Krystal JH, Manji HK. Targeting the glutamatergic system to develop novel, improved therapeutics of mood disorders. *Nature Reviews Drug Discovery*. 2008;7:426–37.
44. Guyton AC, Hall JE. *Textbook of Medical Physiology* (11th ed.). Philadelphia: Elsevier; 2006.
45. Bear MF, Connors BW, Paradiso MA. *Neuroscience: Exploring the brain* (3rd ed.). Baltimore, MD: Lippincott, Williams & Wilkins: 2007.
46. Burt AM. *Textbook of Neuroanatomy*. Philadelphia: Saunders; 1993.
47. Jaume JC. *Endocrine autoimmunity*, In: Gardner DG, Shoack D, (Eds.). Greenspan's Basic and Clinical Endocrinology. NY: McGraw-Hill; 2007: 51–84.
48. Gos T, Gunther K, Bielau H, et al. Suicide and depression in the quantitative analysis of glutamic acid decarboxylase-Immunoreactive neuropil. *Journal of Affective Disorders*. 2009;113:45–55.
49. Cryan JF, Kaupman K. Don't worry 'B' happy!: A role for $GABA_B$ receptors in anxiety and depression. *Trends in Pharmacological Sciences*. 2005;26: 36–43.
50. Krystal JH, Sanacora G, Blumberg H, et al. Glutamate and GABA systems as targets for novel antidepressants and mood-stabilizing treatments. *Molecular Psychiatry*. 2002;7:S71–80.
51. Merali Z, Du L, Hrdina P, et al. Dysregulation in the suicide brain: mRNA expression of corticotrophin-releasing hormone receptors and $GABA_A$ receptor subunits in frontal cortical brain region. *The Journal of Neuroscience*. 2004;24:1478–85.
52. Zahr NM, Mayer D, Pfefferbaum A, Sullivan EV. Low striatal glutamate levels underlie cognitive decline in the elderly: Evidence from *in vivo* molecular spectroscopy. *Cerebral Cortex*. 2008;18:2241–50.
53. Choudary PV, Molnar M, Evans SJ, et al. Altered cortical glutamatergic and GABAergic signal transmission with glial involvement in depression. *Proceedings of the National Academy of Sciences*. 2005;102:15653–8.
54. Rajkowska G, Miguel-Hidalgo JJ, Wei J, et al. Morphometric evidence for neuronal and glial prefrontal cell pathology in major depression. *Biological Psychiatry*. 1999;45:1985–1098.
55. Rot M, Mathew SJ, Charney DS. Neurobiological mechanisms in major depressive disorder. *Canadian Medical Association Journal*. 2009;180: 305–13.
56. Evans SJ, Choudary PV, Neal CR, et al. Dysregulation of the fibroblast growth factor system in major depression. *Proceedings of the National Academy of Sciences*. 2004;101:15506–11.
57. Jones MW, Kilpatrick IC, Phillipson OT. Dopamine function in the prefrontal cortex of the rat is sensitive to a reduction of tonic GABA-mediated inhibition in the thalamic mediodorsal nucleus. *Exploratory Brain Research*. 1988;69:623–34.
58. Benes FM, Vincent SL, Molloy R. Dopamine-immunoreactive axon varicosities form nonrandom contacts with GABA-immunoreactive neurons of the rat medial prefrontal cortex. *Synapse*. 1993;15:285–95.
59. Muller N, Schwartz MJ. The immune-mediated alteration of serotonin and glutamate: Towards an integrated view of depression. *Molecular Psychiatry*. 2007;12:988–1000.
60. Nishikawa T, Scatton B. Evidence for a GABAergic inhibitory influence on serotonergic neurons originating from the dorsal raphe. *Brain Research*. 1983;279:325–9.
61. Petty F, Kramer GL, Gullion CM, Rush JA. Low plasma γ-Aminobutyric acid levels in male Ss with depression. *Biological Psychiatry*. 1992;32: 354–63.
62. Bhagwagar Z, Wylezinaka M, Jezzard P, et al. Reduction in occipital cortex γ-Aminobutyric acid concentrations in medication-free recovered unipolar depressed and bipolar subjects. *Biological Psychiatry*. 2007;61: 806–12.
63. Zink M, Vollmayr B, Gebicke-Haerter PJ, Henn FA. Reduced expression of GABA transporter GAT3 in helpless rats, and animal model of depression. *Neurochemical Research*. 2009 March 15. [Epub ahead of print].
64. Auer DP, Putz B, Kraft E, Lipinski B, Schill J, Holsboer F. Reduced glutamate in the anterior cingulated cortex in depression: An *in vivo* proton magnetic resonance spectroscopy study. *Biological Psychiatry*. 2000;47: 305–13.
65. Mason GF, Anand A, Sanacora G, et al. Different relationships among cortical amino acids in unipolar and bipolar depression. *Proceedings of the International Society of Magnetic Resonance*. 2001;9:557–8.
66. Hassler G, van der Veen JW, Tumonis T, Meyers N, Shen J, Drevets WC. Reduced prefrontal glutamate/glutamine and γ-aminobutyric acid levels in major depression determine using proton magnetic resonance spectroscopy. *Archives of General Psychiatry*. 2007;64:193–200.
67. Sanacora G, Gueorguieva R, Epperson CN, et al. Subtype-specific alterations of γ-Aminobutyric acid and glutamate in Ss with Major Depression. *Archives of General Psychiatry*. 2004;61:705–13.
68. Sanacora G, Mason GF, Rothman DL, et al. Reduced cortical γ-aminobutyric acid levels in depressed Ss determined by proton magnetic resonance spectroscopy. *Archives of General Psychiatry*. 1999;56:1043–7.
69. Sanacora G, Mason GF, Krystal JH. Impairment of GABAergic transmission in depression: New insights from neuroimaging studies. *Critical Reviews in Neurobiology*. 2000;14:23–45.
70. Sanacora G, Mason GF, Rothman DL, Krystal JH. Increased occipital cortex GABA concentrations in depressed *Ss* after therapy with Selected Serotonin Reuptake Inhibitors. *American Journal of Psychiatry*. 2002;159:663–5.
71. Jinno S, Kosaka T. Neuronal circuit-dependent alterations in expression of two isoforms of glutamic acid decarboxylase in the hippocampus following electroconvulsive shock: A stereology-based study. *Hippocampus*. 2009 Mar 12. [Epub ahead of print].
72. Sanacora G, Mason GF, Rothman DL, et al. Increased cortical GABA concentrations in depressed Ss receiving ECT. *American Journal of Psychiatry*. 2003;160:577–9.
73. Mason GF, Sanacora G, Anand A, et al. Cortical GABA reduced in unipolar but not bipolar depression. *Biological Psychiatry*. 2000;47:92S.
74. Thompson M, Weickert CS, Wyatt E, Webster MJ. Decreased glutamic acid decarboxylase$_{67}$ mRNA expression in multiple brain areas of Ss with schizophrenia and mood disorders. *Journal of Psychiatric Research*. 2009; DOI: 10.1016/j.jpsychires. 2009.02.005.
75. Unschild PG, Ising M, Sprecht M, et al. Polymorphisms in the GAD2 gene-region are associated with susceptibility for unipolar depression and with a risk factor for anxiety disorders. *American Journal of Medical Genetics. Part B, Neuropsychiatric Genetics*. 2009. Feb 19. [Epub ahead of print].
76. Rajkowska G, O'Dwyer G, Teleki Z, Stockmeier CA, Miguel-Hidalgo JJ. GABAergic neurons immunoreactive for calcium binding proteins are reduced in the prefrontal cortex in major depression. *Neuropsychopharmacology*. 2007;32:471–82.
77. Price RB, Shungu DC, Mao X, et al. Amino acid neurotransmitters assessed by proton magnetic resonance spectroscopy: Relationship to treatment resistance in Major Depressive Disorder. *Biological Psychiatry*. 2009;65:792–800.
78. Gaillard R, Dehaene S, Adam C, et al. Converging intracranial markers of conscious access. *PLoS Biology*. 2009;7:472–92.
79. Bogen IL, Risa O, Haug K, Sonnewald U, Fonnum F, Walaaes SI. Distinct changes in neuronal and astrocytic amino acid neurotransmitter metabolism in mice with reduced numbers of synaptic vesicles. *Journal of Neurochemistry*. 2008;108:2434–524.
80. Brambilla P, Perez J, Barale F, Schettini G, Soares JC. GABAergic dysfunction in mood disorders. *Molecular Psychiatry*. 2003;8:721–37.
81. Goddard AW, Mason GF, Almai A, Rothman DL, Behar KL, Petroff OAC. Reductions in occipital cortex GABA levels in panic disorder detected with H-Magnetic resonance spectroscopy. *Archives of General Psychiatry*. 2001;58:556–61.
82. WHO. *International Statistical Classification of Diseases and Related Health Problems* 10th Revision. Geneva: World Health Organisation: 2007. http://www.who.int/classifications/icd/en/
83. Stockmeier CA. Involvement of serotonin in depression: Evidence from postmortem and imaging studies of serotonin receptors and the serotonin transporter. *Journal of Psychiatric Research*. 2003;37:357–73.
84. Nezu AM. Problem solving and behavior therapy revisited *Behavior Therapy*. 2004;35:1–33.
85. Beck AT, Rush AJ, Shaw BG, Emery G. C*ognitive theory of depression*. NY: Guilford; 1979.

86. Bartholini G, Lloyd KG, Morselli PL. *GABA and Mood disorders: Experimental and Clinical Research*. NY: Raven Press; 1986.
87. Carpenter LL, Schecter JM, Tyrka AR, et al. Open-label Tiagabine monotherapy for major depressive disorder with anxiety. *Journal of Clinical* Psychiatry. 2006;67:66–71.
88. Pittenger C, Sanacora G, Krystal JH. The NMDA receptor as a therapeutic target in major depressive disorder. *CNS and Neurological Disorders-Drug Targets.* 2007;6:101–15.