Neurotransmitter and Intracellular Mechanisms of Bipolar Disorder; an Explanation of Kato's Theory of Mood-Stabilising Neurons

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Abstract

Investigations into the neurobiology of bipolar disorder have produced evidence of abnormalities within many processes and chemicals in the brain. There are differences between bipolar disorder patients and controls in terms of the functioning of neurotransmitters such as dopamine, intracellular messengers such as GSK-3b, protein kinase C and calcium, and organelles such as mitochondria and the endoplasmic reticulum. A large number of genes have been identified as increasing the risk of bipolar disorder. This article reviews this evidence and examines the hypothesis that these observed abnormalities are contributing towards, or resulting from, a fundamental neurodegenerative process which affects neurons which ordinarily have a 'mood stabilising' effect.

Key words: bipolar disorder, neurobiology, dopamine, calcium, mood stabilisers, neurodegeneration.

Introduction

Bipolar disorder is a disease for which a wide variety of biological markers can be identified which show differences from control groups. Differences can be found at the genetic level, within intracellular messenger and gene expression systems, in neurotransmitter levels, and even on imaging, but none of these appear to be entirely necessary or sufficient to account for the disease. It seems likely that many of these markers we observe to be altered in bipolar disorder are contributing towards, or resulting from, a single main pathological process which is ultimately responsible for the symptomatology of the disorder, and which ties together all the diverse abnormalities that have been identified. Kato has proposed a theory of mood-stabilising neurons, which become dysfunctional in bipolar disorder, and this seems an intriguing candidate for such a 'common pathway'. In this paper, we shall discuss the various observations in the neuropathology of bipolar disorder, including abnormal function of Ca2+ channels, GSK-3b, mitochondria, and the ER stress response (1), and explain how these might fit with the theory of mood-stabilising neurons.

The Neurotransmitter and synaptic cleft level; Dopamine as a neurotransmitter in bipolar disorder

The classical view of bipolar disorder has been of a disorder primarily of neurotransmitter function. Three neurotransmitters, each with their own system of neurons and receptors, play an important role in mood disorders. These are serotonin, noradrenaline and dopamine. Reuptake transporters specific for each of these neurotransmitters regulate their concentration within the synaptic cleft by promoting reuptake of the transmitters into the presynaptic neuron. Hence SSRIs exert their action by blocking the serotonin transporter and venlafaxine blocks both the noradrenaline and serotonin transporters. It is the conventional wisdom that SSRIs and venlafaxine exert their effects in this way, and that the binding of serotonin (and in a similar way noradrenaline) to its receptor causes a second messenger cascade within the postsynaptic neuron, which in turn increases brain derived neurotrophic factor (BDNF) within the cell, which promotes neurogenesis in unipolar depression, thus alleviating the condition.

It appears that there is much evidence for dopamine being an important neurotransmitter in mania and depression. Antipsychotics effective against mania block dopamine neurotransmission, while

psychostimulants, such as amphetamine, by increasing dopamine neurotransmission, cause mania. In the context of bipolar disorder, tricyclic antidepressants can precipitate a rapid 'switch' from depression into mania, but the SSRIs do not tend to cause this (2]. Tricyclic antidepressants block the noradrenaline and serotonin transporters, but have negligible effect on the dopamine transporter. However, in the prefrontal cortex, dopamine transport uses the noradrenaline transporter, such that tricyclics are able to increase the concentration of dopamine within prefrontal cortex synapses, while SSRIs do not (3).

In dopamine-deficient transgenic mice, lower locomotor activity and hypophagia is observed (4, 5). Ventral tegmental area dopamine neuron degeneration is known to cause depression (6). The cerebrospinal fluid concentration of the dopamine metabolite homovanillic acid is seen to alter in a state-dependent manner (7). Thus, dopamine neurotransmission appears to alter with mood state. Serotonin systems, on the other hand, can be seen to alter in a manner that is not dependent on overall mood state. Reduced serotonin activity, as measured by neuroendocrine challenge (8) and decreased cerebrospinal fluid concentrations of HIAA (a serotonin metabolite), were reported in both depressive and manic states (7). Putting this more simply, there is evidence that dopamine in particular is an important neurotransmitter in bipolar disorder. This indicates an important difference in terms of neurotransmitters between bipolar and unipolar depression. It is important to remember, however, that neurotransmitter levels are merely the product of the neurons that produce them, and that these abnormalities might be the result of a number of more fundamental cellular changes in bipolar disorder, most likely effecting the neurogenesis and degeneration of neurons which then, in turn, affect levels of transmitters such as dopamine.

The Role of Calcium Channels

In the platelets of patients with bipolar disorder, it is found that basal levels of calcium, and the degree of calcium influx provoked by agonists such as thrombin, serotonin, and platelet activating factor, are enhanced, regardless of which agonist is used (9, 10). The ER calcium pump can be inhibited using thapsigargin, which results in Ca2+ depletion from the ER stores, and a secondary Ca2+ influx via the SOCC on the plasma membrane, leading to increased cytoplasmic Ca2+ concentrations. Peripheral blood cells taken from patients with bipolar disorder have an enhanced response to thapsigargin (11, 12), and SOCC disruption appears to be contributing towards the Ca2+ signalling changes seen in bipolar disorder (10). Within neurons, Ca2+ signalling could also be disrupted by altered function of the NMDA receptor, Ca2+ permeable AMPA/kainate receptor, and voltage-gated Ca2+ channel. Studies of post-mortem brains from patients with bipolar disorder have shown changes in the genes for these receptors.

The Phosphoinositide pathway

Intracellular calcium levels are also affected by the phosphatidylinositol pathway, the likely target of lithium. Phosphatidylinositol bisphosphate hydrolysis yields diacylglycerol (DAG) and inositol triphosphate (IP3), which in turn causes ER Ca2+ stores to be released. Lymphoblastoid and lymphocyte cell lines from patients with bipolar disorder show lower levels of inositol (13), reduced inositol monophosphatase 2 mRNA (14, 15), and reduced IMPase activity (16). Protein kinase C, which is activated by DAG and Ca2+, is found to be active, bound to membranes, and translocates to the membrane in response to serotonin stimuli, in higher levels in drug-free patients, and this dysregulation is reduced following lithium or valproate treatment (17, 18, 19).
As well as acting on the phosphatidylinositol pathway, mood stabilisers also seem to inhibit glycogen synthase kinase 3b (GSK-3b) (20, 21), and thus the GSK-3b pathway may also have a role in the neurobiology of bipolar disorder. GSK-3b is controlled via intracellular Ca2+ signalling, and has a role in the neurotrophin and Wnt signalling pathways. There is evidence to suggest that GSK-3b overactivity in bipolar disorder may be responsible for a shortening of the circadian rhythm period, and that lithium is able to affect circadian rhythm by GSK-3b inhibition (22).

Mitochondrial dysfunction

Studies using magnetic resonance spectroscopy (MRS) have indicated that differences in energy metabolism are present in patients with bipolar disorder, including reductions in phosphocreatine (23) and creatine (26, 27, 28), a decreased intracellular pH (24), and increased lactate (25). These are similar findings to those seen in mitochondrial diseases like chronic external ophthalmoplegia (CPEO), caused by mitochondrial DNA (mtDNA) deletions and primarily affecting muscle cells. mtDNA deletions were reported to be numerous in the brain of a patient with CPEO who presented primarily with severe retarded depression (29). Thus, it has been suggested that mtDNA deletions in the brain might be a cause for depression. In some mitochondrial cytopathies, convincing associations have been shown with depression (54% of 36 patients with mitochondrial disease,) and bipolar disorder (17%) (30, 31).

These abnormalities of mtDNA, known to be accumulated in the brains of some bipolar disorder patients (33), are likely to effect the pathology of bipolar disorder through mitochondrial Ca2+ dysregulation (32). Mitochondrial-related nuclear gene expression also appears to be decreased in bipolar disorder, for instance in the hippocampus (34). The lymphocytes of bipolar disorder patients appear to down-regulate mitochondria-related nuclear genes in response to glucose deprivation stress, whilst healthy control subjects respond by upregulating these genes (35), suggesting that a cellular stress response impairment may be of importance in bipolar disorder. Transgenic mice have been studied, which show mutations of mtDNA polymerase gamma (POLG), modelling one of the causes of CPOE (36). These mice have accumulations of mtDNA deletions within neurons, and show bipolar disorder-like phenotypes. This included changes to the circadian rhythm, which were exacerbated by tricyclic antidepressants but improved by lithium (37) or electroconvulsive therapy (38). Mitochondria from the brains of these transgenic mice were found to sequester calcium more rapidly (39). Mitochondrial dysfunction in bipolar disorder is also likely to cause oxidative stress, and markers for this, such as thiobarbituric acid reactive substances, are found to be raised in patients with bipolar disorder (40).

Endoplasmic reticulum stress dysfunction

The leucine zipper transcription factor gene X-box-binding protein 1 (XBP1) has been linked with ER stress dysfunction, and may have a role in bipolar disorder. XBP1 response to ER stress within lymphoblastic cells is shown to be weaker in patients with bipolar disorder (41, 42). This weakened response is not dependent on the XBP1 genotype in these patients (42). Within neurons, XBP1 mRNA is spliced as a result of ER stress, induced locally by BDNF as it raises protein synthesis. Neurons with XBP1 knockout show an impairment in the growth and extension of neurites which would be the normal response to BDNF (43). This impaired extension response might be mediated by an impairment in the differentiation of GABAergic interneurons normally induced by BDNF (44). A mutation in Caenorhabditis elegans which prevents XBP1 splicing causes an abnormality in AMPA glutamate receptor transport from the ER (45). Thus, a diminished XBP1 response in the neurons of bipolar disorder patients could cause impaired neurite extension in response to BDNF, impaired GABA interneuron differentiation, and impaired AMPA receptor trafficking.

The endoplasmic reticulum function of protein folding appears to be influenced by a protein with a peptidylprolyl isomerase (PPI) domain, encoded by the peptidylprolyl cis-trans isomerase E like (PPIEL) gene. This is found to be significantly hypomethylated in bipolar II disorder patients and this resulted in raised mRNA expression in lymphoblastoid cells. PPIEL mRNA is expressed throughout the brain, particularly within the substantia nigra and pituitary gland, possibly suggesting a role in dopaminergic neurons (46).

Vulnerability of neurons

The most established neuroimaging finding in bipolar disorder is that of increased numbers of subcortical hyperintensity (SCH) lesions in T2-weighted MRI (47). This increased SCH lesion frequency

in bipolar disorder is thought to be a consequence of increased vulnerability to cellular stress within the neurons or oligodendrocytes. The neuroprotective effect of mood-stabilising drugs supports this idea that bipolar disorder may be associated with some neuronal vulnerability or impaired resilience (48). If this were the case, bipolar disorder would be expected to be associated with neuronal loss. Indeed this is the case, with the anterior cingulate (49, 50, 51), prefrontal cortex (52, 53), hippocampal corpus ammonius (CA2) (54), ventromedial thalamic nucleus (55), hypothalamic paraventricular nucleus (56), and the dorsal raphe ventrolateral subnucleus all showing reduced neuronal density or numbers in patients with bipolar disorder. It is of interest that primarily, the findings of reduced neuronal numbers in these areas are accounted for by reductions in interneurons as opposed to pyramidal neurons (49, 51, 54, 55). Furthermore, of all these areas found to have reduced neurons in bipolar disorder, only the hypothalamic periventricular nucleus also shows gliosis (56). This neuronal vulnerability in bipolar disorder patients appears to be related to altered neurotrophin signalling, impaired calcium signalling, mitochondrial dysfunction, and endoplasmic reticulum (ER) stress response dysfunction. These pathways are closely linked, with neurotrophin regulation vital for correct calcium signalling, and mitochondria and ER important for regulating store-operated calcium channels (SOCC) used in intracellular calcium signalling.

Mechanism of clinical action of mood stabilisers

The mechanism of action of mood stabilisers, particularly lithium and valproate, give useful indications of the important intracellular pathways which affect bipolar disorder. It is known that both lithium and valproate are neuroprotective, and that they act in this way by affecting inositol metabolism, and thus neurogenesis, especially GABAergic neurogenesis (58), (59). The trophic factors BDNF, BAG1 and bcl-2, are important in this process of enhancing neurogenesis. Lithium most probably acts by inhibiting inositol-monophosphatase (IMPase), thus depleting intracellular inositol (57). Both lithium and valproate act to enlarge growth cones (60), and enhance adult neurogenesis (61, 62), particularly of GABA neurones (62).

The mechanisms by which the mood stabilisers cause these neurogenesis effects include inositol depletion (62), bcl-2 upregulation on the outer membrane of mitochondria (22), glycogen synthase kinase 3b (GSK-3b) inhibition (63, 64), BDNF-ERK pathway enhancement, glutamate receptor trafficking effects (65), upregulating the glucocorticoid receptor co-chaperone BAG-1 (66), glucocorticoid receptor functioning inhibition (67), glutathione S-transferase upregulation (68), Notch signalling activation (69), and, in the case of valproate, histone deacetylase inhibition (70). Furthermore, the glutamatergic agents lamotrigine, ketamine and riluzole, which are currently showing some promise as mood-stabilising drugs, all appear to upregulate AMPA receptors, increasing AMPA/NMDA stimulation, and thus may induce neuroproliferation through enhancement of BDNF and other intracellular signalling cascades (71).

Mood-stabilising neuron hypothesis

The progression of bipolar disorder tends to be characterised by a shortening of the interval between episodes and a higher vulnerability to stress. If progression leads to rapid cycling, the effectiveness of lithium is reduced.

This tendency for the disease to progress is usually put down to a 'kindling' theory of repeated external stressors which may precipitate symptoms requiring progressively lower stimulus levels to trigger a response (72). However, a progressive degeneration of neurons with a mood-stabilising role is an alternative explanation. This theory is intriguing as it could tie together much of the known cellular pathology and neurobiology of bipolar disorder discussed above. The inhibitory GABAergic interneurons, which are reported to be reduced in bipolar disorder patients, could fill this role. Impaired ER stress response of bipolar disorder, as discussed above, may result in impairments of differentiation of GABAergic neurons. Cortical inhibition was seen to be decreased in bipolar disorder in a study using transcortical magnetic stimulation (73). In the hippocampal CA2 region, interneurons (74) are found to be reduced and, in particular, the GABAergic marker GAD67 and transcription factors needed for GABAergic interneurons like LHX2 and PAX5 are found to be reduced in the striatum oriens

of the CA2/3 region (75).

Neurons regulating the circadian rhythm, in the retino-hypothalamic pathway, have also been posited as 'mood-stabilising' neurons. Bipolar disorder patients have been reported to show disruptions in the melatonin response to light (76), and social rhythm therapy is effective in preventing relapses in bipolar disorder, by aiming to regularise the social rhythm of patients (77).

Concluding Remarks

It is now quite clear that, although abnormalities are readily detected at the neurotransmitter level in bipolar disorder, the more fundamental intracellular signalling pathologies responsible for these abnormalities must be understood in order to elucidate the neurobiology of the disorder fully. It seems that a diverse number of different genetic, epigenetic and environmental risk factors can have a detrimental effect on the function of key pathways, such as the ER stress response, mitochondrial function, Ca2+ channels, and GSK-3b, and that the ultimate effect of dysregulation of these pathways may be progressive damage to the neurons normally responsible for stabilising mood.

GP Comment

What have I learned from this paper?

Although, on the face of it, a very 'technical' article, this is a useful and comprehensive review of current understanding with regard to the neurobiological variations in neurotransmitter, intracellular messenger and organelle functioning associated with bipolar disease.

It provides a valuable knowledge base to add to the symptomatology, progression and current treatment of bipolar disorder which can underpin information sharing and collaborative work in frontline clinical practice with those who suffer from the disease. This article will also support the clinician to explain and understand the mechanisms by which medication can help.

In addition the article explores the potential relationship between these changes causing progressive damage to the neurons which normally stabilise mood and the observed progression of the disease as characterised by a shortening of the interval between episodes and higher vulnerability to stress, rather than the tendency for repeated external stressors to reduce the level of stimulus required to produce symptoms. It will be interesting to see the future potential of this debate to improve understanding and treatment of the disease.

Jane Leigh, GP.

References

1. Kato T. Molecular neurobiology of bipolar disorder: a disease of 'mood-stabilizing neurons'? Trends Neurosci. 2008 Oct;31 (10):495-503.
2. Peet M. Induction of mania with selective serotonin re-uptake inhibitors and tricyclic antidepressants. Br. J. Psychiatry 1994;164:549–550.
3. Valentini V et al. Noradrenaline transporter blockers raise extracellular dopamine in medial prefrontal but not parietal and occipital cortex: differences with mianserin and clozapine. J.Neurochem. 2004;88:917–927.
4. Zhou QY, Palmiter RD. Dopamine-deficient mice are severely hypoactive, adipsic, and aphagic. Cell 1995;83:1197–1209.
5. Nishii K et al. Motor and learning dysfunction during postnatal development in mice defective in dopamine neuronal transmission. J. Neurosci. Res. 1998;54:450–464.
6. Torack RM, Morris, JC. The association of ventral tegmental area histopathology with adult dementia. Arch. Neurol. 1988;'45:497–501.
7. Goodwin FK, Jamison KR. Manic-Depressive Illness. 2nd edn. Oxford University Press; 2007..
8. Mahmood T, Silverstone T. Serotonin and bipolar disorder. J. Affect. Disord. 2001;66:1–11.

9. Kato T. Role of mitochondrial DNA in calcium signalling abnormality in bipolar disorder. Cell Calcium 2008;44:92–102.
10. Warsh JJ et al. Role of intracellular calcium signaling in the pathophysiology and pharmacotherapy of bipolar disorder: current status. Clin.Neurosci. Res. 2004;4:201–213.
11. Hough C et al. Elevated basal and thapsigargin-stimulated intracellular calcium of platelets and lymphocytes from bipolar affective disorder patients measured by a fluorometric microassay. Biol. Psychiatry 1999;46:247–255.
12. Kato T et al. Mechanisms of altered Ca2+ signalling in transformed lymphoblastoid cells from patients with bipolar disorder. Int. J. Neuropsychopharmacol. 2003;6:379–389.
13. Belmaker RH et al. Reduced inositol content in lymphocyte derived cell lines from bipolar patients. Bipolar Disord. 2002;4:67–69.
14. Nemanov L et al. Effect of bipolar disorder on lymphocyte inositol monophosphatase mRNA levels. Int. J.Neuropsychopharmacol. 1999;2:25–29.
15. Yoon IS et al. Altered IMPA2 gene expression and calcium homeostasis in bipolar disorder. Mol. Psychiatry 2001;6:678–683.
16. Shamir A et al. Inositol monophosphatase in immortalized lymphoblastoid cell lines indicates susceptibility to bipolar disorder and response to lithium therapy. Mol. Psychiatry 1998;3:481–482.
17. Friedman E et al. Altered platelet protein kinase C activity in bipolar affective disorder, manic episode. Biol. Psychiatry 1993;33:520–525.
18. Wang HY et al. Increased membrane-associated protein kinase C activity and translocation in blood platelets from bipolar affective disorder patients. J. Psychiatr. Res. 1999;33:171–179.
19. Hahn CG et al. Lithium and valproic acid treatments reduce PKC activation and receptor-G protein coupling in platelets of bipolar manic patients. J. Psychiatr. Res. 2005;39:355–363.
20. Klein PS, Melton, DA. A molecular mechanism for the effect of lithium on development. Proc. Natl. Acad. Sci. U. S. A. 1996;93:8455–8459.
21. Chen G et al. The mood-stabilizing agent valproate inhibits the activity of glycogen synthase kinase-3. J. Neurochem. 1999;72:1327–1330.
22. Yin L et al. Nuclear receptor Rev-erba is a critical lithium sensitive component of the circadian clock. Science 2006;311:1002–1005.
23. Kato T et al. Reduction of brain phosphocreatine in bipolar II disorder detected by phosphorus-31 magnetic resonance spectroscopy. J. Affect. Disord. 1994;31:125–133.
24. Kato T et al. Alterations in brain phosphorous metabolism in bipolar disorder detected by in vivo 31P and 7Li magnetic resonance spectroscopy. J. Affect. Disord. 1993;27:53–59.
25. Dager SR et al. Brain metabolic alterations in medication free patients with bipolar disorder. Arch. Gen. Psychiatry 2004;61:450–458.
26. Hamakawa H et al. Quantitative proton magnetic resonance spectroscopy of the bilateral frontal lobes in patients with bipolar disorder. Psychol. Med. 1999;29:639–644.
27. Port JD et al. Metabolic alterations in medication-free patients with bipolar disorder: a 3T CSF-corrected magnetic resonance spectroscopic imaging study. Psychiatry Res. 2008;162:113–121.
28. Frey BN et al. Abnormal cellular energy and phospholipid metabolism in the left dorsolateral prefrontal cortex of medication free individuals with bipolar disorder: an in vivo 1H MRS study. Bipolar Disord. 2007;9 (Suppl. 1):119–127.
29. Suomalainen A et al. Multiple deletions of mitochondrial DNA in several tissues of a patient with severe retarded depression and familial progressive external ophthalmoplegia. J. Clin. Invest. 1992;90:61–66.
30. Siciliano G et al. Autosomal dominant external ophthalmoplegia and bipolar affective disorder associated with a mutation in the ANT1 gene. Neuromuscul.Disord. 2003;13:162–165.
31. Fattal O et al. Psychiatric comorbidity in 36 adults with mitochondrial cytopathies. CNS Spectr. 2007;12:429–438.
32. Kato T, Kato, N. Mitochondrial dysfunction in bipolar disorder. Bipolar Disord. 2000;2:180–190.
33. Kato T et al. Increased levels of a mitochondrial DNA deletion in the brain of patients with bipolar disorder. Biol. Psychiatry 1997;42:871–875.
34. Konradi C et al. Molecular evidence for mitochondrial dysfunction in bipolar disorder. Arch. Gen. Psychiatry 2004;61:300–308.
35. Naydenov AV et al. Differences in lymphocyte electron transport gene expression levels between subjects with bipolar disorder and normal controls in response to glucose deprivation stress. Arch.

Gen. Psychiatry 2007;64:555–564.
36. Van Goethem G et al. Mutation of POLG is associated with progressive external ophthalmoplegia characterized by mtDNA deletions. Nat. Genet. 2001;28:211–212.
37. Kasahara T et al. Mice with neuron-specific accumulation of mitochondrial DNA mutations show mood disorder-like phenotypes. Mol. Psychiatry 2006;11:577–593.
38. Kasahara T et al. A marked effect of electroconvulsive stimulation on behavioral aberration of mice with neuron-specific mitochondrial DNA defects. PLoS ONE 2008;3:e1877.
39. Kubota M et al. Abnormal Ca2+ dynamics in transgenic mice with neuron-specific mitochondrial DNA defects. J. Neurosci. 2006;26:12314–12324.
40. Andreazza AC et al. Oxidative stress markers in bipolar disorder: a meta-analysis. J. Affect. Disord. :DOI:10.1016/j.jad.2008.04.013.
41. Reimold AM et al. Plasma cell differentiation requires the transcription factor XBP-1. Nature 2001;412:300–307.
42. So J et al. Impaired endoplasmic reticulum stress response in B-lymphoblasts from patients with bipolar-I disorder. Biol. Psychiatry 2007;62:141–147.
43. Hayashi A et al. The role of brain-derived neurotrophic factor (BDNF)-induced XBP1 splicing during brain development. J. Biol.Chem. 2007;282:34525–34534.
44. Hayashi A et al. Attenuated BDNF-induced upregulation of GABAergic markers in neurons lacking Xbp1. Biochem Biophys Res Commun. 2008;376:758-63.
45. Shim J et al. The unfolded protein response regulates glutamate receptor export from the endoplasmic reticulum. Mol.Biol. Cell 2004;15:4818–4828.
46. Kuratomi G et al. Aberrant DNA methylation associated with bipolar disorder identified from discordant monozygotic twins. Mol.Psychiatry 2008;13:429–441.
47. Videbech P. MRI findings in patients with affective disorder: a meta-analysis. Acta Psychiatr. Scand. 1997;96:157–168.
48. Manji HK, Duman RS. Impairments of neuroplasticity and cellular resilience in severe mood disorders: implications for the development of novel therapeutics. Psychopharmacol. Bull. 2001;35:5–49.
49. Benes FM et al. The density of pyramidal and nonpyramidal neurons in anterior cingulate cortex of schizophrenic and bipolar subjects. Biol. Psychiatry 2001;50:395–406.
50. Bouras C et al. Anterior cingulate cortex pathology in schizophrenia and bipolar disorder. Acta Neuropathol. 2001;102:373–379.
51. Cotter D et al. The density and spatial distribution of GABAergic neurons, labelled using calcium binding proteins, in the anterior cingulate cortex in major depressive disorder, bipolar disorder, and schizophrenia. Biol. Psychiatry 2002;51:377–386.
52. Rajkowska G et al. Reductions in neuronal and glial density characterize the dorsolateral prefrontal cortex in bipolar disorder. Biol. Psychiatry 2001;49:741–752.
53. Beasley CL et al. Selective deficits in prefrontal cortical GABAergic neurons in schizophrenia defined by the presence of calcium-binding proteins. Biol. Psychiatry 2002;52:708–715.
54. Benes FM et al. A reduction of nonpyramidal cells in sector CA2 of schizophrenics and manic depressives. Biol. Psychiatry 1998;44:88–97.
55. Kromkamp M et al. Decreased thalamic expression of the homeobox gene DLX1 in psychosis. Arch. Gen. Psychiatry 2003;60:869–874.
56. Manaye KF et al. Selective neuron loss in the paraventricular nucleus of hypothalamus in patients suffering from major depression and bipolar disorder. J. Neuropathol. Exp. Neurol. 2005;64: 224–229.
57. Nonaka S et al. Chronic lithium treatment robustly protects neurons in the central nervous system against excitotoxicity by inhibiting N-methyl-D-aspartate receptor-mediated calcium influx. Proc. Natl. Acad. Sci. U. S. A. 1998;95:2642–2647.
58. Chen G et al. The mood-stabilizing agents lithium and valproate robustly increase the levels of the neuroprotective protein bcl-2 in the CNS. J. Neurochem. 1999;72:879–882.
59. Williams RS et al. A common mechanism of action for three mood-stabilizing drugs. Nature 2002;417:292–295.
60. Chen G et al. Enhancement of hippocampal neurogenesis by lithium. J. Neurochem. 2000;75: 1729–1734.
61. Hao Y et al. Mood stabilizer valproate promotes ERK pathway-dependent cortical neuronal growth and neurogenesis. J. Neurosci. 2004;24:6590–6599.

62. Laeng P et al. The mood stabilizer valproic acid stimulates GABA neurogenesis from rat forebrain stem cells. J. Neurochem. 2004;91:238–251.
63. Klein PS, Melton DA. A molecular mechanism for the effect of lithium on development. Proc. Natl. Acad. Sci. U. S. A. 1996;93:8455–8459.
64. Chen G et al. The mood-stabilizing agent valproate inhibits the activity of glycogen synthase kinase-3. J. Neurochem. 1999;72:1327–1330.
65. Du J et al. Structurally dissimilar antimanic agents modulate synaptic plasticity by regulating AMPA glutamate receptor subunit GluR1 synaptic expression. Ann. N. Y. Acad. Sci. 2003;1003:378–380.
66. Zhou R et al. The anti-apoptotic, glucocorticoid receptor cochaperone protein BAG-1 is a long-term target for the actions of mood stabilizers. J. Neurosci. 2005;25:4493–4502.
67. Basta-Kaim A et al. Mood stabilizers inhibit glucocorticoid receptor function in LMCAT cells. Eur. J. Pharmacol. 2004;495:103–110.
68. Cui J et al. Role of glutathione in neuroprotective effects of mood stabilizing drugs lithium and valproate. Neuroscience 2007;144:1447–1453.
69. Higashi M et al. Mood stabilizing drugs expand the neural stem cell pool in the adult brain through activation of notch signaling. Stem Cells 2008;26:1758–1767.
70. Leng Y et al. Synergistic neuroprotective effects of lithium and valproic acid or other histone deacetylase inhibitors in neurons: roles of glycogen synthase kinase-3 inhibition. J. Neurosci. 2008;28:2576–2588.
71. Brennan BP et al. Rapid Enhancement of Glutamatergic Neurotransmission in Bipolar Depression Following Treatment with Riluzole. Neuropsychopharmacology 2010;35:834-846.
72. Post RM, Weiss SR. A speculative model of affective illness cyclicity based on patterns of drug tolerance observed in amygdala-kindled seizures. Mol. Neurobiol. 1996;13:33–60.
73. Levinson AJ et al. Cortical inhibitory dysfunction in bipolar disorder: a study using transcranial magnetic stimulation. J. Clin. Psychopharmacol. 2007;27:493–497.
74. Benes FM et al. A reduction of nonpyramidal cells in sector CA2 of schizophrenics and manic depressives. Biol. Psychiatry 1998;44:88–97.
75. Benes FM et al. Regulation of the GABA cell phenotype in hippocampus of schizophrenics and bipolars. Proc. Natl. Acad. Sci. U.S. A. 2007;104:10164–10169.
76. Lewy AJ et al. Manic-depressive patients may be supersensitive to light. Lancet 1981;1:383–384.
77. Frank E et al. Interpersonal and social rhythm therapy: an intervention addressing rhythm dysregulation in bipolar disorder. Dialogues Clin.Neurosci. 2007;9:325–332.