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REVIEW ARTICLE

Neuronal migration, apoptosis and bipolar disorder☆

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Abstract Bipolar disorder, like the majority of psychiatric disorders, is considered a neurodevelopment disease. There is an increased rate of neuronal birth and death during this development period. In the particular case of the processes that determine neuronal death, it is known that those neurons that establish connections have to be removed from the central nervous system. There is a deficit of GABAergic interneurons in the cerebral cortex in bipolar disorder, accompanied by overexpression of proapoptic genes. There is also an alteration in the expression of molecules that mediate in the migration of these neurons and their inclusion in functional synapsis during the foetal stage. The role of these molecules in the neuronal death pathways by apoptosis will be reviewed here in an attempt to establish biological hypotheses of the genesis of bipolar disorder.

PALABRAS CLAVE
Apoptosis;
Trastorno bipolar;
Neurodesarrollo;
Sinapsis;
Migración neuronal;
Interneuronas GABAérgicas

Migración neuronal, apoptosis y trastorno bipolar

Resumen El trastorno bipolar es considerado, al igual que la mayoría de los trastornos psiquiátricos, una enfermedad del neurodesarrollo. Durante dicho período, existe una marcada tasa de nacimiento y muerte neuronal. En el caso particular de los procesos que determinan la muerte neuronal, es sabido que aquellas neuronas que establecen conexiones sinápticas aberrantes deben ser eliminadas del sistema nervioso central. El trastorno bipolar cursa con un déficit de interneuronas GABAérgicas en la corteza cerebral, acompañado de una sobreexpresión de genes proapoptóticos, así como una alteración en la expresión de moléculas que median la migración de dichas neuronas y su inclusión en sinapsis funcionales durante el estadío fetal. Aquí será revisado el rol de dichas moléculas sobre las vías de muerte neuronal por apoptosis en la procura de establecer hipótesis biológicas de la génesis del trastorno bipolar.

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Introduction

Bipolar disorder is currently considered a neurodevelopmental disease[1,2] that involves a considerable loss of quality of life and cognitive faculties in the intermediate term. The theories that back this hypothesis represent the best approximations in the search for the molecular origins of psychiatric disorders,[3,4] after having identified alterations in the expression of different genes that provoke the migration of GABAergic interneurons from their site of origin to their final location in specific cortical circuits. In bipolar disorder, there is a 27% deficit of interneurons in the cerebral cortex[5] and hippocampus.[6,7] There is also a high expression of pro-apoptotic genes[8,9] such as Bcl-2-associated x protein (BAX), Bcl-2-associated death promoter (BAD), caspase-9 and caspase-3, along with a decrease in the expression of anti-apoptotic genes such as brain derived neurotrophic factor (BDNF) and B-cell lymphoma 2 (Bcl-2).[9] When the interneurons migrate, they require the signalling of extracellular molecules that synergically mediate their transfer and posterior incorporation to specific neuronal circuits. The protomap hypothesis formulates that a neuron, from its birth, has defined genetic instructions as to the exact place of migration and synaptic connections that it will establish when it incorporates into functional circuits,[10] so that if it incorporates itself erratically to these circuits, it will establish abnormal synaptic connections that will lead to its death.[11,12] Neuronal death represents a phenomenon needed in the central nervous system, which determines the exact number of cells that will constitute specific neuronal circuits. In spite of the fact that neuronal death is present throughout a normal subject's life, it is much more intense during neurodevelopment because of the high rate of neurogenesis in this period. There are at least 3 types of neuronal death known: apoptosis, autophagy and necrosis. With respect to mental disease and the presence of neuronal death in it, we enter into an intense debate in which the uncertainty of isolated and reductionist research, lacking an overall vision, prevail. Some investigators have recently identified the activation of pro-apoptotic elements such as caspase-3 in some neuronal forms after the abolition of synaptic connections by axotomy[13]; this makes apoptosis the most attractive form of neuronal death when justifying the deficit of interneurons in the cerebral cortex of the subject with bipolar disorder. At any rate, in their migration process, interneurons require the action of molecules that stimulate cell survival, molecules with an alteration in their expression that confers a risk of having the disorder (see further on). In this review article, we present the analysis of 3 of the elements involved in bipolar disorder: BDNF, Neuregulin 1 (Nrg1) and Reelin. We also cover the pro-apoptotic pathways that trigger their abnormal expression.

Migration of GABAergic interneurons and bipolar disorder

The migration of GABAergic interneurons is a complex process mediated by the expression of hundreds of genes synergically, with a fine control that guarantees not only correct migration, but also complete maturation in the search for achieving appropriate inclusion in a specific inhibitory circuit (Fig. 1A). BDNF plays an essential role in the way GABAergic interneurons (molecules deficient in bipolar disorder) migrate to the cortex during neurodevelopment.[14] In rodents lacking expression of the BDNF receptor, tropomyosin-related kinase B (TrkB), tangential migration is reduced in the embryonic period.[15] BDNF production is subject to the expression of molecules of a synaptic nature, such as calcium-dependent activator protein for secretion 2 (CAPS2),[16] in such a way that the greater the number of efficient synaptic connections established, the greater the production of CAPS32 and, consequently, of BDNF.[17] Once tangential migration to the cerebral cortex has occurred, interneurons require extracellular molecule signalling to migrate radially. Reelin is a glycoprotein secreted by the Cajal-Retzius cells that links to specific receptors in the interneuron membrane to provoke radial migration.[18] Studies on rodents lacking expression of the gene for Reelin demonstrate its importance in the laminar configuration of the cerebral cortex. The youngest neurons usually detain their migratory process in the deepest layers, while adult neurons do so in the superficial layers. This process is inverted in zero expression models for Reelin.[19] Consequently, despite not affecting radial and tangential migration directly, the interneurons reach an incorrect place due to the cortical layers being.[20–22] Some variations of the Reelin gene have been identified as a risk factor for developing bipolar disorder in females,[23] and a decrease in its expression would involve the same result in both sexes.[24] In addition, some antidepressants and antipsychotics (drugs commonly used in bipolar disorder) increase Reelin expression in the prefrontal cortex.[25] A direct relationship between alterations in Reelin gene expression and the deficit in glutamic acid decarboxylase (GAD) positive interneurons[26] has recently been identified; patients with bipolar disorder had up to a 40% deficit.[27] Nrg1 comprises a family of extracellular growth factors that require the expression of their receptor ErbB on the surface of the interneuron cell membrane during migration,[28] activating a wide range of second messengers that culminate in the activation of transcription factors in the neuron nucleus. Some polymorphic variations of Nrg1 predispose to the appearance bipolar disorder with its psychotic symptoms[29] and reduced migration of interneurons to the cerebral cortex was found in studies on rodents with the mutation for this gene.[28]

Neuronal apoptosis and abnormal integration into synaptic circuits

After the migratory process, the GABAergic interneurons should integrate in neuronal circuits to carry out a specific role. The molecular processes that mediate migration also stimulate interneuron maturation and there is a deficit of some of these molecules in the brain of a subject with bipolar disorder. Consequently, when they join that circuit, they lack the differentiation needed to establish functional synaptic connections. In any case, whether the interneurons reach the improper place or they reach the correct place and establish aberrant synaptic connections, they must be eliminated from the brain as they develop, as part of a normal synaptic refinement process (Fig. 1B). The prefrontal cortex in the patient with bipolar disorder presents a high

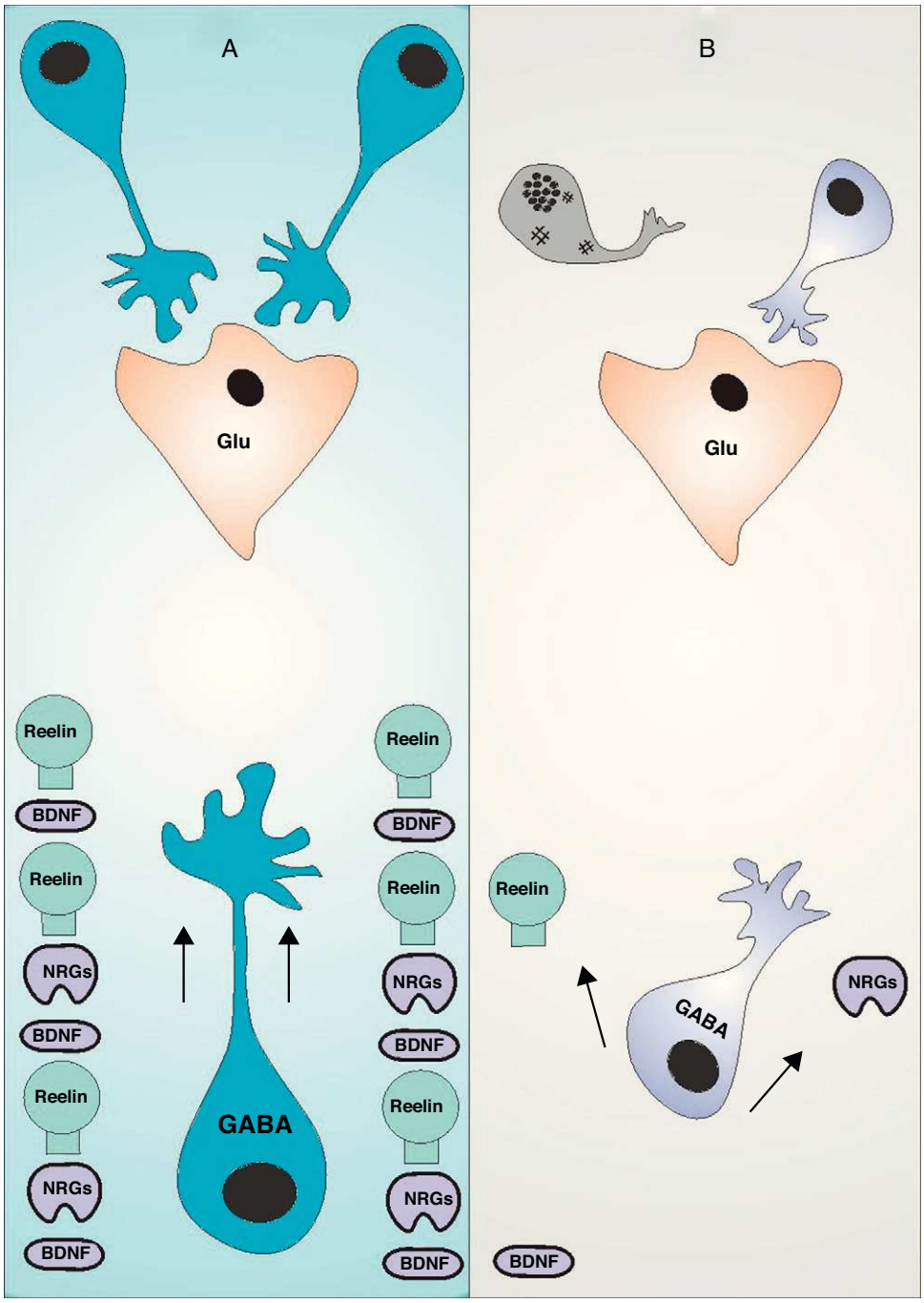

Figure 1 Migration of interneurons in bipolar disorder: (A) showing the influence of BDNF, reelin and Nrg1 on the migration of GABAergic interneurons, in such a way that their correct expression determines correct integration of inhibitory circuits, composed mainly of glutamatergic pyramidal neurons.[15,20,28] (B) Reducing the expression of these molecules not only causes alterations in the direction of GABAergic interneuron migration, it leads to insufficient maturation of these interneurons and the subsequent aberrant integration in the inhibitory circuit and, consequently, death by apoptosis.[12]

expression of pro-apoptotic molecules such as BAD, BAX, caspase-3 and -9 and reduced expression of anti-apoptotic molecules such as Bcl-2.[8] We consequently propose apoptosis as the model of cell death during the neurodevelopment of the bipolar subject, justifying in this way the interneuron deficit existing in these patients. Apoptosis is triggered through 2 pathways. The first is the extrinsic, which is activated by ligands of the tumour necrosis factor family that, upon linking to its receptor in the neuronal surface, promotes caspase-8 activation; this in turn successively activates caspase-3, -6 or -7, finally inducing apoptosis. The 2nd pathway is the intrinsic or mitochondrial; when various molecules in the mitochondrial intermembrane space leave for the neuronal cytoplasm, it is activated. The main one of these molecules is Cytochrome C, which forms a complex with Apaf-1 and dATP nucleosome designated

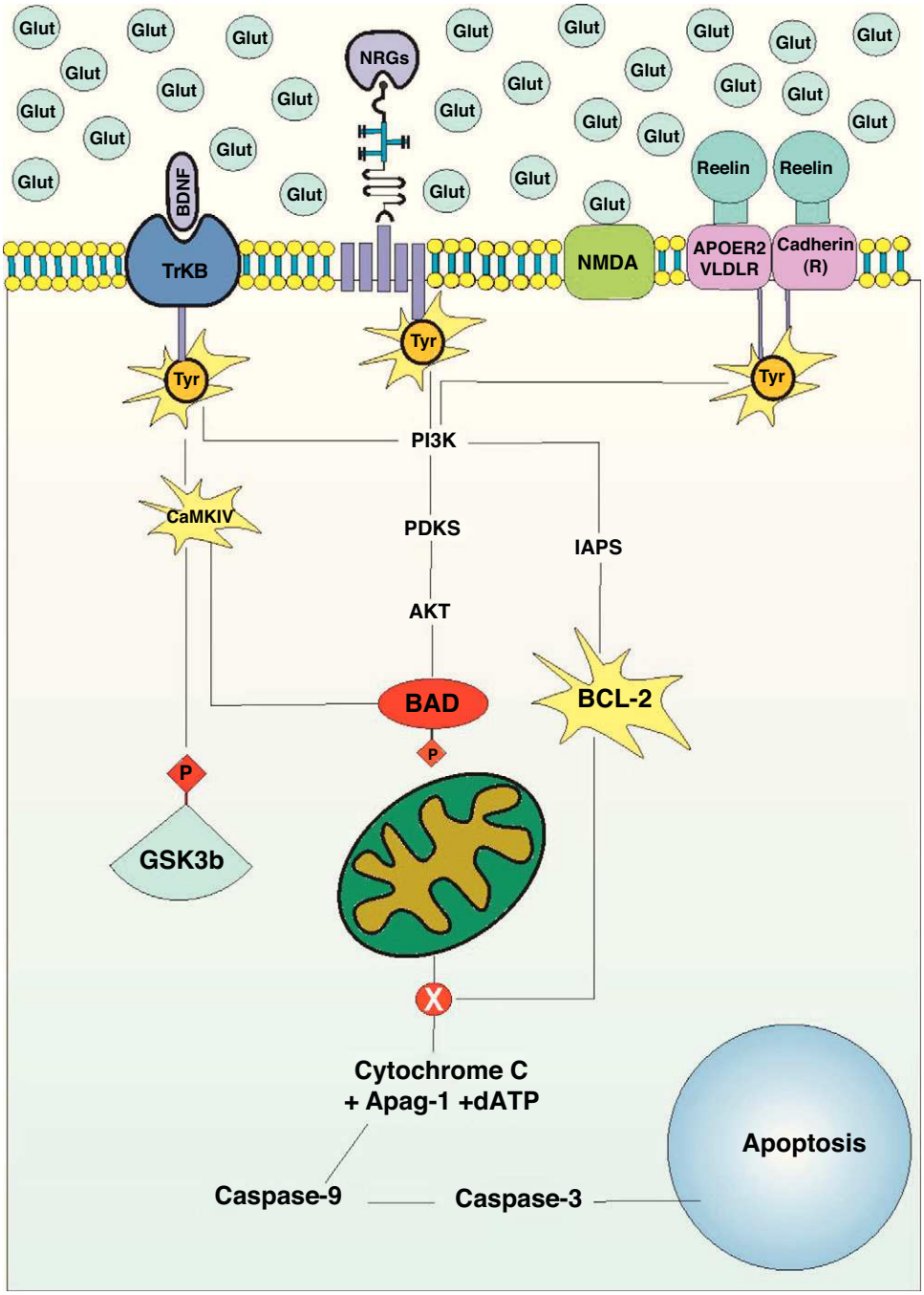

Figure 2 Anti-apoptotic pathways that are deficient in bipolar disorder: the BDNF, Nrg1 and Reelin receptors are transmembrane molecules associated with a tyrosine residue. TrkB activation induces the phosphorylation of GSKb and its consequent exit from the destruction complex, as well as the phosphorylation and inactivation of BAD, a molecule that stimulates the intrinsic apoptosis pathway. Both TrkB and the Nrg1 receptor stimulate PI3K activation, which culminates in BAD inactivation.[48,49] The activity of the Reelin receptor stimulates the activation of BCL-2, which prevents the Cytochrome C from leaving the mitochondria.[42]

apoptosome. Once formed, this complex activates the caspase-9, which in turn will activate the caspase-3 to set off apoptosis (Fig. 2). Bipolar disorder is related to the intrinsic apoptosis pathway; this is known because abnormalities in the mitochondrial structure have been identified in patients that carry this disorder,[30] as well as an alteration in the electron chain transport.[31] Not only do BDNF, Nrg1 and Reelin take part in the migration of GABAergic interneurons to the cerebral cortex, they induce the maturation of these neurons to promote their inclusion in specific neuron circuits. Once there, these molecules perform diverse functions in the mediation of synaptic connections and intracellular signalling ends in favouring neuron survival through anti-apoptotic pathways. In addition, the intracellular signalling of these 3 molecules depends on correct synaptic activity in the neuron in which they are found. BDNF not

only stimulates dendritic and axonal tropism,[32] the degree of synaptic activity mediated by NMDA receptors also strengthens dendrite development; this is in turn mediated by BDNF through a synergic effect,[33] finally promoting connectivity between neuronas.[34] BDNF stimulates the activity of calmodulin-dependent protein kinase II (CaMKII),[35] a protein that induces synaptic plasticity, favouring cell survival through anti-apoptotic mechanisms.[36] Likewise, CaMKII stimulated phosphorylation and inhibition of glycogen synthase kinase-3 (GSK-3), as well as the inactivation of BAD, both mediators of apoptosis, which is a reaction dependent on neuronal depolarization.[37,38] In addition, it has recently been determined that the brain of a patient with bipolar disorder presents a high expression of BAD and a low expression of BDNF,[8] as well as a drop in mRNA CaMKII in the prefrontal cortex.[39] Reelin, in spite of the fact that it is a extracellular matrix protein, plays a crucial role in synaptic maturation during neurodevelopment.[40,41] Its activation also promotes neuron survival when the AKT/PI3-K intracellular pathway is triggered, finally phosphorylating and inactivating BAD, a molecule that induces apoptosis.[42] It was recently demonstrated that AKT/PI3-K inhibition produces caspase-dependent apoptosis,[43] a shared pathway for the 3 molecules under study that presented abnormal expression in the brain of a subject with bipolar disorder (see above). Finally, Nrg1 and its receptor ErbB-4 interact directly with synaptic structures such as PSD-95 and some subunits of the NMDA receptor, fostering their activation.[44,45] The level of neuron activity also determines their expression, principally during neurodevelopment,[46] requiring electron depolarization for proteolytic cleavage of their precursor located in the neuronal membrane.[47] As the receptor agonises, Nrg1 stimulates intracellular signalling of second messengers, culminating in the activation of transcription factors that will mediate cell survival through PI3K/AKT and Bcl-2[48,49] (Fig. 2); the latter is by nature an anti-apoptotic molecule, whose expression is reduced in the brain of the bipolar patient.[50]

Conclusions

Approximately 75% of all the neurons existing during neurodevelopment die as part of a normal process of synaptic refinement. Scientific evidence points to apoptosis as the most attractive form of neuron death to maintain this phenomenon. GABAergic interneurons have been studied in various psychiatric pathologies such as major depressive disorder, bipolar disorder and schizophrenia. In the specific case of bipolar disorder, these interneurons are significantly reduced in the prefrontal cortex and the hippocampus, a deficit that is not accompanied by anatomopathological findings of neuronal death in the adult brain; this suggests that these neurons died during neurodevelopment, being an abnormal exacerbation of a normal process of massive neuronal death.

Bipolar disorder typically presents at the beginning of adulthood, a time when the brain is being submitted to functional and structural changes mainly determined by hormonal activity. The deficit in GABAergic interneurons in the cerebral cortex of the subject with bipolar disorder would then represent an element originating in the foetal state with a clinically relevant appearance at the beginning of adulthood, going unnoticed during childhood and part of adolescence. Bipolar disorder is known to generate cognitive degeneration, which persists even in the state of eutimia[51,52] and seems to be link that is directly proportional to the length of duration of the manic episode[53] and to the chronic course of the disorder.[54] However, even though it is true that these findings suggest that bipolar disorder is a neurodegenerative disease, its neurophysiological bases could arise in alterations in neurodevelopment; this would generate a deficit in GABAergic interneurons that would trigger a long-term stimulatory state, with the consequent neuronal exitotoxicity.[55]

Conflict of interests

The authors have no conflicts of interest to declare.

References

1. Tabarés-Seisdedos R, Escámez T, Martínez-Giménez JA, Balanzá V, Salazar J, Selva G, et al. Variations in genes regulating neuronal migration predict reduced prefrontal cognition in schizophrenia and bipolar subjects from Mediterranean Spain: a preliminary study. Neuroscience. 2006;139:1289–300 [Epub 2006 Mar 23].
2. Sanches M, Keshavan MS, Brambilla P, Soares JC. Neurodevelopmental basis of bipolar disorder: a critical appraisal. Prog Neuropsychopharmacol Biol Psychiatry. 2008;32:1617–27 [Epub 2008 May 7].
3. Huang Z. Molecular regulation of neuronal migration during neocortical development. Mol Cell Neurosci. 2009;42:11–22 [Epub 2009 Jun 10].
4. Jaaro-Peled H, Hayashi-Takagi A, Seshadri S, Kamiya A, Brandon NJ, Sawa A. Neurodevelopmental mechanisms of schizophrenia: understanding disturbed postnatalbrain maturation through neuregulin-1-ErbB4 and DISC1. Trends Neurosci. 2009;32:485–95 [Epub 2009 Aug 26].
5. Benes FM, Vincent SL, Todtenkopf M. The density of pyramidal and nonpyramidal neurons in anterior cingulate cortex of schizophrenic and bipolar subjects. Biol Psychiatry. 2001;50:395–406.
6. Benes FM, Lim B, Matzilevich D, Subburaju S, Walsh JP. Circuitry-based gene expression profiles in GABA cells of the trisynaptic pathway in schizophrenics versus bipolars. Proc Natl Acad Sci USA. 2008;105:20935–40 [Epub 2008 Dec 22].
7. Konradi C, Zimmerman EI, Yang CK, Lohmann KM, Gresch P, Pantazopoulos H, et al. Hippocampal interneurons in bipolar disorder. Arch Gen Psychiatry. 2011;68:340–50 [Epub 2010 Dec 6].
8. Benes FM, Matzilevich D, Burke RE, Walsh J. The expression of proapoptosis genes is increased in bipolar disorder, but not in schizophrenia. Mol Psychiatry. 2006;11:241–51.
9. Kim HW, Rapoport SI, Rao JS. Altered expression of apoptotic factors and synaptic markers in postmortem brain from bipolar disorder patients. Neurobiol Dis. 2010;37:596–603 [Epub 2009 Nov 26].
10. Pasko Rakic, Albert E, Ayoub, Joshua J, Breunig, Martin H, et al. Trends in Neurosciences. Decision by division: making cortical maps. 2009:32.
11. Mattson MP, Keller JN, Begley JG. Evidence for synaptic apoptosis. Exp Neurol. 1998;153:35–48.
12. Peter C. Models of Neuronal Death in vertébrate development: from trophic interactions to network roles. In: van Ooyen A,

editor. Modeling neural development. Crambridge, MA: MIT Press; 2003. p. 167–82.
13. Reid AJ, Mantovani C, Shawcross SG, Terenghi G, Wiberg M. Phenotype of distinct primary sensory afferent subpopulations and caspase-3 expression following axotomy. Histochem Cell Biol. 2011 [Epub ahead of print].
14. Fernandes BS, Gama CS, Maria Ceresér K, Yatham LN, Fries GR, Colpo G, et al. Brain-derived neurotrophic factor as a statemarker of mood episodes in bipolar disorders: a systematic review and meta-regression analysis. J Psychiatr Res. 2011 [Epub ahead of print].
15. Polleux F, Whitford KL, Dijkhuizen PA, Vitalis T, Ghosh A. Control of cortical interneuron migration by neurotrophins and PI3-kinase signaling. Development. 2002;129: 3147–60.
16. Jockusch WJ, Speidel D, Sigler A, Sørensen JB, Varoqueaux F, Rhee JS, et al. CAPS-1 and CAPS-2 are essential synaptic vesicle priming proteins. Cell. 2007;131: 796–808.
17. Shinoda Y, Sadakata T, Nakao K, Katoh-Semba R, Kinameri E, Furuya A, et al. Calcium-dependent activator protein for secretion 2 (CAPS2) promotes BDNF secretion and is critical for the development of GABAergic interneuron network. Proc Natl Acad Sci USA. 2011;108:373–8 [Epub 2010 Dec 20].
18. Massalini S, Pellegatta S, Pisati F, Finocchiaro G, Farace MG, Ciafrè SA. Reelin affects chain-migration and differentiation of neural precursor cells. Mol Cell Neurosci. 2009;42:341–9 [Epub 2009 Aug 19].
19. Pla R, Borrell V, Flames N, Marín O. Layer acquisition by cortical GABAergic interneurons is independent of Reelin signaling. J Neurosci. 2006;26:6924–34.
20. Caviness Jr VS. Neocortical histogenesis in normal and reeler mice: a developmental study based upon [3H]thymidine autoradiography. Brain Res. 1982;256:293–302.
21. Hevner RF, Daza RA, Englund C, Kohtz J, Fink A. Postnatal shifts of interneuron position in the neocortex of normal and reeler mice: evidence for inward radial migration. Neuroscience. 2004;124:605–18.
22. Yabut O, Renfro A, Niu S, Swann JW, Marín O, D'Arcangelo G. Abnormal laminar position and dendrite development of interneurons in the reeler forebrain. Brain Res. 2007;1140:75–83 [Epub 2006 Sep 22].
23. Goes FS, Willour VL, Zandi PP, Belmonte PL, MacKinnon DF, Mondimore FM, et al. Sex-specific association of the Reelin gene with bipolar disorder. Am J Med Genet B Neuropsychiatr Genet. 2010;153B:549–53.
24. Knable MB, Barci BM, Webster MJ, Meador-Woodruff J, Torrey EF. Stanley Neuropathology Consortium, molecular abnormalities of the hippocampus in severe psychiatric illness: postmortem findings from the Stanley Neuropathology Consortium. Mol Psychiatry. 2004;9:544.
25. Fatemi SH, Reutiman TJ, Folsom TD. Chronic psychotropic drug treatment causes differential expression of Reelin signaling system in frontal cortex of rats. Schizophr Res. 2009;111:138–52 [Epub 2009 Apr 9].
26. Nullmeier S, Panther P, Dobrowolny H, Frotscher M, Zhao S, Schwegler H, et al. Region-specific alteration of GABAergic markers in the brain of heterozygous reeler mice. Eur J Neurosci. 2011;33:689–98, doi:10.1111/j.1460-9568.2010.07563.x [Epub 2011 Jan 13].
27. Heckers S, Stone D, Walsh J, Shick J, Koul P, Benes FM. Differential hippocampal expression of glutamic acid decarboxylase 65 and 67 messengerRNA in bipolar disorder and schizophrenia. Arch Gen Psychiatry. 2002;59:521–9.
28. Flames N, Long JE, Garratt AN, Fischer TM, Gassmann M, Birchmeier C, et al. Short- and long-range attraction of cortical GABAergic interneurons by neuregulin-1. Neuron. 2004;44:251–61.
29. Prata DP, Breen G, Osborne S, Munro J, St Clair D, Collier DA. An association study of the neuregulin 1 gene, bipolar affective disorder and psychosis. Psychiatr Genet. 2009;19:113–6.
30. Cataldo AM, McPhie DL, Lange NT, Punzell S, Elmiligy S, Ye NZ, et al. Abnormalities in mitochondrial structure in cells from patients with bipolar disorder. Am J Pathol. 2010;177:575–85 [Epub 2010 Jun 21].
31. Sun X, Wang JF, Tseng M, Young LT. Downregulation in components of the mitochondrial electron transport chain in the postmortem frontal cortex of subjects with bipolar disorder. J Psychiatry Neurosci. 2006;31:189–96.
32. Causing CG, Gloster A, Aloyz R, Bamji SX, Chang E, Fawcett J, et al. Synaptic innervation density is regulated by neuron-derived BDNF. Neuron. 1997;18:257–67.
33. Martin JL, Finsterwald C. Cooperation between BDNF and glutamate in the regulation of synaptic transmission and neuronal development. Commun Integr Biol. 2011;4:14–6.
34. Jacobi S, Soriano J, Moses E. BDNF and NT-3 increase velocity of activity front propagation in unidimensional hippocampal cultures. J Neurophysiol. 2010;104:2932–9 [Epub 2010 Jul 28].
35. Zeng Y, Zhao D, Xie CW. Neurotrophins enhance CaMKII activity and rescue amyloid-induced deficits in hippocampal synaptic plasticity. J Alzheimers Dis. 2010;21:823–31.
36. Easton JB, Royer AR, Middlemas DS. The protein tyrosine phosphatase, Shp2, is required for the complete activation of the RAS/MAPK pathway by brain-derived neurotrophic factor. J Neurochem. 2006;97:834–45 [Epub 2006 Mar 29].
37. Song B, Lai B, Zheng Z, Zhang Y, Luo J, Wang C, et al. Inhibitory phosphorylation of GSK-3 by CaMKII couples depolarization to neuronal survival. J Biol Chem. 2010;285:41122–34 [Epub 2010 Sep 14].
38. Bok J, Wang Q, Huang J, Green SH. CaMKII and CaMKIV mediate distinct prosurvival signaling pathways in response to depolarization in neurons. Mol Cell Neurosci. 2007;36:13–26 [Epub 2007 Jun 27].
39. Xing G, Russell S, Hough C, O'Grady J, Zhang L, Yang S, et al. Decreased prefrontal CaMKII alpha mRNA in bipolar illness. Neuroreport. 2002;13:501–5.
40. Qiu S, Weeber EJ. Reelin signaling facilitates maturation of CA1 glutamatergic synapses. J Neurophysiol. 2007;97:2312–21 [Epub 2007 Jan 17].
41. Groc L, Choquet D, Stephenson FA, Verrier D, Manzoni OJ, Chavis P. NMDA receptor surface trafficking and synaptic subunit composition are developmentally regulated by the extracellular matrix protein Reelin. J Neurosci. 2007;27:10165–75.
42. Ohkubo N, Vitek MP, Morishima A, Suzuki Y, Miki T, Maeda N, et al. Reelin signals survival through Src-family kinases that inactivate BAD activity. J Neurochem. 2007;103:820–30 [Epub 2007 Aug 13].
43. Torre AV, Junyent F, Folch J, Pelegrí C, Vilaplana J, Auladell C, et al. Study of the pathways involved in apoptosis induced by PI3K inhibition in cerebellar granule neurons. Neurochem Int. 2011 [Epub ahead of print].
44. Garcia RA, Vasudevan K, Buonanno A. The neuregulin receptor ErbB-4 interacts with PDZ-containing proteins at neuronal synapses. Proc Natl Acad Sci USA. 2000;97:3596–601.
45. Huang YZ, Won S, Ali DW, Wang Q, Tanowitz M, Du QS, et al. Regulation of neuregulin signaling by PSD-95 interacting with ErbB4 at CNS synapses. Neuron. 2000;26:443–55.
46. Liu X, Bates R, Yin DM, Shen C, Wang F, Su N, et al. Specific regulation of NRG1 isoform expression by neuronal activity. J Neurosci. 2011;31:8491–501.
47. Ozaki M, Itoh K, Miyakawa Y, Kishida H, Hashikawa T. Protein processing and releases of neuregulin-1 are regulated in an activity-dependent manner. J Neurochem. 2004;91:176–88.
48. Guo WP, Fu XG, Jiang SM, Wu JZ. Neuregulin-1 regulates the expression of Akt. Bcl-2, and Bad signaling after focal cerebral ischemia in rats. Biochem Cell Biol. 2010;88:649–54.

49. Croslan DR, Schoell MC, Ford GD, Pulliam JV, Gates A, Clement CM, et al. Neuroprotective effects of neuregulin-1 on B35 neuronal cells following ischemia. Brain Res. 2008;1210:39–47 [Epub 2008 Mar 4].
50. Machado-Vieira R, Pivovarova NB, Stanika RI, Yuan P, Wang Y, Zhou R, et al. The Bcl-2 gene polymorphism rs956572AA increases inositol 1,4,5-trisphosphate receptor-mediated endoplasmic reticulum calcium release in subjects with bipolar disorder. Biol Psychiatry. 2011;69:344–52 [Epub 2010 Dec 16].
51. Normala I, Abdul HA, Azlin B, Nik Ruzyanei NJ, Hazli Z, Shah SA. Executive function and attention span in euthymic patients with bipolar 1 disorder. Med J Malaysia. 2010;65:199–203.
52. Solé B, Bonnin CM, Torrent C, Balanzá-Martínez V, Tabarés-Seisdedos R, Popovic D, et al. Neurocognitive impairment and psychosocial functioning in bipolar II disorder. Acta Psychiatr Scand. 2011, doi:10.1111/j.1600-0447.2011.01759.x [Epub ahead of print].
53. Levy B, Stephansky MR, Dobie KC, Monzani BA, Medina AM, Weiss RD. The duration of inpatient admission predicts cognitive functioning at discharge in patients with bipolar disorder. Compr Psychiatry. 2009;50:322–6 [Epub 2008 Nov 17].
54. Schouws SN, Comijs HC, Stek ML, Beekman AT. Self-reported cognitive complaints in elderly bipolar patients. Am J Geriatr Psychiatry. 2011.
55. Rao JS, Harry GJ, Rapoport SI, Kim HW. Increased excitotoxicity and neuroinflammatory markers in postmortem frontal cortex frombipolar disorder patients. Mol Psychiatry. 2010;15:384–92 [Epub 2009 Jun 2].