REVIEWS ARTICLE

Neuronal migration, apoptosis and bipolar disorder∗

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Abstract Bipolar disorder, like the majority of psychiatric disorders, is considered a neurodevelopmental 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 proapoptotic 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.
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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 estadio 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\textsuperscript{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,\textsuperscript{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\textsuperscript{5} and hippocampus.\textsuperscript{6,7} There is also a high expression of pro-apoptotic genes\textsuperscript{8,9} such as Bcl-2-associated \textit{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).\textsuperscript{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,\textsuperscript{10} so that if it incorporates itself erratically to these circuits, it will establish abnormal synaptic connections that will lead to its death.\textsuperscript{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\textsuperscript{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.\textsuperscript{14} In rodents lacking expression of the BDNF receptor, tropomyosin-related kinase B (TrkB), tangential migration is reduced in the embryonic period.\textsuperscript{15} BDNF production is subject to the expression of molecules of a synaptic nature, such as calcium-dependent activator protein for secretion 2 (CAPS2),\textsuperscript{16} in such a way that the greater the number of efficient synaptic connections established, the greater the production of CAPS2 and, consequently, of BDNF.\textsuperscript{17} Once tangential migration to the cerebral cortex has occurred, interneurons require extracellular molecules signaling 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.\textsuperscript{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.\textsuperscript{19} Consequently, despite not affecting radial and tangential migration directly, the interneurons reach an incorrect place due to the cortical layers being\textsuperscript{20,21} and a decrease in its expression would involve the same result in both sexes.\textsuperscript{24} In addition, some antidepressants and antipsychotics (drugs commonly used in bipolar disorder) increase Reelin expression in the prefrontal cortex.\textsuperscript{25} A direct relationship between alterations in Reelin gene expression and the deficit in glutamic acid decarboxylase (GAD) positive interneurons\textsuperscript{16} has recently been identified; patients with bipolar disorder had up to a 40% deficit.\textsuperscript{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,\textsuperscript{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\textsuperscript{29} and reduced migration of interneurons to the cerebral cortex was found in studies on rodents with the mutation for this gene.\textsuperscript{30}

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
expression of pro-apoptotic molecules such as BAD, BAX, caspase-3 and -9 and reduced expression of anti-apoptotic molecules such as Bcl-2. 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...
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, as well as an alteration in the electron chain transport. 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,\textsuperscript{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,\textsuperscript{33} finally promoting connectivity between neurons.\textsuperscript{34} BDNF stimulates the activity of calmodulin-dependent protein kinase II (CaMKII),\textsuperscript{35} a protein that induces synaptic plasticity, favouring cell survival through anti-apoptotic mechanisms.\textsuperscript{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.\textsuperscript{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,\textsuperscript{8} as well as a drop in mRNA CaMKII in the prefrontal cortex.\textsuperscript{39} Reelin, in spite of the fact that it is an extracellular matrix protein, plays a crucial role in synaptic maturation during neurodevelopment.\textsuperscript{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.\textsuperscript{42} It was recently demonstrated that AKT/PI3-K inhibition produces caspase-dependent apoptosis,\textsuperscript{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.\textsuperscript{44,45} The level of neuron activity also determines their expression, principally during neurodevelopment,\textsuperscript{46} requiring electron depolarization for proteolytic cleavage of their precursor located in the neuronal membrane.\textsuperscript{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.\textsuperscript{48,49} (Fig. 2); the latter is by nature an anti-apoptotic molecule, whose expression is reduced in the brain of the bipolar patient.\textsuperscript{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 euthymia\textsuperscript{51,52} and seems to be linked that is directly proportional to the length of duration of the manic episode\textsuperscript{26} and to the chronic course of the disorder.\textsuperscript{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 excitotoxicity.\textsuperscript{75}

Conflict of interests

The authors have no conflicts of interest to declare.

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