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Pathophysiology in the comorbidity of Bipolar Disorder and Alzheimer's Disease: pharmacological and stem cell approaches

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ABSTRACT

Neuropsychiatric disorders involve various pathological mechanisms, resulting in neurodegeneration and brain atrophy. Neurodevelopmental processes have shown to be critical for the progression of those disorders, which are based on genetic and epigenetic mechanisms as well as on extrinsic factors. We review here common mechanisms underlying the comorbidity of Bipolar Disorders and Alzheimer's Disease, such as aberrant neurogenesis and neurotoxicity, reporting current therapeutic approaches. The understanding of these mechanisms precedes stem cell-based strategies as a new therapeutic possibility for treatment and prevention of Bipolar and Alzheimer's Disease progression. Taking into account the difficulty of studying the molecular basis of disease progression directly in patients, we also discuss the importance of stem cells for effective drug screening, modeling and treating psychiatric diseases, once *in vitro* differentiation of patient-induced pluripotent stem cells provides relevant information about embryonic origins, intracellular pathways and molecular mechanisms.

1. Introduction

Despite the direct relation with neurological diseases, the process of neurodegeneration naturally occurs in the aging brain at different intensities according to the individual. The combination of genetic and environmental conditions stimulates different factors that play a role in this phenomenon, such as inflammatory processes, oxidative stress and immune response (Wyss-Coray, 2016). When a particular neuronal cell type is sporadically affected, causing dysfunction and death, it can lead to the development of neurodegenerative diseases, *e.g.* Alzheimer's Disease (AD), Parkinson's Disease, Huntington's Disease and Amyotrophic Lateral Sclerosis (Przedborski et al., 2003).

In contrast, limited areas of the adult brain – the subgranular zone (SGZ) of hippocampal dentate gyrus (DG) and the subventricular zone (SVZ) of the lateral ventricle – present adult neural stem cells (aNSC) that are capable of differentiating into distinct neural cell types and migrate to other brain areas, following activation by intrinsic and extrinsic signals (Doetsch et al., 1999; Gage et al., 1998). Pro-neurogenic stimuli include growth factors, hormones, drugs and behavioral factors, such as physical activity and learning, while aging, stress and pathological insults, such as those triggered in individuals with neurodegenerative diseases, compromise neurogenesis (Ming and

Abbreviations: 4-HNE, 4-Hydroxynonenal; AA, Arachidonic acid; AD, Alzheimer's Disease; AMPA, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic; AMPAR, α-Amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor; aNSC, Adult neural stem cells; APC, Adenomatous polyposis coli; ApoE, Apolipoprotein E; APP, Amyloid precursor protein; Axin-1, 2, Axis inhibition protein-1, 2; Aβ, Amyloid-beta peptide; BD, Bipolar Disorder; BD-I, II, Bipolar Disorder type I, type II; BDNF, Brain-derived neurotrophic factor; BrdU, Bromodeoxyuridine; CA1, 2, 3, 4, Cornu ammonis 1, 2, 3, 4; CaMKII, Calcium/calmodulin-dependent protein kinase II; CNS, Central nervous system; COX-2, Cyclooxygenase 2; CREB, cAMP response element binding; CSF, Cerebro spinal fluid; DCX, Doublecortin; DG, Dentate gyrus; DKK-1, Dickkopf-1; DLP-1, Dynamic-like protein 1; Drp1, Dynamin-related protein; EAAT 1–2, 3–4, Excitatory amino acid transporter 1–2, 3–4; ER, Endoplasmic reticulum; Fzd, Frizzled receptor; GDNF, Glial cell line-derived neurotrophic factor; GFRα1, GDNF family receptor α1; GPC, Glial progenitor cells; GSK-3β, Glycogen synthase kinase 3 beta; HPA, Hypothalamic–pituitary–adrenal axis; iDG, Immature DG; IFN-γ, Interferon gamma; IL-1, 1β, 10, 4, Interleukin 1, 1β, 10, 4; iNOS, Inducible nitric oxide synthase; IP_3, Inositol trisphosphate; IP_3R, Inositol trisphosphate receptor; iPSC, Induced pluripotent stem cells; LRP5/6, lipoprotein receptor-related protein 5/6; LTD, Long-term depression; LTP, Long-term potentiation; M1,M2 type, Microglial type 1,2; MAP, Microtubule-associated protein; MSC, Mesenchymal stem cells; NeuN, Neuronal nuclei; NGF, Nerve growth factor; NMDAR, *N*-methyl-D-aspartate receptor; nNOS, Neuronal nitric oxide synthase; NPC, Neural progenitor cells; NSC, Neural stem cells; NT-3, 4/5, Neurotrophins 3, 4/5; P75NTR, p75 neurotrophin receptor; PS1, 2, Presenilin 1, 2; ROS, Reactive oxygen species; SGZ, Subgranular zone; SNO, s-Nitrosylated; SVZ, Subventricular zone; TCF/LEF, T-cell factor/lymphoid enhancer factor; TNF-α, Tumor necrosis factor alpha; TBS, Tris-buffered saline; TrkA, B, Tropomyosin kinase receptor A, B

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Song, 2005). Other evidence that neurogenesis is affected in those diseases comes from the fact that these are often preceded by cognitive symptoms related to the damage of neurogenic areas, such as olfactory dysfunction, depression and anxiety (Lauterbach et al., 2010).

Some neuropsychiatric disorders, which do not fit into the definition of neurodegenerative disease, present cellular dysfunctions that may lead to neuronal death. Many psychiatric conditions can develop before or after neurodegenerative diseases, raising hypotheses of the influence of this comorbidity in the development of these disorders. The neurogenic trait of adult mammalian brain is limited and incapable of reversing pathological neuronal death in neurodegenerative diseases. However, the restoration of the equilibrium in neurodegeneration and neuroregeneration relation has been the subject of search for therapeutic strategies.

There is an emerging evidence for the comorbidity between Bipolar Disorder (BD) and sporadic AD. The relationship between BD and AD has been suggested based on clinical and molecular evidence for a possible connection between these progressive neuropsychiatric diseases. Population-based epidemiological studies across the world demonstrated that BD patients may have an increased risk of developing dementia when compared with controls matched by gender and age of the general population. In a recent meta-analysis (Diniz et al., 2017), the frequency of dementia diagnosis was documented in case-control and registry-based studies conducted with bipolar patients from Australia (Almeida et al., 2016; Zilkens et al., 2014), Brazil (Aprahamian et al., 2014), Taiwan (Chen et al., 2015a; Wu et al., 2013), Denmark (Kessing and Nilsson, 2003) and USA (Preuss et al., 2010). A significantly higher risk of dementia in older adults with history of BD was reported, indicating an association between BD and dementia in individuals with different ethnic backgrounds from these five countries. Among BD patients, the frequency of dementia seems to be also positively related with the number of affective episodes (Geerlings et al., 2008; Kessing and Andersen, 2004) and the presence of psychotic symptoms (Kessing and Andersen, 2004; Robinson et al., 2006; Torres et al., 2007).

Neuropsychiatric disorders, like BD and AD, affect several brain regions and produce a complex array of clinical symptoms, which could probably originate from basic phenotypes triggered at the level of single neurons and simple networks. An accurate understanding of the neural, cellular and molecular pathways of human neuropsychiatric illnesses requires the investigation of human brain tissue in both healthy and pathological state. Stem cells therapy and cell-based models are potentially helpful and powerful therapeutic approaches to understand the common cellular and network properties shared by psychiatric and neurological diseases. In recent years, neurons and glial cells have successfully been generated from stem cells such as embryonic stem cells, induced pluripotent stem cells (iPSC), mesenchymal stem cells (MSC) and neural stem cells (NSC), and extensive attempts have been performed in order to develop stem cell-based brain transplantation therapies (reviewed in Kim et al., 2013b). In order to achieve success in the proposed treatment, either in cell transplantation or in iPSC approaches, more knowledge about the molecular pathways of disease initiation and progression are of extremely importance.

In order to better understand the neurobiology of BD and AD, in this review we will focus on the description of pathological conditions and underlying molecular mechanisms shared by these two disorders. Regarding the pathological outcomes, the observed neurotoxic context and the abnormalities in the neurotrophic factors will be discussed. Moreover, a key common regulation pathway will be presented in the light of therapeutic interventions in BD and AD. Stem cell therapy and the study of the neuropathological cellular background in iPSC from psychiatric patients will be also described. In view of that, pharmacological approaches go in hand with the use of stem cells for understanding psychiatric diseases and providing treatment options.

2. Bipolar Disorder

Bipolar Disorders are neuropsychiatric illnesses characterized by switches in mood between depression and mania, which affects up to 15% of the worldwide population with all its possible manifestations (Dell'Aglio et al., 2013). Bipolar patients show a complex and integrated pathophysiology that leads to cognitive, behavioral, and emotional disturbances, immune, neuroendocrine and circadian dysfunctions, neurodegeneration, severe impairments in social and health-related quality of life and an average of 11 year reduction in life expectancy (Kessing et al., 2015). Due to its multifactorial profile, BD etiology, development, onset and progression are still not well understood, even though genetic, environmental and life style contributions are known. Thus, BD symptoms do not seem to be uniquely correlated to specific pathophysiological alterations, but to a complex integrative network producing diverse effects (reviewed by Maletic and Raison, 2014).

BD can be classified into three main outcomes: a. Bipolar Disorder type I (BD-I) – when patients experience severe manic crisis alternated with severe depression and the possibility of psychotic features; b. Bipolar Disorder type II (BD-II) – when patients show long periods of mild to severe depression intercalated with hypomanic phases, with no psychotic features; and c. Cyclothimia – when patients show numerous cycles between hypomanic and depression-like symptoms in a period of two years, which however do not meet all characteristics of hypomanic or major depressive episodes (American Psychiatric Association, 2013). Among different phases and episodes, BD patients can experience periods of normal-like behavior, named as Euthymia, although studies have shown lifespan alterations in biological markers, such as neurotrophic factor levels and oxidative status in both, euthymic and manic/depressive phases (Andreazza et al., 2007; Barbosa et al., 2011a, 2011b; Soares et al., 2016).

3. Alzheimer's Disease

Alzheimer's Disease is a gradual and highly prevalent neurodegenerative disease that affects millions of people worldwide. It has been estimated that by the year 2050, the population suffering from AD will reach ~100 million (Reitz and Mayeux, 2014). AD is classified into two subtypes: a. early-onset familial outcome, caused by specific mutations in genes that code for presenilin 1 (PS1), presenilin 2 (PS2) and amyloid precursor protein (APP); b. late-onset sporadic disease, related to mutations in genes that code for apopoliprotein E (ApoE), with various environmental and genetic risk factors, which remain, to a great extent, unknown. AD symptoms increase as the disease progresses. According to the National Institute of Aging, an earlier symptom is memory impairment followed by memory loss and language difficulties due to brain damage (NIA/NIH, n.d.). In the latest stages, the patients are unable to communicate and to perform common physical activities such as eating, walking and urinating.

4. Structural and functional alterations underlying BD and AD

4.1. Neurodegeneration

Many brain regions, mechanisms, genes and epigenetic outcomes have been pointed as participants in both, BD and AD neurobiology. During both, BD's and AD's progression, neuroimaging studies showed structural and functional alterations in different brain regions, which include volume alterations in lateral ventricles (Brambilla et al., n.d.; Nestor et al., 2008) and gray and white matters (Moorhead et al., 2007; Nery et al., 2017; Sani et al., 2016), embracing cortical and subcortical areas (Abé et al., 2016; Fox et al., 2001; Hibar et al., 2016; Lange et al., 2017), limbic system (Hajek et al., 2012; Haukvik et al., 2015; Javadapour et al., 2010; Schuff et al., 2009) and cerebellum (Andersen et al., 2012; Brambilla et al., n.d.; Colloby et al., 2014),