Ageing Research Reviews 12 (2013) 67–75

Contents lists available at SciVerse ScienceDirect

Ageing Research Reviews

journal homepage: www.elsevier.com/locate/arr

Review article

A breach in the scaffold: The possible role of cytoskeleton dysfunction in the pathogenesis of major depression

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ARTICLE INFO

Article history:
Received 13 August 2012
Received in revised form 31 August 2012
Accepted 31 August 2012
Available online 17 September 2012

Keywords:
Depression
Cytoskeleton
Post-translational modification
Tubulin
Microtubule
Actin

ABSTRACT

Depression is one of the most common psychiatric disorders with inadequately understood disease mechanisms. It has long been considered that dendritic regression and decrease in the number of dendritic spines are involved in depression. Dendrites made up of microtubules and actin filaments form synapses with neighboring neurons, which come together as an important communication network. Cytoskeletal proteins undergo post-translational modifications to define their structure and function. In depression and other psychiatric disorders, post-translational modifications may be disrupted that can result in altered cytoskeletal functions. The disruption of microtubule and actin in terms of morphology and functions may be a leading cause of dendritic regression and decrease in dendritic spine in depression.

1. Introduction

Major depressive disorder (MDD) is one of the most common psychiatric disorders that leads to significant morbidities and medico-social burdens worldwide. It is typically characterized by persisting low mood, anhedonia, along with other behavioral changes including sleep pattern alteration, appetite change, and motivational deficit (Belmaker and Agam, 2008). Depressed individuals may also have feelings of worthlessness, hopelessness, and suicidal tendencies (Belmaker and Agam, 2008). This disorder affects more than 121 million people including 25% of women and 12% of men worldwide (Bromet et al., 2011; Gelenberg, 2010). Europe alone spends up to 118 billion Euros annually on health care related to MDD (Sobocki et al., 2006). The rapidly rising number of MDD patients has led to a 28% increase in the consumption of antidepressants during 2010, which in turn greatly strains the health care system (Guaiana et al., 2011).

MDD is a complex neuropsychiatric disorder with unclear etiology and many possible risk factors. It has a wide array of etiology ranging from genetic alteration (Ridder et al., 2005; Sallinen et al., 1999), monoamine-deficiency hypothesis (Delgado, 2000; Meyer et al., 2006), hypothalamic pituitary-adrenal (HPA) axis dysfunction (Belmaker and Agam, 2008; Swaab et al., 2005) and alterations in other excitatory and inhibitory neurotransmitters (aan het Rot et al., 2009; Krystal et al., 2002). Furthermore, new evidence has shown that histone deacetylase inhibitor (HDAC) (Covington et al., 2009; Gundersen and Blendy, 2009; Tsankova et al., 2004) and the p11 protein has antidepressant-like effects (Alexander et al., 2010; Svenningsson et al., 2006; Svenningsson and Greengard, 2007). Despite the appearance of new hypotheses, the exact cause of depression remains unclear.

MDD is typically marked by its repeated episodes of low mood, making treatment more complicated and costly (Nierenberg et al., 2003; Post, 1992; Simons et al., 1993). The most common pharmacotherapy for MDD is the use of antidepressants, which range from the earliest form of tricyclic antidepressants and monoamine oxidase inhibitors to serotonin or noradrenalin reuptake inhibitors (Hatzinger, 2010; Jackson et al., 2010). Despite the reduced side effects with the newer antidepressants, the efficacy has not improved significantly over time (Hatzinger, 2010). Many reports now show the importance of treatment until full remission (Nierenberg et al., 2003; Zajecka, 2003). Since MDD is marked by repeated episodes, long-term treatment with antidepressants

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1568-1637/$ – see front matter © 2012 Published by Elsevier B.V.
http://dx.doi.org/10.1016/j.arr.2012.08.004

would be needed, hence possibly causing financial burden. Additionally, a large proportion of patients are treatment-resistant, making treatment options difficult (Nelson, 2003). Deep brain stimulation (DBS) is one of the newest treatments for MDD patients, providing an alternative option for the treatment-resistant population (Kennedy et al., 2011). DBS allows progressive improvement in depression symptoms and behavior (Kennedy et al., 2011). However, it is a very invasive treatment with high surgery cost, risk of infection, and electrical defect (Malone, 2010).

MDD can be accompanied by many other psychiatric disorders such as anxiety disorders (Keenan et al., 2009), obsessive–compulsive disorder (Merrill et al., 2011), Alzheimer's disease (Aznar and Knudsen, 2011), and schizophrenia (Majadas et al., 2012). Taken together, there is an urgent need for researchers to reach a better understanding in the pathology of MDD in order to develop more effective treatments.

Accumulating evidence has shown that cytoskeletal abnormalities cause dendritic regression and decrease in dendritic spine in depressive disorder (Lee et al., 2002). Cytoskeletons are crucial structures in maintaining neuronal health (Gu and Zheng, 2009; Penzes et al., 2009). A number of post-translational modifications help to maintain function and stability of these cytoskeletons (Idriss, 2000; Saha et al., 2010; Sparaco et al., 2006; Westermann and Weber, 2003). The healthiness of the cytoskeleton can determine the fate of neurons in many neurological disorders including depression-associated neurodegeneration. Investigation of the relationship between cytoskeletal dysfunction and pathological observations in depression is therefore necessary.

2. Evidence of cytoskeletal abnormality in depression and other psychiatric disorders

A number of psychiatric disorders have been reported to exhibit dendritic regression or decrease in dendritic spine number that may be related to cytoskeletal abnormality. For example, there is a decrease in mushroom-shaped spine in Down syndrome (Blanpied and Ehlers, 2004). In schizophrenia, microtubule-associated protein (MAP)-2 and -3 are found to be abnormally expressed and there is altered phosphorylation of MAP1B (Blanpied and Ehlers, 2004). Depletion of MAP6 can also cause impairment of cognitive function (Fournet et al., 2012). As a result, synaptic stability and proliferation are disrupted (Gozes, 2011). In Alzheimer's disease (AD), hyperphosphorylated tau causes impairment in the tubulin assembly, causing microtubules in dendrites to become structurally unstable (Jinwal et al., 2010). This could be the eventual cause of decreased dendritic spine number (Knafo et al., 2009). These examples illustrate a likely involvement of cytoskeleton in maintaining synapse and consequently communication among neurons in different psychiatric disorders.

Depression is related to many other psychiatric disorders as mentioned above; therefore, it is not surprising that similar cytoskeletal abnormality is also present in depression. Growing evidence has shown cytoskeleton-related alteration in depression. Chronic stress is one of the important risk factors for depression (Lin and Koleske, 2010; Pittenger and Duman, 2008). During stress, an increase in glucocorticoids has been shown to trigger stress-induced dendritic remodeling (Chen et al., 2008; Magarinos and McEwen, 1995; Pawlak et al., 2005), resulting in regression of dendrites and a decrease in spine density, which leads to a decreased synaptic connectivity (Chen et al., 2008). Chronic stress animal models also show alteration in post-translational modified tubulin isoforms, with a decrease in the ratio of tyrosinated tubulin and increase in the ratio of acetylated tubulin (Yang et al., 2009), which can modulate the dynamics of microtubules (Palazzo et al., 2004; Peris et al., 2006; Yang et al., 2009). In a proteomics study, genetic alteration in tubulin and actin has been reported in an animal model of depression (Piubelli et al., 2011). This disrupts the function and isoform ratio of these proteins (Beasley et al., 2006; English et al., 2009; Kojima and Shirao, 2007). Apart from tubulin and actin, changes in their associated proteins such as a reduction in dendritic MAP in the animal model of depression resulted in a reduction of dendritic spine number (Soetanto et al., 2010). The number of post-translational modified tubulin isoforms also decreased, suggesting a decrease in tubulin post-translational modification (Bianchi et al., 2005, 2009). In contrast, therapeutic approaches that are targeted to reverse these effects help decrease behavior immobility and recover recognition memory deficits in the animal model of depression (Bianchi and Baulieu, 2012).

Actin is another cytoskeletal protein that works hand in hand with microtubules. Many reports have shown the importance of its interaction in dendritic spine morphology and synaptic plasticity (Hoogenraad and Akhmanova, 2010). Similar to microtubules, actin malfunction can play a role in many psychiatric disorders. Decrease in spine head size and the number of dendritic spine due to morphological changes of actin is evident in depression and AD (Aguilera, 2011; Milzani et al., 1997; Sabens Liedhegner et al., 2012). In a stress model using primary cultures of hippocampal neurons to mimic depression, abnormalities have been shown in actin morphology in the dendritic spines (Minamide et al., 2000). The normal actin meshwork became rod forms (Medina et al., 2008; Minamide et al., 2000). Although some reports suggest that these actin rods appear to be neuroprotective (Medina et al., 2008), others show microtubules being displaced by these actin rods, which in turn disrupt dendrite morphology, transport and synaptic plasticity (Davis et al., 2011; Medina et al., 2008; Minamide et al., 2000). These phenomena are also observed in AD (Aguilera, 2011). Additional to the formation of actin rods, there is a decrease in actin turnover in AD, causing an accumulation of aggregated F-actin, contributing to an increase in reactive oxygen reagents and apoptosis.

The evidence above shows the range of cytoskeletal alterations in depression, which suggests their relation to dendritic regression and loss of dendritic spines observed in depression. Moreover, treatments targeting cytoskeleton related proteins are able to reverse pathological effects. This strongly suggests the importance of conducting thorough research in how cytoskeleton can influence the course of depression and provide new therapeutic pathways.

3. Actin filament, microtubule and their interplay

3.1. Actin filaments

Actin filaments are the thinnest amongst the three types of neuronal cytoskeleton with a length of 5–7 nm. They are made up of two subunits: monomeric globular actin (G-actin) and polymeric filamentous actin (F-actin). The actin filament consists of a fast-growing barbed end known as the "plus end", and a slow-growing pointed end known as the "minus end". Upon formation, monomer G-actin binds to ATP to assemble into an actin nuclei that serves as the seed for F-actin (Firat-Karalar and Welch, 2011; Hild et al., 2010). Once this filament becomes stabilized, polymerization occurs to allow filament elongation where free-floating G-actin can be added onto its plus end. Eventually, a steady state is reached when the amount of G-actin added onto the plus end is at equilibrium with the amount of F-actin lost on the minus end. These strands of actin filaments nucleate to form a branching network. Actin-related protein 2/3 (Arp2/3) is one of the actin-nucleating proteins that bind onto matured actin filaments, also known as the mother filament (Dent et al., 2011). Nucleation begins with the activation of Arp2/3 complex by nucleation promoting factors. Once activated, this complex causes a daughter filament to