Neuropharmacology 99 (2015) 527–537

Contents lists available at ScienceDirect

Neuropharmacology

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

Invited review

Forkhead box O transcription factors as possible mediators in the development of major depression

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ARTICLE INFO

Article history:
Received 11 March 2015
Received in revised form
22 July 2015
Accepted 12 August 2015
Available online 14 August 2015

Keywords:
FoxO
Major depression
PI3K/Akt
Neuronal atrophy
Neurogenesis
Antidepressants

ABSTRACT

Forkhead box O (FoxO) transcription factors play important roles in cellular physiology and biology. Recent findings indicate that FoxOs are also involved in the development of major depressive disorder. Alterations in the upstream molecules of FoxOs, such as brain derived neurotrophic factor or protein kinase B, have been linked to depression. Antidepressants, such as imipramine and venlafaxine, modify the FoxOs phosphorylation. Furthermore, FoxOs could be regulated by serotonin and norepinephrine receptor signaling as well as the hypothalamic–pituitary–adrenal axis, all of which are involved in the pathogenesis of depression. FoxOs also regulate neuronal morphology, synaptogenesis and adult hippocampal neurogenesis, which are viewed as candidate mechanisms for the etiology of depression. In this review, we emphasize the possible roles of FoxOs during the development of depression and make some strategic recommendations for future research. We propose that FoxOs and its signaling pathways may constitute potential therapeutic targets in the treatment of depression.

Contents

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http://dx.doi.org/10.1016/j.neuropharm.2015.08.020
0028-3908/

1. Introduction

Major depression is one of the most severe and common psychiatric disorders with high rates of self-harm and suicide attempts (Hegerl et al., 2013). The causes of major depressive disorder are not well understood. A diverse contribution of genetic, neurochemical and environmental factors are involved in the onset and progression of depression. Besides the common monoamine hypotheses, the diathesis stress model is another attempt to explain the etiology of depressed behavior (Gold and Chrousos, 2013). Diathesis interacts with the subsequent stress response of an individual, especially some early life experiences which are known to increase the risk for depression (Kiejna et al., 2010). Antidepressants initially correct imbalances of neurotransmitters in the synapse cleft (Mahar et al., 2014; Werner and Coveñas, 2013), while the therapeutic response may result from above and the downstream adaptive changes that occur as a consequence of increased neuroplasticity. These subcellular events include synaptic transmission, gene expression, neuronal morphological changes and many other molecular events in the brain (Kavalali and Monteggia, 2012; Pilar-Cuéllar et al., 2012; Seo et al., 2014). However, some patients do not tolerate some of the undesirable effects associated with these agents such as nervousness, insomnia or sexual dysfunction (Sussman, 1994). Novel targets and new classes of antidepressant agents are required to improve the therapeutic arsenal for the treatment of depression. In addition, currently available antidepressants are prescribed for both moderately and severely depressed patients (Fournier et al., 2010), and for severe major depression, a combination of antidepressant medication and psychotherapy or electroconvulsive therapy are usually considered (Oudega et al., 2011; Hollon et al., 2014). Antidepressants have unusual temporal responses with many agents having a delayed onset of action since clinical improvement is observed several weeks after initiation of antidepressant drug and usually patients have to take antidepressants for months to get a stable maximal improvement (Kirsch et al., 2008; Mitchell, 2006). Antidepressants require a timescale of minutes to boost the synaptic concentration of serotonin and/or norepinephrine, whereas the onset of the therapeutic action is usually a few weeks after the initiation of therapy. The traditional view about the delayed onset of current antidepressant action relies on neurobiological effects that develop slowly under chronic drug treatment, such as alterations of glucocorticoid receptor systems in patients with depression, and changes of gene and protein expression related to dendritic spines, production of brain derived neurotrophic factor (BDNF), adult hippocampal neurogenesis and enhanced synaptic plasticity (Hajszan et al., 2005; Anacker et al., 2011b; Malberg et al., 2000; Groves, 2007). The pathological mechanisms of depression need to be further explored and the controversy about the mechanism of current antidepressant agents to be resolved.

In recent years, the regulation of gene expression has been implicated in the etiology and treatment of depression; several genes such as BDNF, fibroblast growth factor receptor 1, NCAM1 neural cell adhesion molecule 1, and Calcium/Calmodulin-dependent Protein Kinase II have been identified to be of interest (Groves, 2007; Tochigi et al., 2008). Transcription factor DNA binding peptides are essential for the regulation of gene expression and are themselves regulated by phosphorylation and dephosphorylation. For example, phosphorylated cAMP-response element binding protein (CREB) transcription factor binds to the regulatory site on the *BDNF* promoter and increases BDNF protein levels, both of which have been associated with depression (Breuillaud et al., 2012). Transcription factors could serve as the intermediates between intracellular signaling cascades and gene expression, and therefore be involved in the pathophysiology of depression and represent potential targets for the pharmacotherapy.

Forkhead box O (FoxO) is a transcription factor, which plays a regulatory role in multiple biological and pathological systems, including the central nervous system (CNS). Recent discoveries indicate a role for FoxO in the pathogenesis of depression and other psychiatric disorders (Polter et al., 2009; Weeks et al., 2010; Zheng et al., 2013). Enhanced neurotrophins or serotonin neurotransmission in animal brain phosphorylate and inactivate FoxO3a (Zheng et al., 2002; Polter et al., 2009). BDNF, which is reduced in depression (Karege et al., 2005; Angelucci et al., 2005), promotes phosphorylation of the FoxO protein (Mojsilovic-Petrovic et al., 2009; Zhu et al., 2004); moreover, FoxO3a-deficient mice display an antidepressant-like behavior (Zheng et al., 2002; Polter et al., 2009; Zheng and Quirion, 2004); Furthermore, both the serotonin-norepinephrine reuptake inhibitor antidepressant venlafaxine and the mood stabilizer lithium, suppress FoxO3a activity in mouse brain (Wang et al., 2013; Mao et al., 2007). FoxOs are under the control of neurotransmitters (Liang et al., 2006) and glucocorticoids (Qin et al., 2014). FoxOs also regulate signals for cellular atrophy (Jaitovich et al., 2015), cellular morphology (Aranha et al., 2009) and adult neurogenesis (Zhang et al., 2013) and all of these physiological or pathological conditions contribute to the development of depression (Borre et al., 2014; Mahar et al., 2014; Anacker et al., 2013). Although the role of FoxOs in the process of depression is only beginning to be unveiled, it is reasonable at this time to hypothesize that FoxO transcription factors will be found to be pivotal mediators in psychiatric disorders. In this review, cellular signaling cascades responsible for regulating FoxOs, the possible roles of FoxOs in the development of depression, the effects of antidepressants on the activity of FoxOs as well as the potential mechanistic pathways linking major depression and FoxOs will be discussed.

2. Overview of FoxO signaling pathway

Forkhead box (Fox) proteins are a family of transcription factors characterized by a conserved “forkhead” or “winged helix” DNA binding motif. Foxs bind to the regulatory sequence of the downstream target genes and play important roles in regulating the transcription of genes involved in cell growth, proliferation, differentiation, metabolism, apoptosis and drug resistance (Lam et al., 2013; Accili and Arden, 2004). According to the sequence homology, Fox superfamily genes can be classified from FoxA to FoxS (Lam et al., 2013). Of the Fox subfamilies, the FoxO group is one of the most researched subgroups. FoxOs share a conserved DNA-binding domain, the binding sequence is 5′-TTGTTTAC-3′ (Brent et al., 2008). In mammals, there are four FoxO homologues, FoxO1, FoxO3a, FoxO4 and FoxO6. FoxO2 was shown to be same with FoxO3a and FoxO5 is the ortholog of FoxO3a in the zebra fish (Carter and Brunet, 2007). The activity of FoxO is regulated by post-translational modification, including phosphorylation, acetylation, methylation, ubiquitination and glycosylation (Eijkelenboom and Burgering, 2013; Zhao et al., 2011). Phosphorylation of FoxO by protein kinases has been extensively studied. Protein kinase B (Akt), serum/glucocorticoid inducible kinase (SGK), AMP-activated protein kinase (AMPK), mitogen-activated protein kinases (MAPK), inhibitor of nuclear factor kappa-B kinase (IKK), cyclin-dependent kinase (CDK) and mammalian sterile 20-like kinase (MST) are common upstream kinases for FoxO (Boccitto and Kalb, 2011). Phosphatidylinositol 3-kinase (PI3K)/Akt signal pathway activated by insulin or growth factors mediates the major regulation of FoxO (Woodgett, 2005). Binding of insulin or other growth factors (such