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Crosstalk of metabolic factors and neurogenic signaling in adult neurogenesis: Implication of metabolic regulation for mental and neurological diseases

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ABSTRACT

Metabolic disorders like diabetes and obesity are commonly companied with neurological diseases and psychiatric disorders. Accumulating evidences indicated that cellular metabolic factors affect adult neurogenesis and have modulating effects on neurodegenerative disorders and psychiatric diseases. Adult neurogenesis contains multiple steps including proliferation of neural stem cells, lineage commitments of neural progenitor cells, maturation into functional neurons, and integration into neuronal network. Many intrinsic and extrinsic factors produced from neural stem/progenitor cells and their microenvironment or neurogenic niche take roles in modulating neurogenesis and contribute to the brain repair and functional recoveries in many neurological diseases and psychiatric disorders. In this article, we review current progress about how different growth factors, neurotrophin, neurotransmitters and transcriptional factors work on regulating neurogenic process. In particular, we emphasize the roles of the cellular metabolic factors, such as insulin/IGF signaling, incretins, and lipid metabolic signaling molecules in modulating adult neurogenesis, and discuss their impacts on neurological behaviors. We propose that the metabolic factors could be the new therapeutic targets for adult neurogenesis. Plus, the metabolism-regulating drugs have the potentials for treatment of neurodegenerative diseases and mental disorders.

Contents

Abbreviation: NSPCs, Neural stem/progenitor cells; SVZ, subventricular zone; RMS, rostral migratory stream; SGZ, subgranular zone; GCL, granule cell layer; AD, Alzheimer's disease; PD, Parkinson's disease; NSCs, neural stem cells; NPCs, neuronal progenitor cells; Shh, Sonic hedgehog; bHLH, basic helix-loop-helix; BDNF, brain-derived neurotrophic factor; FGF-2, fibroblast growth factor 2; NT-3, neurotrophine-3; DISC1, Disrupted-In-Schizophrenia 1; Klf-9, Krüppel-like factor 9; Cdk, cycle-dependent kinases; CREB, cAMP response element (CRE)-binding protein; EGF, Epidermal growth factor; VEGF, endothelial growth factor; OB, olfactory bulb; HD, Huntington's disease; NTFs, Neurotrophin or neurotrophic factors; CNS, central nervous system; CNTF, ciliary neurotrophic factor; GDNF, glial cell-derived neurotrophic factor; GPI, glycosylphospatidylinositol; GFAP, glial fibrillary acidic protein; RGL, sradial glia-like stem cells; GABA, γ-aminobutyric; NMDA, *N*-methyl-D-aspartate; AMPA/KA, 2-(aminomethyl) phenylacetic acid/kainate; iGluRs, ionotropic glutamate receptors; mGluRs, metabotropic glutamate receptors; SSRIs, selective serotonin reuptake inhibitors; NE, Noradrenergic; GR, glucocorticoid receptor; GPCR, G-protein coupled receptor; Pax, paired box; cav-1, caveolin-1; APPLs, adapter proteins containing pleckstrin homology domain, phosphotyrosine binding domain and leucine zipper motif; PTB, phosphotyrosine binding; FSH, follicle-stimulate hormone; MMPs, metalloproteinases; ApoE, apolipoproteins E; p-STAT3, signal transducer and activator of transcription 3.

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1. Introduction

Impaired neurogenesis is one of the pathological features in different brain disorders such as Alzheimer's disease (AD), Parkinson's disease (PD), stroke and psychiatric disorders (Steiner et al., 2006). Targeting adult neurogenesis becomes an important therapeutic strategy for those neurodegenerative diseases and mental disorders. The process of adult neurogenesis includes the proliferation of neural stem/progenitor cells (NSPCs), the differentiation into certain phenotypes and the formation of functional neurons, eventually integrating into neuronal network for brain repair. In this process, neural stem cells (NSCs) serve as the progenitors to give rise to the neurons and glia cells. In mammalian brains, several regions like the olfactory system and hippocampus have the neurogenic niches, providing a microenvironment to support the proliferation and differentiation of neural stem/progenitor cells (NSPCs). In those plastic neural tissues, the birth, specification, migration, and integration of newly generated young neurons are closely related to animal behaviors (Vadodaria and Jessberger, 2014). In the olfactory system, neural precursor cells residing in the anterior portion of the subventricular zone (SVZ) of the lateral ventricles and migrate along the rostral migratory stream (RMS) into the olfactory bulb to raise into the granule or periglomerular inhibitory interneurons (Doetsch et al., 1999; Lois and Alvarez-Buylla, 1993). In hippocampus, neural precursor cells at the subgranular zone (SGZ) of the dentate gyrus integrate into the granule cell layer (GCL) and develop into functional excitatory granule cells. In those neurogenic niches, NSPCs play a critical role in maintaining cognition and emotion, contributing to life throughout structural plasticity in adult brain (Vivar, 2015). Therefore, modulation of those precursor cells could be a promising therapeutic strategy for brain repairs and regenerative therapy.

Over the last decade, large efforts have been made to explore the underlying mechanisms of adult neurogenesis. Many intrinsic and extrinsic factors have been identified as neurogenic modulators. These factors are not only derived from the NSPCs but also produced from the microenvironment or neurogenic niche. In brief, representative signaling molecules responsible for adult neurogenesis could be summarized below as: (1) Sonic hedgehog (Shh), miR-124, transcription factor Sox2, nuclear receptor Tlx and Wnt/β-catenin signaling pathways could modulate NSPCs proliferation; (2) Basic helix-loop-helix (bHLH) transcription factors, such as Asc1, Neurog2 and Tbr2 and epigenetic factors like Gadd45b, MBD1, MeCP2 and Mll1, contribute to regulating neuronal differentiation and maturation; (3) Insulin-like growth factor-1 (IGF-1) and Shh are essentials for neuroblasts migration; (4) Many extrinsic factors, such as brain-derived neurotrophic factor (BDNF), fibroblast growth factor 2 (FGF-2), GABA, glutamate and neurotrophine-3 (NT-3), are necessary for regulating neuronal survival, dendritic arborization, synaptic plasticity and synapse formation; (5) Many intrinsic factors, including Disrupted-In-Schizophrenia 1 (DISC1), Krüppel-like factor 9 (Klf-9), NeuroD1, cycle-dependent kinases (Cdk) and cAMP response element (CRE)-binding protein (CREB), play crucial roles in the neuronal survival, dendritic arborization and synaptic integration neuronal survival and maturation (Mu et al., 2010). In addition, exercise and environmental enrichment could alter new generated neurons and affect neurological behaviors (Olson et al., 2006). A recent comprehensive review article has discussed and remarked the roles of many environmental factors, drugs and physiological activities in modulating adult neurogenesis. Those factors include opioids, hormones, antidepressant drugs, stress, seizures, as well as physical activities like exercise and learning, etc. (Balu and Lucki, 2009). Thus, adult neurogenesis is a complex process involving multiple signaling network regulations.

Metabolism disorders like diabetes and obesity could be risk factors for many neurological diseases including AD, PD, stroke and depression (Ho et al., 2013; Hu et al., 2007a, 2007b; Roy and Lloyd, 2012; Sander and Kearney, 2009). For example, insulin resistance and type 2 diabetes may increase the risk of AD and cognitive impairments (Biessels et al., 2005). Scientists have paid great attention to understand the roles of metabolic factors in regulating adult neurogenesis and their impacts on neurodegenerative diseases and psychiatric disorders. Until now, many cellular metabolic factors have been confirmed to affect neurogenic molecules and regulate NSCs growth and differentiation during adult neurogenesis. In this review article, we introduce current understanding and knowledge about the neurogenic modulating effects of the cellular signaling molecules closely related to the cognition, stress and mental disorders. We particularly focus on the metabolic factors affecting the neurogenic process and their corresponding behavior modulations. Subsequently we discuss the potential values of metabolism-modulating drugs in promoting adult neurogenesis for the treatments of neurological diseases and psychiatric disorders.

2. Pro-neurogenic factors involved in regulation of neurogenesis related to cognition, stress response, psychiatric and mental activities

For decades, scientists have identified many extrinsic and intrinsic factors that affect different stages of neurogenesis including proliferation of NSPCs, lineage choice of daughter cells, and survival and maturation of NSPCs. Within the neurogenic niches, both growth factors and neurotrophins serve as the dynamic modulating signaling to adult neurogenesis. Many neurotransmitters not only have similar functions with growth factors and neurotrophic factors, but also act as cell signaling for transforming the circuitry information from neurons to NSCs (Meltzer