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Review

Adult hippocampal neurogenesis in the pathogenesis of addiction and dual diagnosis disorders

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ABSTRACT

Background: As knowledge deepens about how new neurons are born, differentiate, and wire into the adult mammalian brain, growing evidence depicts hippocampal neurogenesis as a special form of neuroplasticity that may be impaired across psychiatric disorders. This review provides an integrated-evidence based framework describing a neurogenic basis for addictions and addiction vulnerability in mental illness.
Methods: Basic studies conducted over the last decade examining the effects of addictive drugs on adult neurogenesis and the impact of neurogenic activity on addictive behavior were compiled and integrated with relevant neurocomputational and human studies.
Results: While suppression of hippocampal neurogenic proliferation appears to be a universal property of addictive drugs, the pathophysiology of addictions involves neuroadaptative processes within frontal–cortical–striatal motivation circuits that the neurogenic hippocampus regulates via direct projections. States of suppressed neurogenic activity may simultaneously underlie psychiatric and cognitive symptoms, but also confer or signify hippocampal dysfunction that heightens addiction vulnerability in mental illness as a basis for dual diagnosis disorders.
Conclusions: Research on pharmacological, behavioral and experiential strategies that enhance adaptive regulation of hippocampal neurogenesis holds potential in advancing preventative and integrative treatment strategies for addictions and dual diagnosis disorders.

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1. Introduction

First glimpsed as a dogma defying phenomenon 50 years ago (Altman, 1963), the birth of neurons in the adult mammalian brain is now widely accepted as an ordinary process with extraordinary implications (Eriksson et al., 1998; Kozorovitskiy and Gould, 2004). In describing what may be nature's version of neural stem cell therapy, research on the generation and integration of new neurons in the adult hippocampus, a key structure implicated in most major mental disorders, provides a view of brain remodeling that many psychiatric patients may need to get better (Eisch et al., 2008).

Converging lines of evidence are now providing an increasingly clear picture implicating adult hippocampal neurogenesis in the pathophysiology of drug addiction, magnifying the public health relevance of this phenomena since substance disorders collectively represent the greatest cause of premature illness and death in the US (Mokdad et al., 2004; Olive, 2011). This review integrates translational research outlining adult hippocampal neurogenesis in disease mechanisms of addiction and its comorbidity in mental illness. Starting with a brief summary of hippocampal neurogenesis and its putative role in psychiatric disorders based on several comprehensive reviews (Balu and Lucki, 2009; Eisch et al., 2008; Lledo et al., 2006; Ming and Song, 2005), we consider newer evidence supporting the following inter-related hypotheses: (1) addictive drugs suppress hippocampal neurogenesis; (2) low states of hippocampal neurogenesis heighten addiction vulnerability and/or severity; and (3) augmentation of neurogenic activity is an important therapeutic strategy for addictions and dual diagnosis disorders. Finally, we conclude with an exploration of key research implications and knowledge gaps that warrant further investigation for advancing addictions and integrated dual diagnosis treatment.

2. Fundamentals of adult neurogenesis

Neurogenesis is a process that encompasses the generation and development of individual neurons, and the re-population and structural revision of neural networks as a special form of neuroplasticity (Ming and Song, 2005; Schmidt-Hieber et al., 2004). As demonstrated in neural network modeling, neurogenesis works in conjunction with, and boosts 'conventional' synaptic plasticity, the basic mechanism of learning and memory, to provide a more efficient and reliable method for storing new data (Chambers et al., 2004; Luu et al., 2012). Neurogenesis begins with proliferation, the multiplication of stem cells, followed by differentiation and maturation weeks later, in which glial vs. neuronal phenotypic destinies are programed and fulfilled. Although new astroglial cells continue to divide throughout the adult mammalian brain, in only two structures, the subventricular zone (which supplies cells to the olfactory system), and the dentate gyrus (DG) of the hippocampus, do large quantities of cells become neurons (Ming and Song, 2005). In the young adult rat hippocampus, on the order of 10^3 nascent neurons are generated daily from stem cells, adding to 10^4 immature neurons that migrate into position within the DG granule cell layer which hosts a mature population of about 10^6 (Amrein et al., 2011; Lledo et al., 2006). There, young neurons 'wire in' by growing axo-dendritic connections with adjacent hippocampal compartments (Fig. 1), acquiring physiological and neuroplastic properties of mature DG neurons (Lledo et al., 2006). At any developmental stage, neurogenic neurons could also die (Dayer et al., 2003). Because their information processing and neuroplastic capabilities are dependent on maturational stage (Schmidt-Hieber et al., 2004), their survival is of interest in understanding how they impact overall network function and cognition.

3. Neurogenesis implicated in mental illness and dual diagnosis disorders

Animal and human studies implicate abnormal or maladaptive hippocampal neurogenic activity in the pathogenesis of a range of psychiatric disorders, particularly those associated with hippocampal dysfunction and abnormal psychosocial stress responses (Eisch et al., 2008). These disorders, including schizophrenia, post-traumatic stress disorder (PTSD), major depression and cluster B personality syndromes are highly comorbid with substance use disorders (Kessler, 2004). Similarly, in the general population, mild forms of cognitive dysfunction occurring in combination with impulsive-anxious personality traits are endophenotypic markers of addiction vulnerability (Ersche et al., 2012). This section presents cellular, neuroimaging and cognitive evidence linking neurogenesis with the pathogenesis of mental illnesses that frequently present as dual diagnosis disorders.

Impaired hippocampal neurogenesis has been discovered and replicated across animal models of mental illnesses spanning schizophrenia, PTSD, depression and personality disorder syndromes, even after the face, construct and predictive validities of these models had already been established (Table 1; Borcel et al., 2008; Buwalda et al., 2010; DeCarolis and Eisch, 2010; Duan et al., 2007; Garza et al., 2012; Heine et al., 2004; Hulshof et al., 2011; Ibi et al., 2008; Jayatissa et al., 2006; Kempermann et al., 2002; Kikusui et al., 2009; Lagace et al., 2010; Lieberwirth et al., 2012; Liu et al., 2006, 2008; Maeda et al., 2007; Mirescu et al., 2004; Pieper et al., 2005; Rizzi et al., 2007; Stranahan et al., 2006). As is thought to be the case for the human disorders, these models are heterogeneous in phenotypes and construct etiologies, but share common themes of deranged neuroplasticity or neural network integrity especially involving the hippocampus (Kempermann et al., 2008). Indeed, adult hippocampal neurogenesis is regulated by a host of cellular processes, genetic determinants, and neurochemcial stimuli known to modulate development and morphology of neurons and the course of mental illnesses (Balu and Lucki, 2009; DeCarolis and Eisch, 2010; Eisch et al., 2008).

Surges or sustained high levels of corticosteroids are biological correlates of major psychosocial distress and environmental change that can provoke symptom onset or destabilization across a wide range of psychiatric syndromes. Corticosteroid surges produce atrophic connectivity among neurons throughout the neocortex and hippocampus, and in the hippocampus they can kill neurons and suppress DG neurogenesis (Gould et al., 2000; McEwen, 2007). Subsequently, analogous with the regenerative capacity of a mowed lawn to regrow, neurogenic activity in the DG is renewed upon waning of corticosteroid surges (Cameron and Gould, 1994; Gould et al., 1997). Generally, many neural insults, whether neurochemical, electrical or mechanical, delivered to brain regions connected with, or intrinsic to the DG, are initially destructive but secondarily provocative of neurogenesis (Gould et al., 2000; Lledo et al., 2006). More relevant to recovery from stress-sensitive psychiatric disorders involving cognitive dysfunction, hippocampal neurogenesis is up-regulated by antidepressants (Boldrini et al., 2009; Malberg et al., 2000), lithium (Chen et al., 2000), electroconvulsive therapy (Scott et al., 2000), environmental enrichment (Kempermann et al., 1997) and exercise (Kerr and Swain, 2011).

Neuroimaging has consistently characterized hippocampal atrophy across schizophrenia, post-traumatic stress disorder, major depression and cluster B personality syndromes, potentially reflecting declines in neurogenesis and closely related neuroplastic and information bearing elements (e.g., axodendritic connectivity and neuropil; Bremner et al., 1997; Csernansky et al., 2002; Schmahl and Bremner, 2006; Sheline et al., 1996; Teicher et al., 2012). Accordingly, human postmortem studies are beginning to describe decreases in markers of hippocampal neurogenesis in