Progress in Neuro-Psychopharmacology & Biological Psychiatry xxx (2014) xxx–xxx

Contents lists available at ScienceDirect

Progress in Neuro-Psychopharmacology & Biological Psychiatry

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

Alcohol and adult hippocampal neurogenesis: Promiscuous drug, wanton effects

Chelsea R. Geil, Dayna M. Hayes, Justin A. McClain, Daniel J. Liput, S. Alex Marshall, Kevin Y. Chen, Kimberly Nixon *

Department of Pharmaceutical Sciences, University of Kentucky, Lexington, KY 40536, United States

ARTICLE INFO

Article history:
Received 22 January 2014
Received in revised form 1 May 2014
Accepted 8 May 2014
Available online xxxx

Keywords:
Adult neurogenesis
Alcoholism
Ethanol
Hippocampus
Neural stem cells

ABSTRACT

Adult neurogenesis is now widely accepted as an important contributor to hippocampal integrity and function but also dysfunction when adult neurogenesis is affected in neuropsychiatric diseases such as alcohol use disorders. Excessive alcohol consumption, the defining characteristic of alcohol use disorders, results in a variety of cognitive and behavioral impairments related wholly or in part to hippocampal structure and function. Recent preclinical work has shown that adult neurogenesis may be one route by which alcohol produces hippocampal neuropathology. Alcohol is a pharmacologically promiscuous drug capable of interfering with adult neurogenesis through multiple mechanisms. This review will discuss the primary mechanisms underlying alcohol-induced changes in adult hippocampal neurogenesis including alcohol's effects on neurotransmitters, CREB and its downstream effectors, and the neurogenic niche.

Contents

1. Introduction . . . 0
2. The hippocampus and alcohol use disorders . . . 0
3. Adult neurogenesis — a critical component of hippocampal integrity . . . 0
4. Alcohol and hippocampal neurogenesis . . . 0
5. Potential mechanisms of alcohol's effects on adult neurogenesis . . . 0
5.1. Altered neurotransmission . . . 0
5.2. CREB and its downstream effectors . . . 0
5.3. Direct effects on the neurogenic niche . . . 0
6. Conclusions . . . 0
7. Uncited references . . . 0
Acknowledgments . . . 0
References . . . 0

1. Introduction

Alcohol use disorders (AUDs), more commonly referred to as alcoholism, include alcohol abuse or alcohol dependence, the diagnostic terms for uncontrollable, excessive alcohol intake despite negative consequences. AUDs are major social and economic problems. With nearly 8.5% of the U.S. population meeting the diagnostic criteria for an AUD on any given day, it is not surprising that the economic burden was estimated to be $223.5 billion in 2006 alone (Bouchery et al., 2011; Grant et al., 2004). Further, excessive alcohol consumption is the third leading cause of preventable death in the United States (Mokdad et al., 2004). Despite these tolls, both the incidence of AUDs and the number of new users have increased in past decades (Grant et al., 2004). AUDs are a significant problem across much of the lifespan as experimentation with alcohol begins in adolescence. Indeed, disturbingly similar rates of AUDs exist between adolescents and adults (Clark et al., 2002). Although there are many theories about the development of

* Corresponding author at: University of Kentucky, Department of Pharmaceutical Sciences, 789 S. Limestone St., BPC 473, Lexington, KY 40536, United States. Tel.: +1 859 218 1025; fax: +1 859 257 7585.
E-mail address: kim-nixon@uky.edu (K. Nixon).

http://dx.doi.org/10.1016/j.pnpbp.2014.05.003
0278-5846/

AUDs, all involve the fact that repeated bouts of excessive alcohol intake change the brain in a way that drives a loss of control over consumption (Koob and Le Moal, 1997). This loss of control may be driven by hijacked learning processes, impairments in behavioral control, and/or impaired decision-making (Crews, 1999; Noel et al., 2013). All of these processes involve, at least partially, the contribution of an intact hippocampus, and a wide variety of studies have shown that excessive alcohol intake impacts the structure and function of hippocampal circuitry.

Alcohol (ethanol) is a small, highly lipid soluble and pharmacologically promiscuous drug capable of penetrating virtually every organ system including the brain. Excessive alcohol consumption has widespread deleterious effects on many of these organ systems, but central nervous system injury is a critical consequence as 50 to 75% of alcohol-dependent adults show permanent cognitive impairment (Eckardt and Martin, 1986). These impairments are thought to be due to both structural and functional changes resulting from excessive alcohol consumption (Crews, 1999; Sullivan and Pfefferbaum, 2005). Alcohol appears to target some brain regions more than others with a critical cluster of alcohol-induced impairments in behavioral control, learning, memory, mood, and decision-making attributed, at least in part, to the integrity of the hippocampus (Mechtcheriakov et al., 2007). Because ethanol is so pharmacologically promiscuous, there are many reported and potential mechanisms of alcohol-induced effects on the hippocampus. This review focuses on the emerging role of adult hippocampal neurogenesis in alcoholic neuropathology and the various potential mechanisms involved in alcohol's effects on neural progenitor cells (NPCs) and the neurogenic niche.

2. The hippocampus and alcohol use disorders

Excessive alcohol consumption results in extensive deficits in neuropsychological functions, many of which are subserved by the hippocampus (Chanraud et al., 2007; Ozsoy et al., 2013; Parsons, 1993). As has been reviewed extensively elsewhere (Belujon and Grace, 2011; Eichenbaum, 2001; Gilbert and Kesner, 2006; Johnson et al., 2007), the hippocampus is especially critical for aspects of learning and memory and as such is implicated in the acquisition, consolidation, and expression of context-dependent drug memories (reviewed in Hyman et al., 2006; Nixon et al., 2011). However, many now postulate a role for the hippocampus in relapse and drug seeking as well (Belujon and Grace, 2011; Vorel et al., 2001). This expanded role has emerged from data demonstrating its broader role in cognitive functions, specifically through its interconnections with frontal cortices and reward systems. For example, glutamatergic efferents projecting from the hippocampus and terminating in the prefrontal cortex (PFC) are implicated in the proper processing of executive functions, working memory, and contextual information (Godsil et al., 2013). Therefore, disruptions in the structural integrity of the hippocampus may be an underling substrate for impairments in these functions. Certainly, long-lasting deficits in executive function and working memory are observed following excessive alcohol consumption (O'Daly et al., 2012; Stavro et al., 2012; Stephens and Duka, 2008) and it is hypothesized that compromised hippocampal integrity in alcoholics may contribute to these impairments. In support of this hypothesis, a correlation between deficits in executive function and hippocampal gray matter volume has been reported (Chanraud et al., 2007). Although correlation does not imply causation, increasing new evidence supports that hippocampal integrity influences a broader range of cognitive functions than classically considered.

With newer technology, more consistent reports of hippocampal pathology have emerged in the last several years (Beresford et al., 2006; Ozsoy et al., 2013) including gray matter loss (Mechtcheriakov et al., 2007). Historically, ongoing debate is evident in the literature over whether the hippocampus was impacted by excessive alcohol: whether the left, right, or both hippocampi are affected, whether degeneration is due to effects in white or gray matter, and/or the magnitude of this effect (Agartz et al., 1999; Laakso et al., 2000; Sullivan et al., 1995). Importantly, one commonality that has emerged is that differences in the study population may underlie these discrepancies. For example, early onset drinking has been shown to be associated with greater hippocampal volumetric deficits (Ozsoy et al., 2013) and adolescent AUDs consistently result in hippocampal volume loss (De Bellis et al., 2000; Nagel et al., 2005). However, on the other end of the age spectrum, greater anterior volume loss was reported in the hippocampi of older alcoholics (Sullivan et al., 1995).

Imaging studies thus far, however, lack sufficient resolution to identify specific subregions of the hippocampus or cellular populations. Therefore, post-mortem studies in humans and experimental evidence in animal models have been necessary to offer insight into dentate gyrus specific effects and/or alcohol-induced neuronal loss. One study observed significant reductions in neuron number in all hippocampal subfields, including the dentate gyrus, in alcoholics less than 45 years of age (Bengochea and Gonzalo, 1990). However, a more rigorous stereological estimation failed to observe neuronal loss in any hippocampal subfield, though these subjects were older averaging 55 years of age (Harding et al., 1997). Although Harding et al. (1997) associated hippocampal volume deficits in alcoholic cases with white matter loss, others have proposed that astroglial loss underlies hippocampal neurodegeneration (Korbo, 1999). Nonetheless, animal models of chronic alcohol exposure have shown consistently that alcohol is toxic to hippocampal neurons, including the dentate gyrus granule cells (Cadete-Leite et al., 1988b; Lukoyanov et al., 2000; Walker et al., 1980). Furthermore, animal models allow researchers to examine the effect of dose, duration and/or pattern of exposure which led to the discovery that subtle evidence of damage in the hippocampus is apparent after as little as 24–48 h of high dose, binge-like ethanol exposure (Hayes et al., 2013; Obernier et al., 2002b). In the four-day binge model of alcohol dependence, neurons are lost throughout the corticolimbic pathway with degenerating cells particularly evident in the entorhinal cortex and ventral dentate gyrus (Collins et al., 1996; Crews et al., 2000; Kelso et al., 2011; Obernier et al., 2002a,b). Importantly, these binge models mimic the high blood ethanol concentrations (BECs) experienced by binge drinking alcoholics, which are estimated to be 60% or more of the alcoholic population (Robin et al., 1998; Zeigler et al., 2005). Additionally, alcoholics who drink in a binge pattern are much more likely to have neurodegeneration (Hunt, 1993).

Some portion of alcohol-induced neurodegeneration and impairments in cognitive function can recover with abstinence from alcohol (Bartels et al., 2007; Carlen et al., 1978; Gazdzinski et al., 2005; Mann et al., 1999; Pfefferbaum et al., 1995). For the hippocampus, a host of plastic changes were originally thought to underlie this recovery, such as, dendritic expansion (Cadete-Leite et al., 1988b, 1989) and spine density recovery (King et al., 1988); however, alcohol withdrawal may compromise some of these effects (Durand et al., 1989). Although it has long been hypothesized that this plasticity underlies recovery in hippocampal volume and/or function observed in animals (Lukoyanov et al., 2000) and humans (Bartels et al., 2007), the contribution of these mechanisms seems insufficient to overcome such a significant volume loss. Many of these theories, however, did not take into consideration the newly accepted phenomena of adult neurogenesis in the dentate gyrus (Armstrong and Barker, 2001; Nixon, 2006).

3. Adult neurogenesis — a critical component of hippocampal integrity

Adult neurogenesis, the process by which new neurons are created in the postnatal brain, occurs constitutively in two brain regions, the subventricular zone of the walls of the lateral ventricles and the subgranular zone (SGZ) of the hippocampal dentate gyrus (Altman and Das, 1965; Doetsch et al., 1999). Recent discoveries about the lack of newborn neurons in the adult human olfactory bulb (Bergmann et al., 2012) however, suggest a more critical role for adult neurogenesis

Please cite this article as: Geil CR, et al, Alcohol and adult hippocampal neurogenesis: Promiscuous drug, wanton effects, Prog Neuro-Psychopharmacol Biol Psychiatry (2014), http://dx.doi.org/10.1016/j.pnpbp.2014.05.003