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Introduction

Introduction to a Special Issue: Alcohol and Neural Plasticity

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The diseases and disorders associated with excessive alcohol consumption impact every developmental state and stage of life. The promiscuous pharmacology of alcohol (ethyl alcohol or ethanol) contributes to its broad effects on every organ system in the body (for review see [1]). The brain, however, is a particular target of its detrimental effects, whether exposure is from an individual's consumption of alcoholic beverages or via exposure in the womb, as is the case in fetal alcohol spectrum disorders (FASD). Alcohol, as a small, lipid soluble agent distributes widely across the body and crosses the blood brain barrier to cause brain alcohol levels similar to that in the blood [2]. Although it has relatively low potency, alcohol has a wealth of direct and indirect effects on neurotransmitter and cell signaling systems [3]. As such, alcohol exposure impacts multiple aspects of neural plasticity from the level of the synapse through to the various forms of structural plasticity. This special issue on *Alcohol and Neural Plasticity* provides new discoveries on various derangements in the different aspects of plasticity by alcohol as well as timely, insightful reviews.

The loss of control over alcohol intake concurrent with excessive consumption of alcohol are hallmarks of an alcohol use disorder (AUD), commonly referred to as alcoholism [4]. Fundamentally, both AUDs and FASD result from the misuse of alcohol by an individual. Alcohol misuse remains a major public health problem world wide, causing not only significant harm to the individual, but also a larger impact on society than any other drug of abuse [5]. World wide, rates of AUD range from less than 2% to over 20% of individuals in a given year [1]. In the U.S., nearly 14% of individuals meet the Diagnostic and Statistical Manual V-defined criteria of an AUD in any given year [6]. Regardless of diagnosis, however, excessive consumption of alcohol produces a host of changes in the brain, including brain damage in severe cases [7–9]. The precise mechanisms of the functional and structural impairments caused by alcohol are not fully known, but numerous effects on neural plasticity are implicated in both the causes and consequences of alcohol addiction [3].

Inherent to AUDs is the compulsive use of alcohol despite negative consequences and harm [10], and in the case of pregnant women, despite risks to the developing fetus. FASD is an umbrella term for the spectrum of birth defects and disabilities that result from alcohol exposure during pregnancy. A recent meta-analysis indicates that the worldwide prevalence of FASD averages near 1% (0.8%) of children, with European FASD prevalence at nearly 2% [11]. Indeed, recent estimates of FASD from school aged children in the U.S. range between 1–5% [12] remaining one of the leading causes of intellectual impairment [13, 14]. While prenatal alcohol exposure causes a variety of effects on the body,

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including growth retardation, craniofacial abnormalities, and other birth defects, alcohol's effects on brain development and function are particularly debilitating. A spectrum of impairments have been observed across domains of attention, executive functions, learning and memory, perception, and motor control, with profound intellectual impairment an unfortunate worst case scenario [14]. Development is the ultimate form of neural plasticity and unfortunately, alcohol's teratogenic effects impact nearly all domains of plasticity during development to produce the spectrum of defects and disabilities associated with alcohol exposure in the womb [13].

Neural plasticity, the remarkable ability of the brain to modify and reorganize itself at the synapse, cellular, and circuit levels is effected by and/or in response to excessive alcohol intake or exposure. Multiple articles focus on one of the more recently considered modes of plasticity: structural plasticity, specifically the effect of alcohol on adult neurogenesis. The discovery and evolution of our acceptance of the role of adult neurogenesis in brain structure and function has revolutionized our understanding the brain's response to insult suggesting a potential mechanism of recovery in some regions. It is now well-accepted that the birth and integration of new neurons continues into adulthood in select areas of the brain such as the hippocampus, the subventricular zone of the lateral ventricles and potentially, the hypothalamus [8, 9, 15]. The majority of reviews and reports in this issue focus on the hippocampus as adult neurogenesis in this region is well established in mammals including humans [16, 17]. While the exact rate at which adult neurogenesis occurs in humans is debated [17, 18], there is broad agreement that these new neurons contribute to hippocampal functions [19–21]. Although adult neurogenesis is altered in numerous neuropathological and psychiatric disorders, including AUDs, this plastic process also underlies aspects of pathology in these disorders as will be discussed in several reviews in this issue.

A comprehensive discussion of the contributions of adult neurogenesis as well as other aspects of plasticity in the neurotoxic effects of binge alcohol consumption from adolescence to aging is presented by Leasure and colleagues [22], highlighting the paucity of work on females as well as in models of aging. Basu and Suh [23] then follow up with an innovative review on events that occur with alcohol dependence and specifically the consequences of alcohol withdrawal and its sequelae on adult neurogenesis. This review is one of the first in depth discussions of alcohol's neurophysiological effects on hippocampal excitatory activity, integrated with alcohol's effects on glutamatergic and GABA-ergic signaling and adult neurogenesis. Next, Schlagal and Wu [24] review one of the few findings in the area of polysubstance abuse, the effect of combined alcohol and cocaine exposure on neural stem cells and adult neurogenesis, including in the novel pool of potential stem cells, tanycytes, in the hypothalamus. Finally, the Bartlett group (Cooper Ignatius et al [25]) provides a mechanistically deep and timely review on a hot topic in the alcohol field, neuroimmune activation, as a mechanism of alcohol's effects on synaptic and structural plasticity. This group synthesizes findings from basic science to human subjects to better understand the effect of alcohol on the pro-inflammatory cytokine, tumor necrosis factor, and its broad interactions from glutamatergic and GABAergic plasticity to adult neurogenesis.

These reviews provide a strong foundation for two studies on the effect of alcohol on adult neurogenesis, one in a model of FASD, the other in a model of an AUD. First, Cunningham and colleagues (Gustus et al [26]) follow up on their discovery that prenatal alcohol exposure prevents enrichment-enhanced adult neurogenesis and examine long-term hippocampal structural and functional measures related to adult-generated neurons. Months after prenatal exposure, enrichment enhanced dendritic branching of newborn cells and density of dendritic spine filopodia of these new granule cells were both reduced, while greater c-Fos expression in the dentate gyrus was observed concurrent with poorer performance on a hippocampal-dependent task. Collectively these data underscore long-term negative effects of FASD on multiple aspects of adult hippocampal plasticity. Finally, our own work (Nickell, Thompson et al [27]) in a rat model of an AUD aimed to elucidate the role of new neurons born during compensatory, reactive neurogenesis on the recovery of hippocampal function. Surprisingly, despite blunting the alcohol-induced reactive increase in NSC proliferation and neurogenesis using temozolomide, rats recovered performance on the Morris Water Maze.

Synaptic plasticity is affected by excessive alcohol consumption, whether as direct effects of acute alcohol intoxication or as a consequence of the plastic changes that occur with alcohol dependence. Synaptic plasticity, simply defined, is just that: plastic, activity-dependent changes in synaptic transmission [28], but there are a variety of mechanisms behind those changes. Mandyam and colleagues (Avchalu-

mov and Mandyam [29]) set the stage for the remainder of the issue with their targeted review of alcohol effects on synaptic plasticity in dorsal striatum, neocortex, and hippocampus focused around Koob's [7] heuristic for the stages of an AUD. They emphasize the importance of understanding the effects of alcohol on these synaptic mechanisms as they underlie, fundamentally, the various behavioral deficits that occur with the development of an AUD. Their review provides a comprehensive introduction to their subsequent data paper (Avchalumov et al [30]) that describes enhanced long-term potentiation and basal synaptic transmission, in male and female adult rats in the dorsal striatum with acute alcohol application. Next, fueled by a controversy in the literature, Christie and colleagues (Sawchuk et al [31]) provide an important developmental study of alcohol effects on hippocampal long-term depression and N-methyl-D-aspartate (NMDA) currents. The work offers insight into a gap in our understanding of alcohol's effects at synapses during juvenile development. Their findings concur with the historical perspective that alcohol acts as an antagonist of NMDA receptors, and thus can block forms of LTD that rely on these receptors. The age differences are interpreted appropriately, and highlight the number of complex developmental differences between these ages. Thus, this issue provides a broad array of perspectives and findings in neural plasticity in alcohol-related disorders.

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