HHS Public Access

Author manuscript

Alcohol Clin Exp Res. Author manuscript; available in PMC 2017 November 01.

Published in final edited form as:

Alcohol Clin Exp Res. 2016 November ; 40(11): 2309–2311. doi:10.1111/acer.13227.

Disruption of Integrated Neuronal and Astrocytic Signaling Contributes to Alcohol Use Disorder

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Abstract

Recent research into the pathophysiology of alcohol use disorder suggests that the behavioral and physical manifestations of AUD are produced by hierarchical dysfunction at the cellular, synaptic, and circuit levels. Synaptic and circuit function are highly dependent upon the activity and function of astrocytes. Therefore, dysregulation of astrocytic function may compromise synaptic activity and produce maladaptive modifications of circuit strength. In this commentary, we discuss the extensive crosstalk between neurons and astrocytes that determine synaptic strength and bioenergetic integrity, expounding upon the extensive interactions between glutamatergic neurotransmission and cellular metabolism. Furthermore, we discuss how dysregulation of astrocyte function in AUD may alter astrocyte function and compromise both excitatory neurotransmission and CNS bioenergetics.

INTRODUCTION

Recent investigations of alcohol use disorder (AUD) have focused intensively on the contribution of astrocytic dysfunction and glial pathology. Appropriately, numerous reviews have recently been published citing the relevance of glial activity and astrocyte pathology to the development and symptomology of AUD (Adermark and Bowers, 2016;Nam et al., 2012). In this commentary, we discuss the 2016 review entitled “Disentangling the role of astrocytes in alcohol use disorder” by Adermark and Bowers. These authors concisely describe the role of astrocytes in maintaining homeostasis of the synaptic environment via modulation of the ionic and neurotransmitter composition of the synaptic cleft as well as the role of astrocytic calcium signaling in normal CNS physiology and AUD. As they suggest, a better understanding of the pathophysiology of AUD may only be attained by abandoning

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

the archaic view of astrocytes as passive and supportive elements of the CNS and embracing their indispensible and primary roles in energy homeostasis, synaptic plasticity, and circuit coordination.

Neuron/Astrocyte Molecular Crosstalk: The Lactate Shuttle and Glutamate-Glutamine Cycle

The extracellular and synaptic milieu of the CNS is a complex and relatively heterogeneous solution of ions, amino acids, proteins, and lipids that varies in a region and activity-dependent manner (Oliet and Piet, 2004). Regulation and homeostasis of this environment is reliant upon the action of astrocytes and their interactions with CNS capillaries, synapses, and axons. Furthermore, astrocytic handling of multiple molecular species helps to regulate the bioenergetic profile of the CNS. Type 1 glucose transporters (GLUT1) are specialized high-affinity glucose carriers specifically expressed by the endothelial cells of the blood brain barrier and the abutting astrocytic endfeet. Accordingly, most glucose enters the CNS through astrocytes (although a portion directly enters neurons via GLUT3), where glycolytic processing converts the hexose rings into linear molecules of pyruvate (Benarroch, 2014). Pyruvate may subsequently be converted to lactate by lactate dehydrogenase 5 (LDH5) or enter mitochondria to participate in TCA and oxidative phosphorylation. Molecules of lactate that are shuttled to neurons must traverse the extracellular environment at perisynaptic or extrasynaptic locations. Unbound molecules of lactate are exported from astrocytes via the type 1 monocarboxylate transporter (MCT1), where they traverse the extracellular rift and then re-enter neurons via MCT2. Here, lactate is again converted to pyruvate by LDH1, allowing for its participation in neuronal energy production via TCA and oxidative phosphorylation (Machler et al., 2016).

Adermark et al. highlight that lactate transport into neurons is required for long-term memory and synaptic potentiation, suggesting that astrocytic metabolism is integrally related to neurotransmission and neuroplastic processes. Perhaps more significantly, recent investigations have revealed that disruption of the lactate shuttle persistently reduces conditioned responses to cocaine (Boury-Jamot et al., 2016). Furthermore, the authors imply that glutamatergic neurotransmission, the lactate shuttle, and astrocytic energy metabolism may engage in a counter-regulatory crosstalk allowing mutual modulation of multiple important physiological systems. This is perhaps best illustrated by the observation that glutamate reuptake into astrocytes by the type 2 excitatory amino acid transporter (EAAT2; synonomous with the glutamate transporter type 1, GLT1) is coupled to the cotransport of three sodium ions, raising the intracellular concentration of sodium and increasing the functional demand of the Na^+/K^+-ATPase (Kirischuk et al., 2016). Appropriately, the increased functional drive of this ATP-dependent transporter promotes astrocytic production of ATP. This raises interesting questions regarding the effect of glutamatergic transmission and glutamate uptake on the lactate shuttle and the bioenergetic balance between neurons and astrocytes. More specifically, enhancement of glutamatergic transmission during ethanol intoxication or withdrawal may augment glutamate uptake and thereby promote the production of astrocyte-required ATP, altering the proportion of glucose and other bioenergetic molecules utilized for lactate synthesis and neuronal energy supply. Conversely, ethanol-induced changes in energy handling and astrocytic ATP production may promote or

prohibit efficient uptake of glutamate from the synaptic cleft, altering the efficacy of glutamatergic transmission and modulating neuroplastic responses.

The Role of Mitochondria in Neuron/Astrocyte Crosstalk and Glutamatergic Signaling

Intriguingly, the extensive interaction between glutamatergic signaling and CNS bioenergetics extends far beyond the functional regulation of the Na^+/K^+-ATPase. As Adermark and Bowers indicate, glutamate processing and recycling occurs via a cyclic process involving the astrocytic uptake of glutamate followed by its conversion to glutamine and return to neurons via sodium-coupled neutral amino acid transporters (SNATs). More specifically, synaptic glutamate released from the presynaptic terminal is uptaken by astrocytes primarily by the sodium-dependent excitatory amino acid transporter EAAT2. Here, glutamine synthetase converts glutamate to its non-excitatory precursor glutamine, which is subsequently returned to neurons via astrocytic SNAT3 and SNAT5 transporters and neuronal SNAT 1 and 2. Importantly, glutamate uptaken by astrocytes may also enter mitochondria and participate in the TCA cycle following conversion to alpha-ketoglutarate by the enzyme glutamate dehydrogenase. Similarly, glutamine re-entering neurons must be processed within the mitochondrial matrix by phosphate-activated glutaminase (PAG) for conversion into glutamate, which may subsequently be repackaged into synaptic vesicles or enter TCA following conversion to alpha-ketoglutarate. (Robinson and Jackson, 2016)

The extensive, intimate, and interdependent relationship between the glutamate-glutamine cycle, lactate shuttle, mitochondrial function, and CNS bioenergetics suggests that ethanol and other drugs of abuse may extensively modulate synaptic function and neuronal signaling via isolated effects on one or more of these systems followed by divergent downstream effects on related physiological systems. In this regard, Adermark and colleagues correctly point out that ethanol may disrupt the excitatory and inhibitory balance within the CNS. In support of their argument, the authors cite several publications detailing increased expression of components of the glutamate-glutamine cycle following chronic ethanol exposure in culture and *in vivo* (Zink et al., 2004;Smith, 1997). Furthermore, these results have demonstrated that inhibition of glutamate uptake via pharmacologic or genetic manipulation results in reduced conditioned place preference for ethanol and attenuated voluntary ethanol consumption (Karlsson et al., 2012;Smith et al., 2014). Alternatively, indirect inhibition of glutamate transport via genetic deletion of the circadian clock gene Per2 (Spanagel et al., 2005), activation of the adenosine A1 receptor (Wu et al., 2011), or genetic deletion of ENT1 (Wu et al., 2010) results in increased ethanol consumption. Adermark and colleagues do little to reconcile these seemingly contradictory findings. However, detailed analysis of both the lactate shuttle and glutamate-glutamine cycle suggests that the function and localization of mitochondria are instrumental for the proper functioning of these systems. Therefore, it is possible that the different bioenergetic effects of these individual interventions on astrocyte metabolism and mitochondrial function may exert different downstream effects on glutamate processing and lactate shuttling that result in differential alterations of the glutamatergic system. Recent work by Robinson and colleagues (2016) supports this observation, and suggests the existence of extensive crosstalk between mitochondrial bioenergetics systems and glutamatergic signaling. Furthermore, ethanol itself functions as a metabolic poison, altering blood and brain levels

of multiple metabolites including acetate, lactate, glucose, and ketones (Rawat and Kuriyama, 1972). This may alter the bioenergetic profile of astrocytes, modulating mitochondrial function and lactate shuttling in a manner that disrupts the integrated glutamate signaling cycle. Alternatively, altered efficacy of mitochondria located at synapses utilizing excitatory and inhibitory neurotransmitters may differentially modulate synaptic strength, differentially affecting the viability of excitatory and inhibitory circuits that gate addictive behavior.

Importantly, mitochondrial function and localization are important for the generation of astrocytic calcium transients. In fact, recent research suggests that calcium transients are a direct result of calcium release from mitochondria (Parnis et al., 2013). This event may be initiated by the local actions of neurotransmitters or by locally increased levels of metabolites such as glutamate. As Adermark and colleagues suggest, these calcium transients may be instrumental in synchronizing the activity of neural circuits and facilitating synaptic transmission at distant locations. Disruption of these events by altering the excitatory nature of the synaptic environment or direct modulation of mitochondrial function or bioenergetic signaling events may alter the properties of neural circuits in a manner that promotes aberrant potentiation of synapses responsible for addictive responses while preventing the extinguishment of maladaptive behaviors. As Adermark and colleagues state, neuronal activity may also produce sodium transients. These sodium transients may modulate the regional activity of the Na^+/K^+-ATPase and therefore alter mitochondrial activity, producing downstream effects on calcium transients, glutamate uptake, and synaptic plasticity.

Ethanol affects whole body metabolism in a stereotypic and well-defined manner, increasing blood levels of acetate, ketones, and lactate while reducing the concentration of important metabolites such as glucose. This is at least partially because ethanol inhibits both gluconeogenesis as well as glycogenolysis. Similarly, ethanol inhibits the ability of astrocytes to break down glycogen, inhibiting synaptic plasticity (Suzuki et al., 2011). Other metabolic effects may adversely affect CNS function by modulating the lactate shuttle or glutamatergic signaling. This may also explain why ethanol reduces the concentration of astrocytes within most brain regions, and why abstinence increases the density of astrocytes following chronic ethanol exposure (Miguel-Hidalgo, 2006). Adermark and colleagues succinctly summarize that this effect may also be due to inflammatory responses. However, given that ATP is a potent pro-inflammatory molecule within the CNS, it is possible that the inflammatory and bioenergetic systems engage in a regulatory crosstalk that dictates astrocyte survival and function.

CONCLUSION

Adermark and colleagues argue that ethanol affects the CNS at multiple levels, inducing cellular, synaptic, and circuit dysfunction via disruption of astrocytic function. Countless recent research studies support this hypothesis, indicating that ethanol exerts expansive effects on CNS function. The challenge in the future will be to determine the biological consequences of ethanol intoxication and withdrawal. Although it is possible that ethanol independently affects multiple molecular systems, the principle of parsimony dictates that it

is far more feasible that ethanol exerts its primary function by impairing a system with tremendous branching effects on other physiological systems. Although much work remains to be done, the glutamatergic system, mitochondrial function, and lactate shuttle offer highly integrated candidate pathways that may be modulated by ethanol and alter neuron-astrocyte interactions. Furthermore, all of these pathways function at the cellular, synaptic, and circuit levels to significantly impact the function of the CNS. Therefore, by continuing to investigate the effects of ethanol on synaptic plasticity, bioenergetic systems, and circuitry function, a better understanding of AUD may be attained, perhaps permitting the identification of viable pharmaceutical targets.

Acknowledgments

This work was supported by the Samuel C. Johnson for Genomics of Addiction Program at Mayo Clinic, the Ulm Foundation, the Godby Foundation, the David Lehr Research Award from American Society for Pharmacology and Experimental Therapeutics, and National Institute on Alcohol Abuse and Alcoholism (AA018779) to DSC.

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