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Astrocyte Function in Alcohol Reward and Addiction

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Abstract

Glial cells, particularly astrocytes, play essential roles in the regulation of neurotransmission, metabolism, and supply of energy substrates for synaptic transmission. One astrocyte can receive inputs from several hundreds of synapses, and synchronized neuronal activity correlates with astrocyte calcium signaling. Astrocyte pathology is a common feature of ethanol exposure in both humans and animal models, and brief alcohol intake is sufficient to cause long-lasting changes in astrocyte gene expression, activity and proliferation. Recent research also suggests that astrocytes shape the rewarding sensation of ethanol, and might be involved in modulating alcohol consumption. Considering the role of astrocytes in regulating glutamate homeostasis, a crucial component of alcohol abuse disorders, the astrocyte might be an important target for the development of new pharmacological treatments of alcoholism.

Keywords: Alcohol; Astrocytes; Astroglia; Glia; GFAP; Dopamine; Ethanol

Astrocytes

The astroglial cell, or astrocyte, is the most numerous cell type of the glial cell family. Astrocytes give structural and metabolic support to surrounding neurons and are pivotal for neuronal functioning and signal processing in the CNS [1,2] (Figure 1). The end feet of astrocytic processes encapsulate blood vessels and participate in building up the blood brain barrier [3,4]. The contact with blood vessels also enables the astrocytes to provide neurons with lactate under anaerobic conditions [1,5] (Figure 1). The astrocyte was first acknowledged as the primary cell type responsible for potassium buffering [6], and combined with the clearance of amino acids from the extracellular space, astrocytes warrants a high signal to noise ratio, and reduced receptor desensitization [7,8]. One single astrocyte can enwrap several neuronal somata and receive inputs from thousands of synapses, enabling them to sense and integrate synaptic activity [9,10]. Activation of astrocytes also appears to be a crucial component for the induction of synaptic plasticity mechanisms, and both long-term potentiation (LTP) and long-term depression (LTD) in the hippocampus may be regulated by astrocytes [11,12].

Astrocytes enwrap both presynaptic and postsynaptic terminals, forming the tripartite synapse. Astrocytic end feet encapsulate blood vessels, enabling the astrocyte to give metabolic support to surrounding neurons. Astrocytic clearance of neuroactive substances is crucial for synaptic transmission. The excitatory amino acid glutamate (Glu) is rapidly metabolized to its non-excitable precursor glutamine (Gln), released back to the extracellular space, and taken up by neurons for synthesis of glutamate or GABA. See text for further details.

Astrocytic transporters

One of the most prominent functions of the astrocyte is the clearance of glutamate, and astrocytic glutamate transporters EAAT2 (GLT-1) and EAAT1 (GLAST) are the most abundant transporters for removal of glutamate in the brain [13]. Impaired astrocytic glutamate clearance appears to contribute to neuronal dysfunction and degeneration in Huntington's disease, major depressive disorder and Alzheimer's disease [14-17], and might also play a role in alcohol abuse [18]. Following reuptake, glutamate is converted by glutamine synthetase to its non-excitable precursor glutamine, which is released back to the extracellular space [19] (Figure 1). This astrocyte-dependent glutamate-glutamine cycle is required to maintain active neurotransmission at excitatory terminals, but may also play a vital role for GABAergic neurotransmission [20,21]. Inhibitory transmission is further regulated by astrocytes through glycine transporters GlyT1 and GlyT2, and GABA transporters GAT-1 and GAT-3 [22,23], while adenosine is transported through the equilibrative nucleoside transporter 1 and 3 (ENT1, ENT3) [24,25].

Astrocytic calcium signaling

Even though astrocytes are not electrically excitable they express receptors for the majority of neurotransmitters and neuromodulators [26-31]. Upon activation, astrocytes generate various complex changes in intracellular Ca^{2+}, which can initiate the release of gliotransmittors such as adenosine, D-serine and glutamate [32-35]. The main Ca^{2+}-signaling pathway is mediated via G-protein receptor activated phospholipase C (PLC) and formation of inositol (1,4,5) trisphosphate (IP_3) through hydrolysis of phosphatidylinositol 4,5-bisphosphate (PIP_2), which induces Ca^{2+}-release from internal stores. Photorelease of Ca^{2+} or IP_3 within a single astrocyte is also sufficient to cause glutamate-release and to modulate neuronal excitation [32,34,36-40]. In addition to Ca^{2+} release from internal stores, activation of G-coupled receptors can also initiate influx of Ca^{2+} through different types of voltage-independent Ca^{2+} channels [41,42] (Figure 2).

Intracellular Ca^{2+}-signaling is primarily mediated through IP_3-gated release of Ca^{2+} from internal stores, which may be followed by Ca^{2+}-influx through Ca^{2+} channels. Gap junction channels, which are dynamically regulated by neuronal activity and intracellular homeostasis, allow Ca^{2+} waves to spread through the astrocytic network. (CIF = Calcium Influx Factor; DOCC = Depletion-Operated Calcium

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Channel; SMOCC = Second Messenger-Operated Calcium Channel; ROCC = Receptor-Operated Calcium Channel; ER = Endoplasmic Reticulum).

Gap junction channels

Astrocytes are highly interconnected through gap junction channels, built up by the protein connexin [43]. These gap junction channels concede bidirectional diffusion of charged and uncharged small molecules allowing Ca^{2+} waves to spread through the astrocytic syncytium [44]. Functional gap junctions might also exist between astrocytes and oligodendrocytes and to some extent neurons [45-47]. Coupling at gap junctions is regulated by intracellular ion homeostasis and influenced by neuronal activity and released neuroactive substances such as growth hormones, glutamate, 5-HT, ATP, and potassium [48-53] (Figure 2). Connexins also form plasma membrane channels, hemi channels, through which gliotransmitters can be released [54,55]. Connexin-43 hemi channels are necessary for fear memory consolidation and has been suggested as pharmacological targets for treatment of post-traumatic stress disorder, but dysregulations of hemi channel properties could also be critical during homeostatic imbalances [54,56]. Importantly, the connectivity of the astrocyte network, as well as individual cells, appears to be brain region selective, where astrocytes in the striatum are highly interconnected and primarily categorized as passive, while a larger proportion of astrocytes in the hippocampus are classified as complex [2,49,57].

The Astrocyte during Acute and Chronic Alcohol Exposure

Ethanol effects on signal transduction appear to vary considerable

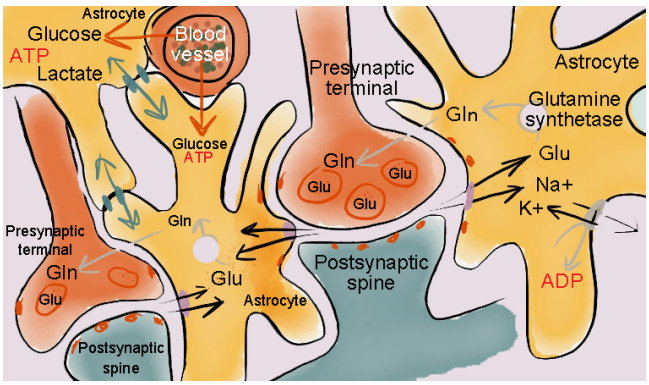

Figure 1: Astrocytes sense and integrate neuronal functioning.

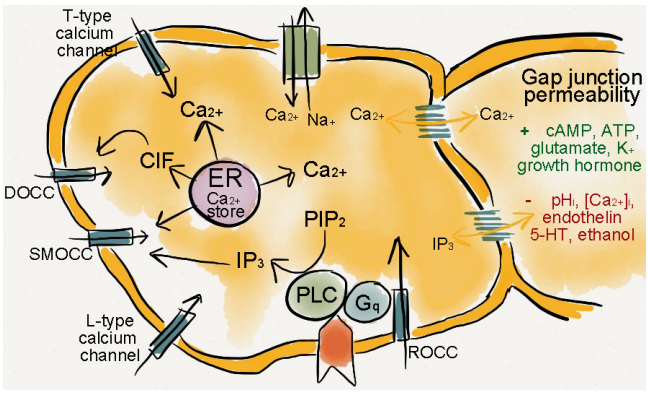

Figure 2: Receptor activated calcium signaling in astrocytes.

with development, differentiation and functional activity [58]. Many membrane proteins, such as ion channels, transporters, receptors, enzymes and G-proteins are affected by ethanol in ways that lead to long-lasting changes in activity and gene expression [59], and astrocytes appear to be important target cells. Brief ethanol-exposure is sufficient to alter astrocytic gene expression and to restrict proliferation [60,61], and may acutely impair astrocytic regulation of neurotransmission. Ethanol elevates intracellular calcium in a subset of astrocytes and reduces gap junction coupling in a brain region selective manner, which could selectively affect signal processing [62-64]. Considering that gap junction coupling equalizes $[Na^+]_i$, the decline in connectivity might also reduce the capacity for amino acid uptake and potassium buffering, as well as lead to failure in coordinating other physiological responses that involves sodium [65,66]. Diminished immunoreactive puncta, and reduced levels of the gap junction protein connexin 43, is also seen in post mortem studies of subjects with alcohol abuse disorder, supporting a role for altered connectivity or hemi channel-based communication in the pathophysiology of alcoholism [67].

Astrocytic cell swelling

Ethanol induces cell swelling in a subset of astrocytes, which could lead to changes in size and geometry of the extracellular space and thereby altered volume transmission [64,68-70]. Swelling of the end feet of astrocytic perivascular processes may also lead to altered cerebral blood flow [71]. Cell swelling is rapidly followed by regulatory volume decrease and the release of organic osmolytes, of which the amino acid taurine is of especial interest [72-75]. Taurine has previously been shown to increase accumbal dopamine levels, and appears to be a key component in ethanol induced dopamine release [76-78]. Considering the role of dopamine in mediating the rewarding sensation of drugs of abuse, it is thus possible that astrocytes are indirectly involved in ethanol-induced reinforcement [65,79,80]. Rapid swelling and regulatory volume decrease is facilitated by astrocytic water channels built up by the protein aquaporin-4 [81,82], and reduced aquaporin-4 expression has in fact also been linked to excessive alcohol consumption [83]. Interestingly, aquaporin-4 expression is depressed by dopamine, while genetic deletion of aquaporin-4 reduces accumbal dopamine [81]. Antagonists targeting dopamine D1 and D2 receptors has also been shown to increase astrocyte calcium excitability, synchrony and gap junction coupling [84], indicating that astrocytes may monitor extra synaptic dopamine levels.

Astrocytic protein expression and morphological transformations

Changes in the expression of the astrocyte specific cytoskeletal protein glial fibrillary acidic protein (GFAP) have been detected in several psychiatric conditions such as Parkinson's disease, schizophrenia, depression and Alzheimer's disease [17,85-89], but it is not clear if this is in response to the injury, or part of the cause of the disorder. Voluntary intake of alcohol, as well as forced exposure, increases both GFAP and GFAP mRNA expression [90-93], while withdrawal reduces the number of GFAP positive cells [94,95]. Alcohol also affects astrocyte morphology and induces rearrangements of actin filaments, which may further impair Ca^{2+} signaling [64,96]. Post mortem analysis of human alcoholics reports reduced GFAP expression and altered astrocyte morphology [97]. These prominent changes in astrocyte morphology are not exclusive to alcoholics with liver pathology, and may persist despite the cessation of alcohol consumption [98,99].

Astrocytic amino acid transporters and ethanol

Astrocytic amino acid transporters are crucial regulators of neurotransmission, and ethanol may cause glutamatergic dysfunction by affecting astrocytic proteins responsible for maintaining extracellular homeostasis [100]. Over all, chronic ethanol exposure causes long-lasting alterations in the expression of glutamatergic receptors and transporters, producing a hyperglutamatergic state [101-104]. Pharmacological modulation of astrocytic clearance of glutamate might thus indirectly mitigate behavioral responses caused by ethanol exposure. Supporting this theory, selective up regulation of the glutamate transporter GLT-1 in the nucleus accumbens shell reduces voluntary ethanol consumption, and impairs methamphetamine and morphine induced conditioned place preference (CPP) [105,106]. However, mice with homozygous GLAST deletion show a pronounced reduction of voluntary alcohol consumption, and inhibited ethanol-induced CPP [107]. In addition, blocking central astrocytic glutamate uptake selectively attenuates ethanol binge drinking behavior in mice [108]. The role of glutamate transporters might thus depend on the brain region targeted, the amount of alcohol consumed, and/or the transporter subtype manipulated. A differential role for astrocyte glutamate transporters is also supported by the selective correlation between GLT-1 and alcohol consumption [106]. Interestingly, changes in adenosine levels, caused by ethanol exposure, may also indirectly alter GLT-1 expression, further affecting alcohol consumption [25,83].

Astrocytes also express transporters for glycine, which has been implemented in the rewarding properties of ethanol through the potentiation of NMDA receptors and activation of glycine receptors [109-111]. Especially, glycine receptors could be important regulators of ethanol induced reinforcement as antagonists targeting glycine receptors both blocks the dopamine-elevating property of ethanol *in vivo*, as well as prevents ethanol-induced changes in striatal neurotransmission *ex vivo* [79,111,112]. In addition, inhibition of the glycine transporter GlyT1 persistently reduces ethanol intake and relapse-like alcohol drinking in rats [113-116], and might thus be a pharmacological target for the treatment of alcohol abuse disorders. However, even though it was recently shown that the GlyT1 transporter inhibitor Org25935 robustly reduces the number of days with heavy drinking, the effect was not significant as compared to placebo [117]. More research is thus required in order to fully elucidate the role of extra synaptic glycine levels in the pathophysiology of alcohol abuse and addiction.

Conclusion

Astrocytes sense and integrate neuronal functioning and activation of astrocytes coincides with synchronized synaptic firing and plasticity. Due to their pivotal role in monitoring extra synaptic transmission, the astrocyte appears to be an important target during both the acute and chronic phase of ethanol exposure and may play a key role in alcohol abuse disorders. Finding ways to modulate astrocyte function might thus lead to novel pharmacological interventions for treatment of alcohol abuse disorders. Especially, restoring ethanol-induced effects on amino acid transporters, and reinstating glutamate homeostasis, might be efficient methods for inhibiting drug seeking, and heavy drinking. However, additional studies are required in order to define ethanol-induced changes in astrocyte function, and to determine the role of astrocytes in the pathophysiology of relapse and alcohol addiction.

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