Review

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Astrocytes: the neglected stars in the central nervous system and drug addiction

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Abstract: With the advent of improved tools to examine the astrocytes, which have been believed to play a supportive role in the central nervous system (CNS) for years, their participation in the operation of the CNS and drug addiction was unveiled. Assisting the formation and function of the CNS, astrocytes are involved in physiological and pathological brain activities. Drug addiction is a pervasive psychiatric disorder, characterized by compulsive drug-taking behavior and high rate of relapse, impacting individual health and society stability and safety. When exposed to drugs of abuse, astrocytes go through a series of alterations, contributing to the development of addiction. Here we review how astrocytes contribute to the CNS and drug addiction. We hope that understanding the interaction between addictive drugs and astrocytes may help discover new mechanisms underlying the addiction and produce novel therapeutic treatments.

Keywords: astrocytes; central nervous system; drug addiction; synaptic plasticity.

Introduction

The two mainstreams of cells that build up the central nervous system are neurons and glia, the latter of which for quite a long time are supposed to act as the background of the former, supporting, nourishing and protecting the neurons [1]. However actually, glia has much more functions. The star-shaped astrocyte, one dominant type of glia, has been implicated in myriad biological processes of the central nervous system (CNS) by interacting with almost all elements of the CNS, including neurons, synapses, glial cells and blood vessels [2]. Widely distributed in the whole brain, astrocytes function complexly varying from physiological activities to pathological changes.

Drug addiction is a chronic relapsing disorder, accounting for the loss of 18 million years of healthy life in 2019 [3]. According to World Drug Report 2021, it was estimated that about 36.3 million people were suffering from drug use disorder in 2019 and the number had rapidly accelerated year by year [3]. Apart from endangering the health of individuals, drug addiction can also lead to crime and violence, and speed up the spread of infectious diseases, seriously affecting social stability and safety [3]. Hence, it is of great significance to reveal the mechanism behind drug addiction, and thanks to the advancing technology in the neuroscience, accumulating studies help people understand how versatile astrocytes work in drug addiction indeed [4].

In the current review, we describe the astrocytic involvement in the operation of the CNS, and then focus on how astrocytes contribute to drug addiction through diversified pathways. Finally, we further discuss the existing problems and prospects of research in astrocytes and drug addiction.

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How astrocytes contribute to the operation of the CNS

Astrocytes are involved in shaping the CNS

Neurogenesis and axon guidance

During the development of the CNS, astrocytes could secrete a variety of trophic factors to support neuronal life, such as brain-derived neurotrophic factor (BDNF), epidermal growth

factor (EGF), fibroblast growth factor 2 (FGF-2) and somatostatin [5–8]. In addition to promoting the growing process of neurons which are created earlier than glia, astrocytes mediate adult neurogenesis as well [9, 10]. Song et al. [11] first proved that astrocytes within adult hippocampus are able to accelerate the proliferation of stem cells and instruct them to become neurons. Following generation, neurons need to extend axons in order to establish synaptic connections, crossing long distances and complicated environment [12]. Astrocytes were also found to be critical for right pathfinding of axons. Minocha et al. [13] showed that Nkx2.1-positive astrocytes could guide axons through the expression of Slit2.

Synapse formation and synapse elimination

Since axons have reached the exact origin, neurons begin to form synapses with the help of astrocytes once again. In terms of the sequence of events, synaptogenesis happens right after the production of astrocytes and the time window of synapse formation overlaps that of the astrocyte maturation [14].

First of all, astrocytes make local contact with immature neurons, permitting them to receive and response to astrocyte-encoded signals. Switch of the receptivity may involve propagation of protein kinase C (PKC) signaling [15, 16]. The signals can be divided into prosynaptogenic ones and antisynaptogenic ones [17]. Prosynaptogenic signals include thrombospondins (TSP1 and TSP2) and Hevin, which could help construct the structure of synapses which contain presynaptic vesicles, N-methyl-D-aspartic acid receptors (NMDARs) and other elements [18, 19]. The synapses are presynaptically active; however, they are postsynaptically inactive so far, due to lack of α-amino-3-hydroxy-methyl-4-isoxazolepropionic acid receptors (AMPARs) [18]. Only with the aid of other prosynaptogenic signals, which could promote AMPARs localization to postsynaptic sites, such as glypicans 4 and 6, can synapses be fully functionally active [20]. Competitively, antisynaptogenic signals like secreted protein acidic rich in cysteine (SPARC) negatively regulate synapse formation [19]. Other astrocyte-secreted molecules also work during the synaptogenesis, including neuroligins, tumor necrosis factor-α (TNF-α), cholesterol, and transforming growth factor β-1 (TGFβ-1) [21–23].

Another important step in synaptic development is the elimination of weakened or redundant synapses, maintaining a proper number of synapses [23]. Astrocytes phagocytose excessive synapses in the developing brain through their phagocytic receptors multiple epidermal growth factor-like domains 10 (MEGF10) and Mer tyrosine kinase (MERTK) [24]. In the adult hippocampus, astrocytes continue to engulf impaired excitatory and inhibitory synapses for circuit homeostasis in an activity-dependent manner [25]. Hevin, which has been mentioned before in the synapse formation, is also a pivotal synapse refinement mediator. During early development, cortical dendritic spines often receive excitatory inputs from both cortex and thalamus, whereas Hevin can stabilize thalamic inputs, eventually forming single-input synapses [26]. On the contrary, in Hevin knockout mice, thalamic inputs are unable to compete with intracortical inputs, and thus ultimately resulting in a situation where the total number of cortical inputs increases and multiple excitatory input synapses persist [26]. Apart from direct mechanisms above, astrocytes can indirectly regulate synapse pruning through initiating microglia [27]. Astrocyte-secreted Interleukin-33 (IL-33) promotes microglial synapse engulfment during neural circuit maturation and remodeling [28].

All in all, astrocytes are involved in the formation of the CNS, assisting in the generation and development of neurons and regulating the synapse formation and elimination.

Astrocytes assist in the running of the CNS

Neuro-glial-vascular coupling

The astrocyte is widely distributed in the CNS. Its direct contact with neurons and blood vessels makes it a modulator in the neurovascular unit, forming the neuro-glial-vascular coupling, which is essential in regulating blood flow, substance and energy metabolism and brain barrier construction [29].

Reliable neural activity within the CNS demands strictly controlled environment and the blood-brain barrier (BBB) is a major interface that isolates brain compartment and circulating blood, adjusting the influx and efflux of solutes [30–32]. The astrocyte, with its endfeet physically ensheathing the capillaries, is located at a strategic position between neurons and endothelial cells [33]. Nutrients can be transported from blood to brain and waste compounds reversely via astrocytes [34, 35]. When the neuronal activity is enhanced, with abundant glutamate released, uptake of glucose by astrocytes from the bloodstream via glucose transporter type 1 (GLUT1) couples with the uptake of glutamate [36]. Through aerobic glycolysis, the glucose is converted to lactate which can be transferred by monocarboxylate transporters (MCT) from astrocytes to neurons [37]. Subsequently, lactate can be oxidized to pyruvate, which is utilized via the tricarboxylic acid cycle to produce vast adenosine triphosphate (ATP) to meet the great demand of energy.

Meanwhile, the endfeet which express water channel aquaporin 4 (AQP4) and Kir4.1 K^+ channel play a special role in ion and volume regulation [31]. Potassium ions released from excited neurons reach astrocyte processes and then diffuse to the perivascular endfeet. Spreading K^+ to a larger area achieves a spatial buffering effect [38]. Water influx, together with ion entry is tuned with water efflux through AQP4 [31]. The highly coordinated work of K^+ channels and AQP4 realizes the clearance of extracellular K^+ and balances ions and water in the microenvironment.

Homeostasis of the brain microenvironment

Aside from AQP4 and Kir4.1 at the endfeet, astrocytes have a mass of other transporters, channels, and enzymes to maintain the homeostasis of the brain microenvironment, such as ions, water, pH and neurotransmitters [39]. Besides the K^+ channel, astrocytes can transfer K^+ through transporters, such as Na^+/K^+ ATPase and $Na^+/K^+/Cl^-$ cotransporter 1, the former of which is also responsible for maintaining transmembrane Na^+ gradient necessary for driving other transporters [40]. CO_2 from neurons can be turned to HCO_3^- by carbonic anhydrase and HCO_3^- can be released by Na^+/bicarbonate cotransporter to balance the pH [39]. Moreover, astrocytes remove and inactivate neurotransmitters, which include glutamate, norepinephrine, γ-aminobutyric acid (GABA) and adenosine, and release gliotransmitters like glutamate, ATP, D-Serine, as well as glutamine, an important source of glutamate and GABA [41].

Synaptic function and plasticity

There is a growing body of evidence that astrocytes are not merely supporting neurons, but also are intimately involved in the modulation of neuronal activity through bidirectional communication with synapses. Araque et al. [42] proposed a term 'tripartite synapse' to refer to the functional and physical structure of the presynaptic membrane, postsynaptic membrane and surrounding astrocyte. Unlike neurons, astrocytes show little electrical excitability, but their Ca^{2+} can be elevated as a result of activation [43]. In the 'tripartite synapse' model, elevation of astrocytic Ca^{2+} level is triggered by neurotransmitters released during synaptic activation, and in turn, activated astrocytes release gliotransmitters to influence synaptic transmission [44]. It is estimated in rodent brain that a single astrocyte oversees 20 to 120 thousand synapses, making it in close relationship with synaptic function and plasticity [45].

Classic long-term potentiation (LTP) relies on NMDA receptors, whose activation needs binding of both glutamate and co-agonist D-serine, and astrocyte-derived D-serine modifies NMDAR plasticity in excitatory synapses nearby [46, 47]. Depletion of D-serine in an individual astrocyte blocks LTP formation, while supply of D-serine rescues LTP blockade induced by clamping astrocytic Ca^{2+} signals [47]. Astrocyte-derived glutamate occurring upon rise of Ca^{2+} level could transiently increase the releasing probability of transmitter, and this short-term plasticity can be transformed to LTP due to the pairing of neuronal depolarization and astrocyte activation [48, 49]. ATP, which is rapidly converted to adenosine extracellularly, is another gliotransmitter. Astrocytes in the hippocampus CA1 region elicit ATP/adenosine, followed by upregulated basal synaptic transmission through presynaptic A_{2A} receptors [50]. In the amygdala of mice, ATP/adenosine could even play different roles by depressing excitatory synapses via A_1 receptors and enhancing inhibitory synapses via A_{2A} receptors [51]. Actually, a single astrocyte could release different gliotransmitters depending on the neuronal activity [52]. For instance, low frequency or short interneuron stimulation induces glutamate release from astrocytes leading to a short-term potentiation, whereas high frequency or prolonged stimulation also induces ATP/adenosine release leading to a short-term depression [52].

Additionally, morphology plasticity of astrocytes plays a key role in local synaptic activity through the structure perisynaptic astrocytic processes (PAPs). PAPs express a large amount of proteins relevant to synaptic transmission, including metabotropic glutamate receptors (mGluRs), glutamine synthetase, glutamate transporters, and $GABA_B$ receptors [45]. The extent to which astrocytes enwrap synapse elements affects the efficacy and activity of transmitter release, further influencing synaptic plasticity [2]. For example, in the supraoptic nucleus of lactating rats, the coverage of PAPs on synapses are reduced, leading to glutamate spillover and reduction of D-serine availability in the postsynaptic NMDARs and thus long-term synaptic changes [46]. A recent study shows that LTP induction prompts withdrawal of PAPs, which boosts extrasynaptic glutamate escape, therefore enhancing nearby synapses [53].

In summary, astrocytes mediate the function of the CNS, participating in neuro-glial-vascular coupling and maintaining the homeostasis of brain microenvironment. Besides, astrocytes are capable of detecting neuronal activity and playing an active role in modulating synaptic transmission.

How astrocytes contribute to drug addiction

Addictive drugs strongly activate dopamine signaling, and recent studies have also shown that astrocyte activity is

fundamental for dopamine-evoked synapse regulation, suggesting that astrocytes may have an emerging role in drug addiction and may serve as a potential therapeutic target [54, 55].

GFAP expression and astrocyte morphology

Astrocytes can be identified by many markers, among which glial fibrillary acidic protein (GFAP) is upregulated after biological injury or during activation by harmful stimuli including drugs of abuse [56, 57]. Almost all kinds of addictive drugs could lead to changes in astrocyte GFAP expression and astrocyte morphology remodeling, yet it is difficult to define specific change patterns in distinct brain regions and in response to different drugs with various training paradigms [58–62].

After both acute and chronic cocaine exposure, GFAP elevation has been observed in the hippocampus [63]. Even after 7 days of cocaine treatment followed by a 3 week withdrawal period, GFAP is found to increase in the prefrontal cortex and both core and shell of the nucleus accumbens (NAc) [59]. However, in a model of cocaine self-administration and extinction training, Scofield et al. [64] pointed out reduction in GFAP expression in the NAc core, making it controversial on the effects of cocaine on changes in GFAP expression. In comparison, the majority of studies which have investigated GFAP expression following drug administration have reported increases consistently in amphetamine, methamphetamine and morphine [60–62]. Further, in human alcoholics, GFAP expression was significantly higher than controls in NAc [65]. Likewise, more GFAP is expressed in rat NAc core during abstinence from ethanol self-administration [66].

With regard to the morphology, astrocytes generally have a decrease in volume and length of processes after drug treatment. Chronic cocaine injection leads to reduced area and length of processes of dorsal hippocampal astrocytes [63]. In the NAc core, cocaine self-administration and extinction reduce astrocyte surface area and volume, as well as communication between astrocytes and synapses. In the same way, the extent of contact made by PAPs is decreased following methamphetamine self-administration and extinction [64, 67]. However, the reduction seems to be region-specific, for no differences in the prelimbic region of the medial prefrontal cortex and basolateral nucleus of the amygdala were observed [68]. As for nicotine, the condition goes totally different. In the prefrontal cortex, CA1 of the hippocampus and the substantia nigra, long-term exposure to nicotine induces extension of processes and increase of cell volume [69].

To sum up, drugs of abuse induce changes in astrocytes from GFAP expression to cell morphology, indicating that astrocytes perform certain functions in drug addiction. Although current outcomes demonstrate distinct responses to drugs, future studies are still needed to explore the influence of different kinds of drugs, administration doses and routes on the properties of astrocytes.

Maladaptive glutamatergic homeostasis

Among the maladaptive responses to addictive substances is the severely impaired glutamatergic homeostasis in the NAc, which is indispensable to the reinstatement of drug-seeking behavior induced by drug-associated cues, contexts, stress and drug itself [70–72].

Three crucial transporters or receptors are responsible for the astrocytic and synaptic glutamate release and elimination. They are glutamate transporter 1 (GLT-1), the cystine/glutamate exchanger (xCT) and mGluR2/3. After presynaptic membrane releases glutamate to postsynaptic membrane, astrocytes could remove extra glutamate from the synapse cleft through Na^+-dependent GLT-1, which is in charge of more than 90% glutamate uptake in the brain [73]. Another transporter controlling extracellular glutamate levels is xCT, one of the several ways of astrocyte releasing glutamate, but the most influential one, through 1:1 exchange for extracellular cysteine, providing approximately 60% of the extrasynaptic glutamate in the NAc core [74]. Besides, mGluR2/3 distributed in presynaptic membranes could limit synaptic release of glutamate and its activation is related with xCT activity [75].

Upregulated glutamatergic transmission within the NAc underlies the reinstatement of drug-seeking behavior [59]. Numerous studies have shown that chronic exposure to drugs of abuse reduces the expression of GLT-1 and induces PAPs retraction, resulting in glutamate spillover in the cleft, accelerating that pathological process [75, 76]. In the same manner, the level of xCT is lowered after administration of drugs [77]. Accordingly, the reduced extracellular glutamate disinhibits regulation of presynaptic mGluR2/3 and enhances glutamate signaling, contributing to relapse behaviors [78]. Ceftriaxone or N-acetylcysteine that could restore expression of GLT-1 and xCT have proved to attenuate the reinstatement in cocaine, methamphetamine and heroin seeking [79–84]. Furthermore, chemogenetic activation of astrocytes by Gq-designer receptors exclusively activated by designer drugs (DREADDs) selectively drives astrocytes glutamate release and inhibits cue-induced cocaine seeking by stimulating mGluR2/3 [85]. Endocannabinoid signaling is another possible pathway to restore glutamate homeostasis,

through which mGluR2/3 function is maintained and priming or cue-induced reinstatement of cocaine seeking is diminished [86].

To sum up, the disruption of glutamatergic homeostasis, which is strictly regulated by astrocytes, promotes vulnerability to reinstatement. Both the augmented synaptic glutamate release and reduced elimination from the synapse cleft could engender abnormal overflow of glutamate linked to the reinstatement of drug seeking behavior.

Astrocyte-neuron signaling in drug addiction

Under physiological circumstances, a huge number of gliotransmitters, transporters and receptors of astrocytes are conducive to its regulation to neuronal activity. Under the pathological conditions of drug abuse, these molecules also work in the reciprocal crosstalk between astrocytes and neurons.

Addictive drugs, despite of distinct action mechanisms, activate the dopamine system consistently [87]. Recently, Corkrum et al. [55] showed that astrocytes in the NAc mediate dopamine-induced synaptic depression through D1 receptors. With elevation of intracellular Ca^{2+} level, activated astrocytes release ATP/adenosine binding to presynaptic A_1 receptors to depress excitatory synapse transmission, which is necessary for amphetamine-related manifestations [55]. Astrocytic adenosine signaling has a significant role in the transition from habitual to goal-directed reward-seeking behavior and alcohol-seeking behavior [88, 89]. In the early stage of drug abuse, drug seeking is controlled and goal-directed, but it gradually turns habitual and compulsive as the addiction develops [90]. Kang et al. [88] demonstrated that chemogenetic activation of astrocytes in the dorsomedial striatum regulates the activity of medium spiny neurons, shifting the reward-seeking behavior patterns from habitual actions to goal-directed ones via adenosine signaling.

Astrocyte-derived D-serine, closely related to synapse plasticity, is also a signal molecule of drug addiction. Curcio et al. [91] proved that exposure to cocaine results in reduced D-serine levels, and therefore subsequently impaired NMDAR-dependent potentiation and depression of glutamatergic synaptic transmission in the NAc. For this reason, exogenous D-serine supply succeeds in rescuing the damaged plasticity and interfering cocaine-related behaviors. As revealed by Kelamangalath & Wagner [92], D-serine treatment facilitates the extinction training and attenuates cocaine-primed drug-seeking behavior. Same effects have been found in cocaine-induced conditioned place preference (CPP) and locomotor sensitization [93, 94]. Moreover, morphine inhibits D-serine release from astrocytes, suppressing the excitability of postsynaptic GABAergic neurons [95].

Lactate is a novel mediator in learning and memory, synapse plasticity and drug addiction, which has been considered only as an energy substrate in brain energy metabolism for long [36]. Since Suzuki et al. [96] found astrocyte-neuron lactate transport is of great importance for long-term memory formation, its role in drug memory, which is associated with drug abuse and relapse, has aroused lots of attention of scientists. Pharmacological inhibition of glycogenolysis in the basolateral amygdala disrupts the lactate production, along with the impaired acquisition and persistence of cocaine-induced CPP [97]. Meanwhile, disruption of astrocyte-neuron lactate transport abolishes the reconsolidation of cocaine reward memory and subsequent expression of cocaine-induced CPP [98]. Lactate is also supposed to be involved in glucocorticoid receptor (GR) –mediated alterations in synapse transmission caused by morphine [99]. While astrocytic GR knockdown inhibits glucocorticoid-induced lactate release, it enhances morphine-induced CPP at the same time, and lactate supplementation could reverse that action [99].

There are still some other astrocyte-related molecules that participate in drug addiction, such as TSP2 and AQP4. By activating its neuronal receptor α2δ-1, astrocyte-secreted TSP2 could promote generation of silent synapses [18]. Through this way, cocaine triggers synaptogenesis in the NAc shell, and disrupting TSP2-α2δ-1 signaling could effectively prevent cue-induced relapse after extinction or withdrawal [100]. Furthermore, ablation of AQP4 reduces heroin consumption in self-administration training and morphine-induced behavioral sensitization, which may be achieved by upregulated expression of dopamine transporter [101].

In conclusion, astrocytes could affect neuronal and synaptic activity through multiple ways to respond to the development of drug addiction. There's no doubt that astrocyte-neuron interaction via glutamate, ATP/adenosine, D-serine, lactate etc., is an essential mechanism of drug addiction.

Future perspectives

For decades, the main character in the neuroscience research has always been the neuron, whose electrical activity is considered to be the foundation of brain activity, while glia plays a secondary and supportive role. However, improved techniques to visualize and manipulate glia have thoroughly expanded our knowledge of glial functions in physiological and pathological conditions, especially those of the astrocytes, the most abundant glial cells [102].

Fruitful findings have prompted us to appreciate the prominent role of astrocytes in the CNS. In terms of shaping the CNS, astrocytes assist neurogenesis and axon guidance, as well as controlling an appropriate number of synapses by participating in synapse formation and elimination. As for the CNS function, astrocytes own diversified receptors, transporters, channels, enzymes and gliotransmitters involved in neuro-glial-vascular coupling, microenvironment homeostasis maintenance, synapse plasticity regulation and many others. These gratifying progresses allow us to re-examine the nervous system and neuropsychiatric diseases from a different perspective.

Since the past few years have witnessed inspiring achievements in acknowledging the function of astrocytes, people began to explore their roles in drug addiction. Most drugs of abuse could activate the astrocytes and alter their morphology and functions towards aberrant levels, which contributes to the development of maladaptive drug-related behaviors. Specifically, the patterns of astrocyte releasing gliotransmitters, such as glutamate, ATP/adenosine and D-serine, are impacted. Among those substances, glutamate has been studied extensively in particular, for the disruption of its homeostasis is believed to promote vulnerability to relapse.

Better understanding of the molecular and cellular changes induced by drugs allows the seeking of effective treatments for drug addiction, among which manipulating astrocytes has risen as a unique approach to prevent relapse. Although growing evidence has demonstrated that some pharmacological means of restoring glutamatergic homeostasis can successfully prevent relapse in rodents, the results of clinical trials in humans are still limited. N-acetylcysteine treatment could potently reduce drug desire following either cocaine cue exhibition or intravenous cocaine injection [103, 104]. In another trial, N-acetylcysteine administration failed to reduce cocaine use in active users, but was able to decrease drug craving in those who had achieved abstinence [105]. Combined with cognitive behavioral therapy, N-acetylcysteine treatment for 8 weeks significantly lessened the craving in veterans with substance use disorder [106]. Recent findings substantiate that N-acetylcysteine could attenuate cocaine-cue attentional bias by reducing the incentive salience of cocaine, and decrease cocaine-seeking behavior possibly by modulating glutamate levels in the rostral anterior cingulate [107, 108]. Although above results are inconsistent, N-acetylcysteine, which is well-tolerated with only mildly adverse effects, displays its potential in preventing drug relapse [109]. Besides N-acetylcysteine, in methamphetamine users, electroacupuncture has the ability to normalize glutamate levels by enhancing astrocytic glutamate clearance in the dorsal hippocampal CA1, suggesting that non-invasive electroacupuncture might be a novel approach to manage drug addiction [110].

As a matter of fact, drug addiction is also a disorder of learning and memory [111]. A major obstacle in addiction treatment is the high rate of relapse due to the persistence of maladaptive drug-associated memories [112]. Even after a long period of withdrawal, individuals have a propensity to generate drug-taking and drug-seeking behaviors when exposed to drug-associated cues and environment [113]. Recently, converging evidence of astrocytic role in memory has been obtained with advanced techniques (including translating ribosome affinity purification, RiboTag, single-cell transcriptomic analyses, super-resolution microscopy, neuron-astrocyte proximity assay, etc. [4]), indicating that astrocyte may also play a part in drug memory as well, which may open a completely new area in pathological mechanism and clinical treatment research [25, 114–116].

In short, it has lately come to light that astrocytes are key participants in drug addiction and they are emerging as a promising therapeutic target of drug addiction.

Conclusions

Here, we highlighted diverse roles of astrocytes in many aspects of the CNS and drug addiction. Notwithstanding that extensive efforts have been made to disentangle the interaction between astrocytes and addictive drugs, further precise exploration in the circuit, cellular, molecular and genetic mechanism of astrocyte-mediated addiction is still needed. With the emergence of new strategies to interrogate astrocytes *in vivo*, a more comprehensive understanding of the roles of astrocytes in drug addiction will be achieved, holding considerable promise for developing feasible therapeutic treatments of drug addiction in the future.

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References

1. Svendsen CN. The amazing astrocyte. Nature 2002;417:29–32.
2. Santello M, Toni N, Volterra A. Astrocyte function from information processing to cognition and cognitive impairment. Nat Neurosci 2019;22:154–66.
3. United Nations Office on Drugs and Crimes. World drug report 2021; 2022. Available from: https://www.unodc.org/unodc/en/data-and-analysis/wdr2021.html [Accessed 25 Apr 2022].
4. Yu X, Nagai J, Khakh BS. Improved tools to study astrocytes. Nat Rev Neurosci 2020;21:121–38.
5. Shetty AK, Hattiangady B, Shetty GA. Stem/progenitor cell proliferation factors FGF-2, IGF-1, and VEGF exhibit early decline during the course of aging in the hippocampus: role of astrocytes. Glia 2005;51:173–86.
6. Schwartz JP, Taniwaki T, Messing A, Brenner M. Somatostatin as a trophic factor. analysis of transgenic mice overexpressing somatostatin in astrocytes. Ann N Y Acad Sci 1996;780:29–35.
7. Reemst K, Noctor SC, Lucassen PJ, Hol EM. The indispensable roles of microglia and astrocytes during brain development. Front Hum Neurosci 2016;10:566.
8. Quesseveur G, David DJ, Gaillard MC, Pla P, Wu MV, Nguyen HT, et al. BDNF overexpression in mouse hippocampal astrocytes promotes local neurogenesis and elicits anxiolytic-like activities. Transl Psychiatry 2013;3:e253.
9. Cope EC, Gould E. Adult neurogenesis, glia, and the extracellular matrix. Cell Stem Cell 2019;24:690–705.
10. Götz M, Huttner WB. The cell biology of neurogenesis. Nat Rev Mol Cell Biol 2005;6:777–88.
11. Song H, Stevens CF, Gage FH. Astroglia induce neurogenesis from adult neural stem cells. Nature 2002;417:39–44.
12. Pasterkamp RJ, Burk K. Axon guidance receptors: endocytosis, trafficking and downstream signaling from endosomes. Prog Neurobiol 2021;198:101916.
13. Minocha S, Valloton D, Ypsilanti AR, Fiumelli H, Allen EA, Yanagawa Y, et al. Nkx2.1-derived astrocytes and neurons together with Slit2 are indispensable for anterior commissure formation. Nat Commun 2015;6:6887.
14. Freeman MR. Specification and morphogenesis of astrocytes. Science 2010;330:774–8.
15. Barker AJ, Koch SM, Reed J, Barres BA, Ullian EM. Developmental control of synaptic receptivity. J Neurosci 2008;28:8150–60.
16. Hama H, Hara C, Yamaguchi K, Miyawaki A. PKC signaling mediates global enhancement of excitatory synaptogenesis in neurons triggered by local contact with astrocytes. Neuron 2004;41:405–15.
17. Allen NJ, Lyons DA. Glia as architects of central nervous system formation and function. Science 2018;362:181–5.
18. Christopherson KS, Ullian EM, Stokes CCA, Mullowney CE, Hell JW, Agah A, et al. Thrombospondins are astrocyte-secreted proteins that promote CNS synaptogenesis. Cell 2005;120:421–33.
19. Kucukdereli H, Allen NJ, Lee AT, Feng A, Ozlu MI, Conatser LM, et al. Control of excitatory CNS synaptogenesis by astrocyte-secreted proteins Hevin and SPARC. Proc Natl Acad Sci USA 2011;108:E440–E9.
20. Allen NJ, Bennett ML, Foo LC, Wang GX, Chakraborty C, Smith SJ, et al. Astrocyte glypicans 4 and 6 promote formation of excitatory synapses via GluA1 AMPA receptors. Nature 2012;486:410–4.
21. Stogsdill JA, Ramirez J, Liu D, Kim YH, Baldwin KT, Enustun E, et al. Astrocytic neuroligins control astrocyte morphogenesis and synaptogenesis. Nature 2017;551:192–7.
22. Augusto-Oliveira M, Arrifano GP, Takeda PY, Lopes-Araújo A, Santos-Sacramento L, Anthony DC, et al. Astroglia-specific contributions to the regulation of synapses, cognition and behaviour. Neurosci Biobehav Rev 2020;118:331–57.
23. Allen NJ, Eroglu C. Cell biology of astrocyte-synapse interactions. Neuron 2017;96:697–708.
24. Chung WS, Clarke LE, Wang GX, Stafford BK, Sher A, Chakraborty C, et al. Astrocytes mediate synapse elimination through MEGF10 and MERTK pathways. Nature 2013;504:394–400.
25. Lee JH, Kim JY, Noh S, Lee H, Lee SY, Mun JY, et al. Astrocytes phagocytose adult hippocampal synapses for circuit homeostasis. Nature 2021;590:612–7.
26. Risher WC, Patel S, Kim IH, Uezu A, Bhagat S, Wilton DK, et al. Astrocytes refine cortical connectivity at dendritic spines. Elife 2014;3:e04047.
27. Wilton DK, Dissing-Olesen L, Stevens B. Neuron-glia signaling in synapse elimination. Annu Rev Neurosci 2019;42:107–27.
28. Vainchtein ID, Chin G, Cho FS, Kelley KW, Miller JG, Chien EC, et al. Astrocyte-derived interleukin-33 promotes microglial synapse engulfment and neural circuit development. Science 2018;359:1269–73.
29. Kugler EC, Greenwood J, MacDonald RB. The "neuro-glial-vascular" unit: the role of glia in neurovascular unit formation and dysfunction. Front Cell Dev Biol 2021;9:732820.
30. Sweeney MD, Sagare AP, Zlokovic BV. Blood-brain barrier breakdown in Alzheimer disease and other neurodegenerative disorders. Nat Rev Neurol 2018;14:133–50.
31. Abbott NJ, Rönnbäck L, Hansson E. Astrocyte-endothelial interactions at the blood-brain barrier. Nat Rev Neurosci 2006;7:41–53.
32. Abbott NJ, Patabendige AAK, Dolman DEM, Yusof SR, Begley DJ. Structure and function of the blood-brain barrier. Neurobiol Dis 2010;37:13–25.
33. Langen UH, Ayloo S, Gu C. Development and cell biology of the blood-brain barrier. Annu Rev Cell Dev Biol 2019;35:591–613.
34. Marina N, Turovsky E, Christie IN, Hosford PS, Hadjihambi A, Korsak A, et al. Brain metabolic sensing and metabolic signaling at the level of an astrocyte. Glia 2018;66:1185–99.
35. Nortley R, Attwell D. Control of brain energy supply by astrocytes. Curr Opin Neurobiol 2017;47:80–5.
36. Wang Q, Hu Y, Wan J, Dong B, Sun J. Lactate: a novel signaling molecule in synaptic plasticity and drug addiction. Bioessays 2019;41:e1900008.
37. Magistretti PJ, Allaman I. Lactate in the brain: from metabolic end-product to signalling molecule. Nat Rev Neurosci 2018;19:235–49.
38. Hibino H, Inanobe A, Furutani K, Murakami S, Findlay I, Kurachi Y. Inwardly rectifying potassium channels: their structure, function, and physiological roles. Physiol Rev 2010;90:291–366.
39. Benarroch EE. Astrocyte signaling and synaptic homeostasis: I: membrane channels, transporters, and receptors in astrocytes. Neurology 2016;87:324–30.
40. Hertz L, Chen Y. Importance of astrocytes for potassium ion (K) homeostasis in brain and glial effects of K and its

transporters on learning. Neurosci Biobehav Rev 2016;71: 484–505.
41. Verkhratsky A, Nedergaard M. Physiology of astroglia. Physiol Rev 2018;98:239–389.
42. Araque A, Parpura V, Sanzgiri RP, Haydon PG. Tripartite synapses: glia, the unacknowledged partner. Trends Neurosci 1999;22:208–15.
43. Perea G, Araque A. Glial calcium signaling and neuron-glia communication. Cell Calcium 2005;38:375–82.
44. Perea G, Navarrete M, Araque A. Tripartite synapses: astrocytes process and control synaptic information. Trends Neurosci 2009;32:421–31.
45. Heller JP, Rusakov DA. Morphological plasticity of astroglia: understanding synaptic microenvironment. Glia 2015;63: 2133–51.
46. Panatier A, Theodosis DT, Mothet JP, Touquet B, Pollegioni L, Poulain DA, et al. Glia-derived D-serine controls NMDA receptor activity and synaptic memory. Cell 2006;125:775–84.
47. Henneberger C, Papouin T, Oliet SHR, Rusakov DA. Long-term potentiation depends on release of D-serine from astrocytes. Nature 2010;463:232–6.
48. Perea G, Araque A. Astrocytes potentiate transmitter release at single hippocampal synapses. Science 2007;317:1083–6.
49. Jourdain P, Bergersen LH, Bhaukaurally K, Bezzi P, Santello M, Domercq M, et al. Glutamate exocytosis from astrocytes controls synaptic strength. Nat Neurosci 2007;10:331–9.
50. Panatier A, Vallée J, Haber M, Murai KK, Lacaille JC, Robitaille R. Astrocytes are endogenous regulators of basal transmission at central synapses. Cell 2011;146:785–98.
51. Martin-Fernandez M, Jamison S, Robin LM, Zhao Z, Martin ED, Aguilar J, et al. Synapse-specific astrocyte gating of amygdala-related behavior. Nat Neurosci 2017;20:1540–8.
52. Covelo A, Araque A. Neuronal activity determines distinct gliotransmitter release from a single astrocyte. Elife 2018;7: e32237.
53. Henneberger C, Bard L, Panatier A, Reynolds JP, Kopach O, Medvedev NI, et al. LTP induction boosts glutamate spillover by driving withdrawal of perisynaptic astroglia. Neuron 2020;108: 919–36.
54. Lüscher C. The emergence of a circuit model for addiction. Annu Rev Neurosci 2016;39:257–76.
55. Corkrum M, Covelo A, Lines J, Bellocchio L, Pisansky M, Loke K, et al. Dopamine-evoked synaptic regulation in the nucleus accumbens requires astrocyte activity. Neuron 2020;105: 1036–47.
56. Linker KE, Cross SJ, Leslie FM. Glial mechanisms underlying substance use disorders. Eur J Neurosci 2019;50:2574–89.
57. Sofroniew MV, Vinters HV. Astrocytes: biology and pathology. Acta Neuropathol 2010;119:7–35.
58. Kim R, Healey KL, Sepulveda-Orengo MT, Reissner KJ. Astroglial correlates of neuropsychiatric disease: from astrocytopathy to astrogliosis. Prog Neuro-Psychopharmacol Biol Psychiatry 2018;87:126–46.
59. Bowers MS, Kalivas PW. Forebrain astroglial plasticity is induced following withdrawal from repeated cocaine administration. Eur J Neurosci 2003;17:1273–8.
60. Frey BN, Andreazza AC, Ceresér KM, Martins MR, Petronilho FC, de Souza DF, et al. Evidence of astrogliosis in rat hippocampus after d-amphetamine exposure. Prog Neuro-Psychopharmacol Biol Psychiatry 2006;30:1231–4.
61. Castellano P, Nwagbo C, Martinez LR, Eugenin EA. Methamphetamine compromises gap junctional communication in astrocytes and neurons. J Neurochem 2016;137:561–75.
62. Garrido E, Pérez-García C, Alguacil LF, Díez-Fernández C. The alpha2-adrenoceptor antagonist yohimbine reduces glial fibrillary acidic protein upregulation induced by chronic morphine administration. Neurosci Lett 2005;383:141–4.
63. Fattore L, Puddu MC, Picciau S, Cappai A, Fratta W, Serra GP, et al. Astroglial in vivo response to cocaine in mouse dentate gyrus: a quantitative and qualitative analysis by confocal microscopy. Neuroscience 2002;110:1–6.
64. Scofield MD, Li H, Siemsen BM, Healey KL, Tran PK, Woronoff N, et al. Cocaine self-administration and extinction leads to reduced glial fibrillary acidic protein expression and morphometric features of astrocytes in the nucleus accumbens core. Biol Psychiatr 2016;80:207–15.
65. Sarkisyan D, Bazov I, Watanabe H, Kononenko O, Syvänen AC, Schumann G, et al. Damaged reward areas in human alcoholics: neuronal proportion decline and astrocyte activation. Acta Neuropathol 2017;133:485–7.
66. Bull C, Freitas KCC, Zou S, Poland RS, Syed WA, Urban DJ, et al. Rat nucleus accumbens core astrocytes modulate reward and the motivation to self-administer ethanol after abstinence. Neuropsychopharmacology 2014;39:2835–45.
67. Siemsen BM, Reichel CM, Leong KC, Garcia-Keller C, Gipson CD, Spencer S, et al. Effects of methamphetamine self-administration and extinction on astrocyte structure and function in the nucleus accumbens core. Neuroscience 2019; 406:528–41.
68. Testen A, Sepulveda-Orengo MT, Gaines CH, Reissner KJ. Region-specific reductions in morphometric properties and synaptic colocalization of astrocytes following cocaine self-administration and extinction. Front Cell Neurosci 2018;12:246.
69. Aryal SP, Fu X, Sandin JN, Neupane KR, Lakes JE, Grady ME, et al. Nicotine induces morphological and functional changes in astrocytes via nicotinic receptor activity. Glia 2021;69:2037–53.
70. Kalivas PW. The glutamate homeostasis hypothesis of addiction. Nat Rev Neurosci 2009;10:561–72.
71. McFarland K, Lapish CC, Kalivas PW. Prefrontal glutamate release into the core of the nucleus accumbens mediates cocaine-induced reinstatement of drug-seeking behavior. J Neurosci 2003;23:3531–7.
72. LaLumiere RT, Kalivas PW. Glutamate release in the nucleus accumbens core is necessary for heroin seeking. J Neurosci 2008;28:3170–7.
73. Danbolt NC. Glutamate uptake. Prog Neurobiol 2001;65:1–105.
74. van der Zeyden M, Oldenziel WH, Rea K, Cremers TI, Westerink BH. Microdialysis of GABA and glutamate: analysis, interpretation and comparison with microsensors. Pharmacol Biochem Behav 2008;90:135–47.
75. Scofield MD, Heinsbroek JA, Gipson CD, Kupchik YM, Spencer S, Smith ACW, et al. The nucleus accumbens: mechanisms of addiction across drug classes reflect the importance of glutamate homeostasis. Pharmacol Rev 2016;68:816–71.
76. Kruyer A, Scofield MD, Wood D, Reissner KJ, Kalivas PW. Heroin cue-evoked astrocytic structural plasticity at nucleus accumbens synapses inhibits heroin seeking. Biol Psychiatr 2019;86:811–9.
77. Kruyer A, Kalivas PW. Astrocytes as cellular mediators of cue reactivity in addiction. Curr Opin Pharmacol 2021;56:1–6.

78. Wang J, Holt LM, Huang HH, Sesack SR, Nestler EJ, Dong Y. Astrocytes in cocaine addiction and beyond. Mol Psychiatr 2022;27:652–68.
79. Knackstedt LA, Melendez RI, Kalivas PW. Ceftriaxone restores glutamate homeostasis and prevents relapse to cocaine seeking. Biol Psychiatr 2010;67:81–4.
80. Shen HW, Scofield MD, Boger H, Hensley M, Kalivas PW. Synaptic glutamate spillover due to impaired glutamate uptake mediates heroin relapse. J Neurosci 2014;34:5649–57.
81. Abulseoud OA, Miller JD, Wu J, Choi DS, Holschneider DP. Ceftriaxone upregulates the glutamate transporter in medial prefrontal cortex and blocks reinstatement of methamphetamine seeking in a condition place preference paradigm. Brain Res 2012;1456:14–21.
82. Reissner KJ, Gipson CD, Tran PK, Knackstedt LA, Scofield MD, Kalivas PW. Glutamate transporter GLT-1 mediates N-acetylcysteine inhibition of cocaine reinstatement. Addiction Biol 2015;20:316–23.
83. Baker DA, McFarland K, Lake RW, Shen H, Tang X-C, Toda S, et al. Neuroadaptations in cystine-glutamate exchange underlie cocaine relapse. Nat Neurosci 2003;6:743–9.
84. Sari Y, Smith KD, Ali PK, Rebec GV. Upregulation of GLT1 attenuates cue-induced reinstatement of cocaine-seeking behavior in rats. J Neurosci 2009;29:9239–43.
85. Scofield MD, Boger HA, Smith RJ, Li H, Haydon PG, Kalivas PW. Gq-DREADD selectively initiates glial glutamate release and inhibits cue-induced cocaine seeking. Biol Psychiatr 2015;78: 441–51.
86. Zhang LY, Zhou YQ, Yu ZP, Zhang XQ, Shi J, Shen HW. Restoring glutamate homeostasis in the nucleus accumbens via endocannabinoid-mimetic drug prevents relapse to cocaine seeking behavior in rats. Neuropsychopharmacology 2021;46: 970–81.
87. Wise RA, Robble MA. Dopamine and addiction. Annu Rev Psychol 2020;71:9–106.
88. Kang S, Hong SI, Lee J, Peyton L, Baker M, Choi S, et al. Activation of astrocytes in the dorsomedial striatum facilitates transition from habitual to goal-directed reward-seeking behavior. Biol Psychiatr 2020;88:797–808.
89. Hong SI, Bullert A, Baker M, Choi DS. Astrocytic equilibrative nucleoside transporter type 1 upregulations in the dorsomedial and dorsolateral striatum distinctly coordinate goal-directed and habitual ethanol-seeking behaviours in mice. Eur J Neurosci 2020;52:3110–23.
90. Lüscher C, Robbins TW, Everitt BJ. The transition to compulsion in addiction. Nat Rev Neurosci 2020;21:247–63.
91. Curcio L, Podda MV, Leone L, Piacentini R, Mastrodonato A, Cappelletti P, et al. Reduced D-serine levels in the nucleus accumbens of cocaine-treated rats hinder the induction of NMDA receptor-dependent synaptic plasticity. Brain 2013;136: 1216–30.
92. Kelamangalath L, Wagner JJ. D-serine treatment reduces cocaine-primed reinstatement in rats following extended access to cocaine self-administration. Neuroscience 2010;169: 1127–35.
93. Hammond S, Seymour CM, Burger A, Wagner JJ. D-serine facilitates the effectiveness of extinction to reduce drug-primed reinstatement of cocaine-induced conditioned place preference. Neuropharmacology 2013;64:464–71.
94. Liu ZQ, Gu XH, Yang YJ, Yin XP, Xu LJ, Wang W. D-serine in the nucleus accumbens region modulates behavioral sensitization and extinction of conditioned place preference. Pharmacol Biochem Behav 2016;143:44–56.
95. Wu J, Zhao R, Guo L, Zhen X. Morphine-induced inhibition of Ca^{2+}-dependent d-serine release from astrocytes suppresses excitability of GABAergic neurons in the nucleus accumbens. Addiction Biol 2017;22:1289–303.
96. Suzuki A, Stern SA, Bozdagi O, Huntley GW, Walker RH, Magistretti PJ, et al. Astrocyte-neuron lactate transport is required for long-term memory formation. Cell 2011;144: 810–23.
97. Boury-Jamot B, Carrard A, Martin JL, Halfon O, Magistretti PJ, Boutrel B. Disrupting astrocyte-neuron lactate transfer persistently reduces conditioned responses to cocaine. Mol Psychiatr 2016;21:1070–6.
98. Zhang Y, Xue Y, Meng S, Luo Y, Liang J, Li J, et al. Inhibition of lactate transport erases drug memory and prevents drug relapse. Biol Psychiatr 2016;79:928–39.
99. Skupio U, Tertil M, Bilecki W, Barut J, Korostynski M, Golda S, et al. Astrocytes determine conditioned response to morphine via glucocorticoid receptor-dependent regulation of lactate release. Neuropsychopharmacology 2020;45:404–15.
100. Wang J, Li KL, Shukla A, Beroun A, Ishikawa M, Huang X, et al. Cocaine triggers astrocyte-mediated synaptogenesis. Biol Psychiatr 2021;89:386–97.
101. Lv Y, Jing MY, Li PY, Zhao TY, Pang C, Lu GY, et al. Aquaporin-4 deletion attenuates opioid-induced addictive behaviours associated with dopamine levels in nucleus accumbens. Neuropharmacology 2022;208:108986.
102. Volterra A, Meldolesi J. Astrocytes, from brain glue to communication elements: the revolution continues. Nat Rev Neurosci 2005;6:626–40.
103. LaRowe SD, Myrick H, Hedden S, Mardikian P, Saladin M, McRae A, et al. Is cocaine desire reduced by N-acetylcysteine? Am J Psychiatr 2007;164:1115–7.
104. Amen SL, Piacentine LB, Ahmad ME, Li S-J, Mantsch JR, Risinger RC, et al. Repeated N-acetyl cysteine reduces cocaine seeking in rodents and craving in cocaine-dependent humans. Neuropsychopharmacology 2011;36:871–8.
105. LaRowe SD, Kalivas PW, Nicholas JS, Randall PK, Mardikian PN, Malcolm RJ. A double-blind placebo-controlled trial of N-acetylcysteine in the treatment of cocaine dependence. Am J Addict 2013;22:443–52.
106. Back SE, McCauley JL, Korte KJ, Gros DF, Leavitt V, Gray KM, et al. A double-blind, randomized, controlled pilot trial of N-acetylcysteine in veterans with posttraumatic stress disorder and substance use disorders. J Clin Psychiatr 2016;77: e1439–e46.
107. Woodcock EA, Lundahl LH, Khatib D, Stanley JA, Greenwald MK. N-acetylcysteine reduces cocaine-seeking behavior and anterior cingulate glutamate/glutamine levels among cocaine-dependent individuals. Addiction Biol 2021;26:e12900.
108. Levi Bolin B, Alcorn JL, Lile JA, Rush CR, Rayapati AO, Hays LR, et al. N-acetylcysteine reduces cocaine-cue attentional bias and differentially alters cocaine self-administration based on dosing order. Drug Alcohol Depend 2017;178:452–60.
109. Jones JD. Potential of glial cell modulators in the management of substance use disorders. CNS Drugs 2020;34:697–722.

110. He T, Li N, Shi P, Xu X, Nie J, Lu X, et al. Electroacupuncture alleviates spatial memory deficits in METH withdrawal mice by enhancing astrocyte-mediated glutamate clearance in the dCA1. Addiction Biol 2022;27:e13068.
111. Hyman SE, Malenka RC, Nestler EJ. Neural mechanisms of addiction: the role of reward-related learning and memory. Annu Rev Neurosci 2006;29:565–98.
112. Hyman SE. Addiction: a disease of learning and memory. Am J Psychiatr 2005;162:1414–22.
113. Milton AL, Everitt BJ. The persistence of maladaptive memory: addiction, drug memories and anti-relapse treatments. Neurosci Biobehav Rev 2012;36:1119–39.
114. Li Y, Li L, Wu J, Zhu Z, Feng X, Qin L, et al. Activation of astrocytes in hippocampus decreases fear memory through adenosine A receptors. Elife 2020;9:e57155.
115. Kol A, Adamsky A, Groysman M, Kreisel T, London M, Goshen I. Astrocytes contribute to remote memory formation by modulating hippocampal-cortical communication during learning. Nat Neurosci 2020;23: 1229–39.
116. Zhang K, Förster R, He W, Liao X, Li J, Yang C, et al. Fear learning induces α7-nicotinic acetylcholine receptor-mediated astrocytic responsiveness that is required for memory persistence. Nat Neurosci 2021;24:1686–98.