Astrocytes in Addictive Disorders

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Overview of Addiction Biology

Circuitry and Transmitters

The elevation of extracellular dopamine in the ventral striatum in response to salient and rewarding stimuli underlies several reinforcement and addiction-related behaviors extensively studied in preclinical models of substance use and relapse (Scofield et al. 2016a). Anatomically, the ventral striatum is divided into two subregions, the nucleus accumbens core (NAcore) and shell (NAshell), which both receive dopaminergic innervation from the midbrain nucleus the ventral tegmental area (VTA) (Ikemoto 2007) and that are both involved in encoding reward and motivation. Increased levels of extracellular dopamine in the ventral striatum are evoked by administration of addictive drugs (reviewed in (Willuhn et al. 2010)) including alcohol (Howard et al. 2008), as well as by sucrose intake (Bassareo et al. 2017), and a substantial body of lesion, microdialysis, voltammetry, and pharmacology studies has led to the general conception that the NAshell is involved in encoding the rewarding effects of addictive drugs, while the NAcore coordinates behavioral outputs in response to salient stimuli (Scofield et al. 2016a; Sellings and Clarke 2003; Salgado and Kaplitt 2015).

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Though natural (i.e., sucrose) as well as pathological (i.e., drugs of abuse) rewards elevate dopamine in the ventral striatum, dopaminergic signaling within this circuit is modulated by glutamatergic transmission, and glutamatergic signaling is uniquely disrupted following repeated intake of addictive substances (Kalivas et al. 1989, 2009; Kalivas 2009). In keeping with important but separable roles for these two transmitters in addiction-related behaviors are recent studies demonstrating that subpopulations of dopaminergic VTA neurons that project to the NAshell co-release glutamate along with dopamine (Stuber et al. 2010; Mongia et al. 2019; Mingote et al. 2019). Glutamate release from dopamine neurons in the NAshell is linked to intake of sucrose and psychostimulants and locomotor responses to acute and repeated psychostimulant administration (Hnasko et al. 2010; Alsio et al. 2011; Birgner et al. 2010; Bimpisidis and Wallen-Mackenzie 2019). Glutamate modulates dopamine neurotransmission through its action on glutamate receptors expressed on dopaminergic terminals (Floresco et al. 1998; Howland et al. 2002) and through facilitation of dopamine loading in synaptic vesicles (Hnasko et al. 2010; Hnasko and Edwards 2012). Though VTA inputs to the NAcore contribute to drug seeking induced by drug prime (Shen et al. 2014a), the impact of dopamine transmission on seeking behavior can be blocked by glutamate receptor antagonists even in the presence of dopamine (Cornish and Kalivas 2000), consistent with a critical role for glutamatergic transmission in drug seeking behavior.

The ventral striatum receives excitatory input from a number of brain regions, in addition to VTA. Cortical regions provide glutamatergic input to the NAcore and NAshell, with prelimbic (PL) cortical afferents in the NAcore or infralimbic (IL) afferents in the NAshell contributing to drug seeking or refraining behavior, respectively. Glutamate transmission in the NAcore is necessary for initial learning of drug-reward associations (Kelley et al. 1997; Smith-Roe and Kelley 2000) and later for retrieval of drug-contingency information during reinstatement of drug seeking following extinction of behavioral responding (Kalivas 2009; Kalivas and Volkow 2005; Koob and Volkow 2010). PL afferents in the NAcore are engaged during cue-, drug-, context- and stress-reinstated seeking of different classes of addictive substances, including opioids, psychostimulants, and alcohol (Rogers et al. 2008; Ball and Slane 2012; Rocha and Kalivas 2010; Doncheck et al. 2020; McFarland et al. 2003; Willcocks and McNally 2013; Chaudhri et al. 2008). The IL input to the NAshell, on the other hand, is recruited during extinction training, whereby operant responding for drug reinforcers is gradually reduced over time when the drug is no longer available (Peters et al. 2008).

The NAcore also receives significant glutamatergic input from basolateral amygdala (BLA) that contributes to both acquisition of self-administration and reinstatement initiated by cues (Carelli et al. 2003; Whitelaw et al. 1996; Di Ciano and Everitt 2004; Puaud et al. 2020), through direct glutamatergic projections to the NAcore and/or projections to the PL (Stefanik and Kalivas 2013). BLA glutamate may also be engaged to a certain extent by operant training for natural reinforcers, since optogenetically stimulating BLA projections to the NAcore can initiate responding for sucrose (Stuber et al. 2011). A number of other brain regions have been strongly implicated in promoting addiction-related behaviors, including dorsal

and ventral hippocampus (Fuchs et al. 2005; Lasseter et al. 2010; Atkins et al. 2008), ventral subiculum (Bossert and Stern 2014), and lateral septum (McGlinchey and Aston-Jones 2018), though not necessarily via direct NAcore projections. Interestingly, excitatory projections to the NAcore can also suppress seeking behavior, since glutamate release from the paraventricular thalamus in the NAcore serves to suppress seeking behavior in the absence of a reinforcer (Do-Monte et al. 2017), arguing that excitatory transmission in the NAcore is necessary, but not sufficient for reward seeking, and that unique innervation of postsynaptic targets may be an important factor in ultimate behavioral outputs.

Astrocytes are likely mediators of the long-lasting excitatory plasticity that arises within the corticostriatal circuitry in response to chronic drug intake. Astroglial processes are positioned proximal to excitatory synapses, and their expression of neurotransmitter transporters regulates stimulation of pre- and postsynaptic receptors. Moreover, astroglia are capable of signaling directly to synapses through transmitter release and play critical roles in homeostatic regulation of synapses. Astroglial adaptations following exposure to addictive drugs are being actively investigated within the circuits outlined above. Given that vast brain region-dependent heterogeneity in astroglial structure and transcriptomic profiles has recently been described (Batiuk et al. 2020; Matias et al. 2019; Cuevas-Diaz Duran et al. 2019; Kohler et al. 2019), astrocyte function as it pertains to addiction is likely unique in each region. Below we explore what is known regarding astroglial contributions to synaptic physiology at baseline and after use of addictive substances.

Transmitter Uptake

Glutamate

The glutamate transporter GLT-1 (EAAT2 in humans) conducts the majority of glutamate uptake and is mostly expressed by astroglia in the adult brain (Danbolt 2001), despite reports of low-level expression in some neurons (Rimmele and Rosenberg 2016). GLT-1 has long been thought to contribute to addiction-related glutamatergic dysregulation in the ventral striatum since its expression and/or function is disrupted after long-term use of psychostimulants, opioids, and alcohol (Roberts-Wolfe and Kalivas 2015). GLT-1 knockdown in astroglia during the early postnatal period leads to repetitive behaviors in drug-naïve animals and enhanced neuronal excitability in the dorsal striatum (Aida et al. 2015). In rats trained to self-administer cocaine, GLT-1 downregulation in the NAcore is dependent upon withdrawal duration as well as cocaine intake, with increasing amounts of either exacerbating the severity of GLT-1 downregulation (Fischer-Smith et al. 2012). Further, extended withdrawal from long-access cocaine self-administration (i.e., daily 6-hour sessions) reduces mRNA levels of the predominant of three GLT-1 isoforms, GLT-1a (Holmseth et al. 2009), in the NAcore, coincident with enhanced

methylation of *Slc1a2*, the gene that encodes GLT-1 (Kim et al. 2018). Since the authors of this study found no changes in GLT-1a or b mRNA levels after withdrawal or extinction from short access cocaine self-administration, but many other studies show GLT-1 downregulation in these paradigms (Roberts-Wolfe and Kalivas 2015), it may be that posttranslational rather than transcriptional mechanisms are responsible for its reduced expression and/or function in short-access models. Interestingly, up- or downregulation of GLT-1 in the striatum disrupts spike-timing dependent plasticity, a type of long-term potentiation that requires a tight temporal relationship between pre- and postsynaptic activity (Valtcheva and Venance 2016). When the action of GLT-1 is blocked, long-term potentiation requires signaling through extrasynaptic GluN2B-containing NMDA receptors. Similarly, signaling through GluN2B is required for cue- or heroin prime-induced reinstatement of heroin seeking (Shen et al. 2011). These data are consistent with diminished function of GLT-1 after extinction from heroin self-administration (Shen et al. 2014b). Further, disrupted forms of synaptic plasticity involving downregulated GLT-1 after drug use and/or withdrawal may conceivably impair mechanisms required for extinction learning, which is somewhat impaired in drug-trained compared with sucrose-trained animals (Martin-Fardon and Weiss 2017). Notably, operant sucrose training does not produce downregulation of GLT-1 (Kruyer and Kalivas 2020a), which may account for these behavioral differences.

A significant body of work has established that compounds that restore GLT-1 expression reduce drug craving and relapse, both in animal models and in human clinical trials (Roberts-Wolfe and Kalivas 2015). For example, the antioxidant N-acetylcysteine, the ß-lactam antibiotic ceftriaxone, and the xanthine derivative propentofylline have all demonstrated promise in restoring GLT-1 expression after drug withdrawal and in blunting reinstated drug seeking in preclinical models (summarized in (Scofield et al. 2016a)). N-acetylcysteine is extremely safe for use in humans but has proven only marginally efficacious in reducing craving and drug use in patients (summarized in (Roberts-Wolfe and Kalivas 2015)), potentially due to limited bioavailability. Given that recent studies indicate that GLT-1 upregulation alone is not sufficient to blunt reinstated cocaine seeking (Logan et al. 2018), it may very well be that additional manipulations are required to adequately suppress relapse vulnerability. Moreover, it may be the case that upregulation rather than homeostatic restoration of GLT-1 expression may not entirely restore mechanisms of synaptic plasticity, as both GLT-1 blockade and overexpression do not properly permit spike timing-dependent plasticity at striatal synapses (Valtcheva and Venance 2016).

Although drug-induced changes in GLT-1 expression after chronic use of addictive drugs have been less well documented in the midbrain when compared to the ventral striatum, astroglial glutamate transporters in the VTA also play an important role in modulating avoidance behaviors (Gomez et al. 2019). As mentioned above, the VTA sends dopaminergic, glutamatergic, as well as GABAergic projections to the nucleus accumbens, and these projections encode the reinforcing and aversive aspects of drug use (Morales and Margolis 2017). Additionally, GABAergic interneurons within the VTA regulate dopaminergic projection neurons that signal

avoidance vs. motivated approach behaviors (McCullough et al. 1993; Tan et al. 2012). This was demonstrated with optogenetic stimulation of VTA astrocytes, which permits excitation of GABAergic interneurons that inhibit dopaminergic projections and promote avoidance behavior (Gomez et al. 2019). It was subsequently shown that astrocyte-dependent facilitation of GABAergic activation depends on GLT-1, as conditional knockout of GLT-1 in VTA astrocytes impairs the optogenetic stimulation-mediated GABAergic excitation (Gomez et al. 2019). While the authors do not clarify the mechanism by which GLT-1 contributes to GABAergic excitation, they illustrate that manipulation of astroglial GLT-1 interferes with conditioned place avoidance, but does not impact conditioned place preference (Gomez et al. 2019), suggesting divergence of these circuits and a contribution of astrocytes through GLT-1 to avoidance, but not approach behavior (Gomez et al. 2019). Although changes in GLT-1 expression have not been as clearly demonstrated in the VTA after drug use and withdrawal compared with the NAcore (Knackstedt et al. 2009), analysis of GLT-1 function may be warranted given these surprising findings. These data also highlight the importance of analyzing transporter function in a pathway-specific manner, rather than in whole tissue, since functional changes that impact discrete subcircuits may not be discernable when protein levels are assessed in tissue extracts.

GABA

While uptake of glutamate release from cortical terminals in the striatum is thought to directly regulate relapse-like behaviors in animal models (Kalivas 2008), cortical stimulation triggers uptake of both GABA and glutamate by striatal astrocytes and clearance of both transmitters contributes to postsynaptic excitation of MSNs (Goubard et al. 2011). These findings illustrate the relevance of local GABAergic signaling on corticostriatal synaptic transmission and the contribution of transporter uptake in regulating striatal outputs. In support of this concept, studies where Ca^{2+} signaling in astrocytes is inhibited in vivo through viral delivery of a genetically encoded plasma membrane Ca^{2+} pump that expels cytosolic Ca^{2+} from astrocytes (CalEx) (Yu et al. 2018) demonstrate the behavioral involvement of GABA transporters expressed on striatal astrocytes in compulsive-like behaviors. Importantly, the CalEx vector reduces astroglial intracellular Ca^{2+} levels at baseline and also reduces the amplitude and duration of Ca^{2+} elevations. When delivered to astroglia in the dorsolateral striatum, CalEx expression results in upregulation of the largely astroglial GABA transporter GAT-3 and produces excessive self-grooming behavior, reminiscent of features of obsessive-compulsive disorder (Yu et al. 2018). Further, GAT-3 upregulation reduces tonic inhibition, a known role for GAT-3 that is expressed most densely in extrasynaptic zones (Melone et al. 2015), selectively at D1 receptor expressing MSNs (D1-MSNs) (Yu et al. 2018). Interestingly, when a different strategy was used to upregulate astroglial GAT-3 in a pathway-nonspecific manner, the authors found no impact on grooming behavior, suggesting that perhaps

the cell selectivity of the effects were necessary for the disrupted behavior observed by the authors.

The dorsal striatum is involved in habit learning (Yin et al. 2004) and is uniquely recruited in cases of substance use disorder characterized by compulsive seeking. For example, in humans who drink socially, but not compulsively, alcohol-associated cues stimulate activation of the ventral striatum. Instead, the same cues stimulate activation of the dorsal rather than the ventral striatum in heavy drinkers, and ventral striatal activity in response to alcohol-associated cues is negatively associated with measures of compulsive craving in these individuals (Vollstadt-Klein et al. 2010). Interestingly, compounds effective in suppressing compulsive behaviors, like N-acetylcysteine, which reduces symptoms of trichotillomania (Farhat et al. 2020) and pathological gambling (Grant et al. 2007), also reduce reinstated drug seeking in animal models (Kalivas and Kalivas 2016). As mentioned above, N-acetylcysteine was most studied in the context of addiction for its ability to upregulate GLT-1 in the ventral striatum, but its impact on astroglial expression of GABA transporters like GAT-3 in the ventral or dorsal striatum has not been assessed.

Dopamine

Although there is in vitro evidence that astrocytes can recover extracellular dopamine through expression of the dopamine transporter (DAT), norepinephrine transporter (NET), and/or plasma membrane monoamine transporter (PMAT) (Pelton 2nd et al. 1981; Takeda et al. 2002; Naganuma et al. 2014), evidence is less clear-cut in vivo. The organic cation transporter 3 (OCT3), a low-affinity monoamine transporter, has been reported on neurons and astroglia in the rodent substantia nigra and striatum (Cui et al. 2009), and electron microscopy studies revealed OCT3 on the plasma membrane of perisynaptic astroglial processes in the rodent amygdala, consistent with its role in monoamine uptake near synaptic sites (Gasser et al. 2017). OCT3 was recently found to function in reverse in the presence of amphetamine, releasing dopamine into the extracellular space (Mayer et al. 2018). The authors also confirmed that while OCT3 was expressed by dopaminergic neurons, the majority of OCT3-expressing cells were likely glia as well as non-dopaminergic neurons (Mayer et al. 2018). Importantly, while astroglia express OCT3 and therefore may also theoretically employ this mechanism, releasing dopamine in the presence of amphetamine, amphetamine enters into dopaminergic neurons through DAT and not through OCT3 (Mayer et al. 2018). Thus, in the absence of a mechanism for amphetamine uptake by astroglia, astroglial OCT3 is not likely to be involved in this process. Because studies on the contribution of OCT3 to dopamine transport in the striatum and elsewhere have emerged relatively recently (Holleran et al. 2020), there are no studies investigating changes in OCT3 expression in astrocytes following drug use and withdrawal in brain regions that contribute to addiction-related behaviors, though it remains a fundamental research question.

Gliotransmission

Glutamate

Gliotransmission by astrocytes is most often described as involving intracellular Ca^{2+} flux and vesicular exocytosis of transmitters, which signal to nearby neurons (Parpura et al. 1994; Araque et al. 2014; Papouin et al. 2017; Scofield 2018). Though electron microscopy and expression studies support the existence of vesicular release machinery in astrocytes, the relevance of this modality for gliotransmission has been contested by studies indicating a lack of glutamate receptor expression in astrocytes in the adult brain in vivo (Sun et al. 2013) as well as studies where deletion of key mediators of intracellular Ca^{2+} flux in astrocytes had little impact on neuronal function (Petravicz et al. 2014; Bazargani and Attwell 2016). Despite this, there are a number of well-established mechanisms by which astroglia signal to neurons through non-exocytotic mechanisms and without associated changes in intracellular Ca^{2+} (Agulhon et al. 2010; Gomez-Gonzalo et al. 2018). Here we will discuss evidence for exocytotic and non-exocytotic mechanisms of transmitter release given the important role for excitatory signaling in formation of drug-cue associations and in reinstatement of drug seeking.

Perhaps the least controversial mechanism for glutamate transmission by astroglia is through the cystine-glutamate antiporter, system xc-, which contributes to 60% of extracellular glutamate in the NAcore in drug-naïve animals (Baker et al. 2002). Extracellular glutamate derived from system xc- tonically stimulates presynaptic autoinhibitory mGluRs on glutamatergic and dopaminergic terminals, regulating transmitter release during neural firing (Baker et al. 2002). System xc-, which is expressed to the greatest extent by astroglia (Pow 2001; Sagara et al. 1993), is downregulated after chronic intake of psychostimulants in the NAcore, and this downregulation is thought to disrupt autoinhibitory tone at presynaptic mGluR2/3 on glutamatergic terminals, leading to enhanced glutamate release in response to drug-associated cues (Baker et al. 2002). It should be noted that system xc- is not similarly downregulated after chronic intake of opioids (Shen et al. 2014b), so this molecular adaptation may not generalize across all substances of abuse. However, the treatments described above that have been tested preclinically for their ability to attenuate reinstated seeking through restoration of GLT-1, including N-acetylcysteine and ceftriaxone, also increase expression of system xc- (Knackstedt et al. 2010), and N-aceytylcysteine may even increase extracellular cystine levels, promoting cystine-glutamate exchange. The contribution of GLT-1 and system xc- upregulation to relapse suppression has been tested by pairing these pharmacological treatments with morpholino knockdown of either GLT-1 or xCT, a subunit of system xc-, in the NAcore prior to reinstatement. In these studies, the authors found that GLT-1, not xCT, had the greatest impact on reinstated drug seeking (Reissner et al. 2015).

Studies exploring the involvement of exocytotic transmitter release by astrocytes in addiction-related behaviors has made use of transgenic mice that express a dominant negative SNARE protein (dnSNARE) in astroglia. These mice lose the

capacity to exocytose transmitter-containing vesicles through SNARE mechanisms in astroglia but retain normal mechanisms for neuronal exocytosis (Pascual et al. 2005). dnSNARE mice exhibit similar operant responding for food compared to wild-type animals but appear to take less cocaine during self-administration, despite similar rates of operant acquisition (Turner et al. 2013). dnSNARE mice also reinstate less robustly to cocaine-paired cues (Turner et al. 2013). Whether this reinstatement deficit derives in part from changes in cocaine intake is an important question, since dnSNARE animals appear to receive fewer cocaine infusions and consequently fewer cocaine-cue pairings during training. However, reinstatement of conditioned place preference (CPP) is also abolished in these mice, supporting a role for vesicular gliotransmission in reinstatement behaviors after exposure to psychostimulants (Turner et al. 2013). One limitation of these studies is that global dnSNARE expression in astroglia does not provide information regarding which brain region(s) orchestrate gliotransmission-dependent modulation of reinstatement. Interestingly, it was found that chemogenetic stimulation of Gq signaling in NAcore astrocytes, a manipulation that engages flux of internal Ca^{2+} and activates SNARE-dependent vesicular release of glutamate, reduces reinstated cocaine seeking initiated by cocaine-associated cues (Scofield et al. 2015). Similarly, astroglial Gq stimulation reduces methamphetamine (Siemsen et al. 2019) and ethanol seeking (Bull et al. 2014). It was demonstrated that the suppression of cocaine seeking using this technique was a consequence of astroglial-glutamate release that stimulated presynaptic mGluR2/3 and ultimately reduced transmitter release from presynaptic terminals (Scofield et al. 2015).

In another study, engaging Gq signaling in cultured astrocytes evoked non-vesicular glutamate release through the glutamate-permeable anion channel Bestrophin 1 (Best1) (Woo et al. 2012). Importantly, Best1 is situated near synapses in vivo and would be expected to raise extracellular glutamate levels less robustly than vesicular release. Consequently, release of glutamate through this modality is more likely to impact high-affinity NMDA receptors, compared with vesicular release which might also engage lower-affinity receptors. Accordingly, it might be expected that separate modalities of glutamate release from astrocytes engage functionally distinct intracellular signaling cascades in nearby neurons, despite both modalities being linked to Gq-coupled receptor activation. Together, the findings described above lead to important questions regarding how these cellular mechanisms are employed within the reward circuitry of drug-naïve animals and how their deployment may be impacted by chronic intake of and withdrawal from addictive substances.

One valid critique of studies where either optogenetic or chemogenetic manipulation of astrocytes is employed to understand astroglial biology is that the abundance of the exogenously expressed proteins, as well as their proximity to synapses, may not reflect normal physiological features of astroglia. Nonetheless, studies in the dorsal striatum and elsewhere clearly illustrate that astrocytes signal to local MSNs using endogenous mechanisms of glutamate release. Dorsal striatal astrocytes are uniquely tuned to respond functionally to electrical stimulation of D1- or D2-MSN subtypes in response to neuronally released endocannabinoids (eCBs), with Ca^{2+} flux and ultimately glutamate release (Martin et al. 2015). Astrocyte glutamate release produces slow inward currents (SICs) in adjacent neurons of the

same subtype as the stimulated neuron, presumably through stimulation of extra-synaptic NMDA receptors (D'Ascenzo et al. 2007), but SICs are rare in heterotypic pairs. These findings are particularly relevant given that stimulation of striatal D1-MSN projections or inhibition of D2-MSN projections trigger reinstated seeking (Heinsbroek et al. 2017; Pardo-Garcia et al. 2019). There is not yet definitive evidence for how astrocytes distinguish between neural subcircuits. It is abundantly clear that striatal astrocytes encompass both D1- and D2-MSN somata within their cellular territories (Octeau et al. 2018), so spatial segregation does not seem a likely possibility. Further, studies using dye-filling strategies illustrate that astrocytes are extensively coupled to one another through gap junctions (Octeau et al. 2018), forming large densely interconnected syncytia. Thus, it does not appear that segregated astrocyte subpopulations are joined into networks through gap junctions, at least not in drug-naïve animals (but see "Homeostatic Functions" for a discussion of drug-induced changes in astrocyte gap junctions). Still, there are a number of hypothetical ways that astrocytes might coordinate signaling within, but not between circuits, when the same receptors and transmitters are employed in both pathways. One possibility is that additional signaling molecules accompany transmitter release and astrocytes selectively express receptors for molecules released by one or the other pathway. As an example, in the ventral pallidum, D1- and D2-MSN terminals co-release unique neuropeptides, with D1-MSNs co-releasing substance P and dynorphin and D2-MSNs co-releasing enkephalin and neurotensin (Kupchik et al. 2014). The same could occur postsynaptically, with the release of different eCBs following postsynaptic excitation of either D1- or D2-MSNs or unique expression patterns of cannabinoid receptors on astroglial subtypes. Whether release of unique pre- or postsynaptic signaling molecules selectively recruits astrocytes to signal to adjacent MSNs in a homotypic manner remains to be shown. Another possibility is that astrocytes are selective in their synaptic proximity, with each astrocyte exhibiting unique proximity to D1- or D2-MSNs in order to receive and transmit signals selectively. While it does not appear that D1 or D2-MSN-containing synapses receive different degrees of astrocyte insulation overall, there is tremendous variability in synaptic insulation by astroglia in the striatum (Octeau et al. 2018; Chai et al. 2017). Thus, it remains possible that each astrocyte may exhibit some selectivity in which synapses it approaches most closely. This concept will be discussed in more depth in the subsequent section on astrocyte morphological plasticity.

D-Serine

D-serine is the R-enantiomer of the amino acid serine and functions as an NMDA receptor co-agonist, with selective affinity for the glycine binding site (Mothet et al. 2000; MacKay et al. 2019). D-serine has been studied for its improvement of positive and cognitive symptoms in schizophrenia patients when co-administered with antipsychotics (Tsai et al. 1998), based on evidence of hypofunctional NMDA receptor activity in the disorder (Coyle 2012). Whether D-serine is released by astrocytes has been a somewhat controversial topic since serine racemase, the

enzyme that converts L-serine to D-serine in cells, is mostly expressed by neurons (Yoshikawa et al. 2007; Benneyworth et al. 2012). It appears that instead, D-serine is produced by serine racemase in neurons and is shuttled between neurons and astroglia for vesicular release (Wolosker 2011; Martineau et al. 2013). Regardless of its cellular origin, D-serine has been shown to play an important role in signaling via NMDA receptors in the accumbens. D-serine is required for NMDA-dependent synaptic potentiation and depression in the NAcore (Curcio et al. 2013), both of which are disrupted after withdrawal from cocaine self-administration (Moussawi et al. 2009). Linking these findings, researchers found that cocaine reduces D-serine concentration in the NAcore through increased expression of D-amino acid oxidase, an enzyme that degrades D-serine (Curcio et al. 2013; D'Ascenzo et al. 2014). The reduction in D-serine levels increases the relative proportion of AMPA/NMDA receptors in neurons postsynaptically and permits locomotor sensitization and CPP (Curcio et al. 2013; D'Ascenzo et al. 2014; Yang et al. 2013). Subsequent studies found that morphine also decreases D-serine in the nucleus accumbens and does so by reducing surface expression of AMPA receptors on astrocytes that normally trigger Ca^{2+} flux and vesicular D-serine release (Wu et al. 2017). Despite these promising findings, additional experimentation is required to determine the precise role of D-serine gliotransmission in mediating addiction-relevant synaptic plasticity.

ATP

Astrocyte-derived adenosine has been shown to contribute to synaptic modulation in various brain regions and in response to synaptically released glutamate as well as dopamine (Pascual et al. 2005; Zhang et al. 2003; Quon et al. 2018; Corkrum et al. 2020). In the dorsolateral striatum, high-frequency stimulation of cortical terminals stimulates astroglial mGluR5, a Gq-coupled receptor, to produce Ca^{2+} increases, ATP release, and adenosine receptor-mediated long-term depression of postsynaptic cells (Cavaccini et al. 2020). In a similar study in the dorsomedial striatum, the authors show that astroglial expression of the adenosine transporter equilibrative nucleoside transporter 1, ENT1 is required for astroglial Gq stimulation to impact neural activity. Interestingly, triggering this signaling cascade alters firing properties of both D1- and D2-MSNs, reducing spontaneous EPSCs in D1- and increasing them in D2-MSNs, promoting goal-directed rather than habitual behaviors (Kang et al. 2020).

Altogether, Gq-dependent signaling in striatal astrocytes has been linked to vesicular glutamate release (Scofield et al. 2015), slow and low-volume glutamate transmission through Best1 (Woo et al. 2012), and adenosine transport through ENT1 (Kang et al. 2020), and activation of astroglial mGluR5, a Gq-coupled receptor, is linked to astrocyte release of ATP (Cavaccini et al. 2020). Perhaps it is not problematic that such a diverse range of outcomes can be recruited using the same tools or by engaging the same signaling cascade in astroglia. In most cases, it cannot be ruled out that multiple forms of gliotransmission occur following Gq receptor stimulation, as exhaustive tests are often not feasible. Also, gliotransmission in vivo

would be expected to be more refined, since local neural signals would be detected by receptors on astrocyte processes to tune local responses. Indeed, it has been demonstrated previously that the same astrocyte is capable of signaling in distinct ways using different gliotransmitters depending on the dynamics of incoming signals (Covelo and Araque 2018), supporting the tremendous plasticity of this cell type.

Synaptic Proximity

Morphological Plasticity of Astrocytes

A central aspect underlying efficacy of transporter uptake and gliotransmission is the physical proximity of astroglial processes with synapses (see Fig. 1). The fidelity of this spatial relationship is crucial for normal neurobiology since perisynaptic astroglial processes (PAPs) express machinery for uptake and release of transmitters and maintenance of homeostatic neuronal function. Interestingly, PAPs display morphological plasticity more dynamic than what is observed in dendritic spines (Haber et al. 2006), and astrocyte morphological plasticity has been reported in the presence of extracellular glutamate (Genoud et al. 2006; Bernardinelli et al. 2014a; Verbich et al. 2012; Perez-Alvarez et al. 2014) and dopamine (Galloway et al. 2018). In the hippocampus, astroglial processes exhibit enhanced physical interaction with
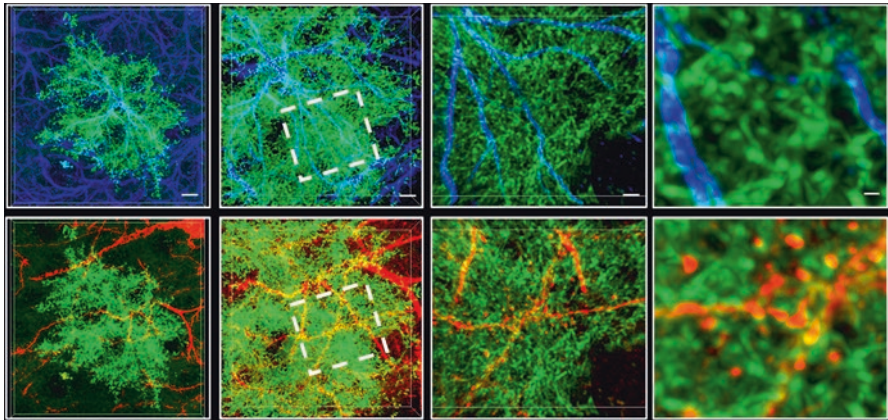
Fig. 1 Super-resolution confocal imaging of an astroglial plasma membrane, GFAP arbor and neighboring dendritic segment on an NAcore-projecting PL neuron. *Top*, plasma membrane labeling of an astrocyte in the PL using the AAV-GFAP-LcK-GFP viral vector from the Khakh laboratory (green) (Shigetomi et al. 2013). Immunohistochemical labeling of the cytoskeletal protein GFAP is shown in blue. *Bottom*, association of the astrocyte plasma membrane (green) with a retrogradely labeled dendritic segment from a neighboring PL neuron that projects to the NAcore (red). Here the neuron was labeled with retrograde delivery of Cre in the NAcore combined with Cre-dependent AAV-DIO-mCherry expression in the PL. For both the top and bottom series, panels transition to higher magnification to show detail from left to right. The dashed box depicts the inset region, scale bars are 10, 5, 2 and 0.5 microns

the postsynaptic compared with the presynaptic compartment (Lehre and Rusakov 2002). Further, astroglial interaction with neurons in this region tends to be biased toward dendritic spines as opposed to the larger dendritic shaft (Gavrilov et al. 2018). The general consensus regarding this conformation is that PAPs are positioned to perform glutamate transport upon transmitter release while also permitting a degree of transmitter spillover presynaptically, allowing for stimulation of presynaptic autoreceptors as a negative feedback loop that maintains elegant regulation of transmitter release probability.

In the striatum, there is a tremendous degree of variability in synaptic insulation by astroglial processes, perhaps due to the different input types (dopaminergic vs. glutamatergic), with astrocytes more closely abutting glutamatergic vs. dopaminergic terminals (Octeau et al. 2018). Regarding postsynaptic selectivity, high-resolution techniques have been applied to astrocytes and different synapse types in the striatum to demonstrate that astrocytes encompass similar numbers of D1- and D2-MSNs, with a slight bias toward D1-MSNs (Octeau et al. 2018). Nevertheless, both neuronal types receive similar degrees of synaptic insulation by astrocytes (Octeau et al. 2018).

Impact of Synaptic Insulation on Synapse Function

Synaptic proximity of astrocyte processes promotes synapse stability and maturation (Bernardinelli et al. 2014b; Nishida and Okabe 2007; Blanco-Suarez et al. 2018), and it is taken for granted that transmitter uptake and release by astrocytes requires a high degree of synaptic proximity to effectively regulate synaptic physiology. Not only would loss of synaptic apposition impact efficacy of these functions, but synaptic retraction of astrocyte processes has been shown to favor synaptic recruitment at excitatory synapses, with transmitter spillover potentiating nearby synapses when astrocyte processes have retracted (Henneberger et al. 2020). Retraction of astroglial processes may also permit stimulation of extrasynaptic glutamate receptors (Pal 2018; Kruyer and Kalivas 2020b) and impact neuronal excitability and plasticity. Extrasynaptic mGluRs pertinent to excitatory signaling underlying relapse include the aforementioned presynaptic mGluR2/3 that serves as a brake on glutamate and dopamine release (Xi et al. 2002) and mGluR5 expressed on nNOS interneurons that initiate degradation of the extracellular matrix and facilitate postsynaptic potentiation (Smith et al. 2017; Kruyer et al. 2019a).

Glutamate spillover permitted by retraction of astrocyte processes also recruits high-affinity NMDA receptors, which play an important role during drug relapse. The GluN2b (NR2b or NMDAR2b) subunit is largely extrasynaptic, as opposed to the mostly synaptic GluN2a (D'Ascenzo et al. 2007). Stimulation of GluN2b-containing NMDA receptors contributes to postsynaptic potentiation during reinstated heroin seeking, and GluN2b knockdown or blockade prevents increases in AMPA/NMDA and spine head diameter induced by a priming heroin injection and reduces reinstated seeking induced by cues or heroin prime (Shen et al. 2011).

Drug-Induced Morphological Plasticity

Astrocytes exhibit profound morphological adaptations after exposure to substances of abuse. For example, astrocyte volume is reduced in the NAcore by exposure to both opioids and psychostimulants (Siemsen et al. 2019; Scofield et al. 2016b; Kruyer et al. 2019b). NAcore astrocytes are also more densely packed after alcohol and astrocyte density correlate positively with breakpoint for ethanol, a measure of motivation to acquire alcohol (Bull et al. 2014). Analysis of astrocyte plasticity is complicated given that both immunological and synaptic events can impact their morphology, and substances of abuse can trigger both types of CNS adaptations. For example, chronic cocaine or morphine exposure causes reactive astrogliosis characterized by changes in GFAP expression, a type of neuroinflammation that induces an altered functional and morphological state in astroglia (Beitner-Johnson et al. 1993; Sil et al. 2018; Bowers and Kalivas 2003). Whether changes in astrocyte proximity to synapses is a by-product of an immunoreactive state and whether synaptic functions of astroglia are interrupted by immunological processes is an ongoing question that necessitates further investigation.

Recent studies show that cues that stimulate drug seeking trigger morphological plasticity in NAcore astrocytes in animals trained to self-administer heroin, but not sucrose (Kruyer et al. 2019b). This plasticity appears homeostatic in nature, resulting from cue-induced neuronal activity and glutamate release. Moreover, interrupting the re-association of astroglial processes with synapse during reinstatement elevates responding for cues that signal heroin availability. Changes in synaptic proximity of astrocyte processes in this case are linked to phosphorylation of ezrin, an actin-blinding protein selectively expressed in astroglial processes (Derouiche and Frotscher 2001). Currently, neither the signaling cascade that drives ezrin phosphorylation nor the mechanism by which astrocyte process motility suppresses reinstated seeking has been uncovered. Additionally, whether NAcore D1- or D2-MSN synapses retain different degrees of astrocyte insulation during withdrawal from drug use or during reinstated seeking is a fundamental remaining question.

Homeostatic Functions

Synaptogenesis

Astrocytes play key roles in both synapse formation and elimination. Astrocytes express and release several signaling factors that contribute to formation of dendritic spines and spine density (Walker et al. 2020; Ikeda et al. 2010; Wang et al. 2020a; Chung et al. 2015), a measure that is aberrantly altered in the striatum after drug use and during reinstated drug seeking (Shen et al. 2011; Dos Santos et al. 2017; Anderson and Self 2017). During development, thrombospondins released by astrocytes promote genesis of new synapses that are postsynaptically silent

(Christopherson et al. 2005). In adult animals, thrombospondin expression is elevated in response to cocaine exposure, and astrocyte thrombospondins in the NAshell contribute to generation of silent synapses (Wang et al. 2020b). In both cases, it is expected that presence of silent synapses facilitates induction of functional synapses rapidly upon further signaling that induces postsynaptic insertion of AMPA receptors. Indeed blocking thrombospondin release by astroglia during exposure to cocaine cues blunts cued reinstatement of seeking (Wang et al. 2020b), which is strongly linked to measures of postsynaptic potentiation (Gipson et al. 2013). Astrocytes also participate in synapse elimination, through phagocytosis directly, and through coordinated signaling with microglia (Chung et al. 2013, 2015; Wilton et al. 2019). While astrocytes prune synapses to refine neural circuits during development, there is evidence that astrocytes express the machinery for synapse engulfment into adulthood (Chung et al. 2015), and recruitment of this process during acquisition of drug taking behavior or extinction learning is a possibility.

BDNF, a growth factor expressed and released by both astrocytes and neurons (Zafra et al. 1991; Ohno et al. 2018; Bergami et al. 2008), confers bidirectional effects on addiction-related behaviors (McGinty et al. 2010). For instance, animals that receive BDNF infusions in the VTA 2 h after a cocaine self-administration session exhibit enhanced reinstated seeking after withdrawal (Lu et al. 2004). Instead, BDNF infusion in the PL attenuates reinstated seeking as well as reinstatement-associated increases in accumbens glutamate according to the same timeline (McGinty et al. 2010). Generally BDNF undergoes activity-dependent upregulation and contributes to synapse stability and plasticity (Gomez-Palacio-Schjetnan and Escobar 2013). Interestingly, BDNF also increases astrocyte morphological complexity (Holt et al. 2019). Whether BDNF expression is altered selectively in astrocytes within corticostriatal or other circuitries pertinent to addiction and relapse or whether neuronal BDNF exerts its effects in part through astroglial signaling has not been determined.

Network Homeostasis

The coupling of astroglia through gap junctions provides them with the unique capacity to scale network activity. Although some connexin proteins are expressed at relatively high levels in the nucleus accumbens of naïve animals, connexin protein expression is reduced up to 21 days after cocaine self-administration (Bennett et al. 1999). Consistent with this finding, methamphetamine reduces gap junction coupling when delivered to cultured astroglia directly, indicated by lack of dye transfer to nearby astroglia that are normally extensively coupled (Castellano et al. 2016). The gap junction protein connexin 30 regulates excitatory synaptic strength broadly in the hippocampus by coordinating widespread synaptic insertion leading to efficient glutamate uptake through increased synaptic proximity, but not increased transporter expression (Pannasch et al. 2014). Perhaps relevant to these findings is

the discovery that inhibiting astrocytes in the medial prefrontal cortex impairs cognitive flexibility, involving coordinated neural oscillations through astroglial transmission (Brockett et al. 2018). How this may relate with flexibility in drug-related learned behaviors, such as extinction, is a relevant question given the involvement of corticostriatal glutamate in measures of drug seeking and refraining. Interestingly, blockade of gap junction proteins in astrocytes in the PL prevents extinction and reinstatement of cocaine CPP (Fitzgerald 2016). Research momentum on the involvement of gap junction proteins in addiction-related behaviors is slowly growing, and there is enthusiasm for the concept of lateral regulation by astroglia, where given their coupling, plasticity, and the multitude of mechanisms by which they impact synaptic function, astrocytes are poised to coordinate synapses that are neither directly nor indirectly linked otherwise (Covelo and Araque 2016).

Conclusions

Emerging research highlights the critical contribution of astrocytes to synaptic function, and astroglial adaptations across a number of brain regions have been shown to contribute to the encoding and expression of motivated behaviors relevant to drug addiction. A majority of early literature on astroglial function was generated in vitro and ex vivo, providing information on general astroglial responses to neural activity or pharmacological manipulation. An accumulating body of work links these early findings with in vivo behavioral measures, highlighting new avenues for research and experimentation. Here, we have highlighted research avenues poised to promote future discovery. Generation of new tools, including CalEx and viruses for astroglial labeling and functional manipulation of gene expression, and improved imaging methodologies are facilitating studies of astroglial function in rodent models of drug addiction and relapse. We expect that advances made in the coming years using these tools will drastically expand our understanding of ways in which astrocytes impact synaptic physiology during normal motivated behavior and in psychiatric disorders such as drug addiction.

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