

The Role of Glial Cells in Drug Abuse

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Abstract: Neuronal dysfunction in the prefrontal cortex, limbic structures, nucleus accumbens and ventral tegmental area is considered to underlie the general physiopathological mechanisms for substance use disorders. Glutamatergic, dopaminergic and opioidergic neuronal mechanisms in those brain areas have been targeted in the development of pharmacotherapies for drug abuse and dependence. However, despite the pivotal role of neurons in the mechanisms of addiction, these cells are not the only cell type in charge of sustaining and regulating neurotransmission. Glial cells, particularly astrocytes, play essential roles in the regulation of glutamatergic neurotransmission, neurotransmitter metabolism, and supply of energy substrates for synaptic transmission. In addition, astrocytes are markedly affected by exposure to ethanol and other substances of abuse. These features of astrocytes suggest that alterations in the function of astrocytes and other glial cells in reward circuits may contribute to drug addiction. Recent research has shown that the control of glutamate uptake and the release of neurotrophic factors by astrocytes influences behaviors of addiction and may play modulatory roles in psychostimulant, opiate, and alcohol abuse. Less is known about the contributions of microglia and oligodendrocytes to drug abuse, although, given the ability of these cells to produce growth factors and cytokines in response to alterations in synaptic transmission, further research should better define their role in drug addiction. The available knowledge on the involvement of glial cells in addictive behaviors suggests that regulation of glutamate transport and neurotrophins may constitute new avenues for the treatment of drug addiction.

Keywords: Addiction, glia, astrocytes, oligodendrocytes, microglia, alcoholism, opiates, psychostimulants.

INTRODUCTION

Drug addiction represents one of the major medical, social and economic burdens of human behavior. Neurons and the circuits they form are the foundation for sensory, motor and behavioral integration, and for all the intermediary processes of emotion, cognition and endocrine control. Thus, alterations in neuronal structure, biochemistry and function have been considered the bases for the initiation and maintenance of drug addiction. Consequently, an overwhelming proportion of the research on the molecular and cellular basis of addiction has concentrated on the effects of drugs on neurons in brain regions that process behavioral and motor functions affected by substances of abuse. Likewise, pharmacological therapies directed to thwart drug addiction or reduce its negative consequences have been directed to molecular pathways in neurons that are known to be affected by drug intake. This neuron-oriented research has been very successful in providing a plethora of knowledge on the neuronal molecular pathways and brain circuits that are altered in drug addiction and on how neuronal alterations determine specific aberrant behaviors. However, despite the pivotal role of neurons in the mechanisms of addiction, these cells are not the only nervous system component in charge of sustaining and regulating neurotransmission. Glial cells, particularly astrocytes and oligodendrocytes, have been shown to play essential roles in the regulation of glutamatergic and GABAergic neurotransmission, conduction of nerve impulses, neurotransmitter metabolism and supply of energy metabolites for

synaptic function. Furthermore glial cells are also markedly affected by exposure to substances of abuse. These features of glial cells suggest that alterations in the morphology and physiology of glial cells in brain areas critical for the manifestation of addictive behaviors, such as the prefrontal cortex, nucleus accumbens (NAcc), ventral tegmental area (VTA), amygdala or hippocampus may contribute to the vulnerability to initiate and persist in drug addiction. Certainly, drug intake, particularly at high doses, is in many instances toxic to neurons and glial cells, and a rich scientific literature addresses the neurotoxicity of substances of abuse. The present review will not focus on the toxic effects of drugs on glial cells. This article will rather review studies of cellular and molecular features of glial cells, and associated drug-induced glial changes that contribute to the vulnerability to and the persistence in drug addiction. It will also consider gliotoxic effects of substance of abuse, but solely as they are thought to increase or regulate behaviors of addiction.

ASTROCYTES

Astrocytes are the most abundant glial cell type in the central nervous system [1]. Like other glial cell types, astrocytes were once thought to play only a secondary, non-regulatory and permissive role in nervous function. However, in recent decades, diverse research lines have demonstrated that astrocytes are critical to the control of neurotransmission, impulse conduction, development and formation of synaptic connections, and energy supply for neuronal activity [2-4]. This multifaceted involvement of astrocytes implies that they are capable of detecting changes in molecules that are released from neurons during transmission or nerve impulse conduction, and that they respond to those molecular changes by regulating the extracellular medium or releasing factors that alter the activity of their neuronal and

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glial neighbors. For example, the cell membranes of astrocytes bear receptors for most neurotransmitters and peptides: glutamate, dopamine, norepinephrine, serotonin, gamma-aminobutyric acid, acetylcholine and opioid peptides [5]. They also bear in their plasma membranes neurotransmitter [6-8] and glucose [9] transporters, and aquaporin-4 channels for water transport [10, 11]. It is not surprising then that many drugs can affect astrocytic physiology not only directly but also through alterations in the release of neurochemicals from surrounding neurons. In addition, recent research has demonstrated that astrocytes release several molecules that fulfill many of the criteria for a transmitter (including glutamate, ATP, D-serine, adenosine, eicosanoids, cytokines) and are capable of modulating the activity of neurons and other glial cells [3].

Administration of cocaine, amphetamines and most psychostimulants induces activation of astrocytes [12-14]. This activation is defined by an increase in the expression of glial fibrillary acidic protein (GFAP), a main component of the cytoskeleton of astrocytes. GFAP is known to be upregulated in response to brain injury and neurotoxicity [15, 16], although changes in GFAP expression are not limited to overt brain injury and many other plastic changes in the neuropil also result in increased GFAP expression [17-19]. For instance, treatment with methamphetamine (METH, "speed") results in loss of dopaminergic terminals without detectable loss of neurons [20], but induces astrogliosis with increased GFAP in the striatum, hippocampus and frontal cortex [21]. Methylenedioxymethamphetamine (MDMA, "ecstasy") is an exception among stimulants because, unlike most of them, its administration in animals models does not result in increased GFAP expression or microglial activation even if it causes transient loss in dopaminergic and serotonergic terminals [21, 22].

Another possible contribution of astrocyte function to the effects of psychostimulants might be mediated through water channels composed of the protein aquaporin-4. Aquaporin-4 is mostly localized to the plasma membranes of the astrocytic endfeet that wrap blood vessels, and aquaporin-4 channels are considered a main route for water regulation in the brain and for regulating levels of amino acids and monoamines in some brain regions [23]. In aquaporin-4 knockout mice, locomotor activity caused by either single or repeated administration of cocaine has been reported to be significantly diminished together with reduction of dopamine and glutamate levels in the NAcc [24].

Recent research on the role of astrocytes in directly regulating addiction to stimulants has used medium collected from cultured astrocytes to determine whether there are soluble factors released by astrocytes that, when applied *in vivo* to the NAcc, alter the rewarding effects of METH and morphine. These studies showed that the astrocyte conditioned medium infused into the NAcc was sufficient to enhance the appearance of rewarding effects by METH and morphine [25, 26]. It is also of interest that the Jak/STAT pathway, which modulates astroglial numbers and astroglioneogenesis [27], mediates those behavioral effects. The same studies show that METH and morphine treatment lead to locomotor sensitization. The sensitization was attenuated after two-month withdrawal for morphine, although not for METH. Persistent sensitization to METH was accompanied

by long-term activation of striatal astrocytes through a PKC-dependent mechanism and reversible behavioral sensitization to morphine was paralleled by a reversible activation of astrocytes [26, 28].

Chronic treatment with morphine also results in increased GFAP expression or enlarged astrocytes in VTA, NAcc, frontal cortex, locus coeruleus and nucleus of the solitary tract of the rat [29-33]. The morphine-induced increases in GFAP expression and the astroglial activation are probably mediated by $\alpha 2$ -adrenoceptors since the antagonist yohimbine inhibits upregulation of $\alpha 2$ -adrenoceptors and prevents the increase in GFAP expression caused by chronic morphine treatment [32, 33]. The responsiveness of astrocytes of morphine administration lead to the proposal by Rönnbäck and Hansson (1988) [34, 35] that astrocytes might contribute to morphine tolerance, and more recent evidence supports that hypothesis [36]. For instance, inactivation of astrocytes by the gliotoxin fluorocitrate attenuates both tolerance to morphine analgesia and morphine-induced increase in GFAP immunostaining [31]. Tolerance to morphine has been also related to downregulation of glial glutamate transporters GLT-1 and GLAST in the spinal cord [37] suggesting a link between structural and functional features of astrocytes involved in tolerance to morphine.

In rats chronically exposed to alcohol, astrocytes increase the expression of GFAP in the first few weeks while longer exposure result in decrease in the expression of GFAP [38], and at those long exposures the numbers of perineuronal glial cells are diminished [39]. *In vitro*, most available evidence has shown that numbers of glial cells are reduced by exposure to ethanol at relevant concentrations [40-44]. As for humans, the possibility that in subjects with chronic alcohol dependence there is a reduction in the packing density of glial cells and astrocytes was explored in our laboratory. We found that in average the density of glial cells is significantly lower in the dorsolateral and orbitofrontal cortex of uncomplicated (absence of Wernicke's encephalopathy and Korsakoff syndrome) alcoholics as compared to controls [45, 46]. Only in relatively older subjects or subjects with the longest duration of alcoholism the levels of GFAP expression and the numbers of glial cells are again as high as in control subjects of the same age. This late relative increase in glial cells might be related to increased damage to neurons, because in the orbitofrontal cortex there is a significant correlation between the loss of neurons and the duration of alcohol dependence [45]. Since relatively young chronic alcoholics in our studies had the lowest glial cell densities there is the possibility that lower numbers of astrocytes are a condition predating the manifestations of alcoholism or that they are involved in increasing the vulnerability to it. An involvement of GFAP-immunoreactive astrocytes in modulating the vulnerability for alcoholism is underscored by our findings that the density of GFAP-IR astrocytes in the PFC is lower in alcohol-preferring rats than in the same regions of Wistar rats or alcohol non-preferring rats [47, 48] and that, in Wistar rats, application of gliotoxins known to preferentially damage astrocytes into the prefrontal cortex results in a transient increase of ethanol preference [49]. In addition, ethanol administration prevents increases in GFAP mRNA associated with moderate traumatic brain injury to the frontal cortex [50] and also reduces levels of GFAP mRNA and protein and hypermethylates GFAP DNA [51].

There are no similar reports of localized glial cell densities and in situ expression of GFAP for the brain of addicts to substances of abuse other than alcohol, so it is difficult to determine if there might be two phases in the responses of glial cells to prolonged drug abuse as it seems to be the case for alcohol. However, available data of functional neuroimaging studies by proton magnetic resonance spectroscopy (MRS) in METH addicts describe an increase in the levels of myo-inositol (which is produced by glial cells and is a measure of glial cell activity) in subjects using METH or MDMA [52]. These increases in myo-inositol (MI) are parallel to decreases in the marker of neuronal integrity N-acetylaspartate [53, 54]. However, there are no descriptions of reduced MI in psychostimulant abusers. These data are consistent with studies done in experimental animals indicating that activation of GFAP by psychostimulants (with the exception of MDMA) and opiates is markedly persistent, and depletion of glial cells or reduction of glial markers have not been reported after the longest exposures to those substances. In the brain of alcoholics however, increases in MI have not been reported in the gray matter, the available studies having found absence of significant change in the frontal cortex [55] or the cerebellum of alcoholics. Myoinositol is not significantly changed after prolonged abstinence, although a study reported elevated MI in frontal gray [56] and white matter [57] of recently (1 month) detoxified alcoholics. Prolonged abstinence appears to result in normalization of MI levels [56]. It is worth mentioning that in rats exposed to 20% ethanol for 8 weeks proton MRS shows a decrease in MI [58], which suggests that in humans examination before withdrawal may have shown MI changes different from those observed after withdrawal and more consistent with lower densities of glial cells found in chronic alcoholics. Interestingly, in major depression patients (which, like alcoholics also have reduced numbers of glial cells in the PFC [59, 60]) there is reduced MI in the prefrontal cortex [61]. At present it is difficult to speculate how altered glial cell responses or numbers in the PFC may contribute to drug or alcohol abuse or what is the relative importance of glial cell abnormalities in each of the relevant brain regions, although the experiments in the NAcc mentioned below clearly point to a specific role of those glial changes in the mechanisms of addiction. Clearly, experiments similar to those in the NAcc [25, 26, 62] (see below) should be performed in other brain areas to determine what direction of glial alterations are related to drug addiction and how the glial changes interact with neuronal alterations to result in the eventual behavioral disturbances.

One of the most important functions of astrocytes in the central nervous system is the reuptake of extracellular glutamate released by neurons during synaptic activity [63]. In fact most of this reuptake is performed by astrocytes through glutamate transporters GLT-1 (EAAT-2) and GLAST (EAAT-1) [64, 65]. The glutamatergic system is heavily involved in learning processes that lead to behaviors of addiction [66, 67] such as those underpinning conditioned place preference (CPP). Accordingly, modulation of glutamate has been targeted to test whether changes in glutamate transport might modulate CPP. In a recent study testing this hypothesis, Nakagawa *et al.* (2005) [68] showed that a glutamate transport activator, MS-153, co-administered with morphine, METH or cocaine, but not when given alone, significantly reduced CPP

for the latter three drugs in mice, without altering their locomotor responses [68]. Also in mice, MS-153 co-administered with morphine attenuated the development of morphine tolerance and physical dependence [69]. Methamphetamine and morphine-induced CPP is also reduced in mice that received adenoviral transfer of the gene for GLT-1 into the NAcc shell [70]. In this model, however, there was no attenuation of morphine withdrawal signs caused by naloxone administration.

Alteration of glutamate transport mediated by astrocytes might be also related to genetically inherited vulnerability to alcoholism. It has been reported that A silent G → A transition at nucleotide 603 in exon 5 of the EAAT2 gene is associated with risk-taking behavior in alcoholics [71, 72]. A gene microarray study in animals with history of alcohol dependence and 3 weeks of abstinence has also shown that among the most significant changes in dependent animals there was an increased expression of EAAT2 transporter mRNA in the cingulate cortex together with increased expression of other mRNAs for proteins involved in glutamatergic neurotransmission [73, 74].

The relevance of the astrocytic modulation of glutamatergic transmission for alcohol addiction is also stressed by the discovery that mice with a mutation of the Period gene ($Per2^{Brdm1}$) show increased alcohol intake [75]. Mice with the $Per2^{Brdm1}$ mutation have diminished expression of the astrocytic glutamate transporter EAAT1 and reduced uptake of extracellular glutamate. The result is higher levels of extracellular glutamate that are associated with increased alcohol intake. Acamprosate, an approved drug shown to reduce craving and relapse in humans very likely by reducing activation of NMDA-type glutamate receptors [76, 77], was capable of reducing glutamate levels and alcohol intake in $Per2^{Brdm1}$ mice [75]. In addition, analysis of the *Per2* gene in humans revealed some single nucleotide polymorphisms that are significantly associated with increases in alcohol intake [75]. A participation of glutamate transport in alcohol addiction is also supported by the work of Melendez *et al.* (2005) [78] with slices from the NAcc, showing that repeated administration (daily for one week) of ethanol to rats caused a decrease of glutamate transport.

The neurotrophic activity of astrocytes may also be relevant to the effects of cocaine in VTA. Glial-derived neurotrophic factor (GDNF) is present in neurons, astrocytes and microglial cells, although it seems to be mainly produced by astrocytes [79, 80]. GDNF supports the survival and differentiation of dopaminergic cells and protects those cells against METH-induced neurotoxicity as shown in wild-type mice [81] and in heterozygous mice with a partial deletion of the GDNF gene [82]. Glial-derived neurotrophic factor, when infused into the VTA reduces the increase in the formation of key proteins induced by cocaine exposure [83]. Furthermore mice lacking expression of GDNF display increase behavioral sensitization to cocaine [84] and treatment of mice with the dipeptide Leu-Ileu an inducer of GDNF (and TNF-alpha, also produced by astrocytes) expression blocked the acquisition of METH-induced place preference and sensitization [85, 86].

Tumor necrosis factor alpha, produced by astrocytes and microglial cells, has been shown recently to prevent METH neurotoxicity and dependence in mice possibly through the enhancement of dopamine uptake in the striatum and the pre-

vention of METH-induced increases in extracellular dopamine [87].

Astrocytes are also a main source of brain derived neurotrophic factor (BDNF) that acts as a survival factor for some neurons and participates actively in synaptic plasticity in the cortex and other subcortical brain centers. Blockage of BDNF activity or inhibition of the BDNF receptor TrkB reduces METH-induced dopamine release and produces dopamine-elicited behavior [88]. Locomotor activity and sensitization following cocaine administration into the NAcc are potentiated by the chronic infusion of BDNF into the NAcc [89]. In addition, in heterozygous BDNF knockout mice there was a reduction of locomotor activity and conditioned place preference caused by cocaine administration [90]. A recent study in the rat has demonstrated that a 4-hour intravenous self-administration of cocaine induces transient expression of BDNF and stimulation of TrkB [62]. Repeated infusion of additional BDNF into the NAcc resulted in persistent increases of cocaine self-administration and infusion of an anti-BDNF antibody diminished cocaine self-administration and relapse. The involvement of NAcc BDNF was demonstrated by using mice with inducible knockout of BDNF in the NAcc. After knocking out the expression of BDNF in neurons of the NAcc cocaine reinforcement was reduced significantly. It remains to be seen whether astrocyte-derived BDNF in the NAcc might also participate in the addictive properties of cocaine.

Unlike GDNF, basic fibroblast growth factor (bFGF, which is also produced by astrocytes), contributes to the development of sensitization to amphetamines [91]. D-amphetamine treatment in rats induces a sustained elevation of bFGF expression in astrocytes of the VTA [92, 93], while antibodies to bFGF applied to the VTA prevent behavioral sensitization to amphetamine exposure [94]. The increase in bFGF is dependent on glutamate acting through NMDA receptors, which stresses that astrocytes are mediators of the interactions between glutamatergic and dopaminergic systems in drug addiction and that changes in astrocytic physiology may result in pathological behavioral sensitization. Confirming an important role of astrocytic bFGF in the effects of psychostimulants are the effects of cocaine administration in rats. In this species, single administration of cocaine results in transient increase in bFGF in the striatum and prefrontal cortex while prolonged exposure (5 or 14 days) produces a persistent increase in bFGF, suggesting that long-term adaptations to drug abuse may involve the expression of bFGF in astrocytes [95]. Other neurotrophic factors enriched in astrocytes, particularly BDNF, have also been found to participate in plastic responses of noradrenergic neurons to intake of opioids and maybe involved in the regulation of withdrawal responses to these substances [96, 97].

MICROGLIA

Microglial cells, unlike astrocytes and oligodendroglia, are not directly involved in the regulation of neurotransmission and impulse conduction. They contain markers of cells of the monocyte/macrophage lineage and expresses many molecules related to inflammatory processes that become activated by neuronal injury or degeneration. However, microglial cells also display receptors to neuropeptides, neurotransmitters and transmitters released by astrocytes [98, 99]. In addition, they

are capable of releasing trophic factors that influence the survival of neurons and are directly involved in functions of repair and debris removal upon brain injury [100]. Microglial cells like other cells of immune system lineage display functional opioid receptors [101, 102]. Overstimulation of these receptors can lead to apoptosis of microglial cells [103].

Methamphetamine administration to rats at doses that induce dependence causes activation of microglial cells in the striatum. Since the activation of microglia follows a course similar to the neurotoxicity caused by METH, it has been suggested that METH neurotoxicity might be at least in part mediated by the METH-activated microglia [104, 105]. Also attenuation of microglial activation mediates tolerance to the neurotoxicity of METH in the striatum [106]. Microglia activity might also be involved in the mediation of the behavioral effects of METH because, in rats, minocycline (an anti-inflammatory known to affect microglia) treatment not only reduced damage to dopaminergic terminals but also significantly attenuated behavioral sensitization caused by repeated administration of METH [107].

Chronic ethanol intake in rats results in the appearance of microglial cells with aberrant morphologies in the hippocampus that clears out after withdrawal from alcohol [108], while during development exposure to ethanol increases the clusters of amoeboid glia in the corpus callosum and microglial cells appear to take into a more differentiated morphology than in alcohol-naïve animals [109]. Whether this sort of changes influences behaviors of alcohol addiction remains to be resolved.

OLIGODENDROCYTES

The effects of drug abuse on the survival and development of oligodendrocytes and the formation and maintenance of myelin have been extensively studied, showing that oligodendrocytes are very sensitive to the exposure to ethanol, even more than astrocytes and neurons, and that the effects of ethanol almost always result in increased likelihood of oligodendrocyte or myelin degeneration [38]. Until recently, there was less information on the effects of other drugs on the oligodendrocytes and the myelin they form. However, recent postmortem gene microarray research is showing that in cocaine abusers one of the most remarkable changes is a marked decrease in the expression of mRNAs for several proteins involved in myelination in the NAcc, which was associated to a reduced number of oligodendrocytes immunoreactive for myelin basic protein [110, 111]. At present there is no information on whether manipulation of oligodendrocyte function in the NAcc or other relevant brain regions can result in modulation of behaviors of addiction. Research on the possibility that oligodendrocyte disturbances influence drug addiction might be important because deficits of myelination in oligodendrocytes caused by loss of erbB signaling are concomitant with increases in dopamine receptors and transporters [112], suggesting a link between the process of myelination and dopaminergic neurotransmission in reward circuits. Oligodendrocytes are also capable of secreting neurotrophic factors in response to surrounding neurons [113].

CONCLUSIONS

Although neurons are the principal players that ultimately integrate and execute behavioral, cognitive and emotional

programs both in the normal and the diseased nervous system, the involvement of glial cells must be taken into account since variations in glial cell numbers or their functions have the potential to affect neuronal physiology. Most of the evidence for a specific role of glial cells in the vulnerability to drug addiction or its maintenance is related to astrocytes because of their multifaceted involvement in several aspects of nervous function. However, as roles for microglia and oligodendrocytes in particular brain locations are better defined, future research should determine if drug addiction might be affected by adaptations in oligodendroglia and microglia.

Besides acknowledging a role for glial cells in the vulnerability to substance abuse, future investigations should also define what aspects of neuronal function are specifically affected by particular glial disturbances and what mechanisms link glial alterations and ensuing neurophysiologic disturbances in drug addiction. Several lines of evidence indicate that the modulation of glutamatergic transmission by astrocytes through their glutamate transporters in prefrontal cortex, striatum and VTA is one of the most important mechanisms that influence behaviors of addiction, and some studies with glutamate transport enhancers even suggest that therapies based on the modulation of glial glutamate transporters may be worth testing. In addition, astroglial, oligodendroglial and microglial cells release growth factors, some of which have been shown to mediate, at least partly, sensitization or tolerance to opiates or psychostimulants, suggesting the possibility of developing anti-addiction therapies based on the regulation of growth factor expression in glial cells.

Key Learning Objectives:

1. Examine the evidence for the contribution of glial cells alterations in relevant brain regions to behavioral features of drug addiction.
2. Identify neuromodulatory systems of glial cells that mediate the influence or glial cell function on behaviors of addiction.
3. Overview the available information on the involvement of each of the three main glial cell types, astrocytes, microglia and oligodendrocytes in the regulation of behaviors of addiction.

Future Research Questions:

1. What are the specific changes in neuronal function caused by glial alterations in drug abusers that contribute to or modify behaviors of addiction?
2. What are the mechanisms by which the glial pathophysiology alters neuronal function in specific brain areas that form the reward circuits?
3. The possible involvement of microglia, oligodendroglia and other intermediate types of glial cells needs to be better characterized to draw a more complete picture of the involvement of glial cells in the vulnerability to drug addiction.
4. Further assess the potential of modulators of glial glutamate transport and neurotrophic activity for the pharmacological treatment of drug addiction.

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