



Review article

A potential role for microglia in stress- and drug-induced plasticity in the nucleus accumbens: A mechanism for stress-induced vulnerability to substance use disorder

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ABSTRACT

Stress is an important risk factor for the development of substance use disorder (SUD). Exposure to both stress and drugs of abuse lead to changes in synaptic plasticity and stress-induced alterations in synaptic plasticity may contribute to later vulnerability to SUD. Recent developmental neuroscience studies have identified microglia as regulators of synaptic plasticity. As both stress and drugs of abuse lead to microglial activation, we propose this as a potential mechanism underlying their ability to change synaptic plasticity. This review focuses on three components of synaptic plasticity: spine density, brain-derived neurotrophic factor (BDNF) and α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor expression. Their roles in addiction, stress, and development will be reviewed, as well as possible mechanisms by which microglia could regulate their function. Potential links between stress, vulnerability to addiction, and microglial activity will be explored.

1. Introduction

Addiction is a major health crisis in the United States. Overdose deaths have doubled in the past decade, with over 64,000 deaths in 2016 (Hedegaard et al., 2017; Kopec et al., 2018). Exposure to stressful life events contributes to vulnerability to substance use disorder (SUD, see Table 1 for acronym definitions) (Breslau et al., 2003; Dembo et al., 1988; Harrison et al., 1997; Widom et al., 1999). A history of trauma is associated with increased drug use in adolescents (Clark et al., 1997; Harrison et al., 1997). Similarly, patients with post-traumatic stress disorder have an increased risk of developing a SUD (Breslau et al., 2003; Snider et al., 2013). Since stress is such an important risk factor for the development of SUD, understanding the biology behind the interaction of stress and drugs of abuse could aid in the development of novel therapeutics.

Lately there has been increased interest in the role of microglia in both substance use and stress (Brown et al., 2018; Crews et al., 2017b; Snider et al., 2013; Weber et al., 2015; Wohleb et al., 2018). Much of this research has focused on the pro-inflammatory response induced by drugs of abuse (Brown et al., 2018; Crews et al., 2017a) and stress (Weber et al., 2015; Wohleb et al., 2018). However, little is known about how microglia modulate neuronal function. Research from the developmental literature suggests that microglia may be contributing to

changes in synaptic plasticity (Paolicelli et al., 2011). Changes in synaptic plasticity are a hallmark of both SUD and responses to stress. Drugs of abuse cause long lasting neuroadaptations in reward-related brain structures, including electrophysiological changes and structural plasticity (Dong and Nestler, 2014). Similarly, stress causes neuroadaptations in a variety of brain regions, such as the amygdala, the hippocampus, and the prefrontal cortex (PFC). In the nucleus accumbens, stress leads to neuroadaptations in the medium spiny neurons which are believed to enhance vulnerability to addiction (Taylor et al., 2014). In the case of both stress and drugs of abuse, synaptic plasticity changes are maladaptive and correlate with depression and drug craving, respectively (Bessa et al., 2013; Loweth et al., 2014).

Along with these forms of stimulus-induced plasticity, normal brain development is also characterized by enhanced synaptic plasticity. Microglia are necessary for these developmental processes, acting as mediators of synaptic plasticity (Miyamoto et al., 2016; Paolicelli et al., 2011). Given that many of the biological mechanisms underpinning normal development are similar to what researchers see in preclinical models of cocaine use disorder, perhaps microglia are also contributing to drug-induced plasticity changes (Dong and Nestler, 2014; see Table 2 for summary). There is also evidence that microglia can influence synaptic plasticity in adulthood, suggesting that microglia do not lose this ability to modulate synaptic plasticity after development (Parkhurst

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Table 1
List of acronyms and definitions.

Acronym	Definition
AMPA	α -amino-3-hydroxy-5-methyl-4-isoxazo- lepropionic acid receptor
BDNF	brain-derived neurotrophic factor
CRF	corticotropin-releasing factor
CX3CL1	fractalkine
CX3CR1	fractalkine receptor
DAMP	danger-associated molecular pattern
MSN	medium spiny neuron
NLRP3	nucleotide-binding oligomerization domain, leucine-rich repeat and pyrine domain protein 3
NMDAR	<i>N</i> -methyl-D-aspartate receptor
PFC	prefrontal cortex
SUD	substance use disorder
TLR4	toll-like receptor 4
TNF- α	tumor necrosis factor- alpha
VTA	ventral tegmental area

et al., 2013).

In this review, we will discuss the role of microglia in synaptic plasticity, BDNF release, and AMPA receptor expression and the ability of stress and drugs of abuse to activate microglia. Although traditionally research has focused on the role of microglia in development, we will discuss our hypothesis that glial cells also participate in synaptic plasticity following exposure to stress and cocaine. Further, we propose that stress may prime microglia to potentiate their response to addictive drugs, thus contributing to stress-induced increases in vulnerability to substance use (Fig. 1).

2. The interplay between stress and substance use

Epidemiological studies have identified stress as an important risk factor for the development of addiction. People exposed to traumatic events, particularly during childhood are more likely to meet criteria for a SUD later in life (Breslau et al., 2003; Clark et al., 1997; Dembo et al., 1988; Harrison et al., 1997; Widom et al., 1999). It is difficult to determine in clinical populations whether the stress was causal in the increased vulnerability to SUD or if there is a common mediating factor. However, studies in animals have demonstrated that following stress, animals will self-administer more nicotine, cocaine, and ethanol (Fosnocht et al., 2018; Sperling et al., 2010; Yu et al., 2014). Additionally, stress will induce drug seeking after forced withdrawal (see Mantsch et al., 2016).

This enhanced vulnerability to addiction-like behaviors following stress may be due, in part, to the ability of stress to modulate drug-induced synaptic plasticity in the nucleus accumbens. For example, male rats that undergo chronic variable stress show increased dendritic complexity of medium spiny neurons (MSNs) in the accumbens core (Taylor et al., 2014). Because activity within the core of the accumbens is associated with compulsive drug consumption, it has been theorized that stress may facilitate the formation of habitual drug-taking behavior (Taylor et al., 2014). Increases in the spine density of MSNs in the accumbens following social defeat or maternal separation stress have also been reported (Christoffel et al., 2011; Warren et al., 2014). It has also been shown that stress alters gene expression of proteins associated with synaptogenesis in male mice (Warren et al., 2014). Taken together, these data suggest that stress is able to alter the structure of neurons in reward-related brain regions such as the nucleus accumbens.

In addition to structural plasticity, stress alters the physiology of neurons in the accumbens and the ventral tegmental area (VTA). Male rats that undergo sleep deprivation stress show both increases in alcohol consumption and Δ FosB, a transcription factor involved in drug-related neuronal plasticity (Reséndiz-Flores and Escobar, 2018). In male mice, cold water stress enhances glutamatergic transmission in the accumbens and in dopaminergic neurons in the VTA (Campioni et al.,

2009; Saal et al., 2003). Repeated social stress has also been shown to enhance *N*-methyl-D-aspartate receptor (NMDAR)-dependent long term potentiation in the VTA, which correlates with an enhanced conditioned place preference score upon later exposure to cocaine (Stelly et al., 2016). Sub-chronic variable stress alters vesicular glutamate transporters in the nucleus accumbens of female mice but not male mice, suggesting that there are likely sex-differences in the effects of stress on plasticity in reward related brain regions (Brancato et al., 2017).

Together these data suggest that stress increases vulnerability to the development of addictive behaviors in part by enhancing synaptic plasticity in the nucleus accumbens. However, more work is needed to elucidate the mechanisms that create this enhanced synaptic plasticity, and how it leads to more severe addictive phenotypes. We propose microglia partially mediate this stress-induced vulnerability to addiction (Brown and Bachtell, 2018; Lo Iacono et al., 2018).

3. Microglial activation following exposure to stress and drug of abuse

Exposure to either stress or drugs of abuse leads to activation of microglia. For example, chronic restraint stress increases Iba1 expression in the PFC and this increase can be reversed by the microglia inhibitor minocycline (Hinwood et al., 2012). Further, it is known that stress activates microglia via the production of danger-associated molecular patterns (DAMPs; Maslanik et al., 2013). DAMPs in turn bind to toll-like receptor 4 (TLR4) on microglia, leading to the activation of the inflammasome nucleotide-binding oligomerization domain, leucine-rich repeat and pyrine domain protein 3 (NLRP3). By engaging TLRs and NLRP3, stress-induced DAMPs cause microglia to produce a variety of pro-inflammatory cytokines (Fleshner et al., 2017). Although the majority of studies on the influence of stress on microglia have been done only in male animals, there is evidence for sex differences in stress-induced microglial response. In contrast to the stress-induced increases in activated microglia in male rats, stress decreases the number of activated microglia in female rats (Bollinger et al., 2016).

Drugs of abuse can activate microglia through similar mechanisms. Minocycline inhibits cocaine-induced locomotor sensitization, suggesting that microglia are responsive to stimulants and contribute to behavioral drug responses (Chen et al., 2009). Additionally, much work has been done examining the involvement of TLR4 in the development of addictive behaviors. Both cocaine and morphine are capable of binding directly to TLR4 (Northcutt et al., 2015; Wang et al., 2012a). Through TLR4 signaling, cocaine and morphine cause microglia to produce pro-inflammatory cytokines (Northcutt et al., 2015; Wang et al., 2012a). Further, inhibiting TLR4 activation in the VTA leads to a decrease in cocaine seeking (Brown et al., 2018). Similarly, VTA inhibition of the interleukin-1 receptor, which binds the pro-inflammatory cytokine interleukin-1 beta also decreases cocaine seeking (Brown et al., 2018). Together this suggests that drug-induced activation of microglia induced by TLR4 activation in the VTA plays a role in cocaine relapse behaviors (Brown et al., 2018). Consistent with this, TLR4 knockout mice have dampened cocaine-induced conditioned place preference relative to wild types (Kashima and Grueter, 2017). Given that TLR4 is expressed primarily on microglia, these TLR4 data suggest that microglia activation is necessary for the development of addiction-like behavior (Kashima and Grueter, 2017).

4. Microglia and synaptic plasticity

While it has been established that exposure to both stress and drugs of abuse elicit a pro-inflammatory response from microglia, the impact of this response on neuronal function is still unclear. Microglia have been shown to survey the brain and transition from a neutral state to a pro-inflammatory state upon detection of danger, similar to macrophages in the periphery (Franco and Fernández-Suárez, 2015).

Table 2
Summary of alterations to synaptic plasticity caused by cocaine, stress and microglia.

	Cocaine	Stress	Microglia
Spine Density	↑ Cahill et al., 2017; Kim et al., 2011a, 2011b; Lee et al., 2006; Robinson and Kolb, 1999; Toda et al., 2010	↑↓ Bessa et al., 2013; Wohleb et al., 2018; Cohen et al., 2014; Skrzypiec et al., 2013; Hains et al., 2015; Luczynski et al., 2015; Radley et al., 2006; Wang et al., 2012a, 2012b	↑↓ Paolicelli et al., 2011; Schafer et al., 2012; Gutiérrez-Martos et al., 2018; Wohleb et al., 2018; Parkhurst et al., 2013; Miyamoto et al., 2016
BDNF Levels	↑ Cotto et al., 2018; Li et al., 2013; Anderson et al., 2017; Bahi et al., 2008; Giannotti et al., 2014; Grimm et al., 2003; Loweth et al., 2014; Lewitus et al., 2016; Loweth et al., 2014; Briand et al., 2014; Famous et al., 2008; Ma et al., 2016	↑ Bessa et al., 2013; Nikulina et al., 2012; Walsh et al., 2014; Yang et al., 2015	↑ Parkhurst et al., 2013; Cotto et al., 2018
AMPA Expression/ Silent Synapses	↑	↑ Yang et al., 2016; Liu et al., 2015; Ito et al., 2015; Suvrathan et al., 2014	↑↓ Beattie et al., 2002*; He et al., 2012*; Leonoudakis et al., 2008*; Lewitus et al., 2016* (via production of TNF-α); Liu et al., 2015

However, microglia may also play a role in processes beyond the typical innate immune response (Paolicelli et al., 2011). For instance, non-activated microglia are still extremely mobile and have constant, dynamic contact with neurons (Nimmerjahn et al., 2005). Much of the research on the role of microglia in neuronal processes has been conducted in animal models of brain development. Microglia have been implicated in a variety of developmental processes, including neurogenesis (Erblich et al., 2011), axon support (Chamak et al., 1994), and synaptic pruning (Paolicelli et al., 2011). Here we focus on several aspects of synaptic plasticity during development and how microglia influence these processes.

4.1. Spine elimination and formation

Dendritic spines are protrusions from dendrites that contain the majority of excitatory synapses in the brain (Harris, 1999; Lai et al., 2016). On spiny neurons, dendritic spine measurements represent an approximation for the number of synapses on a neuron (Alvarez and Sabatini, 2007; Lai et al., 2016). By adulthood the majority of spines are stable, however during development spines are more labile (i.e. heightened spine formation and elimination) (Alvarez and Sabatini,

2007). Microglia have been implicated in both the elimination and formation of synapses/dendritic spines (Paolicelli et al., 2011; Parkhurst et al., 2013).

Spine elimination is due in part to the limited availability of neurotrophic survival signals needed to maintain synapses (Lu and Figurov, 1997). However, there is a growing body of literature that suggests that erroneous synapses are also actively pruned by microglia (Ji et al., 2013; Paolicelli et al., 2011; Schafer et al., 2012; Stevens et al., 2007). The chemokine fractalkine (CX3CL1) and its receptor, CX3CR1, are essential components of microglial migration (Liang et al., 2009). Neurons release CX3CL1 which binds to CX3CR1 expressed solely on microglia (Harrison et al., 1998; Jung et al., 2000). CX3CR1 knockout mice show a decrease in the overall number of microglia in the developing brain and a corresponding increase in post-synaptic density 95 staining (a synaptic marker), as well as increased immature synapses and spine density. This suggests that fractalkine signaling and microglial migration are necessary for synaptic pruning in normal developing brains (Paolicelli et al., 2011). This pruning is not random, as microglia preferentially engulf weak synapses. This marking of weak synapses is mediated by complement signaling (Schafer et al., 2012; Stevens et al., 2007). The primary role of complement signaling is to improve

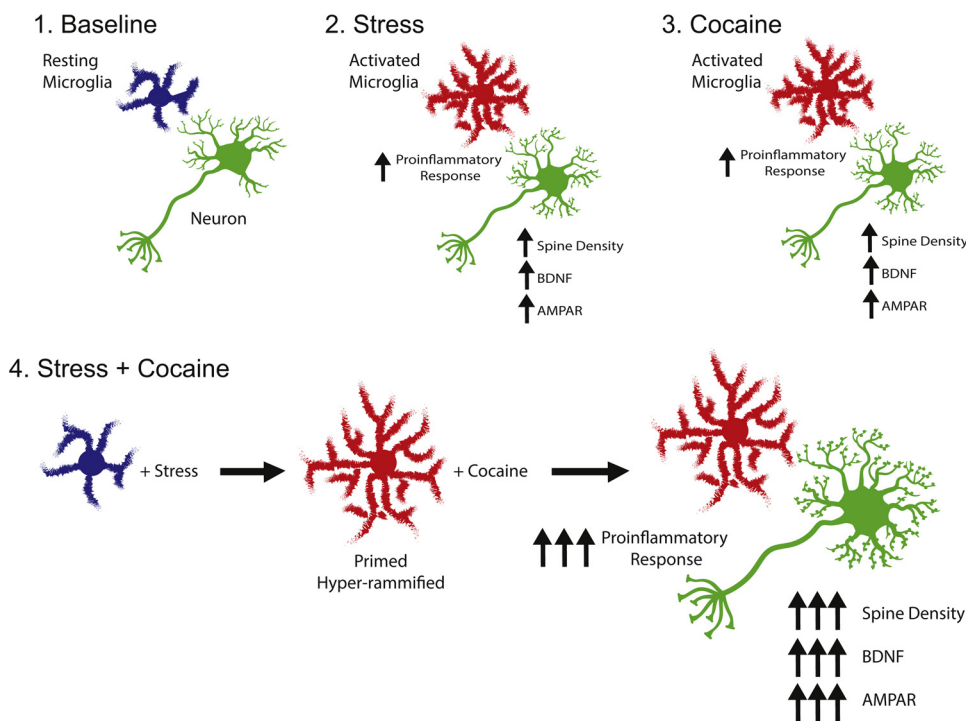


Fig. 1. Proposed mechanism for a role of microglia in stress-induced vulnerability to cocaine addiction. Microglia at rest transition into a “primed” state following exposure to stress. The presence of a second immune challenge, in this case cocaine, leads to enhanced spines, BDNF, and AMPAR expression in the nucleus accumbens.

phagocytosis of antigens, but a similar mechanism seems to be in place to tag synapses to be phagocytosed by microglia (Stevens et al., 2007). Furthermore, genetic variation of the complement component 4 is associated with risk for schizophrenia, suggesting that alterations in complement signaling lead to inappropriate synaptic pruning in development. This indicates that maladaptive synaptic pruning by microglia can lead to pathological outcomes in adulthood (Sekar et al., 2016). Additionally, microglia eliminate D1 receptors tagged by complement proteins in the nucleus accumbens during adolescence in males but not females (Kopeck et al., 2018). This suggests that microglia may regulate developmental synaptic plasticity in a sex-dependent manner.

Along with this role in spine elimination, microglia also seem to be important for the formation of new spines. In vitro experiments have shown that higher concentrations of microglia lead to increased spine density in cultured hippocampal neurons (Lim et al., 2013). Mice with a genetic ablation of microglia show a decrease in both the elimination and formation of dendritic spines (Parkhurst et al., 2013). These mice also show deficits in spine formation as adults that correspond with diminished performance on a motor learning task (Parkhurst et al., 2013). Further, contact between microglia and neurons stimulates the formation of dendritic spines early in development but not in later development (Miyamoto et al., 2016). Taken together, these data suggest that microglia exercise bidirectional regulation of spine density.

4.2. Brain-derived neurotrophic factor

Neurotrophins are growth factors that act as survival signals to neurons and promote cell survival and growth (Cohen-Cory et al., 2010). BDNF is one such neurotrophin and it has been shown to regulate neuron survival, neurite growth, and synaptogenesis during development and learning (Huang and Reichardt, 2001; Parkhurst et al., 2013). Microglia have been shown to assist in learning-related synaptic plasticity through the secretion of BDNF (Parkhurst et al., 2013). Mice with a microglial-specific knockout of BDNF show impaired spine formation following motor task training (Parkhurst et al., 2013). Interestingly, these mice also show impaired learning of the task relative to controls, suggesting that learning-induced spine formation on neurons is dependent on microglial BDNF production (Parkhurst et al., 2013).

4.3. AMPA receptor expression

Microglia may also be able to alter AMPA receptors (AMPA) in developing brains. AMPARs are glutamate receptors that are critical to the development of long-term potentiation and their trafficking in and out of the synapse is an important measure of synaptic plasticity (see Haganir and Nicoll, 2013 for review). During development, the brain has increased levels of a unique type of glutamatergic synapse that does not contain AMPARs, known as silent synapses. Silent synapses are characterized as synapses that contain NMDARs but no AMPARs (Huang et al., 2015b). NMDARs contain magnesium plugs that are only jettisoned when the cell is depolarized (Blanke and VanDongen, 2009). To achieve that depolarization, AMPARs must be present to bind glutamate and allow positive ions to enter the cell (Blanke and VanDongen, 2009). In a silent synapse, there are no AMPARs therefore the NMDARs cannot be activated and the synapse is “silent” (Huang et al., 2015b). AMPARs are extremely dynamic and are trafficked quickly as a result of experience (Zhu, 2009). Therefore, it is theorized that silent synapses serve to prime the brain for periods of heightened synaptic plasticity (Dong and Nestler, 2014). These silent synapses are present in high levels in developing brains and are greatly reduced following puberty (Hanse et al., 2013). The transition of silent synapses to functional synapses is necessary to ending critical periods of heightened plasticity in the visual cortex (Huang et al., 2015a). Prevention of the maturation of silent synapses extended the critical period of visual development, known as juvenile ocular dominance plasticity, into late adulthood (Huang et al., 2015a). The enhanced learning seen in children

compared to adults could be due in part to the concentration of silent synapses (Dong and Nestler, 2014).

Silent synapses become functional upon the insertion of AMPARs into the synapse (Dong and Nestler, 2014). Interestingly, it seems microglia are capable of regulating AMPA receptor expression on neurons via the secretion of the pro-inflammatory cytokine tumor necrosis factor- α (TNF- α) (Beattie et al., 2002; He et al., 2012; Leonoudakis et al., 2004, 2008; Lewitus et al., 2016; Yin et al., 2012). The literature is somewhat mixed, with some researchers finding that TNF- α enhances AMPAR signaling through the insertion of calcium permeable AMPARs (He et al., 2012; Leonoudakis et al., 2008); and other studies finding decreased AMPAR signaling in response to TNF- α (Lewitus et al., 2016). Therefore, it is possible that TNF- α bidirectionally regulates AMPAR expression on neurons. The studies that found that TNF- α enhances AMPAR were both conducted in the hippocampus, while the study that found TNF- α decreases AMPAR was examining the nucleus accumbens, so there may be brain region specific responses of AMPAR to TNF- α (He et al., 2012; Leonoudakis et al., 2008; Lewitus et al., 2016).

5. Synaptic plasticity and cocaine addiction

Due to the many observations that drugs of abuse cause heightened synaptic plasticity in reward-related brain regions, Dong and Nestler (2014) have conceptualized addiction as reward pathways reverting back to a developmental-like state. One measure in particular of synaptic plasticity has received a lot of attention in the addiction literature: spine density. On MSNs in the nucleus accumbens, spine density is altered upon exposure to drugs of abuse. Spines are dynamic and can appear rapidly but are also very long lasting (Lai et al., 2016). These long lasting changes to the neuron morphology are believed to contribute to long-lasting craving in addicts (Christian et al., 2017). However, different drugs of abuse modulate spine density in the accumbens differently (Spiga et al., 2014). While cocaine causes an increase in MSN spine density (Cahill et al., 2017; Kim et al., 2011b; Lee et al., 2006; Robinson and Kolb, 1999; Toda et al., 2010), opioids have been shown to decrease MSN spine density (Miller et al., 2012; Spiga et al., 2014).

Typically, neurotrophins are prevalent in developing brains but present in much lower levels in adulthood (for review see Huang and Reichardt, 2001). In the case of cocaine addiction, adult brains once again have increased levels of neurotrophins, particularly BDNF (McGinty et al., 2010). Increased BDNF levels (both mRNA and protein) have been observed in multiple brain regions related to reward processing such as the medial PFC, VTA, and the nucleus accumbens (Anderson et al., 2017; Bahi et al., 2008; Giannotti et al., 2014; Grimm et al., 2003; Li et al., 2013). In the accumbens, BDNF protein levels correlate with cocaine craving (Li et al., 2013). Following periods of forced abstinence, animals exhibit an increase in drug seeking coined incubation of craving (see Pickens et al., 2011 for review). This same increase in drug craving following periods of abstinence has also been demonstrated in humans with SUD (Bedi et al., 2011; Li et al., 2015; Parvaz et al., 2016). This incubation of craving is dependent on changes in synaptic plasticity (Christian et al., 2017; Li et al., 2013; Loweth et al., 2014). In the case of cocaine, this includes increases in dendritic spine density (Christian et al., 2017). Interestingly, cocaine exposure increases BDNF protein levels in the accumbens on a similar timescale, with levels elevated compared to controls at around withdrawal day 45 and 90 (Li et al., 2013). While the relationship between incubation of craving, spine density, and BDNF is still being elucidated, some researchers hypothesize that BDNF is upregulated following prolonged glutamatergic transmission and contributes to the maintenance of craving (Loweth et al., 2014).

Incubation of craving also correlates with an increased number of silent synapses in the nucleus accumbens following exposure to drugs of abuse (Huang et al., 2015b). In models of cocaine use disorder, silent synapse levels peak during the first days of withdrawal (Huang et al.,

2015b). As the withdrawal period continues, AMPARs are inserted into the silent synapses, thereby “un-silencing” them (Huang et al., 2015b). AMPARs can be divided into two subgroups: GluA2-lacking calcium permeable-AMPA and GluA2-containing, calcium impermeable AMPAR (Ma et al., 2016). This distinction is important because calcium permeable-AMPA have increased conductance compared to calcium impermeable-AMPA (Ma et al., 2016). In the case of cocaine withdrawal, it is specifically calcium permeable-AMPA that are inserted into the silent synapses and correlate with enhanced cocaine craving (Loweth et al., 2014). In fact, methods that promote the insertion of calcium impermeable-AMPA in the synapse over calcium permeable-AMPA actually reduce cocaine-seeking behaviors (Briand et al., 2014; Famous et al., 2008; Ma et al., 2016). Taken together, these data suggest that the development of silent synapses and un-silencing with calcium permeable-AMPA, are an important component of cocaine-related neuroplasticity.

Exposure to cocaine leads to heightened synaptic plasticity in the nucleus accumbens, including increases in spine density, levels of the neurotrophic factor BDNF, and silent synapses. On a molecular level, these synaptic changes resemble normal developmental plasticity. This supports the hypothesis that cocaine inappropriately turns on mechanisms for synaptic plasticity that are supposed to be turned off once the brain is fully developed, leading to addictive phenotypes (Dong and Nestler, 2014). Given the recent discoveries of the role of microglia in developmental synaptic plasticity, it's possible that microglia are also assisting in the drug-related changes in the nucleus accumbens.

6. Possible role for microglia in cocaine addiction-related plasticity

Microglia are potential contributors to the changes in spine density seen following exposure to drugs of abuse, given their established role in regulating spine density during development. Upon exposure to cocaine, microglia may increase contact with MSNs and promote formation of more spines. In support of this possibility, microglia have been shown to modify spine density in the nucleus accumbens of adult mice in an experience-dependent manner. One study has shown that male mice exposed to a high fat/high sugar diet show a decrease in spine density in the nucleus accumbens shell. This decrease in spine density was rescued by minocycline, a microglia inhibitor, suggesting that microglial activation by the high fat/high sugar diet led to altered spine density in the accumbens (Gutiérrez-Martos et al., 2018). Given that microglia have been implicated in the restructuring of neurons in the accumbens in response to rewarding stimuli, their role in addiction-related spine density changes should be investigated.

Multiple studies have shown that incubation of cocaine craving correlates with increased BDNF levels in the accumbens (Christian et al., 2017; Li et al., 2013; Loweth et al., 2014), however most of these experiments have not assessed the origins of this increased BDNF. Given that microglial BDNF facilitates spine growth during the learning of a new task (Parkhurst et al., 2013), it is possible that microglia are responsible for the observed increase in BDNF. That is, following exposure to cocaine, microglial BDNF levels may gradually increase as microglia facilitate the formation of new spines, causing incubation of craving. In support of this, microglial cells incubated with cocaine for 72 h in vitro produce extremely high levels of BDNF compared to those incubated without cocaine in the medium (Cotto et al., 2018). Neurons incubated with cocaine produced much lower levels of BDNF in comparison, suggesting that microglia may be the primary producers of BDNF in response to cocaine (Cotto et al., 2018). Further studies are needed to determine the role of microglial BDNF in vivo, including the importance of microglial BDNF in the incubation of craving. A mouse line generated by Parkhurst et al. (2013) that allows for the knockout of BDNF specifically from microglial cells would be a useful tool in this exploration. One could theorize that mice without microglial BDNF would show fewer addictive behaviors following cocaine exposure.

Microglia could be contributing to the incubation of craving by regulating AMPAR expression on neurons following cocaine exposure. As mentioned above, cocaine is capable of activating microglia through DAMPs which in turn bind to TLRs (Crews et al., 2017b). This sets off a signaling cascade that culminates with the production of pro-inflammatory cytokines, including TNF- α , which regulates AMPA expression on neurons (Beattie et al., 2002; Crews et al., 2017b). Repeated experimenter administered cocaine leads to activation of striatal microglia and increased TNF- α production, which in turn reduces glutamatergic transmission in the nucleus accumbens (Lewitus et al., 2016). Under these conditions, activating microglia following cocaine exposure leads to a reduction in AMPA/NMDA ratios in the accumbens of male mice, while also reducing locomotor sensitization to cocaine. It appears, at least in these experimental conditions, that TNF- α plays a protective role, dampening the pathological synaptic plasticity (Lewitus et al., 2016). Incubation of craving could be mediated by microglia activation. Cocaine self-administration protocols that elicit incubation of cocaine craving result in a prolonged pro-inflammatory response (Loweth et al., 2014). During this time, microglia are producing TNF- α , which may act to prevent the un-silencing of silent synapses by reducing the expression of calcium permeable-AMPA. During withdrawal, microglia are no longer being activated by cocaine, so gradually TNF- α levels will decrease. As TNF- α levels are reduced, more calcium permeable-AMPA will be able to be expressed, leading to un-silencing of synapses, enhanced glutamatergic transmission and increased cocaine craving. It is important to point out that this only one hypothesis. The Lewitus et al. (2016) study uses researcher-administered cocaine injections, which would likely not induce incubation of craving (Loweth et al., 2014). Also, the behavioral output they measured was locomotor sensitization and craving was never assessed (Lewitus et al., 2016). However, given the importance of silent synapses and AMPAR trafficking in cocaine-related plasticity (Dong and Nestler, 2014; Huang et al., 2015b), and the evidence that TNF- α is able to regulate AMPAR expression on neurons (Beattie et al., 2002; He et al., 2012; Lewitus et al., 2016), further exploration into the relationship between microglial TNF- α and cocaine-induced silent synapses is merited. One approach would be to artificially increase TNF- α levels during withdrawal, as the inflammatory response is waning. This may delay the un-silencing of glutamatergic synapses, and reduce craving levels.

7. Synaptic plasticity and stress

The relationship between stress and synaptic changes in the brain is complex, with most of the data suggesting that stress has opposing effects on many measures of synaptic plasticity in different brain regions (see Bennett and Lagopoulos, 2014 for review). For example, the effects of stress on spine density vary depending on the brain region of interest. Generally speaking, chronic stressors tend to increase spine density in the amygdala (Cohen et al., 2014; Skrzypiec et al., 2013), while decreasing spine density in the PFC (Hains et al., 2015; Luczynski et al., 2015; Radley et al., 2006; Wang et al., 2012b).

While less research has been done on the effects of stress on spine density in the nucleus accumbens, several studies indicate that stress increases spine density in the accumbens (Christoffel et al., 2011; Muhammad et al., 2012; Warren et al., 2014; Yang et al., 2015). As stated above, these stress-induced changes in the synaptic plasticity of the accumbens may contribute to the high co-morbidity rates seen between stress disorders and addiction. However, one similar study found no effect of social isolation following weaning on spine density in the nucleus accumbens (Wang et al., 2012b). The other studies used social defeat and foot shock stress paradigms rather than social isolation, which may indicate that the type of stressor is an important factor in determining how stress impacts accumbens spine density. Further research will help elucidate the conditions in which these changes in spine density occur. Like spine density, several studies have found that stress increases BDNF levels in the nucleus accumbens (Bessa et al.,

2013; Nikulina et al., 2012; Walsh et al., 2014; Yang et al., 2015). Male rats show elevated levels of BDNF mRNA following chronic mild stress (Bessa et al., 2013).

Stress has also been shown to alter glutamatergic transmission. Stress alters AMPA/NMDA ratios and AMPA-mediated EPSCs in the nucleus accumbens and the hippocampus (Campioni et al., 2009; Liu et al., 2015). Stress also appears to reduce the phosphorylation of the AMPAR subunit GluA1 at both the S831 and S845 phosphorylation sites in hippocampal neurons (Liu et al., 2015). As the levels of phosphorylation of GluA1 are related to their expression at the membrane (Man et al., 2007), these findings support a stress-induced decrease in AMPAR signaling. Further, animals who have undergone social defeat stress show decreased levels in the GluA1 subunit in the PFC and hippocampus (Yang et al., 2016). However, the same stressor seems to elevate GluA1 levels in the nucleus accumbens (Yang et al., 2016).

To our knowledge, there are no published studies examining whether stress leads to the formation of silent synapses in the nucleus accumbens. However, stressful experiences lead to the generation of silent synapses in the amygdala (Ito et al., 2015; Suvrathan et al., 2014). Interestingly, these silent synapses corresponded with increased fear responses, suggesting that the stressful events led to heightened synaptic plasticity which in turn led to enhanced fear learning (Ito et al., 2015; Suvrathan et al., 2014). When using other measures of synaptic plasticity, such as dendritic spine density, researchers generally see hypertrophy in both the amygdala and the accumbens (Christoffel et al., 2011; Cohen et al., 2014; Skrzypiec et al., 2013; Warren et al., 2014). Since similar stress-induced changes are seen in this measure of plasticity in the amygdala and accumbens, it is possible that stress also causes silent synapses to be formed in the nucleus accumbens. Electrophysiological studies of the accumbens in stressed vs naïve animals could be used to test this hypothesis.

8. Possible roles of microglia in stress plasticity

Microglia are involved in spine elimination and formation during normal development (Miyamoto et al., 2016; Paolicelli et al., 2011). It is possible that microglia also contribute to the increases in spine density and BDNF seen in the nucleus accumbens following stress. Stress leads to the production of glucocorticoid, mineralocorticoid and corticotropin-releasing factor (CRF) (see Joëls and Baram, 2009). It should be noted that all three of these receptors, glucocorticoid receptors, mineralocorticoid receptors, and CRF receptors, are expressed on microglia (Chantong et al., 2012; Kim et al., 2011a). Given that the hormones that contribute to the stress response also bind to microglia, and that stress can activate microglia via DAMPs, it is possible that microglia are also contributing to stress-related neuroadaptations. Chronic unpredictable stress decreases spine density in the PFC of male mice, and this decreased spine density could be prevented by blocking colony stimulating factor 1, which is released by neurons and activates microglia (Wohleb et al., 2018). This indicates that microglial activation is needed for stress-induced changes in spine density (Wohleb et al., 2018). Whether a similar mechanism is happening in the nucleus accumbens remains to be seen.

Microglia also mediate stress-induced changes in AMPAR expression and function. Inhibition of microglia reverses reduction in GluA1 phosphorylation following chronic unpredictable stress (Liu et al., 2015). Again, these data are from hippocampal neurons, and to our knowledge the role of microglia in accumbens AMPAR expression has not been explored. However, this research indicates that microglia actively participate in synaptic plasticity responses to stress.

9. Stress primes microglia: implications for stress-induced vulnerability to cocaine addiction

Stress activates microglia via the production of DAMPs and signaling through TLR4. However it is important to point out that stress

also primes microglia for a second immune challenge, meaning that once the cells are activated by stress, they show enhanced release of pro-inflammatory cytokines when activated a second time (Weber et al., 2015). This enhanced activation is due in part to glucocorticoids, as antagonism of the glucocorticoid receptor attenuates the microglia response in stressed animals to a second pro-inflammatory challenge (Frank et al., 2012). Stress priming of microglia also elevates levels of the DAMP high motility group box-1, which in turn leads to increased inflammasome NLRP3 protein levels (Weber et al., 2015). Additionally, stress-primed microglia are morphologically distinct from control microglia (Hinwood et al., 2013). They exhibit hyper-ramification, or more complex branching than the non-stressed control microglia, which can be prevented by minocycline (Hinwood et al., 2013). It should be noted that many of these studies only examined male animals. A recent study found that both male and female rats undergo stress priming of the immune system, but it appears to be dependent on microglia in males but not females (Fonken et al., 2018). As more studies examine sex differences in stress and immune interactions, the underlying mechanisms will be elucidated.

In many stress-priming studies, the second challenge is the endotoxin lipopolysaccharide, which elicits a strong pro-inflammatory response from microglia (Frank et al., 2012; Weber et al., 2013, 2015). However, mice exposed to early life stress have enhanced pro-inflammatory responses to cocaine later in adulthood (Lo Iacono et al., 2018). This suggests that stress can prime microglia to cocaine as well. The stressed animals also exhibited less dopaminergic transmission in the VTA, which was reversed by the inhibition of microglia (Lo Iacono et al., 2018). Interestingly, this study also investigated the effects of childhood maltreatment in human cocaine users, finding that childhood trauma correlated with higher levels of circulating pro-inflammatory cytokines in response to cocaine (Lo Iacono et al., 2018). Thus, it appears that this animal model for studying early stress and addiction has some translational validity. Another recent study has demonstrated that TNF- α induced by early life stress alters AMPAR subunit expression and enhances cocaine conditioning in male rats. By blocking TNF- α , researchers were able to normalize both AMPAR subunit expression and cocaine response (Ganguly et al., 2019). Given that microglia are known to produce TNF- α in response to stress, it's possible that this stress-enhanced cocaine conditioning is mediated by microglia.

Stress is a major risk factor for the development of addiction in humans (Breslau et al., 2003; Clark et al., 1997; Dembo et al., 1988; Harrison et al., 1997; Widom et al., 1999). Perhaps this is due, in part, to stress altering subsequent microglial activation by drugs of abuse. If in fact microglia contribute to addiction related plasticity, stressed-primed microglia may have greater capacity to alter synaptic plasticity in reward-related brain regions in response to drugs of abuse (Fig. 1). Given the vast literature of synaptic changes following exposure to stress and drugs of abuse, and the role of microglia in similar processes, it seems probable that microglia are important mediators of this synaptic plasticity and could possibly contribute the stress-induced vulnerability to addiction. Recent work by Lo Iacono et al. (2018) and Ganguly et al. (2019) support this hypothesis.

10. Conclusion

While microglia have historically been studied for their role in innate immunity, recent work has focused on the role of microglia in the regulation of synaptic plasticity during development (Paolicelli et al., 2011; Tremblay et al., 2010). Given the similarities in plasticity during development and plasticity during addiction and stress, it seems likely that microglia would also influence plasticity following exposure to stressors and drugs of abuse (Table 2). Exposure to both drugs of abuse and stress lead to increases in circulating pro-inflammatory cytokines (Fox et al., 2012; Levandowski et al., 2016; Nabati et al., 2013) (Weber et al., 2015; Wohleb et al., 2018). In animal models, multiple drugs of abuse have been shown to elicit a pro-inflammatory response in the

brain (Chen et al., 2012; Collier and Hutchinson, 2012; Crawford et al., 2006; Crews et al., 2017a; Hutchinson et al., 2012; Hutchinson and Watkins, 2014; Jacobsen et al., 2014; Lopez-Pedrajas et al., 2015). Given that microglia play such an active role in synaptic changes during normal development and learning, there is potential for microglia to not only influence stress and drug responses through inflammation, but also via regulation of synaptic plasticity.

During development, microglia can regulate synaptic plasticity bidirectionally (see Ueno and Yamashita, 2014 for review). This could be of particular interest in the context of addiction. While this review has focused primarily on cocaine neuroadaptations, different drugs of abuse elicit varied neuroadaptations (Miller et al., 2012). For instance, cocaine and opioids often have polar opposite effects on the brain (Miller et al., 2012). While cocaine increases spine density in the accumbens, opioids decrease it (Miller et al., 2012). Cocaine causes increases in BDNF levels (McGinty et al., 2010), opioids decrease it (Chen et al., 2012). And while incubation of opioid craving has been demonstrated in rodents (Li et al., 2008; Theberge et al., 2012), the molecular underpinnings of that process are not as well characterized as cocaine craving. It is possible that the molecular mechanisms of incubation of cocaine craving look very different from incubation of opioid craving. As microglia have bidirectional control of synaptic plasticity (i.e. can eliminate or form new spines (Paolicelli et al., 2011; Parkhurst et al., 2013) and can upregulate or downregulate calcium permeable AMPAR via cytokine production (Beattie et al., 2002; Lewitus et al., 2016, 2014), they could represent a common mechanism leading to opposing effects on plasticity seen with these different classes of drugs. Further testing is needed to determine the role of microglia on the divergent neuroadaptations of cocaine and opioids. Stress also leads to opposing synaptic changes, with plasticity being enhanced in some brain regions, and inhibited in others (Cohen et al., 2014; Hains et al., 2015; Luczynski et al., 2015; Radley et al., 2006; Skrzybiec et al., 2013; Wang et al., 2012b). Perhaps this is due in part to the bidirectional regulation of synaptic plasticity exerted by microglia.

Of note, the model proposed in this review (Fig. 1) is influenced by the timing of the stressor. When animals are exposed to stress during early development (Lo Iacono et al., 2018), microglia may not only be primed for future cocaine-induced plasticity, but normal developmental processes may be disrupted. Given the stated importance of microglia to healthy development, exposure to stress during sensitive developmental windows may prevent microglia from effectively pruning synapses or sculpting circuits (Brown and Bachtell, 2018). This combined with the primed immune response could make stress during important developmental windows more damaging than stress during adulthood. More experiments are needed to determine the importance of the timing of the stressor.

This review largely does not discuss sex-differences in the immune responses to stress or drugs of abuse. While the data that is available certainly suggests that sex is a major factor in the immune response to stress, there are far fewer studies done in females than males. Generally, the findings of these studies suggest that male immune systems are activated more readily by stress, that microglia play a more active role in the development of reward circuitry in males, and males are more vulnerable to subsequent development of addictive behaviors (Bollinger et al., 2016; Ganguly et al., 2019; Kopec et al., 2018). This line of research is in its infancy, but there is enough evidence of sex-differences in these processes and the importance of using both males and females when studying stress and the immune system should not be overlooked.

While this review focuses on pre-clinical studies, the role of the innate immune system in addiction and stress has also been examined in humans (Chan et al., 2015; Fox et al., 2012; Pedraz et al., 2015). In these studies, drugs of abuse modulate circulating pro-inflammatory cytokines in the periphery (Chan et al., 2015; de Timary et al., 2017; Fox et al., 2012; Pedraz et al., 2015). There have also been advances in technology that allow researchers to study microglia in vivo in the human brain (Cagnin et al., 2002). For instance, positron emission

topography (PET) scans can be used to detect activated microglia (Cagnin et al., 2002). Results from these studies have been mixed, with studies showing increases of microglial activation (methamphetamine; Sekine et al., 2008)), no difference in microglia activation (cocaine; Narendran et al., 2014) and decreased microglia activation (alcohol; Hillmer et al., 2017; Kalk et al., 2017) in response to drugs of abuse. This could possibly be explained by the differences in the abused drugs. Inflammation has also been shown to correlate with stress-related disorders in humans, such as post-traumatic stress disorder and depression (Haapakoski et al., 2015; Passos et al., 2015). PET scans examining microglia activation in depressed patients have been inconsistent, with some finding increases in activation, while other found no differences between depressed patients and healthy controls (Hannestad et al., 2013; Setiawan et al., 2015). These inconsistencies could be explained in part by differences in patient populations, and technological limitations (see van der Doef et al., 2015 for review). However, a recent paper from Lo Iacono et al. (2018) discovered evidence of an immunological link between stress and addiction in humans. They found that cocaine addicts with a history of childhood trauma had elevated levels of circulating pro-inflammatory cytokines compared to cocaine addicts without childhood trauma. This finding is the first evidence seen in humans that supports the model proposed in Fig. 1.

Stress and addiction are both characterized by changes in synaptic plasticity. Recently there have been new insights into the role of microglia in synaptic plasticity during development and learning, however the role of microglia in stress and addiction-induced plasticity remains understudied. Perhaps by studying microglia not only for their inflammatory processes but also as synaptic regulators, we will get a clearer understanding of the link between stress and addiction.

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Declaration of Competing Interest

The authors declare no conflict of interest.

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