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Glial Modulators as Potential Treatments of Psychostimulant Abuse

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Abstract

Glia (including astrocytes, microglia and oligodendrocytes), which constitute the majority of cells in the brain, have many of the same receptors as neurons, secrete neurotransmitters and neurotrophic and neuroinflammatory factors, control clearance of neurotransmitters from synaptic clefts, and are intimately involved in synaptic plasticity. Despite their prevalence and spectrum of functions, appreciation of their potential general importance has been elusive since their identification in the mid-1800s, and only relatively recently have they been gaining their due respect. This development of appreciation has been nurtured by the growing awareness that drugs of abuse, including the psychostimulants, affect glial activity, and glial activity, in turn, has been found to modulate the effects of the psychostimulants. This developing awareness has begun to illuminate novel pharmacotherapeutic targets for treating psychostimulant abuse, for which targeting more conventional neuronal targets has not yet resulted in a single, approved medication. In this chapter, we discuss the molecular pharmacology, physiology and functional relationships that the glia have especially in the light in which they present themselves as targets for pharmacotherapeutics intended to treat psychostimulant abuse disorders. We then review a cross section of preclinical studies that have manipulated glial processes whose behavioral effects have been supportive of considering the glia as drug targets for psychostimulant-abuse medications. We then close with comments regarding the current clinical evaluation of relevant compounds for treating psychostimulant abuse, as well as the likelihood of future prospects.

Keywords

glia; astroglia; microglia; methamphetamine; cocaine; medication

1. INTRODUCTION

Virchow (Virchow, 1856, 1858) penned the term "neuroglia", specifically, *nervenkitt*, which has been translated as "nerve-glue", or perhaps more appropriately as "nerve-putty" (Somjen, 1988). The perception that neuroglia were subservient to neurons and were just the "glue" that held them together persisted as a dominant concept for many decades. It wasn't until the last couple of decades that a more sophisticated vision of some categories of glia became appreciated with greater importance. For instance, it wasn't until nearly the

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beginning of this century that the astroglia were viewed as an integral modular component of a "tripartite synapse" in which they were wed as partners with the presynaptic and postsynaptic nerve terminals regulating neuronal activity and synaptic strength (Araque, Parpura, Sanzgiri, & Haydon, 1999).

Glial cells (astrocytes, microglia and oligodendrocytes) constitute the majority of cells in the brain (Nedergaard, Ransom, & Goldman, 2003; Sherwood et al., 2006). The major subcategories of glial cells include macroglia (most typically defined as astrocytes, oligodendroglia, and ependymal cells) and microglia. Exhaustive reviews on each macroglial cell type and subtype exist and numerous debates on whether additional varieties of macroglia or "stable" populations of oligodendroglial/astroglial progenitors, such as polydendroglia or "NG2" cells (Keirstead, Levine, & Blakemore, 1998; Chang, Nishiyama, Peterson, Prineas, & Trapp, 2000; Zhu, Bergles, & Nishiyama, 2008), continue. Ependymal cells line the ventricles, are important in brain homeostasis and cerebrospinal fluid transport, and are derived from radial glia during embryonic maturation (Spassky et al., 2005). Of the macroglial types, we will only discuss the role of psychostimulants in astroglia, although emerging findings suggest that cocaine (Feng, 2008; George, Mandyam, Wee, & Koob, 2008; Kristiansen, Bannon, & Meador-Woodruff, 2009; Kovalevich, Corley, Yen, Rawls, & Langford, 2012) disrupts myelin and oligodendrocyte genes and/or their function and it seems likely that other macroglial cell types will be found to facilitate significant aspects of psychostimulant action.

Oligodendroglia remain an understudied glial type that have only been minimally explored in the context of psychostimulant abuse (Miguel-Hidalgo, 2009), and will only be passingly mentioned in the present review. Oligodendrocyte numbers (George, Mandyam, Wee, & Koob, 2008) and myelin (Kristiansen, Bannon, & Meador-Woodruff, 2009; Kovalevich, Corley, Yen, Rawls, & Langford, 2012) are reduced following cocaine exposure in rats. Cocaine exposure is also known to cause reductions in myelin basic protein (MBP), proteolipid protein (PLP), and other key oligodendroglial transcripts in gene arrays (Albertson et al., 2004; Bannon, Kapatos, & Albertson, 2005). However, unlike the effects of psychostimulants in microglia and astroglia, which have known effects on neuronal function, it is as yet uncertain whether reduced numbers of cells, decreased levels of MBP, PLP, and other transcripts, or hypothetical alterations in oligodendroglia function induced by psychostimulants (Miguel-Hidalgo, 2009), affect neuronal function. Even less is known about the effects of methamphetamine on oligodendrocytes, except that the drug preferentially disrupts the genesis of oligodendroglial precursors in the adult rat medial prefrontal cortex (mPFC) (Mandyam, Wee, Eisch, Richardson, & Koob, 2007). Additional study of psychostimulant action in oligodendrocytes and how the changes in oligodendrocytes affect other neuronal and glial cell types is warranted and overdue. The discussions that follow are limited to astroglia and microglia.

Glia contain receptors (for reviews see, Kimelberg, 1995; Pocock & Kettenmann, 2007) (see below), secrete neurotransmitters, neurotrophic and neuroinflammatory factors (Benz, Grima, & Do, 2004; Bezzi et al., 1998; Kang, Jiang, Goldman, & Nedergaard, 1998; Parpura et al., 1994; Watkins et al., 2007), control clearance of neurotransmitters from synaptic clefts (Camacho & Massieu, 2006), and are involved with synaptic plasticity (e.g., Ullian,

Christopherson, & Barres, 2004). Given their prevalence, and their multiple modes of controlling neurological functionality, it is not surprising that glia and their secreted products have been reported to modulate, and be modulated by, the drugs of abuse including the psychostimulants (e.g., Bolanos & Nestler, 2004; Clark, Wiley, & Bradberry, 2013; Cooper, Jones, & Comer, 2012; Ghitza et al., 2010; Haydon, Blendy, Moss, & Jackson, 2009; Narita et al., 2006; Pierce & Bari, 2001).

Astroglia and microglia express a multitude of receptors and drug transporters thought to be directly or indirectly affected by psychostimulants. In fact, there are few examples of G-protein coupled receptors (GPCRs) that are expressed by neurons that are not also expressed by astrocytes (Wilkin, Marriott, & Cholewinski, 1990; Zhang & Barres, 2010). Although this refers to both glial types, astroglia display the greatest phenotypic diversity—rivaled only by neurons in the brain. For this reason, unless the glial type of interest is isolated in vitro, it is normally difficult to selectively activate astrocyte (or microglial) receptors without stimulating the same receptor on neurons and vice versa using GPCR agonists or antagonists (Conklin et al., 2008; Fiacco, Agulhon, & McCarthy, 2009). “To date, most direct evidence to unambiguously identify a particular drug target or action in microglia or astroglia rely largely on extrapolating findings from in vitro studies. Obviously, generalizing any results from cell culture studies to the intact animal has serious limitations.

Nevertheless, isolating the response and/or actions of a drug to particular glial type in vivo has been exceedingly challenging. Recently, the use of genetic approaches to direct the expression of engineered GPCRs (Coward et al., 1998) into glia, and the utilization of novel ligands to selectively activate these receptors, has been used as a tactic to unambiguously discern glial versus neuronal functions (Conklin et al., 2008). Strategies using designer receptors exclusively activated by designer drugs (DREADDs) (Armbruster, Li, Pausch, Herlitze, & Roth, 2007) or receptors activated solely by a synthetic ligand (RASSLs) (Conklin et al., 2008; Dong, Rogan, & Roth, 2010), hold considerable promise for discriminating the role of a particular glial type such as astroglia or microglia, or glial subtype such as dopamine D2 versus non-D2 receptor-expressing astroglia, from other cell types. Alternatively, an additional means of differentiating glia from neurons is to examine unique functional markers and their associated responses. Thus, while the “glial” drugs mentioned in this review may preferentially act through a single glial cell type, it is extremely tricky to unambiguously assign the actions of a drug to a particular glial cell type or distinguish a drug’s action in glia versus neurons using current methodology.

Accordingly, even if an action of a drug is preferentially associated with a unique glial function, the glial response may be secondary to the drug’s actions in another cell type and likely to be acting preferentially, but not exclusively, in that glial type. Thus, caution is warranted before asserting “glial” action to most current pharmacotherapeutics.

Manipulating the activity of glia as a target in the development of pharmacotherapeutics for treating psychostimulant disorders is in its infancy, and few mature systematic efforts exist. Thus, this review cannot stand as an inventory of current, glial-related strategies in drug development for the treatment of psychostimulant abuse. Instead, we try to introduce the reader to glial physiology presented with a focus on how altering glial processes may provide opportunities for developing psychostimulant medications. We also provide an overview of key preclinical studies that have reported on drugs that attenuate abuse-related

effects of psychostimulants, which likely act through glial and neuroinflammatory mechanisms. Drugs with the ability to activate or antagonize receptors that mediate the actions of the psychostimulants have automatically marked them as potential pharmacotherapeutics. Astroglia and microglia express most known CNS receptors including dopaminergic, opioidergic, glutaminergic, adrenergic, nicotinic, cannabinergic, serotonergic, ATP/P2X, peptidergic, ionotropic and GPCR classes of purinergic, GABAergic and sigma receptors amongst others (Deschepper, 1998; Durand, Carniglia, Caruso, & Lasaga, 2013; Fumagalli et al., 2003; A. A. Hall, Herrera, Ajmo, Cuevas, & Pennypacker, 2009; Hernandez-Morales & Garcia-Colunga, 2009; E. Hosli & Hosli, 1993; L. Hosli, Hosli, Maelicke, & Schroder, 1992; Khan, Koulen, Rubinstein, Grandy, & Goldman-Rakic, 2001; Kimelberg, 1995; Krisch & Mentlein, 1994; Morioka, 2011; Pocock & Kettenmann, 2007; Stella, 2010). In fact, cortical astroglia account for approximately one-third of the total dopamine D2 receptor binding sites in the cortex (Khan et al., 2001). Although this review does address the structure and function of the glia, including their resident receptors that might modulate psychostimulant effects, it ultimately excludes discussion of potential pharmacotherapeutics having these conventional receptor targets, and instead restricts itself to drugs affecting glia with known anti-neuroinflammatory consequences. This review is consequentially structured into two major sections. The first section covers microglia and astroglia and how their molecular pharmacology and neuroinflammatory effects could serve as provocative targets for psychostimulant pharmacotherapeutic development. The second section reviews *in vivo* evidence of drugs that affect neuroglia and have anti-inflammatory consequences that can ameliorate abuse-related effects of the psychostimulants. This review ends with closing comments regarding the status of glial-drug development for treating psychostimulant abuse, and points to where we think the most interesting targets for future investigation reside.

2. MOLECULAR BIOLOGY AND PHYSIOLOGY OF THE GLIA

2.1. Glial responses to neuronal injury and stress

2.1.1 Innate immune effectors—Unlike neurons, microglia and to a lesser extent astroglia, contribute to innate immunity within the CNS. Microglia, in particular, are the principal immune effectors in the CNS. Microglia express a wide variety of pattern (or “pathogen”, as discussed in proceeding text) recognition receptors (PRRs) associated with innate immune function, including Toll-like receptors (TLRs), scavenger receptors, such as receptors for advanced glycation end-products (RAGE), nucleotide binding and oligomerization domain receptors (NOD-like receptors or NLRs), and Mac-1 complex (see Figure 1). In addition to their role as innate immune effectors, microglia express major histocompatibility complex-I (MHC-I) and MHC-II complexes and can thereby recognize both intracellular and extracellular foreign proteins and process these for presentation as antigens to T-lymphocytes hence contributing to adaptive immunity. While it has long-been known that astrocytes express MHC-I, cumulative evidence suggests that under duress, astrocytes can also express MHC-II (Jensen, Massie, & De Keyser, 2013).

PRRs were initially characterized for their role in host protection against unique pathogen associated-molecular patterns (PAMPs). It was later realized that many of the same cellular

responses that were activated by pathogens could also be triggered by the accompanying damage to the host cell, and that in some instances the damage per se was sufficient to initiate an innate immune response. Consequently, it is not a coincidence that there is considerable overlap in the cellular response to pathogens and damage (Bianchi, 2007; Srikrishna & Freeze, 2009).

Neuronal damage-associated molecular patterns (DAMPs), can directly activate, and in aberrant or pathologic situations, overactivate microglia (Block, Zecca, & Hong, 2007; Biber, Neumann, Inoue, & Boddeke, 2007). DAMPs are released from stressed or injured cells (Bianchi, 2007; Srikrishna & Freeze, 2009). PRRs are activated by DAMPs and are key regulators of innate immune function. Many classes of PRRs have been purported to be directly or indirectly responsive to substance abuse, and especially psychostimulants. Psychostimulants including methamphetamine, cocaine, and ecstasy have been suggested to activate the innate immune system (Clark, Wiley, & Bradberry, 2013), which has been proposed to be a necessary neurobiological step in causing alcohol and cocaine addiction (Crews, Zou, & Qin, 2011). The role of innate immune activation is particularly evident in chronic alcoholism (Crews, Zou, & Qin, 2011; Yakovleva, Bazov, Watanabe, Hauser, & Bakalkin, 2011), but is also thought to contribute to cocaine addiction (Crews, Zou, & Qin, 2011). The diversity of signals that can act as DAMPs permits the injured cell to communicate sophisticated signals to innate immune effectors, which enables a highly coordinated and measured host response to stress or injury.

2.1.2 Pattern recognition receptors (PRRs)

2.1.2.1 Toll-like receptors: TLRs are a primitive part of the innate immune system and respond to novel molecular motifs associated with pathogens such as Gram negative and Gram positive bacteria, or short lengths of single and/or double stranded RNA or DNA suggestive of viral invasion (Beutler et al., 2006; Kawai & Akira, 2007). Multiple TLRs exist. Each is associated with a distinct pathogen motif or related patterns. Although considerable attention has been given to TLR4 in relation to addiction and neuropathic pain due to its ability to bind opiate agonists and antagonists (Hutchinson et al., 2011; Wang et al., 2012b; Theberge et al., 2013), emerging evidence suggests that the expression and function of other TLRs may be influenced by psychomotorstimulants. For example, methamphetamine downregulates TLR9, which attenuates the ability of macrophages to recognize and fight intracellular pathogens such as HIV-1 (Cen et al., 2013). Innate immune genes, including TLRs, have been prosed to be involved in the sequelae of adaptive neurobiological changes underlying alcohol addiction (Crews et al., 2011) and speculates that the same mechanisms may be operative for cocaine and perhaps other addictive drugs (Frank, Watkins, & Maier, 2011; Crews et al., 2011; Clark, Wiley, & Bradberry, 2013).

2.1.2.2 Receptor for advanced glycation end-products (RAGE): RAGE recognizes a wide variety of advanced glycation end-products (AGEs), including S100 β , which is released from damaged astrocytes following brain injury (Egea-Guerrero et al., 2012), and high-mobility group box-1 (HMGB1, a factor that can be released by neurons and glia during stress or inflammation, which is also recognized by TLR2 and TLR4 (Maroso et al., 2010)). Methamphetamine produces a number of abnormal immunogenic protein glycation

products (Dickerson, Yamamoto, Ruiz, & Janda, 2004; Treweek, Wee, Koob, Dickerson, & Janda, 2007; Treweek, Dickerson, & Janda, 2009).

2.1.2.3 Nucleotide-binding and oligomerization domain (NOD) receptors: Less is understood about the potential role of nucleotide-binding and oligomerization domain (NOD) receptors (Strober, Murray, Kitani, & Watanabe, 2006) (NOD-like receptors) in psychostimulant actions. Since several of the NOD-like receptor subfamilies contribute to the formation of inflammasomes (Kanneganti, Lamkanfi, & Nunez, 2007; Schroder & Tschopp, 2010), it is likely that they participate in methamphetamine-induced inflammation and neuronal injury. The NLRP₃ inflammasome, in particular, is involved in interleukin-1 β (IL-1 β) processing by macrophages. IL-1 β is a key cytokine involved in initiating a variety of inflammatory cascades in microglia.

2.1.2.4 Alternative PRRs: Numerous alternative PRRs exist, including C-type lectin receptors (Geijtenbeek & Gringhuis, 2009), RNA helicases, and retinoic acid-inducible gene 1 (RIG-I or RIG-I) protein complexes, and a wide variety of additional receptor types. Several receptor kinase classes sensing internal homeostatic signals including redox, hyperthermia, and aberrant synaptic function also serve as PRRs. Regarding C-type lectin receptors, a class of receptors that display Ca²⁺-dependent binding to carbohydrates, the expression and function of dendritic cell-specific intercellular adhesion molecule-3-grabbing non-integrin (DC-SIGN or CD209) is affected by cocaine (Nair et al., 2004; Nair et al., 2005) and methamphetamine (Nair, Mahajan, Sykes, Bapardekar, & Reynolds, 2006). Disrupting DC-SIGN alters basic immune function and the ability of dendritic cells to present antigens to T-lymphocytes. Numerous reviews describe the mechanisms by which psychostimulants cause aberrant intracellular redox potentials (Rubartelli & Lotze, 2007), oxidative and nitrosative stress, hyperthermia (Thomas, Walker, Benjamins, Geddes, & Kuhn, 2004), mitochondrial energetics, and glucose metabolism in neurons and glia (Davidson, Gow, Lee, & Ellinwood, 2001; Quinton & Yamamoto, 2006; Krasnova & Cadet, 2009; Cadet & Krasnova, 2009; Kita, Miyazaki, Asanuma, Takeshima, & Wagner, 2009; Kaushal & Matsumoto, 2011; Collier & Hutchinson, 2012; Cadet & Jayanthi, 2013).

2.2. Microglia

2.2.1 Direct psychostimulant effects on microglia—Methamphetamine and cocaine directly affect microglia through actions at sigma1-receptors (σ -1R or SIGMA1R). Sigma1-receptors are associated with the membrane of the endoplasmic reticulum (Hayashi & Su, 2007) and can also serve as intracellular chaperones (Su, Hayashi, Maurice, Buch, & Ruoho, 2010). Sigma1-receptors are one of several putative molecular targets of methamphetamine (Hayashi et al., 2010; Kaushal & Matsumoto, 2011) and cocaine (Navarro et al., 2010; Yao et al., 2011; Katz et al., 2011; Narayanan, Mesangeau, Poupaert, & McCurdy, 2011; Fritz, Klement, El, Saria, & Zernig, 2011; Robson, Noorbakhsh, Seminerio, & Matsumoto, 2012; Kourrich et al., 2013). Despite the emerging importance of sigma1-receptors in the neurobiology of psychostimulant addiction and some promising lead compounds (Kaushal, Seminerio, Robson, McCurdy, & Matsumoto, 2012; Xu et al., 2012; Kaushal et al., 2012; Robson et al., 2013), as yet there are no established antagonists highly selective for sigma1-receptors. Microglia, and potentially astroglia, express sigma1-receptors, and therefore can

be directly affected by exposure to methamphetamine and cocaine. Despite some reports that selective $\sigma 1$ -receptor activation has been shown to inhibit microglial motility, cytokine release, and intracellular Ca^{2+} in response to lipopolysaccharide (LPS), monocyte chemoattractant protein-1, and ATP (Hall, Herrera, Ajmo, Jr., Cuevas, & Pennypacker, 2009), while ligands with agonist properties more often found to activate proinflammatory microglial responses (Gekker et al., 2006; Yao et al., 2011; Cuevas, Rodriguez, Behensky, & Katnik, 2011; Behensky et al., 2013). The evidence for astroglial expression of $\sigma 1$ -receptors is less well established and is based on their expression in a human fetal astroglial SVG cell line (Ben-Ami, Kinor, Perelman, & Yadid, 2006), or on ligand binding profiles, or effects in primary astrocytes (Mattson, Rychlik, & Cheng, 1992; Prezzavento et al., 2007) and glioblastoma cell lines (Thomas et al., 1990).

While neurotransmitters tend to be neutral or inhibit the release of proinflammatory cytokines, excess glutamate, extracellular ATP, the tachykinin substance P (Angulo, Angulo, & Yu, 2004), and bradykinin, can augment cytokine production by microglia (Farber, Pannasch, & Kettenmann, 2005; Pocock & Kettenmann, 2007). Imbalances in excitatory and inhibitory neurotransmitters have also been proposed to act as DAMPs (Gao & Hong, 2008), and proposed as a mechanism by which methamphetamine activates glia (Pereira et al., 2012). In this regard, microglial PRRs for glutamate and purine neurotransmitter receptors, specifically AMPA 1 glutamate receptors (GluR1 or GRIA1) (Hemby, 2004; Cadet & Jayanthi, 2013) and P2X4 purinergic receptors (Horvath & Deleo, 2009; Horvath, Romero-Sandoval, & De Leo, 2010), distinguish themselves for their potential involvement in modulating the effects of abused substances directly in microglia. These and other basic steady-state processes are well-established targets of psychostimulants. Thus, by inducing stress and injuring neurons, methamphetamine and cocaine induce the formation of neuronal DAMPs directly, thereby triggering secondary microglial responses. In addition, methamphetamine and cocaine can directly activate the microglia themselves, which may further heighten the innate microglial response to neuronal DAMPs.

2.2.2 Psychostimulant-induced synaptic and neuronal injury result in DAMPs and signals that activate microglia—

Many excellent reviews are available that examine the neurotoxic effects of methamphetamine, cocaine, and other psychostimulants in significant detail (Davidson et al., 2001; Kita et al., 2009; Krasnova & Cadet, 2009; Cadet & Krasnova, 2009; Cadet & Jayanthi, 2013), and will only be concisely mentioned. Instead, our goal here is to consider the role of microglia and astroglia in both contributing to and responding to neuronal injury, and the extent to which glially-directed pharmacotherapies might be advantageous in managing the chronic neuroinflammatory and degenerative effects of these abused substances.

Briefly, methamphetamine can reportedly damage neurons through a variety of mechanisms and the exact sequelae of events resulting in neuronal compromise are not fully understood. Methamphetamine and cocaine are weak bases that restrict intracytoplasmic acidification and reduce the vesicular transmembrane pH gradient necessary for vesicular uptake, while prompting excessive release of biogenic amines from presynaptic terminals (Sulzer & Rayport, 1990). While intracytoplasmic dopamine was initially thought to intrinsically

promote methamphetamine neurotoxicity (Facchinetti et al., 2004), in reality, the non-enzymatic conversion of dopamine to dopamine quinones (LaVoie & Hastings, 1999a; Sulzer & Zecca, 2000) and the concurrent generation of oxyradicals are believed necessary to elicit a cytotoxic microglial response (LaVoie & Hastings, 1999b; Sulzer & Zecca, 2000; Kuhn, Francescutti-Verbeem, & Thomas, 2008; Thomas, Francescutti-Verbeem, & Kuhn, 2008). Despite this evidence, there remains some skepticism regarding the extent to which methamphetamine-induced intraneuronal dopamine quinone formation is causal in neurodegeneration in addicts (Sulzer & Zecca, 2000). This highly localized response may be exacerbated by excessive peripheral ammonia caused by concurrent methamphetamine-induced hepatotoxicity (Halpin & Yamamoto, 2012). The alterations to pH, nitrogen balance, and redox exact the greatest toll on vesicular trafficking at presynaptic boutons, which results in highly localized increases in oxidative and nitrosative stress that disrupt the dopamine transporter (DAT) (Fleckenstein, Metzger, Wilkins, Gibb, & Hanson, 1997) and vesicular monoamine transporter-2 (VMAT2) function (Miller, Gainetdinov, Levey, & Caron, 1999; Larsen, Fon, Hastings, Edwards, & Sulzer, 2002). Disturbing the transporters promotes the pathologic accumulation of dopamine, a weak oxidant, within the cytoplasmic compartment of presynaptic terminals initiating their damage (Miller et al., 1999; Fumagalli et al., 1999; Eyerman & Yamamoto, 2007) and VMAT2 reductions are evident in cocaine addicted individuals (Little, Krolewski, Zhang, & Cassin, 2003). Dopaminergic presynaptic terminal destruction is accompanied by microglial activation, but is thought to be independent of dopamine accumulation in the synaptic cleft or dopamine D1 or D2 receptor blockade (Thomas et al., 2004; Thomas et al., 2004). Moreover, psychostimulants also disrupt the function of GluN2B subunit-expressing *N*-methyl-D-aspartate (NMDA) receptors on neurons (Davidson et al., 2007), which are well known to facilitate the excitotoxic effects of excessive and/or extrasynaptic glutamate.

Methamphetamine and other psychostimulants induce atypical increases in extracellular glutamate in the CNS (Miyatake, Narita, Shibasaki, Nakamura, & Suzuki, 2005; Quinton & Yamamoto, 2006; Cadet, Krasnova, Jayanthi, & Lyles, 2007; Kaushal & Matsumoto, 2011; Pereira et al., 2012). Excessive glutamate, especially at extrasynaptic sites (Sattler, Xiong, Lu, MacDonald, & Tymianski, 2000; Hardingham, Fukunaga, & Bading, 2002), induces excitotoxic injury through actions at specific glutamate receptor types and subtypes expressed by neurons (Rothman & Olney, 1986; Choi, 1988; Olney et al., 1991; Choi, 1992). Overactivation of extrasynaptic GluN2B NMDA receptors causes synaptodendritic injury and neuron death (Ivanov et al., 2006; Liu et al., 2007). Blockade of NMDA receptors with MK-801 or dextromethorphan prevents methamphetamine-induced neurotoxicity (Thomas & Kuhn, 2005). By contrast, some glutamate receptor types are neuroprotective (Venero et al., 2002; Taylor, Diemel, & Pocock, 2003). For example, GluN2A- (GRIN2A) and GluN2B- (GRIN2B) subunit-containing NMDA receptors typically have opposing roles in synaptic stabilization (Kim, Dunah, Wang, & Sheng, 2005). Not inconsequentially, microglia and astrocytes also express many of these same glutamate receptors, which permit both glial types to respond in coordination with neurons and to assume an immediate defensive posture if necessary. Excitotoxic levels of glutamate can trigger a massive inflammatory response in microglia, including the release of TNF- α and numerous other proinflammatory cytokines (Noda, Nakanishi, Nabekura, & Akaike, 2000; Hagino et al.,

2004). While the presence of TNF- α is often assumed to be problematic, depending on the level and duration of TNF- α exposure, it may alert glia to impending danger and can be cytoprotective to neurons (Mattson et al., 1995; Bruce et al., 1996; Figiel, 2008). Lastly, addictive drugs in general (Robison & Nestler, 2011), including methamphetamine (Cadet & Jayanthi, 2013), cause lasting in gene regulation through epigenetic mechanisms that likely to contribute to addiction. because methamphetamine and cocaine cause fundamental epigenetic changes that dysregulate the normal responses to glutamate, normal responses to glutamate are likely to be distorted and/or inappropriate (Robison & Nestler, 2011; Cadet & Jayanthi, 2013). Chronic (2 week) methamphetamine exposure in rats cause epigenetic changes mediated by a co-repressor of RE1 silencing transcription (CoREST), histone deacetylase 2, methyl CpG binding protein 2, and sirtuin 2 complex resulting in the hypoacetylation of histone H4 in the rat striatum (Cadet & Jayanthi, 2013). The epigenetic modification of GluA1 and GluA2 DNA sequences downregulate both AMPA receptor subunit transcripts and these lasting changes likely contribute to the maladaptive neuroplasticity underlying addiction (Cadet & Jayanthi, 2013).

Besides their potential role in activating microglial PRRs (discussed earlier), AMPA 1 glutaminergic (Snyder et al., 2000; Palmer et al., 2005; Davidson et al., 2007; Bowers, Chen, & Bonci, 2010; Yu, Chang, & Gean, 2013; Pierce & Wolf, 2013) and the P2X4 purinergic receptors (Horvath & Deleo, 2009; Horvath et al., 2010), are further distinguished by their pivotal roles in rewiring the key brain areas that underlie addiction through direct actions in neurons. It is noteworthy that many of the same abnormalities in psychostimulant-induced glutamate and/or ATP neurotransmission contributing to addictive behaviors appear to coordinate increases in neuroinflammation by activating microglial PRRs. Several investigators have proposed that glial involvement in general, and glial inflammation in particular, may be a necessary step in the sequelae of events leading to addiction (Crews, Zou & Qin, 2011; Frank, Watkins, & Maier, 2011; Clark, Wiley, & Bradberry, 2013).

The release of ATP from injured neurons activates microglial receptors, including P2Y12, P2X4, and P2X7 (Zhuo, Wu, & Wu, 2011), as well as the NOD-like receptor NLRP₃ (Gombault, Baron, & Couillin, 2012). ATP release from injured cells appears to be highly relevant in the neurotoxicity caused by psychomotorstimulants. As noted, some reports suggest that NLRP₃ inflammasomes cleave nascent IL-1 β into bioactive IL-1 β (Costa et al., 2012), a key pro-inflammatory cytokine released by microglia. The extension of microglial processes in response to neuronal damage in mice is affected by ATP via the P2Y12 receptor (Davalos et al., 2005; Haynes et al., 2006; Ohsawa et al., 2010). Moreover, P2X4 receptor signaling is crucial for the development of neuropathic pain in mice (Tsuda et al., 2003; Tsuda, Inoue, & Salter, 2005). ATP acting via P2X7 receptors is necessary for endotoxin (LPS) dependent release of IL-1 β from microglia (Ferrari, Chiozzi, Falzoni, Hanau, & Di, 1997).

Some neuron-derived signals restrict microglial activation and act as “Off” signals. These include CX3CL1 (fractalkine) (Cardona et al., 2006; Lee et al., 2010; Fuhrmann et al., 2010) and γ -amino-butyric acid (GABA) acting via specific GABA_A receptors (Pocock & Kettenmann, 2007) and GABA_B receptors, which restrict LPS-induced release of IL-6 and IL-12p40 (Kuhn et al., 2004). The interest in receptor systems that mediate “Off” signals is

bolstered by clear evidence implicating them in neurodegenerative processes and the promise of therapeutically switching “Off” over activated microglia. Recent reports suggest that CX3CL1 activation is able to inhibit the dendritic loss and death of striatal neurons induced by the synergistic action of morphine and the pathogenic HIV-1 protein Tat, despite the presence of sustained high levels of TNF- α (Suzuki et al., 2011).

A microglial transcriptional “Off” or “inactivation” regulator, with high potential relevance for psychostimulant abuse, is the Nurr1 transcriptional repressor. Nurr1 is essential for the generation and maintenance of dopaminergic neurons and Nurr1 mutations are responsible for familial Parkinson’s disease, which was recently discovered to inhibit inflammatory responses in microglia and astroglia (Saijo et al., 2009). Posttranslational modifications of Nurr1 promote the formation of Nurr1/CoREST corepressor complexes, which trigger the clearance of NF- κ B-p65 and restore pre-inflammatory transcriptional activity (Saijo et al., 2009). In microglia, Nurr1 expression is upregulated by LPS, and downregulated by increased ERK, JNK and PI3K/Akt pathway activity suggesting ample opportunity for therapeutic manipulation (Fan et al., 2009). Importantly, p65 must be phosphorylated before the NF- κ B-p65 complex can be removed by Nurr1/CoREST, and glycogen synthase kinase-3 β (GSK-3 β) serves an essential role in this function (Saijo et al., 2009).

Interestingly, Nurr1 heterozygote mice display augmented methamphetamine neurotoxicity and greater increases in nNOS activity and 3-nitrosyl adducts (Imam et al., 2005), and show increased neurotoxicity with prolonged methamphetamine exposure (Luo, Wang, Kuang, Chiang, & Hoffer, 2010). Acute methamphetamine exposure (1–3 h following a 4 mg/kg dose) increases Nurr1 transcript levels in several cortical regions and in the ventral tegmental area (VTA) in rats, while chronic exposure (4 mg/kg/day) for 2 weeks attenuates the induction of Nurr1 mRNA levels, suggesting Nurr1 expression becomes blunted with chronic methamphetamine exposure (Akiyama, Isao, Ide, Ishikawa, & Saito, 2008). Thus, in addition to manipulating Nurr1/CoREST activity, drugs and/or small molecule inhibitors of GSK-3 β (Coghlan et al., 2000; Cross et al., 2001) hold additional promise for managing and potentially reversing the deleterious consequences of glial overactivation resulting from psychostimulant abuse.

2.2.3 Consequences Of Microglial Overactivation—As noted earlier in the section on PRRs, many authoritative reviews describe the neurobiological consequences of methamphetamine-induced oxidative, nitrosative damage and neuronal injury and death and need not be repeated here. Microglial activation is triggered to varying degrees by a large number of effectors, which include all the PRRs noted earlier and a combination of key transcriptional regulators. Key aspects of the events triggering microglial activation are briefly summarized below.

The macrophage antigen complex-1 (Mac-1), which is also a commonly used macrophage/microglial (and neutrophil) marker (Tang et al., 1997; Zhang, Goncalves, & Mosser, 2008), is essential for microglial mediated neurotoxicity (Hu et al., 2008). Upon activation, Mac-1 is thought to recruit the p47^{phox} NADPH oxidase subunit to the cell surface, which is requisite for NADPH assembly, superoxide production, and host oxidative defense (Hu et al., 2008). Extracellular reactive oxygen species (ROS) for use in host defense originate from NADPH oxidase, which catalyzes superoxide production from oxygen. NADPH

complex activation increases the production of extracellular ROS and can amplify toxic proinflammatory signals through redox signaling, which can be toxic to bystander neurons (Halliwell, 1992; Block et al., 2007; Block & Hong, 2007; Levesque et al., 2010). Methamphetamine and cocaine cause NADPH complex activation in microglia.

A wide variety of PRRs converge on NF- κ B to trigger proinflammatory responses. Rel/NF- κ B family of transcription factors is central in regulating expression of genes that mediate essential physiological processes, including neuroimmune responses in microglia (Karin, Cao, Greten, & Li, 2002). The family is comprised of five polypeptides (p50, p52, p65/RelA, c-Rel and RelB) that share a homologous N-terminal Rel homology region (Yakovleva et al., 2011). Rel homology domain polypeptides can interact with different affinities and specificities; each is uniquely regulated by inhibitor I κ B proteins, and differentially affects nuclear translocation and DNA binding. ROS are implicated as second messengers promoting the activation of NF- κ B by TNF- α and IL-1 β in microglia (Block, Zecca & Hong, 2007) and similarly in astrocytes (El-Hage et al., 2008). The effects of ROS on NF- κ B activation are cell specific and dependent on subcellular localization (Kabe, Ando, Hirao, Yoshida, & Handa, 2005). NF- κ B activity is associated with microglial proinflammatory responses (Pawate, Shen, Fan, & Bhat, 2004; Guo & Bhat, 2006; Pasparakis, 2009), and NF- κ B pro-inflammatory gene expression is directly exacerbated by ROS (Pawate et al., 2004).

2.2.4 Shades of gray—Intermediate States of Microglial Activation—In reality, the low levels of chronic inflammation that accompany chronic cocaine abuse, and somewhat higher levels of chronic inflammation associated with methamphetamine abuse, are typified by intermediate states of activation/inactivation, rather than all-or-none responses. Colton defines two intermediate states of microglial activation as “alternative activation” and “acquired deactivation” (Colton, 2009).

“Alternative activation” is induced by IL-4 and IL-13 and underscored by reduced levels of proinflammatory cytokine production. This initial state of deactivation is mediated intracellularly by events downstream of STAT6 and highlighted by anti-inflammatory cytokines, the downregulation of nitric oxide synthase 2 (NOS2), and tissue repair and reconstruction. NOS2 is particularly important because it converts arginine into nitric oxide, which is essential in peroxynitrite (ONOO⁻) production and the generation of reactive nitrogen species (RNS). A hallmark of alternative activation is arginine is primarily used to produce polyamines (via enzymatic conversion by arginase 1), rather than nitric oxide, because of the downregulation of NOS2 (Colton, 2009).

“Acquired deactivation” is characterized by a further downregulation of innate immune responses. This “secondary” state of deactivation involves enhanced STAT3/SMAD activity, which is mediated by a downregulation of pro-inflammatory cytokine production, elevated IL-10 and TGF- β anti-inflammatory cytokine release, upregulation of heme-oxygenase 1 (HO-1) and sphingosine-1-phosphate, and typified by heightened “non-immunogenic” phagocytosis of apoptotic cell fragments and immune suppression (Colton, 2009). We propose that chronic psychostimulant abuse, especially cocaine abuse that results in less frank neuropathology than with chronic methamphetamine, results in an “altered”

state characterized by “alternative activation” with abortive attempts at “acquired deactivation”. The sustained partial switch from an acute to a chronic immune profile is likely to be quite maladaptive and seemingly contributes to the prolonged synaptodendritic instability and a protracted weakening of host defenses via partial immunosuppression that is evident with chronic psychostimulant abuse.

2.2.5 Microglial-induced neuroprotection and restoration of neuronal function

—With a long-standing emphasis on cytotoxicity, it is easy to overlook the beneficial role microglia play in supporting normal neuronal function. Microglia serve many beneficial roles by providing trophic support and participate in the repair of damaged neural circuits. For example, during maturation they are essential for selectively pruning excess synaptic connections required for normal function (Paolicelli et al., 2011). In many instances, such as in an experimental model of amyotrophic lateral sclerosis, the morphologic “activation of microglia and astroglia does not predict [cytotoxic] glial function” (Beers, Henkel, Zhao, Wang, & Appel, 2008). A variety of cues act as microglial “Off or inactivation” signals (Block et al., 2007), promoting the release of anti-inflammatory cytokines and trophic factors. These are required for maintaining tissue homeostasis and restricting microglial activation. Anti-inflammatory cytokines include IL-10, while microglial-derived trophic factors include brain-derived neurotrophic factor (BDNF) (Graham et al., 2007; McGinty, Whitfield, Jr., & Berglind, 2010) and transforming growth factor- β (TGF- β) (Streit, 2002; Ransohoff & Perry, 2009). Although microglia can express glial cell-line-derived neurotrophic factor (GDNF) and BDNF, astrocytes generate a significant amount of the BDNF and especially GDNF produced in the brain, which is described in the next section. Tropomyosin receptor kinase B (TrkB) and Ret receptor tyrosine kinase, the cognate receptors for BDNF and GDNF, respectively, are widely expressed by neurons throughout the brain, including the neostriatum and nACC (Yan et al., 1997; Nosrat, Tomac, Hoffer, & Olson, 1997). TGF- β receptors are expressed by neurons, astroglia, and microglia. Thus, psychostimulant-induced increases in glial-derived BDNF and GDNF are strategically positioned to maintain and provide trophic support for neighboring neurons, and these glial-neuron signals are critical in promoting neuroplasticity.

2.3. Astroglia

2.3.1 Critical functions—Astroglia form an intimate association with neurons and are involved with fundamental processes including synaptic transmission that were previously thought to be exclusively neuronal (Parpura, Basarsky, Liu, Jęftinija, & Haydon, 1994; Araque, Parpura, Sanzgiri, & Haydon, 1999; Volterra & Meldolesi, 2005; Haydon & Carmignoto, 2006). As noted earlier, the “tripartite synapse” refers to the intimate structural and functional association between astrocytes and cognate pre- and post-synaptic interconnections. Astrocytes are also critical for interpreting and modifying neuron-to-macrogial communication and vice versa—especially during pathologic situations (Maragakis & Rothstein, 2006). Through the selective uptake and/or release (referred to as gliotransmission) of specific neurotransmitters, astroglia play a vital role in synaptic function and can affect qualitatively and quantitatively affect neurotransmission. Importantly, similar to microglia, astrocytes are also directly affected by psychostimulants. Despite some neuroprotective responses, the net consequences of exposing astroglia to

psychostimulants is they are less likely to aid neurons and assuage overactive microglia following drug exposure.

An essential function of astrocytes is in the reuptake and management of glutamate released by neurons during synaptic activity (Hertz & Zielke, 2004; Boileau et al., 2008). Most of the released glutamate undergoes reuptake by astrocytes through glutamate transporters GLT-1 (EAAT-2) and GLAST (EAAT1) (Rothstein et al., 1996; Tanaka et al., 1997). The glutamate retrieved by astrocytes is converted to glutamine by glutamine synthetase—an enzyme that is not expressed by neurons or other glial types besides astrocytes. The conversion of glutamate to glutamine is critical because excess extracellular glutamate can be excitotoxic to neurons. Neurons rely exclusively on astrocytes to “detoxify” glutamate and return it as glutamine (via phosphate-activated glutaminase), which is referred to as the glutamate-glutamine shuttle. Importantly, the glutamate transport is coupled to the production of the antioxidant glutathione and GABA biosynthesis.

2.3.2 Psychostimulant effects on astroglia—Glutamate is highly involved in learning behaviors associated with addiction (Hyman, 2005; Kalivas, 2009; Kalivas & Volkow, 2011; Stuber, Britt, & Bonci, 2012), including conditioned place preference (CPP). Because of their essential role in managing glutamate, understanding the neurobiological consequences of psychostimulants in astrocytes is likely to reveal significant mechanisms of action. Indeed, EAAT1/2 have been proposed as potential therapeutic targets for methamphetamine and cocaine neurotoxicity (Nakagawa, Fujio, Ozawa, Minami, & Satoh, 2005; Abulseoud, Miller, Wu, Choi, & Holschneider, 2012). The significance of diminished glutamate reuptake in psychostimulant action is revealed by findings demonstrating that a glutamate transport activator, MS-153, given together with methamphetamine or cocaine, significantly decreased CPP without varying locomotor responses in mice (Nakagawa et al., 2005). While few reports of direct actions of methamphetamine or cocaine on EAAT1/2 are reported, Halpin and Yamamoto (2012) suggest that glutamate transporter impairment may result from acute systemic increases in ammonia caused by acute hepatotoxicity. Even slight increases in ammonia decrease EAAT1 expression (Zhou & Norenberg, 1999; Chan, Hazell, Desjardins, & Butterworth, 2000) and limit glutamine synthetase activity (Kosenko et al., 2003). Importantly, the deleterious consequences of methamphetamine and/or ammonia were prevented by co-administering the AMPA receptor antagonist, GYKI 52466, implicating extracellular glutamate and its mismanagement in methamphetamine neurotoxicity (Halpin & Yamamoto, 2012).

Astrocytes express DAT, and can uptake and metabolize extracellular dopamine (Hertz, 1979; Hertz, Chen, Gibbs, Zang, & Peng, 2004; Miyazaki et al., 2011). Striatal astrocytes exposed to methamphetamine in cell culture display decreased 3,4-dihydroxyphenylacetic acid (DOPAC) formation suggesting that monoamine oxidase is selectively inhibited (Kita, Philbert, Wagner, Huang, & Lowndes, 1998). Astrocytes isolated from basal ganglia can express dopamine D1, D2, D3, D4, and/or D5 receptors (Zanassi, Paolillo, Montecucco, Avvedimento, & Schinelli, 1999; Miyazaki, Asanuma, Diaz-Corrales, Miyoshi, & Ogawa, 2004). Dopamine upregulates metallothionein expression and secretion by astrocytes (Miyazaki et al., 2011). Metallothionein binds metals, especially Zn^{2+} , and modulates redox potentials affording indirect protection to methamphetamine-exposed neurons (Miyazaki et

al., 2011). Recent evidence suggests that stimulating dopamine D2 receptors in astrocytes restricts innate immune activation through α B-crystallin release (Shao et al., 2013). Methamphetamine inhibits glucose uptake by astrocytes and neurons resulting in energetic compromise (Abdul Muneer, Alikunju, Szlachetka, & Haorah, 2011).

2.3.3 Astroglial responses to psychostimulant-induced neuronal dysfunction and injury

Besides their role in buffering and managing glutamate, astroglia possess a wide variety of PRRs, respond to DAMPs, and there is an increasing awareness of their key role in innate immune function and its modulation. While astrocytes have long-been known to protect neurons from oxidative damage (Desagher, Glowinski, & Premont, 1996; Wilson, 1997), those effects may be overridden by immune signals such as cytokines produced by microglia, other astrocytes, or other immune effector cells (Chao et al., 1996; Chao, Hu, & Peterson, 1996). Astroglia readily communicate with microglia forming reverberating feedback loops mediating both inflammatory and anti-inflammatory responses—depending on context (Sofroniew & Vinters, 2010). Exposing astrocytes to methamphetamine causes the release of the proinflammatory cytokine IL-6 (Tezuka et al., 2013). The presence or absence of IL-6 coincides with deficits in behavioral correlates of working memory in mice (Tezuka et al., 2013). Moreover, because astrocytes can express numerous classes of neurotransmitter receptors (Prochiantz & Mallat, 1988; Shao & McCarthy, 1994; Shao, Porter, & McCarthy, 1994; Glowinski et al., 1994; Hauser, Fitting, Dever, Podhaizer, & Knapp, 2012), PRRs, and control key neurochemical systems, they are strategically positioned to interpret and convey information regarding neuronal function to microglia and vice versa. In fact, to emphasize the intimate association between neurons, astrocytes, and microglia, especially synaptic remodeling during pathologic processes, it has been suggested that the “tripartite” synapse discussed earlier might be better redefined as “tetrapartite” (De Leo, Tawfik, & Lacroix-Fralish, 2006; Milligan & Watkins, 2009).

Astrocytes are highly plastic and their phenotype can be modified by regional and extrinsic cues within the extracellular environment (Bachoo et al., 2004; Theodosis, Poulain, & Olier, 2008; Zhang & Barres, 2010; El-Hage, Podhaizer, Sturgill, & Hauser, 2011). For instance, astrocytes isolated from different brain regions display fundamental differences in methamphetamine responsiveness in cell culture (Stadlin, Lau, & Szeto, 1998). The diversity and plasticity of receptor expression by astrocytes is not limited to neurotransmitter receptors. PRRs, which recognize conserved microbial molecular motifs, display considerable diversity in astroglia. Moreover, the appearance and level of expression of individual PRRs appears to be plastic and modifiable by environmental factors and xenobiotics (El-Hage et al., 2011). Psychostimulants themselves or local inflammatory factors from microglia or injured neurons may influence the expression of GPCRs, transporters, or PRRs. PRRs expressed by astrocytes include multiple members of the Toll-like receptor (TLR) family including TLR2, TLR3, TLR4, and TLR9 (El-Hage et al., 2011), RAGE (Park et al., 2004a; Ponath et al., 2007; Jones, Minogue, Connor, & Lynch, 2013), a novel NOD-like NLRP₂ receptor that functions as an inflammasome (Minkiewicz, de Rivero Vaccari, & Keane, 2013) and NOD2 receptors (Jiang, Sun, Kaplan, & Shao, 2012), and “laboratory of genetics and physiology 2” (LGP2), an antiretroviral PRR that recognizes double-stranded RNA (dsRNA) (Bruns et al., 2013). Human astrocytes and peripheral blood

mononuclear cells can express a novel RAGE splice variant (δ -RAGE) which is likely to have significant functional implications for the subset of psychostimulant abusers who express this allelic variant (Park et al., 2004b). The expression of TLR2 and TLR9 are particularly important in the host defense response to viral infections, including human immunodeficiency virus (HIV) (Equils et al., 2003) and herpes simplex virus type-1 (HSV-1) (Villalba et al., 2012; Wang et al., 2012a). Methamphetamine exposure has been recently shown to decrease TLR9 expression by macrophages (Cen et al., 2013), but has not yet been explored in astroglia. Based on findings that TLR9 expression by astrocytes is highly plastic and modifiable by other drugs such as opiates or HIV-1 proteins (El-Hage et al., 2011), suggest TLR9 might also be affected by psychostimulants. Collectively, the above results suggest that psychostimulants can affect the innate immune response by altering one or more TLR signaling pathways.

2.3.4 Neuroprotective astroglial responses—As noted earlier, astrocytes exposed to methamphetamine release metallothionein, a free radical scavenger (Kumari, Hiramatsu, & Ebadi, 1998) that protects neurons from the toxic effects of dopamine quinones (Miyazaki et al., 2011). Astrocytes also release heme-oxygenase-1 (HO-1) (Huang, Wu, Lin, & Wang, 2009), which is neuroprotective because it is essential for the production of carbon monoxide, bilirubin, and ferritin (Otterbein, Soares, Yamashita, & Bach, 2003). Pituitary adenylyl cyclase-activating polypeptide 38 (PACAP38) is also released from psychostimulant exposed astrocytes. PACAP38 (1 mg/kg total administered subcutaneously via Alzet minipump for 7 days) counteracts the effects of four doses of 15 mg/kg methamphetamine at 2 h intervals by increasing the expression of VMAT2 significantly attenuating the neurotoxicity (Guillot et al., 2008).

GDNF is mainly produced by astrocytes, although a few reports suggest that subsets of neurons and microglia may express GDNF at low levels (Appel, Kolman, Kazimirsky, Blumberg, & Brodie, 1997; Sandhu et al., 2009). GDNF first binds to its coreceptor, GDNF family receptor $\alpha 1$ (GFR $\alpha 1$), before activating the “rearranged during transfection” (Ret) receptor, which is a member of the tyrosine kinase superfamily (Jing et al., 1996; Trupp et al., 1996; Treanor et al., 1996; Eketjall, Fainzilber, Murray-Rust, & Ibanez, 1999). GDNF is a neurotrophic factor that preferentially protects dopaminergic neurons against methamphetamine neurotoxicity (Cass, 1996; Boger et al., 2007). GDNF is also a potent inhibitor of microglial activation (Rocha, Cristovao, Campos, Fonseca, & Baltazar, 2012). GDNF may be beneficial in treating addiction (Carnicella & Ron, 2009; Gramage & Herradon, 2011), which is discussed in greater detail later in this review.

Similar to GDNF, the neurotrophin, brain-derived neurotrophic factor (BDNF) protects neurons against cocaine neurotoxicity (Graham et al., 2007; McGinty et al., 2010). While BDNF can be expressed by subsets of neurons and glia, the proinflammatory cytokine TNF- α uniquely induces the expression and release of BDNF by primary astrocytes (Saha, Liu, & Pahan, 2006). Pahan and colleagues go on to show that, in astrocytes, BDNF expression is regulated through TNF- α dependent increases in both NF- κ B and C/EBP β transcriptional activity (Saha et al., 2006). Although counterintuitive, the NF- κ B-directed concurrent production of both proinflammatory cytokines and BDNF, which may be unique to astrocytes and not shared by microglia, suggests that astrocytes can provide trophic support

despite adverse inflammatory conditions. Alternative studies show that the immature, proneurotrophin form of BDNF selectively activates p75 neurotrophin receptors (p75NTR), which can increase NF- κ B transcriptional activity; while mature BDNF only stimulates TrkB neurotrophin receptors, which are intrinsically neuroprotective (Reichardt, 2006). Importantly, Nestler and coworkers demonstrate that the selective ablation of the TrkB receptor gene from dopamine D1 or D2 receptor-expressing neurons has diametrically opposing effects on cocaine reward (Lobo et al., 2010). Collectively, these highly provocative findings describe a link between NF- κ B mediated neuroinflammation and BDNF-directed neuroplasticity in the context of psychostimulant addiction.

3. IN VIVO EVIDENCE THAT MODULATING GLIA AND NEUROINFLAMMATION PROVIDE PHARMACOTHERAPEUTIC POSSIBILITIES FOR PSYCHOSTIMULANT ABUSE

3.1. Introduction

Considering the multiple functions of glia, and because glia are the most numerous cell in the brain, it is not surprising that psychostimulants affect their activity (see above). Modulating the activity of the glia has been, in turn, reported to attenuate some of the abuse-related effects of the psychostimulants. Evidence that drugs affecting glial function might emerge as pharmacotherapeutics for treating psychostimulant abuse are reviewed in the next section.. Histopathological and biochemical assessment at autopsy (Buttner, 2011) and positron emission imaging (PET) imaging studies (Sekine et al., 2008) in individuals chronically exposed to psychostimulants suggest that cocaine- (Little et al., 2009) and methamphetamine- (Sekine et al., 2008) can cause astrogliosis and microgliosis with chronic cocaine and methamphetamine abuse. These findings are not universal; however, since several reports fail to or find intermediate changes following prolonged methamphetamine abuse—suggesting reactive astroglial and microglial responses may markedly differ among individuals (Kitamura et al., 2010; Clark, Wiley & Bradberry, 2013). The disparate results are perhaps not surprising considering the inherent differences in genetics, environment, and drug use patterns among individuals. Moreover, the glial response is likely to be even more dynamic, because astroglia and microglia are highly plastic and modifiable by environmental influences.

Most of the drugs included in this section have multiple effects, some of which do not involve glia, but that nevertheless could participate in their potential effectiveness. We can't restrict this review to drugs with only effects specific to the glia. Instead, the minimally inclusive criteria we apply are drugs that are known to affect the glia and neuroinflammatory processes as a dominant effect, and that have consequences for psychostimulant-affected behavior thought to be associated with or predictive of their abuse. With those criteria as a guide, we first discuss drugs affecting glially-derived neurotrophic factors and then consider drugs whose actions in glia are unlikely to involve neurotrophic factors.

Two neurotrophic factors widely expressed in glia are GDNF and BDNF. The molecular pharmacology and biochemical mechanisms of BDNF and GDNF are described in detail in Section 2. In summary, GDNF is present in astrocytes and microglia throughout the brain

being present in the cortex, basal forebrain, and more particularly in the nigrostriatal system (Schaar, Sieber, Dreyfus, & Black, 1993). GDNF is secreted by both neuronal (Oo, Ries, Cho, Kholodilov, & Burke, 2005) and glial (astroglial and microglial) cells (P. S. Chen et al., 2006; Katoh-Semba et al., 2007; Lin, Doherty, Lile, Bektesh, & Collins, 1993; Ohta et al., 2003; Rocha, Cristovao, Campos, Fonseca, & Baltazar, 2012; Satake et al., 2000) in the CNS. The actions of homodimeric GDNF are mediated through specific binding to the GDNF family receptor alpha 1 (GFR α 1) co-receptor, leading to activation of receptor tyrosine kinase (RET) (for review see, Airaksinen & Saarma, 2002). BDNF is distributed widely in the brain including the cortex, cerebellum, hippocampus and other areas (H. T. Zhang et al., 2007), and is contained and secreted by astroglia (F. Zhang, Lu, Wu, Liu, & Shi, 2012) and microglia (Coull et al., 2005; Keller, Beggs, Salter, & De Koninck, 2007). Activation of the P2X4 purinoceptors (P2X4Rs) causes the release of BDNF and it subsequently acts via its cognate receptor, tropomyosin-related kinase B (TrkB) (Trang, Beggs, Wan, & Salter, 2009).

Most of the studies reviewed below that manipulate GDNF and BDNF levels involve their delivery into brain areas, or their general up- or down-regulation through pharmacologic, genetic or other methodology that do not specifically target glia. In fact, most of the reports either lose site or fail to mention that glia, rather than neurons, are the likely source of these neurotrophic factors. Because glia are the major source of these neurotrophic factors, psychostimulant-induced alterations in neurotrophic factors are likely to result from the drugs acting in glia. There have been several, recently published and exhaustive reviews of the importance of GDNF and BDNF in modulating the effects of the drugs of abuse (Bolanos & Nestler, 2004; Carnicella & Ron, 2009; Ghitza et al., 2010; McGinty, Whitfield, & Berglind, 2010; Messer et al., 2000; Minae Niwa, Nitta, Yamada, & Nabeshima, 2007; Pierce & Bari, 2001; Ron & Janak, 2005), and it is beyond our objective to follow similarly. Our more limited objective is to attempt provide a selective review of reports sufficiently compelling to seriously consider the use of GDNF and BDNF as pharmacotherapeutic targets for treating psychostimulant abuse.

3.2. Effects of Manipulating GDNF and TNF- α Levels

One of the earliest demonstrations that GDNF administration into the VTA could attenuate some of the abuse-related effects (biochemical and behavioral) of the psychostimulants were by Messer and colleagues (Messer et al., 2000). This group reported that administration of GDNF (2.5 μ g/day) via osmotic minipumps into the VTA completely blocked the ability of chronic cocaine (20 mg/kg i.p. for 7 days) to increase levels of tyrosine hydroxylase and the NMDAR1 glutamate receptor subunit. Increasing levels of tyrosine hydroxylase, the enzyme responsible for the rate-limiting conversion of the amino acid L-tyrosine to L-3,4-dihydroxyphenylalanine (L-DOPA) (Nagatsu, 1995), the precursor of dopamine, and the NMDAR1 glutamate subunit, which is selectively distributed within astrocytic processes and presynaptic axon terminals within the locus coeruleus (Van Bockstaele & Colago, 1996), are typically increased by cocaine exposure (Beitner-Johnson & Nestler, 1991; Fitzgerald, Ortiz, Hamedani, & Nestler, 1996; Sorg, Chen, & Kalivas, 1993). In behavioral studies they also reported that GDNF-infused rats (2.5 μ g/day into the VTA) showed a dose-

dependent reduction in the levels of cocaine-induced CPP, although this regimen of GDNF didn't abolish place conditioning completely.

In parallel studies, Messer and colleagues (Messer et al., 2000) showed that reducing endogenous levels of GDNF increased the sensitivity to cocaine, and opposite to the effects of exogenously administering GDNF. Reducing endogenous GDNF levels by intra-VTA infusion of an anti-GDNF antibody increased the sensitivity of rats to the ability of cocaine to increase tyrosine hydroxylase levels, and sensitized them to the ability of a threshold dose of cocaine (2.5 mg/kg) to significantly induce CPP. These latter demonstrations illuminate the importance of normal basal levels of GDNF for controlling the sensitivity to respond, biochemically and behaviorally, to cocaine. Genetically reducing levels of GDNF also sensitized rats to the effects of cocaine. Heterozygote GDNF knockout mice (GDNF⁺ / – mice), with diminished levels of GDNF, showed a greater sensitivity for cocaine to establish CPP in that a dose of 5 mg/kg was able to establish CPP in heterozygote but not wild-type mice. GDNF⁺ / – mice also showed a greater sensitivity for cocaine to induce locomotor sensitization following its daily injection (10 mg/kg i.p.) for four days, relative to wild-type littermates, despite having similar levels of locomotor activation on the first day of treatment. The increased sensitivity of GDNF⁺/– mice versus wild-type controls to cocaine's locomotor sensitizing effects were, however, not replicated in a subsequent study that used a similar cocaine dosing regimen (Airavaara et al., 2004). Despite this latter ambiguity involving the locomotor-sensitizing effects of cocaine, Messer and colleagues (Messer et al., 2000) firmly documented the importance of GDNF in controlling the biochemical and behavioral responsivity to cocaine exposure, and their results led them to explicitly suggest, for the first time, the possibility that manipulating levels of GDNF might provide a pharmacotherapeutic route to treat drug dependency.

The ability of increased GDNF levels to attenuate even more relevant, abuse-related behaviors was reported by Green-Sadan and colleagues (Green-Sadan et al., 2003). These researchers observed that increasing GDNF levels, either by augmenting its endogenous production or by exogenous delivery, reduced levels of lever pressing maintained by 1 mg/kg/infusion cocaine under fixed-ratio 1 reinforcement schedules during a 12-day access period in Sprague-Dawley rats, relative to untreated or phosphate-buffered saline (PBS) injection controls. Endogenous generation of GDNF was accomplished by transplanting a human astrocyte-like cell line [simian virus-40 glia (SVG)] into the striatum and nucleus accumbens; SVG secretes GDNF both tonically and following dopaminergic stimulation. Exogenous delivery of GDNF into the striatal/n. accumbens border at a rate of 2.5 µg/day was accomplished by osmotic minipumps. SVG-induced elevation of GDNF levels significantly attenuated levels of cocaine self-administration evidenced by a slower trajectory and lower obtained level of self-administration by Day 12 of cocaine access. This effect on cocaine self-administration appeared not to be due to a general depressant effect, for it did not significantly disrupt rates of lever pressing maintained by water reinforcement in control rats. Exogenous administration of GDNF appeared to completely prevent acquisition of cocaine self-administration, although saline self-administration control groups were not tested to unequivocally make that conclusion.

In other, parallel studies, Green-Sadan and colleagues (Green-Sadan et al., 2003) inversely found that cocaine self-administration affected GDNF levels. Rats that had self-administered cocaine had a 69% reduction of GDNF mRNA in the striatum, with no changes observed in the n. accumbens, relative to non-cocaine treated rats.

The hydrophobic dipeptide, Leu-Ile, induces synthesis of GDNF in vitro and in vivo, and its systemic administration (i.p.) increases the contents of GDNF (and BDNF) in the striatum of mice (Nitta et al., 2004). Leu-Ile (1.5 $\mu\text{mol/kg}$, i.p.) administration with methamphetamine (1 mg/kg, s.c.) for nine days increases levels of GDNF in both neuronal and astroglial cells, relative to the administration of methamphetamine alone (M. Niwa, A. Nitta, Y. Yamada, et al., 2007). When mice were pre-treated with Leu-Ile (1.5 $\mu\text{mol/kg}$, i.p.) 1 h before administration of methamphetamine (1 mg/kg, s.c.), CPP was significantly attenuated relative to treatments with vehicle given prior to methamphetamine administration. Curiously, increasing the dose of Leu-Ile to 15 $\mu\text{mol/kg}$ decreased its effectiveness in attenuating methamphetamine-induced CPP despite inducing similar levels of GDNF (M. Niwa, A. Nitta, Y. Yamada, et al., 2007). This latter effect may be due to the bell-shaped dose-effect curve for Leu-Ile-dependent induction of GDNF (M. Niwa, A. Nitta, Y. Yamada, et al., 2007). When 1 mg/kg s.c. methamphetamine was administered daily to mice for nine days it induced sensitization to its locomotor activity effects. The development of sensitization was significantly attenuated by co-treatment of Leu-Ile (1.5 and 15 $\mu\text{mol/kg}$) with methamphetamine. Leu-Ile, however, was unable to attenuate the locomotor activity effects induced by methamphetamine's initial administration, as it was unable to inhibit the increase in extracellular dopamine levels induced by a single 1 mg/kg methamphetamine treatment, although it was effective in inhibiting subsequent increases during repeated methamphetamine treatment. This lack of effectiveness of Leu-Ile to blunt the locomotor activity effects of methamphetamine's initial administration while blunting its sensitizing effects (M. Niwa, A. Nitta, Y. Yamada, et al., 2007) is reminiscent of the lack of enhanced sensitivity to the locomotor activity effects induced by cocaine's initial administration while displaying enhanced sensitivity to its sensitizing effects in GDNF +/- mice (Messer et al., 2000). Surprisingly, when given for five daily injections Leu-Ile was even effective in attenuating methamphetamine's effects when administered *after* methamphetamine regimens had been completed for inducing CPP and for inducing locomotor sensitizations (M. Niwa, Nitta, Shen, Noda, & Nabeshima, 2007).

Leu-Ile also induces TNF- α in cultured neurons as well as in vivo under treatment conditions inducing GDNF (M. Niwa, A. Nitta, Y. Yamada, et al., 2007). TNF- α , and other inflammatory signals, can induce GDNF expression in glia (Appel, Kolman, Kazimirsky, Blumberg, & Brodie, 1997). Accordingly, Niwa and colleagues (M. Niwa, A. Nitta, Y. Yamada, et al., 2007) suggested that two mechanisms be entertained to explain the ability of Leu-Ile to upregulate GDNF: one is via the expression of TNF- α and another by activating Hsp90/Akt/CREB signaling as reported by Cen (Cen et al., 2006). Observing the lack of effects of Leu-Ile in GDNF +/- and TNF- α -/- mice in attenuating methamphetamine's CPP effects, these researchers speculated that Leu-Ile's inhibitory effects on methamphetamine-induced CPP and locomotor sensitization was likely attributable to the attenuation of

methamphetamine-induced inhibition of dopamine uptake and methamphetamine-dependent increases in extracellular dopamine levels (M. Niwa, A. Nitta, Y. Yamada, et al., 2007).

Yan and colleagues from Nabeshima's laboratory (which included Niwa) extended the importance of endogenous GDNF levels as a determinant of methamphetamine abuse-related behaviors in mice in several directions including to its self-administration and relapse (Y. Yan et al., 2007). In these studies they studied the susceptibility to methamphetamine self-administration in GDNF (+/-) heterozygous knockout mice that had corticolimbic GDNF levels reduced to 54–66% of wild-type littermates. In one study they implanted indwelling venous catheters and trained mice to nose-poke reinforced with 0.1 mg/kg/infusion methamphetamine during 3-h daily experimental sessions. GDNF (+/-) mice required less time to reach stable methamphetamine self-administration than did wild type controls, although their cumulative intake of methamphetamine during training did not differ. When tested under a dose-response for methamphetamine reinforcement, GDNF (+/-) mice nose-poked more often under all doses of methamphetamine, significantly so at the intermediate doses of 0.01 and 0.03 mg/kg/infusion. When subjected to progressive ratio tests at 0.1 mg/kg/infusion methamphetamine, GDNF (+/-) mice demonstrated significantly higher breaking points suggesting a greater "motivation" for methamphetamine. When saline replaced methamphetamine as the infusate, both GDNF (+/-) and wild-type mice extinguished in a similar time course. When tested for the ability of a range of methamphetamine priming doses (0.2–3 mg/kg i.p.) to reinstate extinguished responding, all doses tested between 0.2 and 1.5 mg/kg methamphetamine reinstated greater levels of nose-poking in the GDNF (+/-) mice relative to the wild-types. Relative to saline prime tests, 0.4 and 1 mg/kg methamphetamine significantly elevated nose-poking in GDNF (+/-) mice, but methamphetamine did so only at 1 mg/kg in wild-type mice. Re-presenting the methamphetamine infusion-associated cues continued to reinstate extinguished nose-poking in the GDNF (+/-) mice after six months of methamphetamine withdrawal, although the effectiveness of these cues had withered in wild-type mice after three months. These results suggest that endogenous levels of GDNF can influence the susceptibility to methamphetamine abuse at several points during its abuse cycle, from expanding the range of methamphetamine doses that might come to control behavior and that might precipitate relapse, to determining the persistence of the susceptibility to relapse prompted by re-contact with drug-related stimuli. Observing these results, as well as acknowledging other reports indicating the importance of GDNF in determining methamphetamine-associated behaviors, Yan and colleagues (Y. Yan et al., 2007) echoed Messer and colleagues' (Messer et al., 2000) suggestion that targeting GDNF levels may be a route to developing pharmacotherapies for treating psychostimulant abuse.

Yan and colleagues further extended their earlier studies examining the importance of endogenous GDNF levels as a controller of methamphetamine abuse by comparing mice with elevated GDNF levels induced by bilateral microinjection of adeno-associated virus vectors expressing GDNF (AAV-Gdnf) into their striatum, to control mice similarly injected with adeno-associated virus-mediated enhanced green fluorescent protein (AAV-EGFP) during self-administration and relapse (Yijin Yan et al., 2013). Microinjection of AAV-Gdnf vectors increased the density of GDNF in the striatum by nearly 3-fold relative to AAV-EGFP injected mice at two weeks post-injection. Following intravenous catheterization, the

mice were allowed to nose-poke reinforced with 0.1 mg/kg/infusion methamphetamine during daily, 3-h experimental sessions. No differences were observed between AAV-Gdnf and AAV-EGFP mice during the initial acquisition (Days 1–11) of methamphetamine self-administration. However, once levels stabilized (Days 12–16) during the later phase of self-administration, active nose-poking was significantly lower in the AAV-Gdnf-treated mice than in the AAV-EGFP-treated mice. During extinction of nose-poking, there was no significant difference in active nose-poke responses between the two groups. After meeting extinction criteria, the mice were subjected to dose-response (0.2–2.0 mg/kg i.p.) methamphetamine prime-induced reinstatement tests. AAV-EGFP-treated mice showed a dose-dependent induction of reinstatement with nose-poke responding peaking at the 0.4 mg/kg i.p. methamphetamine-priming dose. In contrast, the AAV-Gdnf-treated mice failed to show any evidence of reinstatement across all priming doses examined. Because of the variability in responding by the AAV-Gdnf-treated mice, it was unclear whether reinstated responding was statistically greater than extinction levels and results of such tests, if conducted, were not provided. Following an additional extinction phase, the mice were subjected to a cue-induced reinstatement test, and then two months later were again tested for cue-induced reinstatement. Methamphetamine-associated cues reinstated responding in both groups during both tests in that nose-poking under cue conditions was more frequent than under no-cue conditions. During both tests, however, nose-poking by the AAV-Gdnf group was lower than that by the AAV-EGFP mice. These latter results not only show the effectiveness of elevated GDNF levels for blunting cue-induced precipitated renewal of responding previously reinforced by methamphetamine, but attest to the enduring effectiveness of the adeno-associated virus vector treatment. Observing the effectiveness of AAV-Gdnf striatal treatment in these studies, and the reports of the relatively non-toxic effects of AAV vectors reported by others (Miyazaki et al., 2012), Yan and colleagues speculated, "...that increased expression of exogenous GDNF protein through the microinjection of AAV-Gdnf vectors in the brain may be a gene therapeutic strategy to treat drug dependence and relapse in a clinical setting" (Yijin Yan et al., 2013).

3.3. Effects of Manipulating BDNF Levels

Horger and colleagues (Horger et al., 1999) tested the effects of exogenous administration of BDNF into the NAc and VTA in Sprague-Dawley rats and manipulation of its endogenous levels through the use of BDNF (+/–) heterozygous mice. Chronic infusion via osmotic minipumps of BDNF into the NAc (1 µg/day/side) resulted in a tripling of the locomotor increasing effects (activity counts) during the 10 min following a 15 mg/kg injection of cocaine relative to control rats. Saline injections also elevated peak locomotor activity by nearly double in BDNF-NAc mice relative to controls that complicated interpretations that the authors attributed to the enhancement of BDNF on mild stress (the injection procedure itself). A subthreshold dose of cocaine (5 mg/kg) in control rats was able to induce locomotor sensitization in BDNF-NAc injected rats. BDNF-NAc injected mice also developed sensitization faster to intermediate doses of cocaine (7.5 and 10 mg/kg) than controls. Mice chronically infused with BDNF into the VTA also showed an elevated locomotor activity response to cocaine (15 mg/kg) but the effects were less dramatic than BDNF infusion into the NAc perhaps, as reasoned by the authors, to ceiling effects of this high dose of cocaine. Intra-NAc BDNF infusion not only enhanced the cocaine (10 mg/kg)-

induced enhancement of light+tone conditioned reinforcers previously paired with water reinforcement, but also enhanced their efficacy in the absence of cocaine. The enhancement of cocaine's effects persisted through repeated (four) tests with cocaine across several days. Although both BDNF (+/-) knock-out mice and wild-type mice developed sensitization to cocaine's (10 mg/kg) locomotor activity effects, albeit delayed in BDNF (+/-) mice, wild-type mice showed a significantly greater (60% greater) response to cocaine upon its first administration.

Other studies reported that genetically manipulating BDNF levels controlled the effects of psychostimulants. Hall and colleagues (F. S. Hall, Drgonova, Goeb, & Uhl, 2003) examined the effects of cocaine on locomotor activity and upon its CPP in heterozygous BDNF (+/-) and wild-type mice. Doses of 5–20 mg/kg s.c. cocaine were tested in each subject during 2-h locomotor activity tests preceded by 1-h habituation periods. BDNF (+/-) mice were less active during wild-type littermates during the first hour of the 3-h test sessions. Although doses of 10 and 20 mg/kg cocaine were able to increase distance travelled in the wild-type mice, only 20 mg/kg cocaine, the highest dose tested, was able to do so in the BDNF (+/-) suggesting a reduced sensitivity to cocaine with the assumed reduction of BDNF levels. Similar differential effects of genotype on cocaine dose were observed during the CPP tests in that doses of 10 and 20 mg/kg cocaine were able to induce CPP in the wild-type mice, but only the 20 mg/kg cocaine dose was able to do so in the heterozygous BDNF (+/-) mice. Although Hall and colleagues observed that there had been reports that heterozygous BDNF (+/-) mice demonstrate altered processes determinative of learning and memory, because a higher dose (20 mg/kg) of cocaine established equivalent CPP in both groups it was unlikely that nonspecific learning deficits could account for the differences in groups at the lower 10 mg/kg cocaine dose. Because CPP involves learning associations between stimuli, and because 10 mg/kg cocaine may represent a more fleeting stimulus than 20 mg/kg if only because of kinetics, dismissing the involvement of learning and memory mechanisms may be premature. Hall and colleagues speculated that because BDNF affects both serotonergic and dopaminergic systems, the effects of partial BDNF deletion on cocaine-induced CPP are largely attributable to the actions of the neurotrophic factor on both of these systems.

Responding previously reinforced by drug delivery can be reinstated during extinction by drug-associated stimuli (de Wit & Stewart, 1981). The level at which responding is reinstated by drug-associated cues may first increase with increases in abstinence and then decrease, and the initial increase in responding with increasing abstinence has been referred by some as an "incubation" effect (Grimm, Hope, Wise, & Shaham, 2001). The "incubation" effect is not special to drug-maintained behavior, and can be characteristic of non-drug maintained behavior as well (Grimm et al., 2003). Lu and colleagues trained rats to self-administer 0.75 mg/kg/infusion cocaine for 10 days during six 1-h daily sessions and then performed intra-VTA infusions of BDNF (0, 0.075, 0.25, or 0.75 µg), or nerve growth factor (NGF) (0, 0.075, or 0.75 µg) and subsequently tested them for reinstatement on days 3 and 10 of withdrawal (Lu, Dempsey, Liu, Bossert, & Shaham, 2004). Responding was greater after 10 days of withdrawal than after 3 days, consistent with an "incubation" effect. Doses of 0.25 and 0.75 µg BDNF increased responding relative to controls on both withdrawal days. In a subsequent study these researchers reported that the enhancement of intra-VTA infusion of BDNF persisted for 30 days into withdrawal (Lu et al., 2004). Infusions of NGF

were without effect. Neither administering 0.75 μ g BDNF into the substantia nigra and testing on days 3 and 10 of withdrawal, nor administering it 2 h before the test session on Day 3 of withdrawal had an effect. Because intra-VTA infusions of BDNF did not appear to affect the slope of the time-response curve, and given observations that increases of BDNF in the VTA don't always track increases in incubated reward seeking, the authors speculated that BDNF "... is probably not directly involved in the basic process underlying the incubation of responsiveness to drug and nondrug reward cues." However, given that BDNF levels were correlated with time-dependent increases in reinstated responding in their previous studies (Grimm et al., 2003), and given the results of the present study, the authors speculated that BDNF-mediated neuroadaptations in mesolimbic areas appear to be involved with persistent cocaine seeking and prolonged withdrawal periods.

Although there have been several other reports in which increasing the presence of BDNF or its receptor, TrkB, in the NAc or VTA (but also including the CA3/dentate gyrus) augments psychostimulant-associated locomotor sensitization, CPP, self-administration or reinstatement of drug-conditioned behavior (e.g., Bahi, Boyer, Chandrasekar, & Dreyer, 2008; Graham et al., 2007), and decreasing their presence diminishes these psychostimulant effects (e.g., Bahi et al., 2008; Graham et al., 2007; Graham et al., 2009; Shen, Meredith, & Napier, 2006), opposite effects have also been reported when BDNF levels are manipulated in the mPFC (Berglind et al., 2007; McGinty, Berglind, Fuchs, & See, 2006). Berglind and See and colleagues were the first to assess the effects of BDNF infusion into the mPFC on psychostimulant (cocaine) abuse-related behaviors (Berglind et al., 2007; McGinty et al., 2006). Berglind and colleagues trained rats to lever press reinforced with cocaine infusion (0.2 mg/infusion) according to FR 1 reinforcement schedules during 2-h daily sessions for 10 consecutive days. In two experiments, BDNF (0.75 μ g/side) was infused into the mPFC (anterior cingulate or prelimbic cortex) immediately following the final self-administration session. When rats were tested during a 30 min extinction test (in which lever pressing was without scheduled consequences) preceded by 22 h of cocaine abstinence, intra-mPFC BDNF-infused rats pressed the previously-reinforced lever less than vehicle-infused rats. Other BDNF-infused rats tested during extinction preceded by six days of abstinence, for cue-reinstatement preceded by six days of extinction, and for cocaine prime-induced (10 mg/kg) reinstatement preceded by six days of extinction, pressed the previously reinforced lever significantly less than controls during each of the three test conditions. Although the first test was identified as an "extinction test", presses of the previously reinforced lever did result in presentations of the light+tone compound stimulus previously associated with cocaine infusion making it, in actuality, also a cue-reinstatement test. Other rats tested during "extinction", but in which lever presses resulted in cocaine-associated cue presentation following six days of cocaine abstinence, responded similarly to controls when intra-mPFC infusions occurred 22 h prior to testing indicating a time-sensitive window existed for the ability of BDNF to exert its effects. Other rats given the BDNF infusions following 10 sessions of food-reinforcement training failed to show differences from controls when tested during extinction (when active lever pressing only resulted in presentation of cues previously associated with food delivery) preceded by six days of abstinence, or during a cue-reinstatement test (whose conditions were little different from the "extinction test") preceded by six days of extinction. These results, contrasted with the

previously reviewed results which indicate that *decreasing* levels of BDNF may *attenuate* the abuse-related behaviors of BDNF, underscore that globally increasing or decreasing BDNF levels in the CNS with psychostimulant medication may not result in a well-controlled, intended therapeutic effect.

3.4. Sigma Receptor Effects

As previously described, this review was not intended to discuss activity of drugs that bind to conventional neuronal receptors for which there may be similar glial receptors. An exception needs to be made regarding the sigma receptor, which we briefly mention here. As discussed above, sigma1-receptors are one of several putative molecular targets of methamphetamine (Hayashi et al., 2010; Kaushal & Matsumoto, 2011) and cocaine (Navarro et al., 2010; Yao et al., 2011; Katz et al., 2011; Narayanan, Mesangeau, Poupaert, & McCurdy, 2011; Fritz, Klement, El, Saria, & Zernig, 2011; Robson, Noorbakhsh, Seminerio, & Matsumoto, 2012; Kourrich et al., 2013). Microglia, and potentially astroglia, express sigma1-receptors, and therefore, can be directly affected by exposure to methamphetamine and cocaine (Gekker et al., 2006; A. Hall, Cruz, Katnik, Cuevas, & Pennypacker, 2006). There have been previous reviews documenting the importance of sigma receptors in modulating the effects of the drugs of abuse (Banister & Kassiou, 2012; Matsumoto, Liu, Lerner, Howard, & Brackett, 2003; Maurice, Martin-Fardon, Romieu, & Matsumoto, 2002; Maurice & Romieu, 2004; Narayanan, Mesangeau, Poupaert, & McCurdy, 2011; Robson, Noorbakhsh, Seminerio, & Matsumoto, 2012), and their potential as pharmacotherapeutic targets for treating psychostimulant abuse is exhaustively reviewed in this volume by Matsumoto. To the extent that sigma receptor binding agents hold promise as pharmacotherapeutics for treating psychostimulant abuse can be attributed to their interactions with glia, especially the microglia, is not definitively known; however, glia should be kept in mind as possible cellular sites of action contributing to any therapeutic effects of this class of agent.

3.5. Nonspecifically Suppressing Glial Processes

Drugs described as having glial modulating or anti-neuroinflammatory effects as part of their overall profile have been reported to attenuate the abuse-related effects of psychostimulants. Often the exact mechanism for their anti-psychostimulant effect hasn't been identified, but their glial/neuroinflammatory-related effects appear to be among the most likely. Some of these drugs include propentofylline, minocycline and ibudilast.

Propentofylline is a phosphodiesterase inhibitor (principally PDF_{1V}) that inhibits induced microglial and astroglia TNF- α release, proliferation and adenosine reuptake (Gregory et al., 2013; Schubert et al., 1997). Methamphetamine-induced (10 μ M) activation of purified mouse cortical astrocytes that is significantly reduced (~34%) by propentofylline (3 μ M) (Narita et al., 2006). Methamphetamine-induced (1 mg/kg) CPP was suppressed by pretreatments with propentofylline (3 mg/kg) (Narita et al., 2006). Supporting the importance of astroglia in mediating the methamphetamine CPP effect, microinjecting astrocyte-conditioned medium (ACM), but not that of microglia-conditioned medium, into the nucleus accumbens the day before the CPP preconditioning test that preceded training with methamphetamine (0.0625, 0.125, 0.25, or 0.5 mg/kg, s.c.) significantly elevated levels

of CPP expression at all doses of methamphetamine at 0.125 and above (Narita et al., 2006). Intra-cingulate cortex (CG) administration of ACM also enhanced the rewarding effect induced by methamphetamine. Treatment with ACM collected from methamphetamine treated astrocytes induced an increase in the level of glial fibrillary acidic protein in mouse purified cortical astrocytes suggesting that methamphetamine exposure caused a release of factors from astrocytes promoting activation. Overall, these results indicate that modulating the effects of glial activity with drugs like propentofylline can obtund the rewarding effects of methamphetamine.

Minocycline is a broad spectrum semi-synthetic tetracycline antibiotic that has been in use for over 30 years whose main indication is acne vulgaris and other skin infections (Garrido-Mesa, Zarzuelo, & Galvez, 2013). Minocycline inhibits microglia and their neuroinflammatory processes including the release of cytokines and chemokines (Cui et al., 2008; Sriram, Miller, & O'Callaghan, 2006). Minocycline has other anti-inflammatory effects including the inhibition of phospholipase A2, prostaglandin E2 and Cox-2. It is protectorant against oxidative stress and apoptosis, and inhibits glutamate excitotoxicity (for review see, Soczynska et al., 2012). While minocycline clearly acts through microglia, and its actions are often categorically assumed to be acting via this cell type, minocycline also directly effects astroglia (Garwood, Pooler, Atherton, Hanger, & Noble, 2011; Alvarez, Rama Rao, Brahmabhatt, & Norenberg, 2011) and astroglia can also produce cytokines, chemokines, and contribute to inflammation. A caveat, noted earlier when discussing DREADDs and RASSLs, is that because astrocytes, microglia, and neurons act in concert and are functionally interdependent, it is not possible to reach unambiguous conclusions regarding the exclusivity of minocycline effects via microglia from in vivo studies—without the use of specialized strategies to discriminate among individual neural cell types.

Minocycline readily penetrates the CNS and has been considered for a broad range of CNS disorders including schizophrenia, depression, stroke, Parkinson's disease, and multiple sclerosis (Abdel-Salam, 2008; Blum, Chtarto, Tenenbaum, Brotchi, & Levivier, 2004; Buller, Carty, Reinebrant, & Wixey, 2009; X. H. Chen et al., 2011; Kim & Suh, 2009; Miyaoka et al., 2007; Soczynska et al., 2012; Stirling, Koochesfahani, Steeves, & Tetzlaff, 2005; Yenari, Kauppinen, & Swanson, 2010). Given minocycline's profile, researchers have begun to investigate its potential application as a pharmacotherapeutic for treating psychostimulant disorders.

Zhang, Hashimoto and colleagues reported several in vivo and in vitro effects of minocycline suggestive of potential in the treatment of methamphetamine abuse. Pretreating mice with minocycline (40 mg/kg) prior to a 3 mg/kg methamphetamine challenge significantly reduced (by ~ 50%) the psychostimulant's hyperlocomotor activity effects (L. Zhang et al., 2006). Doses of 10 and 20 mg/kg of minocycline were without effect. The 40 mg/kg dose of minocycline that was effective did not appear to have locomotor activity effects by itself. Others had reported the ability of a high dose (100 mg/kg, s.c.) of minocycline to attenuate the locomotor activity effects (ambulations) of a moderate dose (0.5 mg/kg; i.p.) of amphetamine in rats (Kofman et al., 1990). At the 100 mg/kg dose, however, minocycline reduced the number of ambulations relative to vehicle treated rats making it less clear regarding the specificity of the effect. This dose of minocycline was

ineffective in blocking the stereotypy induced by 0.5 and 1 mg/kg apomorphine (Kofman et al., 1990). Administering minocycline at 100 and 150 mg/kg intravenously (but not at 25 mg/kg), however, was able to reduce the total, ambulatory and vertical activity of rats elevated by 1 mg/kg i.p. of amphetamine (Kofman, van Embden, Alpert, & Fuchs, 1993). Again, however, these doses effective in attenuating amphetamine's effects appeared to reduce activity when given by themselves suggesting a degree of nonspecificity.

Zhang and colleagues also found that daily treatment with 3 mg/kg methamphetamine for five days induced sensitization to a 1 mg/kg challenge dose of methamphetamine given seven days later as inferred from the greater level of activity induced relative to a vehicle treated group. A group receiving chronic vehicle (i.e., "vehicle" for chronic methamphetamine) followed by a 1 mg/kg methamphetamine challenge was absent to properly infer "sensitization"; however, levels of locomotion elevated by the 1 mg/kg methamphetamine challenge did appear to be at least equal to, if not greater than that induced by the acutely administered 3 mg/kg methamphetamine dose from the earlier study and this suggested a sensitized effect. Sensitization was significantly attenuated by pretreatment with minocycline (40 mg/kg). Minocycline was unable to attenuate some of methamphetamine's *in vivo* effects, however. For instance, it failed (10–40 mg/kg, b.i.d.) to prevent hyperthermia induced by 3 injections of 3 mg/kg. Given the same methamphetamine dosing regimen, however, minocycline dose-dependently (10–40 mg/kg; b.i.d.) attenuated the reduction of dopamine (DA) and its major metabolite, 3,4-dihydroxyphenyl acetic acid (DOPAC) in the striatum, as well as significantly attenuating the reduction of the density of DAT in the striatum. Surprisingly, even when minocycline was given 2 h after the final treatment with methamphetamine, it attenuated the methamphetamine-induced reductions in DA and DAT in the striatum, although its protection was not complete and DOPAC levels were not protected. In *in vivo* microdialysis studies, pretreating mice with 40 mg/kg minocycline prior to a 3 mg/kg methamphetamine challenge significantly inhibited the induced increases in extracellular DA levels. Zhang and colleagues (L. Zhang et al., 2006) speculated that minocycline's inhibition of methamphetamine-induced DA release was likely, in part, responsible for its mechanism for blunting methamphetamine's *acute* behavioral effects, and that its ability to inhibit the activity of p38 mitogen-activated protein kinase (MAPK) could likely be responsible for its inhibition of the induction of methamphetamine-induced sensitization. The neurotoxic effects of methamphetamine, they suggested was most likely attributable to its striatal inhibition of microglial activation.

Fujita, Hashimoto and colleagues examined the effects of 40 mg/kg i.p. minocycline on the establishment of 1 mg/kg s.c. methamphetamine-induced CPP and its elevation of DA levels in the n. accumbens in mice (Fujita, Kunitachi, Iyo, & Hashimoto, 2012). When minocycline was administered before methamphetamine and saline injections during CPP training, it resulted in a complete blockade of methamphetamine-induced CPP. Conditioning with minocycline itself resulted in a small, non-significant induction of place aversion. Pretreating mice with 40 mg/kg minocycline 30 min before administration of 1 mg/kg methamphetamine significantly reduced extracellular DA levels at 30 and 60 min post-methamphetamine administration. Observing their earlier reports that minocycline has neurotrophic effects (Hashimoto & Ishima, 2010), and observing the importance that

neuronal plasticity has in drug dependence (Luscher & Malenka, 2011), these researchers speculated that minocycline's role in neuronal plasticity could possibly account for its ability to block methamphetamine-induced CPP. Because minocycline does not alter the pharmacokinetics of methamphetamine in mice (L. Zhang et al., 2006), it is unlikely that a kinetics explanation could account for its attenuation of methamphetamine's effects. It is also unlikely that the modest level of place aversion induced by minocycline in this study could account for its blockade of methamphetamine's CPP effect, although lack of a dose-effect curve for minocycline administered by itself leaves the robustness and potential importance of that possible effect unanswered.

Ibutilast (aka, AV411; 3-isobutyl-2-isopropyl- pyrazolo-[1, 5-a]pyridine) is a non-selective phosphodiesterase (PDE) inhibitor, glial cell modulator and anti-inflammatory agent (Gibson et al., 2006; Kishi et al., 2001). Ibutilast attenuates the activation of microglia and astroglia, suppressing the lipopolysaccharide- (LPS) and interferon-gamma (IFN- γ)-induced production of inflammatory tumor necrosis factor-alpha (TNF- α), interleukins IL-1 β and IL-6, and nitric oxide (NO), while increasing the productions of NGF, GDNF, neurotrophin-4 and anti-inflammatory cytokine IL-10 (Kawanokuchi, Mizuno, Kato, Mitsuma, & Suzumura, 2004; Mizuno et al., 2004; Suzumura, Ito, Yoshikawa, & Sawada, 1999). Ibutilast also inhibits macrophage migration inhibitory factor (Cho et al., 2010). Ibutilast is marketed in Japan to treat bronchial asthma and ischemic stroke (Kishi et al., 2001), and is being clinically evaluated for treating neuropathic pain (Ledeboer et al., 2006) and opioid dependency (Hutchinson et al., 2009). Because some inhibitors of glial activation and inhibitors of PDE activity can attenuate methamphetamine's effects (see above, for example, Iyo, Bi, Hashimoto, Inada, & Fukui, 1996; M Iyo et al., 1996; Minae Niwa et al., 2007; Y. Yan et al., 2006; L. Zhang et al., 2006), we examined the ability of ibutilast to attenuate the acute and chronic effects of methamphetamine-induced hyperactivity and sensitization in mice, as well as its ability to reduce ongoing levels of methamphetamine self-administration in rats, and to prevent stress- and prime-induced reinstatement of extinguished lever pressing previously reinforced by methamphetamine in rats (see Figure 2). In some studies, we also tested the amino analog of ibutilast, AV1013, which retains ibutilast's ability to inhibit glial cell activation but has minimal PDE inhibitory effects (Cho et al., 2010), to determine whether PDE inhibition was essential for the initial effects we observed with ibutilast.

We examined whether ibutilast and AV411 could attenuate methamphetamine-induced locomotor activity and its sensitization in mice (Snider et al., 2012). In these studies mice were treated b.i.d. with ibutilast (1.8–13 mg/kg), AV1013 (10–56 mg/kg) or their vehicles intraperitoneally for 7 days, beginning 2 days before 5 days of daily 1-h locomotor activity tests. Each test was initiated by either a methamphetamine (3 mg/kg) or a saline injection. Methamphetamine (3 mg/kg) significantly elevated total distance travelled upon its first administration. Each, daily subsequent administration of methamphetamine elevated distance travelled more than the preceding administrations, and distance travelled was significantly greater following its fifth administration compared to its first indicative of sensitization. Neither doses of ibutilast nor AV1013 significantly affected activity when given with methamphetamine's vehicle. Ibutilast reduced distance traveled during all test sessions following methamphetamine administration relative to the vehicle +

methamphetamine treatment group, and significantly so during Testday 2–5 tests at 13 mg/kg ibudilast and during Testday 3 and 4 tests at 7.5 mg/kg ibudilast (Panel A, Figure 2). Ibudilast (13 mg/kg) also significantly prevented the induction of methamphetamine-induced sensitization. AV1013, which lacks ibudilast's potency for inhibiting PDE, but retains its ability to suppress activated glial activity, similarly dose-dependently attenuated methamphetamine's chronic and acute locomotor activity effects, but was ~6–9 fold less potent in doing so. These later observations suggest that the presence of PDE inhibition is not essential for inhibiting methamphetamine's locomotor activity effects, although it likely can contribute if present, and the presence of the other effects of these drugs are sufficient (perhaps including the inhibition of activated glia or upregulation of GDNF).

We also examined whether ibudilast and AV1013, as well as minocycline, could reduce ongoing levels of methamphetamine self-administration in rats (S. E. Snider, E. S. Hendrick, & P. M. Beardsley, 2013). In these studies we trained Long-Evans hooded rats to press a lever for 0.1 mg/kg/inf methamphetamine according to a fixed ratio 1 schedule of reinforcement during 2-h daily sessions. Once stable responding was obtained, twice daily ibudilast (1, 7.5, 10 mg/kg), AV1013 (1, 10, 30 mg/kg), or once daily minocycline (10, 30, 60 mg/kg), or their corresponding vehicles, were given i.p. for three consecutive days during methamphetamine (0.001, 0.03, 0.1 mg/kg/inf) self-administration. Under vehicle pretreatment conditions, 0.03 and 0.1 mg/kg methamphetamine was self-administered above saline self-administration indicating that these doses, but not 0.001 mg/kg/inf methamphetamine, were serving as positive reinforcers. The rats self-administered methamphetamine at an average of 3.7–4.5 mg/kg/2-h session when given access to the 0.1 mg/kg/inf dose, and an average of 2.74–3.2 mg/kg/2-h session methamphetamine at the 0.03 mg/kg/inf dose. Self-administration of both doses were likely high enough to produce pro-inflammatory conditions, as it has been shown that a single dose of 1 mg/kg methamphetamine administered subcutaneously produces a significant enhancement of cytokine and chemokine induction in mice (Loftis, Choi, Hoffman, & Huckans, 2011).

Ibudilast (10 mg/kg) (Panel B, Figure 2), AV1013 (10 and 30 mg/kg), and minocycline (60 mg/kg) all significantly ($p < 0.05$) reduced responding maintained by 0.03 mg/kg/inf methamphetamine, the methamphetamine dose that had maintained the highest level of infusions under vehicle pretreatment conditions. These drugs did not significantly reduce levels of 0.1 mg/kg/inf methamphetamine, however, the highest dose self-administered. These latter observations suggested to us that the effects of the test drugs for reducing methamphetamine self-administration could be rate-dependent (Dews, 1955). To test this possibility, we manipulated the fixed-ratio requirement for methamphetamine infusion and matched response rates obtained at 0.03 and 0.1 mg/kg/inf and then re-tested the effects of 10 mg/kg ibudilast, a dose found previously effective in reducing responding maintained by 0.03 mg/kg/inf methamphetamine. Although 10 mg/kg ibudilast reduced infusion levels of 0.03 mg/kg/inf methamphetamine relative to vehicle control as previously obtained, infusion rates of 0.01 mg/kg/inf methamphetamine in the matched response rate group were again unaffected. These results suggested that the ability of ibudilast to reduce self-administration of the intermediate dose of methamphetamine (0.03 mg/kg/inf), and not at the highest dose (0.1 mg/kg/inf) self-administered, were unlikely attributable to rate-dependent effects, and suggested that the highest dose of methamphetamine could insulate reinforced behavior

from reductions by these drugs. None of the test drugs increased infusion rates of 0.001 mg/kg/inf, the lowest tested dose of methamphetamine and that was not self-administered under vehicle pretreatment conditions. This observation suggested that the infusion-rate reducing effects of these drugs at the 0.03 mg/kg/inf dose of methamphetamine was not attributable to the test drugs "enhancing" the effects 0.03 mg/kg/inf methamphetamine to be functionally experienced as a higher dose (and thus, advancing it along the descending limb of the dose-effect curve).

Bacterial lipopolysaccharide (LPS) is a Gram-negative endotoxin that stimulates inflammation via toll-like receptor-4 (TLR-4) (Chow, Young, Golenbock, Christ, & Gusovsky, 1999). Methamphetamine and LPS both induce inflammation through the AKT/PI3K pathways and induce NF- κ B to translocate to the nucleus and promote transcription of inflammatory cytokines (Ojaniemi et al., 2003; Shah, Silverstein, Singh, & Kumar, 2012). Methamphetamine exacerbates the LPS inflammatory signal (Liu et al., 2012). These effects are likely attributable to both compounds acting via NF- κ B, MAPK, and AKT/PI3K pathways (Liu et al., 2012). Ibudilast and AV1013 antagonize macrophage migration inhibitory factor (MIF) (Cho et al., 2010), a pro-inflammatory factor essential for TLR-4 function and inflammatory response (Roger, David, Glauser, & Calandra, 2001). If LPS and methamphetamine's inflammatory signals are similar, ibudilast and AV1013's antagonism of the TLR-4 receptor via modulation of MIF may be one mechanism by which these compounds are reducing cytokine production and inflammation. Interestingly, morphine's inflammatory response occurs when the glycoprotein, MD-2, forms a complex with TLR-4 and induces inflammation similar to LPS (Wang et al., 2012), thus providing evidence for ibudilast's mechanism of action in reducing opioid-induced inflammation and behavior as well. Minocycline's proposed mechanism also includes interaction with LPS and the NF- κ B pathway. Minocycline prevents LPS-induced degradation of I κ B α , an inhibitory factor, which ultimately prevents NF- κ B translocation to the nucleus and induction of inflammatory cytokine production (Nikodemova, Duncan, & Watters, 2006). Minocycline also decreases binding of NF- κ B to DNA that disrupts transcription (Bernardino, Kaushal, & Philipp, 2009). Thus, all three test compounds are hypothesized to inhibit inflammation and methamphetamine-induced behaviors via a similar neurochemical pathway.

We also examined the ability of ibudilast and minocycline to attenuate the reinstatement of extinguished lever pressing previously reinforced with methamphetamine (Beardsley, 2013; Beardsley, Shelton, Hendrick, & Johnson, 2010; S. E. Snider, E. Hendrick, & P. M. Beardsley, 2013). Male Long-Evans hooded rats were trained to lever press reinforced with 0.1 mg/kg i.v. methamphetamine infusion according to fixed-ratio 1 (FR1) reinforcement schedules during daily, 2-h experimental sessions. After performance had stabilized, lever pressing was extinguished for 12 consecutive sessions. During the sessions, doses of 0 (vehicle), 2.5 and 7.5 mg/kg ibudilast were then administered intraperitoneally b.i.d. on the last 2 days of extinction and then once on the testday to separate groups of 12 rats. During testing, the rats were given 15 min of intermittent footshock or a 1 mg/kg i.p. methamphetamine priming dose followed by a 2-h reinstatement test session that effectively reinstated responding above control levels under vehicle pretreatment conditions. Ibudilast (2.5 and 7.5 mg/kg) significantly ($p < 0.05$) reduced response levels of prime- (7.5 mg/kg methamphetamine) and of footshock-induced reinstatement (Panels C and D, respectively,

Figure 2) of extinguished methamphetamine-maintained responding. Minocycline (15 and 30 mg/kg) was tested under similar methamphetamine prime-induced conditions as described for ibudilast. Minocycline dose-dependently reduced reinstated responding, although the effects did not attain statistical significance. Minocycline (15 and 30 mg/kg) was also tested under cue-induced reinstatement conditions in which the tone-light compound stimulus that had previously accompanied methamphetamine infusions reinstated extinguished lever pressing under vehicle pretreatment conditions. When minocycline was administered as a pretreatment, it dose-dependently reduced cue-induced reinstated responding, significantly so at 30 mg/kg. Overall, these results strengthen interest in ibudilast and minocycline, as well as in other drugs with similar mechanisms of action, as possible candidates for relapse prevention.

4. ONGOING OR PLANNED CLINICAL STUDIES EXAMINING GLIAL MODULATORS IN THE TREATMENT OF PSYCHOSTIMULANT ABUSE

To our knowledge, there are only two drugs reviewed in the behavioral studies above that are either presently in, or proposed for future testing in clinical studies, or for which results pertinent to psychostimulant abuse have been reported using human subjects. Those drugs are ibudilast and minocycline. Unfortunately, given ibudilast's multiple actions including its ability to inhibit release of multiple cytokines and chemokines, its inhibition of MIF and PDE, and its promotion of GDNF, the precise mechanism responsible for its success or failure will be difficult to identify. Minocycline also has its own multiplicity of effects including its antibiotic, anti-inflammatory and neuroprotective effects (Cui et al., 2008; Garrido-Mesa et al., 2013; Soczynska et al., 2012; Sriram et al., 2006) making interpretation regarding its specific mechanism equally challenging.

Reported clinical results with minocycline provided some encouragement that it may eventually have a place in the treatment of d-amphetamine abuse (Sofuoglu, Sato, & Takemori, 1990). In this study healthy non-dependent volunteers were given a 4-day treatment with either minocycline (200 mg/day) or placebo in an outpatient double-blind, placebo-controlled, crossover study. On Days 3 and 4 the subjects were challenged with 20 mg/70 kg d-amphetamine and then were given a variety of physiological, subjective effects and behavioral tests. On the fifth testday the subjects were allowed to self-administer up to four, 5 mg d-amphetamine capsules according to a progressive ratio computer task. Minocycline significantly reduced the rating of "feel good drug effects" and "I feel high" following d-amphetamine challenge, reduced reaction times on a Sustained Attention to Response Test and reduced cortisol levels. Minocycline, however, did not affect d-amphetamine choice behavior during the progressive ratio task. Although there were limitations of this study, as acknowledged by the authors, including the use of healthy volunteers who chose no drugs for 60 percent of the options, and the fact that dose-effect manipulations were neither conducted with minocycline nor d-amphetamine, the attenuation of the subjective effects of d-amphetamine by minocycline offers some encouragement for its future use in the treatment of psychostimulant abuse.

Recently, the interim results of a Phase 1b study involving ibudilast and methamphetamine was reported at the 2013 College on Problems of Drug Dependence Meetings (Shoptaw,

2013). This study was designed to collect safety and tolerability data for ibudilast in the presence of relevant doses of methamphetamine necessary for conducting Phase IIa studies. Specific issues addressed were whether 20 or 50 mg b.i.d. ibudilast altered the cardiovascular, pharmacokinetic and subjective effects of 15 or 30 mg i.v. methamphetamine. The subjects were verified methamphetamine users who were not seeking treatment at the time for their methamphetamine problems. No significant interactions between methamphetamine and either dosage regimen of ibudilast on cardiovascular or subjective (drug effects questionnaire) were observed. The high dosage regimen of ibudilast significantly dampened variability and perseveration on a task of sustained attention. Overall, the findings supported safety for evaluating ibudilast efficacy in subsequent outpatient Phase IIa studies.

Another clinical study (Phase 2) involving ibudilast and methamphetamine is scheduled to begin in mid-2013 that will involve the recruitment of subjects representing those both positively and negatively presenting with HIV (Heinzerling, 2013). The primary aims of this study will address whether ibudilast reduces methamphetamine use more than placebo and whether it improves treatment retention more than placebo. An additional aim specific to HIV positive subjects involves the effects of ibudilast on CD4 count and HIV viral load, anti-retroviral uptake and adherence, neurocognitive function, neuroinflammatory/neurotrophic markers and on serum markers of inflammation.

5. CONCLUSION

This review has provided a molecular and pharmacological basis for targeting CNS glia with drugs as potential pharmacotherapeutics for treating psychostimulant abuse disorders. Additionally, the behavioral studies in which manipulating glial activity was reported to modulate behavioral responses to the psychostimulants further strengthens consideration of medications with glial targets for treating psychostimulant abuse. Developing medications for these targets has challenges, some of which may not be practically surmountable in the near term. For instance, elevating GDNF levels might be of benefit for attenuating the behavioral effects of the psychostimulants under some conditions and times, however, GDNF can't be delivered systemically to penetrate the blood brain barrier (Lin et al., 1993). Even if one could initiate its elevation through other pharmacological methods, timing would be critical, for a rise in GDNF levels may attenuate the acute reinforcing effects of methamphetamine under low consumption conditions (M. Niwa, A. Nitta, L. Shen, et al., 2007; Minae Niwa et al., 2007; M. Niwa, A. Nitta, Y. Yamada, et al., 2007), but may actually augment relapse to methamphetamine use following abstinence from higher consumption conditions (Lu et al., 2009). Considering the pervasiveness of the glia throughout the CNS, nonspecifically (anatomically) elevating or depressing either of these glial neurotrophic factors may result in unintended effects. For instance, injecting BDNF into the PFC has desirable effects (as a medication target) on cocaine-seeking behavior (McGinty, 2013; McGinty et al., 2006; McGinty et al., 2010) but undesirable effects when injected into the VTA (Lu et al., 2004). How could a systemically-administered medication that controlled BDNF levels be expected to have *only* the desirable effect? Other CNS medication candidates, such as the cannabinoid CB1 receptor antagonists, whose targets also have pervasive distribution in the brain (Howlett et al., 2004), have had their development

terminated because of untoward effects (Food and Drug Administration, 2007), likely, in part, because of their activity on non-intended targets. Perhaps glial neuroinflammatory factors, as opposed to their neurotrophic factors, would make easier medication targets in the near term. The two drugs currently being examined clinically for their effects on psychostimulant abuse with those principal targets that we have reviewed include minocycline and ibudilast. Both of these drugs have been used safely as medications for other indications for decades, and initial hints of their positive effects with the psychostimulants are encouraging (Shoptaw, 2013; Sofuoglu, Mooney, Kosten, Waters, & Hashimoto, 2011). Perhaps research and development with drugs having similar mechanisms may lead to the earliest approved medications with important glial activity for the treatment of psychostimulant abuse.

Nonstandard Abbreviations

AGEs	advanced glycation (non-enzymatic glycosylation) end-products
BDNF	brain-derived neurotrophic factor
CD163	cluster determinant 163 (or “cluster of differentiation” 163)
CNS central	nervous system
Co-REST	co-repressor of RE1 silencing transcription
CPP	conditioned place preference
DAMPs	damage-associated molecular patterns
DAT1	dopamine transporter (<i>SLC6A3</i> gene)
DC-SIGN	dendritic cell-specific intercellular adhesion molecule-3-grabbing non-integrin
EAAT	excitatory amino acid transporter
GABA	γ -amino-butyric acid
GDNF	glial cell line-derived neurotrophic factor
GSK-3β	glycogen synthase kinase-3 β
HMGB1	high-mobility group box-1
HO-1	heme-oxygenase 1
IL	interleukin
LPS	lipopolysaccharide
MHC-I	major histocompatibility complex class I
MHC-II	major histocompatibility complex class II
mPFC	medial prefrontal cortex
MBP	myelin basic protein
NMDA	<i>N</i> -methyl-D-aspartate

nACC	nucleus accumbens
NGF	nerve growth factor
NOD-like receptors	Nucleotide-binding and oligomerization domain (NOD) receptors
NOS2	nitric oxide synthase 2
PAMPs	pathogen-associated molecular patterns
PFC	prefrontal cortex
PLP	proteolipid protein
PRRs	pattern recognition receptors
PDE	phosphodiesterase
RIG-1	retinoic acid-inducible gene 1 protein
TLRs	Toll-like receptors
TNF-α	tumor necrosis factor- α
TGF-β	transforming growth factor- β
RAGE	receptor for advanced glycation end-products
SIGMA1R	sigma1-receptors
VMAT2	vesicular monoamine transporter-2 (<i>SLC18A2</i> gene)

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Figure 1.

Psychostimulants increase synaptic damage through direct actions on neurons and glia including both microglia and astroglia. Psychostimulants damage presynaptic terminals of neurons causing the production of reactive oxygen (ROS) and nitrogen (species), and the production of damage-associated molecular patterns (DAMPs) that trigger activation of pattern recognition receptors (PRRs), including Toll-like receptors (TLRs), NOD-like receptors (NLRs) and other PRRs associated with microglia, and to a lesser extent astroglia. Dopaminergic neurons are particularly vulnerable to methamphetamine, which disrupts dopamine transporter (DAT) and vesicular monoamine transporter 1 (VMAT2) function. Importantly, psychostimulants disrupt glial function directly by increasing intracellular Ca^{2+} concentration ($[Ca^{2+}]_i$), NF- κ B transcriptional activity, and by activating sigma1-receptors ($\sigma 1$ -R) and enzyme systems driving oxidative and nitrosative stress especially in microglia (and other cell types). Increases in NF- κ B transcriptional activity result in the increased production of tumor necrosis factor- α (TNF- α), interferon- γ (IFN- γ), and interleukin-6 (IL-6) (among others) cytokines by microglia and to a lesser degree by astroglia. Psychostimulants also obstruct the buffering of extracellular glutamate by

inhibiting excitatory amino acid transporters-1/2 (EAAT1/2) and the conversion of glutamate to glutamine by inhibiting glutamine synthetase, as well as limiting glucose metabolism in astrocytes. Collectively, neuronal damage combined with a heightened state of glial activation promotes positive microglial-astroglial, and neuronal-glial feedback that cause spiraling increases in neuroinflammation and neuronal injury. If unchecked, the cumulative insults result in lasting neurodegenerative changes. Modified and reprinted from reference (Hauser et al., 2012)—an “open access article distributed under the terms of the Creative Commons Attribution License (<http://creativecommons.org/licenses/by/2.5/>), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.”

Figure 2.

Panel A: Results on distance travelled (cm) by mice treated b.i.d. for seven days with ibudilast (IBUD) or its vehicle (VEH1), beginning two days before five days of treatment with 3 mg/kg methamphetamine. Ibudilast was administered at 1.8, 7.5, or 13 mg/kg. Data points represent group means ($\pm$ S.E.M.) obtained during 1-h experimental sessions. Filled data points represent sessions preceded by 3 mg/kg i.p. methamphetamine injections. Unfilled data points represent sessions preceded by i.p. saline injections. N=8 for each treatment group. * $P < 0.05$ with respect to mice treated with ibudilast's vehicle. Modified and reprinted with permission from reference (Snider et al., 2012).

Panel B: Effects of ibudilast or its vehicle on group mean infusions of methamphetamine (0.001, 0.03, and 0.1 mg/kg/inf) obtained during daily 2-h self-administration sessions. Ibudilast was administered at 1, 7.5, or 10 mg/kg i.p. b.i.d. for 3 consecutive days at each methamphetamine self-administered dose. Data points represent the group means of total infusions obtained during the third day of testing at each ibudilast dose. Bars through symbols indicate $\pm$ S.E.M. Data point above "S" on the abscissa indicates results when saline

was self-administered when ibudilast's vehicle was given b.i.d. $N = 4$ rats. $*p < 0.05$ with respect to infusions obtained under ibudilast's vehicle condition. Modified and reprinted with permission from reference (Snider et al., 2013).

Panel C: Mean number of active lever presses during the methamphetamine-primed reinstatement test session as a function of ibudilast dose. Brackets through the bars indicate $\pm$ SEM. "VEH" = results of the vehicle-treatment group. Dashed horizontal lines indicate the range of the means of active lever presses across test groups occurring during the last session of extinction. Asterisk (*) indicates significantly different from vehicle ($P < 0.05$). Modified and reprinted with permission from reference (Beardsley et al., 2010).

Panel D: Mean number of active lever presses during the footshock-induced reinstatement test session as a function of ibudilast dose. Other details as in *Panel C*.