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Review

Glial and neuroinflammatory targets for treating substance use disorders

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ABSTRACT

Background: The plenary session at the 2016 Behavior, Biology and Chemistry: Translational Research in Addiction Conference focused on glia as potential players in the development, persistence and treatment of substance use disorders. Glia partake in various functions that are important for healthy brain activity. Drugs of abuse alter glial cell activity producing several perturbations in brain function that are thought to contribute to behavioral changes associated with substance use disorders. Consequently, drug-induced changes in glia-driven processes in the brain represent potential targets for pharmacotherapeutics treating substance use disorders.

Methods: Four speakers presented preclinical and clinical research illustrating the effects that glial modulators have on abuse-related behavioral effects of psychostimulants and opioids. This review highlights some of these findings and expands its focus to include other research focused on drug-induced glia abnormalities and glia-focused treatment approaches in substance use disorders.

Results: Preclinical findings show that drugs of abuse induce neuroinflammatory signals and disrupt glutamate homeostasis through their interaction with microglia and astrocytes. Preclinical and clinical studies testing the effects of glial modulators show general effectiveness in reducing behaviors associated with substance use disorders.

Conclusions: The contribution of drug-induced glial activity continues to emerge as an intriguing target for substance use disorder treatments. Clinical investigations of glial modulators have yielded promising results on substance use measures and indicate that they are generally safe and well-tolerated. However, results have not been entirely positive and more questions remain for continued exploration in the development and testing of glial-directed treatments for substance use disorders.

1. Introduction

Drug addiction is a pervasive worldwide problem that is characterized by a physical and psychological dependence on drugs such that compulsion to seek and take drugs is increased, control over drug intake is lost, and withdrawal symptoms (e.g., dysphoria, anxiety, irritability, etc.) emerge when drug use is discontinued. The transition from casual drug use to a drug use disorder results from neurobiological changes that produce maladaptive brain functioning in the neurocircuitries that regulate motivated behavior (Koob and Volkow, 2010). An important goal of neurobiological research focused on substance use disorders (SUD) is to identify neuropharmacological targets that will aid in the development of medications for treating these disorders. Thus, it is essential that neurobiological research provide a better understanding of the molecular, cellular and systemic changes that are impacted by drugs of abuse, and how these drug-induced adaptations contribute to behaviors associated with SUD.

Decades of neurobiological research has substantiated the role of dopamine, glutamate and additional neurotransmitter systems in mediating the acute and chronic effects of drugs of abuse. For example, it is well known that many drugs of abuse interact with the mesocorticolimbic dopamine system to produce their acute reinforcing effects (Koob and Volkow, 2010). Chronic administration of abused drugs produces perturbations within this, and other, brain systems (e.g., corticostriatal, extended amygdala, etc.) that ultimately alter emotional regulation and interfere with higher cognitive functions such as impulsive control and self-regulation over drug taking, producing an enduring susceptibility to relapse (Thomas et al., 2008). The focus of a

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majority of these neurobiological studies has highlighted the ability of drugs of abuse to interact with neuronal sites of action, substantiating the role that neuronal sites of action play in the activation of the mesocorticolimbic dopamine system and development of long-term adaptations in the brain that result from chronic use. Despite improved knowledge of the neuronal actions of drugs of abuse, the availability of effective pharmacotherapies is limited for certain drug classes and attempts directed at mesocorticolimbic system dysfunction have been largely unsuccessful.

It has recently come to light that nearly all drugs of abuse also influence non-neuronal glial cells (Beardsley and Hauser, 2014; Crews and Vetreno, 2016; Hutchinson and Watkins, 2014). Glial cells make up the majority of cells in the brain where they play an active role in a variety of brain functions including neurotransmitter release and clearance, synaptic development and maturation, synaptic plasticity, neuronal cell survival, immune responding, and many others (Sofroniew and Vinters, 2010). Glial cells are potently influenced by drugs of abuse and there is emerging evidence that glial cell activity contributes to the behavioral effects of acute and chronic administration of drugs of abuse. These findings raise important questions about the contributions of non-neuronal glial cells in the development and persistence of drug abuse, as well as the clinical implications of glial-directed therapeutic approaches. The Plenary Symposium at the 2016 Behavior, Biology and Chemistry conference provided an opportunity for the speakers to share their latest research findings highlighting the therapeutic potential of glial modulators in the treatment of substance use disorders. Here, we review the literature supporting the notion that glial cells contribute to drug-induced changes in the brain and behaviors, potentially providing an avenue for novel pharmacotherapeutic development.

2. Physiology of glial cells in the brain

Glial cells are extremely abundant throughout the brain and are often categorized based on morphological and physiological characteristics. The primary types of glial cells in the central nervous system include astrocytes, microglia, oligodendrocytes, and ependymal cells. Astrocytes provide numerous structural and metabolic support functions for neurons and regulate the extracellular environment by clearing neurotransmitters, buffering ion concentrations, and releasing signaling molecules (Sofroniew and Vinters, 2010). Microglia are immunocompetent cells that detect pathogens and engage in phagocytosis, lysosomal degradation, and secretion of various pro- and anti-inflammatory substances (Graeber, 2010). Oligodendrocytes are glial cells that wrap around the axons of neurons forming a myelin sheath that insulates the nerve fiber from the extracellular fluid and allows for more efficient propagation of axonal signals (Nave, 2010). Ependymal cells line the spinal cord and brain ventricles where they produce, secrete and circulate cerebrospinal fluid. Collectively, glial cells are an important, and underappreciated, element in nervous system functioning.

Until recently, glial cells were considered to be relatively inactive cells, playing primarily supportive roles for neurons in the brain. It is now abundantly clear that, in addition to their neuronal support function, glial cells actively regulate brain activity through the release and reception of neurochemical signals and homeostatic maintenance of the extracellular environment. They express various neurotransmitter receptors, transporters, and immune signaling complexes that enable them to receive both endogenous and exogenous chemical signals. Glia can also release neurotransmitters, neurotrophic factors, and inflammatory substances that enable them to communicate with neurons and other glial cells. The ability of glial cells to produce various activity states enables them to flexibly regulate the development, maturation, and refinement of neuronal and synaptic functions. Importantly, drugs of abuse modulate the activity of glial cells and alter their interactions with other cells in the brain. While all of the glial cell types have been implicated in drug abuse, the majority of research has focused on the interaction of drugs of abuse with astrocytes and microglia, and these glial cell types will therefore be the focus of this review.

2.1. Astrocytes

Astrocytes are the most abundant glial cell type in the brain (Volterra and Meldolesi, 2005). They have unique cytoarchitectural and phenotypic characteristics that allow them to sense their surroundings and respond dynamically to changes in their microenvironment. Astrocytes are characterized by the expression of the cytoskeletal protein glial fibrillary acidic protein (GFAP) and changes in the expression of GFAP are often used as an indicator of astrocyte activation (Anderson et al., 2014). Although they can take on various structural morphologies, most astrocytes are star-shaped cells with multiple processes originating from the soma. Large diameter vascular processes extending from astrocytes envelop brain capillaries allowing for the regulation of glucose and water homeostasis through the expression of glucose transporters and aquaporin 4, respectively (Amiry-Moghaddam et al., 2003; Iadecola and Nedergaard, 2007; Kacem et al., 1998; Oberheim et al., 2009). Smaller diameter perisynaptic processes form an integral part of the so-called “tripartite synapse” where astrocytic processes engulf the structural elements of the presynaptic neuronal terminal and postsynaptic neuronal membrane (Araque et al., 1999). Perisynaptic processes aid synaptogenesis and synaptic transmission through the expression of various neurotransmitter receptors and transporters, as well as ion channels, cytokine and neurotrophic receptors.

Studies suggest that a single astrocyte residing in cortical gray matter associates with hundreds of dendrites and contacts hundreds of thousands of synapses, perhaps even up to 2,000,000 in humans (Halassa et al., 2007; Oberheim et al., 2009, 2006). Astrocytes are thought to be distributed throughout the brain in microdomains that operate within functional networks that are formed through aqueous channels called gap junctions (Bushong et al., 2004, 2002; Giaume et al., 1991). Gap junctions connect the cytoplasm of astrocytes and allow for direct intercellular communication through the exchange of second messengers, small molecules and ions. The cytoarchitecture of astrocytes and astrocytic networks therefore actively associate with multiple synapses to coordinate neuronal activity. The coordinated release of neurotransmitters, cytokines and neurotrophic factors from astrocytes enables them to broadcast signals to a large area ultimately affecting neuronal activity within multiple networks.

One well characterized function of astrocytes is the clearance of neurotransmitters, such as glutamate, from the synaptic cleft. This function is critical for the termination of synaptic glutamate transmission, maintenance of neuronal excitability, and development of synaptic plasticity. Synaptic clearance of glutamate occurs primarily through the glutamate transporter 1 (GLT-1), a high affinity sodium-dependent transporter expressed exclusively on astrocytes (Chaudhry et al., 1995; Williams et al., 2005). GLT1 is expressed on astrocyte perisynaptic processes that engulf glutamate synapses and engage in glutamate uptake following synaptic release (Yang et al., 2009). Following glutamate uptake, astrocytes convert glutamate to glutamine through the astrocyte-specific enzyme glutamine synthetase (Martinez-Hernandez et al., 1977; Yudkoff et al., 1988). Glutamine is then released out of astrocytes and transported into neurons where it is converted back into glutamate by the enzyme glutaminase. This process is referred to as the glutamate-glutamine cycle and is the primary mechanism for recycling glutamate that is released into the synapse (McKenna, 2007; Yudkoff et al., 1993).

Astrocytes are also capable of releasing chemical transmitters, such as glutamate, D-serine, adenosine triphosphate, and taurine, in a process called gliotransmission. Glutamate gliotransmission plays an integral role in further shaping synaptic transmission and plasticity by modulating extrasynaptic (i.e., beyond the synapse) glutamate receptors on