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SN79, a sigma receptor ligand, blocks methamphetamine-induced microglial activation and cytokine upregulation

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ABSTRACT

Methamphetamine (METH) abuse is associated with several negative side effects including neurotoxicity in specific brain regions such as the striatum. The precise molecular mechanisms by which METH usage results in neurotoxicity remain to be fully elucidated, with recent evidence implicating the importance of microglial activation and neuroinflammation in damaged brain regions. METH interacts with sigma receptors which are found in glial cells in addition to neurons. Moreover, sigma receptor antagonists have been shown to block METH-induced neurotoxicity in rodents although the cellular mechanisms underlying their neuroprotection remain unknown. The purpose of the current study was to determine if the prototypic sigma receptor antagonist, SN79, mitigates METH-induced microglial activation and associated increases in cytokine expression in a rodent model of METH-induced neurotoxicity. METH increased striatal mRNA and protein levels of cluster of differentiation 68 (CD68), indicative of microglial activation. METH also increased ionized calcium binding adapter molecule 1 (IBA-1) protein expression, further confirming the activation of microglia. Along with microglial activation, METH increased striatal mRNA expression levels of IL-6 family pro-inflammatory cytokines, leukemia inhibitory factor (*lif*), oncostatin m (*osm*), and interleukin-6 (*il-6*). Pretreatment with SN79 reduced METH-induced increases in CD68 and IBA-1 expression, demonstrating its ability to prevent microglial activation. SN79 also attenuated METH-induced mRNA increases in IL-6 pro-inflammatory cytokine family members. The ability of a sigma receptor antagonist to block METH-induced microglial activation and cytokine production provides a novel mechanism through which the neurotoxic effects of METH may be mitigated.

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Introduction

Methamphetamine (METH) is an addictive psychostimulant that is currently the second most abused illicit substance in the world behind only Cannabis (Romanelli and Smith, 2006). METH exerts many of its behavioral and physiologic effects by modulating monoaminergic systems within the central nervous system (CNS). METH abuse has several associated side effects including mood disturbances, anxiety, severe dental problems and notably, neurotoxicity (Romanelli and Smith, 2006). Chronic METH usage has been shown in humans to result in dopaminergic damage in the striatum, an effect correlated to relapse rates during clinical addiction treatment (Volkow et al., 2001a,b; Wang et al., 2012). Recently, chronic abusers of METH were also found to have a greater risk of developing Parkinson's disease later in life, which is believed to stem from the neurotoxic consequences of the drug (Callaghan et al., 2010, 2012).

The precise mechanisms by which METH elicits neurotoxic effects are still being elucidated. There are several contributing factors that have been implicated in these effects, such as increased reactive oxygen and nitrogen species (ROS/RNS) generation, dopamine quinone formation, caspase and cell death signaling cascade activation, endoplasmic reticulum (ER) stress induction, and glutamatergic excitotoxicity (Cadet and Krasnova, 2009; Krasnova and Cadet, 2009). Additionally, microglial activation has been implicated in the neurotoxic effects of METH (Escubedo et al., 1998; Kelly et al., 2012; Kuhn et al., 2006; Thomas et al., 2004a; Yue et al., 2012).

Microglia are the resident macrophages of the CNS that function in maintaining homeostasis by sensing deviations from the normal brain environment. Upon activation by perturbations of their surrounding environment, microglia can undergo transformation to different response phenotypes, similar to peripheral macrophages (Perry et al., 2010; Saijo and Glass, 2011). These have classically been categorized

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as M1- and M2-type macrophage/microglia, with M1 microglia being associated with inflammation and degeneration and M2 being associated with regeneration or anti-inflammatory processes (Czeh et al., 2011; Mosser and Edwards, 2008). The classical activation of microglia (M1) is associated with an upregulation of a variety of cell surface proteins, release of pro-inflammatory cytokines, generation of ROS/RNS, and subsequent neuronal damage (Czeh et al., 2011; Mosser and Edwards, 2008; Perry et al., 2010), all of which have been shown to be increased in response to neurotoxic regimens of METH (Escubedo et al., 1998; Kuhn et al., 2006; O'Callaghan et al., 2008; Thomas et al., 2004a,b).

The activation of microglia by METH has been demonstrated in both human studies and preclinical rodent models (Sekine et al., 2008; Thomas et al., 2004a,b). Microglial activation by METH occurs in regions of the brain affected by the neurotoxic actions of the drug and these effects have been shown to be persistent and long lasting even after extended abstinence from the drug (Sekine et al., 2008). The ability of microglia to produce cytokines and reactive species that can compromise synaptic transmission and neuronal function make them logical contributors to METH neurotoxicity and intriguing targets for drug development.

Among the pro-inflammatory cytokines, members of the interleukin-6 (IL-6) family are of particular relevance in the context of METH neurotoxicity. It is believed that the release of cytokines (including IL-6-type cytokines) by activated microglia is relevant to the effects of several neurodegenerative disorders, representing mechanistic overlap between these diseases and the neurotoxic actions of METH (Cadet and Krasnova, 2009; Smith et al., 2012). The upregulation of IL-6 and other members of this cytokine family have been shown in brain regions affected by the neurotoxic actions of METH (Goncalves et al., 2008; Kelly et al., 2012). Moreover, it has previously been shown that mice lacking IL-6 are protected against the neurotoxic actions of METH (Ladenheim et al., 2000), supporting a role of IL-6 in the neurotoxic actions of the drug. Furthermore, it is believed that molecular signaling cascades activated by IL-6-type cytokine signaling are involved in glial cell activation by METH (Hebert and O'Callaghan, 2000).

Presently, there are no FDA approved medications aimed at treating any of the negative side effects of METH abuse, including neurotoxicity. Many potentially promising preclinical treatments have failed to provide clinically effective pharmacotherapies, including those targeting monoaminergic systems. Sigma receptors have recently emerged as a potential target for the production of novel therapeutics aimed at treating many of the negative effects associated with METH usage, including neurotoxicity (Robson et al., 2012; Rodvelt and Miller, 2010). There are currently two known subtypes of sigma receptors, denoted sigma-1 and sigma-2, and sigma receptor antagonists have been shown to mitigate METH-induced behavioral effects and hyperthermia in rodents (Matsumoto et al., 2008; Nguyen et al., 2005). Additionally, sigma receptor antagonists block METH-induced reductions in striatal dopamine and serotonin and their respective transporters in preclinical models of METH-induced neurotoxicity (Kaushal et al., 2012b; Seminerio et al., 2011). The ability of sigma receptor antagonists to mitigate the effects of METH on neuronal cells is well documented; however, it is currently unclear if sigma receptor antagonists also block METH-induced microglial activation.

Sigma receptors are found in microglial cells and sigma receptor ligands have been shown to modulate microglial activation *in vitro* and *in vivo* (Cuevas et al., 2011; Hall et al., 2009). Sigma receptor ligands have been shown to modulate several aspects of microglial activation including migration and cytokine release in response to various activators such as adenosine triphosphate (ATP) and lipopolysaccharide (LPS) (Cuevas et al., 2011; Hall et al., 2009). The sigma receptor ligand SR 31747 has also been reported to block peripheral increases in IL-6 expression in response to peripheral LPS and Staphylococcal enterotoxin B administration, although data from the CNS is currently lacking (Bourrie et al., 1996; Derocq et al., 1995). These studies provide evidence that sigma receptor ligands are capable of modulating the functionality of immune cells, including those present within the CNS. The purpose of the current study was therefore to determine if the putative sigma receptor antagonist and drug development candidate, 6-acetyl-3-(4-(4-(4-flourophenyl) piperazin-1-yl)butyl)benzo[d]oxazol-2(3H)-one (SN79), mitigates microglial activation and cytokine upregulation elicited by METH in the striatum in a preclinical model of METH-induced neurotoxicity. This information will be significant for identifying therapeutically relevant targets for the actions of sigma ligands such as SN79, and sets the stage for future detailed mechanistic studies.

Materials and methods

Drugs and chemicals

(+)-Methamphetamine hydrochloride was obtained from Sigma Aldrich (St. Louis, MO). SN79 was synthesized as previously described (Kaushal et al., 2011b) and provided by Dr. Christopher R. McCurdy (University of Mississippi, University, MS). All administered drugs were dissolved in sterile saline solution (0.1 mL/10 g body weight) (Teknova, Fisher Scientific, Pittsburgh, PA). All other chemicals were obtained from Sigma Aldrich (St. Louis, MO) unless otherwise specified.

Animals

Male, Swiss Webster mice (24–28 g; Harlan, Indianapolis, IN) were utilized for all experiments. Mice were housed in groups of five, on a 12:12 h light/dark cycle with food and water *ad libitum*. Mice were randomly assigned to their respective treatment groups for all experiments. Experiments were performed as approved by the Animal Care and Use Committee at West Virginia University.

Repeated dosing paradigm

Mice were randomly distributed for each experiment into one of four treatment groups: 1) Saline/Saline (0.1 mL/10 g body weight), 2) Saline/METH 5 mg/kg, 3) SN79 3 mg/kg/Saline, or 4) SN79 3 mg/kg/METH 5 mg/kg. The first compound listed in each pair (Saline or SN79) was administered as a pretreatment 15 min prior to the second compound in each treatment group (Saline or METH). Each animal underwent four pretreatments/treatments 2 h apart as previously described (Kaushal et al., 2012b). All injections were administered intraperitoneally.

Core body temperature was measured 1 h after each treatment using a probe (Thermalert TH-S Monitor, Physitemp Instruments Inc., Clifton, NJ) inserted approximately 2.5 cm past the rectum into the colon. Body temperature was recorded after a stable temperature had been reached approximately 10 s post-probe insertion.

The METH dose (5 mg/kg × 4) was selected based upon previous dose response experiments assessing dopaminergic neurotoxicity in this specific model, where it has consistently been shown to result in significant dopaminergic deficits in the striatum (Matsumoto et al., 2008; Seminerio et al., 2012). Similarly, the SN79 dose (3 mg/kg × 4) was selected due to previously reported dose response experiments assessing the ability of this compound to mitigate the striatal dopaminergic deficits elicited by METH (Kaushal et al., 2012b).

At various time points post-treatment (as measured from the last injection) bilateral striatum samples were collected, flash frozen in liquid nitrogen and stored at −80 °C for later use. Samples for protein level analysis were collected 72 h post-treatment and were collected after transcardial perfusion with phosphate buffered saline (PBS) followed by 4% paraformaldehyde. Time points were selected based upon time course experiments contained within this report (microglial markers and cytokine expression levels) and previous data reporting the timeline of METH-induced dopaminergic neurotoxicity and microglial

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