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Glial cell modulators attenuate methamphetamine self-administration in the rat

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ABSTRACT

Neuroinflammation induced by activated microglia and astrocytes can be elicited by drugs of abuse. Methamphetamine administration activates glial cells and increases proinflammatory cytokine production, and there is recent evidence of a linkage between glial cell activation and drug abuse-related behavior. We have previously reported that ibudilast (AV411; 3-isobutyryl-2-isopropylpyrazolo-[1,5-a]pyridine), which inhibits phosphodiesterase (PDE) and pro-inflammatory activity, blocks reinstatement of methamphetamine-maintained responding in rats, and that ibudilast and AV1013, an amino analog of ibudilast, which has similar glial-attenuating properties but limited PDE activity, attenuate methamphetamine-induced locomotor activity and sensitization in mice. The present study's objective was to determine whether co-administered ibudilast, AV1013, or minocycline, which is a tetracycline derivative that also suppresses methamphetamine-induced glial activation, would attenuate active methamphetamine i.v. self-administration in Long-Evans hooded rats. Rats were initially trained to press a lever for 0.1 mg/kg/inf methamphetamine according to a FR1 schedule 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. Ibudilast, AV1013, and minocycline all significantly ($p < 0.05$) reduced responding maintained by 0.03 mg/kg/inf methamphetamine that had maintained the highest level of infusions under vehicle conditions. These results suggest that targeting glial cells may provide a novel approach to pharmacotherapy for treating methamphetamine abuse.

1. Introduction

While neuroinflammation is commonly associated with neurodegenerative conditions, decades of evidence indicate that some CNS-active drugs can induce neuroinflammatory processes via activation of glial cells as well. For example, activated microglia and astrocytes release pro-inflammatory cytokines following methamphetamine administration (Goncalves et al., 2008; Loftis et al., 2011; Nakajima et al., 2004; Yamaguchi et al., 1991). Drug-induced glial activation is involved with methamphetamine's neurotoxicity and alterations of the blood–brain barrier (Clark et al., 2013), and non-neurotoxic levels of methamphetamine-induced neuroinflammation can alter behavior (Miguel-Hidalgo, 2009).

Methamphetamine abuse cost society an estimated 23.4 billion dollars in 2005 (Nicosia et al., 2009; Watanabe-Galloway et al., 2009), and its chronic abuse can lead to hallucinations, pulmonary and cardiac deterioration, dental disease, and suppressed immune function (Hamamoto and Rhodus, 2009; Hauer, 2010; Srisurapanont et al., 2003). Nevertheless, there are currently no approved pharmacotherapies for directly treating methamphetamine abuse, nor any to complement the limited behavioral interventions (Obert et al., 2000; Rawson et al., 2002). Because methamphetamine is best known for disrupting the monoaminergic dopamine, serotonin, and norepinephrine neurotransmitter systems (Cho and Segal, 1994; Creese, 1983), most research has focused on conventional receptor-mediated approaches to develop useful pharmacotherapeutic agents, but heretofore without success (Karila et al., 2010). Furthermore, compounds with varied mechanistic actions such as bupropion, modafinil, and aripiprazole have all had inconsistent efficacy (Brackins et al., 2011). An expanded understanding of methamphetamine's less studied mechanisms, such as glial cell activation, may lead to fresh approaches in drug development.

Developing evidence indicates that attenuating glial activation can reduce methamphetamine-induced behavioral effects (Fujita et al., 2012; Narita et al., 2006; Zhang et al., 2006). Correspondingly,

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an enhancement of neuroprotective growth factors, like glial cell derived neurotrophic factor (GDNF), blocks methamphetamine self-administration and vulnerability towards reinstatement (Yan et al., 2007). Previously our lab reported that the anti-inflammatory glial cell modulator, ibudilast (3-isobutyryl-2-isopropylpyrazolo-[1,5-a]pyridine), and its amino analog, AV1013, attenuates methamphetamine-induced locomotor activity and its sensitization (Snider et al., 2012), and ibudilast attenuates prime- and cue-induced reinstatement of methamphetamine-maintained responding (Beardsley et al., 2010). Among ibudilast's many actions, it is a non-selective phosphodiesterase (PDE) inhibitor (Gibson et al., 2006; Kishi et al., 2001), glial cell modulator, anti-inflammatory agent, and increases production of GDNF (Cho et al., 2010; Mizuno et al., 2004; Rolan et al., 2009; Suzumura et al., 1999). AV1013 exhibits similar glial attenuating actions as ibudilast, but is impotent at inhibiting PDE function (Cho et al., 2010). Other glial-mediated anti-inflammatory drugs attenuate methamphetamine's effects as well. For instance, minocycline hydrochloride significantly attenuates microglial activation (Sriram et al., 2006; Zhang et al., 2006), attenuates methamphetamine and cocaine-induced hyperlocomotion and sensitization (Chen et al., 2009; Zhang et al., 2006), and prevents methamphetamine conditioned place preference (Fujita et al., 2012). Given these reports implicating glial cell activity and methamphetamine's effects, further investigation of anti-inflammatory agents may provide new targets for affecting methamphetamine drug-abuse. In the present study, ibudilast, AV1013, and minocycline were evaluated for their ability to interrupt on-going methamphetamine self-administration in rats.

2. Materials and methods

2.1. Subjects

Adult male Long-Evans hooded rats (Harlan, Indianapolis, IN) weighing 275–300 g at the start of studies were acclimated to the vivarium for at least one week prior to catheter implantation. When not in testing, rats were individually housed in standard plastic rodent cages in a temperature-controlled (22 °C), Association for the Assessment and Accreditation of Laboratory Animal Care International-accredited facility in which they had *ad libitum* access to water. The rats were allowed *ad libitum* rat chow (7012 Teklad LM-485 Mouse/Rat Sterilizable Diet, Harlan Laboratories, Inc., Indianapolis, IN) for at least one week prior to commencement of training, after which they were maintained at 320 g by controlled feedings given after experimental sessions or at a comparable time of day if not tested. The rats were maintained on a reversed, 12 h/12 h light–dark cycle (0600–1800 h lights off) for the duration of the experiment, and they were trained and tested during the dark segment of this cycle.

All procedures were carried out in accordance with the "Guide for the Care and Use of Laboratory Animals" (Institute of Laboratory Animal Resources, National Academy Press, 1996) and were approved by the Institutional Animal Care and Use Committee of Virginia Commonwealth University (IACUC Approval no. AM10032).

2.1.1. Infusion assembly system

Catheters were constructed from polyurethane tubing (Access Technologies, Skokie, IL; 0.044″ O.D. X 0.025″ I.D.). The proximal 3.2 cm of the catheter was tapered by stretching following immersion in hot sesame oil. The catheters were prepared with a retaining cuff approximately 3 cm from the proximal end of the catheter. A second larger retaining cuff was positioned approximately 3.4 cm from the proximal end of the catheter. Mid-scapula cannula connectors were obtained from Plastics One (Roanoke, VA). The cannula connectors consisted of a threaded plastic post through which passed an "L" shaped section of 22 gauge stainless steel needle tubing. The lower surface of the plastic post was affixed to a 2 cm diameter disc of Dacron mesh. During sessions the exposed threaded portion of the infusion cannula was connected to an infusion tether consisting of a 35 cm length of 0.40 mm i.d. polypropylene tubing encased within a 30 cm stainless steel spring to prevent damage. The upper portion of the 0.40 polypropylene tubing was connected to a fluid swivel (Lomir Biomedical, Inc, Quebec, Canada) that was, in turn, attached via 0.40 polypropylene tubing to the infusion syringe.

2.1.2. Surgical procedure

Following acclimation to the laboratory environment, indwelling venous catheters were implanted into the right external jugular vein. Rats were administered 5 mg/kg carprofen s.c. (Rimadyl, Pfizer Animal Health, New York, NY) before surgery. Surgical anesthesia was induced with a combination of 50 mg/kg ketamine (KetaThesia, Butler Animal Health Supply, Dublin, OH) and 8.7 mg/kg xylazine (X-Ject E, Butler Animal Health Supply, Dublin, OH). The ventral neck area and back of the rat were shaved and wiped with povidone–iodine, 7.5% (Betadine, Purdue Products L.P., Stamford, CT) and isopropyl alcohol. The rat was placed ventral side down on the surgical table and a 3 cm incision was made 1 cm lateral from mid-scapula. A second 0.5 cm incision was then made mid-scapula. The rat was then placed dorsal side down on the operating table and a 2.5 cm incision was made longitudinally through the skin above the jugular area. The underlying fascia was bluntly dissected and the right external jugular vein isolated and ligated. A small cut was made into the vein using an iris scissors and the catheter was introduced into the vein and inserted up to the level of the larger retaining cuff. The vein encircling the catheter between the two cuffs was then tied with silk suture. A second suture was then used to anchor the catheter to surrounding fascia. The distal end of the catheter was passed subcutaneously and attached to the cannula connector that was then inserted subcutaneously through the larger incision. The upper post-portion of the cannula connector exited through the smaller mid-scapula incision. All incisions were then sprayed with a gentamicin sulfate/betamethasone valerate topical antibiotic (Betagen, Med-Pharmex, Inc., Pomona, CA) and the incisions were closed with Michel wound clips. Five mg/kg oral carprofen (Rimadyl, Bio-Serv, Frenchtown, NJ) was administered 24 h after surgery, and 8 mg/kg oral enrofloxacin (Baytril, Bio-Serv, Frenchtown, NJ) was administered daily for three days following surgery.

Rats were allowed to recover from surgery for at least 5 days before self-administration training began. Periodically throughout training, ketamine (5 mg/kg) (KetaThesia, Butler Animal Health Supply, Dublin, OH) was infused through the catheters to determine patency as inferred when immediate anesthesia was induced. Between sessions the catheters were flushed and filled with 0.1 ml of a 25% glycerol (Acros, New Jersey)/75% sterile saline locking solution containing: 250 units/ml heparin (Abraxis Pharmaceutical Products, Schaumburg, IL) and 250 mg/ml ticarcillin/9 mg/ml clavulanic acid (Timentin, GlaxoSmithKline, Research Triangle Park, NC). If during the experiment a catheter was determined to be in-patent, the left external jugular was then catheterized and the rat was returned to testing.

2.2. Apparatus

Commercially-obtained test chambers equipped with two retractable levers, a 5-w house light, and a Sonalert® tone generator (MED Associates, Inc., St. Albans, VT) were used. Positioned above each