Brain, Behavior, and Immunity 65 (2017) 210–221

Contents lists available at ScienceDirect

Brain, Behavior, and Immunity

journal homepage: www.elsevier.com/locate/ybrbi

Full-length Article

HIV-1 TAT protein enhances sensitization to methamphetamine by affecting dopaminergic function

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ARTICLE INFO

Article history:
Received 17 January 2017
Received in revised form 28 April 2017
Accepted 6 May 2017
Available online 8 May 2017

Keywords:
TAT expression
Locomotor activity
Dopamine receptors
Adenosine receptors
Brain neurochemistry
HPLC
Gene expression microarrays
Neurotransmitter respecification
Mice

ABSTRACT

Methamphetamine abuse is common among humans with immunodeficiency virus (HIV). The HIV-1 regulatory protein TAT induces dysfunction of mesolimbic dopaminergic systems which may result in impaired reward processes and contribute to methamphetamine abuse. These studies investigated the impact of TAT expression on methamphetamine-induced locomotor sensitization, underlying changes in dopamine function and adenosine receptors in mesolimbic brain areas and neuroinflammation (microgliosis). Transgenic mice with doxycycline-induced TAT protein expression in the brain were tested for locomotor activity in response to repeated methamphetamine injections and methamphetamine challenge after a 7-day abstinence period. Dopamine function in the nucleus accumbens (Acb) was determined using high performance liquid chromatography. Expression of dopamine and/or adenosine A receptors (ADORA) in the Acb and caudate putamen (CPu) was assessed using RT-PCR and immunohistochemistry analyses. Microarrays with pathway analyses assessed dopamine and adenosine signaling in the CPu. Activity-dependent neurotransmitter switching of a reserve pool of non-dopaminergic neurons to a dopaminergic phenotype in the ventral tegmental area (VTA) was determined by immunohistochemistry and quantified with stereology. TAT expression enhanced methamphetamine-induced sensitization. TAT expression alone decreased striatal dopamine (D1, D2, D4, D5) and ADORA1A receptor expression, while increasing ADORA2A receptors expression. Moreover, TAT expression combined with methamphetamine exposure was associated with increased adenosine A receptors (ADORA1A) expression and increased recruitment of dopamine neurons in the VTA. TAT expression and methamphetamine exposure induced microglia activation with the largest effect after combined exposure. Our findings suggest that dopamine-adenosine receptor interactions and reserve pool neuronal recruitment may represent potential targets to develop new treatments for methamphetamine abuse in individuals with HIV.

1. Introduction

There is a high prevalence of methamphetamine abuse in HIV+ humans ranging between 40 and 60% (Rajasingham et al., 2012; Shoptaw et al., 2003). Neurotoxic effects of methamphetamine and HIV disease on the brain are well documented (Ferris et al., 2008; Purohit et al., 2011). However, studies on the brain adaptations that occur during early stages of methamphetamine use and HIV infection are uncommon.

Methamphetamine reward is largely mediated by the dopaminergic system in corticolimbic brain areas including the medial prefrontal cortex (mPFC), nucleus accumbens (Acb), and ventral tegmental area (VTA) (Koob and Volkow, 2010). HIV infection has been associated with impaired dopamine function in the basal ganglia (Kumar et al., 2011) and excessive glutamatergic function in frontal lobes (Nagarajan et al., 2012). Thus, dopamine and glutamate transmitter systems in corticolimbic circuits may be

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http://dx.doi.org/10.1016/j.bbi.2017.05.004
0889-1591/

differentially affected in HIV+ subjects and alter sensitivity to methamphetamine.

HIV viral products may contribute to neuropathology, reward deficits and drug dependence in treated patients (Merino et al., 2011). The viral TAT (trans-activator of transcription) protein is found in the central nervous system of HIV+ humans, even when serum CD4 levels are normalized with antiretroviral drugs (Mediouni et al., 2012). Transgenic mice that express the TAT protein in the brain, under the glial fibrillary acidic protein (GFAP) promoter and inducible by treatment with doxycycline, show neuropathology that is similar to that observed in HIV-infected humans (Kim et al., 2003), therefore providing a useful *in vivo* model to study the temporal impact of TAT protein on brain function. Moreover, TAT-induced dysfunction in corticolimbic dopaminergic neurotransmission (Ferris et al., 2009; Kesby et al., 2016a; Midde et al., 2012; Theodore et al., 2012; Zhu et al., 2009) may lead to alterations in reward function (Kesby et al., 2016a; Koob and Volkow, 2010). We have previously shown that the expression of HIV-associated proteins, such as gp120 and TAT, increase the sensitivity to methamphetamine reward (Kesby et al., 2016a, 2014).

The present studies investigated how HIV-1 TAT expression in the brain impacted dopamine and modified the reward function during methamphetamine-induced locomotor sensitization. Locomotor sensitization is the augmented motor-stimulant response after a period of abstinence that occurs with repeated, intermittent administration of psychostimulants. Such a phenomenon is thought to reflect aspects of the neuronal adaptations underlying drug dependence (Robinson and Berridge, 2008), and mediated by both mesolimbic and mesocortical circuits (Steketee, 2003).

We also determined the activity-dependent induction of neurotransmitter re-specification within a reserve pool of non-dopaminergic neurons to a dopaminergic phenotype in the ventral mesencephalon using quantification of the numbers of tyrosine hydroxylase (TH) – positive neurons (Dulcis and Spitzer, 2008). Activity-dependent homeostatic plasticity in the brain involves changes in synaptic strength, number of synapses, neuronal excitability (Dulcis and Spitzer, 2012; Nelson and Turrigiano, 2008) and neurotransmitter expression (Dulcis et al., 2013). The presence of a reserve pool of neurons that can boost function of an endogenous circuit has been proposed as a novel mechanism of neuroplasticity (Dulcis and Spitzer, 2012; Lewis et al., 2014; Velazquez-Ulloa et al., 2011). Indirect evidence for activity-dependent recruitment of a new population of neurons in amphetamine-sensitized rats (Nordquist et al., 2008) suggests this phenomenon may also be a feature in the development of psychostimulant abuse.

Further, monoamine, glutamate and GABA function in the Acb was determined using high performance liquid chromatography (HPLC). The impact of TAT and methamphetamine on gene expression profile was determined in the brain tissue using microarrays followed by a pathway analyses with a focus on dopamine signaling in the caudate putamen (CPu). Levels of dopamine receptors (DRD) and adenosine receptors (ADORA), that are co-expressed in the basal ganglia (Ferre et al., 1997) and involved methamphetamine reward (Chesworth et al., 2016; Kavanagh et al., 2015; Pierce and Kalivas, 1997; Shimazoe et al., 2000), were assessed and validated in the Acb and CPu using RT-PCR and immunohistochemistry (IHC) analyses. Finally, we also evaluated neuroinflammatory processes in the CPu by assessing expression of the ionized calcium binding adaptor molecule 1 (IBA-1), a marker for microglial activation (microgliosis).

2. Materials and methods

2.1. Animals

A total of 82 male mice (3–5 months old), with 43 containing the GFAP promotor-controlled Tet-binding protein (TAT−) and 39 containing both the GFAP promotor-controlled Tet-binding protein and the TRE promotor-TAT protein transgene (TAT+) were tested. Inducible TAT transgenic mouse colonies with a C57BL/6J background were obtained by generation of two separate transgenic lines Teton-GFAP mice and TRE-Tat86 mice, and then cross-breeding of these two transgenic mouse lines, as previously described (Kim et al., 2003). The mice were housed in groups of 2–4 in a humidity- and temperature-controlled animal facility on a 12 h/12 h reverse light/dark cycle (lights off at 7:00 AM) with *ad libitum* access to food and water. Behavioral testing was conducted during the dark phase of the light/dark cycle from 8 AM to 7 PM with mice from all groups being tested concurrently at any given time throughout the testing period. All of the experiments were conducted in accordance with the guidelines of the American Association for the Accreditation of Laboratory Animal Care and National Research Council's Guide for the Care and Use of Laboratory Animals and approved by the University of California San Diego Institutional Animal Care and Use Committee.

2.2. Locomotor activity testing

Locomotor activity was assessed in four open field arenas (60 × 60 cm) equipped with infrared beams (Med Associates, St. Albans, VT, USA) to calculate total distance travelled. Mice were acclimatised to the testing room at least one hour prior to testing and were tested in the dark for a total of 30 min.

2.3. Doxycycline regimen

All mice were treated with a doxycycline regimen (doxycycline hyclate; Sigma) of 100 mg/kg, intraperitoneally, once a day for 7 days. This regimen is based on the previously demonstrated efficacy of TAT induction at this dose of doxycycline (Carey et al., 2012; Paris et al., 2014a). Doxycycline-induced TAT expression was attenuated by day 7 and significantly decreased 14 days after the termination of doxycycline treatment (Paris et al., 2014a). Only mice containing both the GFAP promotor-controlled Tet-binding protein and the TRE promotor-TAT protein transgene (TAT+) generate TAT protein after doxycycline administration. Mice were administered doxycycline injections in the evening (17:00 h), beginning the day before the methamphetamine acquisition phase.

2.4. Methamphetamine sensitization

The sensitization procedure consisted of an acquisition phase with seven consecutive days of locomotor testing directly after an intraperitoneal injection with either saline (0.9%) or 2 mg/kg methamphetamine (methamphetamine hydrochloride; Sigma, St. Louis, MO, USA). The challenge phase occurred after a seven-day washout period. Mice were tested after either saline or 1 mg/kg methamphetamine. The methamphetamine doses were selected based on the literature (Jing et al., 2014). There were four testing groups: saline acquisition and saline challenge (SAL/SAL), methamphetamine acquisition and saline challenge (METH/SAL), saline acquisition and methamphetamine challenge (SAL/METH), methamphetamine acquisition and methamphetamine challenge (METH/METH).