Progress in Neuro-Psychopharmacology & Biological Psychiatry 53 (2014) 142–148

Contents lists available at ScienceDirect

Progress in Neuro-Psychopharmacology & Biological Psychiatry

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

Minocycline, an antibiotic with inhibitory effect on microglial activation, attenuates the maintenance and reinstatement of methamphetamine-seeking behavior in rat

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ARTICLE INFO

Article history:
Received 2 March 2014
Received in revised form 31 March 2014
Accepted 11 April 2014
Available online 24 April 2014

Keywords:
Glial cell activity
Methamphetamine maintenance
Minocycline
Nucleus accumbens
Reinstatement

ABSTRACT

Methamphetamine (METH) is a major criminal justice and public health problem. Repeated use of METH causes dependence in humans and there are currently no particular pharmacological treatments for METH addiction. Glial cell activation is linked with METH abuse and METH administration causes activation of these cells in many areas of the brain. Many studies have demonstrated that glial cell modulators can modulate drug abuse effects. In this study, we examined the effect of the putative microglial inhibitor, minocycline on maintenance and prime-induced reinstatement of METH seeking behavior using the conditioned place preference (CPP) paradigm. CPP induced with METH (1 mg/kg, i.p. for 3 days) lasted for 11 days after cessation of METH treatment and priming dose of METH (0.5 mg/kg, i.p.) reinstated the extinguished METH-induced CPP. Daily treatment of minocycline (40 mg/kg, i.p.) followed by establishment of CPP blocked the maintenance of METH-induced CPP and also could attenuate priming-induced reinstatement. Furthermore, daily bilateral intra-accumbal injection of minocycline (10 and 20 μg/0.5 μl saline), during extinction period blocked the maintenance of METH CPP but just the highest dose of that could attenuate priming-induced reinstatement. We showed that minocycline administration during extinction period could facilitate extinction and maybe abolish the ability of drug-related cues evoke reinstatement, suggesting that minocycline might be considered as a promising therapeutic agent in preventing relapse in METH dependent individuals.

1. Introduction

Methamphetamine (METH) is a highly abused psychostimulant and its abuse and dependency are major public health problems (Rawson and Condon, 2007). According to the United Nations Office on Drugs and Crime (UNODC, 2011) report, after marijuana, METH is the most abused illicit drug in the world, also the use of it has grown significantly in Iran over the past decade and there are serious social and health concerns about its use. The METH abuse has psychiatric and medical consequences, including psychosis, dependence, overdose and death. However, there are currently no pharmacological treatments for symptoms associated with METH abuse (Sofuoglu, 2010), also a high percentage of users relapse to drug after psychosocial and pharmacological treatments (Elkashef et al., 2008). METH is a powerful psychostimulant that acts primarily to cause the release of the dopamine, serotonin and norepinephrine (Rothman et al., 2001). The nucleus accumbens (NAc) play an important role in reward related phenomena by receiving a large dopaminergic projection from the ventral tegmental area (VTA) and glutamatergic projection from medial prefrontal cortex (Aguilar et al., 2009; Pennartz et al., 1994). It has been found that cue- and METH-induced drug seeking behavior is associated with increased activity in the projection from the prefrontal cortex to the NAc (Rocha and Kalivas, 2010). Also, dopaminergic projections from VTA to NAc and an increase in NAc extracellular dopamine are involved in the maintenance period and drug-induced reinstatement (Romieu et al., 2004; Seiden et al., 1993), Therefore NAc is a critical area in reward related phenomenon.

Glial cells constitute 70% of the total cell population in the central nervous system (CNS) (DeLeo and Colburn, 1999), these non-

Abbreviations: ALS, Amyotrophic lateral sclerosis; ANOVA, Analysis of variance; BDNF, Brain-derived neurotrophic factor; CNS, Central nervous system; CPP, Conditioned place preference; Kg, Kilogram; GDNF, Glial cell-derived neurotrophic factor; GFAP, Glial fibrillary acidic; Hr, Hours; Ip, Intraperitoneal; ICV, Intracerebroventricular; iNOS, Inducible nitric oxide synthase; MDMA, 3-4 methylene dioxymethamphetamine; METH, Methamphetamine; μg, Microgram; μl, Microliter; Mg, Milligram; NO, Nitric oxide; Nac, Nucleus accumbens; TNF-α, Tumor necrosis factor; VTA, Ventral tegmental area.

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http://dx.doi.org/10.1016/j.pnpbp.2014.04.008
0278-5846/

conducting cells were known to provide protection, nutrition and isolation to the neurons of the CNS. Some glial cells contain receptors and contribute to other functions, including ion homeostasis, immune system and neuromodulation (Heneka et al., 2010). Recently, several investigations have shown the role of glial cells in many diseases and disorders as well as drug reward related phenomenon (Miguel-Hidalgo, 2009; Vijayaraghavan, 2009). It has well known that glial cells are involved in many aspects of METH use such as its rewarding effect and neurotoxicity (Narita et al., 2006; Pubill et al., 2003; Snider et al., 2013; Thomas et al., 2004). Minocycline is a second-generation tetracycline that easily crosses the blood–brain barrier and has been applied to various infectious diseases for over 30 years. This drug has powerful neuroprotective properties in several models of neurodegenerative diseases, including Huntington disease, Parkinson disease, amyotrophic lateral sclerosis (ALS) and ischemic stroke (Blum et al., 2004; Jackson-Lewis et al., 2002; Stirling et al., 2005). It's thought that blockade of microglial activation and proliferation by minocycline plays an important role in the neuroprotective effects of this drug (Tikka et al., 2001; Yong et al., 2004).

Recently growing evidences indicate that attenuating glial cell activation by drugs such as ibudilast, propentofylline and minocycline can attenuate the behavioral and molecular effects of repeated exposure to drugs of abuse such as morphine, METH and cocaine (Cooper et al., 2012). For example, in a study by Fujita et al., they showed that minocycline could block the rewarding effect of METH by down regulating dopamine level in NAc (Fujita et al., 2012). It has also been reported that minocycline could reduce self-administration METH in mice (Snider et al., 2013). Furthermore minocycline could attenuate hyperlocomotion and the development of behavioral sensitization after the administration of METH. In addition, minocycline could attenuate the reduction of dopamine and dopamine transporters in the striatum of mouse and monkey brains associated with repeated METH administration (Zhang et al., 2006a). Taken together, these findings suggest that minocycline holds great promise as a therapeutic drug for the treatment of long-term symptoms associated with METH abuse (Hashimoto, 2008; Toolaney, 2007). Reducing the craving and relapse are the most important aspects of therapeutic strategies for the treatment of addiction, and relapse is still a major limitation in drug therapy. Therefore the current study was conducted to investigate whether minocycline could change the maintenance of METH-induced conditioned place preference (CPP) and attenuate reinstatement of drug-seeking behavior induced by priming injection of METH in rats.

2. Material and methods

2.1. Subjects

All experimental procedures conformed to the guide for the care and use of laboratory animals (National Institutes of Health Publication No. 80-23, revised 1996) and were conducted with the approval of an institutional animal care and use committee at the Research and Ethics Committee of Shahid Beheshti University of Medical Sciences. Eighty six male Wistar rats weighing 250–300 g (Pasteur Institute, Tehran, Iran) at the beginning of the experiments were acclimated to the vivarium (a climate-controled environment on a 12 h light/dark cycle), for at least one week prior to the onset of the experiments. The animals were randomly assigned to different experimental groups. Rats were accustomed to their new environment and handled for one week before the experimental procedure was started. Additionally, all efforts were made to minimize animal suffering and to use only the number of animals necessary to produce reliable scientific data.

2.2. Surgery and infusion procedures

Rats were anesthetized with Ketamine–Xylazine (100 mg/kg Ketamine–10 mg/kg Xylazine), placed into the stereotaxic device (Stoelting, USA), the scalp was retracted and permanent guide cannulae (23 gauge) were implanted bilaterally 1 mm above NAc. The stereotaxic coordinates for the NAc were as follows: AP 1.6 mm; ML ± 1.5 mm; DV 6.7 mm (Paxinos and Watson, 2005). To prevent clogging and infection, a stainless steel obturator was used to occlude the guide cannulae during the recovery period. Animals were individually housed and were allowed to recover for 5–7 days from surgery before experiments.

The animals were injected with either minocycline or saline in a volume of 0.5 μl/rat into the NAc, using a Hamilton syringe connected to a 30-gauge injector which was terminated 1 mm below the tip of the guide cannula. Drug solutions or vehicles were slowly administered over a period of 60 s into the nuclei. Needles were left in place for an additional 60 s to facilitate diffusion of the drugs and prevented drug backflow, and then the stylets were reinserted into the guide cannulae. During the infusion procedure, the rats could freely move and all efforts were made to reduce stress of animals.

2.3. Conditioning place preference apparatus and paradigm

CPP paradigm was used to evaluate the effects of intra-peritoneal and intra-NAc administration of minocycline on maintenance and reinstatement of METH. This paradigm has been described in our previous works in detail (Karimi et al., 2014), however, in this study, it is explained briefly.

2.3.1. Apparatus

The CPP apparatus was made of plastic and consisted of three compartments divided by sliding doors, two compartments were identical in size (30 cm × 30 cm × 40 cm) but differed in shading and texture. One compartment had vertical stripes on the walls and the other had horizontal wall stripes also for tactile cue one compartment had a textured floor and another one had smooth floor. The third and middle compartment (start box) was a red tunnel (30 cm × 15 cm × 40 cm). It protruded from the rear of two large compartments and connected the entrances to them. Time spent in each chamber and motor activity was monitored via recorded by a 3CCD camera (Panasonic Inc., Japan) that put 2 m above the apparatus.

2.3.2. Procedures

The rats were transported from the animal housing room to the test room at least 30 min prior to the start of the experiment for habituation. To determine the baseline chamber preference, in Pre-conditioning test (day 1), each animal was placed in start box with the guillotine door removed and rats were allowed to move freely in all three chambers for 10 min and the time spent in each compartment was recorded. In the experimental setup used in this study, the animals did not show any preference for either of the compartments, however, individual rats tended to spend more time in one chamber compared to another, any animal which spent ≥80% of the total test time in each compartment was considered to have initial bias and was excluded from study. Conditioning phase started one day after pre-conditioning test and consist of six, 30-min sessions (three saline and three drug pairing) in a 3-day schedule (days 2–4). On the first day of conditioning phase, rats were administered METH in the morning and immediately confined to the drug-paired compartment for 30 min by closing the removable wall; about 6 h later, the rats were injected with saline and immediately placed in the saline-paired compartment for 30 min. On the next day, animals were injected with saline in the morning and METH in the afternoon. On the third day of conditioning, the schedule of injection was same as the first day. Control animals received only saline instead of METH. On the post-test day (day 6), in a METH free state, rats were placed into CPP box and were tested for CPP with free access to all three chambers. The time spent in each chamber during the 10 min was recorded by a 3CCD camera (Panasonic Inc., Japan) and analyzed using the Ethovision software (Version 7), a video tracking system for automation of behavioral experiments (Noldus Information Technology, the Netherlands). In order to calculate the conditioning