Neurochemistry International 76 (2014) 109–113

Contents lists available at ScienceDirect

Neurochemistry International

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

Rapid communication

Propentophylline increases striatal dopamine release but dampens methamphetamine-induced dopamine dynamics: A microdialysis study

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ARTICLE INFO

Article history:
Received 28 May 2014
Received in revised form 27 June 2014
Accepted 4 July 2014
Available online 15 July 2014

Keywords:
In vivo microdialysis
Dopamine
Methamphetamine
Propentofylline
Caudate nucleus

ABSTRACT

While there are currently no medications approved for methamphetamine (METH) addiction, it has been shown that propentofylline (PPF), an atypical methylxanthine, can suppress the rewarding effects of methamphetamine (METH) in mice. This experiment studied the interactions of PPF with METH in striatal dopaminergic transmission. Herein, the impact of PPF (10–40 mM, intrastriatally perfused (80 min) on the effect of METH (5 mg/kg, i.p.) on striatal dopamine (DA) release was evaluated using brain microdialysis in Sprague–Dawley adult rats. METH was injected at the 60 min time point of the 80 min PPF perfusion. The extracellular levels of DA and its metabolites 3,4-dihydroxyphenylacetic acid (DOPAC) and homovanillic acid (HVA) were determined using high performance liquid chromatography with electrochemical detection (HPLC-ED). PPF induced a concentration-dependent increase in DA release beginning 30 min after the onset of PPF perfusion. DA peak levels evoked by 40 mM PPF were similar to those induced by 5 mg/kg METH i.p. Only the highest concentration of PPF decreased the METH-induced DA peak (circa 70%). The significant decreases in extracellular levels of DOPAC and HVA evoked by METH were partially blocked by 10 and 20 mM PPF. Although 40 mM of PPF also partially blocked the METH-induced DOPAC decrease, it completely blocked HVA depletion after a transient increase in HVA levels in METH-treated rats. Data indicates for the first time that while PPF increases presynaptic striatal DA dynamics it attenuates METH-induced striatal DA release and metabolism.

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1. Introduction

Methamphetamine (METH) abuse and its proneness to target brain dopaminergic (including nigrostriatal) pathways leading to addiction present a major problem worldwide (Kish, 2008). Work in our laboratory have consistently shown that METH induces aberrant striatal dopamine release (Pereira et al., 2004, 2006, 2011). While there are currently no medications approved for treating METH abuse, its pharmacology as an indirect sympathomimetic agent provides opportunities for potential pharmacological strategies for regulation of METH-induced dopaminergic transmission.

Notably, it has been shown that propentofylline (PPF 3 mg/kg; an atypical synthetic methylxanthine (1-[50-oxohexyl]-3-methyl-7-propylxanthine) significantly suppresses place preference produced by either METH or morphine in mice (Narita et al., 2006). This is suggestive that PPF hampered both methamphetamine- and morphine-induced rewarding effects. Moreover, PPF has been studied extensively in several central nervous system (CNS) disease animal models of stroke, opioid tolerance, and acute and chronic pain (Sweitzer and De Leo, 2011). Multiple clinical trials demonstrated that PPF is endowed with a minimal adverse side-effect profile, which further increases the relevance of studying its putative usefulness in multiple CNS disease settings (Sweitzer and De Leo, 2011).

Disclosed mechanisms of this xanthine include inhibition of cyclic AMP (cAMP) and cyclic GMP phosphodiesterases and being a weak antagonist of the adenosine A1 receptor (Fredholm and Lindstrom, 1986). It has also been suggested that PPF is a glial modulator with direct actions on microglia and astrocytes (Jacobs et al., 2012).

Although there is a coherent body of evidence showing that caffeine, which is another methylxanthine, releases striatal DA (Ferré, 2010), the impact of PPF on dopamine (DA) transmission is essentially uncharted. In fact there is only one paper demonstrating that PPF (10 mg/kg) decreases dopamine levels in

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http://dx.doi.org/10.1016/j.neuint.2014.07.003
0197-0186/Published by Elsevier Ltd.

hippocampal perfusates after its i.p. administration. However, the authors failed to show consistent changes in DA release in striatal perfusates (Shimoyama et al., 1988). Additionally, it was reported that intrastriatally-perfused PPF (20 mM) inhibited the release of DA during transient ischemia in rat (Shimizu et al., 1993).

The relevance of dorsal striatal DA to METH addiction (Krasnova et al., 2013) prompted us to probe the effect of PPF on changes in striatal DA release and metabolism exerted by METH.

2. Methods

2.1. Subjects

Thirty-four adult (10–12 weeks), male Sprague–Dawley rats (National Center for Toxicological Research/FDA breeding colony) weighing 400–500 g were housed under controlled environmental conditions (temperature 22 °C, relative humidity 45–55%, 12 h light:dark cycle with lights off at 1800 h). All animals had free access to standard food and tap water. Animal care and use procedures were in accordance with the American Association for Accreditation of Laboratory Animal Care (AAALAC) guidelines and approved by the NCTR/FDA Institutional Animal Care and Use Committee (IACUC). All efforts were made to minimize animal suffering and to reduce the number of animals used.

2.2. Drugs

Methamphetamine hydrochloride and propentofylline were purchased from Sigma–Aldrich, Dallas, TX, USA.

2.3. Microdialysis experiment

Rats were anesthetized with sodium pentobarbital (50 mg/kg; i.p.) and placed into a stereotaxic frame. The dorsal skull was exposed and a small hole was drilled to allow implantation of an intracerebral guide cannula into the caudate nucleus (CN).

The cannula was fixed to the skull with dental acrylic and two anchor screws.

To avoid effects of surgery and anesthesia, the dialysis experiments were started not sooner than seven days or later than ten days after surgery. Carprofen (Rimadyl) was given i.p. at 5 mg/kg immediately after surgery and one day after surgery to minimize pain of surgery. Animals were observed each day for adverse effects of surgery. On the day of tests, animals were hand restrained and the dialysis probe was slowly inserted through the guide cannula into the CN (coordinates: A. 0.2 mm; L. 2.5 mm; V. 5.5 mm). Microdialysis probes and guide cannula used in these studies were CMA-12 (Carnegie Medicine, Sweden). The membrane tip measured 2.0 × 0.5 mm and had an *in vitro* efficiency of 15–18% at a flow rate of 1.0 μl/min with a CMA-100 micrroinfusion pump. The dialysis solution used in these studies was a modified Ringers solution of the following composition, in mM (145 Na^+, 1.2 Ca^{2+}, 2.7 K^+, 150 Cl^-, 1.0 Mg^{2+}), at pH 7.0. Dialysates were analyzed alternately between the two animals under study using a dual channel, on-line injector (BAS, Bioanalytical Systems, West Lafayette, IN) with the injection time set at 10-min intervals. Each sample was analyzed for DA, DOPAC and HVA by HPLC-ED using a Phase-II cartridge column (BAS). The mobile phase consisted of 0.1 M monochloroacetic acid, 1.0 mM sodium octyl sulfate, 0.5 mM EDTA and 6% methanol, degassed and filtered at pH 3.0. Flow through the column was 0.8 ml/min at a controlled temperature of 30 °C and an applied voltage of 0.7 V.

Striatal PPF perfusion began 10 min after the baseline levels were obtained and continued for 80 min. METH (or saline) was administered intraperitoneally (i.p.) at 5 mg/kg, 60 min following the start of PPF perfusion. PPF was intrastriatally perfused instead of being injected because we specifically wanted PPF to target striatal dopaminergic terminals without the confounding contribution of other brain regions, including the substantia nigra, to the dopaminergic dynamics. We perfused the striatum with PPF for a relevant amount of time prior to METH injection to ensure that this methylxanthine would set in motion modifications in dopaminergic dynamics before METH targets the striatum.

Samples were collected for 300 min at 20 min intervals. After each experiment, animals were sacrificed and probe placements were verified histologically. All efforts were made to minimize animal suffering and to reduce the number of animals used.

2.4. Statistical analysis

Three samples were taken to establish baseline levels of extracellular DA, DOPAC and HVA (i.e., 0-time baseline value is plotted as 100%). Statistical analysis was performed applying one-way repeated measures ANOVAs to each drug condition, with time as the repeated measures factor followed by post hoc comparison (Dunnett's multiple comparison test). One-way ANOVA followed by post hoc Newman–Keuls was used for comparisons between the 3 experimental conditions. DA peak effect triggered by the three different PPF concentrations were also compared using one-way ANOVA followed by post hoc Newman–Keuls. Significant differences were defined at $p < 0.05$ level.

3. Results

3.1. Dopamine

Perfusion with the xanthine derivative PPF by reverse dialysis produced a concentration-dependent increase in extracellular striatal DA levels (maximum increase of about 215, 387 and 1505% baseline evoked by 10, 20 and 40 mM PPF, respectively; $p < 0.05$). This release reached the peak 20 min after *the* start of PPF perfusion and returned to baseline 40–60 min following the start of the perfusion (Fig. 1A–C). In fact, DA-peak triggered by PPF40 is significantly higher compared to the DA-peak evoked by the other PPF concentrations (Fig. 1E; $p < 0.001$ vs PPF10, PPF20). Additionally, administration of 5 mg/kg METH (METH5) induced a robust increase in extracellular DA levels that peaked 30 min after dosing (about 1457% of baseline) and remained significantly ($p < 0.05$) above control levels up to 130 min (Fig. 1A–C). Although 10 and 20 mM PPF did not significantly alter the METH-induced DA release profile (Fig. 1A, B), PPF40 (40 mM PPF) significantly attenuated the METH-induced DA peak effect (about 536% of baseline) (Fig. 1C). The Fig. 1D zoomed on the METH5- and saline-treated animals for clarity. It is clearly shown that DA stayed constant throughout the experiment in the saline-treated animals (Fig. 1D).

3.2. Dopamine metabolites: DOPAC and HVA

Administration of 5 mg/kg METH expectedly induced a significant decrease in dialysate DOPAC levels ($p < 0.05$) that began 30 min after METH administration injection and remained significantly lower until the end of the experiment (Fig. 2). Moreover METH triggered a sustained and statistically significant decrease in extracellular HVA levels no sooner than 110 min after administration ($p < 0.05$). Although PPF failed to change striatal extracellular DOPAC and HVA levels as seen in Fig. 2, this xanthine derivative changed the profile of DA metabolites that were evoked by METH5. However, one should stress that PPF40 showed a tendency to transiently increase HVA levels. In fact, PPF at all concentrations delayed 20–60 min. and dampened the decline in extracellular