Psychoneuroendocrinology (2011) 36, 955—969

available at www.sciencedirect.com

ScienceDirect

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

Sex differences in methamphetamine toxicity in mice: Effect on brain dopamine signaling pathways

Mélanie Bourque [a,b], Bin Liu [c], Dean E. Dluzen [c], Thérèse Di Paolo [a,b,*]

[a] *Molecular Endocrinology and Genomic Research Center, Centre de recherche du CHUQ (CHUL), Quebec City, Quebec, G1V 4G2, Canada*
[b] *Faculty of Pharmacy, Laval University, Quebec City, Quebec, G1K 7P4, Canada*
[c] *Department of Anatomy and Neurobiology, Northeastern Ohio Universities College of Medicine and Pharmacy (NEOUCOM), Rootstown, OH 44272, USA*

Received 19 July 2010; received in revised form 13 October 2010; accepted 15 December 2010

KEYWORDS
Methamphetamine;
Dopamine;
Sex Difference;
Akt;
Neurotoxicity;
Striatum

Summary Male mice were reported to display greater methamphetamine-induced neurotoxicity than females. The present study evaluated the involvement of phosphatidylinositol-3 kinase (PI3K)/Akt and extracellular signal-regulated kinase (ERK1/2) pathways in this sex-dependent methamphetamine toxicity. Intact female and male mice were administered methamphetamine (20 or 40 mg/kg) and euthanized a week later. Dopamine transporter (DAT) and vesicular monoamine transporter 2 (VMAT2) autoradiography in the lateral striatum showed a greater sensitivity in male mice treated with 20 mg/kg methamphetamine compared to female mice. Striatal dopamine concentration and DAT autoradiography showed a more extensive depletion in male mice given 40 mg/kg methamphetamine compared to female mice. Mice administered 40 mg/kg methamphetamine showed no sex difference in striatal VMAT2 autoradiography. In the substantia nigra, DAT specific binding was decreased only in male mice treated with 40 mg/kg methamphetamine and DAT mRNA levels decreased in methamphetamine-treated female and male mice. Methamphetamine-treated male mice presented a dose-dependent decrease of VMAT2 mRNA levels. Methamphetamine reduced insulin-like growth factor 1 receptor levels in females at both methamphetamine doses tested whereas it elevated G protein-coupled estrogen receptor 1 (GPER1) only in male mice. Phosphorylated Akt levels decreased only in male mice treated with 40 mg/kg methamphetamine. Glycogen synthase kinase 3β levels were reduced in male mice at both methamphetamine doses tested and in females receiving 40 mg/kg. Bcl-2

Abbreviations: CREB, cAMP-response element-binding protein; DA, dopamine; DAT, dopamine transporter; DOPAC, 3,4-dihydroxyphenylacetic acid; ERK, extracellular signal-regulated kinase; GPER1, G protein-coupled estrogen receptor 1; GSK3β, glycogen synthase kinase 3β; HVA, homovanillic acid; IGF-1R, insulin-like growth factor 1 receptor; MA, methamphetamine; MPTP, 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine; pAkt, phosphorylated Akt at serine 473; pERK 1/2, phosphorylated ERK 1/2; pGSK3β, phosphorylated GSK3β at serine 9; PI3K, phosphatidylinositol-3 kinase; VMAT2, vesicular monoamine transporter 2; [^{125}I]-RTI-121, 3β-(4-[^{125}I]iodophenyl)tropane-2β-carboxylic acid isopropyl ester; [^{3}H]dihydrotetrabenazine, [^{3}H]-TBZ-OH.

* Corresponding author at: Molecular Endocrinology and Genomic Research Center, Centre de recherche du CHUQ (CHUL), 2705 Laurier Blvd, Quebec City, Quebec, G1V 4G2, Canada. Tel.: +1 418 654 2296; fax: +1 418 654 2761.
E-mail address: therese.dipaolo@crchul.ulaval.ca (T. Di Paolo).

0306-4530/$ — see front matter
doi:10.1016/j.psyneuen.2010.12.007

levels were increased in male mice treated with methamphetamine, whereas ERK1/2 and BAD levels were unchanged. These results implicate some of the signaling pathways associated with the sex differences in methamphetamine-induced toxicity.

1. Introduction

Methamphetamine (MA) is a potent and addictive drug of abuse of increasing use. This psychostimulant causes degeneration of striatal nerve terminals in humans and experimental animals as shown by long-lasting depletion in dopamine (DA) concentration, dopamine transporter (DAT) and vesicular monoamine transporter 2 (VMAT2) (Bourque et al., 2007; Moszczynska et al., 2004; Volkow et al., 2001). Gender differences in response to MA have been described (Dluzen and Liu, 2008). Clinical reports show that women have greater behavioural effects related to MA administration but a reduction in striatal DA release following amphetamine challenges as compared to men (Munro et al., 2006; Liu and Dluzen, 2007). Studies in MA treated mice have shown that male mice are more sensitive to MA-induced toxicity showing greater reduction in striatal DA content than comparably treated females (Liu and Dluzen, 2007).

Stimulation of tyrosine kinase receptor (e.g. insulin-like growth factor 1 receptor (IGF-1R)) is shown to mediate activation of the phosphatidylinositol-3 kinase (PI3K)/Akt signaling pathway, an important mediator of cell survival (Manning and Cantley, 2007). The G protein-coupled estrogen receptor 1 (GPER1, also know as GPR30), is able to activate both the PI3K and the extracellular signal-regulated kinase 1/2 (ERK 1/2) pathways is response to estrogen (Prossnitz and Barton, 2009). Moreover, Akt controls expression of the anti-apoptotic molecule Bcl-2 via the cAMP-response element-binding protein (CREB) (Pugazhenthi et al., 2000). Furthermore, Akt can phosphorylate glycogen synthase kinase 3β (GSK3β) and BAD proteins, thereby inhibiting their pro-apoptotic functions (Manning and Cantley, 2007).

The PI3K/Akt pathway was shown to be implicated in the action of psychostimulant drugs on dopaminergic systems. Amphetamine treatment causes inhibition of Akt activation on serine 473 via a mechanism that is PI3K dependent and DA receptor independent (Brami-Cherrier et al., 2002). PI3K signaling is implicated in the regulation of DAT cell surface expression and inhibition of PI3K/Akt by amphetamine contributes to reduction of DAT on the plasma membrane (Garcia et al., 2005).

The ERK 1/2 pathway was shown to be implicated in survival and cellular death (Chu et al., 2004; Hetman and Gozdz, 2004). Activation of ERK 1/2 can be induced by both PI3K and the interaction of DA and glutamate receptors (Valjent et al., 2005). A study with 6-hydroxydopamine has shown that activation of ERK is implicated in toxicity (Kulich and Chu, 2001). Production of nitric oxide by glial cells induced a persistent activation of ERK shown to cause neuronal degeneration (Canals et al., 2003). Furthermore, ERK activation has been associated with oxidative stress in neurodegenerative diseases (Chu et al., 2004). While the dichotomous role of ERK is not well understood, some investigators suggested that its persistent activation could contribute to promote cell death (Chu et al., 2004). ERK also regulates DAT cell surface expression (Moron et al., 2003).

The PI3K/Akt and ERK 1/2 pathways have been associated with the effect of estrogen in the brain (Bryant et al., 2006). By activating these pathways, estrogen can promote cell survival and neuroprotection against neuronal injuries (Bryant et al., 2006). Results from our laboratory have shown that the PI3K/Akt pathway is implicated in the neuroprotective effect of estradiol against 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) toxicity (D'Astous et al., 2006).

The purpose of this study was to investigate the implication of the PI3K/Akt and ERK pathways in toxicity induced by MA in female compared to male mice. Striatal DA concentration as well as DAT and VMAT2 specific binding were used to measure degeneration of DA nerve terminals induced by MA. Moreover, we sought to examine the implication of possible changes in IGF-1R and GPER1 related to these pathways. The investigation of PI3K/Akt and ERK1/2 pathways in a context of the dose-response MA-induced long-term neurotoxicity and sex difference has never been reported. Since MA produces different effects on dopaminergic markers in female and male mice, these findings provide important new information related to the signaling pathway differences in toxicity induced by MA in both female and male mice.

2. Materials and methods

2.1. Animals and treatments

Intact female and male CD-1 mice (2—3 months) were purchased from Charles River Laboratories (Wilmington, MA, USA). Mice were housed individually, to avoid the potential for stress-induced fighting, in plastic cages with free access to food and water, while maintained at room temperature of approximately 22 °C under a 12-h light—dark cycle (lights on at 06:00 h). All conditions were according to NIH regulations and approved by the Institutional Animal Care and Use Committee (IACUC) at Northeastern Ohio Universities College of Medicine (NEOUCOM). All efforts were made to minimize the number of animals used and their suffering.

Mice were treated with 1—2 intraperitoneal injections of 20 mg/kg MA (Sigma, St Louis, MO) in saline at 2-h intervals, to achieve total doses of 20 and 40 mg/kg of MA. A control group of mice received a saline solution.

2.2. Brain preparation

Mice were killed by rapid decapitation one-week post-MA or saline. Brains were removed, bisected and a unilateral striatum was used to assay DA and metabolite concentrations. The contralateral hemisphere was frozen in liquid nitrogen. The striatum (bregma 1.54 at 0.38 mm) and the substantia nigra (bregma −2.80 at −3.88 mm) (Franklin and Paxinos, 1997) of