BRAIN RESEARCH 1520 (2013) 121–133

Available online at www.sciencedirect.com

SciVerse ScienceDirect

www.elsevier.com/locate/brainres

Brain Research

Research Report

Sexually dimorphic intracellular responses after cocaine-induced conditioned place preference expression

Stephanie K. Nygard[a,b,*], Anthony Klambatsen[a,b], Ruhal Hazim[a,b], Mohamed H. Eltareb[a], Jeff C. Blank[a], Anna J. Chang[a], Vanya Quinones-Jenab[a,b], Shirzad Jenab[a,b,*]

[a]Department of Psychology, Hunter College, CUNY, 695 Park Avenue, New York, NY 10065, USA
[b]Biopsychology and Behavioral Neuroscience Subprogram of Psychology, Graduate School and University Center, CUNY, 365 Fifth Avenue, New York, NY 10016, USA

ARTICLE INFO

Article history:
Accepted 28 April 2013
Available online 9 May 2013

Keywords:
Cocaine
CPP
ERK
CREB
FosB/ΔFosB
Sex differences

ABSTRACT

Sex differences in cocaine's mechanisms of action and behavioral effects have been widely reported. However, little is known about how sex influences intracellular signaling cascades involved with drug–environment associations. We investigated whether ERK/CREB intracellular responses in the mesocorticolimbic circuitry underlying cocaine environmental associations are sexually dimorphic. We used a standard 4 day conditioned place preference (CPP) paradigm using 20 mg/kg cocaine—a dose that induced CPP in male and female Fischer rats. In the nucleus accumbens (NAc) following CPP expression, cocaine treated animals showed increased phosphorylated ERK (pERK), phosphorylated CREB (pCREB) and ΔFosB protein levels. In the hippocampus (HIP) and caudate putamen (CPu), pERK and FosB/ΔFosB levels were also increased, respectively. Cocaine females had a larger change in HIP pERK and CPu ΔFosB levels than cocaine males; partly due to lower protein levels in saline female rats when compared to saline males. Prefrontal cortex (PfC) pCREB levels increased in cocaine males, but not females, whereas PfC pERK levels were increased in cocaine females, but not males. CPP scores were positively correlated to NAc pERK, HIP pERK and CPu FosB protein levels, suggesting that similar to males, the ERK/CREB intracellular pathway in mesocorticolimbic regions undergoes cocaine induced neuroplasticity in female rats. However, there seem to be intrinsic (basal) sexual dimorphisms in this pathway that may contribute to responses expressed after cocaine-CPP. Taken together, our results suggest that cellular responses associated with the expression of

Abbreviations: CPP, conditioned place preference; CPu, caudate putamen; CREB, cAMP response element binding protein; DA, dopamine; DAR, dopamine receptor; ERK, extracellular regulated kinase; HIP, hippocampus; MAPK, mitogen activated protein kinases; MEK, mitogen activated extracellular-regulated protein kinase; NAc, nucleus accumbens; pCREB, phosphorylated CREB; pERK, phosphorylated ERK; PfC, prefrontal cortex; VTA, ventral tegmental area

*Corresponding authors at: Department of Psychology, Hunter College, CUNY, 695 Park Avenue, New York, NY 10065, USA. Fax: +1 212 772 4619.
E-mail addresses: stephanienygard@gmail.com (S.K. Nygard), anthonyklambatsen@yahoo.com (A. Klambatsen), swamijie@gmail.com (R. Hazim), meltareb@gmail.com (M.H. Eltareb), ajc473@gmail.com (J.C. Blank), blank.jeff@gmail.com (A.J. Chang), vaquinon@hunter.cuny.edu (V. Quinones-Jenab), sjenab@hunter.cuny.edu (S. Jenab).

0006-8993/$ - see front matter
http://dx.doi.org/10.1016/j.brainres.2013.04.060

learned drug–environment associations may play an important role in sex differences in cocaine addiction and relapse.

1. Introduction

Addiction studies consistently show greater responses among females than males in various cocaine-related outcomes. As more attention is paid to sex-specific and hormonal effects on cocaine abuse, it is increasingly apparent that sex differences are present at all phases of drug abuse, from initiation through escalation of use and progression to addiction. For example, human females report a slower onset of the subjective effects of cocaine, undergo shorter periods of abstinence between cocaine use and experience cravings after cocaine use when presented with cocaine-associated cues more frequently than males (Anker and Carroll, 2011; Elman et al., 2001; Lynch, 2006; Quinones-Jenab and Jenab, 2010). Female rats learn to self-administer cocaine faster (Lynch and Carroll, 1999) and exhibit enhanced locomotor activity and behavioral sensitization to both acute and chronic cocaine administration compared to males (Chin et al., 2001; Craft and Stratmann, 1996; Festa et al., 2004; Sell et al., 2000; Van Haaren and Meyer, 1991). Still to be determined is the contribution of sex differences in central nervous system plasticity and cellular responses for the development of learned drug–environment associations that play an important role in addiction.

Sex differences in the mesocorticolimbic reward circuitry, including dopamine receptor (DAR) distribution, dopamine (DA) binding properties and intracellular signaling, have been postulated to underlie sexually dimorphic responses to cocaine (Becker and Hu, 2008; Festa et al., 2006; Walker et al., 2006). Dopaminergic neurons of the ventral tegmental area (VTA) project to the nucleus accumbens (NAc) and form connections with the hippocampus (HIP), striatum (including the NAc and caudate putamen (CPu)) and prefrontal cortex (PfC) (Hyman and Malenka, 2001). Convergent glutamatergic circuitry is embedded within the reward system and overlap with the circuitry associated with learning and memory processes (Kelley, 2004). Conditioned place preference (CPP) behavioral models exploit this circuitry by using a Pavlovian conditioning procedure to determine the importance of environmental stimuli in cueing drug reward (Bardo and Bevins, 2000; Domjan, 2005). Female rats express cocaine-induced CPP in response to lower cocaine doses (Russo et al., 2003a; Zakharova et al., 2009) and after fewer cocaine-place pairings than males (Russo et al., 2003a). Differences in DAR sensitivity may underlie sex differences in cocaine CPP and the formation of cocaine environment associations. For example, Nazarian et al. (2004) found that regardless of sex, lower doses of a D_1DAR antagonist blocked cocaine CPP acquisition, whereas higher doses of the antagonist only blocked CPP in males. However, the extent to which downstream molecular signaling in response to sexually dimorphic cocaine induced changes in DA activity contribute cocaine CPP remains to be determined.

Acute and chronic cocaine administration induces the phosphorylation of ERK, a signaling molecule of the mitogen activated protein kinase (MAPK) signal transduction family, in a DA dependent manner (Berhow and Nestler, 1996; Jenab et al., 2005; Sun et al., 2008). In male rats, ERK has been repeatedly implicated in the acquisition of psychostimulant-induced CPP and retrieval of cocaine–environment memories (Gerdjikov et al., 2004; Liu et al., 2011; Miller and Marshall, 2005; Pan et al., 2011; Valjent et al., 2006). Cocaine-induced ERK phosphorylation produces rapid increases in membrane excitability that after repeated exposure lead to long-term changes in protein and gene expression associated with signaling reward (Lu et al., 2006; Nestler, 2001). Downstream of ERK, cAMP response element binding protein (CREB), FosB and ΔFosB are transcription factors associated with experience-dependent synaptic plasticity and long-term molecular neuroadaptations in response to cocaine (Carlezon et al., 2005; Larson et al., 2010; Marazziti et al., 2011; Zhang et al., 2006). In male rats, acute cocaine exposure increases striatal CREB phosphorylation and FosB protein levels after cocaine CPP expression and chronic cocaine exposure produces a persistent accumulation of NAc ΔFosB levels (Harris et al., 2007; McClung and Nestler, 2003; Nestler et al., 2001; Rawas et al., 2012; Tropea et al., 2008).

Sex differences in DA response to cocaine combined with the substantial evidence for the important role of ERK, CREB, and Fos proteins in cocaine CPP in males suggest that sex differences may underlie the formation of drug associated memories. However, to our knowledge, studies that have used the CPP paradigm to investigate molecular alterations involved with cocaine-context associations have only used male rats. We aimed to investigate the potential sex differences in the intracellular signaling molecules underlying the expression of cocaine environment associations. Specifically, we examined phosphorylated ERK (pERK), phosphorylated CREB (pCREB), FosB, and ΔFosB protein levels in mesocorticolimbic regions associated with reward, learning, and memory (NAc, CPu, PfC, and HIP), after cocaine CPP expression in male and female rats. We hypothesized that cocaine CPP expression would be associated with similar changes in protein levels in male and female cocaine treated rats. We also expected any sex differences in protein levels to be correlated with sex differences in the magnitude of CPP behavior.

2. Results

2.1. CPP behavior

No differences in any treatment group were observed during the initial preconditioning test in the time spent in each chamber or in total locomotor behavior, confirming the unbiased nature of the CPP apparatus and testing protocol (data not shown). During CPP testing, cocaine treated rats spent significantly more time in the cocaine paired chamber