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SINGLE EXPOSURE TO COCAINE IMPAIRS ASPARTATE UPTAKE IN THE PRE-FRONTAL CORTEX VIA DOPAMINE D1-RECEPTOR DEPENDENT MECHANISMS

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Abstract—Dopamine and glutamate play critical roles in the reinforcing effects of cocaine. We demonstrated that a single intraperitoneal administration of cocaine induces a significant decrease in [^{3}H]-D-aspartate uptake in the pre-frontal cortex (PFC). This decrease is associated with elevated dopamine levels, and requires dopamine D1-receptor signaling (D1R) and adenylyl cyclase activation. The effect was observed within 10 min of cocaine administration and lasted for up to 30 min. This rapid response is related to D1R-mediated cAMP-mediated activation of PKA and phosphorylation of the excitatory amino acid transporters EAAT1, EAAT2 and EAAT3. We also demonstrated that cocaine exposure increases extracellular D-aspartate, L-glutamate and D-serine in the PFC. Our data suggest that cocaine activates dopamine D1 receptor signaling and PKA pathway to regulate EAATs function and extracellular EAA level in the PFC.

Key words: prefrontal cortex, dopamine, cocaine, glutamate, transporter.

INTRODUCTION

Glutamate is the main excitatory amino acid (EAA) transmitter in the mammalian central nervous system (CNS) and plays critical roles in the regulation of complex networks associated with learning, memory, addiction, drug-environment pairing and drug craving (Kalivas, 2004; D'Souza, 2015). Glutamatergic neurotransmission is mediated by ionotropic and metabotropic receptors in the CNS, which are critically associated with drug addiction (Lau and Zukin, 2007). Glutamate release in the *nucleus accumbens* is implicated in reinstatement of cocaine-seeking behavior (Schmidt et al., 2013), suggesting a key role for this neurotransmitter in drug addiction (Kalivas, 2009).

EAAT transporters (EAATs) ensure glutamate uptake into neuronal and glial cytoplasm, thereby finishing the excitatory signal at the synapse (Huang and Bergles, 2004). EAATs are found both in glia and neurons and are classified into five subtypes (EAAT 1–5) based on cell-type localization and sensitivity to different pharmacological blockers (Danbolt, 2001; Nakagawa and Kaneko, 2013). Several consensus sequences for phosphorylation by PKA and protein kinase C (PKC) have been identified on all EAAT subtypes, and phosphorylation on serine residues may alter the activity and expression of the EAATs on the cell surface (Gegelashvili and Schousboe, 1997; Gonzalez and Robinson, 2004). Recent evidence shows that drug-induced increase in EAAT2 expression attenuates cue-induced reinstatement of cocaine-seeking behavior in rats (Sari et al., 2009), showing a significant role for the EAATs in mediating cocaine's effects.

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Abbreviations: ANOVA, analysis of variance; D1R, D1-receptor signaling; DAT, dopamine transporter; DHK, dihydrokainic acid; DL-TBOA, DL-threo-β-benzyloxyaspartate; EAA, excitatory amino acid; EAATs, EAAT transporters; EDTA, ethylenediaminetetraacetic acid; EGTA, ethylene glycol tetraacetic acid; HEPES, 4-(2-hydroxyethyl)-1-piperazineethanesulfonic acid; HPLC, high-performance liquid chromatography; MEM, minimal essential medium; PFC, pre-frontal cortex; PKC, protein kinase C; TTBS, Tween 20 Tris-buffered saline.

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