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BRAIN RESEARCH

Research Report

Effects of dopamine and NMDA receptors on cocaine-induced Fos expression in the striatum of Fischer rats

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ABSTRACT

Cocaine is an addictive psychostimulant that induces immediate early gene (IEG) expression by activating dopamine (DA) D1 and glutamate NMDA receptors in the striatum. In this study, we show that a single cocaine administration (30 mg/kg) time-dependently increases ERK phosphorylation, c-Fos and FosB protein expression, and MKP-1 phosphorylation (p-MKP-1), in the caudate–putamen (CPu) and nucleus accumbens (NAc) of Fischer rats. In the CPu, 1 h after cocaine injection, the increase in c-Fos and FosB protein expressions is totally abolished by pre-administration of DA-D1 receptor antagonist, SCH23390. In the NAc, SCH23390 also inhibits cocaine-induced c-Fos protein expression. The pre-treatment of NMDA receptor antagonist, MK801, partially reduces cocaine-activated c-Fos protein expression in the CPu. Furthermore, the escalation of p-MKP-1 after acute cocaine administration is dependent on both DA-D1 and NMDA receptor activation in both brain regions examined. Our data suggest that cocaine may modulate ERK pathway signaling through the activation of DA-D1 and NMDA receptors, subsequently influencing the IEG protein expression.

1. Introduction

Cocaine is a major drug of abuse in Western countries and induces its psychomotor effects by blocking monoamine transporters. Among three monoaminergic systems, the dopaminergic inputs from the ventral tegmental area (VTA) to the nucleus accumbens (NAc) and the nigrostriatal projections to the caudate–putamen (CPu) have been postulated to be the main regulator of cocaine's behavioral and biochemical effects (reviewed in Hyman and Malenka 2001; Koob and Nestler 1997; Spanagel and Weiss 1999). For example, *in vitro* and *in vivo*, cocaine administration causes a buildup of synaptic dopamine (DA) levels and increases DA neuronal activity in the CPu and NAc (Carboni et al., 1989; Kalivas and Duffy 1988; Maisonneuve and Kreek 1994; Reith et al., 1997). Cocaine also exerts its influence on the glutamatergic system. For instance, in the CPu and NAc, studies have shown that single or repeated cocaine injection modulates extracellular glutamate concentration (Pierce et al., 1996; Reid and Berger, 1996; Smith et al., 1995; Zhang et al., 2001).

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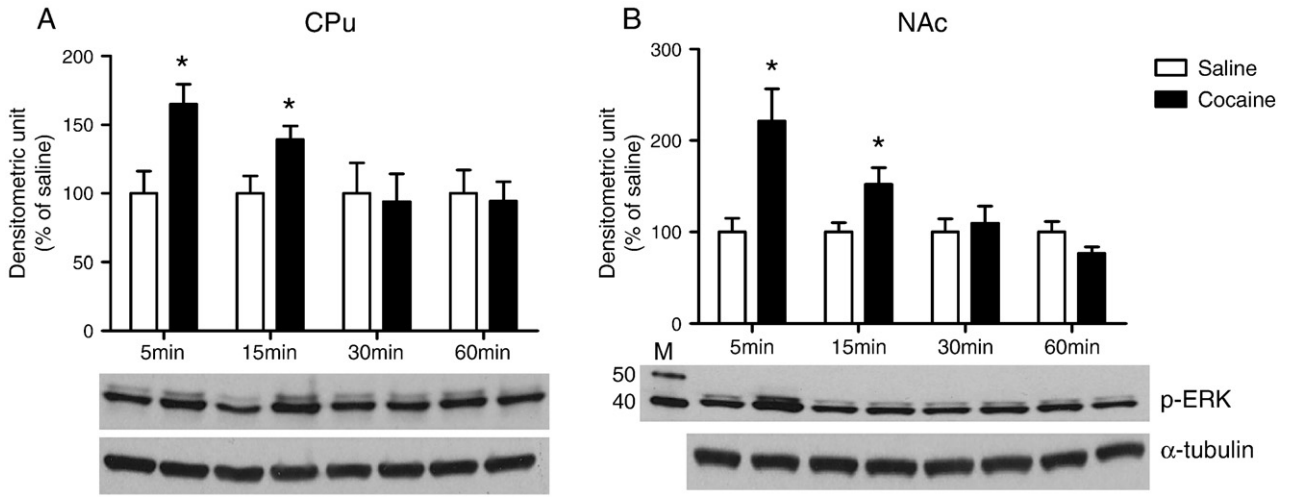

Fig. 1 – The time course of cocaine effects on p-ERK in (A) CPu and (B) NAc. Results represent protein levels over α-tubulin expressed as percentage of saline control (4 animals per group). 5, 15, 30, or 60 min after rats were given injections. M is the molecular marker in kDa. *P<0.05 as compared with respective saline group.

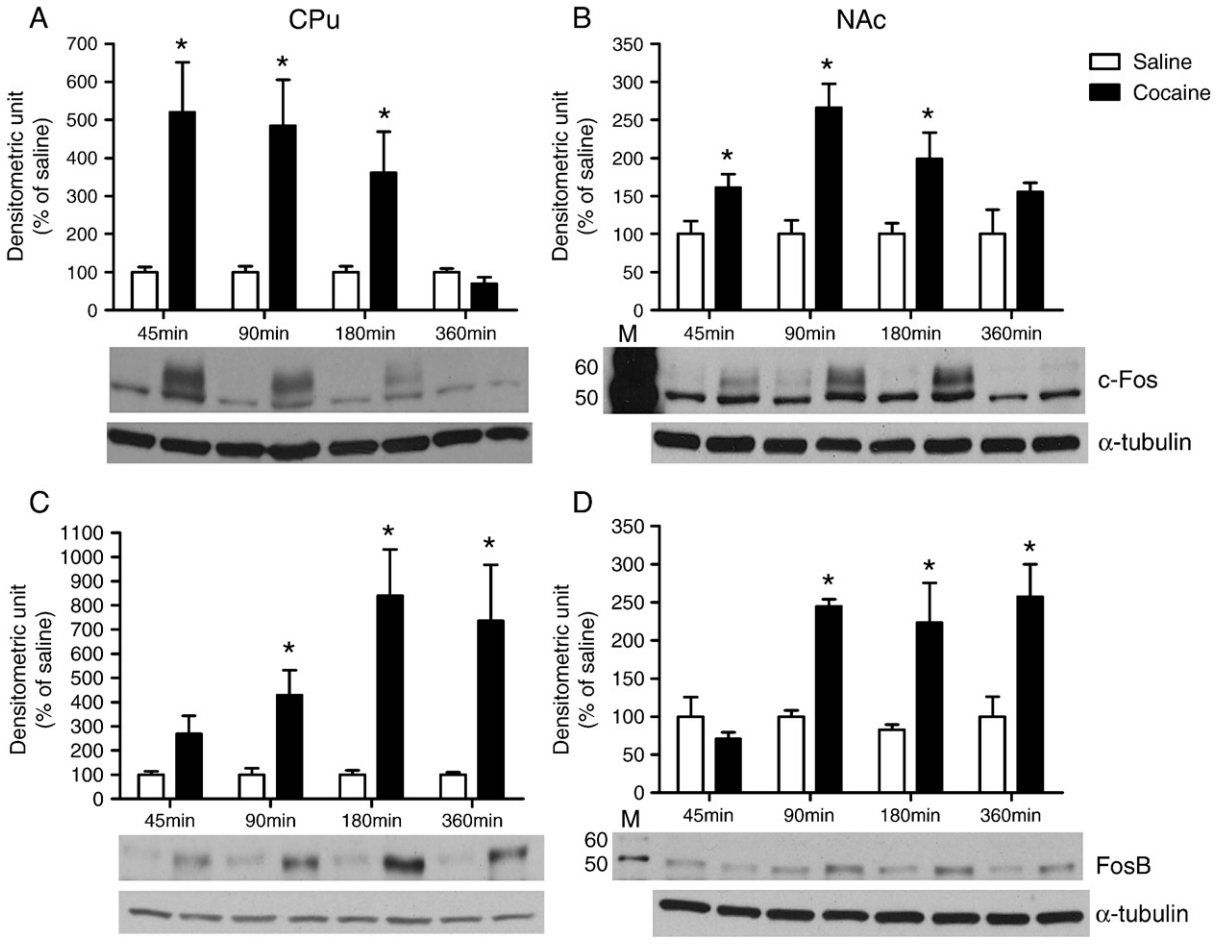

Fig. 2 – The time course of cocaine effects on Fos-like protein expression. c-Fos in (A) CPu and (B) NAc; FosB in (C) CPu and (D) NAc. Results represent protein levels over α-tubulin expressed as percentage of saline control (4 animals per group). 45, 90, 180, or 360 min after rats were given injections. M is the molecular marker in kDa. *P<0.05 as compared with respective saline group.