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Research Report

Striatal patch compartment lesions reduce stereotypy following repeated cocaine administration

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ABSTRACT

Stereotypy can be characterized as inflexible, repetitive behaviors that occur following repeated exposure to psychostimulants, such as cocaine (COC). Stereotypy may be related to preferential activation of the patch (striosome) compartment of striatum, as enhanced relative activation of the patch compartment has been shown to positively correlate with the emergence of stereotypy following repeated psychostimulant treatment. However, the specific contribution of the patch compartment to COC-induced stereotypy following repeated exposure is unknown. To elucidate the involvement of the patch compartment to the development of stereotypy following repeated COC exposure, we determined if destruction of this sub-region altered COC-induced behaviors. The neurons of the patch compartment were ablated by bilateral infusion of the neurotoxin dermorphin-saporin (DERM-SAP; 17 ng/μl) into the striatum. Animals were allowed to recover for eight days following the infusion, and then were given daily injections of COC (25 mg/kg) or saline for one week, followed by a weeklong drug-free period. Animals were then given a challenge dose of saline or COC, observed for 2 h in activity chambers and sacrificed. The number of mu-labeled patches in the striatum were reduced by DERM-SAP pretreatment. In COC-treated animals DERM-SAP pretreatment significantly reduced the immobilization and intensity of stereotypy but increased locomotor activity. DERM-SAP pretreatment attenuated COC-induced c-Fos expression in the patch compartment, while enhancing COC-induced c-Fos expression in the matrix compartment. These data indicate that the patch compartment contributes to repetitive behavior and suggests that alterations in activity in the patch vs matrix compartments may underlie to this phenomenon.

Abbreviations: Dermorphin-saporin, DERM-SAP; unconjugated saporin, SAP; cocaine, COC; saline, SAL

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1. Introduction

The basal ganglia are critically important in the regulation of movement and alterations in the function of the striatum contributes to the development of movement disorders (Crittenden and Graybiel, 2011). The striatum can be divided into the patch (striosome) and matrix compartments based on differential connectivity and the expression of neuropeptides and receptors (Crittenden and Graybiel, 2011; Gerfen et al., 1985; Gerfen and Wilson, 1996; Gerfen and Young, 1988; Graybiel, 1990). The patch compartment is thought to be a limbic channel that runs through the striatum, as it receives inputs from prelimbic cortex and amygdala, while the matrix compartment is considered to be a motor channel traversing the striatum, since it receives inputs from sensorimotor and associative forebrain regions (Bolam et al., 1988; Gerfen, 1984; McDonald, 1992; Ragsdale and Graybiel, 1988). The specific functions of these compartments are not completely understood, but several lines of data suggest that the patch and matrix compartments may sub-serve different aspects of motor activity and behavior. For example, treatment with high or repeated doses of psychostimulants results in enhanced immediate early gene (Canales and Graybiel, 2000; Cole et al., 1995; Graybiel et al., 1990; Horner and Keefe, 2006; Moratalla et al., 1992; Tan et al., 2000; Wang et al., 1995) and neuropeptide expression (Adams et al., 2003; Cole et al., 1995; Fagergren et al., 2003; Horner and Keefe, 2006; Wang et al., 1995) in the patch compartment relative to the surrounding matrix.

Psychostimulant treatment can also result in stereotypy, which is defined as the development of abnormally repetitive motor actions that coincides with an inability to initiate normal adaptive responses (Canales and Graybiel, 2000; Cole et al., 1995; Graybiel et al., 1990; Graybiel and Rausch, 2000). Psychostimulant-induced stereotypic behaviors may be related to enhanced activation of the rostral aspects of the patch compartment relative to the surrounding rostral matrix compartment, as the relative degree of c-Fos expression in the patch compartment in the rostral region of striatum correlates positively with the development of stereotypic behavior following psychostimulant treatment (Canales and Graybiel, 2000). Interestingly, this relationship was specific only for the rostral aspects of striatum, as there was not a significant correlation between psychostimulant-induced patch-enhanced c-Fos expression and stereotypy in more middle or caudal regions of the striatum (Canales and Graybiel, 2000). Furthermore, a recent study from our laboratory found that ablation of the neurons of the rostral patch compartment resulted in reduced levels of stereotypy in

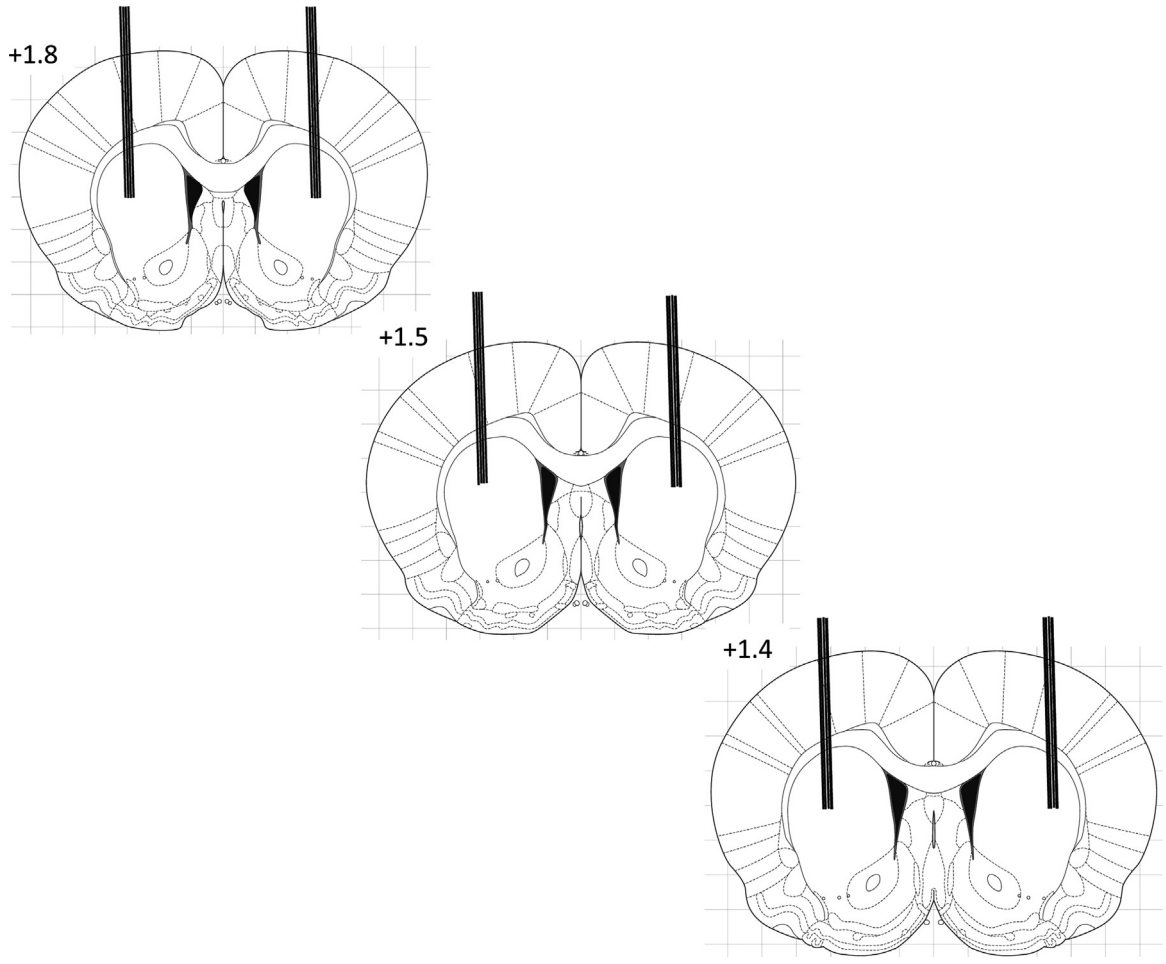

Fig. 1 – Infusion sites in the dorsal striatum. Schematic images showing lines that indicate the placement of microinjection cannulae tips observed during sectioning. Measurements are given in mm relative to bregma.