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STATUS EPILEPTICUS STIMULATES NDEL1 EXPRESSION VIA THE CREB/CRE PATHWAY IN THE ADULT MOUSE BRAIN

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Abstract—Nuclear distribution element-like 1 (NDEL1/NUDEL) is a mammalian homolog of the *Aspergillus nidulans* nuclear distribution molecule NudE. NDEL1 plays a critical role in neuronal migration, neurite outgrowth and neuronal positioning during brain development; however within the adult central nervous system, limited information is available regarding NDEL1 expression and functions. Here, the goal was to examine inducible NDEL1 expression in the adult mouse forebrain. Immunolabeling revealed NDEL1 within the forebrain, including the cortex and hippocampus, as well as the midbrain and hypothalamus. Expression was principally localized to perikarya. Using a combination of immunolabeling and RNA seq profiling, we detected a marked and long-lasting upregulation of NDEL1 expression within the hippocampus following a pilocarpine-evoked repetitive seizure paradigm. Chromatin immunoprecipitation (ChIP) analysis identified a cAMP response element-binding protein (CREB) binding site within the CpG island proximal to the *NDEL1* gene, and *in vivo* transgenic repression of CREB led to a marked downregulation of seizure-evoked NDEL1 expression. Together these data indicate that NDEL1 is inducibly expressed in the adult nervous system, and that signaling via the CREB/CRE transcriptional pathway is likely involved. The role of NDEL1 in neuronal migration and neurite outgrowth during development raises the interesting prospect that inducible NDEL1 in the mature nervous system could contribute to the well-characterized structural and functional plasticity resulting from repetitive seizure activity.
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Key words: seizure, CREB, CRE, hippocampus, NDEL1.

INTRODUCTION

Nuclear distribution element-like 1 (NDEL1/NUDEL) is a mammalian homolog of the nuclear distribution molecule NudE. NDEL1 is broadly expressed, with particularly high levels detected in the brain. NDEL1 interacts with a number of proteins, including dynein, lissencephaly 1 protein (LIS1), disrupted in schizophrenia 1 (DISC1), and 14-3-3ζ (Chansard et al., 2011; Vallee et al., 2012; Bradshaw et al., 2013). Through its interactions with LIS1, and as part of the dynein motor complex, NDEL1 has been shown to play a variety of roles in cytoskeletal organization throughout development. Along these lines, in progenitor cell populations, NDEL1 is concentrated at the centrosome and regulates mitotic spindle pole organization and mitosis (Guo et al., 2006; Moon et al., 2014); whereas in developing postmitotic neurons, NDEL1 redistributes to axons and cell soma and is essential for normal neuronal migration, cortical layering, neurite outgrowth and neuronal polarity (Niethammer et al., 2000; Sasaki et al., 2000; Lambert de Rouvroit and Goffinet, 2001; Toyo-oka et al., 2003; Kamiya et al., 2006; Youn et al., 2009). Consistent with these key developmental processes, germline deletion of NDEL1 is embryonically lethal at the peri-implantation stage (Sasaki et al., 2005).

In the adult central nervous system NDEL1 was found to interact with neurofilament light subunit (NF-L) and to facilitate the polymerization of NFs (Sasaki et al., 2000; Nguyen et al., 2004). Further, the deletion of NDEL1 in the postnatal mouse brain causes NF alterations reminiscent of those observed during neurodegeneration (Nguyen et al., 2004), thus indicating a key role for NDEL1 in neuronal morphology. Additional functional roles for NDEL1 in the soma and cell processes include lysosome transport and organelle positioning (Zhang et al., 2009; Lam et al., 2010). Notably, dysregulation of NDEL1 has been linked to an array of mental and neurodegenerative disorders (Chansard et al., 2011). For example, through its interactions with LIS1 and DISC1, NDEL1 may contribute to the etiology of lissencephaly

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Abbreviations: ChIP, chromatin immunoprecipitation; CREB, cAMP response element-binding protein; DAB, diaminobenzidine; DISC1, disrupted in schizophrenia 1; GCL, granule cell layer; GFP, green fluorescent protein; GFAP, glial fibrillary acidic protein; Hil, hilus; LIS1, lissencephaly 1 protein; NDEL1/NUDEL, Nuclear distribution element-like 1; NF-L, neurofilament light subunit; ML, molecular cell layer; PBS, phosphate-buffered saline; PBST, PBS with 0.1% Triton-X; PCL, pyramidal cell layer; SE, status epilepticus; SO, striatum oriens; SR, stratum radiatum; WT, wildtype.

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and schizophrenia, respectively (Ozeki et al., 2003; Shu et al., 2004; Kamiya et al., 2006; Youn et al., 2009).

Although these studies have revealed functional aspects of NDEL1 in the mature brain, there is still limited information about its neuroanatomical expression and whether NDEL1 is regulated in an activity-dependent manner. Considering the dynamic roles of NDEL1 in transport, neurite outgrowth and the integrity of adult CNS neurons, we posited that NDEL1 may be important for synaptic modification and reorganization following pathophysiological levels of neuronal activity. Here, we begin to address this question with a series of immunolabeling, ChiP Seq, RNA profiling and transgene studies. The findings presented here reveal that NDEL1 expression is regulated by neuronal activity in the mature CNS and that its expression is under the control of the CREB/CRE transcriptional pathway.

EXPERIMENTAL PROCEDURES

Animals and tissue processing

C57BL/6 mice (mixed gender: 7–10 weeks of age) were used for all of the experiments described here. A total of 52 mice were used to generate the data presented in Figs. 1–3 and 6; data presented in Figs. 4 and 5B were curated from our recently published Illumina Sequencing studies (Lesiak et al., 2013; Hansen et al., 2014); data presented in Fig. 5A was derived from a combination of *in silico* studies and cell culture studies published as part of the ENCODE consortium project (for additional details, please see the ChIP seq section below). For immunolabeling assays, mice were anesthetized with an intraperitoneal injection of ketamine (91 mg/ml) and xylaxine (9 mg/ml) and then transcardially perfused with cold saline, followed by 4% paraformaldehyde in phosphate-buffered saline (PBS, pH 7.4). Brains were then post-fixed in 4% paraformaldehyde for 4 h at 4 °C and cryoprotected with 30% sucrose solution in PBS. Coronal sections (40 μm) through the whole brain were prepared using a freezing microtome. For Western analysis, mice were euthanized via CO_2- mediated asphyxiation, brains were isolated and placed in ice-cold oxygenation media, and the striatum were rapidly dissected and stored at −80 °C. A detailed description of the tissue isolation method for the RNA seq analysis is provided in Hansen et al. (2014). All procedures involving mice were approved by the Institutional Animal Care and Use Committee at Ohio State University.

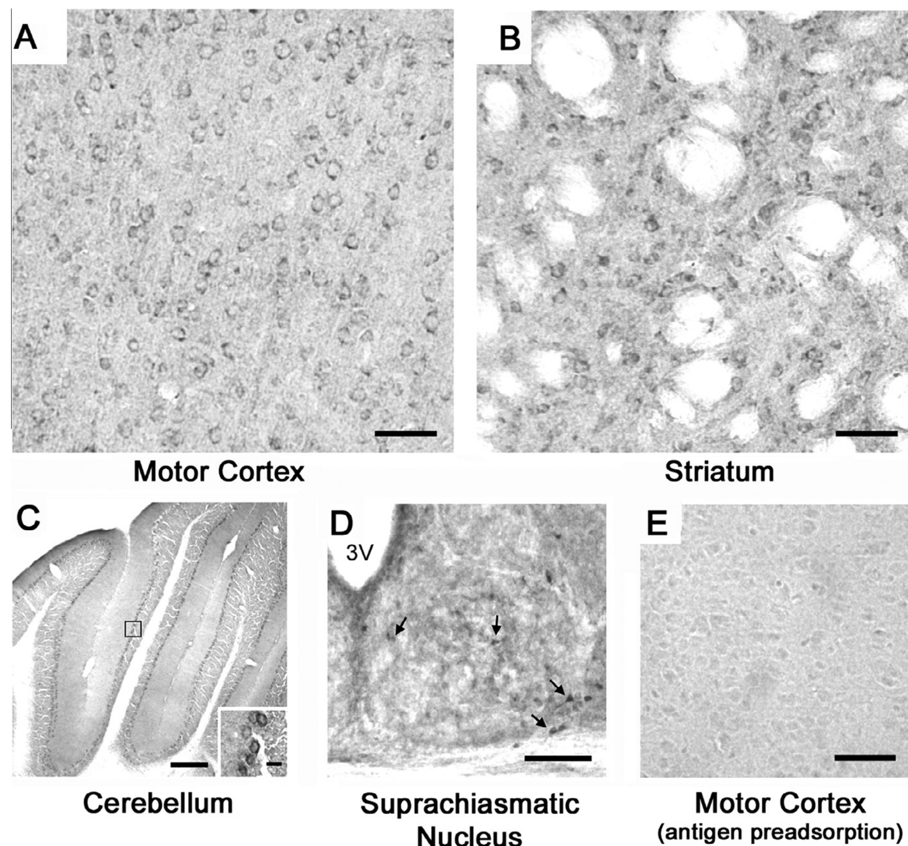

Fig. 1. NDEL1 expression in the adult mouse brain. Representative immunolabeling for NDEL1 is presented for the motor cortex (A), striatum (B), cerebellum (C) and suprachiasmatic nucleus (D). Note the marked cellular expression within all brain regions. (E) As a control, the NDEL1 antibody was incubated with an NDEL1 peptide, and then tissue from the motor cortex was immunolabeled: note the loss of signal relative to the immunostaining shown in *A*. Arrows in D indicate NDEL1 positive cells in the suprachiasmatic nucleus, and the boxed region in C is magnified as a subpanel. Scale bars = 50 μm for A, B and E, 150 μm for C, 10 μm for the high-magnification image in C, and 100 μm for D. Data are representative of 6 animals.

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