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BRAIN RESEARCH

Research Report

NR2A-containing NMDA receptors are required for LTP induction in rat dorsolateral striatum *in vitro*

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ABSTRACT

N-methyl-D-aspartate receptors (NMDARs) have been implicated in various forms of synaptic plasticity. In recent years, studies have been shown that NMDA receptor subunits play different roles in several forms of NMDAR-dependent synaptic plasticity. However, the contribution of NR2A and NR2B subunits in the induction of long-term potentiation (LTP) in the corticostriatal pathway remains unclear. The present study used patch-clamp recordings to study the role of NR2A-containing and NR2B-containing NMDARs in LTP induction in corticostriatal slices from 13–14-day old rats. High-frequency stimulation (HFS) of the corticostriatal pathway readily induced LTP of excitatory postsynaptic currents (EPSCs), and D-APV, a selective NMDAR antagonist, blocked LTP. Moreover, NR2B-containing NMDAR antagonists (Ro 25-6981 and ifenprodil) displayed no influence on LTP induction. However, LTP was not inducible in the presence of Zn^{2+}, an NR2A-containing NMDAR antagonist. These results suggest that the induction of LTP by HFS in the dorsolateral striatum is NMDAR-dependent and requires NR2A-containing NMDARs, not NR2B-containing NMDARs.

1. Introduction

The dorsal striatum (neostriatum) is a brain region that is critical for controlling voluntary motor behaviors (Graybiel et al., 1994), but is also involved in the formation of habits (Yin et al., 2004; Yin and Knowlton, 2006), decision-making (Balleine et al., 2007), and drug addiction (Berke and Hyman, 2000; Everitt and Robbins, 2005). This region receives massive convergent glutamatergic input from the cortex. Corticostriatal pathway synaptic plasticity has been thought to underlie motor-skill learning, cognitive performance, and reward mechanisms (Calabresi et al., 1996; Mahon et al., 2004; Wickens et al., 2003). Previous *in vivo* and *in vitro* studies have demonstrated that long-term potentiation (LTP) and long-term depression (LTD) are induced in corticostriatal glutamatergic synaptic transmission in the dorsal striatum (Calabresi et al., 1992a; Calabresi et al., 2000; Charpier and Deniau, 1997; Partridge et al., 2000; Spencer and Murphy, 2000). Both forms of plasticity are inducible by high-frequency stimulation (HFS). Some of the mechanisms

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responsible for LTP and LTD induction in the dorsal striatum have been recently characterized (Calabresi et al., 2007; Wang et al., 2006). Interestingly, LTP induced by HFS in this region is dependent on activation of NMDA receptors (Calabresi et al., 1992b; Fino et al., 2005; Partridge et al., 2000). However, LTD is NMDAR-independent (Calabresi et al., 1992a; Lovinger et al., 1993).

NMDA receptors, a subtype of glutamate receptors, consist of obligatory NR1 and NR2 (A–D) subunits (Sucher et al., 1996). In the striatum, NR1, NR2A, and NR2B are the predominant subunits that comprise NMDARs (Kosinski et al., 1998; Standaert et al., 1994). Previous investigations revealed that functional and pharmacological properties of NMDARs are determined by the types of NR2 subunits they contain (Neyton and Paoletti, 2006), and that NMDARs containing different NR2 subunits have distinct roles in the striatum. Recent studies have shown that activation of NR2A- and NR2B-containing NMDARs, located in the striatum, differentially modulate GABA and glutamate release in target areas, including the globus pallidus (GP) and substantia nigra reticulata (SNr) (Fantin et al., 2007). In addition, NR2A-containing NMDARs regulate glutamatergic synaptic transmission and evoked-dopamine release in the striatum (Schotanus and Chergui, 2008b). Synaptic plasticity, with regard to its dependence on NR2 subunits, has been investigated in several brain regions, such as the hippocampus, cortex, and nucleus accumbens (NAc) (Liu et al., 2004; Massey et al., 2004; Schotanus and Chergui, 2008a). However, the types of subunits containing NMDARs involved in LTP in the dorsal striatum have not been investigated.

In the present study, whole-cell voltage-clamp recordings were utilized to assess the role of NR2A-containing and NR2B-containing NMDARs in LTP induction in the dorsolateral (DL) striatum.

2. Results

2.1. *EPSC components and LTP induction in the DL striatum*

Glutamatergic synaptic transmission was investigated in the DL striatum using whole-cell recordings from medium spiny neurons (MSNs) in coronal slices containing the cortex and striatum. The recording electrode was placed in the DL striatum and ranged from 3.0 to 3.5 mm, from the midline of the hemi-slice. EPSCs were evoked by 0.05 Hz stimulation with a monopolar glass-stimulating electrode, which was placed in the corpus callosum overlying the DL striatum (Fig. 1A). As shown in Fig. 1B, EPSCs were completely abolished with the addition of both the NMDAR antagonist, D-APV (50 μM), and AMPAR antagonist CNQX (10 μM). The NMDAR-mediated EPSCs were isolated by adding AMPAR antagonist CNQX in Mg^{2+}-free artificial CSF (ACSF). Results indicated that EPSC was composed of NMDAR and AMPAR components. The percentage of NMDAR contribution in EPSCs was 39±5% (n=9). In Mg^{2+}-free ACSF, stable responses were collected for 5 min. After HFS was delivered to the glutamatergic cortical-DL striatum, the EPSC amplitude increased. As illustrated in Fig. 1C, EPSC amplitudes increased gradually after HFS, and remained potentiated for almost 30 min (when the experiment was usually terminated). The corresponding mean value of EPSC potentiation at 30 min was 162±11% and was significantly different (P=0.001, n=8) from the baseline (Fig. 1C).

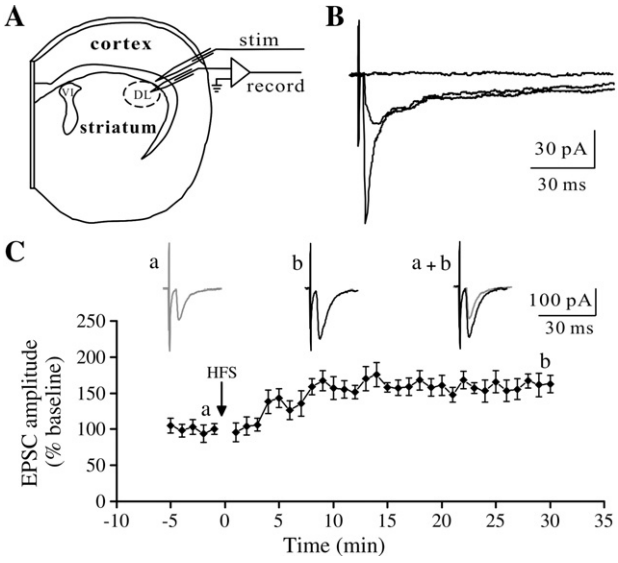

Fig. 1 – HFS-induced LTP in the DL striatum in Mg^{2+}-free ACSF. (A) Schematic diagram depicting placement of stimulating and recording electrodes. A monopolar stimulating electrode was placed in the corpus callosum overlying the DL striatum; the recording electrode was located in DL striatum (circled area) and ranged from 3.0–3.5 mm from the midline of the hemi-slice. (B) Contribution of NMDARs and AMPARs to EPSCs in MSNs. Superimposed current traces were from MSNs clamped at −70 mV in Mg^{2+}-free ACSF, separately representing average EPSCs evoked in control ACSF, CNQX, and both D-APV and CNQX. Each trace was the average of three originals. (C) Long-lasting EPSC amplitude increased after HFS in corticostriatal fibers. The average response, 30 min after HFS, was 162±11% (n=8) of the baseline EPSC amplitude. Each point represented average amplitude of three responses over 1 min. EPSCs (average of 3 individual responses) during baseline (a), 30 min after HFS protocol (b), and overlay (a+b) are shown above the graphs. The arrow indicates when HFS was delivered. Error bars indicate S.E.M.

2.2. *Striatal LTP is dependent on NMDA receptor activation*

To confirm the role of NMDARs in corticostriatal LTP, the selective NMDAR antagonist D-APV was used. As shown in Fig. 2, when HFS was administered in the presence of D-APV (50 μM), potentiation of the EPSC amplitude was blocked, and no significant LTP in synaptic responses was observed (95±11% of baseline EPSC amplitude, 30 min after HFS, P=0.971, n=4). These results suggested that HFS-induced LTP in the DL striatum was fully dependent on NMDARs.