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Properties of the corticostriatal long term depression induced by medial prefrontal cortex high frequency stimulation in vivo

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ABSTRACT

Repetitive stimulation of cognitive forebrain circuits at frequencies capable of inducing corticostriatal long term plasticity is increasingly being used with therapeutic purposes in patients with neuropsychiatric disorders. However, corticostriatal plasticity is rarely studied in the intact brain. Our aim was to study the mechanisms of corticostriatal long term depression (LTD) induced by high frequency stimulation (HFS) of the medial prefrontal cortex *in vivo*. Our main finding is that the LTD induced in the dorsomedial striatum by medial prefrontal cortex HFS *in vivo* (prefrontostriatal LTD) is not affected by manipulations that block or reduce the LTD induced in the dorsolateral striatum by motor cortex HFS in brain slices, including pharmacological dopamine receptor and CB1 receptor blockade, chronic nigrostriatal dopamine depletion, CB1 receptor genetic deletion and selective striatal cholinergic interneuron (SCIN) ablation. Conversely, like in the hippocampus and other brain areas, prefrontostriatal LTD is NMDA receptor dependent. Thus, we describe a novel form of corticostriatal LTD that operates in brain circuits involved in reward and cognition and could be relevant for understanding the therapeutic effects of deep brain stimulation.

1. Introduction

The striatum is the main input nucleus of the basal ganglia and receives topographically ordered inputs from most cortical areas (Hintiryan et al., 2016; Voorn et al., 2004). Projections from prefrontal associative areas are directed mainly to the medial and ventral striatum while those from motor cortical areas reach the dorsolateral striatum. This organization of cortical input relates to functional differences between ventromedial and dorsolateral striatum where the former contributes to more flexible forms of behavior than the latter, which is involved in habits (Everitt and Robbins 2005; Yin and Knowlton, 2006; Graybiel, 2008). It has been proposed that long term changes in corticostriatal transmission underlie the acquisition of goal directed behaviors and habits (Hawes et al., 2015; Reynolds et al., 2001; Costa et al., 2004). The best described form of corticostriatal synaptic plasticity is long term depression (LTD) induced by high frequency stimulation (HFS) of striatal afferents. While corticostriatal LTD can be induced by HFS both *ex vivo* (Calabresi et al., 1992a,b; Lovinger et al., 1993; Walsh, 1993) and *in vivo* (Reynolds and Wickens, 2000), its molecular and pharmacological characterization has mainly been done in brain slices.

Ex vivo studies focused in the dorsolateral striatum show that HFS-LTD depends on dopamine (DA) D2 receptor stimulation (Lovinger, 2010) and postsynaptic endocannabinoid (eCB) release leading to presynaptic CB1 receptor activation and reduced probability of glutamate release (Choi and Lovinger, 1997b). Since HFS-LTD is expressed in striatal medium spiny projection neurons (MSNs) of both the indirect (iMSN) and direct (dMSN) pathways, but DA D2 receptors are only expressed in iMSN, it has been proposed that DA dependent forms of LTD are mediated by striatal cholinergic interneurons (SCIN), which express high levels of D2 receptors and regulate both dMSNs and iMSNs (Wang et al., 2006).

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A few *ex vivo* studies addressing synaptic plasticity in the dorsomedial and ventral striatum revealed regional differences in corticostriatal plasticity (Partridge et al., 2000; Thomas et al., 2000; Dang et al., 2006). For instance, LTD is regarded as NMDA receptor independent in the dorsolateral striatum but it requires NMDA receptors in the ventral striatum (Thomas et al., 2000). The mechanisms of corticostriatal LTD have rarely been addressed with *in vivo* approaches (Reynolds and Wickens, 2000). Whether corticostriatal HFS-LTD requires DA, eCBs, SCIN and NMDA receptors *in vivo* remains to be clarified.

In a previous *in vivo* study we concluded that the local field potential response evoked in the dorsomedial striatum (eLFP) by electrical stimulation of the medial prefrontal cortex (mPFC) of mice reflects cortical input to MSNs based on the following observations: i. its amplitude is linearly correlated to the amplitude of depolarizing postsynaptic potentials simultaneously recorded from MSNs; ii. it is blocked by intrastriatal infusion of an AMPA receptor antagonist; iii. its topographical organization is consistent with the anatomical projections of the mPFC to the dorsal striatum (Galiñanes et al., 2011). In the present study we performed striatal eLFP recordings in mice under urethane anesthesia to analyze the properties of the corticostriatal LTD induced by HFS of the mPFC. We found that this form of LTD is DA and CB1 receptor independent and is unaffected by selective SCIN ablation. Interestingly, we also found that prefrontostriatal HFS-LTD is NMDA receptor dependent.

2. Methods

2.1. Animals

Mice were maintained under a 12 h light:12 h dark cycle with ad libitum access to food and water and cared for in accordance with institutional (IACUC, RS2964/2010 and 2598/13, University of Buenos Aires) and government regulations (SENASA, RS617/2002, Argentina). All efforts were made to minimize the number of animals used and their suffering.

In all pharmacological experiments we used adult CF-1 mice (12–30 weeks old). For SCIN lesion experiments we used ChAT-Cre$^{+/-}$;DTR$^{loxP/wt}$ mice (ChAT-DTR mice) in C57BL/6 homogeneous background (Martos et al., 2017). ChAT-DTR mice were generated by crossing homozygous ChAT-Cre mice (Chat$^{tm(cre)Lowl/J}$, Jackson Laboratories, J06410) with homozygous iDTR mice (Gt(ROSA)26Sor$^{tm1(HBEGF)Awai}$, Jackson Laboratories, J007900). The iDTR line allows expression of the Diphtheria Toxin Receptor (simian Hbegf) after Cre-mediated recombination of a floxed stop cassette, rendering targeted cells susceptible to the toxin. CB1 receptor knock-out mice (CB1 KO) were generated by crossing homozygous CB1 KO mice in CD1 background with wild type CD1 mice (Wolfson et al., 2015).

2.2. Lesions and pharmacology

Neonatal dopamine neuron lesions were done in CF-1 mice as previously described (Avale et al., 2004). PD2 pups received bilateral injections of the catecholaminergic neurotoxin 6-hydroxydopamine (6-OHDA, 6.25 μg/μl; MP Biomedicals) or vehicle (0.1% ascorbic acid) in each lateral ventricle (1.1 mm below the skin, 0.6 mm from midline, and 1.5 mm anterior to the lambda), after desipramine pretreatment (20 mg/kg, s.c.) to protect noradrenergic neurons, under hypothermal anesthesia. Injections were performed at a constant rate of 1.25 μl/min with a 30 gauge needle coupled to a 25 μl Hamilton syringe driven by a microinfusion pump (Bee syringe pump and controller, Bioanalytical Systems). In each litter, half of the pups received the toxin and the other half vehicle. After surgery, they were warmed up and returned to their home cages in groups of up to eight pups per breast-feeding mother until weaning (PD24). Thereafter, control and lesion mice were housed together in the same cage in groups of 4–6 until the electrophysiological experiment (12–30 weeks).

SCIN lesions were performed in ChAT-DTR mice (3–4 month old) as described by (Martos et al., 2017). Under deep surgical anesthesia (isofluorane 1–2%) each mouse was mounted in a stereotaxic frame (Stoelting Co, USA) with a mouse-adaptor and treated with a local anesthetic in the scalp and pressure points (bupivacaine hydrochlorate solution, 5% wv/v, Durocaine, AstraZeneca S.A., Argentina 0.1–0.3 ml). Ophthalmic ointment was applied in both eyes to prevent corneal desiccation. Diphtheria Toxin stocks (DT, Sigma #D0564) were freshly diluted in sterile saline to a concentration of 200 pg/μl. DT solution (lesion) or saline (sham) were microinjected (at a constant rate of 0.22 μl/min) unilaterally in dorsal striatum via a 30 gauge stainless steel cannula coupled to a 10 μl Hamilton syringe driven by a microinfusion pump (Bioanalytical Systems, USA). The injection cannula was left in place for one additional minute before slowly retracting it. DT solution or solvent were injected in three independent sites per hemi-striatum: anterior site: 1.3 mm anterior to bregma, 1.6 mm lateral and −2.8 mm (0.8 μl) and −2.4 mm (0.8 μl) ventral from dura; posterior site: 0.6 mm anterior to bregma, 1.8 mm lateral and -3 mm ventral from dura (1.2 μl) according to the atlas of Paxinos and Franklin (2001). Control and lesion mice were housed together in groups of 3–5 animals per cage until testing.

Chemicals were purchased from Sigma or Tocris. The CB1 receptor antagonist AM-251 was dissolved in DMSO 0.5% and administered at a dose of 5 mg/kg two hours before HFS. DA receptor antagonists eticlopride and SCH23390 were dissolved in saline and co-administered at a dose of 0.25 mg/kg, 90 min before HFS. MK-801, an NMDA receptor antagonist, was dissolved in saline and administered in two 0.375 mg/kg i.p. injections separated by 15 min (final dose: 0.75 mg/kg) due to the lethality observed after delivering the total dose in one injection.

2.3. Electrophysiology

All recordings were performed under urethane anesthesia (1.2–1.5 g/kg i.p.) following published protocols (Galiñanes et al., 2009, 2011). Bupivacaine was applied subcutaneously on the scalp and pressure points and the animal was affixed to a stereotaxic frame. Body temperature was maintained at 36–37 °C with a servocontrolled heating pad (Fine Science Tools, Vancouver, Canada). During the experiment, the level of anesthesia was regularly verified by testing the nociceptive hind limb withdrawal reflex and by online visual examination of the frontal cortex electrocorticogram (see below). Supplemental doses of urethane were customarily given throughout the experiment (0.3 g/kg s.c. every 2–3 h).

A concentric bipolar stimulating electrode (SNE-100, Better Hospital Equipment, New York, NY; outer contact diameter 0.25 mm, central contact diameter 0.1 mm, contacts separation 0.75 mm, contact exposure 0.25 mm) was placed into the prelimbic area of the mPFC (2.0 mm anterior to bregma, 0.4 lateral to midline, 2.0 mm ventral to the cortical surface, ipsilateral to the striatal recording site, Paxinos and Franklin, 2001). A second bipolar electrode was placed into the motor cortex (2.0 mm anterior to bregma, 1.6 lateral, 1.2 mm ventral) to record the electrocorticographic activity (0.1–300 Hz (Galiñanes et al., 2009, 2011). Striatal field potentials were recorded with a 24-channel two-shank silicon probe (100 μm vertical spacing between contacts and 500 μm horizontal shank spacing; NeuroNexus Technologies, Ann Arbor, MI). Each recording site of the silicon probe had a contact area of 413 μm^2 and an impedance of about 0.8 MΩ. The probe was positioned in the coronal plane within the rostral area of the dorsal striatum with an