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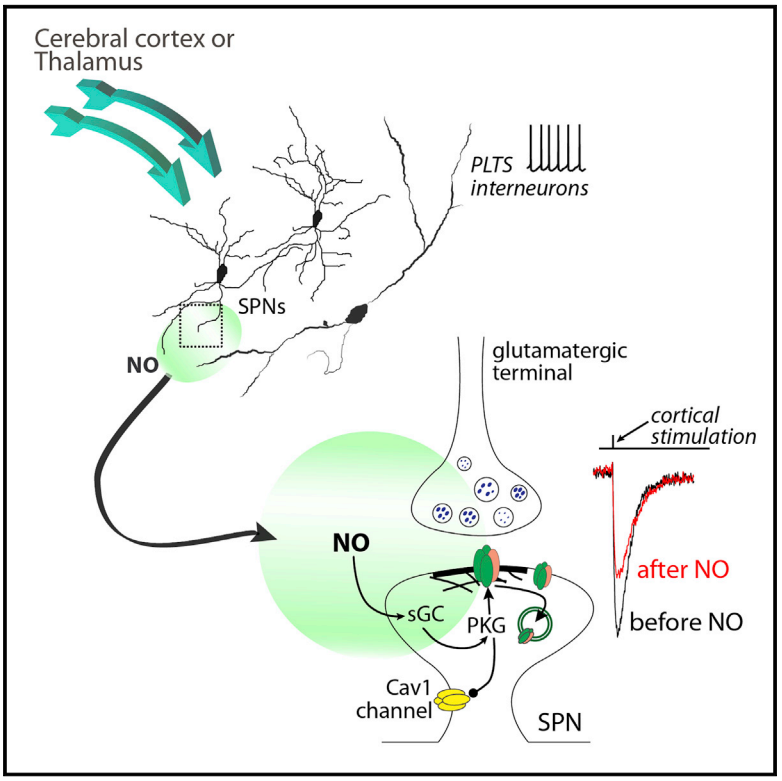
# Interneuronal Nitric Oxide Signaling Mediates Post-synaptic Long-Term Depression of Striatal Glutamatergic Synapses

## Graphical Abstract

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## In Brief

Nitric oxide (NO) is a gaseous neurotransmitter whose intracellular machinery is expressed at abundant levels within the striatum. Historically, NO's role in striatal plasticity has been controversial. Rafalovich et al. have conducted a series of pharmacological and optogenetic studies that reveal that NO is unequivocally a mediator of striatal depression.

## Highlights

- Activation of PLTS interneurons produces NO-LTD at SPN glutamatergic synapses
- NO-LTD is dependent upon cGMP signaling and expressed postsynaptically
- NO-LTD is independent of activity and the origin of presynaptic terminal
- NO blunts presynaptic eCb-LTD by suppressing dendritic L-type $Ca^{2+}$ channels

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# Interneuronal Nitric Oxide Signaling Mediates Post-synaptic Long-Term Depression of Striatal Glutamatergic Synapses

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## SUMMARY

**Experience-driven plasticity of glutamatergic synapses on striatal spiny projection neurons (SPNs) is thought to be essential to goal-directed behavior and habit formation. One major form of striatal plasticity, long-term depression (LTD), has long appeared to be expressed only pre-synaptically. Contrary to this view, nitric oxide (NO) generated by striatal interneurons was found to induce a post-synaptically expressed form of LTD at SPN glutamatergic synapses. This form of LTD was dependent on signaling through guanylyl cyclase and protein kinase G, both of which are abundantly expressed by SPNs. NO-LTD was unaffected by local synaptic activity or antagonism of endocannabinoid (eCb) and dopamine receptors, all of which modulate canonical, pre-synaptic LTD. Moreover, NO signaling disrupted induction of this canonical LTD by inhibiting dendritic $Ca^{2+}$ channels regulating eCb synthesis. These results establish an interneuron-dependent, heterosynaptic form of post-synaptic LTD that could act to promote stability of the striatal network during learning.**

## INTRODUCTION

The striatum has long been implicated in learning goal-directed behavior and habits (Balleine et al., 2007). This learning is thought to reflect changes in the strength of glutamatergic synapses that dictate the timing and pattern of activity of principal spiny projection neurons (SPNs) (Gerfen and Surmeier, 2011). In the dorsal striatum, axospinous glutamatergic synapses on SPNs are formed primarily by cortical pyramidal neurons. Long-term depression (LTD) of these synapses was initially described over 20 years ago and has been extensively studied (Calabresi et al., 1992; Centonze et al., 2001; Gerfen and Surmeier, 2011; Kreitzer and Malenka, 2008; Mathur and Lovinger, 2012). The best-characterized form of LTD is induced by post-synaptic depolarization and activation of metabotropic glutamate receptors and L-type $Ca^{2+}$ channels, which trigger the generation of endocannabinoids (eCbs) by SPNs; expression of LTD is mediated by eCb activation of pre-synaptic CB1 receptors, which results in sustained depression of glutamate release (Kreitzer and Malenka, 2005; Lovinger et al., 1993). Although other neuromodulators can mimic the actions of eCbs at these synapses (Mathur et al., 2011), no post-synaptically expressed form of LTD has been described in SPNs.

One of the signaling molecules implicated in post-synaptically expressed LTD elsewhere in the brain is NO (Garthwaite, 2008). Striatal expression of NO signaling proteins soluble guanylyl cyclase (sGC) and protein kinase G (PKG) are among the highest of any brain region, making a role for NO signaling in striatal plasticity plausible (Ariano, 1983; Ding et al., 2004). Indeed, NO has been implicated in striatal synaptic plasticity, but its role is controversial (Calabresi et al., 1999; Sammut et al., 2007), with most of the available data suggesting it is a permissive modulator of eCb-dependent LTD (eCb-LTD) (Centonze et al., 1999, 2001).

## RESULTS

### NO Signaling Produced LTD of Glutamatergic Synapses

To assess the potential role of NO signaling in striatal synaptic plasticity, excitatory post-synaptic currents (EPSCs) evoked in SPNs by electrical stimulation of corticostriatal axons were monitored before, during, and after the application of the NO donor (*S*)-nitroso-*N*-acetyl-D,L-penicillamine (SNAP, 100 μM) to ex vivo parasagittal brain slices of mouse forebrain (Figure 1A). In this preparation, cortical axons can be stimulated electrically without directly activating striatal neurons, unlike the coronal brain slice (Kawaguchi et al., 1989). Transient application of SNAP led to a persistent depression of corticostriatal EPSCs (Figure 1B). To verify that our electrical stimulus was not directly exciting SPNs, cortical pyramidal neurons were optogenetically activated to evoke EPSCs; SNAP application also produced a persistent depression of optically evoked corticostriatal EPSCs (Figure S1A).

NO can have both direct and indirect effects on proteins involved in synaptic transmission (Garthwaite, 2008). Because

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