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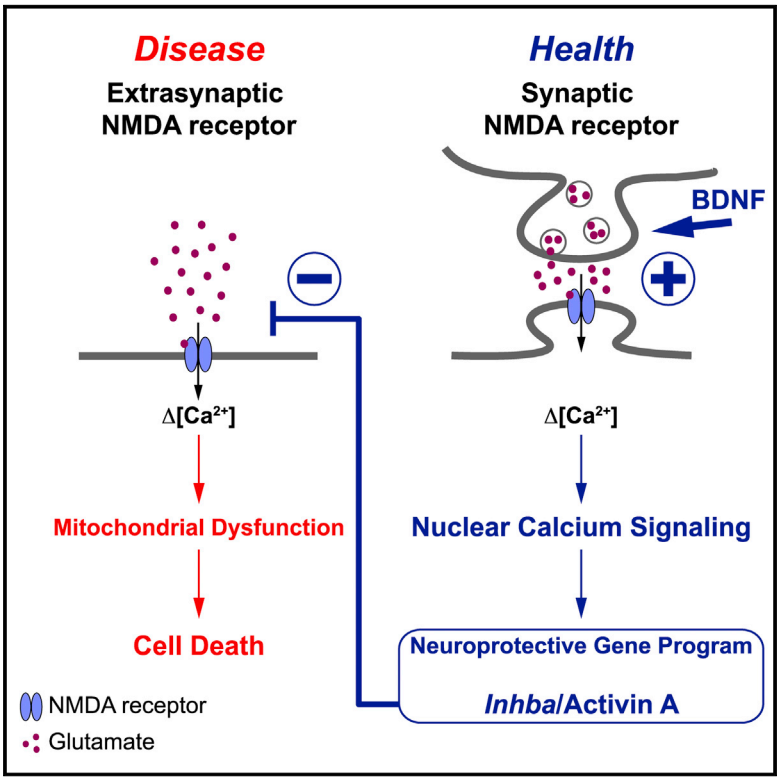
BDNF Reduces Toxic Extrasynaptic NMDA Receptor Signaling via Synaptic NMDA Receptors and Nuclear-Calcium-Induced Transcription of *inhba*/Activin A

Graphical Abstract



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In Brief

Lau et al. show that BDNF-induced neuroprotection is mediated by synaptic NMDA-receptor-dependent nuclear calcium signals activating transcription of inhibin β-A (activin A). Activin A in turn reduces toxic extrasynaptic NMDA-receptor-mediated calcium influx, shields neurons from mitochondrial dysfunction, and protects against stroke-induced brain damage.

Highlights

- BDNF-induced neuroprotection requires synaptic NMDA receptors and nuclear calcium
- BDNF-nuclear calcium signaling induces transcription of *inhba*/activin A
- Activin A reduces toxic extrasynaptic NMDA receptor signaling, shielding mitochondria
- Activin A protects against excitotoxic cell death in cultured neurons and in vivo

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BDNF Reduces Toxic Extrasynaptic NMDA Receptor Signaling via Synaptic NMDA Receptors and Nuclear-Calcium-Induced Transcription of *inhba*/Activin A

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SUMMARY

The health of neurons is critically dependent on the relative signaling intensities of survival-promoting synaptic and death-inducing extrasynaptic NMDA receptors. Here, we show that BDNF is a regulator of this balance and promotes neuroprotection by reducing toxic NMDA receptor signaling. BDNF acts by initiating synaptic NMDA-receptor/nuclear-calcium-driven adaptogenomics, leading to increased expression of *inhibin* β-A (*inhba*). Inhibin β-A (its homodimer is known as activin A) in turn reduces neurotoxic extrasynaptic NMDA-receptor-mediated calcium influx, thereby shielding neurons against mitochondrial dysfunction, a major cause of excitotoxicity. Thus, BDNF induces acquired neuroprotection by enhancing synaptic activity and lowering extrasynaptic NMDA receptor death signaling through a nuclear calcium-*inhibin* β-A pathway. This process, which confers protection against ischemic brain damage in a mouse stroke model, may be compromised in Huntington's disease, Alzheimer's disease, or aging-related neurodegenerative conditions that are associated with reduced BDNF levels and/or enhanced extrasynaptic NMDA receptor signaling.

INTRODUCTION

BDNF is a versatile and multifunctional growth factor implicated in the control of a wide spectrum of adaptive processes in the developing and adult brain, ranging from modulation of synaptic connectivity and excitability to neuroprotection (Park and Poo, 2013). BDNF acts through the high-affinity tyrosine receptor kinase B (TrkB) receptor, which upon ligand binding activates downstream effector kinases and signaling pathways including phosphatidylinositol 3-kinase (PI3K)/Akt and the Ras/extracellular-signal-regulated kinase 1/2 (ERK1/2) cascade. The induction of these signaling pathways is generally thought to mediate the neuroprotective effects of BDNF against toxic insults such as bath-applied glutamate, hypoxic ischemia, serum deprivation, or camptothecin-induced apoptosis (Almeida et al., 2005; Atwal et al., 2000; Han and Holtzman, 2000; Hetman et al., 1999). The PI3K/Akt and Ras/ERK1/2 pathways are indeed potent neuroprotectors and are also involved in pro-survival processes activated by neuronal activity (Papadia et al., 2005; Perkinton et al., 2002). However, the buildup of a long-lasting neuroprotective shield upon induction of synaptic activity, known as "acquired neuroprotection" (Bading, 2013; Zhang et al., 2009), results primarily from the activation of synaptic NMDA receptors and the subsequent generation of nuclear calcium transients that serve as the on switch of a neuroprotective gene program (Hardingham et al., 2001, 2002; Papadia et al., 2005; Zhang et al., 2007, 2009). The induction of this survival-enhancing set of genes is part of a broad, nuclear-calcium-regulated change in the transcriptional profile of synaptically activated neurons, here termed "adaptogenomics," which is required for the long-term implementation of virtually all structural and functional adaptations in the brain (Bading, 2013).

Both synaptic dysfunction and impaired NMDA receptor signaling as well as decreased BDNF levels are implicated in the etiology of several neurodegenerative diseases (Zuccato and Cattaneo, 2009). We therefore reasoned that BDNF-induced survival and acquired neuroprotection are mechanistically linked and share the requirement for synaptic NMDA receptors and nuclear-calcium-regulated transcriptional events. This hypothesis is supported by previous observations that BDNF can increase synaptic AMPA- and NMDA-receptor-mediated currents, as well as whole-cell NMDA currents and calcium responses (Carmignoto et al., 1997; Poo, 2001). Our study revealed that, under our conditions, the buildup of a neuroprotective shield following BDNF treatment of hippocampal neurons is not mediated by PI3K/Akt and Ras/ERK1/2 signaling but instead is the result of the ability of BDNF to promote synaptic activity and to induce the expression of *inhibin* β-A (*inhba*)—an activity-driven neuroprotective gene regulated by synaptic NMDA receptors and nuclear calcium (Zhang et al., 2009). The mechanism through which the BDNF-*inhibin* β-A-signaling pathway boosts resistance against excitotoxicity involves a dephosphorylation of NMDA receptor subunit NR2B at tyrosine residue 1472, a decrease in neurotoxic extrasynaptic NMDA-receptor-mediated calcium influx, and reduced calcium-overload-induced mitochondrial dysfunction. These results indicate that BDNF induces neuroprotection primarily through the control of the balance between