Superoxide generation via the NR2B-NMDAR/RasGRF1/NOX2 pathway promotes dendritogenesis

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N-methyl-D-aspartate receptors (NMDARs) that contain the NR2A and NR2B subunits play a critical role in neuronal plasticity and dendritogenesis. Gain-and-loss-of function studies indicate that NR2B, but not NR2A, promotes dendritic branching. Accumulating evidence indicates that stimulation of NMDARs activates NADPH oxidase (NOX2), thereby generating superoxide. However, the molecular underpinnings of this process are not understood. RasGRF1, a guanine nucleotide exchange factor, is key for several forms of neuronal plasticity and interacts directly with the tail of NR2B. We investigated whether the NR2B-NMDAR/RasGRF1 pathway regulates the activity of NOX2 and whether superoxide production is required for dendritogenesis. We measured superoxide production in developing primary cultures of hippocampal neurons from 3 to 25 days in vitro (DIV) with the probe dihydroethidium (dHE). We found the highest dHE levels at early and intermediate developmental stages (3?15 DIV), when the NR2B-NMDAR expression is abundant. During these early/intermediate developmental stages, but not in mature neurons (>15 DIV), NMDAR activity is required for superoxide production. We also found that disrupting the NR2B-RasGRF1 interaction led to reduced dHE fluorescence intensity and moreover inhibited dendritic branching in hippocampal neurons. Together, our data indicate that superoxide production is induced by the NR2B-NMDARs/RasGRF1/NOX2 pathway and promotes dendritogenesis. © 2019 Wiley Periodicals, Inc.

cultures

dendrites

neuron

NMDAR

RasGRF1

superoxide

chlorpheniramine maleate plus phenylephrine

guanine nucleotide exchange factor

n methyl dextro aspartic acid receptor 2B

RasGRF1

reduced nicotinamide adenine dinucleotide phosphate oxidase 2

superoxide

unclassified drug

Cybb protein, rat

guanine nucleotide exchange factor

n methyl dextro aspartic acid receptor

NR2B NMDA receptor

Rasgrf1 protein, rat

reduced nicotinamide adenine dinucleotide phosphate oxidase 2

superoxide

animal cell

animal cell culture

animal experiment

Article

dendritogenesis

developmental stage

female

hippocampal neuronal culture

in vitro study

morphology

nerve cell growth

nerve cell plasticity

nonhuman

primary culture

priority journal

rat

signal transduction

animal

dendrite

dendritic cell

gene expression regulation

genetics

growth, development and aging

hippocampus

metabolism

nerve cell

nervous system development

Animals

Dendrites

Dendritic Cells

Gene Expression Regulation, Developmental

Hippocampus

NADPH Oxidase 2

Neurogenesis

Neuronal Plasticity

Neurons

ras-GRF1

Rats

Receptors, N-Methyl-D-Aspartate

Signal Transduction

Superoxides