

**Nitrous Oxide activates layer 5 prefrontal neurons via SK2 channel inhibition for antidepressant effect**

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**Abstract:**

Nitrous oxide (N<sub>2</sub>O) induces rapid and durable antidepressant effects. The cellular and circuit mechanisms mediating this process are not known. Here we find that a single dose of inhaled N<sub>2</sub>O induces rapid and specific activation of layer V (L5) pyramidal neurons in the prefrontal cortex of rodents exposed to chronic stress conditions. N<sub>2</sub>O-induced L5 activation rescues a stress-associated hypoactivity state, persists following exposure, and is necessary for its antidepressant action. While NMDA-receptor antagonism has been N<sub>2</sub>O's purported mechanism of action, L5 neurons activate independently from NMDA-receptor function and synaptic activity. By examining different molecular and circuit targets, we identify N<sub>2</sub>O-induced inhibition of calcium-sensitive potassium (SK2) channels as a primary molecular interaction responsible for driving specific L5 activity along with ensuing antidepressant-like effects.