Wnt5a inhibits K+ currents in hippocampal synapses through nitric oxide production

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Hippocampal synapses play a key role in memory and learning processes by inducing long-term potentiation and depression. Wnt signaling is essential in the development and maintenance of synapses via several mechanisms. We have previously found that Wnt5a induces the production of nitric oxide (NO), which modulates NMDA receptor expression in the postsynaptic regions of hippocampal neurons. Here, we report that Wnt5a selectively inhibits a voltage-gated K+ current (Kv current) and increases synaptic activity in hippocampal slices. Further supporting a specific role for Wnt5a, the soluble Frizzled receptor protein (sFRP-2; a functional Wnt antagonist) fully inhibits the effects of Wnt5a. We additionally show that these responses to Wnt5a are mediated by activation of a ROR2 receptor and increased NO production because they are suppressed by the shRNA-mediated knockdown of ROR2 and by 7-nitroindazole, a specific inhibitor of neuronal NOS. Together, our results show that Wnt5a increases NO production by acting on ROR2 receptors, which in turn inhibit Kv currents. These results reveal a novel mechanism by which Wnt5a may regulate the excitability of hippocampal neurons.

Hippocampal neurons

K+ current

ROR2 receptor

Wnt5a

7 nitroindazole

nitric oxide

receptor tyrosine kinase like orphan receptor

voltage gated potassium channel

Wnt5a protein

7-nitroindazole

enzyme inhibitor

indazole derivative

n(g) methylarginine

nitric oxide

potassium

potassium channel

receptor tyrosine kinase like orphan receptor

Ror2 protein, rat

Wnt protein

Wnt5a protein, rat

animal cell

animal tissue

Article

brain cell culture

controlled study

hippocampal neuron

hippocampus potential

male

nerve cell

nerve cell excitability

neuromodulation

nonhuman

potassium current

priority journal

protein interaction

rat

regulatory mechanism

synaptic transmission

Wnt signaling pathway

animal

C57BL mouse

cell culture

cytology

drug effects

excitatory postsynaptic potential

genetic transduction

genetics

hippocampus

in vitro study

mammalian embryo

metabolism

mouse

nerve cell

physiology

Sprague Dawley rat

synapse

Animals

Cells, Cultured

Embryo, Mammalian

Enzyme Inhibitors

Excitatory Postsynaptic Potentials

Hippocampus

In Vitro Techniques

Indazoles

Mice

Mice, Inbred C57BL

Neurons

Nitric Oxide

omega-N-Methylarginine

Potassium

Potassium Channels

Rats

Rats, Sprague-Dawley

Receptor Tyrosine Kinase-like Orphan Receptors

Synapses

Transduction, Genetic

Wnt Proteins