A novel function for Wnt signaling modulating neuronal firing activity and the temporal structure of spontaneous oscillation in the entorhinal-hippocampal circuit.

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Abstract

During early and late postnatal developments, the establishment of functional neuronal connectivity depends on molecules like Wnt that help the recently formed synapses to establish and consolidate their new cellular interactions. However, unlike other molecules, whether Wnt can modulate the firing properties of cells is unknown. Here, for the first time we explore the physiological effect of the canonical and non-canonical Wnt pathways on a circuit that is currently generating oscillatory activity, the entorhinal cortex-hippocampal circuit. Our results indicate that Wnt pathways have strong influence in the circuital and cellular properties depending on the Wnt protein isoforms, concentration, and type of neuronal circuit. Antibodies against canonical and non-canonical ligands, as well as WASP-1 and sFRP-2, demonstrate that constitutive release of Wnts contributes to the maintenance of the network and intrinsic properties of the circuit. Furthermore, we found that the excess of Wnt3a or the permanent intracellular activation of the pathway with BIO-6 accelerates the period of the oscillation by disrupting the oscillatory units (Up states) in short units, presumably by affecting the synaptic mechanisms that couples neurons into the oscillatory cycle, but without affecting the spike generation. Instead, low doses of Wnt5a increase the period of the oscillation in EC by incorporating new cells into the network activity, probably modifying firing activity in other places of the circuit. Moreover, we found that Wnt signaling operates under different principles in the hippocampus. Using pyrvinium pamoate, a Wnt/β-catenin dependent pathway inhibitor, we demonstrated that this pathway is essential to keep the firing activity in the circuit CA3, and in less degree of CA1 circuit. However, CA1 circuit possesses homeostatic mechanisms to up-regulate the firing activity when it has been suppressed in CA3, and to down-modulate the cellular excitability when exacerbated circuital activity has dominated. In summary, the amount of Wnt that is being released can exert a fine tuning of the physiological output, modulating firing activity, improving reliability of communication between neurons, and maintaining a continuous
self-regulatory cycle of synaptic structure-function that can be present during all postnatal life.