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A Serotonergic Axon-Cilium Synapse Drives Nuclear Signaling to Maintain Chromatin Accessibility

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Chemical synapses between axons and dendrites mediate the brain's intercellular communication. Here we describe a new kind of synapse, the axo-ciliary synapse, between axons and primary cilia. By employing enhanced focused ion beam – scanning electron microscopy on samples with optimally preserved ultrastructure, we discovered synapses between the serotonergic axons arising from the brainstem, and the primary cilia of hippocampal CA1 pyramidal neurons. Functionally, these cilia are enriched in a ciliary-restricted serotonin receptor, 5-hydroxytryptamine receptor 6 (protein: 5-HT6; gene: HTR6). Using a newly developed cilia-targeted serotonin sensor, we show that opto- and chemogenetic stimulation of serotonergic axons releases serotonin onto cilia. Using fluorescence lifetime imaging microscopy to measure Förster resonance energy transfer changes of biosensors, we showed that ciliary 5-HT6 stimulation activates a non-canonical $G_{\alpha q/11}$-RhoA pathway. Activation of this pathway modulates nuclear actin and increases histone acetylation and chromatin accessibility. Ablation of this pathway reduces chromatin accessibility in CA1 pyramidal neurons. Axo-ciliary synapses serve as a distinct mechanism for neuromodulators to program neuron transcription through privileged access to the nucleus [1]. As HTR6 was recently discovered as one of the potential contributors to bipolar disorders [2], studying the ciliary 5-HT6 signaling may yield novel mechanistic insights of these diseases.

References

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