New serotonergic pathways regulating gene transcription and neuronal morphology

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Serotonin (5-hydroxytryptamine or 5-HT) is an important neurotransmitter involved in a wide range of central and peripheral physiological and pathological functions. A number of different G-protein coupled 5-HT receptors are known to sensitively modify different neuronal networks by their specific action on synaptic transmission and postsynaptic excitability. Here we show for the first time that serotonin 5-HT4 receptor is coupled not only to the heterotrimeric Gs, but also to G13 protein. Activation of this signaling pathway results in modulation of gene transcription and in reorganization of the actin cytoskeleton. We also demonstrated that serotonin receptor 5-HT7 can activate heterotrimeric G12 protein in addition to the Gs protein, leading to the selective activation of small GTPases RhoA and Cdc42. Agonist-dependent activation of the 5-HT7 receptor induced pronounced filopodia formation paralleled by cell rounding. Analysis of hippocampal neurons demonstrated that activation of the endogenous 5-HT7 receptors significantly increased neurite length, whereas stimulation of the endogenous 5-HT4 receptors lead to a pronounced decrease in the length and number of neurites. These data demonstrate distinct roles for the 5-HT_7R/G12 and 5-HT_4R/G13 signaling pathways in the neurite outgrowth/retraction, and also suggest that serotonin plays a prominent role in regulating the neuronal cyto-architecture in addition to its classical role as neurotransmitter.