

Insights into physiological versus pathological Notch signaling in neurons.

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Our previous work showed that synaptic activity facilitates Notch activation and that this cascade is essential for synaptic plasticity and memory formation. In addition, we confirmed that hypoxia-ischemia (HI) aberrantly induces Notch in neurons and that this affects cell survival. We speculate that reduction in Notch function is instrumental in the cognitive impairment in Alzheimer's Disease; whereas aberrant induction of Notch may substantially contribute to the neuronal damage following stroke. Based on the evidence that under increased synaptic activity *Hes1* and *Hes5* are unchanged, whereas there is strong induction of the *Hes* genes after ischemia, we hypothesize that that physiological Notch signaling acts through a non-canonical (non-transcriptional) pathway whereas pathological Notch signaling through a canonical (transcriptional) one. In this work we aim to address the mechanism behind what we call "physiological" and "pathological" Notch signaling. In this study we show that in condition of increased synaptic activity, "physiological" condition, Notch processing depends on endocytosis as opposed to extra-synaptic stimulation, as in "pathological" conditions. A microarray analysis from *Notch1cKO* and wt hippocampi in basal condition and after maximal activity (MECS) showed that the number of differentially expressed genes significantly increased upon maximal activity and that both transcriptional and non-transcriptional targets are affected by the absence of Notch.