Role of the neuronal primary cilia-autophagy axis in the regulation of cognition and brain plasticity

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Abstract:

Normal brain aging is characterized by a decline in cognitive functions that develop around midlife. One of the most commonly affected regions of the brain is the hippocampus, leading to learning and memory deficits. With increased life expectancies in developed societies, the number of individuals affected by age-related memory loss is bound to dramatically increase. Therefore, a deeper understanding of how a healthy brain ages is now a highly prioritized challenge and it is crucial to identify mechanisms that favor neuronal plasticity in the hippocampus to ensure the maintenance of cognitive functions. We recently showed that brain autophagy, a lysosomal catabolic process that controls cell homeostasis, is pivotal for memory formation and maintenance during aging. We identified Osteocalcin (Ocn), a youthful hormone, as a direct inducer of autophagy in hippocampal neurons and its administration to aged mice improved memory in an autophagy-dependent manner. These findings suggest a novel role for autophagy in the communication between systemic milieu and neurons to foster cognitive fitness and brain plasticity. The primary cilium (PC) is an extracellular organelle that acts as a cellular antenna sensing systemic signals, such as hormones. Interestingly, the PC can transduce information about extracellular changes in various tissues by modulating autophagy. We hypothesize that PC constitutes a gateway in hippocampal neurons through which youthful systemic factors modulate autophagy and cognitive fitness. Accordingly, we show that alteration of PC activity selectively in hippocampus impaired autophagic machinery and led to severe memory deficits. During aging, we found abnormal PC morphology associated with a reduction of major PC-associated proteins. Lastly, we found that GPR158, the receptor for Ocn, is highly present in neuronal PC upon Ocn treatment. Taken together, these findings advance our understanding of how HpC neurons sense the systemic milieu, which intracellular mechanisms mediate their adaptive responses to environmental changes and provide novel molecular mechanistic insight into these processes.