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A novel approach of Compensation for Neurodegeneration and Aging Induced Cognitive Decline

The significant increase in life expectancy intensifies the need for novel therapies for age- and neurodegenerative-related (Alzheimer's and Parkinson's) cognitive decline. Learning-related cellular changes include modifications that occur at synapses and modifications in the intrinsic properties of neurons. While it is commonly agreed that changes in strength of connections between neurons in the relevant networks underlie memory storage, increasing amount of evidence show that modifications in intrinsic neuronal play a key role in learning related behavioral changes. We have been revealing the cellular and molecular mechanisms underlying learning-relevant modifications in intrinsic excitability. Moreover, we show that such modifications are causally related to a higher form of learning termed meta-learning, or learning how to learn. Using knockout mice of a specific subtype of glutamate neuronal receptor, and virus-induced overexpression of the receptor, we were able to show a novel role for this receptor in mediating these long-lasting neuronal modifications which result in cognitive enhancement in animal models of complex learning.

The data we have generated validates a role for receptor in enhancing learning via regulating neuronal plasticity and excitability by dampening AHP. Moreover, pharmaceutical regulation of receptor-mediated activity presents a novel approach for cognitive enhancement via a highly relevant pathway which is not yet targeted by current therapies. Since an increase in neuronal excitation is central to high-order learning, pharmaceutical decrease of AHP via receptor activation may offer an opportunity for cognitive enhancement in both neurological disorders and aging. Due to the limited expression pattern of receptor, side effects resulting from activation of this receptor are expected to be limited. Since this particular receptor represents a novel pathway for intervention in cognitive impairment, pharmaceutical agents acting at this target may be used in conjunction with current therapies which target other pathways.