Increased dosage of p44 causes memory loss, neurodegeneration and premature death

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INTRODUCTION

The communication between a cell and its environment is achieved by the use of cellular receptors. Molecules attach to their specific receptors located in the cell surface, and the receptors in turn send signals to the interior of the cell to induce a change. IGF-1R is one of these receptors, and it has been shown to regulate the life span of several organisms.

In mammals, IGF-1R signaling is, at least in part, controlled by p44. In the mouse, an increase in p44, a short and naturally occurring form of p53, leads to increased IGF-1R signaling, which accelerates aging and shortens lifespan.

1. Aging is the single most important risk factor for sporadic (late-onset) Alzheimer’s Disease (AD).
2. Our group has shown that IGF-1R controls the generation of Aβ, which accumulates in the brain of AD patients.
3. We studied the effect of increased IGF-1R signaling and accelerated aging in mice with increased dosage of p44. In addition, to assess the role of IGF-1R signaling in AD pathology, we bred p44 mice to mice over-producing the human precursor of Aβ (APP), which develop an AD-like pathology at old age.

RESULTS

p44/+ mice show memory impairment and synaptic defects

Brain sections of 5-month-old male p44/+ and APP695/swe mice were immunostained for GFAP (astrocytic marker; green) and NeuN (neuronal marker; red). Higher magnification of reactive astrocytes is shown in (A). Images were obtained in the dentate gyrus sectors of the hippocampus of p44/+ mice (B) and p44/+;APP695/swe mice (C). Values are mean±SEM. *P < 0.05; **P < 0.005.

Reduced IGF-1R signaling improves the synaptic deficits caused by the accumulation of Aβ in APP695/swe mice.

CONCLUSION

In transgenic mice, increased IGF-1R signaling accelerates Alzheimer’s Disease-like pathology, whereas reduced IGF-1R signaling prevents it.

By regulating IGF-1R signaling, p53 may play a role in the cognitive decline associated with both normal aging and late-onset Alzheimer’s Disease.

Our results suggest that IGF-1R could be a valid pharmacological target for the treatment and/or prevention of both the memory loss that accompanies aging and the neuropathy that characterizes Alzheimer's disease.