
The authors note that, due to a printer’s error, the affiliation for Kaitlin L. Ingraham should instead appear as “Laboratory of Molecular NeuroTherapeutics, Departments of Pharmacology and Experimental Therapeutics and Neurology, and Alzheimer’s Disease Center, Boston University School of Medicine, Boston, MA 02118.” The corrected author and affiliation lines appear below. The online version has been corrected.

Tomomi Kiyota*, Kaitlin L. Ingraham*, Michael T. Jacobsen*, Huangui Xiong*, and Tsuneya Ikezu*,b,1

*Departments of Pharmacology and Experimental Neuroscience, University of Nebraska Medical Center, Omaha, NE 68198; and bLaboratory of Molecular NeuroTherapeutics, Departments of Pharmacology and Experimental Therapeutics and Neurology, and Alzheimer’s Disease Center, Boston University School of Medicine, Boston, MA 02118
FGF2 gene transfer restores hippocampal functions in mouse models of Alzheimer’s disease and has therapeutic implications for neurocognitive disorders

Tomomi Kiyota*, Kaitlin L. Ingraham*, Michael T. Jacobsen*, Huangui Xiong*, and Tsuneya Ikezu†§

*Departments of Pharmacology and Experimental Neuroscience, University of Nebraska Medical Center, Omaha, NE 68198; and †Laboratory of Molecular NeuroTherapeutics, Departments of Pharmacology and Experimental Therapeutics and Neurology, and Alzheimer’s Disease Center, Boston University School of Medicine, Boston, MA 02118

AUTHOR SUMMARY

The adult hippocampus is a brain region that plays a central role in memory formation, synaptic plasticity (i.e., the ability of a neuron to change the strength of its response to stimulation from other neurons), and neurogenesis in the subgranular zone (SGZ), the process by which neurons are generated from cells that can differentiate into specific types of cells called progenitor cells. Reduced hippocampal neurogenesis is strongly associated with memory dysfunction in humans with age-associated cognitive dysfunction, further substantiating the emerging role of neurogenesis in hippocampal functions in the aged brain. In the Alzheimer’s disease (AD) brain, hippocampal neurogenesis shows proliferation of neuronal progenitor cells in response to the disease but impairment in their maturation. Thus, there is a significant therapeutic potential for restoring functions in the aging or disease-impaired hippocampus through the proper enhancement of neurogenesis, with an emphasis on normal neuronal maturation in AD brains. Indeed, neurotrophic factor therapy is a promising approach for the enhancement of neuroprotection and neuronal maturation in the brain (1, 2). In this research article, we report that the gene transfer of FGF2 restores the function of a brain region, the hippocampus, including learning and neurogenesis, in animal models of AD.

FGF2 is a neurogenic factor that promotes the proliferation and differentiation of multipotential neural progenitor cells isolated from the adult mouse brain (3). However, an elevation of FGF2 levels has been documented in the AD brain. Moreover, the treatment of primary cultured neurons with FGF2 has been characterized as rather inhibitory to neuronal differentiation (4, 5). These studies have led to the opinion that the increase in FGF2 levels in response to neurodegeneration may be antagonistic to the maturation of newly synthesized neurons and is potentially inhibitory to neuroregeneration in the AD brain. However, the latter conclusion was drawn from a study of the low molecular weight isoform (LMW) of FGF2 (an isoform is one of several forms of a protein), which did not include all the isoforms, including the high molecular weight (HMW) FGF2. HMW FGF2 has distinct cellular localization and signaling pathways and is involved in neuroprotection and neuronal differentiation.

The AAV serotype 2/1 hybrid virus (AAV2/1) is a modified virus used for gene therapy; that is, the virus delivers a particular gene to target cells, and thereby results in the gene being expressed in those target cells. In this study, we have demonstrated that AAV2/1-mediated expression of the FGF2 gene in transgenic (genetically modified) mouse model of AD (called APP+PS1 mouse) significantly restores spatial learning and neurogenesis and partially clears amyloid-β peptide (Aβ)—a molecule that accumulates in the AD brain and results in destructive plaques—in the hippocampal regions after both pre- and postsymptomatic treatments. These results suggest that gene therapy with FGF2 is effective in potentially ameliorating cognitive dysfunction after the onset of symptoms. Our study also shows that AAV2/1-FGF2 infection directly enhances neuronal differentiation of neuronal progenitor cells in cell culture system. Moreover, this enhancement is through an apparently different mode of action from the effect of LMW FGF2. This difference can be explained by the predominant gene expression of HMW FGF2 and its distinct nuclear localization after AAV2/1-FGF2 infection. FGF receptor 1 (FGFR1) exists as a nuclear protein and specifically binds to the HMW isoforms but not

Fig. P1. Schematic diagram of FGF2, Aβ, and hippocampal functions. (A) The proliferation of self-renewing neuronal stem cells in the SGZ of the dentate gyrus is enhanced by a secreted LMW isoform of FGF2 mainly from astrocytes in the SGZ, and potentially by direct stimulation with Aβ. AAV-FGF2 infection in neuronal stem cells expresses intracellular and HMW FGF2 and enhances neuronal differentiation via a distinct mechanism from that of the LMW FGF2. (B) Neuronal maturation is enhanced by HMW FGF2 expression in the neuronal stem cells and is inhibited by Aβ. Neurons also produce Aβ, which is partially inhibited by the expression of HMW FGF2. (C) HMW FGF2 enhances hippocampal neuronal c-fos gene expression and CA1 LTP, and confers the synaptic inhibition by Aβ. Enhanced neuronal plasticity may facilitate learning and memory. (D) LMW FGF2 activates microglia and enhances Aβ uptake, leading to the reduction of Aβ plaques in the brain.


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*To whom correspondence should be addressed. E-mail: tikezu@bu.edu.

†Laboratory of Molecular NeuroTherapeutics, Departments of Pharmacology and Experimental Therapeutics and Neurology, and Alzheimer’s Disease Center, Boston University School of Medicine, Boston, MA 02118.
to the LMW FGF2 isoform. The FGFR1 pathway may activate CREB-binding protein, thereby up-regulating (i.e., increasing) the gene expression associated with neural differentiation and development. Thus, intracellular HMW FGF2 may enhance neuronal differentiation and potentially synaptic plasticity.

In addition, AD mice injected with AAV2/1-FGF2 show a modest reduction in Aβ deposition, which is accompanied by the enhanced presence of microglia—immune cells in the central nervous system—around the plaque regions, suggesting that microglia may play an important role in Aβ clearance after the AAV2/1-FGF2 injection. This was confirmed in our in vitro study showing that FGF2 directly activates Aβ engulfment by primary cultured microglia. These results prompted us to develop a hypothesis that unifies the biological interaction of FGF2, Aβ, and hippocampal functions (Fig. P1).

In summary, we have demonstrated that AAV2/1-FGF2 gene transfer significantly restores spatial learning, neurogenesis, and partial Aβ clearance in the hippocampal regions of APP+PS1 mice after both pre- and postsymptomatic treatments. Further investigation is warranted to dissect the mode of action between HMW and LWM FGF2 for their effects on neurogenesis, synaptic plasticity, and neurocognitive function for the potential therapeutic applications to AD and other neurocognitive disorders.