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Editorial Comment

Fibroblast Growth Factor 21 in the Elderly: Where Do We Stand?

Fibroblast growth factor 21 (FGF21), together with FGF19 and FGF23, belongs to an FGF subfamily known as the endocrine FGFs. Serum FGF21 is mainly secreted from the liver and adipose tissue and circulating in the bloodstream.[1] The downstream signaling of FGF21 is mediated by a classic tyrosine kinase FGF receptor and co-receptor β-Klotho. In addition to its versatile roles in the regulation of energy homeostasis and the adaptive starvation response, FGF21 is gaining considerable attention in aging research.

Zanini and colleagues now report in the *International Journal of Gerontology* the results of a cross-sectional study of the association between cognitive assessment and serum FGF21 levels.[2] The authors found a positive correlation between FGF21 and learning ability, immediate and delayed memory, and global cognition in the oldest participants. Despite the relatively small number of participants, this study adds another piece to the puzzle of FGF21 biology. FGF21 was associated with cognitive impairment in non-elderly but not in elderly patients with metabolic syndrome.[3] By contrast, in another small study of patients with bipolar disorder, higher FGF21 was associated with better cognitive performance in terms of letter fluency and motor speed.[4] These apparently contradictory findings highlight the complexity of FGF21's physiology and pathophysiology.

Exogenous administration of FGF21 or analogs improved metabolic disorders in animal models. Nonetheless, FGF21 can serve as a biomarker for a number of diseases, including diabetes mellitus, chronic kidney disease, coronary heart disease, and fatty liver disease.[5] It has been proposed that the increased level of endogenous FGF21 results from an impaired response to FGF21 signaling, a state known as FGF21 resistance. However, the concept is not supported by current clinical evidence.[6] Another hypothesis is that FGF21 is a part of the 'longevity assurance program'.[7] Elevated circulating FGF21 levels represent a protective mechanism in an attempt to increase survival. In parallel, increasing age consistently showed a positive correlation with serum FGF21 levels.[6,8] Of interest, the age-related increase in serum FGF21 levels may be attenuated by habitually performing moderate-to-vigorous-intensity physical activity.[9]

FGF21 has been shown to cross the blood-brain barrier, and there is a linear relationship between FGF21 levels in the serum and cerebrospinal fluid.[10] Through acting on the central nervous system, FGF21 regulates the circadian behavior and hypothalamic-pituitary-adrenal axis. Intriguingly, pharmacological FGF21 seems to have potential neuroprotective benefits. Peripherally derived FGF21 promoted proliferation of oligodendrocyte precursor cells and structural remyelination.[11] In a mouse model of traumatic brain injury, FGF21-overexpressing mesenchymal stem cells more efficiently restored memory deficits and dendritic morphology.[12] While it remains an open question whether higher circulating FGF21 levels in the elderly reflect FGF21 resistance or a compensatory response, understanding and exploiting FGF21 as a cognitive indicator require further investigation.

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