Nicotinamide phosphoribosyltransferase

Nicotinamide phosphoribosyltransferase (NAMPT) is the key enzyme for the synthesis of nicotinamide adenine dinucleotide (NAD) in the salvaging pathway. Though NAMPT inhibitors such as FK866 were originally developed as anti-cancer drugs, they also display neuroprotective effects. Here we show that the administration of FK866 at 0.5 mg/kg (ip, qod) for four weeks, i.e., ~1% of the dose used for the treatment of cancer, significantly alleviates the aging-induced impairment of cognition and locomotor activity. Mechanistically, FK866 enhanced autophagy, reduced protein aggregation, and inhibited neuroinflammation indicated by decreasing TNFα, IL-6, GFAP, and Iba1 levels in the aged mouse brain. Though FK866 did not affect the total NAD and nicotinamide mononucleotide (NMN) levels in the mouse brain at the dose we used, FK866 increased nicotinamide (NAM) level in the young mouse brain and decreased NAM level in the aged mouse brain. On the other hand, FK866 did not affect the serum glucose, cholesterol, and triglyceride of young and aged mice and exhibited no effects on the various indices of young mice. Thus, the NAMPT inhibitor can be repurpose to counteract the cognitive impairment upon aging. We also envision that NAMPT inhibitor can be used for the treatment of age-related neurodegenerative diseases [1)].

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Zeng M, Wei TF, Chen C, Shen C, Gao TY, Xie X, Wu M, Lu YB, Zhang WP. Nicotinamide phosphoribosyltransferase inhibitor ameliorates mouse aging-induced cognitive impairment. J Cereb Blood Flow Metab. 2021 Apr 4:271678×211006291. doi: 10.1177/0271678×211006291. Epub ahead of print. PMID: 33818184.