Healthy aging: How science and daily habits preserve brain function

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Key nutrients like omega-3 fatty acids, curcumin, and NAD+ are important for maintaining cognitive function, but their effective delivery to the brain is hindered by the blood-brain barrier (BBB) and age-related declines in nutrient transport. Dr Rebecca Crews and Heather Makar explore the importance of overcoming these delivery challenges to enhance strategies for cognitive longevity and healthy aging

The traditional view that cognitive decline is an unavoidable consequence of aging is being increasingly questioned by modern research. While aging is associated with structural and functional changes in the brain – such as reduced volume and slower processing speeds – these changes are not entirely beyond our control. Environmental and lifestyle factors, including regular exercise and balanced dietary habits, play a significant role in shaping cognitive function. For example, aerobic exercise has been shown to preserve hippocampal volume, whereas obesity and excessive caloric intake may accelerate brain atrophy (Mattson et al., 2018).

Nutrients and bioactive compounds hold promise for supporting brain health and mitigating age-related cognitive decline. However, a major obstacle lies in delivering these compounds effectively to the brain. The blood-brain barrier (BBB), which acts as a protective shield for the brain, can block many of these compounds from reaching their target. This challenge has inspired innovative research into overcoming these barriers to enhance strategies for cognitive longevity over time.

Key nutrients for brain health

Extensive research highlights the role of bioactive compounds and nutrients in shaping brain function and promoting healthy aging. Several key compounds have emerged as particularly influential in cognitive health:

- Omega-3 fatty acids:

  Docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA) are essential omega-3 fatty acids vital for maintaining neuronal integrity, synaptic plasticity, and neuroprotection. DHA, the most abundant omega-3 in the brain, is a structural component of neuronal membranes and influences cell signaling, neuroinflammation, and mitochondrial function, while EPA modulates inflammation and vascular health, indirectly supporting cerebral function (Iwao et al., 2023).

- Curcumin:

  A polyphenol derived from turmeric, curcumin exhibits antioxidant, anti-inflammatory, and amyloid-beta clearing properties. It modulates pathways implicated in cognitive decline by reducing oxidative stress, inhibiting pro-inflammatory cytokines, and enhancing brain- derived neurotrophic factor (BDNF), which supports neuronal survival and plasticity (Benameur et al., 2021).
- NAD+:

  As an essential coenzyme, NAD+ plays a critical role in energy metabolism, DNA repair, and cellular resilience. It serves as a substrate for sirtuins, poly (ADP-ribose) polymerases (PARPs), and CD38, all of which regulate neuronal health, mitochondrial function, and neuroinflammation (Hong et al., 2020).

Nutrient delivery challenges: BBB, healthy aging, and bioavailability

Despite the potential of these compounds, their effective delivery to the brain remains a significant hurdle. The BBB tightly regulates the transport of substances into the brain, often favoring specific nutrient forms. For instance, lysophosphatidylcholine (LPC)-bound DHA is more efficiently transported across the BBB than free DHA. Age-related declines in transport protein activity, such as Mfsd2a, further hinder DHA uptake, contributing to neuroinflammation, impaired cognitive function, and increased risk of neurodegenerative diseases (Iwao et al., 2023).

Aging exacerbates these challenges. NAD+ levels decline sharply with age, impairing ATP production and increasing oxidative stress. Similarly, curcumin's therapeutic potential is limited by its poor bioavailability. Its lipophilic nature, rapid metabolism in the liver and intestines, and low water solubility restrict its ability to reach the brain in therapeutic concentrations (Benameur et al., 2021, Fang et al., 2019).

Breakthroughs in brain-directed nutrient delivery

To address these challenges, researchers are leveraging innovative strategies to enhance the delivery of neuroprotective compounds to the brain. Nanotechnology is a promising solution, improving the stability, absorption, and targeting of neuroprotective compounds. Lipid-based nanocarriers, like liposomes, are biocompatible and capable of transporting both hydrophilic and lipophilic molecules, improving their ability to cross the BBB. For instance, liposomal nicotinamide riboside (NR) increased brain NR levels nearly threefold and reduced infarct volume by 35.4% in a mouse model of cerebral ischemia (Xie et al., 2024). Non-lipid-based carriers, such as PLGA nanoparticles, have also shown success, increasing curcumin uptake in the mouse brain by 2.8-fold compared to standard formulations (Tiwari et al., 2013).

A key strategy for enhancing BBB penetration is the use of targeting ligands. These molecules, such as lactoferrin, bind to specific receptors on the BBB, facilitating transport across the barrier. This approach has led to increased brain NAD+ levels and improved cognitive function in preclinical models (Cai et al., 2024). More sophisticated

nanocarriers, like multifunctional liposomes, combine multiple features for optimized delivery. These might include a PEG coating for extended circulation, a targeting ligand for BBB crossing, and a specially designed drug derivative to improve target binding, as seen with curcumin delivery to amyloid plaques in Alzheimer's disease models (Mourtas et al., 2014).

The route of administration significantly impacts bioavailability. Intranasal delivery offers a non-invasive pathway to the brain, bypassing the BBB via olfactory and trigeminal nerve pathways. Intranasal NAD+ administration in a rat model of traumatic brain injury effectively restored hippocampal NAD+ levels and provided greater neuroprotection than injections (Wong et al., 2012). Similarly, quercetin-loaded transferosomes (a type of liposome designed to enhance permeability) improved nasal mucosa absorption and increased brain accumulation in rats (Elkomy et al., 2023).

A new era for cognitive wellbeing

Accumulating evidence shows that diet, exercise, and lifestyle significantly impact brain health, giving us real opportunities to take control of our cognitive longevity. At the same time, cutting-edge technologies like nanotechnology, receptor-targeted delivery, and intranasal administration are revolutionizing how neuroprotective therapies are delivered to the brain, overcoming challenges like bioavailability and blood-brain barrier penetration. As research advances, refining these approaches and prioritizing human studies will be key to developing personalized strategies that promote cognitive function and healthy aging.

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