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The future of healthy brain aging will be metabolic: a predictive lesson from data-driven modeling

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A Viewpoint on the Frontiers in Science Lead Article
Breakdown and repair of metabolism in the aging brain

Key points

- Preserving our cognitive abilities throughout life will require addressing the challenge of metabolic decline.
- Considering their important metabolic role, glial cells are becoming primary targets for the development of interventions/treatments to preserve brain function in the aging brain.
- Data-driven mathematical models could help to evaluate and predict the outcome of interventions intended to preserve or restore brain metabolic proficiency.

Introduction

Advances in modern medicine, public health, and living standards over the last century have significantly extended life expectancy. However, with the increase in longevity, the prevalence of aging-related neurological diseases, such as dementia and simple cognitive decline, has grown significantly and will continue to rise with the projected aging of the population. We urgently need to identify the critical causative factors for these conditions and find ways to counteract or reverse their effects to promote healthy brain aging and further extend healthy life expectancy. In their lead article, Shichkova and colleagues (1) used data-driven modeling to identify the major metabolic alterations that can impact neuronal activity in the aging brain and suggested how these may be reversed.

Aging and metabolic decline

A reduction in glucose consumption (or hypometabolism), as identified in specific brain regions using ^{18}F-fluorodeoxyglucose positron emission tomography (^{18}F-FDG PET), has

become a hallmark of both normal and pathological brain aging. Indeed, clear evidence of hypometabolism has been reported in neurodegenerative diseases such as Parkinson's disease and Alzheimer's disease (AD) (2). Moreover, these metabolic alterations have also been observed in asymptomatic, at-risk individuals—sometimes years before any detectable signs of disease—suggesting that such metabolic deficits are not merely a consequence of neurodegeneration. Hypometabolism has been detected in normal brain aging and is associated as a risk factor for cognitive decline. The exact causes of hypometabolism and its link to potential cognitive deficits remain unclear at present. Elucidating these relationships and the underlying pathological processes that affect brain metabolism may allow the design of adequate interventions to delay or even prevent cognitive decline.

Importance of astrocyte-neuron metabolic interactions for cognition

Based solely on histological observations, 19th-century neuroanatomists had already suggested that glia, and more specifically astrocytes, could regulate the supply of essential metabolites to neurons. However, only in the last 30 years has clear evidence implicated astrocytes in this critical function. Two seminal observations sparked the investigations that led to these findings. First, brain activation triggered by sensory stimulation or cognitive tasks was shown to produce a concomitant increase in blood flow to the associated cortical area. This "neurovascular coupling" was proposed to ensure a sufficient supply of oxygen and nutrients to neurons in the active area. Its cellular and molecular bases remained elusive for decades despite intense research efforts. Only recently has the role of astrocytes in the regulation of cerebral blood flow upon neuronal activation been uncovered, revealing intricate metabolic interactions between neurons, astrocytes, and blood vessels (3). The second key finding followed the development of a method to measure and visualize localized glucose consumption in the brain. The 2-deoxyglucose method revealed the close relationship between activation of a specific brain area and localized glucose consumption, giving rise to the concept of neurometabolic coupling. Again, the prominent role of astrocytes and the description of the associated mechanism—the so-called astrocyte-neuron lactate shuttle—foregrounded the tight metabolic interactions between astrocytes and neurons (4). These findings also raised the question of the importance of these interactions for cognition.

Indeed, interference with the transfer of energy substrates from astrocytes to neurons led not only to alterations in neuronal responses upon brain activation but also to deficits in behavioral performance requiring intact activation of the associated brain areas (5). These observations highlighted the fact that neurons are not energetically autonomous; their activity (and the cerebral functions they subserve) critically depends on interactions with their astrocytic partners. Suddenly, we must consider a new factor that contributes to both cognition and pathological processes affecting cognition. Indeed, astrocytes are emerging as a novel therapeutic target for neurological diseases affecting cognition, such as AD (6). Considering their role in neuroenergetic regulation, astrocytes may constitute a priority target for interventions aimed at restoring or preserving metabolic proficiency in the central nervous system.

Targeting metabolism as a strategy against cognitive decline

Interestingly, conditions that affect peripheral energy homeostasis, such as diabetes, can directly cause cognitive decline or are a risk factor for the development of dementia, notably via alterations in brain energy metabolism (7). Indeed, some investigators consider AD to be a "type 3" form of diabetes. Brain insulin resistance and dysfunction of insulin signaling pathways are suspected of being responsible for cognitive impairment, and drugs that treat these pathologies have been proposed as potentially effective solutions. Insulin and other hypoglycemic agents such as metformin have shown beneficial effects in animal models and patients with AD. Insulin sensitizers such as rosiglitazone and pioglitazone, which are agonists of the nuclear receptor peroxisome proliferator-activated receptor-γ (PPARγ), have reversed behavioral deficits in preclinical AD models and in patients. Similarly, analogs of the gut hormone glucagon-like peptide-1 (GLP-1), such as liraglutide and semaglutide, have demonstrated neuroprotective activity against the toxicity of Aβ oligomers (produced in abnormal quantities in AD) and the decline in behavioral performance normally exhibited by genetic mouse models of AD. In addition, fibroblast growth factor 21 (FGF21), a hormone primarily produced by the liver and involved in glucose and lipid homeostasis, has been shown to improve behavioral performance in a mouse model of diabetes-induced cognitive decline and a genetic mouse model of AD, by modulating components of the astrocyte-neuron lactate shuttle.

Pharmacological agents are not the sole therapeutic option with the potential to prevent aging-related cognitive decline. There is accumulating evidence that physical exercise exerts cognitive benefits in both young and aging subjects, although the precise mechanisms involved are certainly pleiotropic and not yet well-defined. One hypothesis is that physical exercise might benefit cognition by improving brain energy metabolism. For example, effects on brain mitochondrial activity have been observed. However, interestingly, exercise also improves cognitive function by modulating various components of the astrocyte-neuron lactate shuttle, and by allowing muscle-derived lactate to enter the brain and sustain brain activity (8). Further investigation is necessary to decipher the critical impact of exercise on cerebral metabolic processes and how this might improve cognition, but the improvement of astrocyte-neuron metabolic interactions already appears to be important.

Mathematical models to guide the development/evaluation of anti-aging treatments

The brain is a complex organ involving different cell types and multiple interactions among them, particularly in the domain of

neuroenergetics. To elucidate how such interactions are important for cognition, we need to use tools that account for this complexity while extracting the key elements to guide our quest for interventions to prevent aging-associated cognitive decline. Some successful examples show how mathematical modeling could help identify mechanisms underlying complex biological data or predict the impact of an external stimulus or treatment on a particular biological response. The brain presents a particular challenge in this respect but recent efforts, such as those of Shichkova and colleagues (1), promise to take us one step further. Considering the labor-intensive and costly nature of biological investigations, along with the ethical aspects of animal experimentation, computational modeling should provide a useful approach to rapidly develop and evaluate anti-aging strategies aimed at preserving metabolic proficiency, thereby preventing cognitive decline.

Conclusion

A paradigm shift is underway in the field of aging-related studies, with efforts dedicated to promoting healthy aging. The increased incidence of neurodegenerative diseases associated with longer life expectancy is mobilizing substantial resources to uncover the underlying causes and develop therapeutic solutions. Along with several clinical trial failures, the realization that genetics-driven hypotheses alone are not providing successful options to prevent aging-related cognitive decline has led to a reappraisal. Mounting biological evidence, together with data-driven modeling, points to metabolic dysfunction during aging as a fundamental event and a potential therapeutic target. We should pay attention to these lessons now if we are to prepare ourselves for a long and bright future.

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Author contributions

LP: Conceptualization, Writing – original draft, Writing – review & editing.

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