Trimethylamine N-Oxide in Normal Cognitive Aging

Subjects: Clinical Neurology

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Trimethylamine-N-oxide (TMAO), a gut microbiota-derived metabolite from dietary precursors, might emerge as a promising biomarker of cognitive dysfunction within the context of brain aging and NCD. TMAO may increase among older adults, Alzheimer's disease patients, and individuals with cognitive sequelae of stroke. Higher circulating TMAO would make them more vulnerable to age- and NCD-related cognitive decline, via mechanisms such as promoting neuroinflammation and oxidative stress, and reducing synaptic plasticity and function.

Keywords: neurocognitive disorders ; brain aging ; cognitive dysfunction ; trimethylamine-N-oxide

1. Introduction

The increased pace of aging has been both a challenge and a triumph for public health. Globally, 1 in 6 people will be aged 60 years or above by 2030 [1]. Advanced age is one of the strongest risk factors for neurocognitive disorders (NCD) such as Alzheimer's disease (AD) and poststroke cognitive impairment (PSCI) [2]. Driven by the aging population, the number of individuals with dementia is doubling every 20 years, and even among dementia-free seniors, 1 in 5 have mild NCD syndromes [3]. Patients with NCD typically exhibit longitudinal declines in cognitive and functional abilities, posing an increased risk for higher health expenditure [4] and all-cause mortality [2]. Although age increases risk, there are marked individual differences in the vulnerability for older adults in terms of NCD. Indeed, the onset of these disorders could be prevented or delayed, given that a wide range of predictive features, such as bio-behavioral factors, psychosocial characteristics, and cardiovascular diseases, are potentially modifiable [5][6]. Among them, gut microbiota and their metabolic products, including trimethylamine-N-oxide (TMAO), have recently emerged as a promising disease modifier and might play a putative role in aging and the development and progression of NCD [7][8][9].

TMAO is synthesized from the oxidation of trimethylamine (TMA) by hepatic flavin monooxygenases (FMO), and TMA is a microbiota-derived metabolite, generated in the gut from dietary precursors, mainly choline, L-carnitine, and betaine [10]. The TMAO level is affected by dietary intake, renal clearance, and host and microbial enzymes [11][12]. In contrast with a positive correlation observed between the dietary intake of TMAO precursors and cognitive function [13][14][15], elevated TMAO levels are detected in healthy aging [16] and associated with the pathogenesis of several diseases—for example, metabolic abnormalities, autoimmune disorders, colon cancer, and most prominently, atherosclerotic diseases [17][18]. A circulating TMAO level in the range of 1.5 μM to 10.5 μM has been shown to have a dose-dependent relationship with incident cardiovascular risk [19], the exposure of which serves as a vital target for cognitive health [20]. On top of that, TMAO itself contributes to cognitive decline both with aging [21] and NCD [22], suggesting an effect of higher TMAO levels on NCD per se, as well as their risk factors. Evidence shows that TMAO may be involved in the processes of brain aging and cognitive impairment via promoting neuroinflammation and oxidative stress, as well as reducing synaptic plasticity and function [23]. Despite this, opposing findings that TMAO had positive effects upon the blood–brain barrier (BBB) integrity and murine cognitive function in response to inflammatory challenge [24] illuminated the complex nature of the relationship that remains to be elucidated.

2. Normal Cognitive Aging

The TMAO level may rise during the normal aging process [21][25] (**Table 1**). Healthy individuals aged above 65 years had significantly increased plasma TMAO levels, with a mean plasma concentration of 9.8 μM, in comparison to 4.4 μM in adults aged 45 to 64 years, and 2.8 μM in adults aged 18 to 44 years, revealing that TMAO was positively related to age (r^2 = 0.161, p < 0.001) [25]. Moreover, brain TMAO levels were also higher in old vs. young mice, and were highly correlated to the levels in circulation [21], indicating a direct effect of TMAO on the brain and cognitive function.

Indeed, in healthy middle-aged to older adults, circulating TMAO levels inversely predicted working memory and fluid cognition independent of traditional risk factors [21]. In mice, 16-week treatment of TMAO at a concentration of 1.5% could induce and aggravate brain aging and aging-related cognitive dysfunction as a result of neuron senescence, and the

underlying mechanism would be the mitochondrial impairments driven by oxidative stress and the reduced expression of synaptic plasticity-related proteins by inhibiting the mammalian target of rapamycin (mTOR) signaling pathway [25]. Likewise, preexisting higher circulating TMAO may sensitize sevoflurane-induced cognitive impairment in aged rats, probably via downregulating antioxidant enzyme methionine sulfoxide reductase A in the hippocampus, then leading to microglia-mediated neuroinflammation [26]. Furthermore, TMAO would induce aging-like cognitive impairments in young animals, as TMAO-supplemented young adult mice performed worse on the novel object recognition test compared to the controls, with higher concentrations of pro-inflammatory cytokines and the reactive astrocyte marker, suggesting that TMAO might mediate cognitive aging by inducing neuroinflammation and astrocyte activation [21] (**Table 1**).

Table 1. Main studies of TMAO involved in healthy aging.

Authors (Year)	Subjects/Models	Interventions	Main Related Findings	Conclusions
	The elderly > 65 years (*n* = 141), middle-aged adults between 45–64 years (*n* = 118), and young adults aged 18–44 years (*n* = 168)	**N/A**	**Plasma TMAO: higher in the elderly than in the middle-aged and young groups (9.83 ± 10.63 vs. 4.42 ± 4.39 vs. 2.85 ± 3.10 μM), positively related to age (r^2 = 0.1610, p < 0.001) TMAO precursors (choline, carnitine, betaine, and butyrobetaine): did not differ significantly in the three groups**	**The plasma level of TMAO increased with age in humans, but TMAO precursors did not increase with age**
Li et al. (2018) [25]	**24-week-old male SAMP8 (*n* = 12) and SAMR1 (*n* = 12) mice**	**1.5% TMAO in drinking water vs. sterile water for 16 weeks**	**Plasma TMAO: increased with age in SAMR1 and SAMP8 mice Cognition (Y-maze, novel object recognition, and Morris water maze): aggravated by TMAO Hippocampus: TMAO increased senescent neurons in CA3 region; damaged ultrastructure of chemical synapses in CA1 region; increased oxidative stress; reduced expressions of synaptic plasticity-related proteins; down-regulated activity of the mTOR signaling pathway**	**TMAO could deteriorate brain aging and cognitive function by promoting neuron senescence, damaging synapses, down-regulating the expression of synaptic plasticity-related proteins, and inhibiting the mTOR signaling pathway**
Li et al. (2019) [27]	**20 ± 2 g male ICR mice (*n* = 10), aging induced by daily intraperitoneally injected D-gal (120 mg/kg) and $NaNO_2$ (90 mg/kg) for 3 months**	**On the 25th day of aging induction, daily intragastric administration of vitamin E (100 mg/kg) or Fructus Ligustri Lucidi aqueous extract (4.9 g/kg) for 65 days**	**Serum TMAO: aging mice were higher than controls (0.38 ± 0.08 vs. 0.24 ± 0.07 μM); could be decreased to 0.28 ± 0.09 μM after Fructus Ligustri Lucidi administration; associated with several bacterial taxa (Sutterella↑, Unclassified_Clostridiales↑, Corpococcus↑, Clostridium↑, Unclassified_S24-7↑, SMB53↑, Aldercreutzia↑, Oscillospira↑, Desulfovibrio↑, Bifidobacterium↓, and Lactobacillus↓)**	**Fructus Ligustri Lucidi may have an anti-aging effect by regulating the imbalance in the intestinal microbiota and the increase in serum TMAO levels in aging mice induced by D-gal and $NaNO_2$**

Authors (Year)	Subjects/Models	Interventions	Main Related Findings	Conclusions
Brunt et al. (2021) [21]	Middle-aged and older healthy adults aged 50–79 years (*n* = 103), and young healthy adults aged 18–27 years (*n* = 22)	N/A	Plasma TMAO: higher in the middle-aged and older adults vs. young adults; not differ between men (7.4 ± 7.4 μM) and women (6.2 ± 6.6 μM) TMAO precursors: higher plasma choline in the middle-aged and older adults vs. young adults (13.9 ± 6.1 vs. 7.9 ± 3.2 μM), comparable L-carnitine and betaine Cognition (NIH toolbox cognition battery test, trail-making test): inversely related to TMAO in subdomains of working memory, episodic memory, and fluid cognition	Concentrations of TMAO increased with aging and had no sex differences Plasma TMAO could predict working memory and fluid cognition independent of cardiovascular risk in middle-aged to older adults
	Male C57Bl/6 young mice at 8 weeks of age (*n* = 34) and old mice at 20–24 months of age (*n* = 16)	a defined 0.07% choline diet with or without 0.12% TMAO for 6 months	Plasma and brain TMAO: highly correlated, higher in old vs. young mice, greater in TMAO-supplemented mice vs. controls Plasma and brain TMAO precursors (choline, betaine, and L-carnitine): not correlated, differed in old vs. young mice, and not affected by TMAO supplementation Cognition (novel object recognition): TMAO impaired memory and spatial learning Whole-brain lysates: TMAO-supplemented mice had increased IL-1β, TNF-α, phosphorylated NF-κB, and reactive astrocyte marker LCN2 vs. controls Cultured human astrocytes: increased LCN2 and CD44 if treated with 100 μM TMAO	TMAO may cross the BBB to a greater extent than TMAO precursors Increased plasma and brain levels of TMAO, induced by either natural aging or supplementation, could cause cognitive decline accompanied by astrocyte activation and neuroinflammation

Abbreviations: ↑, increase; ↓, decrease; CA, cornu ammonis; CD44, cluster of differentiation 44; LCN2, lipocalin 2; mTOR, the mammalian target of rapamycin; NF-κB, nuclear factor-κB; NIH, National Institutes of Health; SAMP8, senescence-accelerated prone mouse strain 8; SAMR1, senescence-accelerated mouse resistant; TMAO, trimethylamine-N-oxide; TNF-α, tumor necrosis factor α.

Therefore, the potential of TMAO as a prevention and/or treatment target for cognitive declines in aging has been exploited (**Table 1**). The aging mice demonstrating deficits in memory and cognitive function revealed an improvement in cognition after *Fructus Ligustri Lucidi* (i.e., the ripe fruit of *Ligustrum lucidum Ait*) treatment, possibly by lowering oxidative stress subsequent to decreased circulating TMAO levels via the altered gut microbiota, characterized as a reduction in *Bifidobacterium* and *Lactobacillus*, and an increase of the *Sutterella*, *Unclassified_Clostridiales*, *Corpococcus*, and *Clostridium*, among others [27]. However, nutritional intake of TMA precursors might have cognitive protection capacities. For instance, a randomized clinical trial has shown that the supplementation of 2 g L-carnitine taken orally once a day for six months significantly improved the cognitive function in subjects above 100 years of age, showing significant improvements in the mini-mental state examination (MMSE) score (4.10 compared with 0.60) when compared to the placebo group [28].

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