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RESEARCH HIGHLIGHT

Taurine as a possible therapy for immunosenescence and inflammaging

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Cellular & Molecular Immunology (2024) 21:3–5; https://doi.org/10.1038/s41423-023-01062-5

In their recent Science article, Singh et al. identified taurine as an endogenously produced anti-inflammatory, anti-immunosenescence, and anti-aging molecule. The authors also show that restoring taurine to its "youthful" levels prevents inflammation, boosts the immune response, and delays inflammaging/aging.

Much scientific effort has been invested in therapeutic strategies to increase our lifespan and healthspan, and there is a general belief that inflammaging and, particularly, immunosenescence can be manipulated to delay or reverse aging-associated degeneration [1]. In this context, many exogenous and endogenous "anti-aging" molecules are being investigated to extend the number of years we spend in good health [1].

One potential endogenous anti-aging molecule is the sulfur-containing amino acid taurine, which was first investigated in the context of bone formation and osteoporosis [2]. At the same time, it was discovered that taurine levels correlate with immune function, obesity and nervous system function [2, 3]. Not surprisingly, taurine deficiency is associated with myriad adverse health conditions, including diabetes, hypertension, liver disease, inflammation and obesity, which also lead to anomalous immune phenotypes [3, 4]. Taurine, chemically 2-aminoethanesulfonic acid, is a quasi-essential nutrient found in all eukaryotic organisms and highly expressed in mammalian tissues. It is synthesized from cysteine through the action of cysteine sulfinic acid decarboxylase [4], although it can also be obtained from the diet (meat, fish, and milk/dairy) and transported into cells by the Slc6a6 transporter [5].

A recent exceptional paper by Singh et al. [6] addressed the physio(patho)logic roles of taurine. Their findings indicate that taurine "reduces cellular senescence, protects against telomerase deficiency, suppresses mitochondrial dysfunction, decreases DNA damage, and attenuates inflammation". In humans, taurine levels correlate negatively with several age-associated diseases and positively with acute endurance exercise, situations that are often related to the depression and the activation of immune system responses, respectively [1].

The origin of the study stems from the examination of taurine levels in the blood of mice (*Mus musculus* [4-week-old mice *versus* 56-week-old mice]), nonhuman primates (*Macaca mulatta* [5-year-old *versus* 15-year-old macaques]), and humans, which revealed that taurine concentrations substantially declined with age in all three species. For example, taurine levels decreased by 70 and 85% in mice and monkeys, respectively, with aging and were found to be > 80% lower in elderly humans than in their younger peers.

The authors thus questioned whether taurine deficiency drives aging in mice (Fig. 1A). They used approximately 250 male and female mice (14 months old, equivalent to 45 years old in humans) and split them into two groups, and mice were fed daily placebo or taurine (1000 mg per kg body weight until the end of life). At the end of the experiment, the authors found that taurine supplementation increased life expectancy by an average of 12% in females and 10% in males, and life expectancy at 28 months increased by 18 to 25%, an additional three to four months of life (equivalent to approximately seven to eight human years). These results showed that taurine deficiency is a driver of aging in mice because its reversal increased lifespan (Fig. 1A). Singh et al. also found that taurine supplementation slowed the aging process and increased lifespan in worms (10 to 23%) but not in budding yeast, a unicellular organism, possibly due to organismal differences in taurine metabolism. The authors suggested that the effects of taurine on lifespan are conserved in metazoans (invertebrates and mammals).

To identify how taurine affected health, the authors studied the effect of taurine supplementation on the health and life expectancy of female mice. The results showed that at the age of 2 years (60 human years), animals fed taurine for one year were healthier than controls in almost every respect. Specifically, taurine supplementation: i) suppressed age-associated weight gain (even in 'menopausal' mice), ii) increased energy intake, iii) boosted bone mass, iv) improved muscular endurance and strength, v) reduced anxious and depression-like behaviors, vi) reduced insulin resistance, vii) rejuvenated the immune system (myeloid-leukocyte axis); and viii) resulted in longer and healthier lives (Fig. 1A).

At the cellular level, taurine supplementation improved many functions that are associated with the "hallmarks" of aging [7]. Using adult mice lacking *Slc6a6* (taurine transporter) [5], the authors found that taurine supplementation reduced the number of senescent cells, which should die but instead persisted and activated the senescence-associated secretory phenotype. Additionally, using a zebrafish model of telomerase deficiency [8], taurine supplementation was found to increase survival. Other positive benefits of taurine supplementation included i) a decrease in oxidative DNA damage; ii) evident epigenetic changes in DNA and histone methylation, which could alter chromatin conformation and affect transcription; iii) an improved ability of cells to detect nutrients and maintain proteostasis pathways; iv) a decrease in the proportions of myeloid and lymphoid cells by

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Received: 13 June 2023 Accepted: 16 June 2023
Published online: 7 July 2023

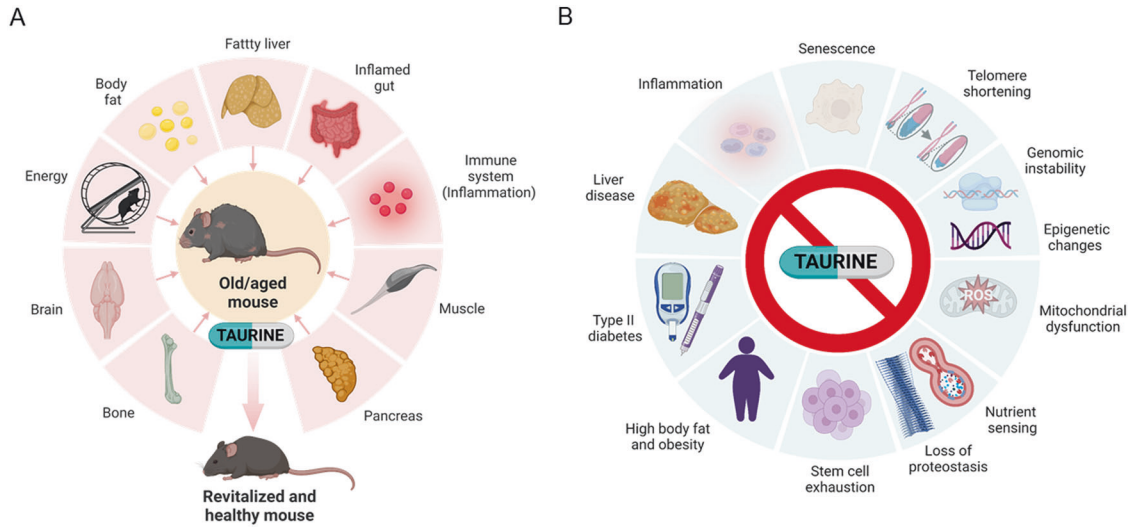

Fig. 1 Effects of taurine supplementation on physiopathologycal aspects associated with healthspan. **A** Taurine supplementation facilitates organic rejuvenation of old/aged mice. **B** Taurine supplementation increases healthy lifespan in animals (worms, mice, and monkeys), potentiates the immune system, and reduces aging traits and inflammaging including human aging-associated pathologies. This figure was created with Biorender.com

preventing the proinflammatory state associated with aging (inflammaging); v) an increase in the abundance of stem cells in some tissues (which help tissues regenerate after injury); and vi) an improvement in mitochondrial homeostasis (Fig. 1B). Interestingly, mitochondria are taurine dependent, as a pool of cytosolic taurine is transported for the generation of specific tRNAs necessary for the translation of the NADH-ubiquinone oxidoreductase chain 6 protein, a complex I subunit of the electron transport chain [9].

To question whether taurine supplementation would improve health or increase longevity in humans, the authors conducted two studies on the correlation or concomitance between the levels of taurine and its derivatives with the pathological conditions associated with aging and physical exercise. They first determined the blood levels of taurine pathway metabolites (taurine, hypotaurine and N-acetyltaurine) in a cohort of 11,966 individuals with aging-associated pathologies from the EPI-Norfolk study, integrating more than 50 clinical risk factors [10]. They observed that increases in taurine and hypotaurine levels were associated with a lower body mass index and abdominal obesity and an increase in all taurine-related metabolites was associated with a lower prevalence of type II diabetes, lower glucose levels, and less liver damage and inflammation (Fig. 1B). Second, using a physical exercise test, they found an increase in blood taurine and its metabolites after exercise irrespective of whether the participants were athletes (sprinters, endurance runners, and bodybuilders) or sedentary individuals undergoing a cycling session. These results suggest that some of the health benefits of exercise may be explained by increased taurine levels.

Similar health effects were observed in middle-aged nonhuman primates that received taurine daily for six months, which prevented weight gain, reduced fasting blood glucose and markers of liver damage, increased bone density in the spine and legs, and improved immune system health (immunophenotype) [6].

As levels of taurine decline with age, restoring the levels to those found in young individuals may be a promising anti-aging strategy. In addition, as a supplement, taurine has some advantages since it occurs naturally in our bodies, it can be obtained from the diet, it has no known toxic effects (although it is rarely used at the concentrations used in the Singh et al. study), and it can be enhanced by exercise. Furthermore, as a naturally occurring biomolecule, taurine cannot be exploited through a commercial patent.

For many years, scientists have struggled to understand the molecular bases of immunosenescence and organic aging in a battle not only to increase life expectancy but also to improve the quality of life. It is possible that maintaining or restoring taurine to its "youthful" levels during the passage of years could be a promising anti-immunosenescence and anti-aging strategy. Accordingly, the results of the Singh et al. study represent an opportunity to perform large-scale clinical trials with different age groups to establish a causal relationship between taurine as a 'source' of life/health that rejuvenates our immune system, extends our healthy life expectancy, and delays the onset of diseases associated with aging and even aging itself.

The findings of Singh et al. [6] have several implications and raise interesting questions. Future studies should evaluate i) the general and specific molecular mechanisms through which taurine elicits pleiotropic effects on many aging-associated processes and immune health consequences in different metazoan species; ii) the regulatory mechanisms operating on endogenous taurine levels throughout development, from juvenile to elderly stages; iii) the regulation of the gene expression and enzymatic activity of cysteine sulfinic acid decarboxylase; iv) the conditions to sustain taurine and its derivatives at levels that are beneficial for maintaining the operability and efficiency of the immune system; v) whether known derivatives of taurine can reproduce or even augment its effects without the toxicity of taurine itself; vi) the regulatory role of taurine in mitochondrial health/homeostasis and the participation of mitochondria in the mechanism of action of taurine; vii) the impact of taurine on epigenetic regulation and how it affects the regulation of chromatin structure and gene transcription; and viii) the realistic possibilities of extrapolating these findings to regenerative medicine (e.g., sports performance, sports injuries, sarcopenia, muscle disorders, inflammatory pathologies, and inflammaging) and to other aging-associated pathologies and their treatments, such as diabetes, mental illness and depressive disorders.

In summary, Singh et al. [6] presented a conceptual explanation of the occurrence, with evolutionarily conserved dynamics, and consequences of taurine deficiency and/or supplementation as a driver/preventer of aging-associated diseases, highlighting a potential therapy to be advanced in regenerative medicine. This work is a proof of concept that taurine supplementation in vivo could facilitate immune, tissue, and organ rejuvenation.

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ACKNOWLEDGEMENTS

Research in the author's laboratory is supported by the Ministry of Science and Innovation and the Spanish Research Agency through FEDER funds (PID2021-1261520B-100) (MICINN/AEI/FEDER, EU). CBMSO receives an institutional grant from the Fundación Ramón Areces, Spain.

COMPETING INTERESTS

The author declares no competing interests.

ADDITIONAL INFORMATION

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