In Major UK Biobank Analysis Higher Tyrosine Levels Linked to Shorter Lifespan

Researchers investigated the role of phenylalanine and tyrosine in human lifespan.

Dietary protein restriction has been reported to increase lifespan. Amino acids that respond to protein restriction may influence lifespan. For instance, tyrosine has been demonstrated to regulate physiological responses to a low-protein diet in an animal study. Further, restricting tyrosine intake modulates amino acid-sensing pathways, reduces endogenous tyrosine, and extends lifespan in experimental models.

Further, elevated levels of phenylalanine, which is the precursor of tyrosine, are associated with telomere loss, type 2 diabetes, and inflammatory diseases. Evidence shows that phenylalanine is oxidized to meta-tyrosine, a toxic metabolite reported to reduce lifespan in Caenorhabditis elegans. However, the role of these amino acids has been rarely studied in humans.

Study

In the present study, researchers assessed the role of phenylalanine and tyrosine in human lifespan. First, they used Cox regression to evaluate associations between baseline plasma levels of tyrosine and phenylalanine and all-cause mortality in the United Kingdom Biobank (UKB) cohort; the analysis was adjusted for sex, age, smoking, alcohol intake, ethnicity, body mass index, physical activity, education, and the Townsend Deprivation Index.

In addition, associations of tyrosine and phenylalanine levels with cancer and cardiovascular disease (CVD) mortality were assessed. Next, the researchers conducted combined and sex-specific genome-wide association studies (GWASs) of tyrosine and phenylalanine in the UKB. Single-nucleotide polymorphism (SNP)-based heritability was calculated. Genetic instruments for circulating tyrosine and phenylalanine were derived from the GWASs.

Specifically, SNPs linked to circulating tyrosine or phenylalanine at genome-wide significance were selected. The team used genome-wide significant SNPs associated with tyrosine and phenylalanine in the UKB in a two-sample Mendelian randomization (MR) analysis, and applied them to a GWAS of parental attained age (a proxy for lifespan) in a European ancestry population to estimate the effect on lifespan. Finally, multivariable MR analyses were performed to assess the independent effects of tyrosine and phenylalanine.

About 272,475 individuals from the UKB cohort with data on amino acid levels, confounders, and death status were included. Among these, 23,964 deaths occurred, including 9,734 deaths in females and 14,230 in males. Plasma phenylalanine was associated with higher all-cause

mortality overall, and in both sexes. Similarly, plasma tyrosine was associated with an elevated risk of mortality overall and in males alone.

These associations persisted in a sensitivity analysis that excluded deaths from accidents. A higher tyrosine-to-phenylalanine ratio was associated with a lower risk of all-cause mortality overall and in females. In disease-specific mortality analysis, plasma phenylalanine was associated with cancer and CVD mortality, whereas tyrosine showed no associations. Restricted cubic spline analyses suggested potential non-linearity in the associations, with turning points near the population mean concentrations, indicating that associations were more pronounced at higher circulating levels.

Findings

In the GWAS, the heritability estimates for tyrosine and phenylalanine were 0.09 and 0.04, respectively. In total, 2,422 and 11,379 genome-wide significant SNPs were identified for phenylalanine and tyrosine, respectively. In sex-specific analysis, 1,099 and 946 SNPs were identified in males and females for phenylalanine, and 5,297 and 4,840 variants were identified in males and females for tyrosine, respectively.

Following exclusion of correlated genetic variants, 74 and 21 SNPs were used as genetic instruments for tyrosine and phenylalanine in the combined analysis. In sex-specific analyses, 12 SNPs in males and 10 in females were used as genetic instruments for phenylalanine; for tyrosine, 45 SNPs in males and 29 in females were used. SNPs associated with these amino acids were located in genes crucial for amino acid regulation, metabolism, and transport.

The essential genes for phenylalanine were phenylalanine hydroxylase (PAH), solute carrier family 17 member 1 (SLC17A1), SLC43A1, SLC38A4, carbamoyl phosphate synthase 1 (CPS1), glutathione S-transferase mu 1 (GSTM1), and glutathione S-transferase alpha 2 (GSTA2). For tyrosine, these were PAH, GSTM1, 4-hydroxyphenylpyruvate dioxygenase (HPD), and CPS1.

Genetically predicted elevated phenylalanine levels were associated with a longer lifespan in males only. In contrast, genetically predicted increases in tyrosine levels were associated with a shorter lifespan in the overall population and showed directionally consistent inverse associations in both sexes, although the statistical strength varied by analytic method in univariable MR analyses. In multivariable MR, phenylalanine was no longer associated with lifespan in either sex after controlling for tyrosine. In contrast, tyrosine was associated with shorter lifespan, particularly in males, after controlling for phenylalanine, with weaker and less consistent evidence in females, depending on the analytic method used.

Effect sizes in Mendelian randomization were expressed in estimated life years per standard deviation increase in genetically predicted amino acid levels, with the strongest independent effect observed in men (approximately one year of life per SD increase in tyrosine).

Conclusion

In sum, genetically predicted higher tyrosine levels were associated with a shorter lifespan, and the association was sustained in males independent of phenylalanine; in contrast, phenylalanine was not independently associated with lifespan.

These results underscore the potential role of tyrosine in human longevity and warrant further investigation. Importantly, Mendelian randomization estimates reflect the lifelong effect of endogenous circulating levels rather than short-term dietary supplementation.

The authors also noted limited statistical power to detect sex differences and acknowledged that partial sample overlap between the exposure and outcome datasets could introduce bias, although sensitivity analyses showed consistent effect directions.

Source:

https://www.news-medical.net/news/20260301/Higher-tyrosine-levels-linked-to-shorter-lifespan-in-major-UK-Biobank-analysis.aspx