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The impact of trimethylamine on the function of the cardiovascular system and kidneys

w dyscyplinie nauki medyczne

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The impact of trimethylamine on the function of the cardiovascular system and kidneys

In recent years, an increasing number of studies have focused on the impact of gut microbiota on human health. A particular area of interest is Trimethylamine oxide (TMAO), a metabolite produced through the oxidation of trimethylamine (TMA) by flavin-containing monooxygenases (FMOs) in the liver. Gut microbiota generate TMA from dietary sources such as choline and carnitine. Additionally, TMA and TMAO are present in fish and seafood, which are dietary sources of these compounds. Excretion of TMA and TMAO predominantly occurs through urine.

The bulk of research concentrates on the role of TMAO. Investigations have consistently shown a positive correlation between elevated levels of TMAO in blood and urine and the onset of cardiovascular and kidney diseases. However, the underlying mechanisms remain partially understood. While most studies indicate a detrimental effect of TMAO on human health, there are some that propose beneficial impacts.

Conversely, the role of TMA in the pathogenesis of cardiovascular and kidney diseases has received limited attention, and studies on the role of TMA in cardiovascular and renal diseases are scarce.

This doctoral thesis aimed to establish the physiological concentrations of TMA, TMAO, and their precursors in various laboratory animals (house mouse, brown rat, guinea pig). The thesis further sought to enhance understanding of FMOs and TMA/TMAO metabolism (Publication No. 1) and to investigate the impact of TMA on kidney and cardiovascular system functions (Publication No. 2).

This research is the first to compare concentrations of TMA and TMAO in tissues of laboratory animals, as previous studies focused solely on blood or urine. Our findings reveal significant differences in the concentrations of carnitine, choline, TMA, and TMAO in blood, urine, and various tissues (heart, lungs, liver, kidneys) among these species. Notably, TMAO blood concentrations were consistent across species and aligned with human and animal studies. The highest TMAO concentration was observed in the rat's renal medulla, and the lowest in the mouse liver. Conversely, TMA concentrations were highest in the mouse's renal medulla and lowest in the rat's lungs. We also evaluated the activity of FMO1, FMO3, and FMO5 in the

heart, lungs, liver, and kidneys, observing notable species-specific differences in FMO expression.

The effects of chronic TMA administration via drinking water on rat kidney and cardiovascular system functions were also examined. Rats receiving TMA exhibited increased systolic blood pressure, elevated levels of glucose, protein, Kidney Injury Molecule-1 (KIM-1) in urine, and a higher protein/creatinine ratio in urine, alongside histological kidney changes indicative of chronic progressive nephropathy. This suggests that chronic TMA exposure adversely affects kidney and cardiovascular health.

Furthermore, TMA-treated rats showed a 7-30 fold increase in tissue TMAO concentration, while TMA levels rose minimally. These rats also demonstrated a daily increase in TMA and TMAO excretion and reduced renal FMO1 and FMO3 expression, indicating efficient TMA-to-TMAO conversion.

This thesis contributes new insights into the concentrations of TMA, TMAO, and their precursors in commonly used laboratory animals, as well as the activity of FMOs. These findings enhance our understanding of TMA and TMAO metabolism and their roles in cardiovascular and kidney diseases. Additionally, our research may aid in selecting appropriate animal models for future studies. Importantly, this thesis provides data on the negative impact of chronic TMA administration on cardiovascular and kidney functions.