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Trimethylamine Oxide (TMAO): A New Toxic Kid on the Block

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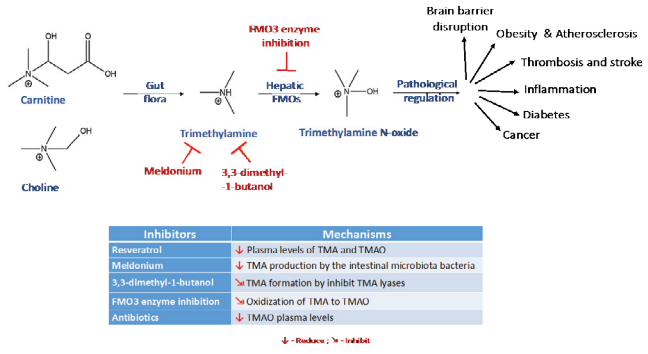
Trimethylamine N-oxide (TMAO), a small, organic, oxygenated product of trimethylamine (TMA), belongs to the class of amine oxides [1]. Most of the TMA derived from the metabolism of choline, L-carnitine by bacteria in the gut and is absorbed into the bloodstream. TMA is rapidly oxidized to TMAO by the hepatic enzyme, flavin-containing monooxygenase-3 (FMO3) [2-4]. Systemic concentration of TMAO in normal healthy individuals ranges from 0.5–5 μM [1,5]. 50% of the TMAO does not get metabolized and is excreted unchanged within 24 h through urine, sweat and breath [6-8].

Clinical findings suggest that there is a potential link between the metabolites produced by the gut flora and the risk factors for cardiovascular and other diseases such as kidney failure, thrombosis, atherosclerosis, obesity, diabetes, and cancer [2]. Several studies have reported an association between plasma TMAO and choline levels in patients with heart failure [9-12]. TMAO negatively regulates glucose metabolism which leads to diabetes mellitus [13]. An observational clinical study reveals elevated levels of plasma TMAO were a strong risk marker for diabetes. Diabetic patients with high plasma TMAO levels was a marker of adverse cardiovascular outcomes, such as death (HR 2.7), myocardial infarction (HR 4.0), heart failure (HR 4.6), unstable angina (HR 9.1) and other cardiovascular complications (HR 2.0) [14]. Though the mechanisms behind the risk are undefined, TMAO could be a valuable marker to predict the risk of diabetes and its complications. The contribution of TMAO to the progression of renal dysfunction shows that chronic dietary intake elevates the plasma TMAO levels directly and leads to progressive renal fibrosis and dysfunction [15]. TMAO levels were considerably elevated in ischemic kidney damage triggered by either cold ischemia or transplantation [16,17].

Studies have shown that TMAO activates inflammatory pathways in cells of the vasculature leading to augmented endothelial cell-leukocyte interactions and atherosclerosis. Studies on both *in vivo* and *in vitro* cultured human aortic endothelial cells and vascular smooth muscle cells showed that elevated levels of TMAO induce expression of proinflammatory cytokines and adhesion molecules mediated by the NF-κB signaling pathway [18]. TMAO enhances monocyte activation as well as adhesion by activating endothelial cells to express VCAM-1 [19,20]. Interestingly, recent findings reported that a raised systemic concentration of TMAO (100 μM) showed increased platelet hyper reactivity and platelet aggregation *in vitro* and *in vivo*. A couple of clinical data indicated that colorectal cancer is positively linked to plasma TMAO levels. Similarly, experimental findings suggested that urinary TMAO could be used as a prognosticator for gastric tumorigenesis [21,22]. In contrast, TMAO also corrects the mutant protein-folding defect and protective from carcinogenesis [23,24].

Since the microbiome is considered to be the source of TMAO, antibiotic treatment should reduce its circulating levels. However, antibiotics are not an ideal treatment since it could have other unwanted consequences, and also chronic treatment may lead to bacteria resistant. Meanwhile, removing TMAO producing bacteria, use of specific bacteria to increase its metabolism has also been attempted [25]. Furthermore, controlled intake of dietary precursors of TMAO is a possible approach. Besides, several pathway inhibitors are reported to reduce the TMA and TMAO levels in plasma (Figure 1). Indeed, people who eat plant-based diet appear to form a negligible amount of TMAO [26]. Our understanding of the diet and microbial metabolites interaction and their influence on human health is at an initial stage. Nevertheless, increasing evidence suggests that a plant-based diet may be beneficial for this interaction in many ways. On the other hand, there is accruing clinical and laboratory-based findings convincing a pathogenic role to TMAO. It is essential to commence studies examining intracellular levels of TMAO in mammals, cellular signaling and also define the effects of TMAO on enzymes and other proteins to establish the role of TMAO in health and disease in humans. Also, comparing the infection models with germ-free mice models could support our understanding of how gut flora influence various diseases.



Inhibitors	Mechanisms
Resveratrol	↓ Plasma levels of TMA and TMAO
Meldonium	↓ TMA production by the intestinal microbiota bacteria
3,3-dimethyl-1-butanol	↘ TMA formation by inhibit TMA lyases
FMO3 enzyme inhibition	↘ Oxidization of TMA to TMAO
Antibiotics	↓ TMAO plasma levels

↓ - Reduce ; ↘ - Inhibit

Figure 1: TMAO synthesis, pathological complications, and known inhibitors.

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