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Unraveling the Effects of Trimethylamine N-Oxide on Stroke: "The lower, the better?"

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Trimethylamine *N*-oxide (TMAO) is a small organic compound generated from choline, carnitine, and betaine via gut microbial and host metabolism (**Fig. 1**)[1]. Increased TMAO levels are associated with a higher risk of major adverse cardiovascular events (death, myocardial infarction, or stroke)[2] as TMAO involves increased foam cell formation, decreased reverse cholesterol transport, and enhanced platelet aggregation[3, 4]. Since solid evidences are reported, considerable research interest has arisen on clinical use of TMAO as a biomarker or therapeutic target as well as TMAO productivity of gut microbiota in many prevalent disorders such as heart failure, coronary artery disease, and other atherosclerotic diseases including stroke. Potential therapeutic strategy of diet and drugs in reducing TMAO levels have emerged[3, 5].

Until now, several studies from China have addressed the relationship between TMAO and stroke[6-8]. Two case-control studies of Chinese population confirm that higher serum TMAO levels were associated with increased risk of first stroke[6, 7]. Hypertensive patients in the upper tertile (TMAO≧3.19 μmol/L) had 37% higher risk of first stroke than those in the lowest tertile (TMAO <1.79 μmol/L)[6]. Higher TMAO levels were associated with an increased risk of first attack and the severity of stroke in patients[6, 7]. Conversely, another case-control study of Chinese patients with stroke and transient ischemic attack showed that plasma TMAO levels of patients with stroke and transient ischemic attack were lower compared with control patients with asymptomatic atherosclerosis, which was the opposite of our expectations[8]. The authors postulated that either stroke event or the treatment may reduce TMAO levels; however, this postulation must be verified in the future.

In this issue of the journal, Sun *et al.*[9] conducted a large-scale case-control study enrolled 953 ischemic stroke cases and same control subjects and presented a positive association between plasma TMAO and the risk of ischemic stroke in Chinese population. The authors performed multivariable conditional logistic regression analysis to diminish effects of confounding factors and demonstrated that subjects with highest plasma TMAO (TMAO >3.83 μmol/L) had 80% higher risk of first ischemic stroke compared to those with lowest plasma TMAO (TMAO ≦1.53 μmol/L). The results of increased odds were consistent with prior observations of cardiovascular events and supported the idea that plasma TMAO involved stroke incidence and was an independent risk factor for stroke. More interestingly, the authors demonstrated that ischemic stroke risk increased steeper at less than 2.46 μmol/L of plasma TMAO and increased slowly when the TMAO levels rose more than 2.46 μmol/L. This data is extremely suggestive when we consider molecular mechanisms of TMAO underlying stroke incidence. For instance, biological action of TMAO may not be in a dose-dependent manner when TMAO levels become higher; or TMAO-mediated functional changes of target cells may occur in different TMAO concentrations and cell dependent. We hope to understand the implication of the truth behind clinical research results.

There are some points to be considered when we interpret their results. First, the exact mechanism underlying the correlation between TMAO and stroke is still unknown. It is assumed that TMAO activates inflammation and thrombus formation and results in increased cardiovascular events, so far. Second, we did not possess detailed information regarding medications of study participants. Taken medication have a

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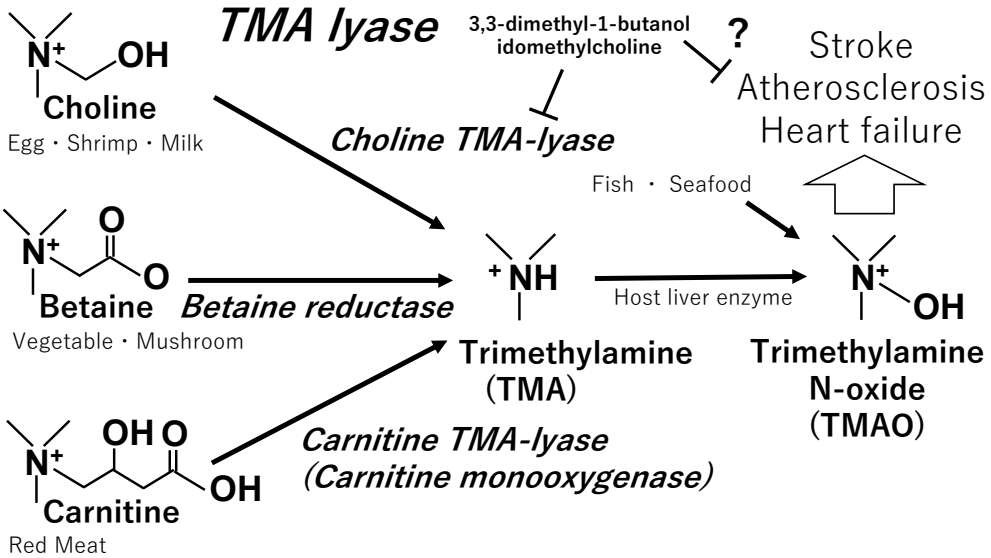

Fig. 1. Gut microbial and host pathways in trimethylamine *N*-oxide (TMAO) metabolism

Trimethylamine (TMA) is generated from choline (derived from egg, shrimp, and milk); betaine (vegetable and mushroom); and carnitine (red meat) by three specific TMA lyases; namely, choline TMA lyase, betaine reductase, and carnitine monooxygenase, respectively. Produced TMA is metabolized by liver host enzyme and is changed to TMAO. TMAO was shown to be associated with increasing cardiovascular events in several clinical studies. In animal experiments, 3,3-dimethyl-1-1butanol or iodomethylcholine was reported to reduce plasma TMAO and inhibit mouse atherosclerosis. Whether reducing the plasma TMAO is effective for prevention of stroke or which enzyme should be inhibit to prevent human cardiovascular events is still unknown.

substantial effect on gut microbiota and TMAO levels; therefore, medication-matched controls is required to elucidate the impact of TMAO on stroke. Third, the plasma TMAO levels in the current study population are lower than those in the Western countries, while it is comparable to some other Chinese populations[6, 8, 9]. Dietary factors and gut microbiota diversity across ethnicities may contribute to the difference in TMAO levels between Chinese and Western populations[1, 2, 6, 8, 9]. However, as another Chinese study indicated rather high TMAO values[7], the sample treatment and method of measurement might be critical. The study suggests that it might be difficult to set the same cutoff value to predict stroke incidence in a different population, although it does not mean that TMAO is not suitable as a biomarker. As the authors indicate, "the lower TMAO levels is better" seems to be true. Further studies are needed to evaluate the dose–response relationship of TMAO concentration with stroke.

Therapeutic approaches have emerged for reducing TMAO levels, including the use of prebiotics, probiotics, and antibiotics to elicit a favorable impact on gut microbiota, 3,3-dimethyl-1-butanol or iodomethylcholine by suppressing the activity of microbial choline trimethylamine (TMA) lyase[5, 10], and diet modification to reduce the intake of choline and carnitine (Fig. 1). Recent studies in association with gut microbial functional genes revealed that there are at least three types of TMA-producing enzymes; namely, choline TMA lyase, carnitine TMA lyase (carnitine monooxygenase), and betaine reductase. It is still unknown which gut microbial enzyme is the best target for prevention of cardiovascular diseases, including stroke. We believe that future research will uncover these new therapeutic pathways, and the number of stroke incidence will decrease via reducing plasma TMAO levels.

Conflicts of Interest

The authors (K.H. and E.T) declare no conflicts of interests. T.Y. is doing joint research with Nitto Pharmaceutical Industries, Ltd. N.Y. was awarded a clinical research grant from the Japanese Circulation Society.

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