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RAPID COMMUNICATION

DIMETHYLAMINE FORMATION IN MAN

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Trimethylamine N-oxide, a common food component, has been identified as a major source of urinary dimethylamine in man. The potential pathophysiological consequences of exposure to dietary derived dimethylamine are raised.

INTRODUCTION

Dimethylamine is the most abundant short-chain aliphatic amine present in human urine; the usual daily excretion of 15-25mg being significantly increased following the ingestion of fish. The amine is also present in other body fluids including saliva, gastric juice, blood and vaginal secretions [1,2]. There are at present two important unresolved issues with respect to its occurrence in body fluids, namely its origin and significance. Much work points to it originating from dietary chemicals, and such food components as lecithin, choline and trimethylamine when given orally elicit small increases in the levels of urinary dimethylamine [3]. These studies also suggest a role for the gut flora in this metabolic process. However, the list of possible dietary precursors is by no means exclusive and others almost certainly await identification. In addition, endogenous biosynthetic pathways for the formation of dimethylamine may also exist and the N-methylation of monomethylamine, metabolically derived from sarcosine or glycine, has been proposed [3,4].

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The presence of dimethylamine in body fluids also raises the question of its potential significance, especially from a pathophysiological point of view. Dimethylamine is well-known to undergo nitrosation under weak acid conditions to give dimethylnitrosamine, an animal carcinogen. Dimethylnitrosamine has been detected and quantified in human urine samples and it has been postulated that it may arise from the nitrosation of dimethylamine by the nitrogen dioxide present in urban environments [5]. It was therefore deemed important to extend the survey of dietary chemicals that could be potentially responsible for the formation of dimethylamine. Investigations within our laboratories have drawn particular attention to trimethylamine N-oxide, a common food component present in high concentrations in marine fish, which apparently has not been previously considered for this role. This paper reports the results of studies in human subjects which demonstrate trimethylamine N-oxide as a source of urinary dimethylamine.

METHODS

Four healthy adult male subjects (mean age 23.5 ± 0.5 years) who had not been exposed to any recent drug medication, did not smoke tobacco and refrained from alcohol for seven days before and during the study were selected. Their normal diet was maintained throughout the study but the subjects were asked to omit fish and sea foods. Urine was collected into plastic bottles containing hydrochloric acid (15ml; 6M) for the 0-24 hours preceding dosing to act as a control. The subjects then ingested 375mg, 750mg, 1125mg, or 2250mg of trimethylamine N-oxide and collected the following 0-24 hour urine as described above. Each individual dosing was separated by at least 14 days. The total urine volumes were recorded and aliquots (4 x 50ml) analyzed for dimethylamine, trimethylamine and trimethylamine N-oxide by head-space gas chromatography as previously described in detail [6].

RESULTS AND DISCUSSION

The urinary excretion of both dimethylamine and trimethylamine N-oxide under normal dietary conditions and following challenge with oral doses of trimethylamine N-oxide are shown in Table 1. The mean urinary excretion levels for dimethylamine and trimethylamine N-oxide observed for the four volunteers over the four control periods were 22.2mg/day and 44.4mg/day respectively, values which were in agreement with previously published data [6].

Table 1. Urinary excretion of dimethylamine (DMA) and trimethylamine N-oxide (TMAO) before and after oral administration of various doses of trimethylamine N-oxide to healthy volunteers.

TMAO dose (mg; mM)	Dimethylamine			Trimethylamine N-oxide		
	before	after	percentage	before	after	percentage
	(mg/day)		TMAO dose	(mg/day)		TMAO dose
375; 5	25.1±3.9	37.6± 4.9	5.6±3.5	66.8±25.1	399.6± 51.1	88.8±17.9
750; 10	20.6±3.9	48.1± 6.8	6.1±1.3	35.9±27.3	617.0±107.6	77.5±17.4
1125;15	21.4±3.8	90.0±23.8	10.2±3.4	30.0±10.2	849.4±143.4	72.8±12.7
2250;30	21.5±4.4	221.5±72.9	14.9±5.6	44.9±28.9	1541.3± 88.2	66.5± 4.4

Values are mean ± S.D. for four volunteers

At all dose levels, following oral administration of trimethylamine N-oxide there occurred significant increases in urinary dimethylamine output. Following the ingestion of 375 and 750mg of the N-oxide some 5.6% and 6.1% respectively of the dose could be accounted for in terms of dimethylamine, this conversion rising to 14.9% at the highest N-oxide dose level. At this higher dose level there also occurred a marked decrease in the urinary recovery of the N-oxide (66.5% dose) which was consistent with its increased conversion to dimethylamine.

It is thus clear that orally administered trimethylamine N-oxide can be converted to dimethylamine which is excreted in the urine. The behaviour of the N-oxide in this respect is in marked contrast to that of its parent amine, trimethylamine. Various studies have shown that less than one percent of an administered dose of trimethylamine is converted to dimethylamine and dietary precursors of trimethylamine, such as choline and lecithin, elicit only relatively small increases in urinary dimethylamine levels [7,8].

Unfortunately, little can be said at this juncture concerning the mechanism of formation of dimethylamine from orally administered trimethylamine N-oxide. Clearly, the extent of conversion is dose-dependent. It is known that some bacterial species can convert the N-oxide directly to dimethylamine with the elimination of formaldehyde [9]. It is speculated that a large oral presentation of trimethylamine N-oxide (2250mg N-oxide as would be present in to 200g skate or 450g plaice) may be incompletely absorbed and part may therefore be exposed to and metabolised by the gut bacterial flora to dimethylamine. Indeed, recent work with rats has shown that

only oral administration of trimethylamine N-oxide produces a significant increase in urinary dimethylamine; intravenous or intraperitoneal injection of the N-oxide is without this effect. Additionally, the oral administration of molar equivalents of the parent amine, trimethylamine, also failed to produce significant increases in urinary dimethylamine output [10]. The fact that exposure to dietary trimethylamine N-oxide increases exposure to dimethylamine raises questions of what foodstuffs contain this N-oxide. Highest levels are found in fish, particularly marine fish, and it might be anticipated therefore that fish-rich diets may be associated with exposure to high levels of dimethylamine. The significance of this in respect of dimethylnitrosamine formation and potential deleterious sequelae is under investigation.

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