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Metabolism and Excretion of Orally Ingested Trimethylarsenic in Man

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Fishes and shellfishes are rich in trimethylarsenic (TMA) (Yamauchi and Yamamura 1980). Edmonds and Francesconi (1977) as well as Edmonds et al. (1977) revealed that the chemical structure of TMA occurring in western rock lobsters and stringrays is arsenobetaine. TMA is also known to occur in other chemical structures such as arsenocholine (Irgolic et al. 1977) and trimethylarsonium lactic acid (Cooney et al. 1978). In *in vivo* experiments, it was revealed that dimethylarsinic acid (DMAA) is converted to TMA *in vivo* (Yamauchi and Yamamura unpublished data). The reports of the chemical structure of TMA in organisms and the production of TMA *in vivo* have been on the steady increase in recent years. On the other hand, there are only a few reports of the *in vivo* metabolism and excretion of TMA.

For purposes of unveiling the mechanisms of *in vivo* metabolism and excretion of TMA in man, we observed the chemical species and output of arsenic in the urine and the TMA levels in the blood with the passage of time following oral ingestion of TMA-rich foods once only.

MATERIALS AND METHODS

The meat portion of prawns (*Pandalus borealis*) was used as foods rich in TMA. The total arsenic in the ingested foods was made up of 98.8% TMA, 0.96% inorganic arsenic and 0.14% DMAA: in other words, TMA accounted for most of the total arsenic. No methylarsonic acid (MAA) was detected. The subject was an adult Japanese man, and this subject was given the agent twice with a 2-week interval. The ingested amount of TMA was 10 μg/kg of As. In the first experiment, 747 μg of As (756 μg of As as the total arsenic intake) was ingested orally once only, and in the second experiment, 750 μg of As (759 μg of As as the total arsenic intake) was likewise ingested. During either experiment period, the subject was totally restricted from the ingestion of other marine products, so as to minimize the influence of dietary arsenic. The urine was collected at specified intervals during the period from 24 hr before the ingestion of TMA to 72 hr after the ingestion. All urine samples were preserved at -20°C. For the arsenic assay, 5 ml of the urine was used. The sample was transferred into a 50-ml glass-stoppered test tube, and after the addition of 5 ml of 2 N NaOH, was heated in a hot water bath for 3 hr. Twenty ml of 10% oxalate solution and 20 ml of 10% phthalate solution were then added as buffers. The arsenic contained in the mixture was reduced to arsines with 2 ml of 20% $NaBH_4$ in 0.2 N NaOH solution, and the arsines were fixed with liquid nitrogen. From the fixed arsines were separated the component arsines, which were determined by arsine-generator flameless atomic absorption spectrophotometry (Braman

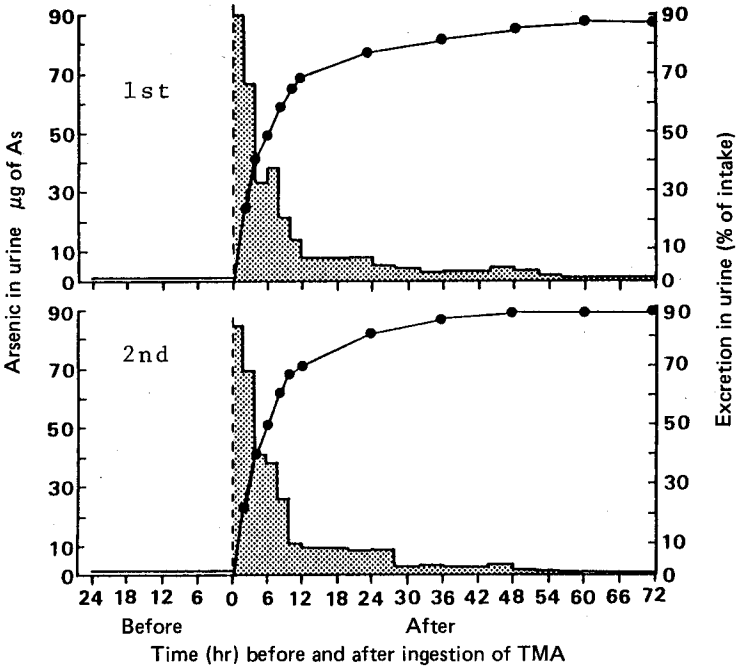

Fig. 1. Excretion pattern and rate of trimethylarsenic (TMA) in the urine with time after single oral ingestion of TMA (747 μg of As in the 1st, and 750 μg of As in the 2nd experiment).

et al. 1977; Yamauchi and Yamamura 1979a).

RESULTS AND DISCUSSION

Table 1 shows the background arsenic concentrations in the urine during the experimental period (with restricted intake of seafoods). The output of TMA in the urine during the first 72 hr after the single oral ingestion of TMA corresponded to 86.4% of the ingested amount of TMA in the first experiment, and to 89.2% in the second experiment (Table 2). It was shown that the most of the TMA ingested was excreted in the urine without undergoing any change in its chemical species *in vivo*. An amount of TMA corresponding to 50% of the ingested amount was excreted in the urine during the first 6 hr after the ingestion (Fig. 1). The TMA output reached a peak 2 hr after ingestion, decreased rapidly from then on, and was very low from 24 hr after the ingestion onward. A trace of or no TMA was detected in the urine from 60 hr after the ingestion onward.

From the experiments on hamsters, it is known that TMA is chiefly excreted in the urine but not in the feces (Yamauchi and Yamamura unpublished data). In this study, 90% of the ingested amount of TMA was excreted in the urine, and this finding again proved that TMA is chiefly excreted in the urine even in man. The TMA output pattern in the urine is characterized by the occurrence of its peak as early as 2 hr after the ingestion. In this study, the biological half-life of TMA in man was shown to be about 6 hr (Fig. 1). From the results of the experiments by Creceli-

Table 1. Background values of arsenic in the urine during the restricted ingestion of marine products

Experiment No.	Inorganic As (μg As/hr)	MAA (μg As/hr)	DMAA (μg As/hr)	TMA (μg As/hr)	Total (μg As/hr)
1st	0.76±0.26	0.08±0.03	0.60±0.15	0.67±0.16	2.10±0.45
2nd	0.44±0.09	0.05±0.02	0.40±0.07	0.82±0.19	1.71±0.32

The above values are the mean ± SD for 5 samples, respectively.
MAA: methylarsonic acid; DMAA: dimethylarsinic acid; TMA: trimethylarsenic.

Table 2. Arsenic outputs in the urine after one oral dose of trimethylarsenic

Experiment No.	Time after intake (hr)	Inorganic As (μg As)	MAA (μg As)	DMAA (μg As)	TMA (μg As)	(%*)	Total (μg As)	(%†)
1st	0~ 2	0.25	0.57	0.58	174.5	23.6	175.9	23.3
2nd		2.30	0.12	1.60	165.4	22.1	169.4	22.3
1st	2~ 4	0.62	0.30	0.01	128.4	17.3	129.3	17.1
2nd		0.82	0.02	0.44	135.4	18.1	136.7	18.0
1st	4~ 6	2.58	0.64	0.60	63.1	8.5	66.9	8.9
2nd		1.72	0.20	1.42	78.9	10.5	82.2	10.8
1st	6~ 8	4.32	0.48	0.24	72.3	9.8	77.4	10.2
2nd		0.90	0.12	0.18	73.5	9.8	74.7	9.8
1st	8~10	–	–	0.54	39.4	5.3	40.0	5.3
2nd		0.60	0.16	0.28	50.0	6.7	51.0	6.7
1st	10~12	1.48	0.14	0.36	23.4	3.2	25.4	3.4
2nd		0.20	–	–	19.2	2.6	19.4	2.6
1st	12~24	0.48	0.52	–	68.0	9.2	69.0	9.1
2nd		14.0	0.44	–	86.9	11.6	101.7	13.4
1st	24~36	4.77	1.03	–	32.7	4.4	38.5	5.1
2nd		4.84	0.40	–	39.9	5.3	45.2	5.9
1st	36~48	1.28	0.61	–	27.9	3.8	29.8	3.9
2nd		9.84	0.76	–	17.2	2.3	27.8	3.7
1st	48~60	5.91	0.10	–	13.0	1.8	19.0	2.5
2nd		2.40	0.68	–	2.56	0.3	5.64	0.7
1st	60~72	–	–	–	3.02	0.4	3.02	0.4
2nd		–	–	–	–		–	
Total								
1st		21.7	4.39	2.33	645.7	87.3	674.2	89.2
2nd		37.6	2.90	3.92	669.1	89.2	713.9	94.1

Ingested amount of trimethylarsenic: 747 μg of As in the 1st, and 750 μg of As in the 2nd experiment.
The arsenic outputs in the urine after oral ingestion of TMA once only are corrected by the background values of the above-mentioned 4 chemical species of arsenic (Table 1).
* Percent of the ingested amount of TMA excreted in urine.
† Percent of the ingested amount excreted in urine (756 μg of As as the total arsenic intake in the 1st, and 759 μg of As as the total intake in the 2nd experiment).
– Not detected.

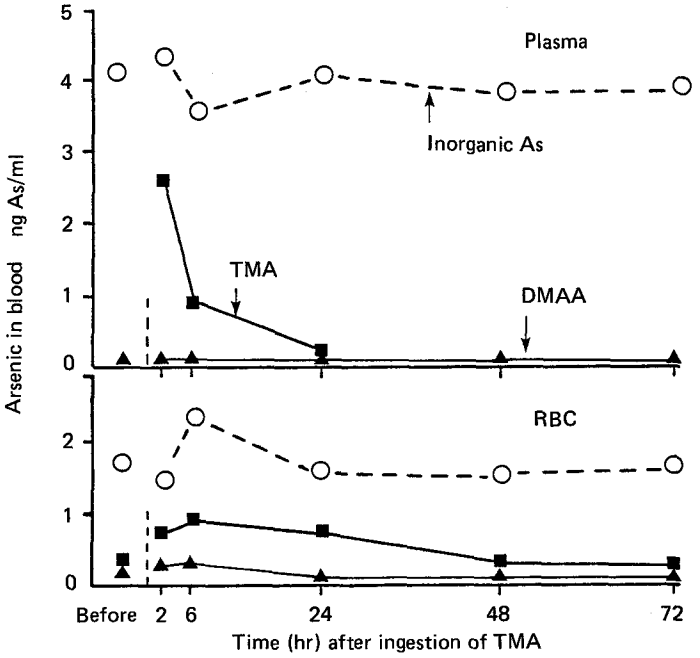

Fig. 2. Changes in the blood level of arsenic with time after single oral ingestion of trimethylarsenic (750 μg of As) (2nd experiment)

us (1977), on the other hand, the biological half-life of organic arsenic (methylarsenic compounds) in marine products may be estimated to be no more than 20 hr. In other words, the biological half-life of TMA has proved to be very short. Comparison of the excretory rates of TMA and arsenic trioxide (Yamauchi and Yamamura 1979b) indicates that TMA is excreted at twice as high a rate as arsenic trioxide during the first 24 hr after its ingestion. Because of this difference in excretion rate, TMA may be less toxic to humans than arsenic trioxide.

Ninety percent of the ingested amount of TMA was excreted in the urine without undergoing any change in its chemical species, while 3~5% was excreted as the other species of arsenic (inorganic arsenic, MAA and DMAA). The latter indicated differences of the background values of arsenic (Table 1) and the species of arsenic other than TMA in the foods (materials) deducted from the determined values. These slight increases in such chemical species of arsenic suggest that TMA may partly be demethylated *in vivo*. From their experiments, Crecelius (1977), Stevens et al. (1977) and Buchet et al. (1981) drew the conclusion that no organic arsenic compounds (methylarsenic compounds) are converted into inorganic arsenic. However, Andreae (1981) reported the fact that the organic arsenic compounds in seaweeds are converted into arsenate *in vivo*. We do not entirely agree with the opinion that TMA and DMAA are not demethylated *in vivo*, but are of the opinion that they are less likely demethylated.

Fig. 2 illustrates the behavior of arsenic in the blood following the oral ingestion of TMA in the second experiment. The TMA taken up by the blood tended to be

distributed in the plasma rather than into the blood cells. The plasma TMA showed a peak 2 hr after the ingestion of the agent, which was consistent with the peak output of TMA in the urine. TMA then disappeared rapidly from the plasma, being no longer detected in the plasma 48 hr after the ingestion. In the meantime, the inorganic arsenic and DMAA levels did not change. Three chemical species of arsenic, i.e., inorganic arsenic, DMAA and TMA, occurred in the blood cells before the ingestion of TMA. Out of these species, TMA, DMAA and inorganic arsenic increased with the ingestion of TMA, though slightly. No MAA was detected in the blood.

In the experiments on rats, DMAA had an affinity for red blood cells, resulting in its slow disappearance from the blood (Yamauchi et al. 1980). On the other hand, DMAA or TMA had less affinity for red blood cells in hamster blood, disappearing from the blood very rapidly (Yamauchi and Yamamura unpublished data). In this study, it was shown that the excess TMA in the blood is distributed into the plasma, and that it disappeared from human blood very rapidly. These findings are consistent with the findings in hamsters.

Fishes and shellfishes are rich in TMA and DMAA (Yamauchi and Yamamura 1980). Although humans ingest large amounts of TMA and DMA through fishes and shellfishes, there has been no report of any impairment of health with the arsenic contained in fishes and shellfishes. In our opinion, the very rapid excretion of methylarsenic compounds and its low retention *in vivo* in humans obviates health concerns.

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