Effect of Muscular Exercise on the Concentration of Uridine and Purine Bases in Plasma—Adenosine Triphosphate Consumption–Induced Pyrimidine Degradation

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To identify whether muscular exercise increases the plasma concentration of uridine and of purine bases, the effect of rigorous muscular exercise was determined in five healthy men with a bicycle ergometer. Twenty-five–minute muscular exercise at 65% maximum O_2 consumption increased the concentration of uridine, purine bases, and inorganic phosphate in plasma and of NH_3 and lactic acid in blood. These results suggest that exercise-induced excessive adenosine triphosphate (ATP) consumption enhanced not only purine degradation but also pyrimidine degradation (uridine triphosphate [UTP] → uridine diphosphate [UDP] → uridine monophosphate [UMP] → uridine) in exercising muscles.

RECENTLY, WE DEMONSTRATED that fructose- and ethanol-enhanced pyrimidine degradation and purine degradation resulted in an increase in the concentration of uridine and purine bases (hypoxanthine, xanthine, and uric acid) in plasma.[1] Fructose infusion or ethanol ingestion consumes adenosine triphosphate (ATP) in the respective metabolism, leading to a decrease in ATP and increases in adenosine diphosphate (ADP) and adenosine monophosphate (AMP). Since these changes enhance purine nucleotide degradation as described previously,[1] plasma purine bases (the end products of purine degradation) increase. On the other hand, since uridine diphosphate (UDP) is phosphorylated to uridine triphosphate (UTP) using ATP as a phosphate donor, the fructose- or ethanol-induced decrease in ATP reduces the production of UTP, resulting in increases in UDP and uridine monophosphate (UMP). The decrease in ATP and increases in UDP and UMP enhance pyrimidine degradation. Since fructose and ethanol are mainly metabolized in the liver, the fructose- or ethanol-induced increase in the concentration of plasma uridine is ascribable to enhanced pyrimidine degradation in the liver. Rigorous muscular exercise is well known as a condition in which ATP is excessively consumed with resultant enhanced purine degradation.[2,3] Muscular exercise consumes ATP excessively, disturbing ATP production by oxidative phosphorylation because of the ischemia of exercising muscles. As a result, ATP markedly decreases while both ADP and AMP increase. These changes of adenine nucleotides enhance purine degradation (AMP → inosine monophosphate → inosine → hypoxanthine), resulting in hypoxanthine leakage from the exercising muscles into the plasma. Since rigorous muscular exercise consumes ATP, it may also enhance pyrimidine degradation in the muscle as do ethanol ingestion or fructose infusion in the liver. Therefore, we investigated whether rigorous exercise enhanced pyrimidine degradation in the muscle, as well as purine degradation.

SUBJECTS AND METHODS

Chemicals

All chemicals, including hypoxanthine, xanthine, and uridine, were purchased from Wako Pure Chemical Industries (Osaka, Japan).

Subjects and Protocol

The study was conducted on five healthy men aged 20 to 23 years and weighing 48 to 62 kg. The subjects had normal laboratory data. After informed consent was obtained, they exercised on a bicycle ergometer. Heparinized blood samples were drawn from both the right femoral vein and the right radial artery at the same time before and immediately after the subjects performed workloads of 65% of maximum oxygen uptake for 25 minutes on the bicycle ergometer. Maximum oxygen uptake was determined as follows. The subjects were asked to pedal a bicycle ergometer (Takei Kiki, Tokyo, Japan) at approximately 50 rpm at an initial setting of 0 W. The workload was increased incrementally every minute until the pedaling frequency could no longer be maintained. During exercise, oxygen uptake and heart rate were monitored every minute and maximum oxygen uptake was determined.

Blood and Urine Analyses

Plasma concentrations of hypoxanthine, xanthine, and uridine were determined by the method reported by Yamamoto et al[4] using high-performance liquid chromatography. The column was a Wakosil 5C-18 (4.6 mm ID × 25.0 mm; Wako Pure Chemical Industries). Uric acid levels in plasma and urine were measured by the uricase method using an autoanalyzer. The blood concentration of lactic acid was measured by enzymatic methods using a Determinar LA kit (Kiyowa Medix, Tokyo, Japan), and blood NH_3 was determined using an Ammonia Test kit (Wako Pure Chemical Industries).

Statistics

Results are expressed as the mean ± SD. The significance of differences was assessed by the two-tailed paired Student's t test for all variables. A P value less than .05 was considered statistically significant.

RESULTS

Plasma Concentration of Uridine and Purine Bases Before and After Exercise

Muscular exercise increased plasma concentrations of uridine in the femoral vein and the radial artery from 3.96 ± 0.78 μmol/L to 5.04 ± 0.72 μmol/L ($P < .01$) and from 3.51 ± 0.59 μmol/L to 5.12 ± 0.52 μmol/L ($P < .05$), respectively (Fig 1). The concentration of uridine in plasma did not differ between the femoral vein and the radial artery before and after exercise. In the femoral vein and radial artery, muscular exercise increased plasma concentrations of hypoxanthine 14.2-fold ($P < .01$) and 13.4-fold ($P < .01$), xanthine 2.6-fold ($P < .05$)

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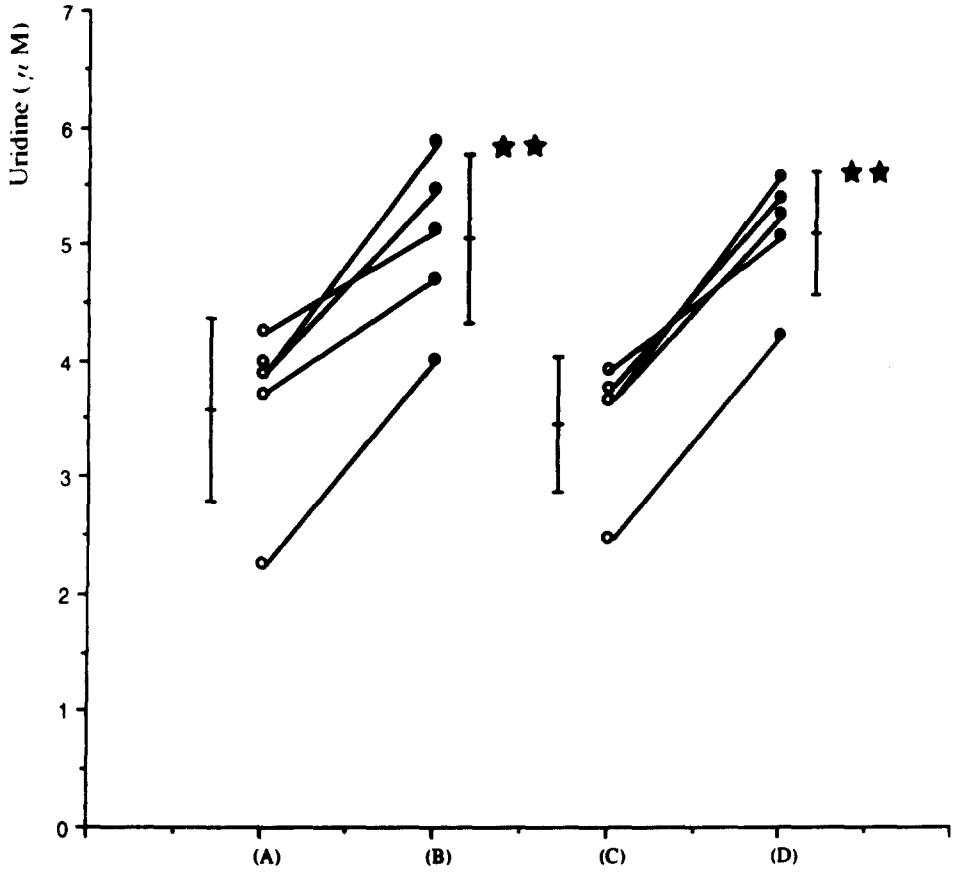

Fig 1. Concentration of uridine in plasma (N = 5). (A) Femoral vein before exercise, (B) femoral vein after exercise, (C) radial artery before exercise, (D) radial artery after exercise. **$P < .01$.

and 2.8-fold ($P < .05$), and uric acid 1.1-fold ($P < .05$) and 1.1-fold ($P < .05$), respectively (Table 1). Plasma concentrations of hypoxanthine, xanthine, and uric acid did not differ in the femoral vein versus the radial artery before muscular exercise. Nor did the respective plasma concentrations of hypoxanthine, xanthine, and uric acid differ in the femoral vein versus the radial artery after muscular exercise. However, an increase in the plasma concentration of hypoxanthine was 11.5 and 7.6 times more than that of uridine in the femoral vein ($P < .01$) and the radial artery ($P < .01$), respectively (Table 1).

Concentrations of NH_3 and Lactic Acid in Blood and Inorganic Phosphate in Plasma

The concentration of NH_3 in blood increased 6.7-fold ($P < .01$), lactic acid in blood 8.6-fold ($P < .01$), and inorganic phosphate in plasma 1.3-fold ($P < .05$) in the femoral vein after exercise (Table 2).

Table 1. Plasma Concentration of Purine Bases (N = 5)

	Hypoxanthine (μmol/L)	Xanthine (μmol/L)	Uric Acid (μmol/L)
Before exercise			
Femoral vein	1.22 ± 0.36	0.51 ± 0.17	321 ± 52
Radial artery	0.99 ± 0.20	0.49 ± 0.25	329 ± 59
After exercise			
Femoral vein	17.37 ± 5.03†	1.34 ± 0.26*	360 ± 57*
Radial artery	13.32 ± 3.08†	1.36 ± 0.54*	365 ± 69*

*$P < .05$, †$P < .01$: *v* before exercise.

pH, Pao_2, $Paco_2$, and Hemoglobin in Arterial and Venous Blood

In the femoral vein and radial artery, muscular exercise decreased both the pH ($P < .01$) and $Paco_2$ ($P < .05$), whereas it did not affect Pao_2 or hemoglobin (Table 3).

DISCUSSION

In previous studies,[5-7] it has been shown that ischemia increases purine degradation, followed by pyrimidine degradation, resulting in leakage of uridine and hypoxanthine from the ischemic tissues into the blood. In addition, recent studies[1,8] suggest that excessive consumption of ATP enhances pyrimidine degradation, as well as purine degradation, whatever the substance causing the consumption of ATP. Therefore, we

Table 2. Concentration of Lactic Acid and NH_3 in Blood and Inorganic Phosphate in Plasma in the Femoral Vein (N = 5)

	NH_3 (mmol/L)	Lactic Acid (mmol/L)	Inorganic Phosphate (mmol/L)
Before exercise	22.7 ± 3.5	0.86 ± 0.14	1.1 ± 0.1
After exercise	151.8 ± 45.3†	7.4 ± 1.7†	1.4 ± 0.2*

*$P < .05$, †$P < .01$: *v* before exercise.

Table 3. Blood Gas Analysis Before and After Exercise (N = 5)

	pH	$Paco_2$ (torr)	Pao_2 (torr)	Hemoglobin (g/dL)
Before exercise				
Femoral vein	7.35 ± 0.02	48.3 ± 2.1	32.6 ± 10.4	15.0 ± 1.5
Radial artery	7.40 ± 0.01	36.5 ± 0.7	96.3 ± 7.6	15.0 ± 1.3
After exercise				
Femoral vein	7.24 ± 0.05†	42.4 ± 5.5*	41.5 ± 6.6	15.5 ± 1.2
Radial artery	7.33 ± 0.04†	31.2 ± 2.5*	100.2 ± 10.1	14.8 ± 1.0

*$P < .05$, †$P < .01$: *v* before exercise.

examined whether rigorous exercise, which causes excessive consumption of ATP in muscle, induces pyrimidine degradation.

The present study demonstrated that muscular exercise increased lactic acid and NH_3 levels in venous and arterial blood after exercise and inorganic phosphate in plasma, and it was also demonstrated that muscular exercise decreased the pH of venous and arterial blood despite a decrease in $Paco_2$ in venous and arterial blood. The increase in lactic acid and the decrease in pH indicate that exercising muscles became hypoxic and anaerobic glycolysis increased, and the increases in NH_3, inorganic phosphate, and purine bases indicate that adenine nucleotides were dephosphorylated and AMP deamination was accelerated in exercising muscles, resulting in enhanced purine degradation.[9] As a result, plasma hypoxanthine, the end product of purine degradation in muscle, markedly increased, leaking from the exercising muscles into the blood. These results indicated that any energy crisis during exercise increased the degradation of adenine nucleotides, as described previously[9-11] (Fig 2). As expected, muscular exercise increased the plasma uridine level in the present study, although the change was modest in contrast to the changes of hypoxanthine, suggesting that excessive exercise-induced degradation of adenine nucleotides is accompanied by degradation of pyrimidine nucleotides. In a previous study,[12] 2-minute intense exercise increased both hypoxanthine and xanthine in the plasma but not uridine or uric acid. However, in the present study, 25-minute rigorous exercise on a bicycle ergometer increased both pyrimidine and purine degradation, resulting in an increase in plasma uridine together with an increase in plasma oxypurine. Furthermore, it was demonstrated that the increase was markedly greater for hypoxanthine than for uridine. The difference in the results seems ascribable to the degree of exercise. Namely, the 2-minute intense exercise in the previous study[12] was not

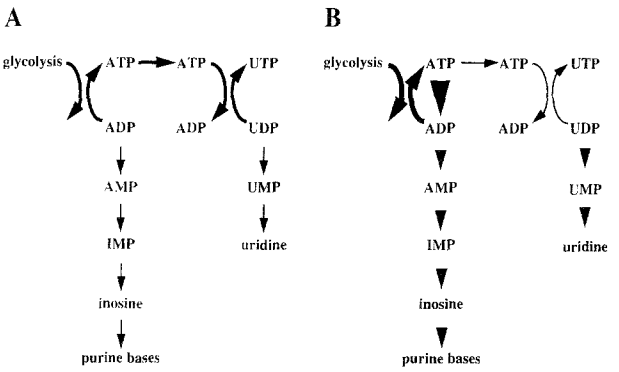

Fig 2. Scheme of pyrimidine and purine degradation induced by muscular exercise. (A) Before exercise, (B) after exercise. Thick downward arrows indicate increased degradation.

sufficient to increase plasma uridine but was sufficient to increase plasma hypoxanthine, whereas a 25-minute exercise in the present study was sufficient to increase both plasma uridine and hypoxanthine. Therefore, an increase in plasma hypoxanthine seems to be a more sensitive indicator of ischemia-induced purine degradation in exercising muscle than the plasma uridine level (Fig 1 and Table 1), although both reflect ischemia-induced purine degradation in exercising muscle. Muscular exercise increased both the inorganic phosphate level in plasma, albeit slightly, and the NH_3 level in blood (Table 2). In contrast, fructose, ethanol, or xylitol decreased inorganic phosphate levels in plasma[1,8] and did not affect NH_3 levels in blood (T. Yamamoto, unpublished data, June 1993). These results indicate that the mechanism of purine degradation with muscular exercise differs from that obtained with administration of fructose, xylitol, or ethanol, as described previously.[9-11,13-15] Namely, the mechanism of ATP breakdown with fructose and xylitol is related to the trapping of inorganic phosphate as phosphorylated sugars. In contrast, in exercising muscle, excessive consumption and breakdown of ATP occurs, releasing inorganic phosphate. Furthermore, fructose, xylitol, and ethanol cause ATP degradation in the liver, whereas muscular exercise causes ATP degradation in muscles, as shown by the present study. Therefore, the present study and previous studies[1,8] suggest that the abrupt loss of ATP causes pyrimidine degradation and purine degradation regardless of the mechanism or site (Fig 2), although the biological implications of exercise-induced modest changes in uridine levels are unclear.

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