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ORIGINAL COMMUNICATIONS

Ammonia metabolism during exercise in man

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Summary. Physical exercise is accompanied by increased plasma levels of ammonia but it is not known whether this rise primarily reflects accelerated formation in muscle or decreased removal by the liver. Consequently, leg and splanchnic exchange of ammonia was examined, using the catheter technique, in 11 healthy subjects at rest, during three consecutive 15 min periods of bicycle exercise at gradually increasing work loads (35%, 55% and 80% of maximum oxygen uptake) and for 60 min during post-exercise recovery. The basal arterial ammonia level was 22±2 μmol/l, the concentration rose curvilinearly in response to increasing work loads (peak value 84±12 μmol/l), and fell rapidly after exercise, reaching basal levels after 30–60 min. A linear regression was found for ammonia levels in relation to lactate concentrations at rest and during exercise (r=0·85, P<0·001). A significant relationship was also observed between arterial ammonia and alanine levels (r=0·75, P<0·001). Leg tissues showed a net uptake of ammonia in the basal state (2·4±0·5 μmol/min). During exercise this changed to a net production, which increased curvilinearly with rising work intensity (peak value 46±15 μmol/min) but reverted to a net ammonia uptake at 30–60 min after exercise. Splanchnic ammonia uptake (basal 12±2 μmol/min) did not change in response to exercise but increased transiently during the early post-exercise period.

From the above observations we conclude that the hyperammonaemia of exercise comes primarily from muscle release, while the splanchnic removal of ammonia is essentially unaltered. Part of the ammonia formed in contracting muscle is most likely used in the synthesis of amino acids, mainly glutamine and probably alanine.

Introduction

Even though the metabolism of ammonia has received much attention, its regulation in varying physiological and clinical situations is still not well understood. While several organs show a net uptake and utilization of ammonia, other tissues release

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ammonia, and the blood concentration accordingly reflects the net balance of this uptake and release. In the resting state, ammonia is formed in the kidneys by deamidation of glutamine, a reaction catalysed by glutaminase and partly controlled by renal pH changes. The major part of the circulating ammonia, however, is absorbed from the intestinal tract where, in turn, it is derived from enzymatic degradation of nitrogenous compounds. A substantial amount of this ammonia is taken up by the liver and converted to urea. Consequently, the ammonia concentration is higher in the portal vein than in arterial blood (White *et al.*, 1955).

Skeletal muscle plays a limited role in ammonia metabolism in the basal state. Ammonia is utilized in the formation of glutamine and usually a small muscle uptake of ammonia is observed (Bessman & Bradley, 1955). In contrast, heavy or prolonged exercise is accompanied by the formation and release of large amounts of ammonia from muscle tissue (Parnas *et al.*, 1927; Allen & Conn 1960). In this situation, ATP is used as an anaerobic energy source, resulting in increased formation of AMP. The activity of the purine-nucleotide cycle is enhanced during physical exercise (Lowenstein 1972), converting AMP to inosinic acid (IMP) with the formation of ammonia. Ammonia production serves to limit the exercise-induced fall in intracellular pH in muscle tissue and may also influence the amino acid metabolism.

It is generally believed that the exercise-induced increase in blood ammonia concentration is derived primarily from this accelerated ammonia production in muscle. However, in view of the decreased liver blood-flow that is associated with exercise (Wahren *et al.*, 1971), another important contributing factor could be a reduced removal of ammonia by the liver. The present study was therefore undertaken to examine the effect of exercise on the inter-organ flux of ammonia.

Material and Methods

SUBJECTS

Eleven healthy, non-obese male subjects were studied in the basal post-absorptive state. Their mean age was 27 years (range 21–41) and mean weight 74 kg (range 64–84). The purpose and possible risks of the study were carefully explained to all subjects before obtaining their consent to participate. The experimental protocol was reviewed and approved by the institutional ethics committee.

PROCEDURE

The studies were performed in the morning after an overnight fast (12–14 h). Teflon catheters were inserted percutaneously into a femoral vein, a brachial artery and an antecubital vein. A Cournand catheter (No. 8) was introduced percutaneously into another antecubital vein and advanced into a right-sided hepatic vein under fluoroscopic control. The catheter tip was placed 3–4 cm from the wedge position and its location was checked repeatedly by fluoroscopy before and after the exercise period.

Basal blood samples were collected 30–45 min after catheterization with the subjects resting in the supine position. The subjects then performed exercise in the upright position on a bicycle ergometer (Elema Schönander, Stockholm, Sweden) for three consecutive 15-min periods, at work intensities corresponding approximately to 25%, 50% and 75% of their maximal oxygen uptake, determined on a separate occasion before the study. After exercise, blood samples were collected for 60 min with the subjects in the supine position. Throughout the study, the subjects' ECG was monitored continuously.

Samples for determination of ammonia, urea and lactate were drawn from the artery and the femoral and hepatic veins in the basal state, after 7½ and 15 min at each work load and at 5, 15, 30 and 60 min after exercise. Amino acid concentrations were measured simultaneously in the artery and femoral vein. Hepatic blood-flow was measured by the continuous infusion technique (Bradley, 1948) using indocyanine green dye (Rowell *et al.*, 1964). Leg blood-flow was estimated from the pulmonary oxygen uptake and leg oxygen arterio-venous differences (Jorfeldt & Wahren, 1971).

ANALYSES

Ammonia concentration was measured with a flow injection technique (Svensson & Anfält, 1982), based on calorimetric measurements using phenol red as indicator. Urea (Fawcett and Scott, 1960) and lactate (Wahren, 1966) were determined enzymatically in whole blood, after precipitation with 3M perchloric acid.

Individual amino acids were measured in plasma by an automated ion exchange chromatograph (Liquimat III, Kontron, Basle, Switzerland) using a single column of Aminex 9 (Biorad Laboratories, Richmond, Calif., U.S.A.) and Lithium Pico Buffer System W (Durrum Chemical Corporation, Sunnyvale, Calif., U.S.A.). The proteins were precipitated with 30% sulphosalicylic acid within 1 h after sampling and the supernatant was stored at −20°C until analysed. Oxygen content was determined in expired air collected in Douglas bags and analysed using the Scholander microtechnique. Haemoglobin concentration and oxygen saturation were determined spectrophotometrically (Drabkin, 1950).

Standard statistical methods were employed, using the paired *t*-test when applicable. Data given in the text and tables are presented as mean values ±SEM.

Results

The pulmonary oxygen uptake, relative work intensity, heart rate and haematocrit before, during and after exercise are shown in Table 1. Although the three work loads were intended to correspond to 25%, 50% and 75% of maximal pulmonary oxygen uptake, the actual work intensity was slightly higher during each exercise period: 35±2%, 55±3% and 80±3%, respectively. The heart rate rose from 61±10 beats/min at rest to a maximum of 184±4 beats/min. Exercise resulted in a transient

Table 1. Pulmonary oxygen uptake, relative work intensity, heart rate and haematocrit before, during and after exercise

		Exercise work load			After exercise	
	Basal	1st	2nd	3rd	30 min	60 min
VO_2 (l/min)	0·25±0·01	1·21±0·07	1·89±0·08	2·70±0·11	0·28±0·01	0·28±0·02
Relative work intensity	—	35·0±2·2	55·1±2·8	80·1±3·4	—	—
Heart beats/min	61±10	113±4	154±3	184±4	—	—
Haematocrit	42·7±0·7	45·0±0·9***	45·5±0·9***	46·4±1·1***	42·9±1·0	43·2±1·2

Data are given as mean±SE. Asterisks denote the probability that the value is different from the corresponding basal observation. *** $P<0·001$.

Table 2. Arterial concentration and regional exchange of ammonia, lactate and urea before, during and after exercise

		Exercise work load			After exercise	
	Basal	1st	2nd	3rd	30 min	60 min
Arterial concentrations						
Ammonia (μmol/l)	21·8±1·7	27·4±2·1**	45·6±5·8**	84·4±12·1***	27·2±3·5	20·4±1·7
Lactate (mmol/l)	0·51±0·03	1·01±0·24	2·26±0·50**	7·68±1·60**	2·26±0·56**	0·97±0·19*
Urea (mmol/l)	4·85±0·21	4·77±0·18	4·78±0·17	4·97±0·17	4·82±0·18	4·91±0·17
Leg exchange						
Ammonia release (μmol/min)	−2·4±0·5	3·6±2·5***	14·4±1·9*	45·7±15·3**	0·1±0·7	−1·8±0·9
Lactate release (mmol/min)	0·05±0·01	0·33±0·19	1·32±0·60	1·35±0·72	0·18±0·06	0·14±0·02
A-FV O_2 (ml/l)	62·5±3·2	148±4	166±5	188±5	64·6±10·9	54·5±4
Estimated leg blood-flow (l/min)	0·49±0·03	2·31±0·15***	3·55±0·14***	4·74±0·18***	0·67±0·08	0·63±0·05
Splanchnic exchange						
Ammonia (μmol/min)	12·4±1·8	11·4±1·1	13·7±1·3	14·8±3·6	16·6±2·1	12·0±1·5
Lactate (mmol/min)	0·23±0·04	0·34±0·10	0·55±0·11*	1·05±0·31*	0·73±0·09***	0·54±0·09**
Estimated hepatic blood-flow (l/min)	1·27±0·12	1·01±0·06**	0·72±0·06***	0·40±0·07***	1·40±0·05	1·55±0·09*

Data are given as mean±SE. Asterisks denote the probability that the value is different from the basal observation. * $P<0·05$, ** $P<0·01$, *** $P<0·001$.

haemoconcentration, as demonstrated by a rise in haematocrit from 42·7±0·7% at rest to 46·4±1·1% at the end of the third exercise period, but within 30 min after the end of exercise the haematocrit had returned to its basal level.

ARTERIAL CONCENTRATIONS

The arterial concentrations of ammonia, lactate and urea are summarized in Table 2. Exercise at the lowest work intensity resulted in a small increase in ammonia levels (+25%, $P<0·01$), but during the second work load the levels doubled and at the highest work load there was a fourfold rise (peak value 84±12 μmol/l). Cessation of exercise was followed by a rapid decrease in ammonia concentration; 5 min after exercise the ammonia level had fallen to 59±10 μmol/l and after 15 min to 36±5 μmol/l. There was a further, slower decline, so that after 60 min of recovery the arterial ammonia levels were similar to those in the basal state (Table 2).

Arterial lactate concentrations increased continuously during exercise, the maximal rise occurring between the second and third work load (Table 2), when lactate levels rose threefold from 2·26±0·50 to 7·68±1·60 mmol/l. As in the case of ammonia, the arterial lactate levels decreased rapidly during the first 15 min after work to 3·87±1·12 mmol/l ($P<0·05$ as compared to basal), followed by a slower decline (Table 2). A significant direct correlation was observed between the arterial lactate and arterial ammonia levels ($r=0·85$, $P<0·001$, Fig. 1). The arterial concentration of urea was 4·85±0·21 mmol/l in the basal state and did not change significantly either during or after exercise.

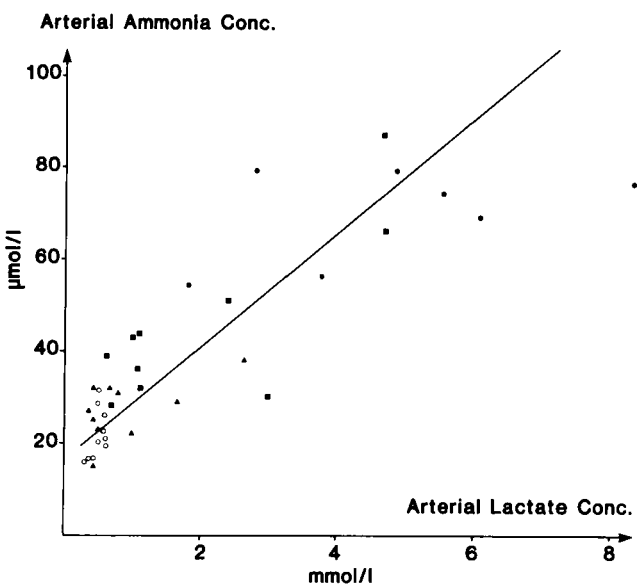

Fig. 1. The relationship between arterial ammonia and lactate concentrations at rest (○) and during the first (▲), second (■) and third (●) work loads. $r=0·85$, $P<0·001$.

Table 3. Arterial concentrations of plasma amino acids before, during and after exercise

		Exercise work load			After exercise	
	Basal	1st	2nd	3rd	30 min	60 min
Taurine	48±3	55±4*	54±4*	59±4***	45±3	41±3
Serine	106±5	107±6	98±4	96±5*	94±5	94±6
Glutamate	58±2	37±3***	31±4***	27±3***	60±3	60±4
Glutamine	538±15	616±17***	606±17*	666±23***	594±18**	605±35*
Glycine	180±4	199±6*	190±6*	193±7**	160±5**	172±11
Alanine	195±6	284±11***	326±17***	430±19***	308±28**	260±22**
Valine	208±12	221±12	201±12	201±11	192±10	180±7
Methionine	18±1	21±1**	21±1***	23±1***	18±0	18±1
Isoleucine	57±4	61±4	58±3	59±4	49±2*	47±2*
Leucine	123±7	129±8	124±7	128±7	112±4	105±4*
Tyrosine	45±2	48±2**	50±2*	53±2***	45±2	45±2
Phenylalanine	42±2	49±2**	45±1**	52±3***	44±1	43±2
Ornithine	45±2	48±2	42±1	42±2	39±2*	38±2*
Lysine	144±7	162±7**	154±6*	165±8***	136±5	138±9
Histidine	72±2	80±3**	77±2**	84±2***	78±3	77±3*
Arginine	74±4	86±4**	82±4***	87±4***	71±3	71±5

Data are given as mean±SE. Asterisks denote the probability that the value is different from the corresponding basal observation, * $P<0.05$, ** $P<0.01$, *** $P<0.001$.

Table 3 presents the arterial concentrations of plasma amino acids. During exercise significant increases were observed for taurine, glutamine, glycine, alanine, methionine, tyrosine, phenylalanine, lysine, histidine and arginine in all three work periods. Alanine rose most markedly, by 45%, 65% and 120%, respectively, during the three work loads. A significant positive correlation was observed between the arterial levels of alanine and ammonia (r=0·75, P<0·001). The increments for the other amino acids varied between 8% and 30% during the three exercise periods. For alanine, glutamine and histidine the arterial levels were still significantly above basal level at 60 min after exercise. In contrast, the arterial glutamate concentration declined progressively during exercise (−55%, P<0·001) and the serine concentration also decreased significantly at the heaviest work load (−10%, P<0·05). The concentration of glutamate had returned to basal level at 30 min after exercise.

LEG EXCHANGE

In the basal state there was a small, but significant, uptake of ammonia to the leg tissues (−2·4±0·5 μmol/min, Table 2). At the lowest work load the uptake turned into a net release, which increased almost fourfold during the second work load. During the third work load ammonia output from the leg muscles rose further, to 46±15 μmol/min (P<0·01). Thirty minutes after exercise a net release of ammonia was no longer detectable and after 60 min of recovery, an uptake was observed, similar in magnitude to that in the basal state. For lactate, a net release from muscle tissue was demonstrated in the basal state. As could be expected, the release of lactate increased more than 20-fold during exercise (Table 2).

In the basal state there was a net output of 16 amino acids from the leg tissues. The release of alanine and glutamine (17·2±1·0 and 14·3±3·6 μmol/min, respectively) exceeded that of all the other amino acids and accounted for 60% of the total output. Leg alanine release increased significantly during exercise at the second and third work load (47±11 and 153±50 μmol/min, respectively, P<0·05, Fig. 2), while glutamine exchange remained unaltered. For glutamate a net uptake was found in the basal state (9·0±2·0 μmol/min) and this increased significantly during the first work load (19·8±3·6, P<0·05, Fig. 2). The leg exchange of the other amino acids did not change significantly during or after exercise.

SPLANCHNIC EXCHANGE

The splanchnic exchange of ammonia showed an unaltered net uptake of approximately 12–14 μmol/min before and during exercise (Table 2). Immediately after exercise, however, splanchnic ammonia uptake rose transiently to 25·0±5·3 μmol/min (P<0·05). This was followed by a gradual decline, reaching basal levels 30–60 min after exercise. In contrast, the splanchnic uptake of lactate (Table 2) increased continuously during exercise, from 0·23±0·04 mmol/min at rest to 1·05±0·31 mmol/min at the third work load (P<0·05). Immediately after the end of

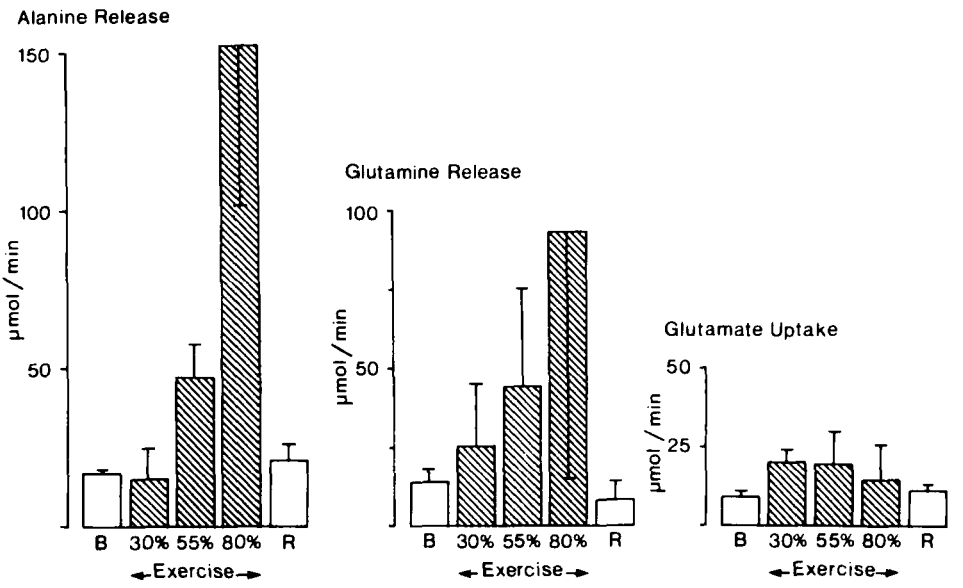

Fig. 2. Leg exchange of alanine, glutamine and glutamate in the basal state (B), during exercise (hatched columns) and during recovery after exercise (R). Mean values±SE are indicated.

exercise the transient rise for ammonia was accompanied by a further increase in the splanchnic uptake of lactate, to 1·67±0·25 mmol/min ($P<0·001$). The lactate uptake then gradually declined but after 60 min it was still significantly above the basal level.

Splanchnic blood-flow decreased during exercise in relation to work load, from a basal level of 1·27±0·12 to 0·40±0·07 l/min after 15 min on the final work load. Simultaneously, the estimated leg blood-flow increased, also in relation to the work load, from 0·49±0·03 l/min in the basal state to 4·74±0·18 l/min.

Discussion

In the resting state, detoxification of ammonia occurs primarily in the liver but a small amount of ammonia uptake has also been observed in skeletal muscle (Bessman & Bradley, 1955). The present results, which demonstrate a net uptake of ammonia by the liver and a small but significant uptake by the legs in the basal state (Table 2), thus confirm previous studies.

The situation during physical exercise is less well understood. The plasma-ammonia concentration is, however, known to increase during exercise. In the present study this rise in plasma-ammonia was curvilinear in relation to work load (Fig. 3) and was already statistically significant at 35% of maximal oxygen uptake. Previous studies have demonstrated a significant accumulation of blood ammonia only during exercise at work loads corresponding to 50–70% or more of maximal oxygen uptake

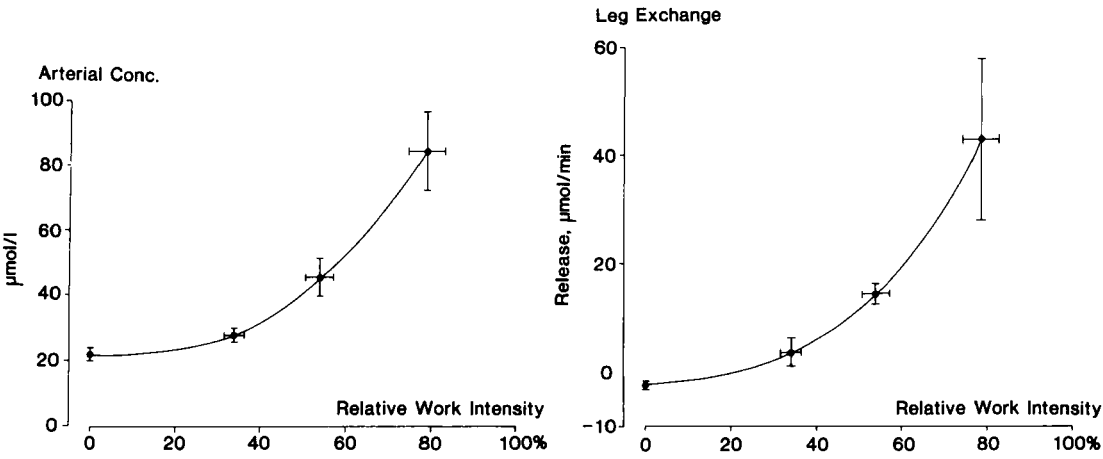

Fig. 3. Arterial concentration of ammonia in relation to relative work intensity (left panel) and leg output of ammonia in relation to relative work intensity. Mean values±SE are indicated.

(Allen & Conn, 1960; Wilkerson *et al.*, 1977; Babij *et al.*, 1983; Maughan & Sadler, 1983; Buono *et al.*, 1984). One possible explanation for this discrepancy is that arterial blood samples were used in the present study whereas venous determinations were used in the previous ones. Although working muscle generates ammonia during exercise, it is conceivable that the non-exercising muscles may continue to take up ammonia, thereby rendering venous blood less suitable than arterial blood for the detection of changes in systemic ammonia fluxes.

During exercise there was a net release of ammonia from the leg tissue. A tendency to this effect was already apparent at the lowest work load (35% of maximal oxygen uptake) and exercise at heavier work loads was accompanied by a curvilinear increase (Fig. 3). Skeletal muscle is the likely site of this ammonia formation, ammonia production being the result of AMP deamination in the purine-nucleotide cycle (Lowenstein, 1972). According to recent reports, ammonia formation is more apparent in the fast-twitch than in the slow-twitch muscle fibres (Meyer *et al.*, 1980; Dudley *et al.*, 1983). During work of rising intensity, the fast-twitch muscle fibres become progressively more activated, which probably explains the curvilinear rather than linear relationship between net ammonia production by leg tissue and work intensity.

The net splanchnic uptake of ammonia remained virtually unchanged during exercise even though splanchnic blood-flow decreased considerably (Table 2). This finding represents the net result of a rising arterial ammonia concentration and a diminishing hepatic blood-flow (−70%), since the fractional extraction of ammonia was unchanged during exercise. This means that, in healthy man, the exercise-induced hyperammonaemia is exclusively an effect of accelerated ammonia formation in

muscle, while no alteration of ammonia metabolism in the liver seems to occur. The transient increase in splanchnic ammonia uptake immediately after cessation of exercise is similarly explained by the rapid rise of splanchnic blood-flow together with a persistently elevated arterial concentration of ammonia in the first 15 min of the recovery period.

As expected, the arterial lactate concentration increased during exercise (Wilkerson *et al.*, 1977; Maughan & Sadler, 1983; Ohno *et al.*, 1983; Babij *et al.*, 1983). Like ammonia, lactate is considered to be formed predominantly in the glycolytic fast-twitch fibres which, to an increasing degree, are activated during work of rising intensity (Meyer *et al.*, 1980; Dudley *et al.*, 1983). This could explain the linear correlation between ammonia and lactate found in the present (Fig. 1) and other studies (Babij *et al.*, 1983).

The accelerated alanine formation in working skeletal muscle, demonstrated in the present as well as previous studies (Felig & Wahren, 1971; Babij *et al.*, 1983; Ohno *et al.*, 1983), could be accounted for by an increased glycogen degradation as well as augmented peripheral uptake and utilization of glucose, which is a major substrate for muscle oxidation during exercise (Bergström & Hultman, 1967; Wahren *et al.*, 1971). Glucose metabolism in skeletal muscle involves the formation of alanine via transamination of pyruvate, alanine is subsequently released to the circulation (Fig. 2) and taken up by the liver, where it is reconverted to glucose (Felig *et al.*, 1970). There was a significant correlation between the arterial concentrations of alanine and ammonia during exercise ($r=0{\cdot}75$, $P<0{\cdot}001$), suggesting that ammonia may have contributed to part of the amino groups used in alanine synthesis. The rise in arterial glutamine concentration during exercise, previously noted also by Babij *et al.* (1983), is of particular interest with regard to the simultaneous decline in glutamate levels (Table 3). Glutamate was taken up by the working leg muscles and this uptake increased significantly during exercise (Fig. 2). It can therefore be assumed that glutamate was converted into glutamine in the muscle tissue, thereby reducing the intracellular elevation of ammonia during exercise. In addition, rising arterial levels for ten other amino acids were observed at all levels of work intensity. Since the increments varied between 8 and 30%, they are only partly attributable to the haemoconcentration that accompanies exercise (maximum 9%, Table 1). The altered amino acid concentrations may possibly be due instead to augmented amino acid catabolism, in turn a possible effect of increased protein breakdown and reduced protein synthesis during exercise (Rennie *et al.*, 1981). After exercise, the whole-body protein synthesis increases again, this time exceeding the breakdown (Rennie *et al.*, 1981), which could explain the rapid normalization of the arterial amino acid pattern (Table 3).

The unaltered urea levels during and after exercise (Table 1) are consistent with a largely unchanged splanchnic uptake of ammonia. In contrast, a rise in blood urea concentration and urea pool size during more prolonged forms of exercise (1–3 h), are reported to occur (Rennie *et al.*, 1980; Haralambie & Berg, 1976).

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