The Purine Nucleotide Cycle

STUDIES OF AMMONIA PRODUCTION BY SKELETAL MUSCLE IN SITU AND IN PERFUSED PREPARATIONS

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Ammonia production by hind limbs of rat was studied in perfused preparations during rest, exercise, and hypoxia, and while the perfusate contained epinephrine or cyanide. Ammonia production by hind limbs was also studied in situ during rest and exercise. Strong correlations were observed between ammonia, IMP, and lactate formation. Adenylosuccinate was not present in detectable amounts in resting muscle (~1 nmol/g dry weight) but it appeared and rose sharply in exercising muscle, and then declined during recovery. The maximum found was about 18 nmol/g dry weight. When IMP accumulation exceeded 2.8 pmol/g dry weight, the formation of adenylosuccinate diminished, presumably because of an inhibition of adenylosuccinate synthetase by excess substrate.

Exercise resulted in a greatly increased output of ammonia and a decreased output of alanine and glutamine. The tissue contents of aspartate and glutamate were decreased, while that of alanine was increased. The content of malate increased 3-fold during exercise.

Epinephrine, hypoxia, and cyanide each caused an increased output of ammonia at the expense of the amino acid content of the tissue. These results provide evidence for the operation of the purine nucleotide cycle in skeletal muscle under various conditions that are associated with an increased rate of glycolysis.

Extracts of skeletal muscle produce ammonia from aspartate under conditions that mimic muscle doing work. The conversion of aspartate to fumarate and ammonia occurs via the purine nucleotide cycle, which consists of the reactions catalyzed by adenylate deaminase, adenylosuccinatase, and adenylosuccinate (1, 2). In the present paper we report a study of ammonia production and associated metabolic changes in intact skeletal muscle of rat under various conditions. Exercise causes a drop in total adenine mononucleotides that is accompanied by accumulation of ammonia, IMP, and adenylosuccinate. The levels of IMP and adenylosuccinate decline again during recovery. The time course of these changes is consistent with the operation of the purine nucleotide cycle in skeletal muscle.

MATERIALS AND METHODS

Animals - Male rats of the Sprague-Dawley strain and laboratory chow were obtained from Charles River Breeding Laboratories, Wilmington, Mass. The animals received food and water ad libitum, and weighed 180 to 230 g at the time of use.

Perfusion Technique - The perfusion apparatus, anaesthetization, and surgical procedure were as described by Ruderman et al. (3) with minor modifications. The spermatic artery and vein were ligated and the testis and seminal vesicles were removed. The perfusate was pumped from a central mixing reservoir through a nylon filter into a water-jacked oxygenator maintained at 38° (P. A. Brooks, Witney, Oxon, OX8 5HT, England). The gas phase oxygenator was gassed with humidified 95% O₂, 5% CO₂ at a flow rate of 300 ml/min. From the oxygenator the perfusate was sent to the preparation using a multichannel pump (Buchler Instruments, Fort Lee, N. J. 07024). The flow rate was approximately 12 ml/min. The entire apparatus and animal were enclosed in a cabinet maintained at 38°.

The perfusate consisted of Krebs-Ringer bicarbonate buffer (4) containing 3% bovine serum albumin (Fraction V, fatty-acid poor, Miles Laboratory, Kankakee, Ill.). Washed bovine erythrocytes (hematocrit 20%, hemoglobin 6 to 7 g/100 ml), substrates, and hormones. Endogenous lactate (0.3 to 0.6 mM) was always present after washing and diluting the erythrocytes; because of this, pyruvate was added initially to obtain a [lactate]/[pyruvate] ratio of approximately 10. The pH of the perfusion medium was monitored and kept between 7.35 and 7.40. The initial volume of perfusion medium was 150 ml. The first 20 ml of perfusate that passed out of the venous drainage were discarded; thereafter the perfusate was recirculated. At the end of each perfusion a portion of the right musculature, mainly gastrocnemius and posteriorinferior thigh muscle, was rapidly frozen in situ with aluminum clamps cooled in liquid nitrogen.

Exercise Studies - The sciatic nerve of the perfused hind limb was exposed and a Dastre's electrode (Palmer Co., London, England) was attached around the nerve in its gluteal course. The leg was fixed to the perfusion platform at the ankle with adhesive tape. Isometric contractions were induced by square-wave electrical pulses from a stimulator (Grass Instruments, Quincy, Mass.). The pulses were applied for a duration of 10 ms with a frequency of 1, 4, or 6/s. The voltage was usually maintained between 0.5 and 10 V; however, at times it was necessary to increase the voltage to as much as 50 V in order to maintain vigorous contractions at high frequencies of stimulation. The intensity of the contractions was assessed by palpation of the exercising muscles. Approximately one-third to one-half of the muscle tissue of the hindquarter contracted when the nerves were stimulated.

Composition of Perfused Tissue and Expression of Results - Analyses of a series of 15 perfusions with rats weighing 125 to 280 g showed that the perfused material consisted of 81% soft tissue (mainly...
Ammonia Production by Skeletal Muscle

Adenylosuccinate in tissue extracts was measured on a Perkin-Elmer model 556 double wave length spectrophotometer by following absorbance change at 292 nm minus absorbance changes at 310 nm using an E_M of 10.0 (2). The assay mixture contained 50 mm triethanolamine, pH 7.4, 1 mm EDTA, 0.6 ml of tissue extract, and about 0.1 unit of enzyme, in a total volume of 2.0 ml. Known amounts of adenylosuccinate were recovered quantitatively when added to tissue extracts and to the frozen tissue powders prior to extraction.

Adenylosuccinate in neutralized tissue extracts stored at -20°C was stable for at least 6 months.

Results

Ammonia, Alanine, and Glutamine Output by Perfused Muscle—Resting perfused hind limbs slowly released ammonia into the perfusate. The rate of release of ammonia was not affected by glucose or insulin (Table I). The ammonia released was produced by the muscle, and was not due to washout of pre-existing intracellular ammonia, since the muscle content of ammonia was maintained or increased during the course of the perfusion. For example, in a set of control perfusions the ammonia content of resting muscle was 0.47 ± 0.07 (n = 5) and 0.83 ± 0.13 (n = 4) μmol/g dry weight after 10 and 45 min of perfusion, respectively. The initial concentration of ammonia in the perfusate was between 50 and 100 μM. It was contributed in part by the erythrocytes and reagents used for preparing the perfusate. Arterial blood of humans and rats normally contains 25 to 75 μM ammonia (20-22). When the initial concentration of ammonia in the perfusate was raised to between 0.20 and 12 mm by adding ammonium chloride, resting muscle preparations always took up ammonia, in accord-
in the presence of methionine sulfoximine was 47 μmol over 2 h, which is equal to a production rate of 0.39 μmol/30 g/min. This result is in close agreement with the increment in ammonia plus glutamine obtained in the absence of methionine sulfoximine (0.43 μmol/30 g/min).

Addition of 5 mM aspartate, glutamate, or leucine, or of 2 mM glutamine to the perfusate did not alter the rate of ammonia output by resting muscle (data not shown)

**Effect of Exercise on Ammonia, Nucleotide, Nucleoside, and Hypoxanthine Content of Perfused Skeletal Muscle**—The ammonia and IMP contents of muscle increased upon exercise, in a manner that was related to the severity of the exercise (Table I). There was no stoichiometry between the changes in ammonia and IMP contents, and none was to be expected since ammonia but not IMP was diffusing from the tissue. Exercise resulted in a large decrease in the content of creatine phosphate, a proportionately smaller decrease in ATP, and a small increase in the content of AMP. Similar changes in creatine phosphate and ATP contents have been described previously (1, 16, 29-31) and are repeated here simply to facilitate comparison.

Exercise led to decreases in the total adenine mononucleotide pool of 7, 19, and 32% for 1, 4, and 6 shocks/s,

### Table I

**Effect of exercise, epinephrine, hypoxia, cyanide, and insulin on ammonia, alanine, and glutamine output by perfused muscle**

Metabolite outputs into the perfusate are expressed as means ± S.E. Outputs of metabolites were linear with time over both control and test periods. The number of perfusions is given by n. The control period for Groups a, b, and c was 45 min. In the case of Groups d, e, and f the initial control period lasted 15 min, after which insulin was added and the control period was continued for another 15 min. The exercise period was then started; it lasted 15 min for Groups d and e, and 30 min for Group f. In the case of Groups g, h, and i the control period lasted 30 min, and the test period lasted an additional 30 min. The rates quoted are the averages of those observed over the entire control period in the case of Groups a, b, and c, and over the test period only in the case of Groups d through i. The perfusate used for Group a contained no added glucose, for all other groups it contained 6 mM glucose initially. Insulin, 5 milliunits/ml, was added at the start of the control period for Group c, and 15 min after the start of the control period for Groups d, e, and f.

<table>
<thead>
<tr>
<th>Controls</th>
<th>Exercise</th>
<th>Epinephrine (30 μm)</th>
<th>Hypoxia</th>
<th>Cyanide (1 mM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>n=5</td>
<td>n=3</td>
<td>n=3</td>
<td>n=3</td>
<td></td>
</tr>
<tr>
<td>Ammonia output</td>
<td>Alanine output</td>
<td>Glutamine output</td>
<td>Glucose uptake</td>
<td>Lactate output</td>
</tr>
<tr>
<td>0.073 ± 0.018</td>
<td>0.059 ± 0.019</td>
<td>0.079 ± 0.017</td>
<td>0.206 ± 0.020</td>
<td>0.086 ± 0.017</td>
</tr>
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<td>0.206 ± 0.020</td>
<td>0.086 ± 0.017</td>
</tr>
</tbody>
</table>

### Table II

**Effect of exercise, epinephrine, and hypoxia on content of selected metabolites of perfused muscle**

Metabolite contents are expressed as means ± S.E. The lower case letter designation of the perfusion groups identifies identical groups in Tables I and II. The number of preparations analyzed is given by n. Only five samples each from perfusion Groups b and c were used for metabolite analyses. All perfusions were started with 6 mM glucose. Where indicated, 5 milliunits of insulin/ml were added at the start of the control period. For other details see legend to Table I.

The average wet weight/dry weight ratio was 4.68.

<table>
<thead>
<tr>
<th>Controls</th>
<th>Exercise</th>
<th>Epinephrine</th>
<th>Hypoxia</th>
</tr>
</thead>
<tbody>
<tr>
<td>n=5</td>
<td>n=3</td>
<td>n=3</td>
<td>n=3</td>
</tr>
<tr>
<td>Creatine phosphate</td>
<td>ATP</td>
<td>ADP</td>
<td>AMP</td>
</tr>
<tr>
<td>81.0 ± 4.17</td>
<td>24.4 ± 1.1</td>
<td>2.78 ± 0.13</td>
<td>0.315 ± 0.018</td>
</tr>
<tr>
<td>76.0 ± 5.5</td>
<td>26.6 ± 0.7</td>
<td>3.71 ± 0.27</td>
<td>0.38 ± 0.01</td>
</tr>
<tr>
<td>43.8 ± 3.8</td>
<td>23.8 ± 0.4</td>
<td>3.98 ± 0.66</td>
<td>0.75 ± 0.062</td>
</tr>
<tr>
<td>30.2 ± 2.0</td>
<td>20.2 ± 0.78</td>
<td>4.07 ± 0.41</td>
<td>0.675 ± 0.090</td>
</tr>
<tr>
<td>25.5</td>
<td>16.9</td>
<td>3.49</td>
<td>0.489</td>
</tr>
<tr>
<td>81.3 ± 1.1</td>
<td>5.85 ± 0.05</td>
<td>3.52 ± 0.25</td>
<td>5.94 ± 0.069</td>
</tr>
</tbody>
</table>

* Only two samples were analyzed from each group.
respective. The adenine nucleotides lost were largely accounted for by the IMP formed. Adenylosuccinate was not detected in the resting preparations (< I nmol/g dry weight) and was only detected in some of the exercised preparations. Adenylosuccinate was not counted for by the IMP formed. Adenylosuccinate was not detected under our assay conditions, observed for IMP and ATP. Low but significant amounts of IMP and ATP were found in resting muscle. (Table III).

*Effect of Exercise and Exercise Followed by Recovery on Content of Selected Metabolites of Muscle in Situ*

Metabolite contents are expressed as means ± S.E. The muscle was stimulated using pulses of 10 ms at a frequency of 5/s, as described under "Materials and Methods." The number of animals analyzed is given by n. (Only two samples in each group were analyzed for inosine and hypoxanthine.) The average weight/dry weight ratio was 4.97.

Table III

<table>
<thead>
<tr>
<th>Metabolite</th>
<th>Resting control</th>
<th>Exercise</th>
<th>Recovery period after exercise</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n = 5</td>
<td>n = 5</td>
<td>2.5 min, n = 4</td>
</tr>
<tr>
<td>Creatine phosphate</td>
<td>84.0 ± 3.6</td>
<td>28.7 ± 3.0</td>
<td>70.4 ± 4.2</td>
</tr>
<tr>
<td>ATP</td>
<td>25.9 ± 1.7</td>
<td>18.9 ± 0.8</td>
<td>20.7 ± 1.0</td>
</tr>
<tr>
<td>ADP</td>
<td>3.12 ± 0.21</td>
<td>3.31 ± 0.15</td>
<td>2.67 ± 0.12</td>
</tr>
<tr>
<td>AMP*</td>
<td>0.48 ± 0.048</td>
<td>0.324 ± 0.028</td>
<td>0.395 ± 0.023</td>
</tr>
<tr>
<td>Sum of AMP, ADP, and ATP</td>
<td>28.5 ± 1.3</td>
<td>22.7 ± 0.8</td>
<td>24.0 ± 1.1</td>
</tr>
<tr>
<td>IMP</td>
<td>0.167 ± 0.014</td>
<td>2.97 ± 0.46</td>
<td>2.15 ± 0.37</td>
</tr>
<tr>
<td>Adenylosuccinate</td>
<td>&lt;0.001</td>
<td>0.017 ± 0.003</td>
<td>0.021 ± 0.004</td>
</tr>
<tr>
<td>Sum of AMP, ADP, and IMP, and ATP</td>
<td>28.7 ± 1.3</td>
<td>25.7 ± 0.6</td>
<td>26.2 ± 0.74</td>
</tr>
<tr>
<td>Inosine</td>
<td>0.045</td>
<td>0.0302</td>
<td>0.121</td>
</tr>
<tr>
<td>Hypoxanthine</td>
<td>0.019</td>
<td>0.089</td>
<td>0.025</td>
</tr>
<tr>
<td>Ammonia</td>
<td>0.932 ± 0.182</td>
<td>1.2 ± 0.32</td>
<td>1.41 ± 0.13</td>
</tr>
<tr>
<td>Aspartate</td>
<td>1.40 ± 0.22</td>
<td>1.87 ± 0.25</td>
<td>1.42 ± 0.40</td>
</tr>
<tr>
<td>Glutamate</td>
<td>5.93 ± 0.53</td>
<td>3.73 ± 0.31</td>
<td>4.04 ± 0.57</td>
</tr>
<tr>
<td>Glutamine</td>
<td>15.9 ± 1.0</td>
<td>14.1 ± 0.7</td>
<td>14.2 ± 1.3</td>
</tr>
<tr>
<td>Alanine</td>
<td>8.24 ± 0.89</td>
<td>7.84 ± 0.63</td>
<td>7.08 ± 0.80</td>
</tr>
<tr>
<td>Lactate</td>
<td>4.82 ± 1.59</td>
<td>25.3 ± 3.1</td>
<td>15.0 ± 2.8</td>
</tr>
</tbody>
</table>

I and II. Thus, the increases in ammonia and amide nitrogen are largely balanced by decreases in aspartate, glutamate, and alanine.

Recently, a report appeared in which epinephrine was shown to diminish the output and content of alanine and glutamine by epitochlaris muscle of rat incubated in vitro (32).

*Glycolysis by Perfused Muscle—Exercise Stimulated Glucose Uptake and Lactate Output* (Table I, compare Group c with Groups d, e, and f). The \[lactate\]/\[pyruvate\] ratio in the perfusate was 11 for muscle at rest; it rose to 15, 17, and 27 during exercise induced by 1 and 4 shocks/s, respectively. These ratios do not agree with ratios of lactate and pyruvate production rates (Table I) because the rates are calculated from initial and final perfusate concentrations of lactate and pyruvate. At rest oxygen consumption was 12.7 pmol/30 g of muscle/min; it rose to 17.5 and 25.3 pmol/30 g of muscle/min during exercise induced by 1 and 4 shocks/s.

Addition of 25 nM epinephrine increased lactate and pyruvate output, and caused a small increase (from 11 to 14) in the \[lactate\]/\[pyruvate\] ratio. At the concentration used, epinephrine did not cause vasoconstriction, but it tended to do so at

1 These changes were obtained from the data in Tables I and II as follows (output is expressed as \(\mu\)mol/30 g fresh weight/30 min and content as \(\mu\)mol/30 g fresh weight):

<table>
<thead>
<tr>
<th>Metabolite</th>
<th>Output Change</th>
<th>Content Change</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ammonia</td>
<td>12.7</td>
<td>+6.60</td>
</tr>
<tr>
<td>Glutamine</td>
<td>11.6</td>
<td>+4.49</td>
</tr>
<tr>
<td>Ammonia plus amide N</td>
<td>24.3</td>
<td>+11.1</td>
</tr>
<tr>
<td>Aspartate</td>
<td>-5.0</td>
<td>-5.0</td>
</tr>
<tr>
<td>Glutamate</td>
<td>18.0</td>
<td>18.0</td>
</tr>
<tr>
<td>Alanine</td>
<td>4.3</td>
<td>-26.4</td>
</tr>
<tr>
<td>Asp + Glu + Ala</td>
<td>-49.4</td>
<td>-45.1</td>
</tr>
<tr>
<td>Corrected for loss of glutamate into glutamine</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Thus only 35.4 - 22.0 - 6.4 pmol of the ammonia plus amide nitrogen output cannot be accounted for in terms of the amino acids measured.
higher concentrations. Hypoxia and cyanide increased glucose uptake and lactate output. The [lactate]/[pyruvate] ratio was 4.97, it can be calculated that 2.3, and 9 μmol of IMP/g of dry weight correspond to concentrations of 0.8, 1.2, and 3.6 mM. The maximum activities of adenylosuccinate synthetase and adenylosuccinase in hind leg of rat are about the same (33). High [IMP] inhibits adenylosuccinate synthetase. The inhibition is competitive with respect to GTP, and the Kᵢ for IMP is about 2 mM. An intracellular concentration of 3.6 mM IMP is therefore sufficient to cause a substantial inhibition of adenylosuccinate synthetase.

Effect of Exercise on Malate and Citrate Content of Hind Limb—The malate content of hind limbs in situ and in perfused preparations rose from 0.373 ± 0.012 (n = 8) μmol/g dry weight in resting controls to 1.120 ± 0.060 (n = 6) μmol/g dry weight after 15 min of exercise. The citrate content did not change significantly in the same experiments (0.71 ± 0.08 μmol/g dry weight). The most probable source of the additional malate is the purine nucleotide cycle, the operation of which results in a net conversion of aspartate to fumarate and malate (1, 2).
The activities of adenylosuccinate synthetase and adenylosuccinate in skeletal muscle of rat are 0.74 and 0.61 μmol/g fresh weight/min, respectively, at 38°C (23). These activities can account for the rate of disappearance of IMP and the rate of appearance of adenylosuccinate and AMP. In addition to the inhibition by IMP, adenylosuccinate synthetase is inhibited strongly by GDP, and to a lesser extent by AMP, adenylosuccinate, and orthophosphate (1, 2, 39, 40). The Km values for IMP, GTP, and aspartate are 200, 10, and 300 μM, respectively. Adenylosuccinate from mammalian skeletal muscle has a Km for adenylosuccinate of about 9 μM (41).

ADP and AMP showed little or no change between rest, exercise, and recovery from exercise. The average ADP and AMP contents shown in Table III are 2.96 ± 0.08 and 0.52 ± 0.09 μmol/g dry weight, which correspond to 0.596 and 0.105 μmol/g wet weight, respectively. Skeletal muscle actin contains one tightly bound molecule of ADP per actin monomer; the binding is so tight that the ADP is not available to the pool of free ADP. The content of actin monomer is about 0.6 μmol/g fresh weight (42). This is about the same as the total ADP content. The standard error of these determinations is too great to use the total and bound ADP to calculate the capacity of adenylate deaminase even at the very low concentration of AMP calculated to be freely available. This implies that the activity of adenylate deaminase is under control. The regulation of adenylate deaminase is complex; suffice it to say here that the muscle enzyme is activated by ADP and alkali metal ions and is inhibited by GTP and ATP (1, 45).

The equilibrium constants for 38°C used in the calculations were those given by Kuby and Noltmann (43). In some cases they are the same as those used by McGilvary and Murray (42). The method of calculating ADP and AMP concentrations was that of McGilvary and Murray (42). In the equations given on page 5845 in Ref. 42, the concentration of ADP in terms of ATP should read

\[
[ADP] = \frac{d[ATP^*]}{2K_{pm}} \left[ \left( \frac{d^2 - 4K_{pm} + 4K_{pm} [ATOTL]}{[ATP^*]} \right)^{1/2} - d \right]
\]

The equilibrium constants for 38°C used in the calculations were those given by Kuby and Noltmann (43). In some cases they are the same as those used by McGilvary and Murray (42), but all are quoted here for clarity.

\[
K_1 = [ATP^*]/[ATP] = 7.94 \times 10^6 \text{ M}^{-1}
\]

\[
K_2 = [HADP'/H][ADP'] = 5.01 \times 10^3 \text{ M}^{-1}
\]

\[
K_3 = [HAMP'/H][AMP'] = 2.82 \times 10^3 \text{ M}^{-1}
\]

\[
K_4 = [HCrP'/H][CrP'] = 3.16 \times 10^3 \text{ M}^{-1}
\]

\[
K_5 = [MgATP'/Mg][ATP'] = 7.0 \times 10^6 \text{ M}^{-1}
\]

\[
K_6 = [MgADP'/Mg][ADP'] = 3.0 \times 10^6 \text{ M}^{-1}
\]

\[
K_7 = [MgAMP]/[Mg][AMP] = 4.9 \times 10^4 \text{ M}^{-1}
\]

\[
K_8 = [MgCrP'/Mg][CrP'] = 2.4 \times 10^4 \text{ M}^{-1}
\]

\[
K_9 = [AMP]/[ATP][ADP'] = 0.364
\]

\[
K_{10} = [ATP^*]/[H][ATP] = 1.52 \times 10^6 \text{ M}^{-1}
\]

Total adenine nucleotides used in the calculations were taken to be the contents of ATP + ADP + AMP less 0.6 μmol/g fresh weight (the amount bound to actin). The free Mg²⁺ concentration used was 5 \times 10^{-4} \text{ M} (44).

The contents of freely available AMP of 0.12 to 0.56 nmol/g fresh weight are equivalent to concentrations of about 0.24 to 1.1 μM (assuming that the intracellular water is 50% of the fresh weight, and that this AMP is evenly distributed throughout the intracellular water). Adenylate deaminase of rat skeletal muscle has an activity of about 200 pmol/min/gram weight; this activity is about 0.094 nmol/g fresh weight, respectively, assuming an intracellular pH of 6.6. After 2.5 min of recovery from exercise the contents of freely available ADP and AMP fall back to 0.084 nmol/g fresh weight, respectively, assuming an intracellular pH of 6.8. The lack of change in the total AMP content is thus explained in terms of most being bound to actin and being unavailable. The ADP that is freely available accounts for only 0.11 and 0.50% of the total AMP in muscle at rest and during vigorous exercise, respectively.

If the myokinase reaction is indeed in equilibrium, as is assumed in the above calculations, then freely available AMP accounts for only 3.2 and 5.4% of the total ADP in muscle at rest and during vigorous exercise, respectively. Thus virtually all of the total AMP is not available. Unlike ADP, there is no readily identifiable protein to which most of the AMP binds tightly. Perhaps muscle has a compartment which stores most of the total AMP in such a manner that it is not available to myokinase or adenylyl deaminase.

References

1. Lowenstein, J. M. (1972) Physiol. Rev. 52, 382-414
Ammonia Production by Skeletal Muscle

The purine nucleotide cycle. Studies of ammonia production by skeletal muscle in situ and in perfused preparations.

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