AMP Deamination Delays Muscle Acidification during Heavy Exercise and Hypoxia*

Bernard Korzeniewski

From the Faculty of Biotechnology, Jagiellonian University, 30-387 Kraków, Poland

Mechanical work of muscle is driven by the hydrolysis of ATP to ADP (and P). Under most conditions the total adenine nucleotide pool (ATP + ADP + AMP) remains constant, and therefore ADP must be reconverted to ATP in order to maintain energy delivery for exercise. Three main processes are responsible for ATP resynthesis: conversion of PCr to creatine by creatine kinase takes place at the onset of exercise, anaerobic glycolysis (AG) is an important ATP supplier during intensive short term muscle work, and oxidative phosphorylation (OP) is a major source of ATP in most muscles under most conditions. Additionally, during heavy exercise two molecules of ADP may be converted to one molecule of ATP and one molecule of AMP (reaction catalyzed by adenylate kinase) that is further converted to IMP (reaction catalyzed by AMP deaminase) (1–5). The concerted action of adenylate kinase and AMP deaminase leads to production of some additional ATP and consumption of some additional ADP but at the same time to a decrease in the total adenine nucleotide pool. This is a kind of debt run up by muscle during exercise, and it is given back during muscle recovery after exercise when the size of the adenine nucleotide pool slowly returns to its initial value. The reduction in the total adenine nucleotide pool during short term heavy exercise in skeletal muscle may amount to 10, 20, or even 50% (6–12). In ischemic heart the decrease in the total adenine nucleotide pool caused by AMP deamination (manifesting itself by a decrease in ATP concentration) is also observed (13–15). A general scheme of the adenine nucleotide metabolism in heavily working and/or ischemic skeletal muscle/heart is presented in Fig. 1.

The stoichiometry of the adenylate kinase + AMP deaminase system is one ATP molecule produced and two ADP molecules consumed per one IMP molecule produced. The net effect of all the reactions producing and consuming ATP that causes the reduction in the total adenine nucleotide pool occurs mostly at the cost of ATP concentration (6). Although ATPases (in muscle mostly actomyosin-ATPase and calcium-ATPase) produce and consume the same amount of ADP and ATP, respectively, the adenylate kinase + AMP deaminase system consumes more ADP than produces ATP. Therefore, for the ATP production/consumption and ADP production/consumption, both cannot be well balanced at the same time. Absolute (in mM) changes in [ADP] are over 1 order of magnitude smaller than absolute changes in [ATP] (6) (ADP is more important for the regulation of metabolism than ATP, and therefore [ADP] is kept more constant than [ATP] when the total pool of adenine nucleotides decreases; this is not the case during rest-to-work transition in skeletal muscle, where elevated [ADP] stimulates ATP production). In other words, the ADP production/consumption is much better balanced than ATP production/consumption. Therefore, in the present paper (see Figs. 2–7) ADP balance will be mostly considered rather than ATP balance.

The physiological role of AMP deamination is not certain. It has been postulated that this process helps to keep a possibly high value of the ATP/ADP ratio and phosphorylation potential (4, 5). However, a similar effect could be achieved by an additional activation of anaerobic glycolysis, the rate of which is not limited, as the rate of oxidative phosphorylation, by oxygen supply. Other authors postulate that the adenylate kinase + AMP deaminase system prevents significant ADP and/or AMP accumulation (6, 17). It was demonstrated in a recent study (16) that in skeletal muscle lacking adenylate kinase [ADP] rises to a very high level during heavy exercise. The progressive accumulation of AMP deamination products, IMP and NH3, has been proposed to cause the development of fatigue (17). However, essentially no correlation between fatigue and IMP level was observed (18). Creatine depletion and creatine kinase deficiency lower the AMP deaminase level (19, 20), but the physiological role of this phenomenon is unclear. People with AMP deaminase deficiency are much more susceptible to fatigue than healthy individuals (21), which suggests some role of this enzyme in fatigue resistance.

The present theoretical study suggests that the role of AMP deamination is to decrease the rate of ATP production by anaerobic glycolysis through diminishing the increase in the concentration of effective glycolysis activators, ADP and AMP, during heavy exercise. This delays muscle acidification and thus lengthens the duration of exercise and/or diminishes damages of muscle cells.
AMP Deamination and Muscle pH

**THEORETICAL PROCEDURES**

The computer model of oxidative phosphorylation and anaerobic glycolysis in skeletal muscle developed previously (22), being a modification of the model of oxidative phosphorylation in skeletal muscle (23), was used for the *in silico* studies carried out in the present paper. Within this model a simple phenomenological kinetic description of glycolysis is used as shown in Equation 1.

\[
V_{GLYC} = k_{GLYC} \cdot ADP_{le} \cdot \left(\frac{H^{+}}{H_{\text{rest}}^{+}}\right)
\]  

(Eq. 1)

where \(ADP_{le}\) is free (not bound to proteins), total (magnesium-free and magnesium-bound) cytosolic ADP concentration; \(H_{\text{rest}}^{+}\) is resting proton concentration (\(= 10^{-7}\) M); \(H^{+}\) is current proton concentration, and \(k_{GLYC}\) is a rate constant. The linear dependence of the glycolytic flux on [ADP] (including implicitly the dependence on [AMP]) was extracted (22) from the comprehensive model of glycogenolysis and glycolysis developed by Lambeth and Kushmerick (24). The dependence of ATP production by oxidative phosphorylation on [ADP] within the model used in the present paper is saturable, with the half-saturating ADP concentration equal to about 25 \(\mu\)M. The complete description of the computer model of oxidative phosphorylation + anaerobic glycolysis in skeletal muscle used in the present study is given in Ref. 22 and can be accessed at the following web site: awe.mol.uj.edu.pl/~benio/.

In this work some modifications were introduced to the model developed in Ref. 22. First of all, a very simple kinetic description of AMP deaminase has been introduced; a constant rate of AMP deamination was assumed as shown in Equation 2.

\[
V_{DEAM} = c
\]  

(Eq. 2)

where \(c\) is equal to 0.5 and 1 \(\text{mM/min}\) for moderate and high AMP deaminase activity, respectively. These values were chosen to reflect approximately the rates of adenine nucleotide depletion encountered in different experimental studies (6–12). Several *in vitro* activators and inhibitors of AMP deaminase have been postulated (1, 7), including ADP, AMP, H\(^+\), P\(_i\), ATP, and GTP. Nevertheless, the role of these effectors under physiological conditions remains controversial (10, 25, 26). Because the topic of the present study is the effect of AMP deamination on muscle energetics and not the regulation of AMP deaminase, the simple kinetic description appearing in Equation 2 seems to be entirely sufficient. The linear decrease in the total adenine nucleotide pool with time resulting from Equation 2 reflects well the experimental results (6).

Additionally, the dependence of the stoichiometry (s) of proton production by the Lohmann reaction (\(\text{PCr} \rightarrow \text{creatinine} + \ P_i + \ sH^{+}\)) on cytosolic pH (pH\(_{j}\), extracted from Ref. 27, was introduced, where \(s = 0.63 - (\text{pH}_{j} - 6.0) \times 0.43\).

In computer simulations the transition from rest to heavy exercise, the energy demand (rate constant of ATP usage) was elevated 100 times.

It was postulated previously that both oxidative phosphorylation (28, 29) and glycolysis (22) must be directly activated during rest-to-work transition by some external cytosolic factor/mechanism in order to explain numerous experimental data, this is the so-called parallel-activation mechanism. Therefore, the rate constants of oxidative phosphorylation complexes and glycolysis block were also increased in computer simulations at the onset of exercise as in Ref. 22; oxidative phosphorylation was activated 100\(^{0.35}\) times and glycolysis was activated 100\(^{0.9}\) times.

In absolute units, in computer simulations ATP usage was increased from 0.73 \(\text{mM/min}\) (2.9 \(\mu\)mol/g dry weight/min) at rest to 73 \(\text{mM}\) (292 \(\mu\)mol/g dry weight/min) during heavy exercise. This resulted in an increase in \(\text{VO}_{2}\) from 0.3 \(\text{mL/min}\) (1.2 \(\mu\)mol/g dry weight/min) to about 9–11 \(\text{mL/min}\) (36–44 \(\mu\)mol/g dry weight/min) (compare with Ref. 23). The maximal \(\text{VO}_{2}\) in human skeletal muscle is 16 \(\text{mL/min}\) during single muscle exercise (23, 30, 31) and about two times lower during whole body exercise (e.g., cycling) (23, 32, 33) (the difference is probably because of oxygen supply limitations (32)).

It is worth emphasizing that the 100-fold increase in ATP usage caused a 70–90-fold increase in ATP supply by oxidative phosphorylation but only a 30–40-fold increase in \(\text{VO}_{2}\), because in resting muscle over 50% of oxygen consumption is because of proton leak and not ATP consumption (34, 35) and because some fraction (7–28%) of ATP production is taken over by anaerobic glycolysis during heavy exercise. The significant contribution of proton leak in rest to standard metabolic rate is related to its thermogenic function in warm-blooded animals (34). A proton leak results (within the model) in a phenomenological ATP/O\(_{2}\) ratio of about 2.5 at rest, although the model predicts a mechanistic ATP/O\(_{2}\) ratio of about 5.7. As discussed elsewhere (34, 36, 37), higher phenomenological ATP/O\(_{2}\) ratios measured using \(^{31}\)P NMR at rest may be significantly overestimated. In fact, it is commonly thought that oxidative phosphorylation in resting muscle is near state 4, in which the phenomenological ATP/O\(_{2}\) ratio by definition equals 0, and not in state 3, in which phenomenonological ATP/O\(_{2}\) approaches the mechanistic ATP/O\(_{2}\). Nevertheless, during heavy exercise the relative contribution of proton leak to \(\text{VO}_{2}\) is negligible, because in these conditions oxygen is mostly consumed for greatly elevated ATP synthesis by oxidative phosphorylation, and a decreased \(\Delta p\) inhibits proton leak. Therefore, the relative intensity of proton leak at rest is not very important for the simulations carried out in the present theoretical study.

The model involves explicitly only ATP usage and not mechanical work or thermodynamic energy balance. Therefore, neither phosphorylation efficiency nor contraction coupling efficiency (38) is taken into account (these efficiencies are implicitly assumed to be constant). The only way in which the mechanical work and/or efficiency may affect the system taken into account explicitly within the model is through changing the ATP usage during exercise. Therefore, a decrease (down-regulation) in the mechanical work would decrease ATP usage, although a decrease in the efficiency would increase ATP usage for a given mechanical work intensity. In the computer simulations shown in Figs. 2–6, ATP usage during muscle work was kept constant. Therefore, some additional computer simulations were made in which ATP usage either gradually decreased or increased during exercise (theoretical results not shown). A decrease in ATP usage slowed down and diminished the decrease in the ATP/ADP ratio and muscle acidification, whereas an increase in ATP usage had the opposite effect. However, in both cases the decrease in the total adenine nucleotide pool had a similar effect as for constant ATP usage, and muscle acidification was significantly delayed. Therefore, changes in mechanical work and/or efficiency do not affect the general effect of AMP deamination on the system.
The simulations show what would be the values of these parameters after 4 min if the exercise was not terminated earlier because of fatigue.

| Conditions               | pH    | ATP/ADP |
|-------------------------|-------|---------|
| Normoxia                |       |         |
| No AMP deamination      | 6.46  | 131     |
| Low AMP deamination     | 6.52  | 118     |
| High AMP deamination    | 6.60  | 96      |
| Hypoxia                 |       |         |
| No AMP deamination      | 5.87  | 19      |
| High AMP deamination    | 6.06  | 15      |

TABLE 2
Simulated contribution (in %) of different processes to ADP consumption after 4 min of heavy exercise for different AMP deamination intensities at normoxia and hypoxia

100% corresponds to 73 mM/min. The simulations show what would be the values of these parameters after 4 min if the exercise was not terminated earlier because of fatigue. CK indicates creatine kinase; AK indicates adenylate kinase; AMP-d indicates AMP deaminase.

| Conditions               | CK    | OP    | AG    | AK + AMP-d |
|-------------------------|-------|-------|-------|------------|
| Normoxia                |       |       |       |            |
| No AMP deamination      | 0.4   | 87.7  | 11.9  | 0          |
| Low AMP deamination     | 0.4   | 88.4  | 9.8   | 1.3        |
| High AMP deamination    | 0.8   | 89.3  | 7.3   | 2.6        |
| Hypoxia                 |       |       |       |            |
| No AMP deamination      | 0.1   | 72.3  | 27.5  | 0          |
| High AMP deamination    | 0.2   | 75.8  | 21.1  | 2.6        |

Only free (not bound to proteins) ADP is taken into account in the model (22, 23) used for computer simulations in this study. ADP bound to actomyosin dissociates very slowly (39) and therefore can be treated as a completely separate pool that is not effectively exchangeable with the free cytosolic pool. This assumption is confirmed by the observation (6) that changes in free ADP and total ADP during the rest-to-work transition are roughly similar, suggesting that the bound ADP pool remains approximately constant. Therefore, only free ADP enters the total adenine nucleotide pool in the computer simulations carried out in this theoretical study. Both magnesium-bound and magnesium-free forms of ATP, ADP, and AMP are taken into account within the discussed computer model (22, 23). In simulations with normoxia, the saturating oxygen concentration was used (240 μM), although in simulations with hypoxia the oxygen concentration was set at 2 μM.

THEORETICAL RESULTS

Computer simulations were carried out for three AMP deamination intensities (none, low, and high AMP deamination intensity) and for two oxygen saturation levels (normoxic and hypoxic conditions). The theoretical results are presented in Figs. 2–6. In all cases the intensity of ATP usage and ADP usage is expressed in % of the ATP turnover imposed at heavy exercise, 73 mM/min. Tables 1 and 2 show some chosen parameter values at the end of particular simulations that are difficult to read directly from these figures. It is worth emphasizing that the simulations indicate what would happen during 4 min of exercise if muscle work is not terminated earlier because of fatigue caused by low pH or other related factors (40).

Fig. 2 presents the computer simulation of the transition from rest to heavy exercise in normoxic conditions without any activity of AMP deaminase. During 4 min of work, VO2 increases over 37 times (from 0.3 to 11.2 mM/min); [ADP] rises from 7 to 51 μM; [PCr] falls from 29 to 5 mM; [Pi] increases from 2.7 to 22 mM; and [AMP] rises from 0.02 to 1.1 μM. The total adenine nucleotide pool remains constant of course, and there are no significant changes in [ATP]. Cytosolic pH drops from 7.0 to 6.46 (see Table 1). At the onset of exercise, ADP is mainly consumed by creatine kinase, but ATP resynthesis is quickly taken over by oxidative phosphorylation and anaerobic glycolysis. After 4 min of exercise, the contribution of creatine kinase to ADP usage (amounting 73 mM/min) is negligible (0.4%), and most (87.7%) of the ADP is consumed by oxidative phosphorylation, and anaerobic glycolysis is responsible for utilization of 11.9% of ADP (see Table 2).

Fig. 3 and Fig. 4 present computer simulations analogous to that shown in Fig. 2, but with moderate and high AMP deamination intensity, respectively. Increased AMP deaminase activity causes of course a greater depletion of the total adenine nucleotide pool during heavy exercise. This is accompanied by a greater decrease in [ATP] (after 4 min of exercise, ATP concentration decreases from 6.7 to 4.7 mM and 2.7 mM at moderate and high AMP deamination activity, respectively). During exercise [ADP] first rises, but then begins to drop; generally, AMP deamination significantly lowers the final [ADP] at the end of exercise to 40 and 28 μM at moderate and high AMP deaminase activity, respectively. The final [AMP] also decreases with the increase in AMP deamination. On the other hand, AMP deamination elevates the final [Pi]. VO2 is not significantly affected by the decrease in the total adenine nucleotide pool. However, moderate and high rates of AMP deamination lead to some ADP consumption by the adenylate kinase plus AMP deaminase system, constituting the fourth (after creatine kinase, oxidative phosphorylation, and anaerobic glycolysis) ADP consumer (39). This study demonstrates that the activity of the adenylate kinase plus AMP deaminase system, constituting the fourth (after creatine kinase, oxidative phosphorylation, and anaerobic glycolysis) ADP consumer and (to a less extent because of adenylate kinase stoichiometry) ATP producer in muscle, leads to a decrease in the activity of another ADP consumer/ATP producer, i.e. anaerobic glycolysis. This effect is exerted through a decreased concentration of ADP and AMP, effective activators of glycolysis. The cytosolic proton concentration is determined by the balance between different processes that produce/consume H+ ions, namely creatine kinase, anaerobic glycolysis, and proton efflux/
FIGURE 2. Simulated time courses of selected parameter values during rest-to-intensive-work transition in normoxia for no AMP deaminase activity. A, VO$_2$, [ATP], [ADP], [P], and [PCr]; B, cytosolic pH, [AMP] and [total adenine nucleotides]. C, ATP usage, ADP usage by creatine kinase, by oxidative phosphorylation (plus aerobic glycolysis) and by anaerobic glycolysis. 100% of ATP or ADP usage corresponds to 73 mmol/min.
influx to/from blood (22). Anaerobic glycolysis leads to muscle acidification during intensive exercise. Therefore, a decrease in the anaerobic glycolysis intensity elevates cytosolic pH during such an exercise.

Adenylate kinase converts two ADP molecules to one ATP molecule and one AMP molecule. In the absence of AMP deaminase activity, this enzyme just maintains [ATP], [ADP], and [AMP] close to thermody-
namic equilibrium with each other. On the other hand, when the intensity of AMP deamination to IMP is significant, AMP deaminase constitutes a net consumer of AMP (see Fig. 1). In this case the reaction catalyzed by adenylate kinase is driven toward ATP synthesis (the reaction ADP → AMP → IMP drives the coupled reaction ADP → ATP). Thus, the concerted action of adenylate kinase and AMP deaminase

FIGURE 4. Simulated time courses of selected parameter values during rest-to-intensive-work transition in normoxia for high AMP deaminase activity. A, VO₂, [ATP], [ADP], [Pi], and [PCr]. B, cytosolic pH, [AMP] and [total adenine nucleotides]. C, ATP usage, ADP usage by creatine kinase, by oxidative phosphorylation (plus aerobic glycolysis), by anaerobic glycolysis, and by adenylate kinase (AK) + AMP deaminase (AMP-d). 100% of ATP or ADP usage corresponds to 73 μmol/min.
leads to ATP production and ADP consumption but also to a decrease in the total adenine nucleotide pool. Because two ADP molecules are consumed for one ATP molecule produced, [ATP] and [ADP] production/consumption cannot both be balanced at the same time. As discussed above, [ADP] production/consumption is much better balanced than [ATP] production/consumption, and therefore the reduction in

FIGURE 5. Simulated time courses of selected parameter values during rest-to-intensive-work transition in hypoxia for no AMP deaminase activity. A, $\text{VO}_2$, [ATP], [ADP], $[P_i]$, and [PCr]. B, cytosolic pH, [AMP] and [total adenine nucleotides]. C, ATP usage, ADP usage by creatine kinase, by oxidative phosphorylation (plus aerobic glycolysis), and by anaerobic glycolysis. 100% of ATP or ADP usage corresponds to 73 $\text{mM}/\text{min}$.
FIGURE 6. Simulated time courses of selected parameter values during rest-to-intensive-work transition in hypoxia for high AMP deaminase activity. A, VO$_2$, [ATP], [ADP], [Pi], and [PCr]. B, cytosolic pH, [AMP] and [total adenine nucleotides]. C, ATP usage, ADP usage by creatine kinase, by oxidative phosphorylation (plus aerobic glycolysis), by anaerobic glycolysis, and by adenylate kinase (AK) + AMP deaminase (AMP-d). 100% of ATP or ADP usage corresponds to 73 mm/min.
the total adenine nucleotide pool is mostly reflected by a decrease in [ATP]. Therefore, in this study (see e.g. Figs. 2–7), ADP production/consumption rather than ATP production/consumption is considered.

One can see from Figs. 2–6 and Table 2 that the decrease in the total adenine nucleotide pool caused by AMP deamination decreases the contribution of anaerobic glycolysis, but not of oxidative phosphorylation, to the overall ADP consumption. The absolute reduction in the contribution to ADP usage is not great, 2.1–4.6 and 6.4% in normoxia and hypoxia, respectively. However, this is equivalent to a relative decrease in the anaerobic glycolysis intensity by about 20–40%, which means quite a large effect. Therefore, it can be concluded that the adenylate kinase plus AMP deaminase system can diminish significantly the anaerobic glycolysis flux.

Fig. 7 explains why the decrease in [ADP] (and [AMP]) during heavy exercise caused by AMP deamination inhibits significantly anaerobic glycolysis (AG) but not oxidative phosphorylation (OP). During heavy exercise and, especially, hypoxia, [ADP] is much higher than the half-saturation (or Michaelis-Menten) constant of oxidative phosphorylation for ADP (equal to about 25 μM). On the other hand, the rate of glycolysis still depends strongly (near linearly) on [ADP] (and [AMP]) (compare Equation 1). Therefore, a decrease in the [ADP] (and [AMP]) during exercise caused by AMP deamination significantly inhibits anaerobic glycolysis but has only a small effect on oxidative phosphorylation.

In fact, the rate of oxidative phosphorylation and its contribution to ADP consumption even slightly increases when the total adenine nucleotide pool is reduced. This is caused by the fact that AMP deamination elevates [Pi] during heavy exercise/hypoxia. Pi is an activator of oxidative phosphorylation, although not so effective as ADP.

Creatine kinase consumes significant amounts of ADP only at the beginning of exercise. However, its contribution to ADP usage is similar during different AMP deaminase activities (compare Figs. 2–4 as well as Figs. 5 and 6 and also see Table 2).

Simulations presented in Figs. 3 and 4 predict that in the presence of AMP deamination, [ADP] first increases during the transition from rest to heavy exercise and then starts to decrease after about 3 min. Such a behavior is encountered in experimental studies (6).

In silico studies demonstrate that hypoxia decreases the contribution of oxidative phosphorylation to ADP usage and increases the contribution of anaerobic glycolysis to ADP usage (compare Fig. 2 and Fig. 5). This takes place because low oxygen concentration inhibits ATP supply by oxidative phosphorylation, which leads to an increase in [ADP] and [AMP]. The elevated level of ADP and AMP activates in turn the glycolytic flux.

The decrease in the anaerobic glycolysis intensity brought about by AMP deamination leads to a decrease/delay of cytosol acidification, as can be seen from Figs. 2–6 and Table 1. The effect can be as high as 0.2 pH units at a given moment of exercise. Low pH could lead (directly or through some related factors) to myocyte damage and/or to earlier termination of exercise because of fatigue (40). The last possibility is supported by the observation that patients with AMP deaminase deficiency fatigued after performing only 28% as much work as control healthy individuals (21). In the natural environment a few more seconds of skeletal muscle work may decide survival, for instance when a prey escapes from a predator. In an ischemic heart prolonged work is also crucial for life. Therefore, it is postulated here that the reduction/delay of muscle acidification during heavy exercise/hypoxia in skeletal muscle/heart constitutes the main physiological benefit of AMP deamination. This hypothesis is supported by the fact that H⁺ ions activate AMP deaminase at least in some experimental conditions (1, 6, 7).

It has been postulated by several authors (4, 5) that the role of AMP deamination is to keep a possibly high ATP/ADP ratio and phosphorylation potential during heavy exercise. However, the in silico studies performed here do not confirm this proposal. As shown in Table 1, a decrease in the adenine nucleotide pool results in a lower ATP/ADP ratio during exercise. (The same is true for the phosphorylation potential proportional to log(ADP/[ATP × Pi]) (data not shown.) This happens because ADP is more important as a metabolic regulator than ATP, and its concentration is kept more constant when the overall pool of adenine nucleotides decreases.

In the simulation concerning no AMP deaminase activity in hypoxic conditions (Fig. 5), the cytosolic pH drops to very low values, below 5.9. Such low values are never encountered in experimental studies. First, however, it is likely that in such conditions AMP deaminase is always highly active, which prevents a very high cytosol acidification. Second, the simulations presented in Figs. 2–6 show what would happen in the system during 4 min of heavy exercise if the exercise is not terminated earlier because of fatigue. An extremely intensive voluntary exercise, in which creatine kinase and anaerobic glycolysis constitute the main source of ATP and during which the total adenine nucleotide decreases by 34%, can last only 30 s (8). In such an exercise the AMP deamination activity is even higher than that considered here, and its effect on cytosolic pH and duration of exercise may be even greater.

In conclusion, adenylate kinase plus AMP deaminase constitute an additional ADP consumer and, to a smaller extent (because of adenylate kinase stoichiometry), an ATP producer. Therefore, AMP deamination during heavy exercise and/or hypoxia in skeletal muscle/heart allows other processes that consume ADP/produce ATP to be slowed down. This especially concerns the anaerobic glycolysis that is significantly inhibited by a decreased [ADP] and [AMP] during exercise. As a result, proton production by this process decreases, and cytosol acidification is diminished and/or delayed. This seems to be the main benefit of AMP deamination, because a decrease in the total adenine nucleotide pool does not help to keep a high ATP/ADP ratio and phosphorylation potential, as was postulated by several authors.

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