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ORIGINAL ARTICLE

The effect of AMP deamination on skeletal muscle is stronger and more beneficial in extremely intense exercises to exhaustion and/or extremely stressing conditions

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Abstract

Purpose The effect of AMP deamination (AD) on the skeletal muscle bioenergetic system in constant-power exercise to exhaustion of different durations/intensities is studied.

Methods A computer model of the skeletal muscle bioenergetic system, involving the each-step-activation mechanism of system activation during work transitions and P_i double-threshold mechanism of muscle fatigue, is used.

Results The effect of AD on the system is stronger and more beneficial in extremely intense exercise (EIE) than in very intense exercise (VIE) and intense exercise (IE). Namely, in IE, AD accelerates P_i increase, shortens very significantly the time to exhaustion, slightly enhances the ATP/ADP decrease (harmful effects), does not affect significantly AMP and pH, and attenuates ADP increase (beneficial effect). In VIE and EIE, AD accelerates P_i increase and moderately shortens the duration of exercise (harmful effects), significantly attenuates the ATP/ADP and pH decrease (beneficial effects), and very significantly lowers the ADP and AMP increase (strong beneficial effects). Generally, the more intense the exercise, the greater are the beneficial effects and the smaller are the harmful effects. AD prevents significant cytosol acidification during muscle recovery after exercise. The slow AMP and total adenine nucleotide pool (especially ATP) resynthesis during recovery accelerates ADP and pH, and delays P_i return to the resting value.

Conclusion The main advantageous physiological role of AMP deamination is attenuation of the harmful effects of the AMP, ADP, and H^+ increase during and after very intense exercises.

Keywords ATP decrease · Adenine nucleotide pool · Intense exercise · Work transition · Bioenergetic system · Computer model

Abbreviations

A_{tot}	Total adenine nucleotide pool
AD	AMP deamination
AD−	AD absent
AD+,	AD present
ADD	AMP deaminase deficiency
EIE	Extremely intense exercise
IE	Intense exercise
VIE	Very intense exercise
ESA	Each-step activation
OXPHOS	Oxidative phosphorylation
P_i^-	H_2PO4^-; Pi_{crit}, critical P_i, above which the additional ATP usage, underlying the VO_2 and metabolite slow component, appears
Pi_{peak}	Peak P_i at which exercise is terminated because of fatigue
PP_i	Pyrophosphate

Introduction

The enzyme AMP deaminase (EC 3.5.4.6) catalyzes the reaction of AMP deamination: decomposition of adenine monophosphate (AMP) to inosine monophosphate (IMP) and ammonia (NH_3) (Sahlin et al. 1978; Lowenstein 1990; Tullson and Terjung 1991; Hancock et al. 2006a):

$$AMP \rightarrow IMP + NH_3.$$

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Together with the reaction catalyzed by adenylate kinase (EC 2.7.4.3) of very quick and reversible conversion of two adenine diphosphate (ADP) molecules to one adenine triphosphate (ATP) molecule and one AMP molecule:

$$2\ \mathrm{ADP} \rightleftharpoons \mathrm{ATP} + \mathrm{AMP},$$

they lead during skeletal muscle work to a decrease in the total free adenine nucleotide pool (A_{tot} = ATP + ADP + AMP), especially in ATP that constitutes the main component of this pool. The extent of AD-related ATP decrease can be very different, from < 10% to > 50%, depending on exercise type and intensity, muscle/fiber type (oxidative vs. glycolytic), type of muscle stimulation (cortical vs. electrical), muscle perfusion type (natural vs. external), oxygen availability, training status, and other factors (Meyer and Terjung 1979; Meyer et al. 1980; Sabina et al. 1984; Dudley and Terjung 1985; Katz et al. 1986; Sahlin and Bloberg 1990; Harris et al. 1991; Söderlund and Hultman 1991; Hellsten et al. 1999; Parolin et al. 1999; Tullson et al. 1995; Zhao et al. 2000; Norman et al. 2001; Hancock et al. 2006a; Sundberg et al. 2019; Smith et al. 2024).

AMP deamination takes place in some cases during skeletal muscle exercise and is particularly intense in strong energy crisis related to high ADP and AMP increase during high muscle work and/or in hypoxia (see e.g., Hancock et al. 2006a for discussion). The physiological role of AD is still not fully understood. Several potential benefits have been proposed (see Zoladz et al. 2025 for recent discussion): attenuation of the decrease in the ATP/ADP ratio and decrease in the phosphorylation potential ΔG_P during muscle exercise (Sahlin and Broberg 1990; Tullson and Terjung 1991; Smith et al. 2024), prevention of an excessive ADP and/or AMP accumulation (Sahlin et al. 1992; Hellsten et al. 1999; Hancock et al. 2006a), delay in muscle acidification (Korzeniewski 2006), and increase in the muscle H^+ buffering capacity by the produced NH_3 (Hochachka and Mommsen 1983). Of course, the last mechanism also leads to a delay in muscle acidification. However, the direct mechanism (Korzeniewski 2006) and the NH_3-mediated mechanism (Hochachka and Mommsen 1983) do not exclude each other and can act in parallel.

AMP and A_{tot} (and thus ATP) are resynthesized very slowly during recovery after exercise: this process lasts from minutes to tens of minutes (Taylor et al. 1986; Zhao et al. 2000; Smith et al. 2024) and occurs through reactions catalyzed by adenylosuccinate synthetase (EC 6.3.4.4) and adenylosuccinate lyase (EC 4.3.2.2). The reason for the slow rate of this process also remains unknown.

The previous article devoted to AMP deamination by the author (Korzeniewski 2006) led to the conclusion that a major benefit of this process is attenuation of cytosol acidification during exercise. However, while this conclusion can still remain valid, that study used an earlier version of the computer model of the skeletal muscle bioenergetic system that lacked the fatigue component, that is, the P_i double-threshold mechanism that allows to simulate the exercise duration in constant-power exercise, which was impossible in the previous model version. That version also lacked additional ATP usage underlying the $\dot{V}O_2$ and metabolite slow component and contained an older version of the kinetic description of glycolysis and some other minor elements. Additionally, the previous article only dealt with a relatively long and not very intense exercise lasting 4 min. Therefore, the theoretical results and conclusions obtained in Korzeniewski (2006) should be significantly updated and extended, especially in the context of muscle fatigue and very short/intense exercises. Indeed, the predictions of the two studies differ quite significantly: while the main effect of AMP deamination in the previous article was an attenuation of cytosol acidification, in the present article the main effect is a delay in ADP and AMP increase, while the delay in H^+ increase is a secondary effect (see below).

Overall, it seems that the extent of AMP deamination, expressed as a relative ATP decrease during exercise, tends to be larger in more intense exercises to the limit of tolerance, in fast-twitch fibers/glycolytic muscles, sedentary/untrained subjects, and generally in conditions of muscle stress and severe energetic crisis (highly elevated ADP and AMP), for instance very high work, hypoxia/anoxia, and/or electrical stimulation of externally perfused muscles (Meyer and Terjung 1979; Meyer et al. 1980; Sabina et al. 1984; Dudley and Terjung 1985; Katz et al. 1986; Sahlin and Bloberg 1990; Harris et al. 1991; Söderlund and Hultman 1991; Hellsten et al. 1999; Parolin et al. 1999; Tullson et al. 1995; Zhao et al. 2000; Norman et al. 2001; Hancock et al. 2006a; Sundberg et al. 2019; Smith et al. 2024). Nevertheless, the effects of AMP deamination on the skeletal muscle bioenergetic system in exercises of different intensities (or, more generally, various magnitudes of bioenergetic stress) have not been compared in a single study using the same group of individuals (it is not possible to have the same individuals with (different intensities of) and without AD) or the same model.

This *in silico* study is intended to compare the effects of AMP deamination in three constant-power exercises to exhaustion of different durations and intensities: intense exercise (IE), very intense exercise (VIE), and extremely intense exercise (EIE) lasting 4 min, 30 s, and 10 s in the presence of increasing rates of AD (AD+) (and longer in the absence of AD (AD−)), respectively, on system variables (especially metabolite levels) and to estimate the beneficial (improvement of muscle performance, health, and condition) and harmful (worsening of muscle performance, health, and condition) consequences of this phenomenon in each case.

The second aim is to test the effect of the very slow AMP and the total adenine nucleotide pool (chiefly ATP) resynthesis during muscle recovery after exercise on the system variables. It is hypothesized that the beneficial and harmful effects will be different in exercises of different durations/intensities, with the beneficial effects being strongest and harmful effects weakest in the shortest/most intense exercises. It is supposed that the most beneficial result of AMP deamination is an attenuation of the ADP, AMP, and H^+ increase. It is expected that AMP deamination accelerates P_i increase and thus muscle fatigue (shortens exercise duration to the limit of tolerance) as a consequence of an attenuation of ADP increase (see below, Theoretical results). It is hypothesized that the slow AMP resynthesis and thus total adenine nucleotide pool (especially ATP) recovery after termination of exercise accelerate the return of ADP and H^+ to the resting values and thus hasten the myocyte repair after bioenergetics stress-generated damage (as proposed previously for the PCr recovery overshoot, Korzeniewski 2003). Generally, the present study is intended to determine the role of AMP deamination in the skeletal muscle bioenergetic system during and after intense exercise.

Theoretical procedures

Ethical approval

This is a purely a theoretical study that did not involve any experiments on humans or animals.

Computer model

A dynamic computer model of the skeletal muscle bioenergetic system (Korzeniewski 1998, 2019; Korzeniewski and Zoladz 2001; Korzeniewski and Liguzinski 2004; Korzeniewski and Rossiter 2015, 2020) was used in the present study. The model comprises the ATP usage block (actomyosin-ATPase, Ca^{2+}-ATPase, resting ATP usage), particular OXPHOS complexes, NADH supply block (TCA: tricarboxylic acid cycle, fatty acid β-oxidation, MAS: malate/aspartate shuttle), glycolysis block, creatine kinase, adenylate kinase, proton leak through the inner mitochondrial membrane, and proton efflux/influx through the cellular membrane.

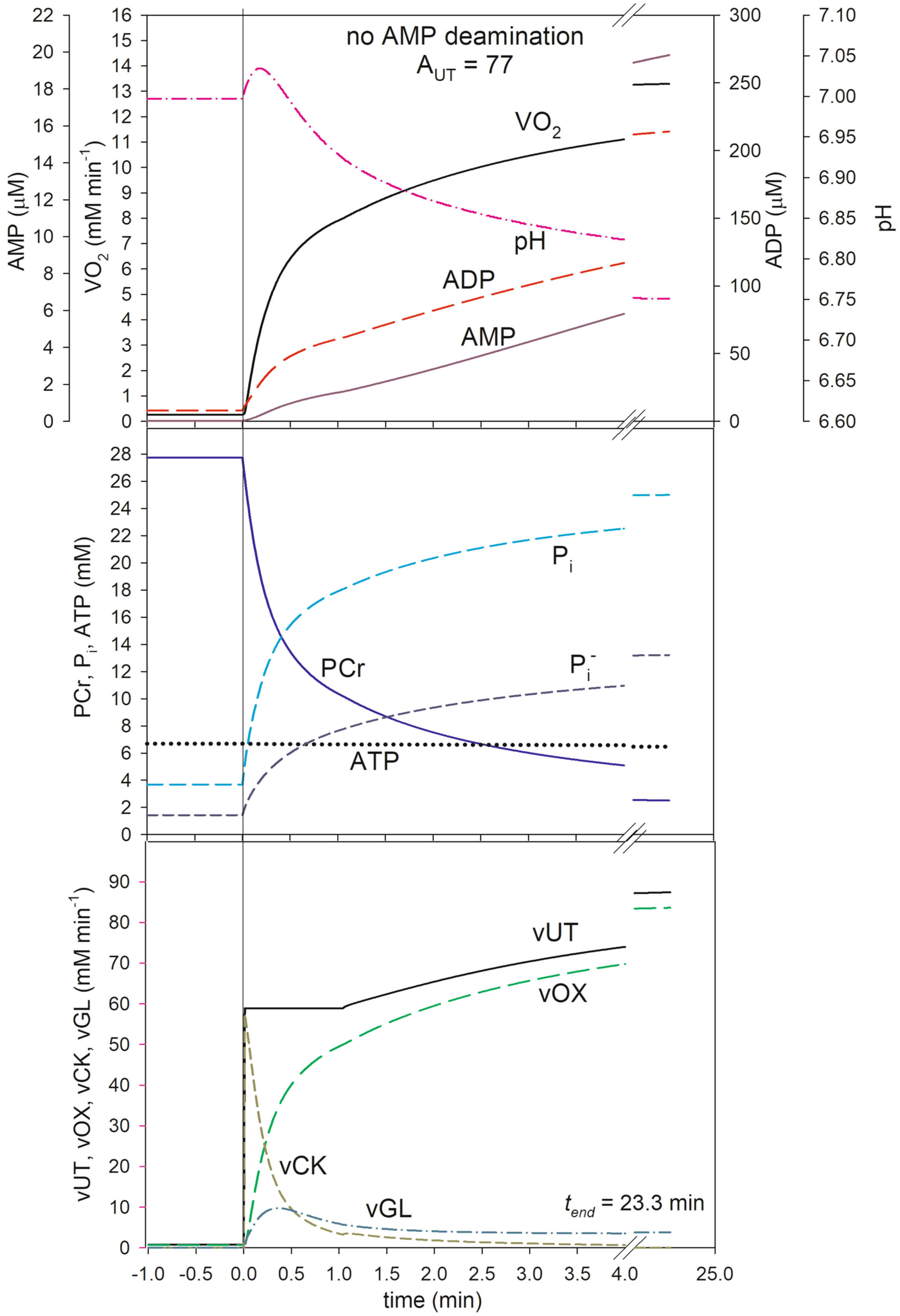
The model involves the each-step-activation (ESA) mechanism of the activation of the system during work transitions (Korzeniewski 1998, 2003, 2007, 2017; Korzeniewski and Rossiter 2015). According to this mechanism, not only ATP usage is activated by cytosolic Ca^{2+} ions, but also all steps of the ATP supply system taken into account explicitly within the model, namely all OXPHOS complexes (complex I, complex III, complex IV, ATP synthase, ATP/ADP carrier, P_i carrier), NADH supply system and (anaerobic) glycolysis are directly activated by some cellular mechanism, likely to involve cytosolic and mitochondrial Ca^{2+} ions and protein (de)phosphorylation, during rest-to-work or low-to-high-work transition in skeletal muscle, heart, neural tissue, liver and perhaps other.

The model also involves the P_i double-threshold mechanism of muscle fatigue (Korzeniewski and Rossiter 2020). This mechanism is based on three assumptions: (i) the additional ATP usage, underlying the VO_2 and metabolites slow component, is initiated when P_i exceeds the critical concentration Pi_{crit}; (ii) exercise is terminated because of fatigue (exhaustion, reaching the limit of tolerance) when P_i reaches the peak level Pi_{peak}; (iii) the P_i increase and additional ATP usage increase stimulate each other, forming a positive feedback. The P_i double-threshold mechanism received recently strong experimental support (Hureau et al. 2022). This mechanism was preceded by the "fatigue-factor-F-double-threshold" mechanism based on a similar logic, where F represented a group of fatigue-related metabolites (ADP, AMP, IMP, NH_3, P_i) (Korzeniewski and Zoladz 2003).

The model has been extensively tested by comparison with a wide range of experimental data and is able to account for and explain numerous properties of the skeletal muscle bioenergetic system (see Korzeniewski 2017 for a relatively recent review of earlier studies, and Korzeniewski 2019, 2021, 2022, 2023a, b, 2024; Korzeniewski and Rossiter 2020, 2021, 2022). The complete model description is given in Korzeniewski (2019), still without complete P_i double-threshold mechanism, and located on the website: http://bernardkorzeniewski.pl.

Computer simulations

The simulation of the rest-to-work transition in constant-power exercise to the limit of tolerance was initiated by an instantaneous increase of the ATP usage activity (rate constant A_{UT}) from 1 (scaled rest value) to a desired active value. Three active A_{UT} values of 77 (intense exercise, IE), 130 (very intense exercise, VIE), and 245 (extremely intense exercise, VIE) were adjusted to obtain the duration of exercise to exhaustion of 4 min, 30 s, and 10 s in the presence of AMP deamination (AD +) with the rate of 0.33. 5.0 and 20.0 mM min^{-1}, respectively. This meant that during exercise, the ATP usage activity was 77, 130, and 245 times greater than that at rest. One A_{UT} unit corresponds to about 3 W during whole-body exercise (about 2–4 W depending on the working muscle mass and exercise type). These values were adjusted to obtain the relative decrease in ATP during exercise and exercise duration to exhaustion, characteristic for experimental data or reflect extremely intense/stress-generating exercise (Meyer and Terjung 1979; Meyer et al. 1980; Sabina


no AMP deamination
A_{UT} = 77
AMP (μM)
0
2
4
6
8
10
12
14
16
18
20
22
VO_2 (mM min^{-1})
0
1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
ADP (μM)
0
50
100
150
200
250
300
pH
6.60
6.65
6.70
6.75
6.80
6.85
6.90
6.95
7.00
7.05
7.10
VO_2
pH
ADP
AMP
PCr, P_i, ATP (mM)
0
2
4
6
8
10
12
14
16
18
20
22
24
26
28
P_i
PCr
P_i^-
ATP
vUT, vOX, vCK, vGL (mM min^{-1})
0
10
20
30
40
50
60
70
80
90
vUT
vOX
vCK
vGL
t_{end} = 23.3 min
-1.0
-0.5
0.0
0.5
1.0
1.5
2.0
2.5
3.0
3.5
4.0
25.0
time (min)

◂**Fig. 1** Simulated time courses of selected fluxes and metabolite concentrations during constant-power intense exercise (IE) to the limit of tolerance with ATP usage activity $A_{UT} = 77$ and no AMP deamination ($v_{AD} = 0$ mM min^{-1}). *vUT* ATP usage flux, *vOX* ATP supply by OXPHOS (+aerobic glycolysis) flux; *vGL* ATP supply by anaerobic glycolysis flux; *vCK* ATP supply by creatine kinase (CK) flux

et al. 1984; Dudley and Terjung 1985; Katz et al. 1986; Sahlin and Bloberg 1990; Harris et al. 1991; Söderlund and Hultman 1991; Hellsten et al. 1999; Parolin et al. 1999; Tullson et al. 1995; Zhao et al. 2000; Norman et al. 2001; Hancock et al. 2006a; Sundberg et al. 2019; Smith et al. 2024).

At the same time, OXPHOS complexes, NADH supply, and glycolysis were directly activated (their rates were increased) in parallel with ATP usage with some delay (the ESA mechanism of the system activation during work transitions) (Korzeniewski 1998, 2017; Korzeniewski and Rossiter 2015). Analogous simulations were carried out for the same parameter values in the absence of AD.

The rate of AMP deamination was approximated by a very simple equation, as in Korzeniewski (2006):

$$vAD = c, \tag{1}$$

which means that a constant rate of AD during exercise was assumed. This simple kinetics was completely sufficient, as the topic of the present study is not the regulation of AMP deaminase, but the effect of AMP deamination on the system properties. The near-linear decrease in ATP with a short lag in the initial stage of exercise (Hellsten et al. 1999) confirms that this is a reasonably good approximation. c equaled 0 in the absence of AD (AD−) and 0.33, 5.0, and 20.0 mM min^{-1} for IE, VIE, and EIE in the presence of AD (AD+), respectively.

Summing up, three types of exercise were simulated: 1. intense exercise (IE): $A_{UT} = 77$, $v_{AD} = 0$ (AD−) or 0.33 mM min^{-1} (AD+); 2. very intense exercise (VIE): $A_{UT} = 130$, $v_{AD} = 0$ (AD-) or 5.0 mM min^{-1} (AD+); and 3. extremely intense exercise (EIE): $A_{UT} = 245$, $v_{AD} = 0$ (AD−) or 20.0 mM min^{-1} (AD+).

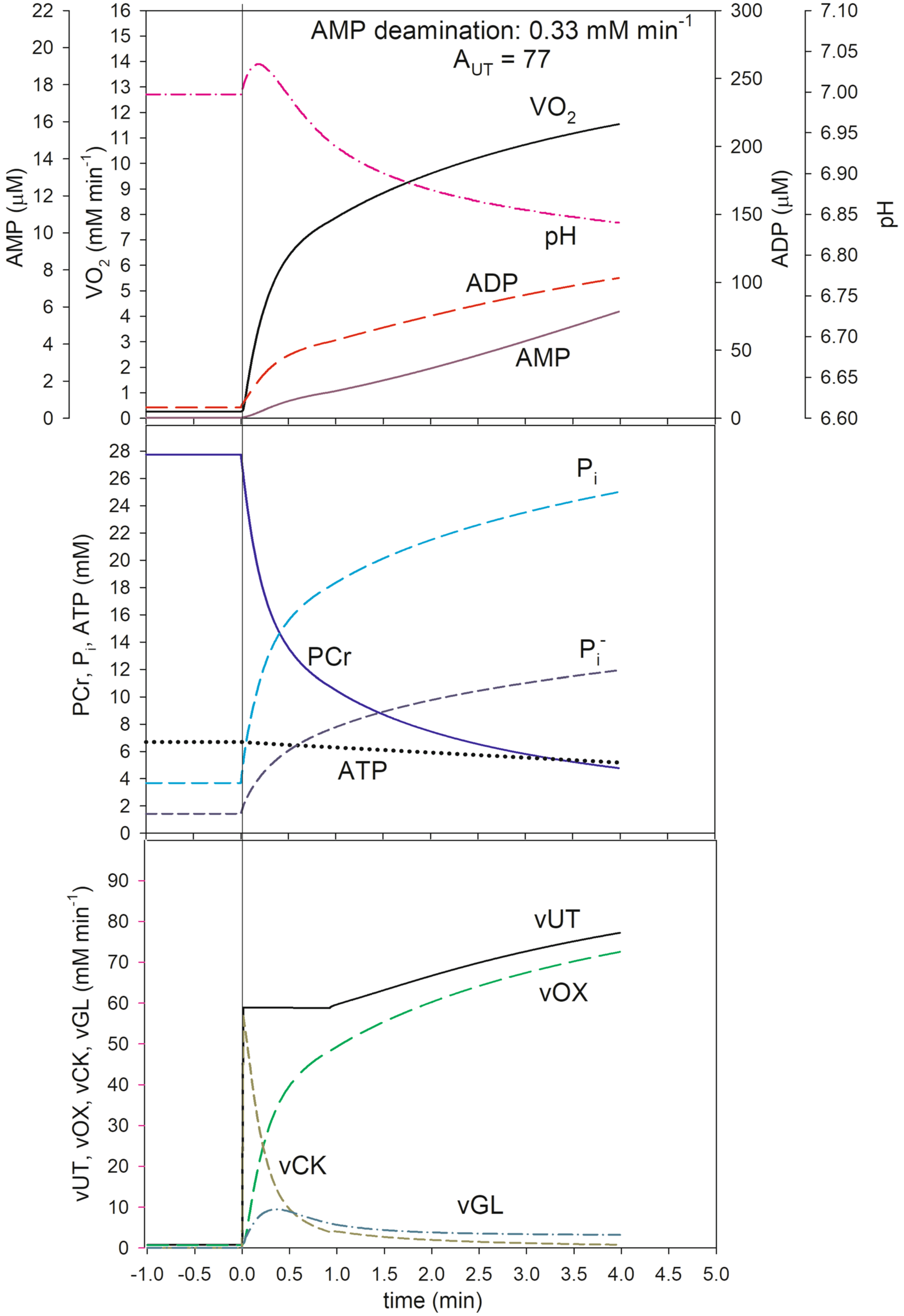
Exercise was terminated because of fatigue at the moment P_i reached Pi_{peak} (= 25 mM) (severe or very heavy exercise intensity domain). In the first set of simulations of IE, VIE, and EIE for AD− and AD+, simulations were terminated at this point. In the second set of simulations, concerning only VIE (as an illustration), also muscle recovery was simulated after the termination of exercise. The rate of AMP resynthesis c was either 0 (AD−) or equaled − 0.2 mM min^{-1} (AD+, slow AMP resynthesis) or − 5.0 mM min^{-1} (AD+, fast AMP resynthesis). The resynthesis was instantaneously switched off the moment ATP recovered to the initial (resting) value.

Theoretical results

AD− and AD+ in IE ($A_{UT} = 77$) differ in several important aspects. This is demonstrated in Figs. 1 and 2 and Table 1. While the figures show the variable time courses to the termination of exercise for AD− and AD+, Table 1 shows the variables values after the time of the termination of exercise in AD+ IE (4 min) both in AD− and AD+ to enable a direct comparison. Therefore, the end values are the same in the figures and the table for AD+, but not for AD−. In fact, AD− IE is actually terminated after as long as 23.3 min (Fig. 1). This is a huge, almost sixfold difference compared to 4 min in AD+ IE. This is caused by a much faster reaching of Pi_{peak} by P_i in AD+ than AD− IE – the exercise duration is very sensitive to the attenuation/acceleration of P_i increase, as in this duration region P_i rises relatively slowly (shallow increase slope) and a small acceleration/delay in the P_i increase can affect very significantly the time when it reaches Pi_{peak}. AMP deamination causes the acceleration of P_i increase through the attenuation of ADP increase (see below). Both ADP and P_i are activators of OXPHOS, so if ADP decreases then P_i must increase to keep ATP supply unchanged and thus match ATP usage. Of course, at the end of exercise, in both cases P_i reaches the Pi_{peak} value = 25 mM. However, after 4 min in AD− exercise P_i equals 22.5 mM (Table 1), while in AD + exercise $P_i = Pi_{peak} = 25$ mM. Also H_2PO4^- (P_i^-) rises more slowly in AD− than AD+ (Fig. 1 vs. Figure 2).

After 4 min of AD+ IE, ATP drops by 23%, mostly due to AMP deamination (Fig. 2, Table 1), while in AD− IE, ATP decreases by only 2% after 4 min (3% at the end) of exercise, due to the hydrolysis of ATP to ADP (and AMP) (Fig. 1, Table 1). AMP deamination somewhat attenuates the ADP increase and does not affect significantly H^+ increase after 4 min of exercise, although at the end of AD− IE (23.3 min) ADP and H^+ rise to much higher values than in AD+ exercise (Fig. 2 vs. Fig. 1, Table 1). The ATP/ADP ratio after 4 min of exercise is slightly lower in AD+ than in AD− IE (Table 1). The AMP level increases to a similar value in both cases after 4 min of exercise, although at the end of exercise AMP is over twice higher in AD− IE than in AD+ IE (Fig. 1 vs. Fig. 2). In both AD− and AD+ IE, the additional ATP usage begins (P_i exceeds Pi_{crit}) after 1 min of exercise or slightly later. Creatine kinase (CK) is the main ATP supplier during first 15 s of exercise, while later ATP synthesis is taken over by OXPHOS, with a small contribution of anaerobic glycolysis.

The differences between AD− and AD + become greater in VIE ($A_{UT} = 130$). The duration of exercise to the limit of tolerance is here only moderately longer in AD –than in AD+: 50.4 s vs. 30 s (Fig. 3 and Fig. 4, Table 1). This


AMP deamination: 0.33 mM min^{-1}
A_{UT} = 77
AMP (μM)
VO_2 (mM min^{-1})
ADP (μM)
pH
VO_2
pH
ADP
AMP
0 2 4 6 8 10 12 14 16 18 20 22
0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16
0 50 100 150 200 250 300
6.60 6.65 6.70 6.75 6.80 6.85 6.90 6.95 7.00 7.05 7.10
PCr, P_i, ATP (mM)
0 2 4 6 8 10 12 14 16 18 20 22 24 26 28
P_i
PCr
P_i^-
ATP
vUT, vOX, vCK, vGL (mM min^{-1})
0 10 20 30 40 50 60 70 80 90
vUT
vOX
vCK
vGL
-1.0 -0.5 0.0 0.5 1.0 1.5 2.0 2.5 3.0 3.5 4.0 4.5 5.0
time (min)

◂**Fig. 2** Simulated time courses of selected fluxes and metabolite concentrations during constant-power intense exercise (IE) to the limit of tolerance with ATP usage activity $A_{UT}=77$ and AMP deamination rate $v_{AD}=0.33$ mM min^{-1}. *vUT* ATP usage flux, *vOX* ATP supply by OXPHOS (+aerobic glycolysis) flux; *vGL* ATP supply by anaerobic glycolysis flux; *vCK* ATP supply by creatine kinase (CK) flux

is again caused by an accelerated P_i increase in AD+, but because in this duration region P_i rises more quickly (more steep increase slope), the relative difference in the time to reach Pi_{peak} is lower. In AD+ VIE, ATP decreases by 40%, and in AD− by 2% after 30 s (and by 4% at the end) of exercise. The increase in ADP during exercise is almost twice greater in AD– VIE than in AD VIE after 30 s of exercise and over three times greater at the end of AD– VIE (Figs. 3 and 4 and Table 1). The rise in AMP in AD– VIE after 30 s of exercise is over three times higher, and at the end of AD– VIE about eight times higher, than at the end (30 s) of AD+ VIE. Unlike in IE, the ATP/ADP ratio is slightly higher in AD+ than in AD− after 30 s (the end of AD+ VIE) (Table 1). Therefore, the tendency of the impact of AD on ATP/ADP is reversed. The increase in H^+ is quite significantly lower in AD+ VIE than in AD– VIE after 30 s, and markedly lower than in AD– VIE at the end of exercise.

In VIE, creatine kinase is the main ATP supplier during first 10 s of exercise, and later this function is taken over by OXPHOS and anaerobic glycolysis. However, the contribution of the latter to ATP supply is significantly higher than in IE.

The relative shortening of the exercise duration between AD+ and AD− is even less in EIE than in VIE: 10 s vs. 13.9 s (Figs. 5 and 6, Table 1). P_i (and P_i^-) rises more quickly in AD+ than in AD– EIE and its increase is still steeper than in VIE. ATP drops by 54% in AD+ and by 2% in AD– EIE after 30 s (4.5% at the end) of exercise. The increase in ADP after 10 s of exercise is three times lower in AD+ than in AD– EIE and almost six times lower than at the end of AD– EIE, so the difference is significantly greater here than in VIE. The ATP/ADP ratio is significantly higher in AD+ EIE, than in AD– EIE (Table 1). The huge difference between AD+ and AD– EIE can be observed at the AMP level: 2 µM vs. 9 µM after 10 s of exercise (Figs. 5 and 6 and Table 1). At the end of AD– EIE exercise, AMP increases to over 30 µM, and thus is over 15 times greater, than at the end of AD+ exercise! The cytosol pH (7.04) is moderately higher in AD+ than in AD– EIE after 10 s of exercise (6.99) and significantly higher than at the end of AD− (6.90). Generally, the most prominent difference between AD+ EIE and AD– EIE in 10 s exercise to exhaustion (in AD+) is a much lower increase in ADP, H^+, and especially AMP during exercise in the former.

CK is the main ATP supplier during the first 6–7 s of EIE and later ATP delivery is to some extent taken over by OXPHOS and anaerobic glycolysis; the contribution of both is similar in AD− and greater of OXPHOS in AD+ (Figs. 5 and 6).

Figures 7, 8, 9 show differences in system variables during the recovery after VIE ($A_{UT}=130$) (taken as an example) for AD− (Fig. 7) and AD+ with slow (0.2 mM min^{-1}) (Fig. 8) and fast (5.0 mM min^{-1}) (Fig. 9) AMP resynthesis. AMP resynthesis is of course related to A_{tot}, especially ATP, return to the resting value. A discontinuity can be seen in the variable time courses in Fig. 9 after ~ 30 s of recovery. It is simply caused by an instantaneous switching off of AMP resynthesis when ATP reaches the resting value. Of course, this is a rough simplification made within the model and most probably does not represent the real situation, where the transition is likely more smooth.

Some significant differences can be observed between AD− and AD+ exercise and between AD+ exercise with slow and fast AMP resynthesis.

Of course, in the simulations presented in Figs. 7, 8, 9 (AD– VIE and AD+ VIE with slow and fast AMP resynthesis, respectively) during the muscle work period, the system variables behave as in simulations presented in Figs. 3 and 4 (AD− and AD+ VIE), resulting in their different end-exercise values. They constitute different starting points for the return of these variables to the resting values during muscle recovery after exercise. Nevertheless, these differences can be enhanced during recovery. The most spectacular example is pH that drops to 6.70 after about 20 s of recovery in AD– VIE starting from 6.80 at the end of exercise. The reason for this phenomenon is the "reverse" creatine kinase (CK) reaction: resynthesis of PCr and ADP from ATP and Cr, in which H^+ is released. On the other hand, pH drops only to 6.90 in AD+ VIE during muscle recovery in both slow and fast AMP resynthesis.

The return to the resting values of VO_2, ADP, and PCr is faster, of AMP and pH is of similar duration, and of P_i is slower in AD+ VIE with slow than with fast AMP resynthesis (it does not make much sense to compare AD+ with AD− in this respect, as the changes in variable values in them differ very significantly). Namely, the half-transition times between exercise end and resting steady-state $t_{0.5off}$ equal 8 s and 12 s for VO_2, 3 and 6 s for ADP, 20 and 28 s for PCr, 2 and 2 s for AMP, 185 and 207 s for pH, and 26 and 20 s for P_i for slow and fast AMP resynthesis, respectively.

Discussion

Benefits and harms of AMP deamination

The most prominent beneficial effect of AMP deamination during skeletal muscle contraction is a very significant

Table 1 Simulated selected variable values in constant-power exercise to exhaustion without ($v_{AD} = 0$) and with ($v_{AD} > 0$) AMP deamination for three exercise intensities (ATP usage activities) $A_{UT} = 77$ (intense exercise, IE), 130 (very intense exercise, VIE), and 245 (extremely intense exercise, EIE)

Simulation	$A_{UT} = 77$		$A_{UT} = 130$		$A_{UT} = 245$	
Variable	$v_{AD} = 0$ mM min^{-1}	$v_{AD} = 0.33$ mM min^{-1}	$v_{AD} = 0$ mM min^{-1}	$v_{AD} = 5.0$ mM min^{-1}	$v_{AD} = 0$ mM min^{-1}	$v_{AD} = 20.0$ mM min^{-1}
t_{end}	23.3 min	*3.99 min*	52.4 s	*30.6 s*	13.9 s	*10.0 s*
ATP_{AD+end}	6.58 mM	*5.18 mM*	6.57 mM	*3.90 mM*	6.54 mM	*3.07 mM*
ΔATP_{AD+end}	↓ 2%	*↓ 23%*	↓ 2%	*↓ 40%*	↓ 2%	*↓ 54%*
ADP_{AD+end}	117 µM	***103 µM***	122 µM	***64 µM***	141 µM	***46 µM***
ATP/ADP_{AD+end}	56	*50*	54	***61***	46	***67***
AMP_{AD+end}	6 µM	6 µM	10 µM	***3 µM***	9 µM	***2 µM***
Pi_{AD+end}	22.5 mM	*25.0 mM*	22.0 mM	*25.0 mM*	22.1 mM	*25.0 mM*
Pi^{-}_{AD+end}	11.0 mM	*11.9 mM*	9.6 mM	*10.2 mM*	8.7 mM	*9.4 mM*
pH_{AD+end}	6.82	6.84	6.91	***6.96***	6.99	***7.04***
H^{+}_{AD+end}	151 nM	145 nM	123 nM	***110 nM***	102 nM	***91 nM***

v_{AD}, AMP deamination rate; AD+end in a subscript, value at the time at which the exercise of a given intensity is terminated in the presence of AMP deamination: 4 min, 30 s, and 10 s, respectively; italic characters, harmful effect; bold-italic characters, profitable effect; underlined characters, neutral/uncertain effect

attenuation of ADP and AMP increase during exercise and delay in muscle acidification during and, especially, after exercise (Figs. 2, 4 and 6 vs. Figs. 1, 3, and 5, respectively, Table 1). A significant harmful effect (apart from the decrease in the total adenine nucleotide pool A_{tot} itself) is an acceleration of P_i increase, leading to a significant shortening of exercise duration to exhaustion (Figs. 2, 4 and 6 vs. Figs. 1, 3 and 5, respectively, Table 1). P_i must increase more in the case when ADP increases less to activate the ATP supply by OXPHOS (both ADP and P_i are OXPHOS activators). Moreover, the effect of AD strongly depends on the intensity of exercise and the rate of AD related to it (Figs. 1, 2, 3, 4, 5, 6, Table 1). The beneficial effects are stronger and the harmful effects are weaker in shorter and more intense exercises to exhaustion, where the decrease in the total adenine nucleotide pool (A_{tot}), especially in ATP, is greater.

AMP deaminase is activated by ADP and AMP and inhibited by P_i (Wheeler and Lowenstein 1979, 1980). On the other hand, computer simulations show that AMP deamination attenuates the ADP and AMP increase and enhances P_i increase during exercise (Figs. 1, 2, 3, 4, 5, 6). Therefore, the effect of AD on bioenergetic metabolite levels constitutes a self-limiting mechanism.

High ADP and AMP levels can exert various disadvantageous effects in the skeletal muscle cell. A huge number of enzymatic reactions and transport processes are driven by the hydrolysis of ATP to ADP and P_i and some by hydrolysis of ATP to AMP and PP_i (pyrophosphate) (e.g., aminoacyl-tRNA synthetases). The products of ATP hydrolysis, especially at high concentrations, can inhibit these reactions/processes and the effect of ADP and AMP is kinetically different from the effect of P_i and PP_i.

For instance, ADP is a strong inhibitor of Na^+/K^+-ATPase (sodium–potassium pump) (Apell et al. 1986; Kennedy et al. 1986; Peluffo 2004), a crucial transporter responsible, among others, for maintaining the ionic homeostasis of the cell and the ionic and electrical gradient across the cell membrane. ADP also inhibits the Ca^{2+}-ATPase (SERCA) and increases Ca^{2+} leak from SR cisterns (Macdonald and Stephenson 2001; Inesi and Tadini-Buoninsegni 2014; Zhang et al. 2022). Hundreds of other reactions/processes are driven by ATP hydrolysis and are likely to be inhibited by high levels of ADP and AMP. Of course, this can also potentially concern P_i and PP_i, but the kinetic effect of all these metabolites is different, as they participate in different stages of particular reactions. Additionally, relative changes in ADP and AMP are much greater than in P_i and PP_i. The very moderate effect of AD on P_i increase is not likely to have a significant impact on the Na^+/K^+-ATPase or Ca^{2+}-ATPase activity.

Of course, ADP and AMP (and also P_i and PP_i) are effective activators of different bioenergetic processes, for instance glycolysis (Connett and Sahlin 1996; Lambeth and Kushmerick 2001; Korzeniewski and Liguzinski 2004), pyruvate oxidation and TCA cycle (Arnold and Finley 2022), and OXPHOS (Chance and Williams 1956; Liguzinski and Korzeniewski 2006) that are crucial for meeting the ATP supply of highly elevated ATP demand during muscle contraction and thus maintaining metabolite homeostasis. Also, AMPK (AMP-activated protein kinase) plays a key role in the regulation of bioenergetic metabolism during exercise (Richter and Ruderman 2009). Therefore, from this point of view, the increase in ADP, AMP, P_i, and PP_i could be considered as advantageous. However, this most probably concerns a moderate increase. A large increase could disturb or even strongly inhibit many of the reactions/processes discussed above.

AMP deamination and phosphorylation potential

Frequently, the phosphorylation potential ΔG_P is considered as the key variable for the cell bioenergetics, as an "energy charge" measure in the cell that controls most bioenergetic processes (Hancock et al. 2006a; Smith et al. 2024). ΔG_P or Gibbs free energy or free enthalpy of the ATP hydrolysis reaction (ATP → ADP + P_i) is defined as follows:

$$\Delta DG_P = \Delta DG_P^0 + RT\ln\left(\left(\mathrm{ADP} \times \mathrm{P_i}\right)/\mathrm{ATP}\right), \tag{2}$$

where $\Delta G^0{}_P = - 32$ kJ mol^{-1} is ΔG_P defined at "standard" equilibrium conditions (involving, e.g., Mg^{2+}, K^+, and H^+ ion concentrations), R is the gas constant, and T is absolute temperature (in K) (Nicholls and Ferguson 2002). Of course, a certain minimal level of ΔG_P is necessary to drive various reactions/processes for purely thermodynamic reasons. However, once this level is exceeded, this is not ΔG_P, but its components: ATP, ADP, P_i, and H^+ that kinetically regulate particular reactions/processes (see Wiseman et al. 2023 for a recent discussion). A given level of ΔG_{ATP} can result from different combinations of ATP, ADP, P_i, and H^+ levels, and their impact on the muscle bioenergetic system can be very different. Additionally, AMP and PP_i that do not "enter into the composition" of ΔG_P also regulate the cellular metabolism. This is the main reason why ΔG_P is not dealt with in the present study. Additionally, the exact value of ΔG_P depends on several factors, for instance, ion (e.g., Mg^{2+} and K^+) concentrations that are different according to different sources. Nevertheless, the ATP/ADP ratio is calculated that is (to some extent) proportional to ΔG_P to approach to some extent the cell "energy charge".

Smith et al. (2024) postulated a smaller decrease in ΔG_P in the presence of AMP deamination (fall in ATP by 19%) during an 8-min incremental protocol (2-min stages of isotonic knee extensions). However, the authors did not take into account the AD-induced augmented P_i increase during exercise in their considerations on the impact of AD on ΔG_P.

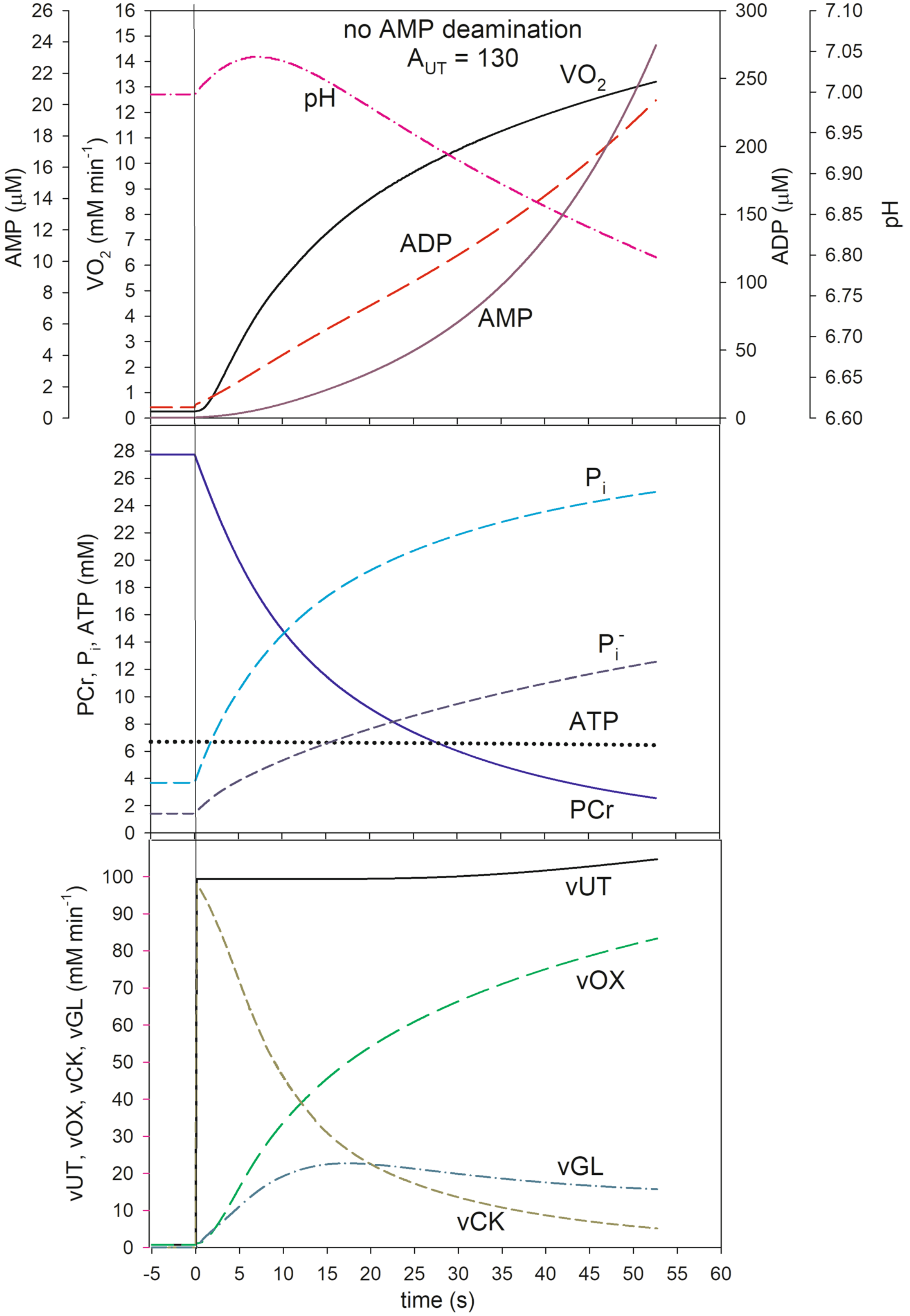
In the absence of AMP deamination, there is a unique relationship between ATP, ADP, P_i, and H^+ during rest-to-work transition. However, AMP deamination decouples this unique relationship. This is another reason why the effect of ATP, ADP, P_i, and H^+ (and also of AMP and PP_i) should be considered in separation.

Effect of ADP, AMP, P_i, PP_i and H^+ on cell metabolism

Particular energy-related metabolites (ADP, AMP, P_i, PP_i, H^+) regulate kinetically various reactions/processes within the system in a different way and to a different extent. For instance, most probably the main metabolite related to muscle fatigue (both peripheral and central) is P_i, with H^+ as an additional factor and ADP playing essentially no (at best minor) role (Allen et al. 2008; Hureau et al. 2022; see also Korzeniewski and Rossiter 2020). Other authors (Wilson et al. 1988; Sundberg et al. 2019) suggest that this is not P_i itself, but rather its deprotonated form $H_2PO_4^-$ (P_i^-) that is the "real" fatigue factor. It was shown (Cooke and Pate 1986; Hendry et al. 2025) that P_i is the main metabolite inhibiting actomyosin-ATPase (at the stage of power stroke generation of the cross-bridge cycle coupled with P_i release from the myosin head) with a smaller contribution of H^+ and essentially no impact of ADP. P_i precipitates with Ca^{2+} ions within the sarcoplasmic reticulum, which lowers free Ca^{2+} concentration and thus weakens muscle contraction (Allen and Westerblad 2001; Hureau et al. 2022). As discussed above, ADP is a strong inhibitor of Na^+/K^+-ATPase and Ca^{2+}-ATPase. ADP and P_i activate OXPHOS to a different extent (Chance and Williams 1955; Korzeniewski and Brown 1998; Liguzinski and Korzeniewski 2006), while ATP and H^+ do not affect OXPHOS in the physiological range of concentrations (Suleymanlar et al. 1992). TCA cycle is markedly activated by ADP (Arnold and Finley 2022). Glycolysis is differently regulated by ADP, AMP, P_i,and PP_i (all of them being activators of glycolysis) (Connett and Sahlin 1996; Lambeth and Kushmerick 2001; Korzeniewski and Liguzinski 2004).

Factors promoting AMP deamination

AMP deamination is favored by stressing conditions leading to high ADP and AMP increase during exercise: (1) high exercise intensity (Sabina et al. 1984; Katz et al. 1986; Sahlin and Bloberg 1990; Harris et al. 1991; Hellsten et al. 1999; Parolin et al. 1999; Tullson et al. 1995; Hancock et al. 2006a, b; Sundberg et al. 2019; Zhao et al. 2000; Norman et al. 2001; Smith et al. 2024); (2) hypoxia/anoxia (Meyer and Terjung 1979; Meyer et al. 1980; Dudley and Terjung 1985; Söderlund and Hultman 1991; Hancock et al. 2006a, b)); (3) low capacity for ATP supply by OXPHOS: fast-twitch fibers vs. low-twitch fibers (Meyer and Terjung 1979; Meyer et al. 1980; Dudley and Terjung 1985; Söderlund and Hultman 1991; Hancock et al. 2006a, b) (because of low OXPHOS complexes activity and/or low/absent ESA, Korzeniewski 2003); (4) electrically stimulated, externally perfused muscle (Meyer and Terjung 1979; Dudley and Terjung 1985) (because of low/absent ESA, Korzeniewski 2003); (5) untrained/sedentary individuals (Dudley and Terjung 1985; Hancock et al. 2006a, b) (because of lower OXPHOS activity, Korzeniewski and Rossiter 2021). Additionally, the intensity of AD seems to have a tendency to increase with the intensity of the enumerated factors (Meyer and Terjung 1979; Meyer et al. 1980; Sabina et al. 1984; Dudley and Terjung 1985; Katz et al. 1986; Sahlin and


no AMP deamination
A_{UT} = 130
VO_2
pH
ADP
AMP
AMP (μM)
VO_2 (mM min^{-1})
ADP (μM)
pH
0 2 4 6 8 10 12 14 16 18 20 22 24 26
0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16
0 50 100 150 200 250 300
6.60 6.65 6.70 6.75 6.80 6.85 6.90 6.95 7.00 7.05 7.10
P_i
P_i^-
ATP
PCr
PCr, P_i, P_i^-, ATP (mM)
0 2 4 6 8 10 12 14 16 18 20 22 24 26 28
vUT
vOX
vGL
vCK
vUT, vOX, vCK, vGL (mM min^{-1})
0 10 20 30 40 50 60 70 80 90 100
-5 0 5 10 15 20 25 30 35 40 45 50 55 60
time (s)

◂**Fig. 3** Simulated time courses of selected fluxes and metabolite concentrations during constant-power very intense exercise (VIE) to the limit of tolerance with ATP usage activity $A_{UT} = 130$ and no AMP deamination ($v_{AD} = 0$ mM min^{-1}). *vUT* ATP usage flux, *vOX* ATP supply by OXPHOS (+aerobic glycolysis) flux; *vGL* ATP supply by anaerobic glycolysis flux; *vCK* ATP supply by creatine kinase (CK) flux

Bloberg 1990; Harris et al. 1991; Söderlund and Hultman 1991; Hellsten et al. 1999; Parolin et al. 1999; Tullson et al. 1995; Zhao et al. 2000; Hancock et al. 2006a, b; Sundberg et al. 2019; Norman et al. 2001; Smith et al. 2024). For instance, all cases where the fall in ATP exceeded 30% involved very intense exercise, fast-twitch fibers, hypoxia/anoxia, and/or electrical stimulation of externally perfused muscles (Meyer and Terjung 1979; Meyer et al. 1980; Dudley and Terjung 1985; Harris et al. 1991; Söderlund and Hultman 1991; Zhao et al. 2000; Norman et al. 2001). It was postulated (Korzeniewski 2003) that each-step activation (ESA) that elevates the effective OXPHOS activity/capacity during muscle work (but not at rest) about fivefold (Korzeniewski and Rossiter 2015; Korzeniewski 2017, 2019) is highly active in cortically stimulated oxidative muscles in situ and slightly active or completely switched off in electrically stimulated externally perfused glycolytic muscles. Generally, ESA attenuates the ADP, P_i, and AMP increase (e.g., Korzeniewski 2017). This could help to explain points 3 and 4 above. In the present work, various conditions leading to different extents of ADP and AMP increase (bioenergetic stress) were approximated by constant-power exercises to exhaustion of different intensities (ATP usage activity, A_{UT}) and AMP deamination rates (v_{AD}). However, it should be stressed that AMP deamination to be initiated requires not only bioenergetic stress (elevated ADP and AMP), but also high work intensity/ATP turnover (Sahlin et al. 1990).

AMP deaminase deficiencies

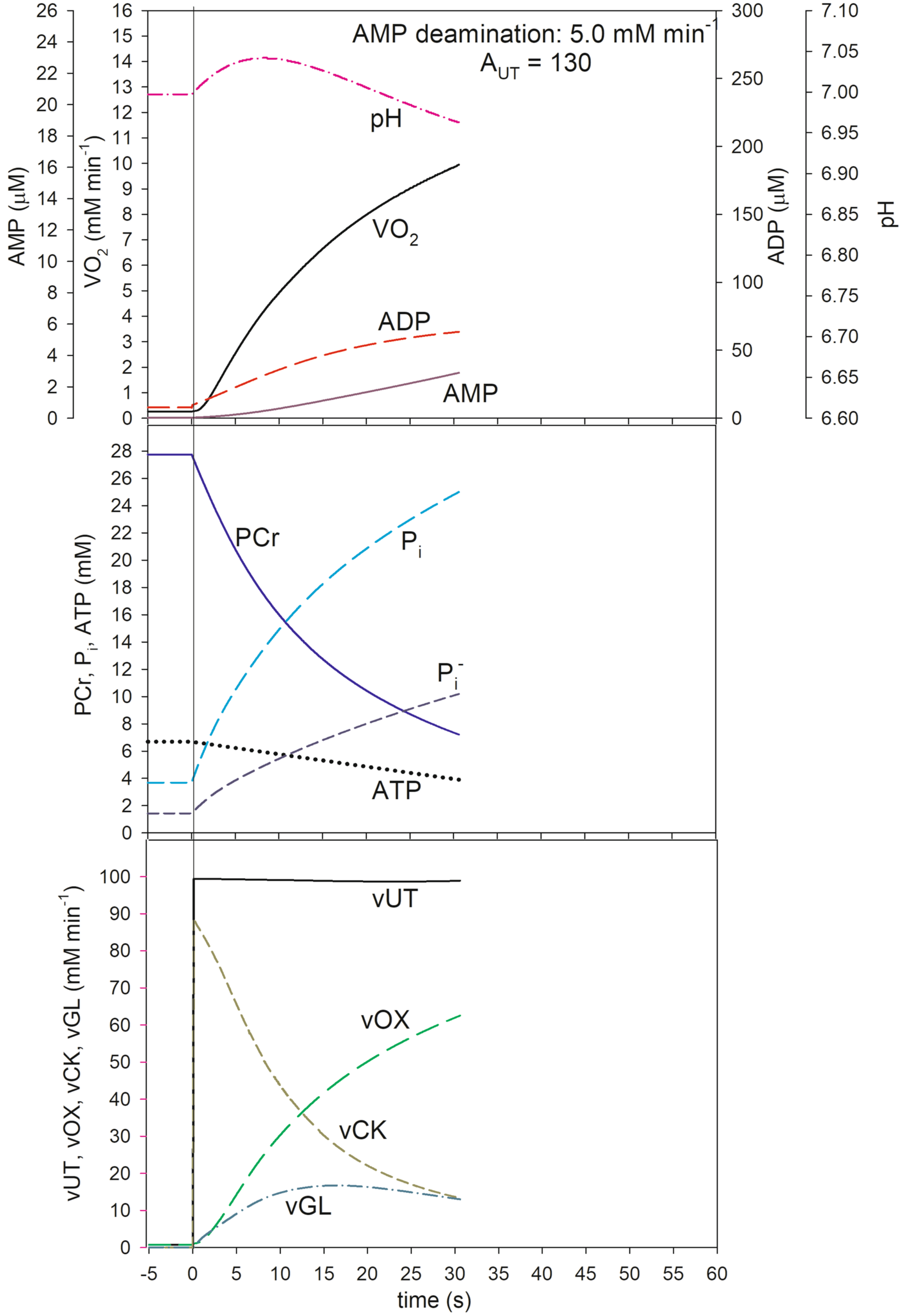
The AMP deaminase deficiency (ADD) is the most common muscle enzyme defect in man, found in about 2–3% of all muscle biopsies. It can lead to various exercise-induced muscle symptoms such as early fatigue, cramps, and/or myalgia (Kelman et al. 1982; Sabina et al. 1984; Gross 1997). However, the vast majority of homozygous subjects do not develop a metabolic myopathy (Gross et al. 1997; Sabina 2000; Norman et al. 2001; de Ruiter 2002). In mice, an induced deficiency of adenosine monophosphate deaminase 1 (AMPD1) slows down the rate of muscle contraction and relaxation, thus significantly impairing muscle function (Hafen et al. 2022). The reason for this heterogeneity remains uncertain (Gross 1997). It can be related to the compensative capabilities of other biochemical pathways or the exercise type. Perhaps, AMP deamination exerts some milder long-term effects that gave our ancestors an evolutionary advantage (better fitness) over their competitors. The lack of pathological syndromes in most ADD patients does not imply that the presence of AD does not improve muscle performance and intactness over long periods of time. Certainly, this process would not appear during human (and animal) evolution without playing a certain beneficial role. Additionally, as AD certainly exerts some harmful effects (depletion of the total adenine nucleotide pool, shortening of the exercise duration to the limit of tolerance), the advantages it brings must prevail over these disadvantages. The lack of pathological symptoms in many (most?) ADD bearers does not mean that AD does not improve muscle performance during exercise or especially during continuously repeated series of exercises during human (and animal) lifetime. The present study is intended to investigate some of the potential advantages and disadvantages of AMP deamination.

It is possible that the attenuated increase in ADP, AMP, and H^+ during muscle exercise exerts a long-term effect that is difficult to observe in one exercise, but cumulates over tens and hundreds of subsequent exercises. This could involve, e.g., less muscle damage according to stress and/or more efficient muscle repair after stress during lifetime, so that damages acquired in subsequent exercises do not accumulate. Some cases of ADD patients with severe pathological symptoms seem to support this possibility.

It was demonstrated that in skeletal muscle lacking adenylate kinase, ADP rises to a very high level during heavy exercise (Hancock et al. 2006b). This is an effect analogous to the effect of ADD. Therefore, most probably the role of the concerted action of AMP deaminase and adenylate kinase is to attenuate the exercise-induced ADP (and AMP) increase.

Of course, the differences between AD− and AD+ exercises shown in Figs. 1, 2, 3, 4, 5, 6 are conclusive provided that all other system parameters/properties remain unchanged. However, this does not have to be the case in ADDs, where numerous compensative changes are likely to develop during lifetime.

It may seem contradictory that the model predicts that AMP deaminase deficiency attenuates task failure and lengthens exercise, while in reality the deficiency decreases muscle performance or has no visible effect. The prolongation of exercise seems beneficial when considered in isolation. However, one should bear in mind that AMP deamination deficiency causes harmful effects through ADP and AMP increase acceleration during the entire life, affecting muscle function and causing overall decline in muscle performance. It is likely that the skeletal muscle bioenergetic system adapts somehow to the absence of AMP deamination. Therefore, various effects, both harmful and compensatory, accumulate for a long time. The resultant effect of all these phenomena is difficult to predict and probably depends on a combination of factors in a given case (e.g., the size of


AMP deamination: 5.0 mM min-1
AUT = 130
pH
VO2
ADP
AMP
AMP (μM)
VO2 (mM min-1)
ADP (μM)
pH
0
2
4
6
8
10
12
14
16
18
20
22
24
26
0
1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
0
50
100
150
200
250
300
6.60
6.65
6.70
6.75
6.80
6.85
6.90
6.95
7.00
7.05
7.10
PCr
Pi
Pi-
ATP
PCr, Pi, ATP (mM)
0
2
4
6
8
10
12
14
16
18
20
22
24
26
28
vUT
vOX
vCK
vGL
vUT, vOX, vCK, vGL (mM min-1)
0
10
20
30
40
50
60
70
80
90
100
-5
0
5
10
15
20
25
30
35
40
45
50
55
60
time (s)

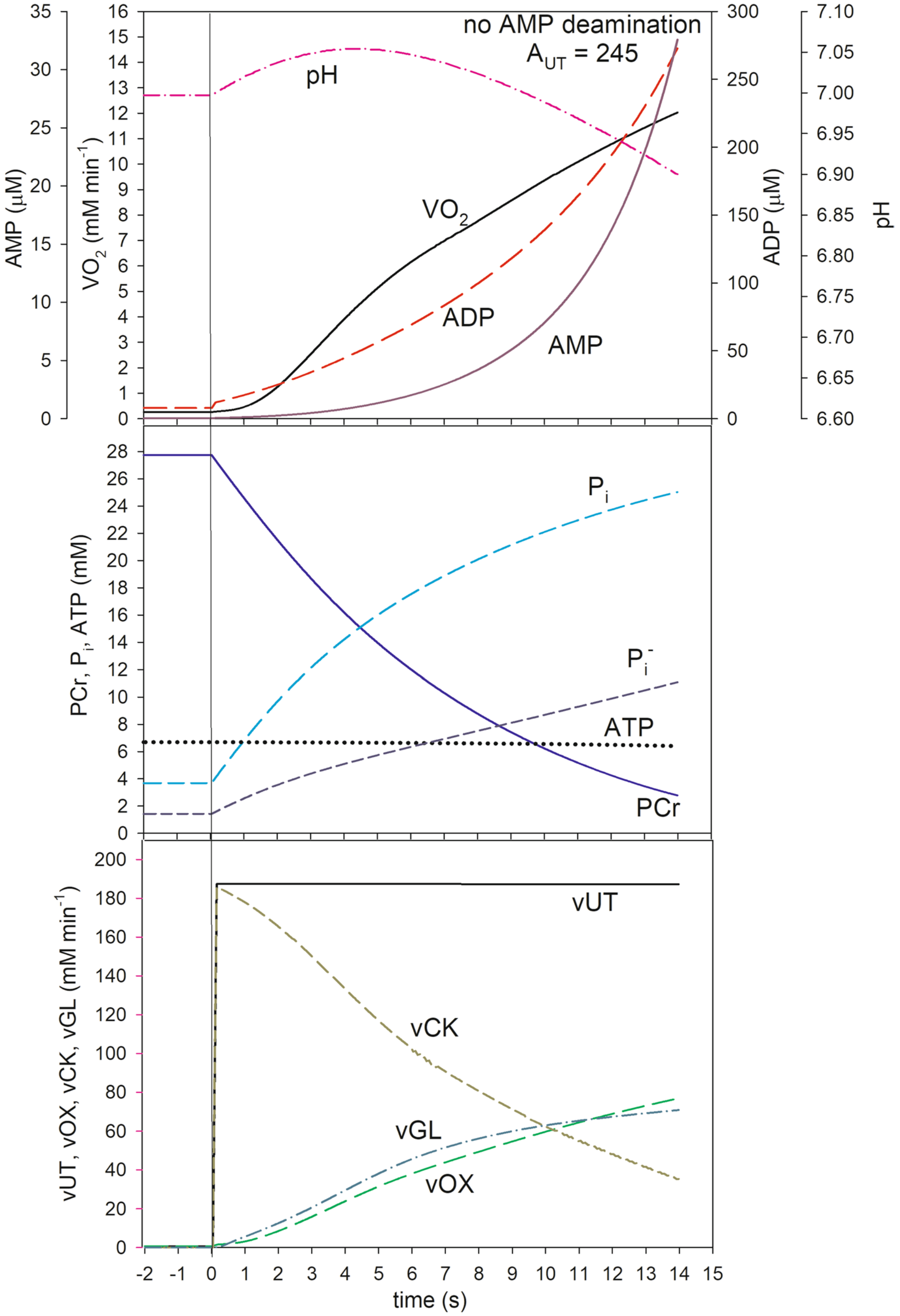
◂**Fig. 4** Simulated time courses of selected fluxes and metabolite concentrations during constant-power very intense exercise (VIE) to the limit of tolerance with ATP usage activity $A_{UT} = 130$ and AMP deamination rate $v_{AD} = 5.0$ mM min^{-1}. *vUT* ATP usage flux, *vOX* ATP supply by OXPHOS (+ aerobic glycolysis) flux; *vGL* ATP supply by anaerobic glycolysis flux; *vCK* ATP supply by creatine kinase (CK) flux

deficiency, compensatory mechanisms). For instance, the value of Pi_{peak} could be higher in subjects with intact AMP deaminase, which would delay task failure and thus lengthen the exercise. This is perhaps the reason for the huge variability of the effect of AMP deaminase deficiency in different individuals and cases. The model predicts the effect of AMP deaminase deficiency, provided that all other factors are kept unchanged. In reality, this is most probably not the case.

Slow AMP resynthesis during muscle recovery

AMP and ultimately A_{tot} (chiefly ATP) is resynthesized very slowly—it takes minutes/tens of minutes—during muscle

Fig. 5 Simulated time courses of selected fluxes and metabolite concentrations during constant-power extremely intense exercise (EIE) to the limit of tolerance with ATP usage activity $A_{UT} = 245$ and no AMP deamination ($v_{AD} = 0$ mM min^{-1}). *vUT* ATP usage flux, *vOX* ATP supply by OXPHOS (+ aerobic glycolysis) flux; *vGL* ATP supply by anaerobic glycolysis flux; *vCK* ATP supply by creatine kinase (CK) flux



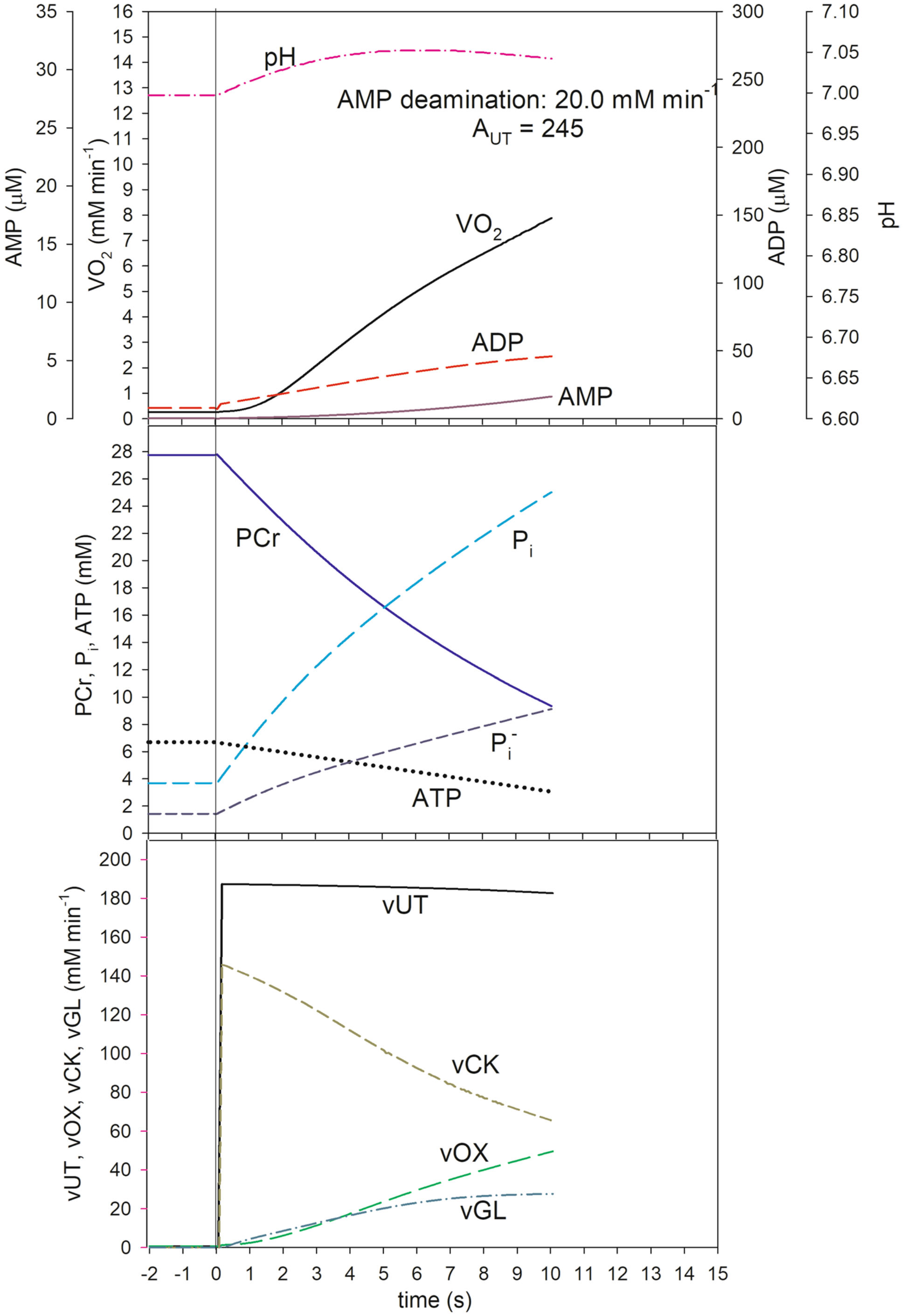


Fig. 6 Simulated time courses of selected fluxes and metabolite concentrations during constant-power extremely intense exercise (EIE) to the limit of tolerance with ATP usage activity $A_{UT} = 245$ and AMP deamination rate $v_{AD} = 20.0$ mM min^{-1}. *vUT* ATP usage flux, *vOX* ATP supply by OXPHOS (+ aerobic glycolysis) flux; *vGL* ATP supply by anaerobic glycolysis flux; *vCK* ATP supply by creatine kinase (CK) flux

recovery after exercise (Taylor et al. 1986; Zhao et al. 2000; Smith et al. 2024). The reason for this phenomenon is not known. Rather moderate effects of low vs. high AMP resynthesis rate during muscle recovery were predicted by computer simulations (Fig. 9 vs. Fig. 8). They comprise a certain acceleration of the return of ADP and pH and slowing down of the return of P_i to the rest values. However, low ATP resynthesis rate can be important for subsequent exercises with significant AMP deamination that could lead to (almost) complete depletion of ATP, which seems decidedly disadvantageous. Therefore, slow AMP and A_{tot} resynthesis remains a puzzle.

It was postulated that the PCr recovery overshoot—related to ADP undershoot—observed in some cases during muscle recovery and lasting several minutes is caused by a slow decay of ESA during recovery (Korzeniewski 2003; Korzeniewski and Zoladz 2013). The role of this phenomenon could be activation of muscle cell recovery/

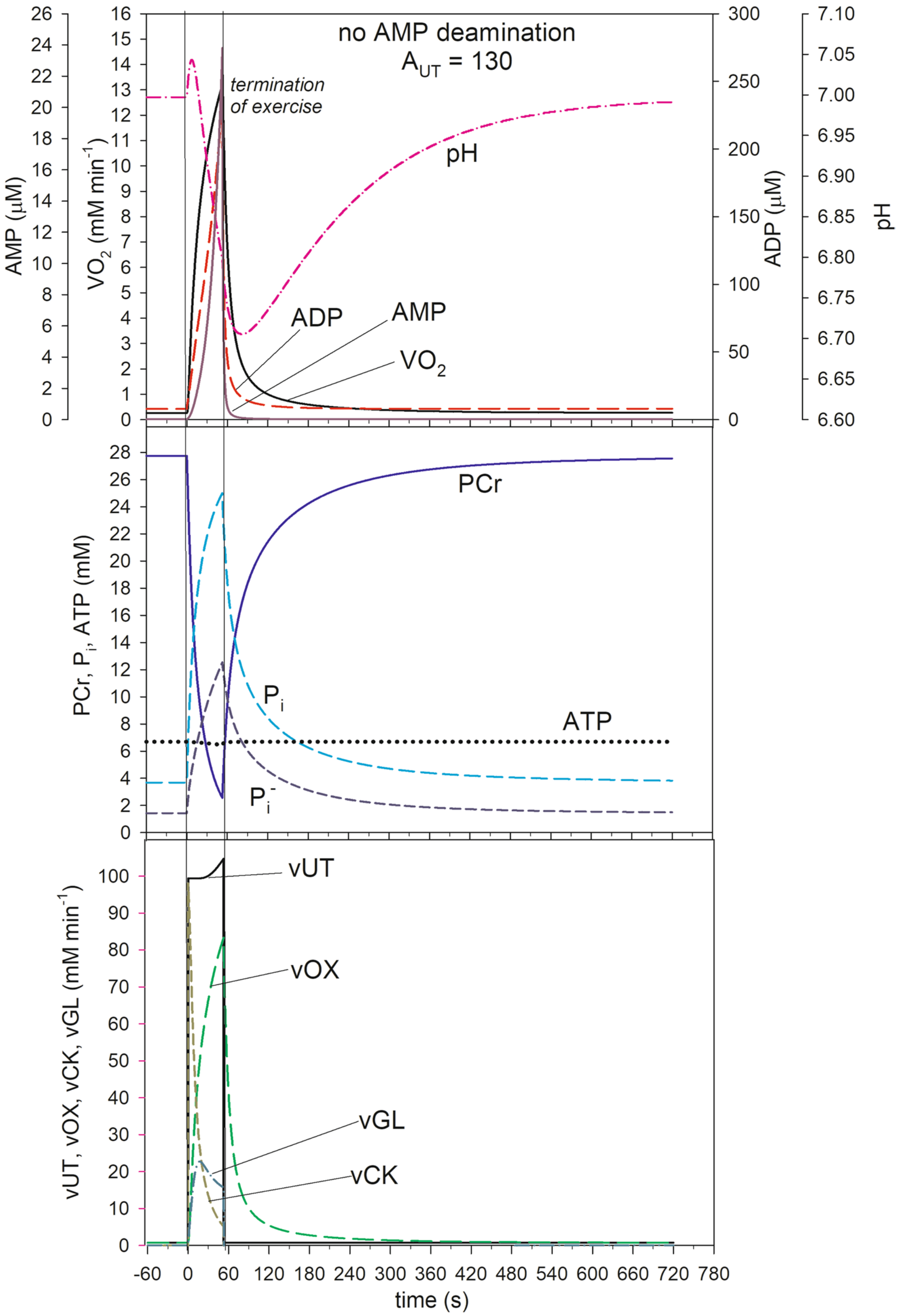


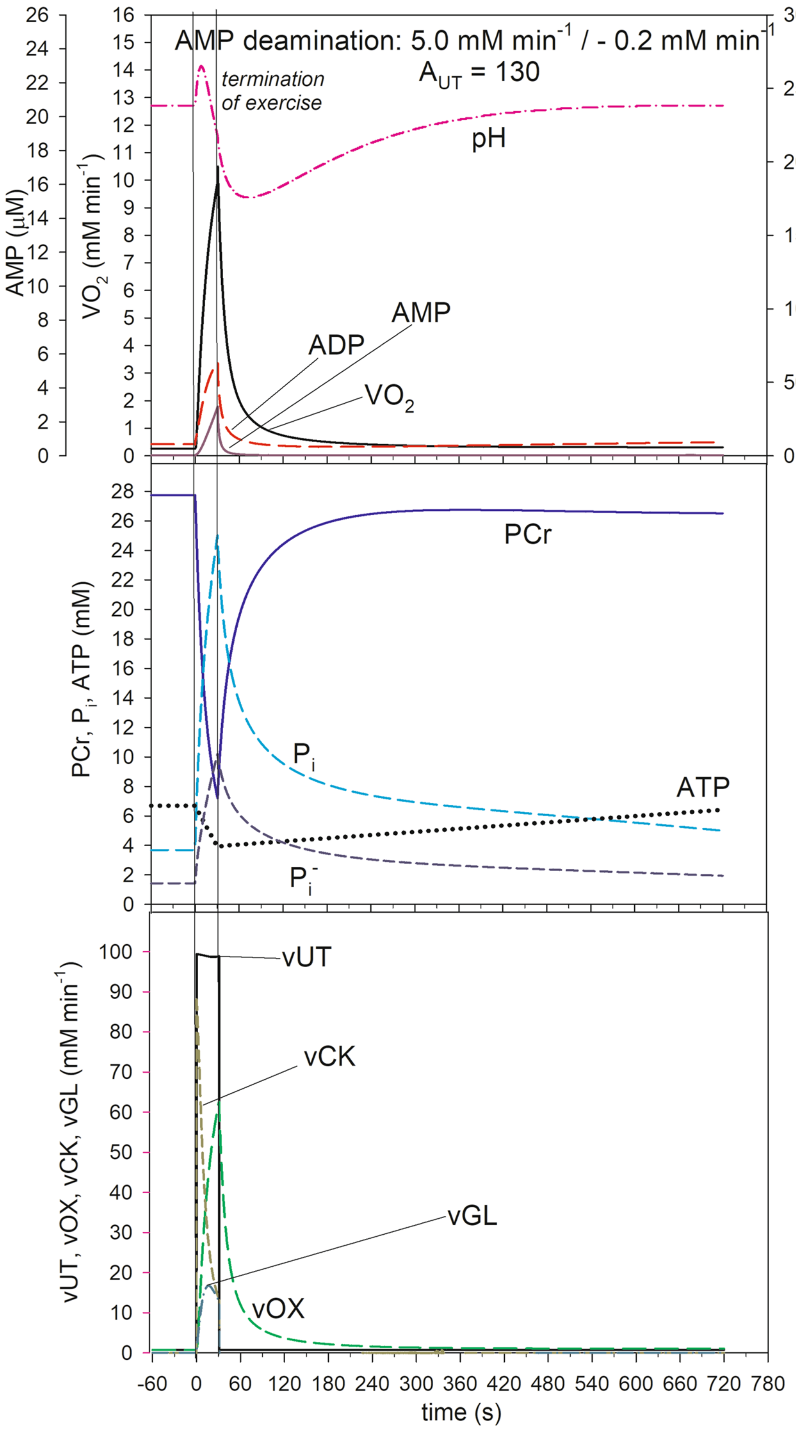
Fig. 7 Simulated time courses of selected fluxes and metabolite concentrations during constant-power very intense exercise (VIE) to the limit of tolerance and recovery after exercise, with ATP usage activity $A_{UT} = 130$ and no AMP deamination ($v_{AD} = 0$ mM min^{-1}). vUT, ATP usage flux, vOX, ATP supply by OXPHOS (+ aerobic glycolysis) flux; vGL, ATP supply by anaerobic glycolysis flux; vCK, ATP supply by creatine kinase (CK) flux

repair after stressing exercise—such anabolic processes as protein and RNA synthesis are stimulated by a high ATP/ADP ratio (or not inhibited by a low ADP level). Therefore, the somewhat faster return of ADP to the low resting level at slow than at fast AMP resynthesis during recovery (Fig. 9 vs. Fig. 8) could have a similar effect. Nevertheless, the difference between both cases is disappointingly small.

General discussion

A dynamic computer model was used in this theoretical study. An advantage of a well-tested model is that it allows to formulate quantitative and explicit and not only qualitative and intuitive explanations. The very structure of the model enables to investigate true causal relations as opposed

Fig. 8 Simulated time courses of selected fluxes and metabolite concentrations during constant-power very intense exercise (VIE) to the limit of tolerance and recovery after exercise with ATP usage activity $A_{UT} = 130$, AMP deamination rate during exercise $v_{AD} = 5.0$ mM min^{-1} and slow AMP resynthesis (reamination) during recovery $v_{AD} = -0.2$ mM min^{-1}. *vUT* ATP usage flux, *vOX* ATP supply by OXPHOS (+aerobic glycolysis) flux; *vGL* ATP supply by anaerobic glycolysis flux; *vCK* ATP supply by creatine kinase (CK) flux

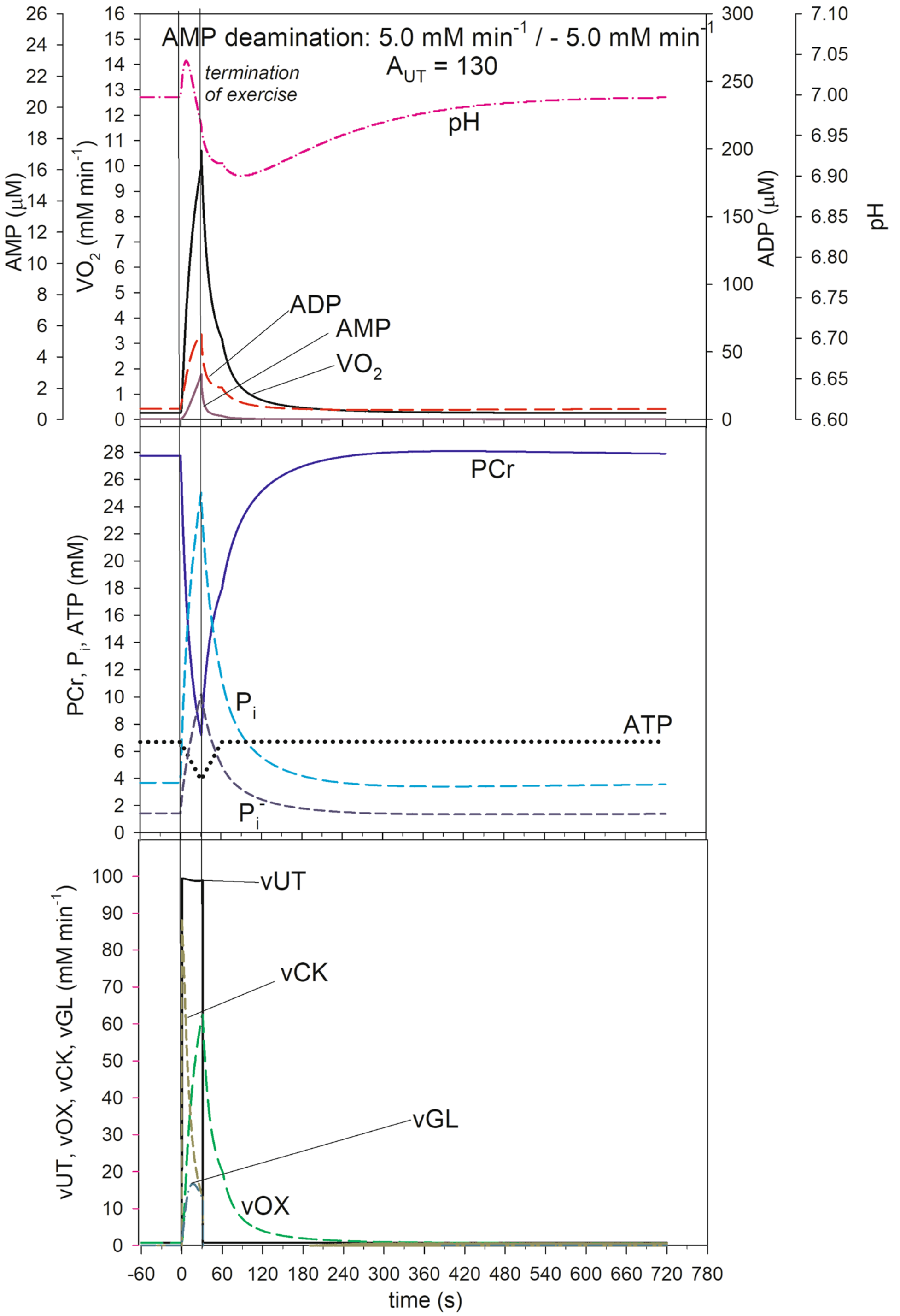


to correlations between various variables. As such, a good model can be a valuable supplement of experimental studies that helps to explain and integrate them.

Constant-power exercise to exhaustion was used in the present study, although in reality in VIE and especially EIE all-out exercise would probably be a better approximation of the real situation. However, this study is not intended to refer to any particular kind of exercise, but to stressful exercise/conditions in general. IE, VIE, and EIE are intended to reflect different conditions/situations where bioenergetic stress in the form of highly elevated ADP and AMP is present: e.g., hypoxia/anoxia, fast-twitch muscle fibers, electrical stimulation/external perfusion, and untrained/sedentary individuals.

The absolute AMP concentration is uncertain, as different (although usually roughly around 1) equilibrium constants

Fig. 9 Simulated time courses of selected fluxes and metabolite concentrations during constant-power very intense exercise (VIE) to the limit of tolerance and recovery after exercise with ATP usage activity $A_{UT} = 130$, AMP deamination rate during exercise $v_{AD} = 5.0$ mM min^{-1} and fast AMP resynthesis (reamination) during recovery $v_{AD} = -5.0$ mM min^{-1}. *vUT* ATP usage flux, *vOX* ATP supply by OXPHOS (+aerobic glycolysis) flux; *vGL* ATP supply by anaerobic glycolysis flux; *vCK* ATP supply by creatine kinase (CK) flux



of adenylate kinase (AK) are reported (they depend on conditions, e.g., assumed Mg^{2+} concentration). The values of a few micromoles at the end of exercise obtained in this study are comparable to, e.g., those reported in Parolin et al. (1999), see also Tullson and Terjung (1990). However, relative changes in AMP are most relevant, and they are essentially the same at different equilibrium constants of AK (simulations not shown).

Study limitations

Of course, the dynamic computer model of the skeletal muscle bioenergetic system used in this study, as in every model of this kind, constitutes only an approximation and simplification of the complex reality.

In the present study, all conditions of bioenergetic stress during exercise (especially strongly elevated ADP and AMP), for instance intense constant-power exercise to exhaustion, incremental exercise and all-out exercise, hypoxia/anoxia, glycolytic muscles/muscle fibers, electrically stimulated externally perfused muscles, and so on, are approximated by three constant-power exercises of different intensities and with different rates of AMP deamination. Of course, this constitutes a significant simplification. However, it is not of prime importance how ADP, AMP, and H^+ are elevated to a high value, but how the initiated AMP deamination counteracts (the effect of) their further increase.

This study used a “one-compartment” model that does not take into account different fiber types and is averaged over the whole muscle. However, it was developed based on “averaged”, “one-compartment” experimental data, such as pulmonary and muscle $\dot{V}O_2$ and muscle ATP, ADP, AMP, P_i, and H^+, and generates predictions concerning this kind of system variables that can be measured experimentally.

AMP deamination in heart is not the topic of the present study. However, some difference in this process and its effect can be expected between these tissues. For instance, primarily because of a significantly lower total phosphate pool in heart, this organ is much less susceptible to an increase in P_i and fatigue, which is important for tissue specificity of mitochondrial myopathies (Korzeniewski 2016) or ischemic conditions.

The model used in this study does not involve explicitly IMP and NH_3 concentrations. However, it is reasonable to assume that their values are increased in the result of AMP deamination.

Nevertheless, it does not seem that these simplifications and approximations affect significantly the general conclusions drawn in the present study.

Conclusions

AMP deamination (AD) in skeletal muscle during intense work and/or in bioenergetic stress conditions has both benefits (improvement of muscle performance, health, and condition) and harms (worsening of muscle performance, health, and condition). The harmful effect is of course the decrease in the total adenine nucleotide pool, especially ATP, particularly when a series of subsequent intense exercises following each other is considered. Another disadvantage is acceleration of P_i increase and thus shortening of exercise duration to the limit of tolerance, according to the P_i double-threshold mechanism of muscle fatigue. These harms must be overcompensated by profits; otherwise, the considered phenomenon would not be created during biological evolution. The main advantageous effect of AMP deamination is the attenuation of ADP, AMP, and H^+ increase in intense exercise/bioenergetic stress. These metabolites at high levels inhibit several reactions/processes in the cell essential for its functioning, chiefly during exercise, such as Ca^{2+}-ATPase and Na^+/K^+-ATPase. The more intense/stressing the exercise, the stronger is this advantageous effect. An additional benefit of AD is prevention of significant cytosol acidification in the initial phase of muscle recovery after exercise. The slow AMP resynthesis during recovery somewhat accelerates the return of ADP and pH to the resting level, which could help in muscle repair after intense exercise and/or stress-induced damages. However, this effect is rather modest. Therefore, further studies are needed to fully explain the role of AMP deamination during intense stressing exercise and of slow AMP resynthesis during recovery after exercise.

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Declarations

Conflict of interest The author declares that there are no competing interests associated with the manuscript.

References

Allen DG, Westerblad H (2001) Role of phosphate and calcium stores in muscle fatigue. J Physiol 536:657–665. https://doi.org/10.1111/j.1469-7793.2001.t01-1-00657.x

Allen DG, Lamb GD, Westerblad H (2008) Skeletal muscle fatigue: cellular mechanisms. Physiol Rev 88:287–332. https://doi.org/10.1152/physrev.00015.2007

Apell HJ, Nelson MT, Marcus MM, Läuger P (1986) Effects of the ATP, ADP and inorganic phosphate on the transport rate of the Na+, K+-pump. Biochim Biophys Acta 857(1):105–115. https://doi.org/10.1016/0005-2736(86)90103-3

Arnold PK, Finley LWS (2022) Regulation and function of the mammalian tricarboxylic acid cycle. J Biol Chem 299(2):102838. https://doi.org/10.1016/j.jbc.2022.102838

Chance B, Williams GR (1955) Respiratory enzymes in oxidative phosphorylation. IV. The respiratory chain. J Biol Chem 217(1):429–38.

Connett R, Sahlin K (1996) Control of glycolysis and glycogen metabolism. In: Rowell L, Shepherd J (eds) Handbook of physiology. Oxford University Press, New York, pp 870–911

Cooke R, Pate E (1986) The effects of ADP and phosphate on the contraction of muscle fibers. Biophys J 48(5):789–798. https://doi.org/10.1016/S0006-3495(85)83837-6

de Ruiter CJ, May AM, van Engelen BG, Wevers RA, Steenbergen-Spanjers GC, de Haan A (2002) Muscle function during repetitive moderate-intensity muscle contractions in myoadenylate deaminase-deficient Dutch subjects. Clin Sci (Lond) 102:531–539. https://doi.org/10.1042/cs20010190

Dudley GA, Terjung RL (1985) Influence of acidosis on AMP deaminase activity in contracting fast-twitch muscle. Am J Physiol 248(1):C43–C50. https://doi.org/10.1152/ajpcell.1985.248.1.C43

Gross M (1997) Clinical heterogeneity and molecular mechanisms in inborn muscle AMP deaminase deficiency. J Inherit Metab Dis 20(2):186–192. https://doi.org/10.1023/a:1005352605421

Hafen PS, Law AS, Matias C, Miller SG, Brault JJ (2022) Skeletal muscle contraction kinetics and AMPK responses are modulated by the adenine nucleotide degrading enzyme AMPD1. J Appl Physiol 133:1055–1066

Hancock CR, Brault JJ, Terjung RL (2006a) Protecting the cellular energy state during contractions: role of AMP deaminase. J Physiol Pharmacol 57(Suppl 10):17–29

Hancock CR, Janssen E, Terjung RL (2006b) Contraction-mediated phosphorylation of AMPK is lower in skeletal muscle of adenylate kinase-deficient mice. J Appl Physiol 100(2):406–413. https://doi.org/10.1152/japplphysiol.00885.2005

Harris RC, Marlin DJ, Snow DH, Harkness RA (1991) Muscle ATP loss and lactate accumulation at different work intensities in the exercising Thoroughbred horse. Eur J Appl Physiol 62:235–244. https://doi.org/10.1007/BF00571546

Hellsten Y, Richter EA, Kiens B, Bangsbo J (1999) AMP deamination and purine exchange in human skeletal muscle during and after intense exercise. J Physiol 520:909–920. https://doi.org/10.1111/j.1469-7793.1999.00909.x

Hendry JI, Erol ME, Layec G, Debold EP, Tewari SG, Wallqvist A, Pannala VR (2025) A human skeletal muscle cross-bridge model to characterize the role of metabolite accumulation in muscle fatigue. Exp Physiol. https://doi.org/10.1113/EP092843

Hochachka PW, Mommsen TP (1983) Protons and anaerobiosis. Science 219:1391–1397. https://doi.org/10.1126/science.6298937

Hureau TJ, Broxterman RM, Weavil JC, Lewis MT, Layec G, Amann M (2022) On the role of skeletal muscle acidosis and inorganic phosphates as determinants of central and peripheral fatigue: a ^{31} P-MRS study. J Physiol 600:3069–3081. https://doi.org/10.1113/JP283036

Inesi G, Tadini-Buoninsegni H (2014) Ca^{2+}/H^{+} exchange, lumenal Ca^{2+} release and Ca^{2+}/ATP coupling ratios in the sarcoplasmic reticulum ATPase. J Cell Commun Signal 8(1):5–11. https://doi.org/10.1007/s12079-013-0213-7

Katz A, Sahlin K, Henriksson J (1986) Muscle ammonia metabolism during isometric contraction in humans. Am J Physiol 250:C834–C840. https://doi.org/10.1152/ajpcell.1986.250.6.C834

Kelemen J, Rice DR, Bradley WG, Munsat TL, DiMauro S, Hogan EL (1982) Familial myoadenylate deaminase deficiency and exertional myalgia. Neurology 32:857–863. https://doi.org/10.1212/wnl.32.8.857

Kennedy BG, Lunn G, Hoffman JF (1986) Effects of altering the ATP/ADP ratio on pump-mediated Na/K and Na/Na exchanges in resealed human red blood cell ghosts. J Gen Physiol 87:47–72. https://doi.org/10.1085/jgp.87.1.47

Korzeniewski B (1998) Regulation of ATP supply during muscle contraction: theoretical studies. Biochem J 330:1189–1195. https://doi.org/10.1042/bj3301189

Korzeniewski B (2003) Regulation of oxidative phosphorylation in different muscles and various experimental conditions. Biochem J 375:799–804. https://doi.org/10.1042/BJ20030882

Korzeniewski B (2006) AMP deamination delays muscle acidification during heavy exercise and hypoxia. J Biol Chem 281:3057–3066. https://doi.org/10.1074/jbc.M510418200

Korzeniewski B (2007) Regulation of oxidative phosphorylation through parallel activation. Biophys Chem 129:93–110. https://doi.org/10.1016/j.bpc.2007.05.013

Korzeniewski B (2016) Faster and stronger manifestation of mitochondrial diseases in skeletal muscle than in heart related to cytosolic inorganic phosphate (P$_i$) accumulation. J Appl Physiol 121:424–437. https://doi.org/10.1152/japplphysiol.00358.2016

Korzeniewski B (2017) Regulation of oxidative phosphorylation through each-step activation (ESA): evidences from computer modeling. Prog Biophys Mol Biol 125:1–23. https://doi.org/10.1016/j.pbiomolbio.2016.12.001

Korzeniewski B (2019) Pi-induced muscle fatigue leads to near-hyperbolic power–duration dependence. Eur J Appl Physiol 119:2201–2213. https://doi.org/10.1007/s00421-019-04204-8

Korzeniewski B (2023a) Sensitivity of $\dot{V}o_{2max}$, critical power and $\dot{V}o_2$ on-kinetics in skeletal muscle. Resp Physiol Neurobiol 307:103977. https://doi.org/10.1016/j.resp.2022.103977

Korzeniewski B (2023b) Training-induced increase in VO_{2max} and critical power, and acceleration of $\dot{V}O_2$ on-kinetics result from attenuated P$_i$ increase caused by elevated OXPHOS activity. Metabolites 13:1111. https://doi.org/10.3390/metabo13111111

Korzeniewski B (2024) P$_i$-based biochemical mechanism of endurance-training-induced improvement of running performance in humans. Eur J Appl Physiol 125:49–59. https://doi.org/10.1007/s00421-024-05560-w

Korzeniewski B, Brown GC (1998) Quantification of the relative contribution of parallel pathways to signal transfer: application to cellular energy transduction. Biophys Chem 75:73–80. https://doi.org/10.1016/s0301-4622(98)00193-8

Korzeniewski B, Liguzinski P (2004) Theoretical studies on the regulation of anaerobic glycolysis and its influence on oxidative phosphorylation in skeletal muscle. Biophys Chem 110:147–169. https://doi.org/10.1016/j.bpc.2004.01.011

Korzeniewski B, Rossiter HB (2015) Each-step activation of oxidative phosphorylation is necessary to explain muscle metabolite kinetic responses to exercise and recovery in humans. J Physiol 593:5255–5268. https://doi.org/10.1113/JP271299

Korzeniewski B, Rossiter HB (2020) Exceeding a "critical" P$_i$: implications for $\dot{V}O_2$ and metabolite slow components, muscle fatigue and the power-duration relationship. Eur J Appl Physiol 120:1609–1619. https://doi.org/10.1007/s00421-020-04388-4

Korzeniewski B, Rossiter HB (2021) Factors determining training-induced changes in $\dot{V}o_{2max}$, critical power and $\dot{V}o_2$ on-kinetics in skeletal muscle. J Appl Physiol 130:498–507. https://doi.org/10.1152/japplphysiol.00745.2020

Korzeniewski B, Rossiter HB (2022) Skeletal muscle biochemical origin of exercise intensity domains and their relation to whole-body $\dot{V}O_2$ kinetics. Biosci Rep 42:BSR20220798. https://doi.org/10.1042/BSR20220798

Korzeniewski B, Zoladz JA (2001) A model of oxidative phosphorylation in mammalian skeletal muscle. Biophys Chem 92:17–34. https://doi.org/10.1016/s0301-4622(01)00184-3

Korzeniewski B, Zoladz JA (2003) Possible factors determining the non-linearity in the VO_2-power output relationship in humans" theoretical studies. Jpn J Physiol 53:271–280. https://doi.org/10.2170/jjphysiol.53.271

Korzeniewski B, Zoladz JA (2013) Slow VO2 off-kinetics in skeletal muscle is associated with fast PCr off-kinetics–and inversely. J Appl Physiol 115:605–612. https://doi.org/10.1152/japplphysiol.00469.2013

Lambeth MJ, Kushmerick MJ (2001) A computational model for glycogenolysis in skeletal muscle. Ann Biomed Bioenerg 30:808–827. https://doi.org/10.1114/1.1492813

Liguzinski P, Korzeniewski B (2006) Metabolic control over the oxygen consumption flux in intact skeletal muscle: in silico studies. Am J Physiol Cell Physiol 291:C213–C224. https://doi.org/10.1152/ajpcell.00078.2006

Lowenstein JM (1990) The purine nucleotide cycle revisited [corrected]. Int J Sports Med 11(Suppl 2):S37-46. https://doi.org/10.1055/s-2007-1024853. (**Erratum in: Int J Sports Med 11:411,1990**)

Macdonald WA, Stephenson DG (2001) Effects of ADP on sarcoplasmic reticulum function in mechanically skinned skeletal muscle fibres of the rat. J Physiol 532(Pt 2):499–508. https://doi.org/10.1111/j.1469-7793.2001.0499f.x

Meyer RA, Terjung RL (1979) Differences in ammonia and adenylate metabolism in contracting fast and slow muscle. Am J Physiol

237(3):C111–C118. https://doi.org/10.1152/ajpcell.1979.237.3.C111

Meyer RA, Dudley GA, Terjung RL (1980) Ammonia and IMP in different skeletal muscle fibers after exercise in rats. J Appl Physiol Respir Environ Exerc Physiol 49(6):1037–1041. https://doi.org/10.1152/jappl.1980.49.6.1037

Nicholls DG, Ferguson SJ (2002) Bioenergetics 3. Academic Press, London

Norman B, Sabina RL, Jansson E (2001) Regulation of skeletal muscle ATP catabolism by AMPD1 genotype during sprint exercise in asymptomatic subjects. J Appl Physiol 91:258–264. https://doi.org/10.1152/jappl.2001.91.1.258

Parolin ML, Chesley A, Matsos MP, Spriet LL, Jones NL, Heigenhauser GJF (1999) Regulation of skeletal muscle glycogen phosphorylase and PDH during maximal intermittent exercise. Am J Physiol 277:E890–E900. https://doi.org/10.1152/ajpendo.1999.277.5.E890. (**Endocrinol Metab**)

Peluffo RD (2004) Effect of ADP on Na^+-Na^+ exchange reaction kinetics of Na,K-ATPase. Biophys J 87:883–898. https://doi.org/10.1529/biophysj.103.030643

Richter EA, Ruderman NB (2009) AMPK and the biochemistry of exercise: implications for human health and disease. Biochem J 418(2):261–275. https://doi.org/10.1042/BJ20082055

Sabina RL (2000) Myoadenylate deaminase deficiency. A common inherited defect with heterogeneous clinical presentation. Neurol Clin 18:185–194. https://doi.org/10.1016/s0733-8619(05)70184-5

Sabina RL, Swain JL, Olanow CW, Bradley WG, Fishbein WN, DiMauro S, Holmes EW (1984) Myoadenylate deaminase deficiency. Functional and metabolic abnormalities associated with disruption of the purine nucleotide cycle. J Clin Invest 73(3):720–730. https://doi.org/10.1172/JCI111265

Sahlin K, Broberg S (1990) Adenine nucleotide depletion in human muscle during exercise: causality and significance of AMP deamination. Int J Sports Med 11(Suppl 2):S62-67. https://doi.org/10.1055/s-2007-1024856

Sahlin K, Palmskog G, Hultman E (1978) Adenine nucleotide and IMP contents of the quadriceps muscle in man after exercise. Pflug Arch 374(2):193–198. https://doi.org/10.1007/BF00581301

Sahlin K, Gorski J, Edstrom L (1990) Influence of ATP turnover and metabolite changes on IMP formation and glycolysis in rat skeletal muscle. Am J Physiol 259:C409–C412. https://doi.org/10.1152/ajpcell.1990.259.3.C409

Smith ZH, Hayden CMT, Hayes KL, Kent JA (2024) Skeletal muscle inosine monophosphate formation preserves ΔG_{ATP} during incremental step contractions in vivo. Am J Physiol Regul Integr Comp Physiol. https://doi.org/10.1152/ajpregu.00192.2024

Söderlund K, Hultman E (1991) ATP and phosphocreatine changes in single human muscle fibers after intense electrical stimulation. Am J Physiol 261(24):E737–E741. https://doi.org/10.1152/ajpendo.1991.261.6.E737. (**Endocrinol Metab**)

Suleymanlar G, Zhou HZ, McCormack M, Elkins N, Kucera R, Reiss OK, Shapiro JI (1992) Mechanism of impaired energy metabolism during acidosis: role of oxidative metabolism. Am J Physiol 262(6 Pt 2):H1818–H1822. https://doi.org/10.1152/ajpheart.1992.262.6.H1818

Sundberg CW, Prost RW, Fitts RH, Hunter SK (2019) Bioenergetic basis for the increased fatigability with ageing. J Physiol 597:4943–4957. https://doi.org/10.1113/JP277803

Taylor DJ, Styles P, Matthews PM, Arnold DA, Gadian DG, Bore P, Radda GK (1986) Energetics of human muscle: exercise-induced ATP depletion. Magn Reson Med 3:44–54. https://doi.org/10.1002/mrm.1910030107

Tullson PC, Terjung RL (1990) Adenine nucleotide degradation in striated muscle. Int J Sports Med 11:47–55. https://doi.org/10.1055/s-2007-1024854

Tullson PC, Terjung RL (1991) Adenine nucleotide metabolism in contracting skeletal muscle. Exerc Sport Sci Rev 19:507–537

Tullson PC, Bangsbo J, Hellsten Y, Richter EA (1995) IMP metabolism in human skeletal muscle after exhaustive exercise. J Appl Physiol 78(1):146–152. https://doi.org/10.1152/jappl.1995.78.1.146

Wheeler TJ, Lowenstein JM (1979) Adenylate deaminase from rat muscle. Regulation by purine nucleotides and orthophosphate in the presence of 150 mM KCl. J Biol Chem 254:8994–8999

Wheeler TJ, Lowenstein JM (1980) Effects of pyrophosphate, triphosphate, and potassium chloride on adenylate deaminase from rat muscle. Biochemistry 19:4564–2567. https://doi.org/10.1021/bi00561a004

Wilson JR, McCully KK, Mancini DM, Boden B, Chance B (1988) Relationship of muscular fatigue to pH and diprotonated P_i in humans: a ^{31}P-NMR study. J Appl Physiol 64:2333–2339. https://doi.org/10.1152/jappl.1988.64.6.2333

Wiseman RW, Brown CM, Beck TW, Brault JJ, Reinoso TR, Shi Y, Chase PB (2023) Creatine kinase equilibration and ΔG_{ATP} over an extended range of physiological conditions: implications for cellular energetics, signaling, and muscle performance. Int J Mol Sci 24:13244. https://doi.org/10.3390/ijms241713244

Zhang Y, Kobayashi C, Cai X, Watanabe S, Tsutsumi A, Kikkawa M, Sugita Y, Inaba K (2022) Multiple sub-state structures of SERCA2b reveal conformational overlap at transition steps during the catalytic cycle. Cell Rep 41(10):111760. https://doi.org/10.1016/j.celrep.2022.111760

Zhao S, Snow RJ, Stathis CG, Febbraio MA, Carey MF (2000) Muscle adenine nucleotide metabolism during and in recovery from maximal exercise in humans. J Appl Physiol 88:1513–1519. https://doi.org/10.1152/jappl.2000.88.5.1513

Zoladz JA, Majerczak J, Korzeniewski B (2025) Possible role of muscle AMP deamination. Am J Physiol-Regul Integr Comp Physiol. https://doi.org/10.1152/ajpregu.00030.2025