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Physiology of Muscle Fatigue during Intense Exercise

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1. INTRODUCTION

During maximal exercise fatigue, defined as a loss of force output, occurs within seconds (Fig. 1). The question is "what causes fatigue during intense exercise?" It could be central (cortical), but it appears that in well-motivated subjects, a substantial component of fatigue can be localized in the muscle [1]. It is difficult to identify a single factor in muscle responsible for the reduction in performance during intense exercise, but there are various suggestions for the cause of fatigue. This review will mainly be focused on a few selected variables, such as ATP, lactate, protons and potassium, which have been implicated in the development of fatigue during intense exercise in humans.

2. AVAILABILITY OF MUSCLE ATP

Fatigue does not appear to be related to lack of energy, since muscle ATP rarely fails bellow 60% of pre-exercise level during exhaustive voluntary exercise [2], and even in highly fatigued fibres, the ATP concentration is over 100-fold higher than the micromolar amounts required for peak force [3]. In addition, it has been observed that when intense dynamic exercise was repeated, muscle ATP concentration was significantly lower at the end of the second exercise bout, indicating that lack of ATP was not the cause of fatigue during the first exercise period [2]. Furthermore, in a study where single fibre analysis was performed on muscle biopsies taken immediately after exercise no fibre was totally depleted of ATP, even after electrical stimulation that resulted in a large decline in force [4,5].

Performance of high intensity intermittent exercise has been observed to be increased after a period of creatine intake [16], which in other studies has been shown to increase muscle creatine and creatine phosphate (CP), and it has been suggested that low CP levels cause fatigue [6,7]. In line with that notion is the finding in several studies of a reduced muscle function in animals where creatine (Cr) and CP have been depleted by a period of feeding with beta-guanidinopropionic acid (GPA), an analog of Cr [8,9]. On the other hand, it has been observed that CP declines rapidly in the initial phase of exercise and that subjects are

able to maintain the exercise intensity for several minutes even though the CP concentration remains low [10]. Therefore, it is doubtful that low CP levels *per se* cause fatigue.

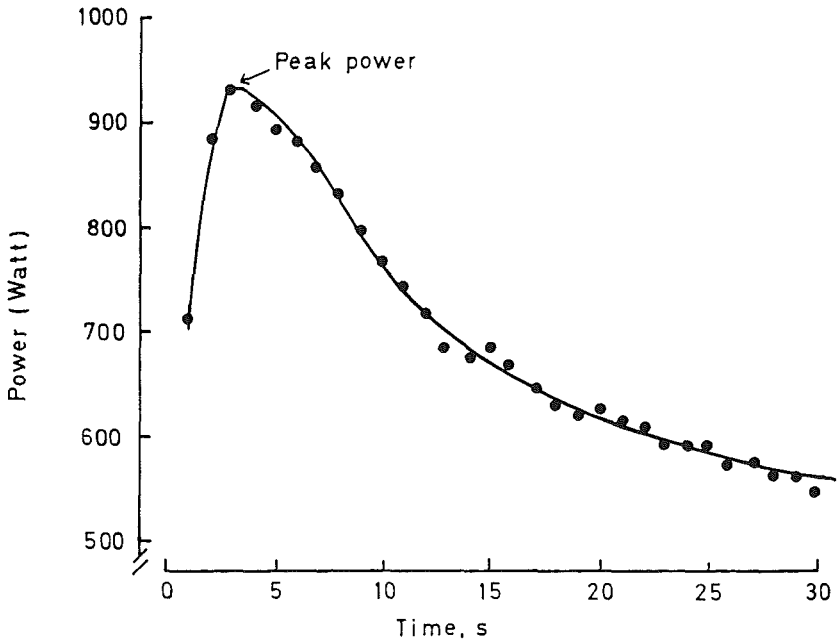

Figure 1. Power output and fatigue profile generated during cycle ergometer sprints.

It could be argued, however, that the role of ATP and CP as limiting factors during intense exercise can not be revealed from measurements of muscle ATP and CP. The ATP may not be equally distributed in the muscle cell [11-13]. Thus, the measured ATP may not reflect the actual ATP concentration at the sites of ATP utilization. It may be that during intense exercise the ATP concentration falls below a critical level in the vicinity of the ATP utilization sites thereby causing a drop in contractile capacity. Bessmann and Savabi [15] showed that the ATP produced by bound myofibrillar CK has better access to myofibrillar ATPase than does the general pool of ATP.

Furthermore, McLellan and Vinegrad [16] demonstrated that there is an ADP pool in myofibrills which can easily be rephosphorylated into ATP by myofibrillar CK but which is not accessible for mitochondrial CK. However, it should be pointed out that all data supporting ATP compartmentation are indirect and definitive evidence for physiologically important compartmentation has not yet been demonstrated.

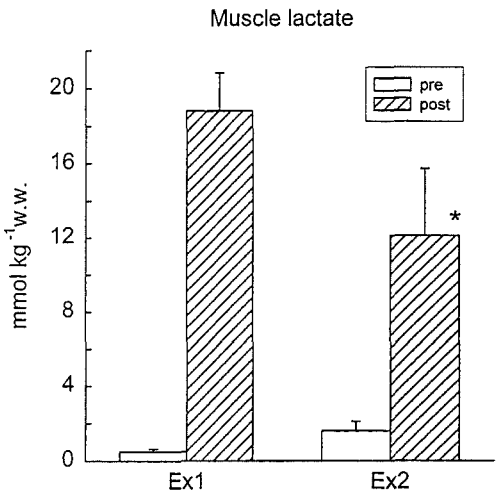

Figure 2. Muscle lactate prior to and at the end of two exhaustive knee-extensor exercise bouts separated by 1 h of recovery. Note that the muscle lactate concentration at exhaustion was significantly lower at the end of exercise. Data used with permission from Journal of Physiology.

3. ACCUMULATING MUSCLE LACTATE AND PROTEINS

Lactate ions *per se* have been observed to inhibit rabbit SR Ca^{2+} channel activity [17]. Furthermore, increased lactate concentrations have been reported to impair development of tension in intact dog muscle [18]. However, in the latter study the effect of lactate could not be differentiated from the associated change in pH. In addition, lactate anions *per se* had no effect on maximal Ca^{2+} activated force in skinned fibres [19]. Thus, it is questionable whether lactate *per se* causes fatigue. This notion is supported by findings in a study in which subjects repeated intense exhaustive knee-extensor exercise after a 60 min recovery period [20]. At the point of exhaustion the muscle lactate concentration in the second exercise bout was only 65% of the concentration at the end of the first exercise bout (Fig. 2).

A large production of lactate during intense exercise is associated with elevated acidity within the exercising muscles. Decreases in muscle pH from about 7.1 to 6.5-6.8 are often observed during intense exhaustive exercise [2, 21-22], and based on NMR studies it has been suggested that pH in individual fibres can be even lower [23-24]. This may affect the function of the muscle cells, as it is known from *in vitro* studies that low pH has an inhibitory effect on various functions within the muscle cell, e.g. the activity of phosphorylase and PKF, the excitation-contraction coupling, the affinity for Ca^{2+} to bind to troponin, the coupling between the contractile elements and the re-uptake of Ca^{2+} in the sarcoplasmatic reticulum [SR; 19,25-30].

It is generally believed that lowered pH causes fatigue [31,32]. However, lactate and pH may not be exclusive determinants of fatigue [2,21,33]. In order to examine the effect of

muscle pH on development of fatigue during intense exercise, seven subjects performed intense exhaustive leg exercise on two occasions: with (leg+arm; LA) and without (leg; L) preceding intense intermittent arm exercise [33]. The duration of the exercise was shorter in LA than in L (3.46±0.28 (±SE) vs. 4.67±0.55 min; $p<0.05$). Before exercise muscle pH was the same in L and LA, but at the end of exercise muscle pH was lower in LA than in L (Fig. 3). The latter finding suggests that there is no definitive muscle pH that leads to fatigue and that low pH is not the only factor causing fatigue during intense muscle contractions *in vivo.*

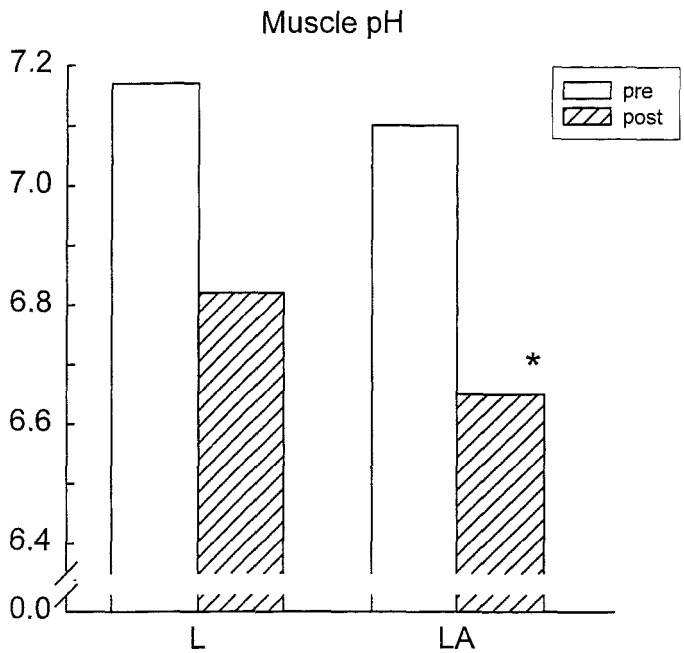

Figure 3. Muscle pH prior to and at the end of exhaustive knee-extensor performed without (L) and with (LA) prior arm exercise. Note that the muscle pH was significantly lower when the exhaustive exercise was preceded by intense intermittent arm exercise. Data use with permission from Journal of Physiology.

The results from the studies on humans are also supported by findings in a study where single fibres from mouse skeletal muscle were repetitively stimulated [34]. Under certain conditions a pronounced decline in tension and slowing in relaxation could not be explained by an intracellular acidification. Similarly, both studies on frog and human muscles have

shown that the rapid phase of recovery in force cannot be explained by the decline in H^+ accumulation, since muscle pH decreases after an intense muscle contraction [31,35-36].

4. ACCUMULATING POTASSIUM IN MUSCLE INTERSTITIUM

It has been speculated that a progressive accumulation of potassium in the interstitium during intense exercise may be implicated in the fatigue process [2,22,37]. In the study mentioned above [33] with and without prior arm exercise, the release of potassium during the exercise was higher in LA than in L. The greater release of potassium in LA led to the same arterial and venous potassium concentration at the point of exhaustion in LA and L, even though the exercise duration was shorter in LA. Furthermore, in both L and LA conditions, the potassium efflux to the blood was reduced at the end of exercise, possibly due to the increasing arterial potassium concentrations, suggesting that potassium in the interstitium accumulated progressively towards the end of exercise. The finding of the same arterial and venous potassium concentrations at exhaustion under the two conditions are in accordance with observations in studies where intense exercise was repeated [2,22]. They are also in agreement with the observation of similar arterial and venous potassium concentrations at exhaustion, whether intense exercise was performed with or without β-blockade, although the exercise time was shorter with β-blockade [38].

The mechanism behind the possible effect of potassium on the development of fatigue is unclear. It may be that the accumulating potassium stimulates sensory receptors of group III and IV nerve fibres leading to inhibition at the spinal level [Fig. 4; 1,39]. Another coupling between fatigue and potassium could be an inhibition of the propagation of the action potential due to ion disturbances over the sarcolemma and a possible block in its propagation into the t-tubules [37]. The latter hypothesis is supported by the observation that rather small increments in extracellular potassium led to a reduction in tension in subsequent contractions when isolated mouse muscles were stimulated [40]. It is possible that a continuous efflux of potassium from the exercising muscle, together with a limited reuptake and a reduced release to venous blood, leads to a progressive accumulation of potassium in the interstitium which may have been implicated in the fatigue process. Even though the results from this experiment indicate that lowered pH *per se* does not cause fatigue, a decrease in pH in LA may promote the development of fatigue during exercise by increasing the release of potassium from the muscle cell through potassium channels [41-42].

The scheme which may prevail is that an elevated potassium concentration around the muscle fibres blocks prolongation of the action potential over some fibre membranes and possibly at the same time stimulates the sensory input, which causes inhibition of spinal motor nerves [39]. This is likely to be a gradual phenomenon, and can at first be overcome by the drive from the motor cortex as the firing rates are elevated and new motor units are activated. However, a point is reached when the number of new muscle fibres that can be activated is considerably reduced and the reflex inhibition causes such a reduction in spinal motor activity output, that the muscles are unable to maintain the exercise intensity [39].

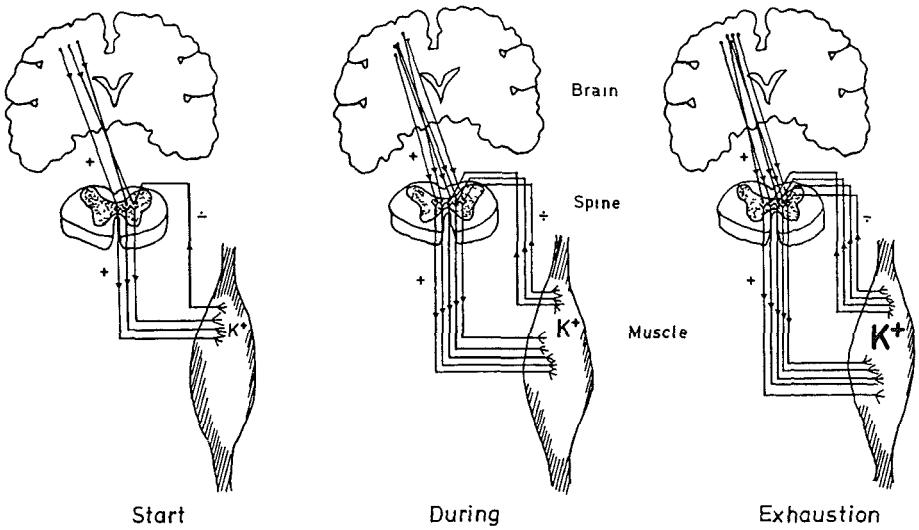

Figure 4. A hypothesis of how accumulating interstitial potassium within a muscle may cause fatigue. As exercise progresses potassium accumulates more and more which stimulates inhibitory signals from the muscle leading to greater and greater activation of motor nerves until it is not possible to activate more fibres.

5. OTHER FACTORS

There are various other suggestions for the cause of fatigue during intense exercise. Just a few potential candidates will briefly be mentioned.

It has been suggested that fatigue may be caused by a decreased capacity to rephosphorylate ADP in combination with a high rate of ATP turnover [32]. This does not appear to be related to an elevated free ADP concentration, as the ADP concentration within the physiological range had no effect on the cross-bridge interaction studied in a skinned fibre preparation [43]. On the other hand, an elevated P_i concentration was shown to reduce the contraction force [43]. A role for P_i is supported by the NMR observations of a relationship between the diproteinated form of P_i ($H_2PO_4^-$) and the decline in force [22,44], and further by the finding of a relationship between recovery of P_i and peak tetanic force of frog muscles [45], but other studies have failed to show such a coupling [46-47].

Fatigue may also be related to a failure in the coupling between t-tubular depolarization and Ca^{2+} release from sarcoplasmatic reticulum (SR), or to a decreased rate of Ca^{2+} re-uptake to SR, which would slow the rate of relaxation [28]. In support of this theory is the observation that the Ca^{2+} uptake by the SR-system was depressed after intense exhaustive exercise and that this reduction was inversely related to the relaxation half-time [48]. It was also coupled to a reduced MVC, indicating that the release of Ca^{2+} from the SR-system was

affected as well. For further discussion of the role of Ca^{2+} in the development of fatigue see Westerblad *et al.* [49].

6. CONCLUSIONS

Fatigue during intense exercise appears to be due to local factors in the exercising muscle. It is difficult to identify a single factor in the muscle responsible for the reduction in performance during intense exercise. Based on measurements of ATP and CP in muscle biopsies obtained during and at the end of intense exhaustive exercise, it seems that muscle fatigue is not caused by a lack of energy. However, it is possible that ATP is compartmentalized and that the ATP concentration can fall below a critical level in the vicinity of the ATP utilization sites, thereby causing a drop in contractile capacity. Many *in vitro* studies have shown that elevated muscle acidity has an inhibitory effect on several reactions within the muscle cell. However, *in vivo* studies have demonstrated that lowered muscle pH is not the only factor in the development of fatigue during intense exercise. Instead, fatigue during intense exercise may be associated with an excitation-coupling failure and possibly a reduced nervous drive due to reflex inhibition at the spinal level. In the latter hypothesis accumulation of interstitial potassium in muscle may play a major role.

7. ACKNOWLEDGEMENT

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Discussion: Physiology of Muscle Fatigue during Intense Exercise

A.J.M. Wagenmakers:

You conclude that ATP and creatine phosphate are not failing to very low levels and therefore do not play a role in muscle fatigue. But you have shown that in quite a few of the fibres, there are remarkable reductions in the concentration of ATP and creatine phosphate. Probably the drop in ATP is attended by an increase in the free ADP concentration and the drop in creatine phosphate must be attended by an increase in the inorganic phosphate concentration in these fibres. Both inorganic phosphate and free ADP are inhibitors of the Na^+/K^+ pump and this may lead to potassium accumulation in the interstitial fluid. So this provides a way to directly link the factors that you exclude to the cause of fatigue.

J. Bangsbo:

That is a very good point. I did not discuss all points of fatigue and I did not discuss phosphate, as such, and you are definitely right. The accumulation of phosphate inhibits the different ATPase reactions and contraction may be affected. However, several studies have not seen a correlation between phosphate and the development of fatigue. Anyway it could be that the inhibitory role of phosphate at the Na^+/K^+ pumps could reduce the re-uptake of potassium, leading to a further increase in potassium in the interstitium and that is then causing the fatigue. There is a complex interplay between many of these factors we are dealing with.

F. Brouns:

One should also consider the energy charge of the cell, because there may be synergistic effects and all these factors change at the same time. Together with an increase in lactate, you see also an increase in ammonia, meaning that there is a depletion of the adenylate-rich pool which may change the energy charge. Did you look at that?

J. Bangsbo:

We see different levels of AMP, nucleotide degradation and ammonia at fatigue indicating that those are not *per se* causing the fatigue. They may however influence the ΔG_{ATP}, but this is very difficult to determine as we are talking about the free concentration of ADP, phosphate and so.

S. Erill:

Just a comment. Fatigue is a very common and ill-explained side effect of anti-hypertensive medication or anti-hypertensive drugs. I wonder whether this potassium channel hypothesis does not provide a lead for further studies into the mechanism of antihypertensive medication induced fatigue.

M. Orme:

Some of the newer drugs (unlike diuretics which mostly lower serum potassium) such as ACE-inhibitors and many beta blockers actually increase serum potassium and so might be expected to cause a rise of intracellular potassium in tissues such as skeletal muscle.

J.R. Barbany:
Could you comment on the effects of hypoxia on muscle fatigue and its mechanisms?

J. Bangsbo:
It is dependent on what type of exercise we are dealing with. If you look at submaximal exercise, there you have almost the same oxygen uptake but you have an earlier type of fatigue at hypoxia and it may be difficult to explain the exact mechanism of that type of fatigue. If you look at more intense exercise, you also have an effect on performance. You have reduced oxygen uptake during intense exercise, and therefore, a higher need for anaerobic energy production that leads to lower pH. That may have a link to the potassium and may then create an earlier type of fatigue during those conditions.

J.R. Barbany:
What about fatigue during hypoxia conditions at high altitude?

J. Bangsbo:
The aerobic ATP producing system is reduced which may influence the Na^+/K^+ pumps and may influence the pH. Unless you get at a very high altitude where you have the so-called lactate paradox where muscle lactate concentrations are low at exhaustion, showing that there are other mechanisms that cause fatigue under those conditions.

T.E. Graham:
A number of speakers have presented pH data and it appears that they looked at it in a variety of ways statistically. And you should keep in mind that pH is a log scale. One should really be converting it to hydrogen ion, because it is amazing until you actually do that, how different these small changes in pH are and they are not anything close to linear changes. Especially once you get into muscle changes, which are bigger than blood, it can be quite a big factor.

D.P.M. MacLaren:
Going back to the accumulation of potassium. There are data that tend to suggest that the accumulation of potassium may in some way influence either calcium release or calcium re-uptake by the sacroplasmic reticulum and therefore relaxation rates, so inducing fatigue. Have you any comments to make on that?

J. Bangsbo:
There have been studies that have focused specifically on potassium in the muscle cell. We have to remember that the potassium concentration is pretty high at rest and it decreases markedly during exercise but it is still fairly high at the point of fatigue. So it is questionable how forceful that effect may be.

If potassium is the fatigue agent, it may have implications for training. The question is how we can decrease the accumulation of potassium in the interstitium. An increase in the number of Na^+/K^+ pumps has been reported after training and therefore, you expect a more efficient uptake of potassium and in that way, this may explain a delay of fatigue or we could call it, increased performance after the training.