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Lactic Acid and Exercise Performance
Culprit or Friend?

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Abstract

This article critically discusses whether accumulation of lactic acid, or in reality lactate and/or hydrogen (H^+) ions, is a major cause of skeletal muscle fatigue, i.e. decline of muscle force or power output leading to impaired exercise performance. There exists a long history of studies on the effects of increased lactate/H^+ concentrations in muscle or plasma on contractile performance of skeletal muscle. Evidence suggesting that lactate/H^+ is a culprit has been based on correlation-type studies, which reveal close temporal relationships between intramuscular lactate or H^+ accumulation and the decline of force during fatiguing stimulation in frog, rodent or human muscle. In addition, an induced acidosis can impair muscle contractility in non-fatigued humans or in isolated muscle preparations, and several mechanisms to explain such effects have been provided. However, a number of recent high-profile papers have seriously challenged the 'lactic acid hypothesis'. In the 1990s, these findings mainly involved diminished negative effects of an induced acidosis in skinned or intact muscle fibres, at higher more physiological experimental temperatures. In the early 2000s, it was conclusively shown that lactate has little detrimental effect on mechanically skinned fibres activated by artificial stimulation. Perhaps more remarkably, there are now several reports of protective effects of lactate exposure or induced acidosis on potassium-depressed muscle contractions in isolated rodent muscles. In addition, sodium-lactate exposure can attenuate severe fatigue in rat muscle stimulated *in situ*, and sodium lactate ingestion can increase time to exhaustion during sprinting in humans. Taken together, these latest findings have led to the idea that lactate/H^+ is ergogenic during exercise.

It should not be taken as fact that lactic acid is the deviant that impairs exercise performance. Experiments on isolated muscle suggest that acidosis has little detrimental effect or may even improve muscle performance during high-intensity exercise. In contrast, induced acidosis can exacerbate fatigue during whole-body dynamic exercise and alkalosis can improve exercise performance in events lasting 1–10 minutes. To reconcile the findings from isolated muscle fibres through to whole-body exercise, it is hypothesised that a severe plasma acidosis in humans might impair exercise performance by causing a reduced CNS drive to muscle.

With repeated contraction of skeletal muscle there is eventually a decline of muscle force or power output leading to impairment of whole-body exercise performance, that is, fatigue develops. The aetiology of fatigue is controversial, although it has been associated with diminished motor drive from the CNS and/or changes of metabolites, electrolytes or ultrastructural damage within muscle.[1-7] The relative contribution of these factors seems to depend on the nature of the exercise or the fatigue model employed.[5,6,8] During high-intensity exercise, the intramuscular accumulation of lactic acid has long been considered one of the most important factors in fatigue.[5,6,9-12] In 1907, Fletcher and Hopkins[13] were the first to demonstrate that lactate was produced in amphibian muscle electrically stimulated under anaerobic conditions. The concept that this metabolite is a major player in fatigue was then evolved through their student, AV Hill, with studies on isolated frog muscle and with plasma lactate measurements in exercising humans.[14-16] It should be noted that virtually no lactic acid exists in the body in this neutral form; instead it is represented by two ionic species: lactate ions and hydrogen (H^+) ions.[10,12,17-19] Therefore, when evaluating the 'lactic acid hypothesis for muscle fatigue' (see section 1) it must be acknowledged that this is a construct and that a possible role for both lactate and H^+ ions needs to be addressed separately.

With the advent of the muscle biopsy technique and then nuclear magnetic resonance spectroscopy in the 1960s and 1970s, detailed studies appeared on the build up of lactate and H^+ (i.e. acidosis) in working muscle[12,20-23] and support for this hypothesis grew. It is largely because of these early findings that lactic acid and fatigue have become intimately linked, with the idea being indoctrinated into us.[24] Moreover, a view made popular by Arthur Lydiard (the late great distance running coach from New Zealand) is that lactate and the associated acidosis during anaerobic exercise can be extremely detrimental for both exercise performance and health.[25] For these reasons, the viewpoint common to many sport scientists and coaches worldwide is that lactic acid is the major villain limiting performance during intense exercise.

Despite these historical findings, an increasing body of evidence has appeared since the early 1990s suggesting that accumulated lactate and acidosis have little detrimental effect on muscle performance. In the early 2000s, some elegant experiments have been interpreted to mean that lactic acid is actually ergogenic. Clearly, the validity of the lactic acid hypothesis has been questioned. The aim of this article is to provide an update on the role of lactic acid in fatigue. It will include a brief look at key evidence supporting a role of lactic acid and the fragility of some interpretations, a discussion and critique of some recent high-profile studies adverse to a role of lactic acid, and some speculative ideas on the roles of lactic acid in exercise.

1. The 'Lactic Acid Hypothesis for Muscle Fatigue'

1.1 Lactate and H^+ Production

During muscle contraction, the energy molecule adenosine triphosphate (ATP) is used by myosin adenosine triphosphatase (ATPase) to allow cross-bridge cycling between actin and myosin filaments, resulting in force production. However, ATP concentrations are normally low so that with repeated contractions the phosphocreatine (PCr) stores in muscle are used to resynthesise and maintain ATP concentrations. With an increasing number of contractions, the PCr concentration declines resulting in a need to utilise other fuels. Consequently, muscle glycogen is called upon with glycogenolysis being activated, leading to an increased flux through the glycolytic pathway with formation of pyruvate and ATP. With intense dynamic exercise, this pathway must be used to produce the necessary ATP to meet the demand of the cross-bridge cycle (increased myosin ATPase activity) and muscle ion pumps (increased Ca^{2+}-ATPase and Na^+-K^+-ATPase activities). With lower intensity exercise, pyruvate is destined for oxidation by aerobic metabolic processes in the mitochondria. Unfortunately, the mitochondria are unable to oxidise all of the pyruvate

produced during intense exercise, such that modest increases in pyruvate leads to its conversion to lactate in the myoplasm.[10] It is generally thought that this accumulation of lactate is directly associated with the production of H^+ and leads to a fall in intramuscular pH (pH_m) or acidosis.[23,26] However, a recent thought-provoking review[17] and follow-up publication[18] discuss H^+ formation and conclude that it is not due to a lactic acidosis, i.e. H^+ is not formed during lactate production from pyruvate. Instead, they propose that H^+ formation occurs during glycolytic reactions that involve ATP hydrolysis.[17,18] An alternative explanation based on physical chemistry principles is that production of lactate, as a strong acid anion, leads to H^+ formation from water.[19] Inside the muscle fibre, the H^+ are mostly buffered but some lactate along with H^+ are thought to be extruded via lactate-proton transporter proteins in the cell membrane.[27]

This leads to the lactic acid hypothesis for muscle fatigue which is 'accumulation of lactate or an acidosis in working muscle causes inhibition of contractile processes, either directly or via metabolism, resulting in diminished exercise performance'. Undeniably, it is an attractive and conceptually simple idea to have metabolic end products as the major cause of fatigue. There are parallels with this idea and product inhibition of enzymes as occurs in many biochemical reactions, and studies on cardiac muscle have suggested that lactate/H^+ can cause impaired contractility and arrhythmias during myocardial ischaemia.[28-31]

1.2 Observations from Correlation-Type Studies

Many early studies found that lactate had increased in fatigued frog muscle at the endpoint, or in blood following exhaustive exercise in humans,[5,7,13-16] which makes lactate a potential fatigue candidate. In 1976, Fitts and Holloszy[32] were the first to strengthen this claim by revealing a tight linear relationship between lactate accumulation and loss of twitch force as fatigue progressed in frog muscle. This observation was soon repeated using a variety of stimulation protocols,[20] and then in mammals using isolated skeletal muscles from rats[33] or in human quadriceps muscle activated by electrical stimulation.[26,34] Moreover, temporal relationships were also apparent between the decline of force and accumulation of H^+ in each of these studies.[20,26,33,34]

Two further correlations used to support the lactic acid hypothesis are that the accumulation of intramuscular lactate or H^+, and the decline of force both occurred more slowly after physical training[33] and in more fatigue-resistant slow-twitch than fast-twitch muscle.[33,35,36] Although these correlation studies are suggestive, they do not prove cause and effect. In fact, the very same studies show that relationships also exist between the decline of force and decrease of ATP,[32] increase of inorganic phosphate (P_i),[20] increase of adenosine diphosphate (ADP)[20] and PCr depletion.[20,33] If the correlation argument remains steadfast, then these other metabolic changes must surely also be considered as fatigue factors. Moreover, an important point is that all of the above studies involved an imposed anaerobic environment, either by gassing the muscle with N_2 rather than O_2,[20,32] using cyanide,[20] making the muscle ischaemic with a cuff,[26,34] or by using isolated whole muscles where diffusion restrictions are likely to render central fibres hypoxic.[33] This condition is most likely to have a considerable bearing on the mechanisms of fatigue.[8]

Adams et al.[35] compared fatigue during repeated tetanic stimulation of cat soleus muscles with and without perfusion. The authors observed a 60% greater loss of force and a 0.3 pH unit greater acidosis in the ischaemic situation. In contrast, there should be a good O_2 supply and adequate blood flow during many forms of dynamic exercise in humans. Therefore, the only real conclusion to be gleaned from these particular correlation studies is that lactate or H^+ ions are potential candidates to cause fatigue.

Table I. Intramuscular pH (pH_m) values obtained at rest and after different exercise events

Exercise event	Typical pH_m value (range)[a]	References
Rest	7.0 (6.9–7.2)	12,21-23,43-52
Dynamic exercise – continuous		
10 sec sprint	6.94	45
20 sec sprint	6.82	45
30–60 sec sprint	6.7 (6.6–6.9)	46,49,52
1.5–11 min (maximal)	6.5 (6.3–6.9)	21-23,46,47
>60 min (submaximal)[b]	7.0 (6.95–7.05)	43,44
Dynamic exercise – intermittent		
20 min (all-out for 30–40 sec, repeated)	6.46	21
Static exercise		
>45 sec (60–100% MVC)	6.5 (6.4–6.9)	12,49-51

a $pH_m = -\log_{10}[H^+]_m$ (assayed in homogenates of biopsy samples from quadriceps or gastocnemius muscles after cycling or running in humans). Range is given for mean values.

b Exercise intensities are typically 60–90% of peak oxygen consumption.

MVC = maximal voluntary isometric contraction.

2. Could Lactate Ions or Acidosis Be the Culprit?

2.1 Intramuscular Lactate Accumulation

During intense exercise in humans, the lactate concentration can increase by up to 40 mmol/L in muscle fibres and 25 mmol/L in plasma.[5,7,23,26] Increases of extracellular lactate do not seem to directly influence force production,[37,38] hence more interest has centred on effects of intramuscular lactate on myofilament function or excitation-contraction coupling. When experiments are performed on skinned muscle fibres (where the cell membrane has been removed) the myofilament proteins can be exposed to a milieu resembling that which occurs during fatigue, e.g. one with raised lactate. These types of experiments have shown that lactate does not appreciably influence maximal cross-bridge function.[39-41] Other studies indicate that lactate can impair calcium (Ca^{2+}) release from isolated sarcoplasmic reticulum[42] and when using artificial methods to trigger Ca^{2+} release in skinned fibres.[40] However, under more physiological conditions, application of 20–30 mmol/L lactate only slightly (<10%) impairs Ca^{2+} release and force.[40,41] Such effects have not been regarded to be of any major importance in fatigue.

2.2 Intramuscular Acidosis

A prerequisite to support the idea that myoplasmic acidosis is responsible for fatigue is that intramuscular H^+ concentration must increase (or pH_m decrease) during exercise (table I). This requires invasive sampling with biopsies taken from the large working muscles when the interest is dynamic exercise. In 1972, Hermansen and Osnes[21] were the first to demonstrate using biopsy analysis that a large acidosis occurred in quadriceps muscle during maximal cycling or running. Data from similar studies on other types of exercise events are shown in table I. During prolonged submaximal exercise, the pH_m is only slightly affected[43,44] and with short-duration maximal exercise (<30 seconds) small to moderate pH_m changes occur.[45,46] Thus, H^+ is unlikely to be a major player in these types of events. The largest acidosis occurs with maximal continuous or intermittent exercise of 1–10 minutes duration; the pH_m can fall by 0.5 pH units to ~6.5, although a large spread in these values occurs.[12,21-23,46,47] This variation possibly arises because of different proportions of fast- and slow-twitch fibres recruited amongst subjects[48,49] and given that a greater acidosis occurs in fast-twitch fibres.[33,35,36] When static contractions are studied, the nuclear magnetic resonance technique can be used to measure pH_m non-invasively; the pH_m can

fall to ~6.5 depending on the contraction duration.[12,49-51] The largest acidosis in human muscle fibres that appears to be realistic is around pH_m 6.2.[5,22,48]

Measurements of pH_m have also been made at the single fibre level during fatigue using pH-selective glass microelectrodes or fluorescence indicators in frog[37,53,54] or mouse muscle fibres.[27,38,55,56] A key observation is that acidosis is more pronounced in amphibian than mammalian fibres even when using an identical stimulation regime.[38,54-56] This would suggest that ideas formulated when using amphibian muscle most likely involved an excessive acidosis.[5,13,32,37,53,54] Also, some fatigue protocols involve virtually no change of pH_m in mammalian fibres and hence a role for acidosis can be eliminated.[38,56] Moreover, several studies may have an artificially greater acidosis than during normal exercise because of the imposed experimental conditions. In authentic dynamic exercise, the pH_m seldom falls to <6.7 because either the duration is too brief or the intensity is too low. It is only during maximal exercise for about 1–10 minutes that a severe acidosis can occur (table I).

2.3 Plasma Acidosis

The acid-base balance of plasma can also be disturbed with moderate- to high-intensity exercise; plasma pH can fall from ~7.4 to 6.9–7.0 with maximal exercise.[21,22,57] Changes of interstitial pH can be greater than for plasma pH,[58] although an acidosis of 0.1–0.2 pH units is much more common.[44-46,52,57,58] Notably, the largest extracellular acidosis usually occurs minutes after exercise cessation[21,52,58] when force is usually recovering. Researchers have tested the effect of induced extracellular acidosis on fresh muscle and have generally shown that peak tetanic force does not decline.[37,38,53,59] Hence, an extracellular acidosis is thought not to cause fatigue. Since the focus of many studies is on an intramuscular acidosis, some of these studies and the solidness of their conclusions will now be discussed.

3. Detrimental Effects of Acidosis on Muscle Performance

3.1 Relationship Between Intramuscular pH and Force Production in Fatigued Muscle

Several groups have measured pH_m and force throughout the course of fatiguing activity in human or animal muscles.[1,20,26,33-36] Figure 1 shows the relationship between the pH_m and reduction of force due to fatigue processes, constructed using data from two of these studies in human subjects.[1,26,34] In both cases, the pH_m could fall by 0.3–0.4 pH units to ~6.7 with only a moderate loss of force, and when the acidosis was more severe there was a marked reduction of force. These relationships may indicate that some form of safety margin exists beyond which force decreases sharply with further declines of pH_m. In line with this safety margin idea, a cycling study demonstrated that an acidosis to pH_m 6.9 was without effect on peak power, and at pH_m

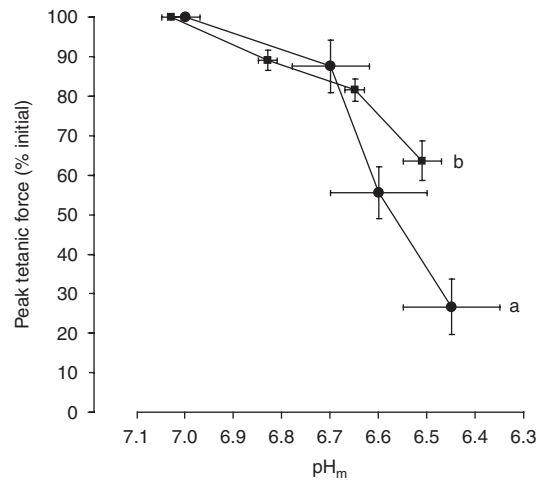

Fig. 1. Relationship between peak tetanic force and intramuscular pH (pH_m) during fatigue in human muscles. Data points are mean values ± standard deviations. (**a**) Fatigue was evoked by repeated tetanic stimulation (20Hz for 1.6 sec, with 1.6-sec rest periods, for 100 contractions) in quadriceps muscle (n = 7), pH_m determined from biopsy samples.[26,34] (**b**) Fatigue was evoked by three repeated maximal voluntary contractions (15 sec each) of the first dorsal interosseous muscle. Peak tetanic force was evoked at 100Hz for 0.5 sec, pH_m was measured using nuclear magnetic resonance spectroscopy (n = 4).[1] In both (**a**) and (**b**) the blood supply to the muscle was occluded with a cuff.

6.8 there were only small effects (<10% decrease).[45] When a severe acidosis occurred, there was a greater force loss in the quadriceps than first dorsal interosseous muscle (figure 1). This may be due to the quadriceps muscle having a greater proportion of fast-twitch fibres than the first dorsal interosseous muscle, since fast-twitch fibres are more susceptible to force depression with acidosis.[29,33,35,36,39] Also, the relationship would be expected to be shifted upwards if factors other than H^+ contribute to the decline of force with fatigue in these studies, i.e. more force is generated at each pH_m. Moreover, force can be partially restored following exercise cessation when pH_m remains acidotic;[1,36,50] an observation used to question the lactic acid hypothesis. However, it is plausible that H^+ may depress force by interacting with other factors that change in muscle cells (e.g. electrolytes) but that these factors recover more quickly than pH_m after exercise, so that interactive effects are lost. Nevertheless, fatigue can be associated with an intracellular acidosis (figure 1), even though the relationship between pH_m and force does not appear to be simple and may require interactive effects with other fatigue factors.

3.2 Effect of Induced Acidosis on Force Production in Fresh Muscle

Another test of the lactic acid hypothesis is to impose an acidosis on fresh muscle of similar magnitude to that seen during fatiguing activity. If the hypothesis is to remain valid then this intervention should reduce force by a similar extent to that of fatigue. Such experiments can readily be undertaken with isolated muscle preparations. Indeed, increasing the CO_2 content in the bathing solution causes pH_m to fall[12,38,53,56] and reduces force in intact amphibian[53] and mammalian skeletal muscle.[12,38,53] Also, an induced acidosis can reduce maximum force and shortening velocity in skinned muscle fibres.[29,39,60,61] Notably, this effect appears to be small in skinned fibres (<10% reduction) when using more physiological activation methods.[62] It has also been argued from these types of experiments that a large acidosis *per se* is insufficient to account for all the force loss during fatigue.[53] A modification of these experiments is that a smaller extracellular acidosis (induced with ammonium chloride or CO_2) can exacerbate the force loss that occurs with repeated tetanic stimulation of perfused hindlimb muscles in animals[59] and quadriceps muscle in humans,[63] or can shorten the time to exhaustion during maximal exercise.[64,65] However, an imposed acidosis does not cause significant fatigue in short-duration (30-second) all-out exercise.[66]

3.3 Mechanism(s) of Contractile Impairment with Acidosis

There also needs to be cellular mechanism(s) by which intramuscular acidosis can diminish muscle force or power output. A large number of cellular processes may contribute to such effects (table II). These processes have usually been investigated with only H^+ concentration being altered in isolated muscle preparations, e.g. skinned muscle fibres, sarcoplasmic reticulum vesicles, isolated ion channels or enzymes. However, in more intact systems, the negative effects are not always seen. For example, acidosis can reduce charge movement[67] or directly impair Ca^{2+} release from isolated sarcoplasmic reticulum[42] or isolated Ca^{2+} release channels,[68] but acidosis has no depressive effect on Ca^{2+} release with normal voltage-activation in mechanically skinned[62] or intact single fibres.[9] Also, increased H^+ concentration can inhibit the activity of phosphofructokinase when the enzyme is isolated,[69] but not in whole-body exercise when various enzyme activators may counteract this effect.[12,26,70] The most popular proposed site of impairment is the myofilament proteins, whereby reductions of maximum cross-bridge activity,[29,39,53,60-62,71-73] Ca^{2+} activation of troponin[5,9,29,56] and myosin ATPase activity[5,9,72,74] could allow H^+ to be the culprit (table II). Still, there should be some caution about the interpretation of these studies for two reasons. First, many of these studies involve working with extremely acidic conditions (pH_m <6.5), which occurs in few exercise situations (table I) and second, interactive effects with other fatigue factors have seldom been studied,

Table II. Proposed mechanisms for impaired muscle performance with intramuscular acidosis

Mechanism	References
Contractile processes	
Myofilament function	
↓ maximum force[a] (↓ maximum cross-bridge cycling)	29,39,53,60-62,71-73
↓ Ca^{2+} sensitivity (↓ Ca^{2+} binding to troponin)	5,9,29,56
↓ maximum velocity of shortening (↓ myosin ATPase activity)	5,9,72,74
Excitation-contraction coupling	
↓ Ca^{2+} release by SR (↓ Ca^{2+} release channel activity, ↓ charge movement)	42,67,68
↓ Ca^{2+} uptake by SR (↓ calcium ATPase activity)	5,9
Metabolic processes	
↓ free energy from ATP hydrolysis	20
↓ rate of glycolysis/glycogenolysis (↓ PFK, ↓ GP activities)	5,51,69
↓ rate of cAMP production	51
Other cellular processes	
↑ K_{ATP} channel conductance	75

a Maximum force is that evoked when using a very high Ca^{2+} concentration so that troponin is saturated with Ca^{2+}.

ATP = adenosine triphosphate; **ATPase** = adenosine triphosphatase; **cAMP** = cyclic adenosine monophosphate; **GP** = glycogen phosphorylase; $\mathbf{K_{ATP}}$ = ATP-dependent K^+ channel; **PFK** = phosphofructokinase; **SR** = sarcoplasmic reticulum; ↓ indicates decrease; ↑ indicates increase.

as only H^+ is changed and other factors are held constant. Indeed, Nosek et al.[61] showed that H^+ and P_i could interact to reduce force with the implication being that the diprotonated P_i species was functioning as the detrimental metabolite.

3.4 Consensus by the Late 1980s

At this point in time, several reviews expressed the view that H^+ is likely to be a major cause of fatigue when there is an exercise-induced intramuscular acidosis.[5,9,11,12,71] The evidence supporting this is as follows: (i) intense exercise or electrical stimulation leads to an intracellular acidosis in fatigued muscle; (ii) temporal relationships exist between myoplasmic lactate or H^+ accumulation and decline of force during fatigue; (iii) correlation studies show that the rate and extent of intramuscular acidosis is attenuated and fatigue is slowed after physical training or in slow-twitch compared with fast-twitch muscle; (iv) an induced acidosis reduces muscle force and shortening velocity in fresh muscle and exacerbates fatigue during subsequent contractile activity; and (v) mechanisms exist whereby elevated H^+ could impair contractile and metabolic processes.

4. Acidosis is Really not that Bad

In the 1990s, several findings have strongly challenged the lactic acid hypothesis, all of which involved less harmful effects of acidosis on muscle function at more physiological temperatures. Three types of such experiments are presented. Firstly, the earlier studies showing detrimental effects of H^+ on skinned fibres were usually done at 10–20°C where the preparation was more stable. When methods allowed investigation at 25–30°C the relative effects of acidosis on isometric force and shortening velocity were abolished or attenuated.[72,73] Secondly, the relative effects of CO_2-induced acidosis on contractile performance of fresh muscle were attenuated at 25–37°C,[35,36,73,74] whereas similar pH_m changes during fatigue occurred in association with a large decrement of force.[35] Thirdly, a pre-conditioning CO_2 exposure at 28°C did not seem to accelerate fatigue in isolated single fibres from mice even though it resulted in a greater acidosis during fatigue.[55] Taken together, these muscle physiology experiments show that an acidosis does not exert large negative inotropic effects and cannot, by itself, cause severe fatigue. Consequently, they have been used to discredit the lactic acid hypothesis, at least

via direct effects of H^+ on muscle.[10,76] Nevertheless, the smaller negative effects of acidosis on muscle performance (<10% decline) may still be sufficient to limit whole body exercise performance in competition.[77] Besides, an induced acidosis can exacerbate fatigue in intact animals and humans,[63-65] in contrast to the isolated single muscle fibre results.[55] Hence, it is conceivable that H^+ may interact with some other change in muscle (e.g. with decreased Ca^{2+} release from the sarcoplasmic reticulum) or in the body to impair exercise performance.

5. Lactate and Acidosis Have Performance-Enhancing Effects

5.1 Possible Benefits with Lactate/H^+

Many observations suggest that lactate/H^+ production is likely to have value rather than be hazardous but the beneficial effects are seldom preached. Well documented effects of acidosis including greater release of O_2 from haemoglobin for working muscle fibres (the Bohr Effect), stimulation of ventilation, enhancement of muscle blood flow, and afferent feedback to the CNS to increase cardiovascular drive,[27,58,64,78] may all help during exercise. Lactate may also be advantageous as Brooks proposed with his 'lactate shuttle hypothesis' where lactate released by working muscle fibres are taken up and utilised by other cells or muscle fibres as a metabolic fuel.[10,24] Also, sodium lactate ingestion has recently been shown to improve performance during intense exercise in humans[79] and during fatiguing stimulation of perfused hindlimb muscle in rats.[80] Finally, lactate production is associated with an oxidation-reduction (redox) potential that helps sustain intramuscular ATP production and performance.[81,82] This is clearly revealed in patients with McArdle's disease whom lack glycogen phosphorylase and cannot produce lactate/H^+, since they fatigue more rapidly than normal subjects whom are indeed faced with an acidosis.[1,82] This clinical situation shows categorically that glycolysis helps to preserve human performance and that processes other than lactate/H^+ accumulation contribute to fatigue.

5.2 Lactic Acid: Potassium Interaction

Scientists usually endeavour to do experiments by systematically changing one factor and keeping all other aspects constant, but this is not the situation during whole-body exercise. Two prominent and large changes that occur simultaneously during high-intensity exercise involve H^+ and potassium (K^+) ions.[5,7,22,30,31,47,70] Leitch and Paterson[30] and Paterson[31] made use of this information and demonstrated that hyperkalaemia (raised extracellular K^+ concentration) and acidosis have additive detrimental effects on cardiac muscle performance. However, with skeletal muscle, the response to these ionic changes is strikingly different. In 1992, Renaud and Light[83] were the first to show that acidosis has a protective influence against K^+-induced force depression in frog skeletal muscle. However, it took Nielsen et al.[84] in 2001 to perform similar experiments on mammalian skeletal muscle (but with lactate exposure) before the news that acidosis protects against K^+-induced force paralysis gained prominence (see figure 2). These studies have now been reproduced and extended[85-88] with similar beneficial effects of acidosis seen on depolarisation-induced impairment of Ca^{2+} release and force in mechanically skinned fast-twitch fibres.[88] These recent observations have indeed caused a major headache for the lactic acid hypothesis supporters.[24] Controversy now exists to explain the mechanism by which acidosis restores contractility in K^+-depressed muscles. Pedersen et al.[87] demonstrated that acidosis restores excitability in association with a reduced chloride (Cl^-) conductance in muscle membranes. However incubation in low Cl^- solutions may restore[87-89] or depress force at raised extracellular K^+[4] leaving the mechanism uncertain.

The above dramatic findings have made such an impact that Allen and Westerblad[90] entitled their recent *Science* publication '*Lactic acid – the latest performance-enhancing drug*'. This idea certainly makes one think about this possibility, but one wonders about whether the extrapolation from the acido-

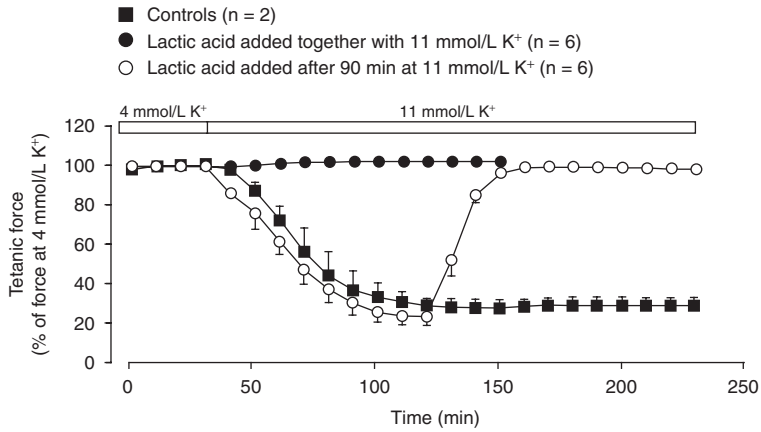

Fig. 2. Protective effect of 20 mmol/L lactic acid on tetanic force in rat soleus muscles exposed to an extracellular [K+] of 11 mmol/L. Tetanic contractions were evoked every 10 min (30Hz, 1.5 sec) at 30°C. Data points are mean values ± standard error of the mean (reproduced from Nielsen et al.,[84] with permission).

sis-K^+ interaction on isolated muscle to exercise performance is too extreme. Lactate exposure or acidosis had no effect on fatigue induced with repeated tetanic stimulation of isolated muscle preparations,[55,85] although it slowed fatigue *in situ*;[80] this apparent conundrum may be attributed to the different fatigue models employed.[8] An induced acidosis in humans has never been shown to enhance exercise performance and, in contrast, the effects are often negative.[63-65] Moreover, fatiguing stimulation of isolated muscle shows that a large intracellular acidosis and large depolarisation (which represents effects of K^+) occur together in the same fibres, and in this situation tetanic force is considerably reduced.[37,53] This observation and traditional thinking using a correlation type of approach could be used to argue a case that both H^+ and K^+ are fatigue factors. This finding could be interpreted in two ways: (i) that both acidosis and K^+ cause fatigue but by interacting with some other factor; or (ii) that acidosis indeed protects against deleterious effects of K^+ and something else causes all the fatigue. There is little doubt that H^+ with K^+ alone cannot explain much fatigue, and several recent studies have looked more closely at the role of several other interacting factors.[3,4,30,31,67,86-89] The important message to be extracted from these latest findings[84-88] is that there is a genuine need for caution about whether lactate/H^+ is detrimental during fatigue.

6. What About Performance Enhancement with Bicarbonate?

It has been postulated that ingestion of H^+ buffers, such as sodium bicarbonate, might diminish any acidosis during exercise and therefore attenuate fatigue.[11,44,57,64-66,71] Although the literature on this topic appears contradictory, it seems that bicarbonate does enhance exercise performance, but is mostly restricted to intense exercise lasting 1–10 minutes[11,57,64,65,71] or when large acid-base disturbances occur,[91] but there is no protective effect without a large acidosis.[44] Moreover, such beneficial effects are not limited to bicarbonate, as ingestion of other H^+ buffers also improves exercise performance.[79] The H^+ buffer appears in plasma but does not enter muscle[71,79,92] and the ergogenic effect is postulated to be mediated by greater H^+ extrusion from working muscle fibres[27,91,92] to delay or attenuate the fall in pH_m.[91] There is evidence suggesting that bicarbonate can act on muscle to improve contractile performance,[92] but a disparity exists as this is not always the case.[93] Consistent with the latter results is the possibility that a large extracellular acidosis may exert negative effects via the CNS. Indeed, bicarbonate loading can dampen

the plasma acidosis with exercise[57] and improve performance in association with lower ratings of perceived exertion[11,57,94] or by an attenuation of the arterial desaturation of haemoglobin (lowering the partial pressure of O_2) which occurs during competitive rowing.[57] Hypoxic conditions may exert detrimental effects via the CNS,[95,96] which could possibly be alleviated with bicarbonate. Both of these ideas lead to the very intriguing thought that bicarbonate may work by reducing central fatigue. This clearly cannot be investigated in experiments with reduced muscle preparations[8] and a more complete understanding of the role of lactate and acidosis in exercise performance would therefore necessitate whole-body exercise studies.

7. Future Directions

To develop a greater understanding of the role of lactate/H^+ in exercise performance requires much more than one type of experiment or the use of one fatigue model.[8] Studies to address the following questions could be valuable:

- Whether an induced acidosis or alkalosis influences various mechanical fatigue measures (e.g. power output) that are relevant for different types of exercise in humans?
- Whether a plasma acidosis or altered muscle afferent feedback due to lactate or acidosis[78] causes an increased perception of effort, diminished motor drive from the CNS, diminished coordination or lessened steadiness in humans?
- Whether negative interactive effects occur between elevated H^+ and other factors that change during intense exercise? This needs to be expanded from K^+[83-88] to include Na^+,[2,22,57] Cl^-,[4,22,87-89] Ca^{2+}[3,5,22,57,67] and phosphate metabolites,[1,5,6,33,45,46,50] to name a few.

These studies need to be both mechanistic and performance based, and keeping in mind possible contributing effects from hormonal changes that occur simultaneously during exercise, such as with elevated catecholamines.[30,31,46,86]

8. Conclusions

There is absolutely no doubt that the glycolytic pathway is extremely important for muscle function. Indeed, patients with McArdle's disease who cannot use this pathway are unable to sustain intense exercise[1,82] and this pathway is well developed with sprint training.[33,46] In addition, blood lactate concentration is a very useful marker of exercise intensity and adaptation to training. However, a role for 'lactic acid' in fatigue is more controversial with a variety of studies involving work on isolated muscle preparations and with human subjects having addressed this issue. The main points raised in this article are as follows:

- Correlation-type studies have implicated lactate/H^+ accumulation as a cause of fatigue that has become embedded in our psyche. Many of these studies were done on amphibian muscle (under anaerobic conditions) that more readily generates lactate/H^+ than mammalian muscle.
- Some effects of increased lactate and acidosis during exercise are likely to be beneficial via either systemic or direct effects on muscle.
- Recent work by muscle physiologists, which show that induced acidosis has limited effects on muscle contractile function at body temperatures and is protective against hyperkalaemia, have made us rethink that H^+ is hazardous and that it may be ergogenic.
- Many forms of exercise have little or no change in lactate or pH_m (table I). Only a few types of dynamic exercise involve a severe acidosis, which is needed to cause a large reduction of force (figure 1). This possibly involves H^+ interacting with other cellular changes, and is more important in fast-twitch than in slow-twitch fibres.
- Whole-body studies show that induced acidosis can impair muscle or exercise performance, and that induced alkalosis may be ergogenic for events lasting 1–10 minutes.

This latter point seems to provide the strongest support for the proposal that lactic acid is a culprit for exercise performance. What is absolutely certain is that lactate/H^+ is not the sole cause of fatigue, and

even with a severe exercise-induced acidosis we can not yet be dogmatic that 'lactic acid' is a major player in fatigue.

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