

Monocarboxylate Transporters and Lactate Metabolism in Equine Athletes: A Review

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Pösö AR: Monocarboxylate transporters and lactate metabolism in equine athletes: A review. Acta vet. scand. 2002, 43, 63-74. – Lactate is known as the end product of anaerobic glycolysis, a pathway that is of key importance during high intensity exercise. Instead of being a waste product lactate is now regarded as a valuable substrate that significantly contributes to the energy production of heart, noncontracting muscles and even brain. The recent cloning of monocarboxylate transporters, a conserved protein family that transports lactate through biological membranes, has given a new insight into the role of lactate in whole body metabolism. This paper reviews current literature on lactate and monocarboxylate transporters with special reference to horses.

Horse; MCT; skeletal muscle; Red blood cell; Exercise.

Introduction

Horses are superb athletes in comparison to other athletic species. Exceptionally high maximal oxygen uptake, a splenic reserve of red blood cells released into the circulation during exercise, and a high amount of energy stored as glycogen in the muscles contribute to the high performance capacity of a horse (Jones 1989, Derman & Noakes 1994). Furthermore, equine muscles and blood are equipped with properties that increase their tolerance to lactic acid, the formation of which is necessary for maximal performance. The buffer capacity of muscles of trained horses is higher than in other athletic species, and red blood cells appear to function as a lactate sink, both of which phenomena may increase the anaerobic capacity (McCutcheon *et al.* 1987, Pösö *et al.* 1995). Because the lactic acid-induced acidification is the single most important factor causing fatigue, the regulation of its concentration in exercising muscle plays a central role in muscle function. Recent characterisation of monocarboxylate transporters, a protein family involved in the transport of lac-

tate across biological membranes, has added a new perspective to our knowledge of lactate metabolism in exercise physiology (Poole & Halestrap 1996, Halestrap & Price 1999). At the moment the physiological importance of these transporters is not completely understood, but the number of isoforms of monocarboxylate transporters and the conservative nature of these proteins suggest that the pathways of lactate are far more complex than generally believed.

Formation of lactate in muscle

Formation of lactic acid in muscle tissue is basically a question of the capacity of different metabolic pathways. Both at rest and during exercise, the rate of ADP rephosphorylation must meet the demand of ATP for contraction and other functions of the muscle cell. During light work, the demand for ATP lies within the limits of aerobic capacity, and ATP is produced by oxidative phosphorylation, but with increasing intensity, anaerobic pathways of energy produc-

tion, i.e., substrate-level phosphorylation, become more important. It has been calculated that during a 400-m Quarter Horse race, about 60% of the energy is derived from anaerobic metabolism, and in longer races, such as in 1600- to 2100-m Thoroughbred and Standardbred races, estimated values range from 10% to 30% (Eaton 1994).

Aerobic capacity varies among breeds of horses, among muscles and also among fiber types. Slow-twitch, type I, fibers usually have higher aerobic capacity than the fast-twitch, especially type IIB, fibers, which usually rely more on the anaerobic metabolism (McMiken 1986). The characteristics of type IIB fibers are species specific and also depend on training. For example, in reindeer and in well trained horses also type IIB fibers have high oxidative capacity (Ronéus *et al.* 1994, Pösö *et al.* 1996). Availability of oxygen and the capacity to use it are the limiting factors for aerobic metabolism. This includes the cardio-respiratory function, hemoglobin concentration in the blood, transit time of the blood in the muscle, capillarization, myoglobin concentration in the muscle, and finally the number of mitochondria in the muscle fibers (Booth & Thomason 1991). Within the animal kingdom, horses have a high oxidative capacity, as indicated by maximal oxygen uptake of about 160 ml/kg body weight \times min (Evans & Rose 1988, Rose *et al.* 1988), more than twice the uptake in human elite athletes. Theoretically, if it is assumed that during intense exercise 90% of oxygen is consumed by exercising muscles and that approximately 40% of the body weight is muscle, it can be calculated that with this oxygen uptake, aerobic ATP production in the equine muscle may approach $2 \mu\text{mol} \times \text{g}^{-1} \times \text{s}^{-1}$. This value is, however, well below the approximated maximal ATP demand, the calculated value of which for human muscle is about $3 \mu\text{mol} \times \text{g}^{-1} \times \text{s}^{-1}$ (Newsholme & Leech 1983), and the difference indicated by these 2

figures has to be met by anaerobic glycolysis, an uneconomical but high-capacity pathway.

In human athletes, ATP production in glycolysis may be as high as $3 \mu\text{mol/g}$ body weight \times s (Newsholme & Leech 1983), and although similar estimations from equine muscle are unavailable, the comparison of the activities of key glycolytic enzymes in equine muscles to those in human muscles (Essén-Gustavsson *et al.* 1984, Henriksson *et al.* 1986, Ronéus *et al.* 1991, Cutmore *et al.* 1993) indicates that anaerobic ATP production may be equally important in horses. Another product of glycolysis is NADH, which increases the cytosolic NADH/NAD⁺ ratio, which would rapidly slow down the rate of glycolysis. When the NADH/NAD⁺ ratio increases, glycolysis switches to the anaerobic mode. Instead of oxidation, pyruvate is reduced to lactate, and simultaneously NADH is oxidized to NAD⁺, which allows glycolysis to continue at the maximum rate. The need for NADH reoxidation in the cytoplasm means that the formation of lactic acid is essential for anaerobic energy production.

All muscle fibers contain the necessary enzyme lactate dehydrogenase. The activity of lactate dehydrogenase is, however, highest in those fibers that have the lowest volume density of mitochondria and the lowest number of capillaries per fiber area both in horses (Karlström *et al.* 1994) as well as in other species (McCullagh *et al.* 1996, Grichko *et al.* 1999). In horses these are usually the fast-twitch type IIB fibers (Valberg & Essén-Gustavsson 1987). In addition to this, lactate dehydrogenase activity in type IIB fibers is due almost exclusively to the muscle type isoenzyme that favors the reaction towards the formation of lactate, whereas in the slow-twitch fibers the isoenzyme that favors the oxidation of lactate to pyruvate is also present (McCullagh *et al.* 1996, Grichko *et al.* 1999). Recently the activity of lactate dehydrogenase

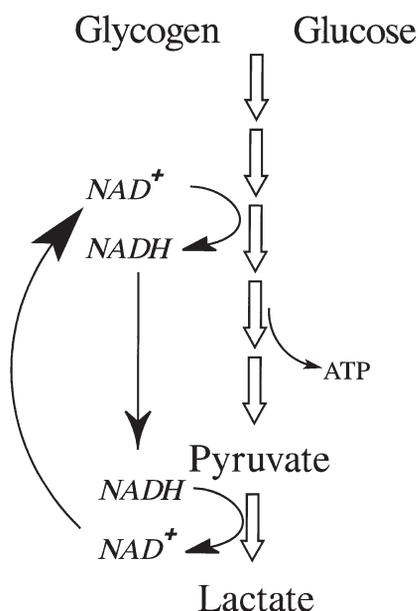


Figure 1. Oxidation of carbohydrates in glycolysis

has been demonstrated also in mitochondria, which allows for an intracellular lactate shuttle and suggests that some of the lactate oxidation may occur in these organelles (Brooks *et al.* 1999b).

Effects of lactate on muscle metabolism

Accumulation of lactate in the muscle cells initiates a cascade that eventually leads to fatigue. In horses after intermittent maximal exercise lactate concentrations of the middle gluteal muscle may increase up to 200 mmol/kg dry weight, but in other maximal exercise tests values around 100 mmol/kg dry weight have been reported (Snow *et al.* 1985, Schuback & Essén-Gustavsson 1998, Valberg *et al.* 1999). Also in exercising human subjects muscle lactate concentrations may reach 100 mmol/kg dry weight (Sahlin *et al.* 1989, Juel *et al.* 1990). Lactic acid increases the osmotic pressure of the muscle cell, which allows the extracellular water to

move into the cell and increase the cell volume (Kingston & Bayly 1998). Interestingly, recent studies have suggested that cell volume is one of the major regulators of cell function. Increased volume may have a direct effect on energy metabolism, because swelling has an inhibitory effect on glycogen breakdown (Lang *et al.* 1998).

Because lactic acid is a relatively strong acid with a pK_a -value of 3.86, at cellular pH it will be dissociated into a lactate anion and a proton, both of which have marked effects on metabolism (Hyypää & Pösö 1998). Acidification of the cell will impair the function both of Ca^{2+} -pumps and of Ca^{2+} -channels on the sarcoplasmic reticulum and thus increase the relaxation time of the muscle sarcomeres (Fitts 1994, Hyypää & Pösö 1998). Protons also have a direct effect on the conformation of the myosin ATP-ase which is necessary for contraction (Fitts 1994, Hyypää & Pösö 1998). Furthermore, energy production will be slower, because protons inhibit the activity of the rate limiting enzyme of the glycolysis, phosphofructokinase, and also inhibit glycogen phosphorylation (Fitts 1994, Hyypää & Pösö 1998). In addition, the lactate anion has an inhibitory effect on the function of sarcomere. Because of all these events, muscles will work less efficiently, i.e., be fatigued (Fig. 2).

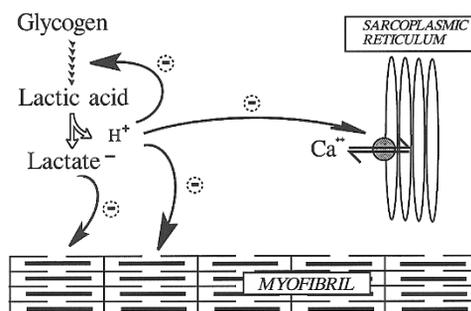


Figure 2. Effects of protons and the lactate anion on cell metabolism.

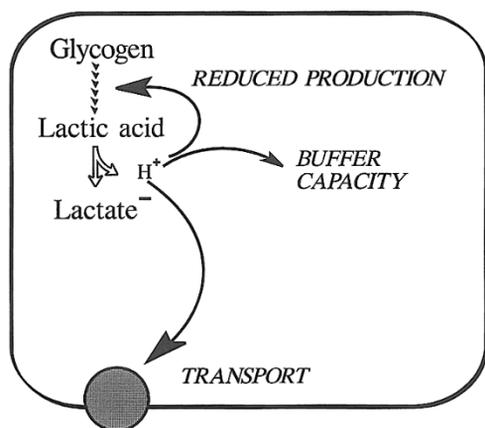


Figure 3. Regulation of pH in the muscle cell.

Several mechanisms in the muscle cell operate to prevent acidification and its consequences (Fig 3). The most important of these are buffer capacity and export of lactic acid from the muscle. The pH of the cell is maintained by buffer systems that include bicarbonate, protein, phosphate, and carnosine (Sahlin & Henriksson 1984, Harris *et al.* 1990). The most efficient of these is the bicarbonate system, because it is an open system via the circulation and respiration. Protein content within the cell is high, and proteins function as buffers, as does the dipeptide carnosine. The concentration of the latter is especially high in equine muscles and is concentrated in the type IIB fibers (Marlin & Harris 1989, Dunnett & Harris 1995) which have the highest glycolytic and the lowest oxidative capacity (Valberg 1987). Even though the buffer capacity of the trained equine muscle may be 50% higher than in human athletes (Fox *et al.* 1987, McCutcheon *et al.* 1987, Sewell *et al.* 1991), it is not high enough to prevent acidification. In horses after intense exercise muscle pH may drop to 6.5 to 6.4, while in human subjects the reported values range from 6.2 to 6.9 (Lovell *et al.* 1987, Harris *et al.* 1989, Juel 1997).

Transport of lactate from muscle

To delay acidification and thus to extend the time to exhaustion, lactate anions and protons can be exported from the muscle into interstitial space and blood plasma (Fig 4). Only the unprotonated form of lactic acid can freely diffuse through plasma membrane, because the phospholipid bilayer of the biological membranes prevents the passage of protons and lactate anions (Juel 1997). The role of nonionic diffusion increases with increasing lactic acid concentration and also when pH decreases. It can be calculated that at physiological pH, 7.4, 99.97% of lactic acid is dissociated, and at pH 6 the percentage is still 99.3. The role of nonionic diffusion is, however, greater than the proportion of undissociated lactic acid, because its high permeability through the membranes. From the muscle, protons formed during dissociation of lactic acid can be transported by the monocarboxylate transporter (MCT), or by the Na^+/H^+ -exchange protein (Juel 1997). Comparison of the capacity of each of these systems - diffusion, Na^+/H^+ exchange and MCT - shows that MCT plays the major role; for instance, in hu-

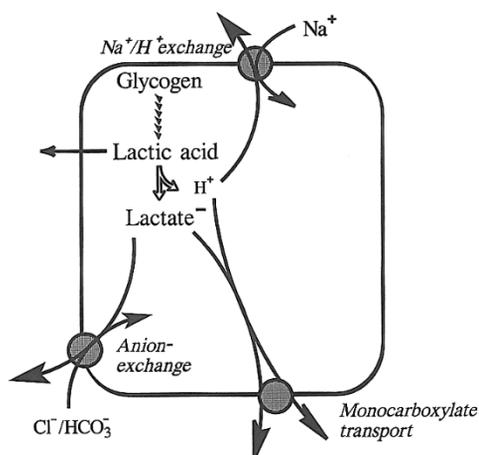


Figure 4. Transport of lactate and protons across membranes.

man muscles the capacity of MCT to transport protons is markedly higher than the other two mechanisms combined (Juel 1996).

Monocarboxylate transporters form a conserved protein family, the members of which are expressed in a species- and tissue-specific manner (Halestrap & Price 1999). As indicated by their name, these proteins are not specific for lactate only, but transport other monocarboxylic acids, such as pyruvate, volatile fatty acids, and ketone bodies, as well. In all cases the transport is electroneutral; one monocarboxylate anion is transported together with a proton (Poole & Halestrap 1993, Juel 1997). The most extensively characterised MCT isoform is MCT1, which is expressed in most tissues. This isoform has been labeled by Halestrap and his group the "housekeeping" MCT (Poole *et al.* 1996). Two isoforms of MCTs have been identified in the muscle tissue. Isoform 1 (MCT1) is the predominant isoform in the oxidative fibers, whereas in the fast-twitch, least oxidative, fibers, isoform 4 (MCT4) plays a major role (McCullagh *et al.* 1997, Wilson *et al.* 1998). Several studies have shown that the expression of MCT1 is upregulated by training (McCullagh *et al.* 1997, Baker *et al.* 1998, Bonen *et al.* 1998, Pilegaard *et al.* 1999, Dubouchaud *et al.* 2000). Interestingly, the activity and the amount of MCT1 appears to correlate with the percentage of oxidative fibers (Baker *et al.* 1998, Wilson *et al.* 1998), and it has been speculated that in oxidative fibers the role of MCT1 is to transfer lactate into the cells for oxidation, whereas MCT4 functions in the efflux of lactate from the muscle (Baker *et al.* 1998). This notion is supported by the finding that the upregulation of MCT1 is accompanied by an increase in the activity of LDH1, the heart-type isoenzyme, indicating coexpression between the substrate transfer protein and the immediate enzyme the substrate faces in the cell (McCullagh *et al.* 1997, Dubouchaud *et al.*

2000). Since the MCT on the mitochondrial membranes is MCT1, the effect of training on the MCT1 expression may in part be due to the exercise-induced increase in the number of mitochondria (Brooks *et al.* 1999a). MCT4 also increases with training (Pilegaard *et al.* 1999, Dubouchaud *et al.* 2000), but interindividual variation in this activation is large (Dubouchaud *et al.* 2000). MCTs are activated at low pH (Poole & Halestrap 1993). Another important regulatory factor is the concentration gradient across the sarcolemma; as soon as lactate concentrations in the extracellular space approach that in the muscle, the efflux of lactate is attenuated.

In human subjects at exhaustion after dynamic knee extensor exercise, large interindividual differences in muscle pH occur (Juel *et al.* 1990, Mannion *et al.* 1995), which suggests that muscle sensitivity to low pH varies individually. It has also been shown that large interindividual differences exist in the post-exercise muscle-plasma lactate gradients (Tesch *et al.* 1982). Together, these results suggest that lactate transport across the sarcolemma provides a control site in lactate accumulation in the exercising muscle. It can be speculated that an individual with a high lactate transport capacity may produce more ATP from glycogen/glucose before the critical pH inside the cell is reached than an individual with a low lactate transport capacity. This is supported by two lines of evidence: First, some elite athletes have exceptionally high MCT activities, and second, human beings with a deficiency in MCT also suffer from exercise intolerance (Fishbein 1986, Pilegaard *et al.* 1994). More research will be needed to clarify the precise role of MCT in exercise performance and in the pH regulation of muscle.

Distribution of lactate in blood

The lactate anion as well as lactic acid is freely

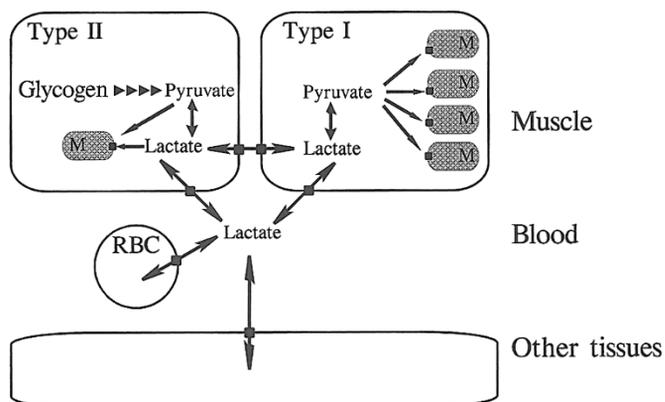


Figure 5. Monocarboxylate transporters in lactate metabolism. Black squares mark monocarboxylate transporters, M = mitochondria.

soluble in water and can thus be dispensed into the entire water space of the body, assuming that the necessary transport protein is available. From plasma, lactate is transported into red blood cells (RBC), liver, heart, all noncontractive muscles and other tissues (Fig 5). The direction of the lactate flow is determined mainly by the concentration gradient across the membranes of those tissues. The flow of lactate into the tissues will tend to decrease the plasma concentration of lactate and thus increase the efflux from the muscle which is determined by the muscle - plasma concentration gradient.

In the horse, RBC water space is especially interesting, because, during exercise, RBC account for about 60 per cent of the blood volume. RBC have active MCT on their plasma membranes, and they efficiently and rapidly take up lactate from plasma (Väihkönen & Pösö 1998, Skelton *et al.* 1995). Because the transporter has a rather high K_m -value, about 20 mmol/l (Skelton *et al.* 1995, Väihkönen & Pösö 1998), it thus cannot be saturated at physiological lactate concentrations. The activity of MCT in RBC is also activated by low pH (Väihkönen *et al.* 1999). It was recently suggested that high MCT activity in RBC membranes is a feature of athletic animal species such as dogs and horses

(Skelton *et al.* 1995). In horses, RBC lactate is highly variable and has been connected with performance capacity, because among Standardbred trotters, those horses with the best individual performance index values have the highest lactate concentration in their RBC (Pösö *et al.* 1995, Räsänen *et al.* 1995). The accumulation of lactate in RBC is also a function of MCT activity (Väihkönen *et al.* 1999). Our own studies of more than 100 Standardbred horses have demonstrated that in approximately 30% of the horses MCT activity in their RBC membranes is extremely low, and in these horses RBC lactate concentration is low after races (Väihkönen & Pösö 1998, Väihkönen *et al.* 1999). From our studies, it can be concluded that accumulation of lactate in RBC during exercise may have some impact on performance, but the issue is extremely complex, and the differences in the performance capacity between elite horses are small; thus, the causal relationship is extremely difficult to show conclusively. Interestingly, this high inherent interindividual variation seems to be a property of horses, because other athletic species that have been tested, human athletes, racing reindeer, sled dogs, and greyhounds, fail to show it (Väihkönen *et al.* 2001).

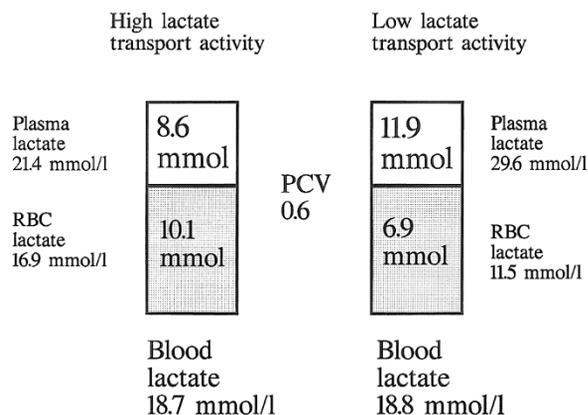


Figure 6. Distribution of post-exercise lactate in blood samples of two horses. Samples for the measurement of whole blood lactate and plasma lactate were taken about 5 min after a 2100-m race. The sample for plasma lactate analysis was immediately cooled in ice-water and centrifuged at +4 °C for separation of plasma.

Lactate accumulation in RBC during and after exercise has, however, a very large effect on the practice of lactate measurements, and on the question whether the post-exercise lactate concentration should be measured in whole blood or in plasma. On the basis of a large number of samples, there seems to be a good correlation between whole blood and plasma lactate concentrations (Persson *et al.* 1995, Pösö *et al.* 1995), but the situation differs completely if viewed on an individual basis. This can be demonstrated with “a real-life” example based on blood samples taken from two horses after a trotting race (Fig 6). One of these horses had high MCT activity in its RBC but in the other, this activity was low. In a blood samples taken from these two horses about 5 min after a race, the whole-blood lactate concentration was the same, 18.7-18.8 mmol/l, which may be taken as an indication that the amount of lactate transported from the muscle was the same. However, when part of the blood samples mentioned was immediately put on ice-water and plasma was rapidly separated by centrifugation and the plasma lactate concentrations were measured, the difference was striking: the horse having a low MCT activity had a high lactate concentration in plasma, whereas for the other horse

more lactate had accumulated in the red blood cells and thus the plasma lactate concentration was low. This difference was not due to hematocrit values. This example demonstrates that if post-exercise lactate concentration is analysed in plasma samples, it is very difficult to make horse-to-horse comparisons. Interestingly, similar great individual muscle-blood lactate gradients exist in human athletes (Tesch *et al.* 1982). MCT activity is not the only factor influencing the accumulation of lactate in RBC *in vitro* (Väihkönen *et al.* 1999). The time from sampling to centrifugation and also the temperature at which the sample is stored have a great impact. If the blood sample is kept warm, the transport of lactate into RBC in the sample test tube is rapid, whereas if the samples are kept on ice no transport can be detected up to one hour. This may also be correlated with the ambient temperature, i.e., summer versus winter conditions. However, all these speculations on lactate distribution are unnecessary if whole blood lactate values are used.

Elimination of lactate during exercise and recovery

Transport of lactate into RBC is only a passive means to increase the muscle-plasma concen-

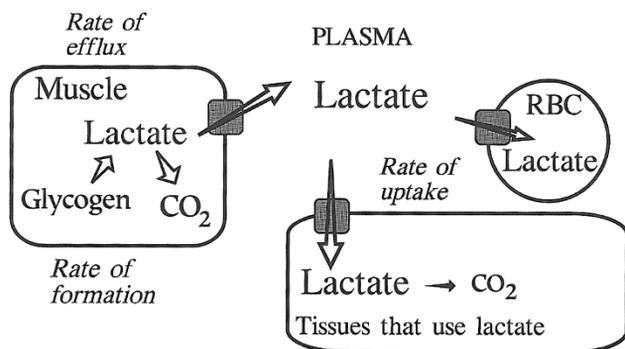


Figure 7. Factors affecting plasma lactate concentration

tration gradient; the oxidation of lactate is more efficient. The latter occurs in the heart, liver, type I muscle fibers, and other noncontracting tissues both during exercise and especially after it (Brooks 1991). The use of lactate differs between muscle tissue and liver. In the muscle, lactate is used for oxidation and energy production, and retains still over 90% of the energy of glucose. In liver, especially during exercise, lactate is metabolised back to glucose and circulated again to working muscles. During recovery, some lactate can be used for the synthesis of glycogen, although this matter is still under debate (Stevenson *et al.* 1987, Ryan & Radziuk 1995). This cell-to-cell lactate shuttle is well accepted, and recently a similar shuttle has been suggested to operate also within cell cytosol and mitochondria (Brooks *et al.* 1999b). It is generally accepted that light exercise during recovery increases lactate disappearance from blood both in human subjects and in horses (Marlin *et al.* 1987, Bangsbo *et al.* 1994, Francaux *et al.* 1995). During recovery, muscle tissue, which on a percentage basis is the largest tissue of the body, changes from lactate producer to lactate consumer, because lactate is a good energy substrate and readily available. During light exercise, the oxygen consumption of muscle may be twice that at rest, an increase that is small in comparison to the 20-fold in-

crease from rest to maximal aerobic exercise. This small increase in muscle oxygen consumption will also double the utilisation of lactate in muscle, seen as faster disappearance (Halperin & Rolleston, 1993).

Lactate as a marker of performance

Several factors affect blood lactate concentration (Fig. 7), and at least some of these factors are influenced by training. The rate of lactate production in exercising muscles is influenced by oxidative capacity, and thus training which is often accompanied with an increase in the number of mitochondria may reduce lactate production. Another factor that may regulate blood lactate concentration is the rate of efflux from the muscle, and as mentioned earlier, training increases the number of monocarboxylate transport proteins on the sarcolemma, which would have the effect of increasing blood lactate concentration. The third factor that markedly influences blood lactate concentration is its uptake by tissues that oxidize lactate. Several studies in humans have shown that lactate is taken up by the liver and inactive muscles and that lactate clearance is increased by training (Donovan & Brooks 1983, Pagliassotti & Donovan 1990, Phillips *et al.* 1995). Increased clearance during and after exercise would tend to lower the lactate concentration in blood. All

these factors have to be taken into account when blood lactate concentration serves as a marker of performance.

What does blood lactate concentration tell us about performance? Primarily, it is a useful marker for the estimation of aerobic capacity. It is well known that the trained horses have high aerobic capacity and at a certain absolute work intensity produce less lactate than do horses that are not equally well trained (Snow & MacKenzie 1977, Persson 1983). In races, horses perform at maximal intensity and use their anaerobic capacity, as well. For this anaerobic capacity, lactate is not an equally good marker, because we still have insufficient basic knowledge of those systems contributing to blood lactate concentration. For two horses working at maximal intensity, one with a high lactate and the other a substantially lower maximal lactate concentration, there are still several factors that remain question marks in this equation. Did one horse have a low concentration of lactate because it did not have high activity of MCT on its sarcolemmal membranes, or did it have less lactate production in its muscles because of higher aerobic capacity or because of lower activity of its glycolytic enzymes? Was the fiber recruitment pattern the same in the two horses? Or was the buffer capacity different in the muscles; did one horse tolerate lower lactate concentrations in its muscles? What if the uptake of lactate into liver and other user tissues differed between these two horses? From a practical point of view, knowledge of aerobic capacity is valuable, because high capacity would mean that lactate concentration for a major part of the race will be lower than that of a horse with low oxidative capacity. We should not, however, forget that what is important is not the blood lactate, but the lactate concentration in the muscle and perhaps also the activity of MCT in muscle membranes.

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Sammanfattning

Monokarboxylat transportörer och laktat metabolismen hos tävlingshästar

Mjölksyra är en känd slutprodukt av den anaeroba glykolysen, en reaktionskedja som är viktig under hårt arbete. Nyligen klonade transportproteiner för monokarboxylsyror, som formar en konserverad protein familj och som transporterar mjölksyra genom biologiska membraner, har givit en ny inblick i mjölksyrans roll i kroppsmetabolismen. Istället för att vara en värdelös slutprodukt anses mjölksyra nu vara ett värdefullt substrat som i väsentlig grad deltar i energiproduktionen i hjärtat, okontraherande muskler och även hjärnan. I den här artikeln refereras ny litteratur om mjölksyra och om monokarboxylsyra transportörer med speciell hänvisning till hästar.

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