Lactate and Fatigue

LAKTAT VE YORGUNLUK

Şeref ERDOĞAN*, S.Sadi KURDAK*

* Dr., Çukurova University, School of Medicine, Department of Physiology, Adana, TURKEY

Summary

Muscle fatigue may be defined as a decreased power output in terms of force production and speed and discussed in central and peripheral origin. Peripheral fatigue is caused by an impairment of force generation by the muscle. During intensive muscle contraction, as a result of anaerobic glycolysis, H^+ and lactate accumulates in the muscle cell and they may negatively effect the force output. For many years fatigue-inducing action of lactate was discussed together with pH. But in 1995, Hogan et al. showed pH independent fatigue-inducing effect of lactate ion on skeletal muscle and changed this idea. Following to this report, investigators were concentrated on the mechanism of lactate's direct effect (pH independent) on tension development. This review is focused on to distinguish lactate ion and lactic acid induced fatigue from each other.

Key Words: Lactate, Lactic acid, Fatigue

T Klin J Med Sci 1999, 17:366-369

Özet

Kas yorgunluğu, güç oluşumu ve hızındaki azalma olarak tanımlanabilmekte, merkezi ve periferik kaynaklı olarak irdelenebilmektedir. Periferik yorgunluk kas tarafından oluşturulan güçteki azalmadan kaynaklanır. Yoğun kas kasılması süresince, anaerobik glikoliz sonucu H^+ ve laktat kasta birikmekte ve bunlar da güç oluşumunu olumsuz yönde etkileyebilmektedir. Yıllardır laktatın yorgunluk yapıcı etkisi pH ile beraber değerlendirilmiştir. Ancak 1995'de, Hogan ve ark. laktat iyonunun iskelet kası üzerinde yorgunluk yapıcı etkisinin pH'dan bağımsız olarak da gerçekleşebildiğini gösterdi ve bu konudaki görüş değişti. Bu bildiriden sonra araştırıcılar laktatın gerim oluşumu üzerine olan direkt (pH'dan bağımsız) etkisinin mekanizması üzerine yoğunlaştı. Bu derlemede laktat iyonu ve laktik asidin yorgunluk oluşturma etkilerinin birbirinden ayrılması üzerinde durulmuştur.

Anahtar Kelimeler: Laktat, Laktik asit, Yorgunluk

T Klin Tıp Bilimleri 1999, 17:366-369

Muscle fatigue may be defined as a decreased power output in terms of force production and speed. During the contraction of the skeletal muscle, impulses originated from the central nervous system are transferred by the peripheral motor nerve fibers towards the neuromuscular junction and then to the skeletal muscle as the target tissue. Voluntary muscle activity involves many steps from the brain to the formation of actin - myosin cross bridges within the muscle. Therefore muscle fatigue may occur as a result of failure at any one of these steps and this phenomena may be discussed in two main groups: i. Central fatigue, is caused by a failure in neural drive; ii. Peripheral fatigue is impairment of force generation by the muscle, which may occur at 3 different sites (1):

1. Excitation; spreading of the stimulus within the neuromuscular junction.

2. Activation; mechanisms involved with Ca^{2+} releasing from the sarcoplasmic reticulum.

3. Contraction; actin - myosin interaction.

Factors involved with peripheral fatigue phenomenon may be affected by the intramuscular metabolic changes occurred during contraction. In literature, there are two main hypothesis proposed

Geliş Tarihi: 20.04.1999

Yazışma Adresi: Dr.Şeref ERDOĞAN
Çukurova Üniversitesi Tıp Fakültesi
Fizyoloji AD,
01330 Balcalı, ADANA

to explain these intramuscular metabolites changes (1):

1. Exhaustion hypothesis,

2. Accumulation hypothesis.

While the exhaustion hypothesis mainly concentrated on the insufficiency of energy substrates, in terms of ATP, creatinine phosphate, and glycogen, the accumulation hypothesis explained the force reduction by increased amount of metabolites such as H^+, Pi, and lactate within the muscle cell. In the present review we are concentrated on sole or combined effect of accumulated end products (H^+ and lactate), and/or insufficient washout of these metabolites. Especially one of these end products, lactate, is identified as fatigue-inducing agent and many experiments were performed to clarify the effect of this metabolite on fatigue.

Terminology: Lactic acid versus Lactate

Lactic acid is present in lactate form in body fluids. Since the pK value of lactic acid is 3.9, at the pH values of 6.4, which measured in the fatigued muscle and at the physiological pH of 7.4, 99.5 % of the lactic acid is in ionized form (2,3). It is well known that lactate is the end product of anaerobic glycolysis and, there are different possible pathways which determine the fate of this metabolite. Thus lactate; i. accumulates in the muscle cell; ii. is converted to glucose/glycogen (gluconeogenesis), or alanine via pyruvate (4); iii. leaves the muscle cell may oxidate lactate by another tissue in tricarboxylic acid cycle (TCA) (3,5-7). Since entering to this cycle requires equal amount of protons to lactate, and oxidation of this metabolite has an alkalizing effect for muscle cell (3). On the other hand the oxygen level in intracellular milieu is one of the main determining factors for the amount of utilized lactate in TCA, oxygen insufficiency results in accumulation of this metabolite with proton and, this reaction ends up with acidification of the intracellular milieu (8).

Previous studies had shown the presence of a stereospecific lactate carrier protein on the skeletal muscle cell membrane for the L-(+) isomer (4). Lactate and proton are transferred with this carrier protein together and especially during exercise this cotransporter is an important regulator of intracellular pH (4,9,10). Because of this interaction between lactate and H^+, for many years fatigue-inducing effect of lactate was explained with acidification of the muscle cell (9-12).

Lactate - H^+ relationship during fatigue

For many years, all of the studies related to fatigue was concentrated on the accumulation of H^+, and changes at the muscle pH (measured pH in fatigue muscle 6.00-6.30) (13-19). Reduction of the muscle pH results in:

1. Inhibition of the glycolytic enzymes (20).

2. Failure of excitation - contraction coupling (12,16,18,21,22).

3. Inhibition of sarcoplasmic reticulum Ca^{2+} release (18,23,24).

4. Competition with Ca^{2+} for binding to troponin (25,26)

5. Direct inhibition of the cross bridges between actin and myosin (27).

Observation of synchronous changes at the intracellular H^+ concentration with lactate concentrated investigators on lactic acid instead of lactate ion (11,12). On the other hand, recent studies in intact animal models, where muscle pH was measured directly, had shown that the reduction of tension development during fatigue was more prominent comparing to the changes at muscle pH, and reported as an interesting finding (28). This study had shown that at least another factor (such as Pi or inappropriate Ca^{2+} release) might also involve in fatigue. However, in a previous study, elevation of the intracellular H^+ concentration together with Pi was measured and additive effect of these two metabolites was shown (29). On the other hand, influence of another metabolite, lactate with H^+ on muscle tension was also studied and isolated effect of lactate was reported in one of these studies (28). In that experiment, Chase and Kushmerick (28) used skinned fiber preparation in a solution at pH of 7.1 and published the nonsignificant molecular effect of lactate ion at 50 mM concentration.

Molecular mechanisms of lactate induced fatigue

In 1995, the idea of pH-dependent fatigue inducing effect of lactate was changed by Hogan et al. (30). These investigators infused in situ isolated dog gastrocnemius muscle with L-(+)-Lactate solu-

tion at physiological pH and showed 17 % reduction at the muscle tension development. Data from our laboratory and others had also shown pH independent inhibitor effect of lactate on muscle tension by using different experimental models such as skinned fiber (31), and in vitro rat diaphragm muscle (32). By putting all of these data together, beside the acidic effect of lactate, fatigue inducing effect of this molecule was found. After discovery this direct action of lactate, recent studies related to lactate-fatigue relationship are concentrated to understand the mechanism of lactate's molecular effect.

Possible explanations of reduced tension development with high lactate at isopH may be highlighted as; changes at the ionic distribution, inhibition of calcium release from sarcoplasmic reticulum or reduced calcium sensitivity of the contractile proteins (20).

Since lactate is carried through the cell membrane with lactate-proton cotransporter, H^+ carried together with lactate may change the intracellular ionic balance (such as Na^+, K^+, Ca^{2+}) (20, 33) and thus by effecting the electrical properties of the muscle cell, it may reduce tension development. However, the data from our laboratory had shown the reduction of tension development (approx. 20%) without changing the excitability of the rat diaphragm muscle in 20 mM lactate solution at iso pH (34).

On the other hand, Andrews et al. (31) examined the sensitivity of the contractile proteins to calcium on the skinned fiber preparations. These investigators found a small but significant effect on the maximal Ca^{2+}-activated force with 15, 20, 25 mM lactate and showed the reduction at the tension development by 97.47 %, 96.28 %, and 98.78 %, respectively. Interestingly, at that study beside the low (5 -15 mM) lactate concentrations, no significant inhibitor effect was reported for high concentrations (30-50 mM) as well. Actually this minimal inhibitor effect of 50 mM lactate on tension development at skinned fiber preparations was also reported by Chase and Kushmerick (28) on 1988. Even 20% reduction at the tension development was recorded at in vitro and in situ skeletal muscle preparations with 20 mM lactate at isopH, only 4% reduction was measured at Ca^{2+}-activated force in skinned fiber preparations for the same lactate concentration. This finding had shown the possible inhibitor effect of lactate molecule on the Ca^{2+} sensitivity of contractile proteins, but in addition to that even more prominent mechanisms have to the responsible from this reduction.

To study the mechanisms of the molecular effect of lactate ion on rabbit white skeletal muscle, in 1997, Favero et al. (35) was isolated the sarcoplasmic reticulum. These investigators recorded the channel activity of this organelle at 10 to 30 mM lactate concentrations and found that lactate reduced the Ca^{2+}- and caffeine-stimulated Ca^{2+} release nearly 50% by binding to the 3H ryanodine receptor (35). Data from our laboratory had also shown a 16% reduction at tension development with 20 mM of lactate was compensated with 10 mM of caffeine (36). By putting these data together, the prominent mechanism of lactate ion-induced fatigue may be explained with reduced sarcoplasmic reticulum Ca^{2+} release.

Conclusion

For many years, lactate is known as a fatigue-inducing agent. Insufficient washout of lactate that induce intracellular acidity impairs the excitation, contraction and metabolic processes; thus may depress the maximal power output and ends up with muscle fatigue. However, in addition to lactate's mentioned properties, following the discovery of the inhibitor effect on tension development as a molecule, number of studies concentrated on the mechanisms of isolated molecular effects are increasing.

Studies had shown that molecular effect of lactate may reduce Ca^{2+} release by binding to sarcoplasmic reticulum ryanodine receptor. Beside that, small but significant reduction at the sensitivity of the contractile proteins was also underlined. It would be interesting to distinguish the acidic and molecular effect of lactate from each other. Thus it will be possible to clarify another effect of lactate on this multifactorial phenomena, "fatigue".

REFERENCES

1. MacLaren DPM, Gibson H, Parry-Billings M, Edwards RHT. A review of metabolic and physiological factors in fatigue. Exerc Sport Sci Rev 1989; 17: 29-66.
2. Wilkie DR. Muscular fatigue: effects of hydrogen ions and inorganic phosphate. Fed Proc 1986; 45: 2921-3.

3. Gladden LB. Lactate uptake by skeletal muscle. Exercise Sports Sci Rev 1989; 17: 115-55.

4. Roth DA, Brooks GA. Lactate transport is mediated by a membrane-bound carrier in rat skeletal muscle sarcolemmal vesicles. Arch Biochem Biophys 1990; 279: 377-85.

5. Bangsbo J, Graham T, Johansen L, Saltin B. Muscle lactate metabolism in recovery from intense exhaustive exercise: impact of light exercise. J Appl Physiol 1994; 77: 1890-5.

6. Gladden LB. Net lactate uptake during progressive steady-level contractions in canine skeletal muscle. J Appl Physiol 1991; 71: 514-20.

7. Lindinger MI, McKelvie RS, Heigenhauser GJ. K+ and Lac-distribution in humans during and after high-intensity exercise: role in muscle fatigue attenuation? J Appl Physiol 1995; 78: 765-77.

8. Gladden LB, Yates JW. Lactic acid infusion in dogs: effects of varying infusate pH. J Appl Physiol : Respirat Environ Exerci Physiol 1983; 54:1254-60.

9. Juel C. Lactate/proton co-transport in skeletal muscle. regulation and importance for pH homeostasis. Acta Physiol Scand 1996; 156: 369-74.

10.Juel C. Lactate-proton cotransport in skeletal muscle. Physiol Rev 1997; 77:2 321-58.

11.Hogan MC, Welch HG. Effect of varied lactate levels on bicycle ergometer performance. J Appl Physiol : Respirat Environ Exerci Physiol 1984; 57: 507-13.

12.Fitts RH. Cellular mechanisms of muscle fatigue. Phys Rev 1994; 74:49-85.

13.Metzger JM, Fitts RH. Role of intracellular pH in muscle fatigue. J Appl Physiol 1987; 62: 1392-7.

14.Renaud JM: The effect of lactate on intracellular pH and force recovery of fatigued sartorius muscles of the frog, Rana pipiens. J Physiol (Lond) 1989; 416: 31-47.

15.Westerblad H, Lee JA, Lannergren LJ, Allen DG. Cellular mechanisms of fatigue in skeletal muscle. Am J Physiol 1991; 261 (Cell Physiol 30): C195-C209.

16.McKenna MJ. The roles of ionic processes in muscular fatigue during intense exercise. Sports Med 1992; 13: 134-45.

17.Williams JH, Ward CW, Klug GA. Fatigue-induced alterations in Ca2+ and caffeine sensitivities of skinned muscle fibers. J Appl Physiol 1993; 75: 586-93.

18.Fitts RH, Balog EM. Effect of intracellular and extracellular ion changes on E-C coupling and skeletal muscle fatigue. Acta Physiol Scand 1996; 156:169-81.

19.Bangsbo J, Graham T, Johansen L, Strange S, Christensen C, Saltin B. Elevated muscle acidity and energy production during exhaustive exercise in humans. Am J Physiol (Regulatory Integrative Comp Physiol 32) 1992; 263: R891-R9.

20.Bosca L, Aragon JJ, Sols A. Modulation of muscle phosphofructokinase at physiological concentration of enzyme. J Biol Chem 1987; 260:2100-7.

21.Lindinger MI, Heigenhauser GI. The roles of ion fluxes in skeletal muscle fatigue. Can J Physiol Pharmacol 1991; 69: 246-53.

22.Balog EM, Thompson LV, Fitts RH. Role of sarcolemma action potentials and excitability in muscle fatigue. J Appl Physiol 1994; 76: 2157-62.

23.Favero GT, Zable CA, Bowman MB, Thompson A, Abramson JJ. Metabolic end products inhibit sarcoplasmic reticulum Ca2+ release and [3H] ryanodine binding. J Appl Physiol 1995; 78: 1665-72.

24.Byrd SK, Bode AK, Klug GA. Effects of exercise of varying duration on sarcoplasmic reticulum function. J Appl Physiol 1989; 66: 1383-9.

25.Metzger JM. Effects of troponin C on pH sensitivity of contraction in mammalian fat and slow skeletal muscle fibers. J Physiol 1996; 492: 163-72.

26.Blanchard EM, Solaro RJ: Inhibition of activation and troponin Ca binding of dog cardiac myofibrils by acidic pH. Circ Res 1984; 55: 382-90.

27.Metzger JM, Moss RL. pH modulation of the kinetics of a Ca2+-sensitive cross bridge state transition in mammalian single skeletal muscle fibers. J Physiol 1990; 428: 751-64.

28.Chase PB, Kushmerick MJ. Effects of pH on contraction of rabbit fast and slow skeletal muscle fibers. J Biophys Soci 1988; 53: 935-46.

29.Cooke R, Franks K, Luciani GB, Pate E. The inhibition of rabbit skeletal muscle contraction by hydrogen ions and phosphate. J Physiol 1988; 395: 77-97.

30.Hogan MC, Gladden LB, Kurdak SS, Poole DC. Increased [lactate] in working dog muscle reduces tension development independent of pH. Med Sci Sport Exerc 1995; 27: 317-77.

31.Andrews MA, Godt ER, Nosek TM. Influences of physiological L(+)-lactate concentrations on contractility of skinned striated muscle of rabbit. J Appl Physiol 1996; 80: 2060-5.

32.Erdogan S, Kurdak SS, Dogan A. L-(+)-Lactate reduced tension development in invitro rat diaphragm muscle at iso pH. Experimental Biology '95 (FASEB), 1995; Abstracts part I, page A-351.

33.Lindinger MI, Heigenhauser GJ. Ion fluxes during tetanic stimulation in isolated perfused rat hindlimb. Am J Physiol 1988;254: Pt 2 R117-26.

34.Kurdak SS, Erdogan S, Dogan A. L-(+)-Lactate reduce tension development at iso pH without changing excitability in rat diaphragm muscle. (Med Sci Sport Exerc; has been evaluating).

35.Favero GT, Zable CA, Colter D, Abramson JJ. Lactate inhibits Ca^{+2}-activated Ca^{+2} channel activity from skeletal muscle sarcoplasmic reticulum. J Appl Physiol 1997; 82: 447-52.

36.Kurdak SS, Erdogan S, Ergen N, Dogan A. High doses of caffeine recovers the lactate-induced fatigue in vitro rat diaphragm muscle at iso pH. XXXIII. International Congress of Physiological Sciences (St. Petersburg, Russia), 1997; Abstracts P034.30.