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Original article

The importance of lactic acid in migraines and fibromyalgia☆

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ABSTRACT

Background: Lactic acid is a byproduct of both muscle metabolism and the central nervous system. Changes in metabolism are related to various physiological and pathological conditions. The aim of this study was to determine the relationship between migraine and fibromyalgia with the levels of lactic acid in the blood.

Methods: We study 93 patients divided into five groups: (1) patients with fibromyalgia ($n = 20$); (2) episodic migraine ($n = 20$); (3) chronic migraine ($n = 20$); (4) fibromyalgia and episodic migraine ($n = 13$); and (5) fibromyalgia and chronic migraine ($n = 20$), and 20 healthy subjects (control group). Blood levels of lactic acid were measured at four different time points: at rest, during aerobic exercise, during anaerobic physical activity and while resting after anaerobic exercise.

Results: Lactic acid increased in all groups during anaerobic physical activity without predominance for either group. During aerobic physical activity, all groups increased lactic acid levels, but the increase was more expressive in the chronic migraine group and the chronic migraine with fibromyalgia group without statistical significance.

Conclusions: We did not found abnormalities involving the metabolism of lactic acid in episodic and chronic migraine with or without fibromyalgia.

☆ The study was conducted at the Neurology, Cardiology and Rheumatology Services, Hospital de Clínicas, Universidade Federal do Paraná (UFPR), Curitiba, PR, Brazil.

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A importância de ácido láctico na enxaqueca e na fibromialgia

Palavras-chave:
Enxaqueca crônica
Enxaqueca episódica
Ácido láctico
Fibromialgia

RESUMO

Introdução: O ácido láctico é um subproduto do metabolismo muscular e do sistema nervoso central. As alterações no metabolismo estão relacionadas com diversas condições fisiológicas e patológicas. O objetivo deste estudo foi determinar a relação entre a enxaqueca e a fibromialgia com os níveis de ácido láctico no sangue.

Métodos: Foram estudados 93 pacientes, divididos em cinco grupos: 1) fibromialgia (n = 20); 2) enxaqueca episódica (n = 20); 3) enxaqueca crônica (n = 20); 4) fibromialgia e enxaqueca episódica (n = 13); e 5) fibromialgia e enxaqueca crônica (n = 20), além de 20 indivíduos saudáveis (grupo controle). Os níveis sanguíneos de ácido láctico foram medidos em quatro momentos: em repouso, durante o exercício aeróbico, durante a atividade física anaeróbica e durante o descanso depois do exercício anaeróbico.

Resultados: O ácido láctico aumentou em todos os grupos durante a atividade física anaeróbica, sem predominância em qualquer grupo. Durante a atividade física aeróbica, todos os grupos apresentaram um aumento nos níveis de ácido láctico, mas esse aumento foi mais expressivo nos grupos de enxaqueca crônica e enxaqueca crônica com fibromialgia, sem significância estatística.

Conclusões: Não foram encontradas anormalidades que envolvessem o metabolismo do ácido láctico na enxaqueca episódica e crônica, na presença ou não de fibromialgia.

Introduction

Migraine is a chronic neurological disorder with high prevalence and severe impact on a patient's quality of life. This disorder has genetic characteristics that modulate a dysfunction in brain electrical activity. This neurological condition is characterized by recurrent episodes of headache with unilateral throbbing characteristics of moderate to strong severity that worsens with physical activity. This worsening is associated with vomiting, nausea, phonophobia and photophobia.[1,2]

Many biochemical changes can be observed during and between migraine attacks. Lactic acid levels, for example, may be altered, exhibiting an increase compared with patients with tension-type headache and healthy controls.[3] These data suggest that migraine patients have an abnormality in mitochondrial metabolism. It was demonstrated that lactate levels within the visual occipital cortex is elevated in migraine patients during the inter-ictal period and could suggest the presence of anaerobic glycolysis in cortical regions.[4] However, other studies have not confirmed these changes and, as a result, do not support this hypothesis.[5]

Lactic acid usually increases during high-intensity physical activity and is related to a decline in muscle strength and pain generation during exercise.[6–8] Additionally, the increase in lactic acid observed during exercise has been shown to trigger migraine attacks with aura.[9,10] Despite this causal relationship, lactic acid is not considered an algogenic substance.[11]

Fibromyalgia is a chronic pain condition of unknown etiology characterized by widespread spontaneous muscle pain and tenderness to palpation. The diagnostic criteria used for fibromyalgia comes from the American College of Rheumatology 2009 and 2010.[12,13] Fibromyalgia can also display co-morbidities, such as psychiatric disorders and other pain syndromes. The correlation between fibromyalgia and migraine varies from 22 to 50% of cases.[14] This association contributes to a decreased quality of life for patients and enhances the presence of co-morbidities. The pathophysiological relationship between these two disorders has not yet been established in the medical literature.

Patients with fibromyalgia may experience high levels of lactic acid at rest[15,16] or during aerobic physical activity.[17] However, other studies show that changes in glycolysis and lactic acid at rest or during physical activity were slight increased among fibromyalgia patients.[18,19]

The ratio of lactic acid production in patients with migraine and fibromyalgia, as well as the influence of this metabolite in the pathophysiology of these diseases, is controversial or nonexistent. The goal of this study is to determine whether the metabolism of lactic acid changed in episodic migraine or chronic migraine, with or without associated fibromyalgia.

Patients and methods

We selected from out-patient headache clinic cases with chronic and episodic migraine who were also suffering from fibromyalgia and from the out-patient rheumatology clinic for patients with only fibromyalgia. All patients with chronic and episodic migraine met the criteria proposed by the International Headache Society Classification (IHS-2004).[2] The fibromyalgia patients fulfilled all of the criteria of the American Society of Rheumatology (2009 version).[13] For the control group, we recruited employees belonging to the clinical staff of the Hospital de Clínicas da Universidade do Paraná. All patients and controls underwent a clinical and laboratory investigation to rule out silent diseases, such as diabetes, kidney failure, liver disease, lung disease and heart disease.

Medications

A portion of patients continuously used one or more of the following medications: selective inhibitors of serotonin uptake ($n = 23$), tricyclic antidepressants ($n = 20$), selective receptor of serotonin inhibitors, norepinephrine and dopamine ($n = 5$), antipsychotics/dopamine blockers ($n = 6$), benzodiazepines ($n = 14$), sleep inducers ($n = 1$), muscle relaxants ($n = 19$), anti-inflammatory drugs ($n = 9$), antimalarials ($n = 2$), antihistamines for allergy ($n = 4$), statins ($n = 3$), proton pump blockers ($n = 6$), anticonvulsants ($n = 10$), angiotensin converting enzyme inhibitors ($n = 10$), diuretics ($n = 10$), oral anticoagulants ($n = 1$), alendronate ($n = 1$), levothyroxine ($n = 15$), metformin, insulin and orlistat ($n = 4$).

Symptoms during testing

The tests were performed despite the painful muscle symptoms in patients with fibromyalgia. The patients with episodic migraine underwent the test only if they were free of a headache crisis for at least five days. Patients with chronic migraine were tested during periods of lower headache intensity.

Exercise stress testing

The patients underwent exercise stress testing using a treadmill with progressive increments of effort and while using the software MicromedErgoPC 13. Initially, the patients had an electrocardiogram at rest (baseline control phase) followed by exercises with a mean duration of 30 min. The treadmill was in a flat position, started at speeds of 2.0 mph and increased by 1.0 mph every minute until reaching 9.0 mph. The test was divided into different stages: aerobic, anaerobic exercise and rest post exercise. To differentiate between aerobic and anaerobic exercise, we used the Karvonen formula (220 minus subject age = maximum heart rate for the age). We considered aerobic metabolic activity when the heart rate was between 50 and 69% of the predicted value found in the Karvonen formula for the age and anaerobic exercise when the heart rate was from 70% to 85% of the predicted maximum. All subjects sustained the exercise at the necessary heart rate for at least 3 min.[19] All subjects were considered to be sedentary.

Lactic acid determination

Lactic acid was determined by capillary blood samples via a transdermal skin punch of the left index finger at four time points: (1) resting baseline before exercise; (2) after 10 min of aerobic activity; (3) after 3 min of anaerobic activity; and (4) after 6 min of rest following anaerobic exercise. A drop of blood was placed on a specific paper tape (Roche Diagnostics Brazil) and introduced into a device for reflectance photometry (Accutrend Lactate, Roche Diagnostica, Brazil), which automatically determined the levels of lactic acid.

Ethics study

All patients signed an informed consent form. The procedures in this study were approved by the ethics committee for human research at the Hospital de Clinicas, Universidade Federal do Paraná.

Statistical analysis

In addition to descriptive statistical tests, we used the *t*-test for independent samples (homogenization of cases) and the Mann–Whitney *U* test for making comparisons between the levels of lactic acid in the various stages of the study ($p < 0.05$ for statistical significance). To confirm the results we applied the Bonferroni correction. Statistical analysis and plots were done using the SPSS software version 11.0 (Chicago, IL).

Results

Study subjects

The study subjects were grouped by age, weight, height and body mass index (BMI). All subjects and controls were females. Patients were divided into six groups: Group I – the healthy subjects using no medication ($n = 20$); Group II – patients with only fibromyalgia ($n = 20$); Group III – patients with only episodic migraine ($n = 20$); Group IV – patients with only chronic migraine ($n = 20$); Group V – patients with fibromyalgia plus episodic migraine ($n = 13$); and Group VI – patients with fibromyalgia plus chronic migraine ($n = 20$) (Table 1). All groups were similar, and there was no statistically significant difference between them with respect to age, weight, height or body mass index (BMI) (Table 1).

Lactic acid blood levels

The lactic acid was measured in 113 cases in four occasions (452 analyses): the baseline phase, aerobic phase, anaerobic phase and rest after physical activity. The lactic acid average of all groups underwent elevation during anaerobic activity and remained high during the rest period. Comparison of all subjects lactic acid level at the baseline phase (2.70 ± 1.32 mmol/L) with the anaerobic phase (3.81 ± 1.81 mmol/L) showed a significant increase ($p = 0.0001$). The lactic acid level at the baseline phase compared with the post-exercise rest (3.28 ± 1.34 mmol/L) was also significant ($p = 0.001$). The aerobic phase lactic acid also increased (3.01 ± 2.20 mmol/L) but was not significantly different from the baseline ($p = 0.125$) (Fig. 1).

No significant difference was found between aerobic exercises when compared with the baseline phase in all groups. Anaerobic exercise increased the lactic acid compared with baseline in the control group ($p = 0.0001$), fibromyalgia group ($p = 0.0001$) and chronic migraine group ($p = 0.008$). In the post-exercise rest group, the lactic acid remained elevated in the control group ($p = 0.008$) and the fibromyalgia group ($p = 0.003$). In the groups of episodic migraine, chronic migraine, fibromyalgia plus episodic migraine and chronic migraine plus fibromyalgia, the levels of lactic acid remained slightly elevated or near the basal control without statistical significance (Table 2).

When the levels of lactic acid were compared among the groups, the variation was not statistically significant between

Table 1 – Subjects characteristics of the controls, fibromyalgia and migraine cases.

Group	Number of cases[a]	Age (years-old) Mean ± SD Min–max	Weight (kg) Mean ± SD Min–max	Height (m) Mean ± SD Min–max	Body index mass Mean ± SD Min–max
Controls	20	42.60 ± 9.36 (22–56)	66.75 ± 9.15 (53–84)	1.64 ± 0.76 (1.53–1.80)	24.95 ± 3.90 (18.59–34.17)
Fibromyalgia	20	47.35 ± 6.33 (32–57)	65.75 ± 12.38 (46–90)	1.60 ± 0.54 (1.49–1.70)	25.65 ± 4.98 (18.81–34.07)
Episodic migraine	20	37.75 ± 10.54 (21–59)	65.95 ± 12.68 (46–90)	1.62 ± 0.67 (1.50–1.76)	25.24 ± 5.21 (17.85–35.15)
Chronic migraine	20	39.15 ± 12.13 (26–67)	65.15 ± 11.88 (45–100)	1.60 ± 0.78 (1.47–1.79)	25.71 ± 5.34 (20.00–42.16)
Episodic migraine plus fibromyalgia	13	46.92 ± 8.64 (30–62)	71.08 ± 4.70 (65–80)	1.61 ± 0.55 (1.53–1.72)	27.33 ± 2.35 (23.87–30.86)
Chronic migraine plus Fibromyalgia	20	44.30 ± 6.45 (31–57)	66.45 ± 12.39 (44–92)	1.61 ± 0.73 (1.50–1.76)	25.56 ± 4.16 (19.04–31.59)

SD, standard deviation; min, minimal; max, maximal.
[a] All cases were females.

Table 2 – Lactic acid levels at rest and the type of exercises phases.

Group	Number of cases	Rest (mmol/L) Mean ± SD	Aerobic (mmol/L) Mean ± SD	Anaerobic (mmol/L) Mean ± SD	Rest post exercise (mmol/L) Mean ± SD
Controls	20	2.39 ± 0.88	2.82 ± 2.41	3.64 ± 1.31	3.34 ± 1.24
Fibromyalgia	20	2.33 ± 1.08	2.38 ± 1.71	4.32 ± 1.96	3.37 ± 1.56
Episodic migraine	20	2.93 ± 1.38	3.22 ± 2.70	3.22 + 0.96	3.25 ± 1.39
Chronic migraine	20	2.79 ± 1.25	3.40 ± 1.91 $p = 0.048$[a]	4.21 ± 1.56	3.44 ± 1.19
Episodic migraine plus fibromyalgia	13	2.40 ± 0.83	2.05 ± 0.81	4.15 ± 3.40	3.05 ± 1.60
Chronic migraine plus fibromyalgia	20	3.23 ± 1.95	3.87 ± 2.53 $p = 0.042$[a]	3.43 ± 1.48	3.16 ± 1.27

SD, standard deviation.
[a] Statistical significance in relation to the control group before Bonferroni Correction (Mann–Whitney *U* test).

the phases of anaerobic exercise and rest after exercise phase. In the aerobic phase we found that the levels of lactic acid increased in the chronic migraine group ($p = 0.048$) and chronic migraine plus fibromyalgia group ($p = 0.042$) when compared with the other groups. However, if we applied the Bonferroni correction, this statistical significance disappears (Table 2).

No patients with fibromyalgia reported increased of muscle pain in all phases of the exercise. All patients with migraine and controls had no new complaints related tests during the study.

Discussion

The lactic acid blood level increased during exercise, with the skeletal muscle being the largest production site.[20] The increase in lactic acid production occurs after an increase of glycogenolysis and glycolysis. These changes promote a reversal of systemic genesis of energy, increasing circulating levels of catecholamines and altering the systemic glucose metabolism.[21,22] The energy source in the central nervous system (CNS) originates from glucose and lactic acid. The latter serves as energy source after overcoming the blood–brain barrier or when being produced directly in glial cells.[23] In the CNS, lactic acid is essential for maintaining the metabolic interactions between astrocytes and neurons, and its increases in lactic acid influence neuronal activity in the hypothalamus and the solitary tract.[24,25]

The diffusion of lactic acid is known to be mediated by transporters, such as monocarboxylate transporters 1 (MCT1) and 2 (MCT2), allowing greater ATP synthesis, closure of K channels and neuronal depolarization.[26] The sub-forms of MCT1 and MCT2 are expressed in the sites of lactic acid production (muscle and glial cells) and local of utilization (astrocytes, blood vessels, hippocampus, cerebellum, cerebral cortex and hypothalamus).[27] In humans, the amount of intracellular lactate is determined by the balance between the amount produced in the cell from increased glycolysis (physical activity) and the quantity transported out of the cell or into the mitochondria (influenced by MCT1). Acute physical activity alters the expression of MCT1 in the first minutes, and this change is maintained within 24 hours after exercise.[28]

A central mechanism that may alter lactate removal is the plasma volume (PV). Exercise is a potent inducer of PV increase, which occurs immediately after the onset of physical activity. The increased PV also influences cardiovascular

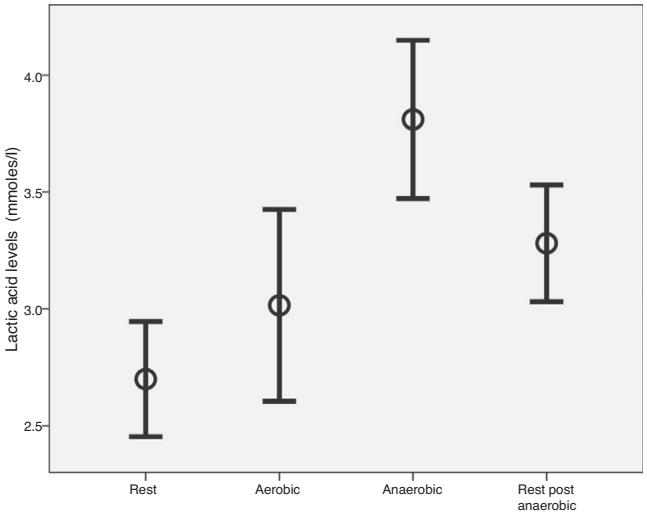

Fig. 1 – Lactic acid levels and response to the type of exercises in 113 female cases (controls 20; fibromyalgia 20; episodic migraine 20; chronic migraine 20; episodic migraine plus fibromyalgia 13; and chronic migraine plus fibromyalgia 20).

function, peripheral blood flow and the elevation of catecholamine levels (norepinephrine and epinephrine).[29] However, the main removal capacity of lactate during exercise is determined by the action of cellular MCT1, which is expressed in large amounts in the first minutes following the onset of physical activity. This relationship occurs such that the increased amount of circulating MCT1 is directly related to the reduction of the levels of muscle lactic acid.[30,31]

Conclusion

In conclusion our groups of chronic migraine and chronic migraine plus fibromyalgia showed significant increased levels of lactic acid during aerobic physical activity in relation to the controls. However, they did not reach a statistical significance level after Bonferroni correction. The increased levels seems to be more dependent on the presence of chronic migraine than fibromyalgia and may be due to the increased production, by the decreased metabolism of lactic acid or to the several medications used by the patients. Our findings cannot support the suggestion of abnormal metabolism of lactic acid in patients with episodic and chronic migraine associated with fibromyalgia. No causal relationship between migraine, fibromyalgia and lactic acid production was found.

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Conflicts of interest

The authors declare no conflicts of interest.

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