Comparison of Magnesium (Mg^{2+}) and ATP Abnormalities in Muscle Disorders: Fibromyalgia, Dermatomyositis and Scleroderma

Kenneth J. NIERMANN[1], Jane H. PARK[1], Rebecca J. MEYER[1], David A. GILPIN[1], Lloyd E. KING[1], Nancy J. OLSEN[1]
[1]Departments of Radiology and Medicine, Vanderbilt University, School of Medicine, Nashville, TN USA;

Introduction

Magnesium deficiency is known to produce neuromuscular symptoms of fatigue, weakness, and abnormal EMG (1). Magnesium is important because it is required for almost all enzyme reactions involving ATP. This includes enzymes in the glycolytic and Krebs cycles, which produce the ATP required for muscle contraction. Levels of free and ATP-bound magnesium can be determined in human muscles using P-31 MRS (2,3).

In this report, abnormalities in magnesium and ATP levels are compared in three different muscle disorders: fibromyalgia, dematomyositis, and scleroderma. Fibromyalgia (FM) is a disease characterized by widespread pain with tender points which is associated with disordered sleep. Dermatomyositis (DM) is characterized by a typical rash and severe proximal muscle weakness. Sclreoderma (Scl) is a connective tissue disorder which results in damaging fibrosis of the skin, lungs, kidneys, vascular system, and muscles. For each of these diseases, the muscle involvement results in the clinical complaints of weakness and fatigue. The observed decreases in the levels of free and ATP-bound magnesium in the diseased muscles are consistent with the degree of weakness and fatigue in the patient groups.

Methods

P-31 MRS spectra of the quadricep muscles of 11 normal control subjects, 12 fibromyalgia, 11 dermatomyositis and 13 scleroderma patients were acquired using a 1.5 T magnet. Spectra were obtained during each minute of a 6 minute rest period. During exercise, a weight corresponding to 25% MVC was secured on the ankle, and the subject raised his foot by contraction of the quadricep muscles once every 5 sec for 6 min. The exercise was repeated at 50% MVC for another 6 min period. The protocol concluded with a recovery period of 6 to 10 min. ATP levels were determined as previously described (4). Free and ATP-bound magnesium were calculated from the spectra according to the methods of Gupta and Mottet (2,3).

Results

During the initial rest period, there were no statistically significant differences between the [Mg free] levels in the muscles of the patients and controls. By contrast the [Mg-ATP], which is the enzymatically active form of ATP, was 12% lower in the FM muscles as compared to normal values ($P<0.013$) and approximately 40% lower in the DM or Scl muscles ($P<0.00001$). During the more strenuous exercise at 50% MVC, the [Mg free] levels decreased in the muscles of FM, DM and Scl patients by 24%, 52%, and 15%, respectively. Thus [Mg free] in the diseased muscles became significantly lower than the control values (P value range: 0.046 to 0.014) (Table 1). With exercise [Mg-ATP] levels remained unchanged in the control subjects and FM patients, but dropped by 10% in the two other patient groups. The data are in accord with the increases in the percentage [ATP-free] in the patient groups, which also became significantly different from the normal controls.

In comparing the patient groups, FM patients showed [free Mg] levels that were not statistically different from that of DM or Scl patients. The [Mg-ATP] values for FM patients were significantly higher than the DM or Scl values ($P<0.0001$). Thus FM subjects were the group closest to normal controls.

Discussion

Levels of intracellular free Mg and MgATP have been determined in a variety of human tissues, including red blood cells, brain and muscle. Magnesium deficiency in tissues has been reported in a number of clinical conditions such as hypertension, arteriosclerosis, cardiac arrythmias, diabetes, and eosinophilia myalgia. In the present study, levels of free Mg and MgATP were determined in the quadricep muscles which are markedly affected in various myopathies. Free Mg is one of the rate determining factors in the generation of ATP via oxidative phosphorylation in the Krebs cycle, and MgATP is the enzymatically active form of the nucleotide.

During exercise and recovery, free Mg and MgATP were significantly lower in the diseased muscles as compared to normal muscles. Low levels of magnesium may be related to the weakness and fatigue observed in these patients. It also has been observed that magnesium deficiency results in phosphaturia and loss of phosphate from muscle as well as other tissues. The mechanisms for this loss are not understood. P-31 MRS examination showed that the total phosphate (measured as the sum of Pi, PCr, ATP, PME and PDE) showed significant decreases in all three groups of patients.

In general, FM patients had a better magnesium and phospate profile than the DM or Scl patients. The higher levels of Mg in the FM muscles may be related to the almost normal morphology demonstrated with MRI. By contrast, DM and Scl muscles showed a wide variety of abnormalities, including inflammation, fat infiltration, fascia fibrosis, and atrophy. The presence of variable fiber diameter and fragmentation suggest that membrane abnormalities may permit increased Mg loss and even ATP hysdrolysis.

In the case of DM or juvenile DM patients, prednisone and immunosuppressive therapy promoted higher magnesium levels, which correlated with the resolution of inflammation, improved muscle strength, and greater endurance (5, 6). The data suggest that Mg may be important in the recovery of myopathic patients since this element is essential for the generation and maintenance of ATP in muscles.

In summary, low levels of [Mg free] and [MgATP] correlate with severity of muscle weakness and fatigue in FM, DM, and Scl. The MRS data indicate a significant role for magnesium in the pathology of these diseases.

References

1. Shils ME. Ann. Rev. Nutrition. 8: 429-460, 1988.
2. Gupta RK, Bemkovic JL, Rose ZB. J. Biol. Chem. 253: 6172-6176, 1978.
3. Mottet I, Demeure R, Gallez B, Grandin C, vanBeers BE, and Pringot J. MAGMA 2: 101-107, 1994.
4. Park JH, Vital TL, Ryder NM, Hernanz-Schulman M, Partain CL, Price RR, Olsen NJ. Arthritis Rheum. 37: 736-747, 1994.
5. Park JH, Olsen NJ, Phothimat P, Carr BN, King LE. ISMRM 5:163, 1997.
6. Niermann KJ, Henanz-Schulman M, Olsen NJ, Park JH. ISMRM 8:1886, 2000.

Muscle Mg^{2+} Levels in Fibromyalgia (FM), Dermatomyositis (DM) and Scleroderma (Scl) during exercise (mmol/kg ± SE)

	Mg free	Mg-ATP	ATP total	%ATP free
Controls (n=11)	0.96 ± 0.12	4.98 ± 0.19	5.31 ± 0.20	6.0 ± 0.4
FM (n=12)	0.67± 0.05	4.4 ± 0.13	4.80 ± 0.13	7.8 ± 0.6
DM (n=11)	0.57 ± 0.14	2.90 ± 0.20	3.30 ± 0.30	11.5 ± 1.6
Scl (n=13)	0.61 ± 0.06	3.08 ± 0.22	3.37 ± 0.23	8.8 ± 0.9
P value:	**Control vs**	**Patients**		
Ctl vs FM	0.027	0.012	0.033	0.026
Ctl vs DM	0.046	<0.0001	<0.0001	0.004
Ctl vs Scl	0.014	<0.0001	<0.0001	0.01
P value:	**FM vs DM**	**or Scl**		
FM vs DM	NS	<0.0001	<0.0001	0.042
FM vs Scl	NS	<0.0001	<0.0001	NS
P value:	**DM vs Scl**			
DM vs Scl	NS	NS	NS	NS