ROLE OF INTRACELLULAR CALCIUM IONS IN THE PHYSIOPATHOLOGY OF FIBROMYALGIA SYNDROME

M. Magaldi, L. Moltoni, G. Biasi, R. Marcolongo

Institute of Rheumatology, University of Siena

INTRODUCTION

Today fibromyalgia syndrome (FM) is considered to be a generalized non-articular rheumatic condition. It shows typical symptoms such as chronic pain, asthenia, muscular tension and/or rigidity in articular, periarticular subcutaneous tissues, ligaments and tendon insertions. It is associated with a specific tenderness on palpation at tender points (TP)(1,2). FM is one of the most frequent rheumatic diseases affecting from 6% to 20% of rheumatology out-patients. It has a higher incidence in women aged between 25 and 45 years. Painful symptoms may be exacerbated by cold and wind and relieved by heat. Headache, irritable bowel syndrome and menhorragia are also typical symptoms of FM. The etiopathogenesis of FM is still unclear. Authors discuss whether FM should be considered an organic disorder or a somatization of an anxiety syndrome, since no anatomic-pathological lesion or other kind of alteration has ever been detected. On the other hand, even in the presence of somatic symptoms, many authors consider FM to be induced by biochemical modifications in neurons and in the serotonergic system in particular. Patients report sleep disorders, altered nociceptive threshold, muscular pain and tension which give rise to a sort of vicious circle (3,4). At present, the relation between muscular tension and lowering of nociceptive threshold is still under investigation. Researches into a "central" and a "peripheral" basis of FM is open: no conclusion has been reached as to whether muscles are altered in the first place or they are a target of neurohormonal dysfunction (5). Histologic findings did not show either significative or distinctive alterations of muscles (6,7) and studies on energetic metabolism did not

produce conclusive results (8,9). It is well known that muscular contraction depends on entrance of calcium ions into myocells. These ions may therefore play a primary role in cellular alterations occurring in FM. Our interest in the behavior of calcium ions in intracellular space stems from this observation.

MATERIALS AND METHODS

Two groups of patients were recruited: 100 patients affected by FM and 40 healthy controls. Measuring of ions was performed by using polymorphonuclear cells (PMNs) drawn from venous blood. PMNs were separated by phycoll gradient, counted and suspended in PBS (calcium free buffer): the final PMNs concentration was 40 mmoli. They were then incubated with FURA-2AM (calcium probe) and put in a thermostat at 37°C for 30 minutes. PMNs were separated by centrifugation at 120 rpm. This operation was performed twice. Them PMNs were tested using a RF-5000 (Shimadzu) spectophotometer. Two wavelengths were chosen for excitation (340 and 380 nm) and one wavelength for emission light.

RESULTS

We registered a heavy reduction of intracellular calcium concentration in patients diagnosed with FM as compared to healthy controls. Statistic analysis performed by one tail t-student test, showed $p<0.0001$ (tab. 1).

Tab. 1 - Results of intracellular calcium concentration.

	Intracellular calcium
FM	46.048 nMoli/L ± 29.025
Controls	146.48 nMoli/L ± 22.35

DISCUSSION

These results highlight the biochemical likeness between spasmophylia and

FM, both disorders being characterized by intracellular calcium reduction. Spasmophylia is caused by hyperexcitability of neurons and muscles in central and peripheral systems, which may involve all organs and systems as a reaction to strain and stress. It also tends to evolve over the years in relation to adrenergic reactivity. Many symptoms such as asthenia, anxiety-tension, and headache are common to both FM and spasmophylia whereas muscular pain, tender points, irritable bowel syndrome and menhorragia are typical symptoms of FM. Intracellular calcium reduction in FM may therefore induce a peripheral and neuromuscular excitability with an excessive response to external stimuli and microtraumas. Observations made on intracellular calcium reduction in FM may be supported by the hyperexcitability shown by patients in stressful situations. However, typical manifestations of spasmophylia as tetanic strokes and electromyographic alterations are never detected in FM.
Further studies are needed in order to evaluate the pathogenetic role and proper meaning of intracellular calcium reduction, of symptoms and diagnosis.
May drugs effective on calcium metabolism be used in the treatment of FM? Researches into this field are still open to contributions.

Calcium ions have a key role in the physiology of muscular contraction: changes in calcium ion concentration may be involved in the pathogenesis of fibromyalgia. Although, since the plasmatic level of calcium in fibromyalgia patients is always in the normal range, it seemed interesting to evaluate the intracellular calcium concentration. The study was carried out on two groups of subjects: 70 affected by fibromyalgia and 40 healthy controls. The result obtained show that in fibromyalgia patients the intracellular calcium concentration is significantly reduced in comparison to that of healthy controls: the reduced intracellular calcium concentration seems to be a peculiar characteristic of fibromyalgia patients and may be potentially responsible for muscular hypertonus. The effective role of this anomaly in the physiopathology of fibromyalgia and the potential role of drugs active on the calcium homeostasis are still to be confirmed.

1) MARCOLONGO R., GIORDANO N., FIORAVANTI A., "Reumatismo fibromialgico", p. 377-386 in: Le malattie reumatiche, Fisiopatologia e clinica, UTET, Torino, 1991.
2) WOLFE F. et al., Arthritis and Rheum., 1990, 33, 160-172.
3) ZIMMERMANN M., Clin. J. Pain, 1991, 7, 8-15.
4) YUNUS M.B., J. Rheumatol., 1992, 19, 846-852.
5) WEIGENT D.A., BRADLEY L.A., BLALOCK J.E., ALARCON G.S., Am. J. Med. Sci., 1998, 315, 405-412.
6) SIMMS R.W., Am. J. Med. Sci., 1998, 315, 346-350.
7) McCAIN G.A., J. Musculoskel. Pain, 1994, 2, 93-104.
8) WILKE W.S., Rheum. Dis. Clin. North Am., 1995, 21, 247-260.
9) RUSSELL I.J., Bull. Rheum. Dis., 1998, 3, 45-48.

KEY WORDS: fibromyalgia, intracellular calcium, muscle contraction.

Lectured at the meeting held in Siena on October 5, 1999.
Received: October 10, 1999; accepted: October 29, 1999.

Address reprint requests/correspondence to Dr. M. Magaldi, Institute of Rheumatology, University of Siena, Policlinico Le Scotte, Viale Bracci 1, I-53100 Siena.