Oxidative stress and mitochondrial dysfunction in fibromyalgia

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Abstract

Fibromyalgia (FM) is a chronic pain syndrome with unknown etiology and pathophysiology. Recent studies have shown some evidence demonstrating that oxidative stress may have a role in the pathophysiology of FM. Furthermore, it is controversial the role of mitochondria in the oxidant imbalance documented in FM. Signs and symptoms associated with muscular alteration and mitochondrial dysfunction, including oxidative stress, have been observed in patients with FM. To this respect, Coenzyme Q_{10} (CoQ_{10}) deficiency, an essential electron carrier in the mitochondrial respiratory chain and a strong antioxidant, alters mitochondria function and mitochondrial respiratory complexes organization and leading to increased ROS generation. Recently have been showed CoQ_{10} deficiency in blood mononuclear cells in FM patients, so if the hypothesis that mitochondrial dysfunction is the origin of oxidative stress in FM patients is demonstrated, could help to understand the complex pathophysiology of this disorder and may lead to development of new therapeutic strategies for prevention and treatment of this disease.

REVIEW

INTRODUCTION

Fibromyalgia (FM) is a common chronic pain syndrome accompanied by other symptoms such as fatigue, headache, sleep disturbances, and depression. FM is diagnosed according to the classification criteria established by the American College of Rheumatology (ACR) (Lawrence *et al.* 2008) and routine laboratory investigations usually yield normal results (Yunus *et al.* 1981), therefore, new diagnostic markers for FM are needed. FM affects predominantly females and, despite being a common disorder (it affects at least 5 million individuals in the United States (Lawrence *et al.* 2008)), its pathogenic mechanism remains elusive.

Recent years added new information to our understanding of FM pathophysiology. Some genetic and biochemical markers and antibodies have been documented in FM, as the serotoninergic system genotype of 5–HTT, catechol-O-methytransferase gene polymorphism, D4 dopamine

receptor exon II repeat polymorphism, and antibodies against serotonin (Bazzichi *et al.* 2006; Offenbaecher *et al.* 1999); Cohen *et al.* 2002; Tander *et al.* 2008; Gursoy *et al.* 2003; Buskila *et al.* 2004; Klein *et al.* 1992; Werle *et al.* 2001; Greenfield *et al.* 1992). It has been also postulated alterations in serotonin metabolism (Schwarz *et al.* 2002; Staud 2002; van Denderen *et al.* 1992; Alnigenis *et al.* 2001) and in substance P (Staud and Spaeth 2008), and cytokines has been considered to play a role in the pathogenesis of FM (Wallace 2001a; 2006b; Lloyd *et al.* 1994); but in last years increased oxidative stress levels have been observed in fibromyalgia. These last findings may support the hypothesis of fibromyalgia as an oxidative disorder.

OXIDATIVE STRESS IN DISEASE AND FIBROMYALGIA

In general, oxidative and nitrosative stress (IO&NS) could be defined as an imbalance between the presence of high levels of reactive oxygen species (ROS) and reactive nitrogen species (RNS), and the antioxidative defense mechanisms (Thannickal and Fanburg 2002; Haddad 2004; Carmody and Cotter 2001). These toxic molecules are formed via oxidation-reduction reactions and are highly reactive since they have an odd number of electrons. ROS generated under physiological conditions are essential for life, as they are involved in bactericidal activity of phagocytes, and in signal transduction pathways, regulating cell growth and reduction–oxidation (redox) status (Davies 1995). ROS includes free radicals, such as hydroxyl and superoxide radicals, and nonradicals, including hydrogen peroxide and singlet oxygen. Oxidative stress and generation of free radicals, as primary or secondary event, have been related in a great number of diseases (Zhou *et al.* 2008; Stack *et al.* 2008; Praticò 2008; Cachofeiro *et al.* 2008; Fibach and Rachmilewitz 2008; Orrell *et al.* 2008; Bagis *et al.* 2005; Ozgocmen *et al.* 2006). Like ROS, RNS could also play a significant role in the pathogenesis of many diseases, and have drawn significant attention in recent years. Nitric oxide (.NO), generated by the enzyme inducible nitric oxide synthase (iNOS), is one of the most important and widely studied RNS.

It has been hypothesized that oxidative stress is linked to both initiation and the progression of Parkinson´s disease (Zhou *et al.* 2008), and strong evidence exists for early oxidative stress in Huntington´s disease (Stack *et al.* 2008). Moreover, numerous studies demonstrate that different biomarkers of oxidative-stress-mediated events are elevated in the Alzheimer disease (Praticò 2008), renal disease (even in early chronic kidney disease) (Cachofeiro *et al.* 2008), and oxidative stress is believed to aggravate the symptoms of many diseases, including hemolytic anemias (Fibach and Rachmilewitz 2008) and amyotrophic lateral sclerosis (Orrell *et al.* 2008).

Recent studies have shown some evidence that oxidative stress may have a role in the pathophysiology of FM. Bagis *et al.* reported, in a group of female patients with FM, increased malondialdehyde (MDA) levels as an indicator of lipid peroxidation and decreased superoxide dismutase (SOD) enzyme activity compared to controls (Bagis *et al.* 2005). At the same time, Ozgocmen *et al.* observed higher levels of thiobarbituric acids reactive substance (TBARS), reflecting lipid peroxidation and lower levels of nitrite (indicating nitrosothiols levels) (Ozgocmen *et al.* 2006). Hein *et al.* showed significantly higher pentosidine serum levels in FM patients than in healthy subjects (Hein and Franke 2002).

Total antioxidant capacity (TAC) of plasma has been described to be significantly lower in patients with FM, being the total peroxide level of plasma significantly higher (Altindag and Celik 2006). Recently, Kaufmann *et al.* have observed elevated spontaneous hydrogen peroxide production in neutrophils, inducing alterations in neutrophil function respect to stress hormones and the endocannabinoid anandamide (Kaufmann *et al.* 2008). Moreover, we have demonstrated an alteration of coenzyme Q_{10} (CoQ_{10}) distribution in plasma and mononuclear cells from FM patient and higher levels of reactive oxygen species (ROS) production in mononuclear cells from FM patients compared to control (Cordero *et al.* 2009).

These results confirm the oxidative stress background of FM, probably due to a defect in the antioxidant system (SOD, CoQ_{10}) and a high production of ROS. Finding the origin of oxidative stress could help us to understand the pathophysiology of FM, and to offer new therapeutic strategies for this disease.

Interestingly, in there is evidence showing IO&NS may have a role in the pathophysiological mechanisms of myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS), a disorder with a strong comorbidity with FM and considered by some authors to be the same disorder (McKay *et al.* 2009). So, increased 8-hydroxydeoxyguanosine (8-OhdG), a marker of oxidative damage to DNA has been observed in ME/CFS (Maes *et al.* 2009). High levels of MDA has been observed in serum and erythrocyte from ME/CFS patients (Manuel y Keenoy *et al.* 2001; Richards *et al.* 2007), and Vecchiet *et al.* have observed low level of vitamine E, an important lipophilic antioxidant, and high level of TBARS in plasma from ME/CFS patients (Vecchiet *et al.* 2003).

MITOCHONDRIAL DYSFUNCTION AND COQ_{10}

Mitochondria play a pivotal role in mammalian cell metabolism, hosting a number of important biochemical pathways, being oxidative phosphorylation the most important. In this process the energy released by electron transfer in the respiratory chain is conserved in the form of ATP. Mitochondria are known to be involved in the etiology and pathogen-

esis of a variety of diseases and in aging (Neustadt and Pieczenik 2008; Genova *et al.* 2004), as a consequence of some aspect of the dysfunction of mitochondria.

Mitochondria are also known to be strong producers of ROS, and particularly susceptible to damage by their action on lipids, protein and DNA (Lenaz 1998; Ernster and Dallner 1995). To this respect, radicals derived from oxygen represent the most important class of radical species generated in living systems. Molecular oxygen (dioxygen) has a unique electronic configuration and is itself a radical. The addition of one electron to dioxygen forms the superoxide anion radical. Superoxide anion, arising either through metabolic processes or following oxygen "activation" by physical irradiation, is considered the "primary" ROS, and can further interact with other molecules to generate "secondary" ROS. The mitochondrial electron transport chain is the main source of ATP in the mammalian cell and thus is essential for life. During energy transduction, a small number of electrons "leak" to oxygen prematurely, forming the oxygen free radical superoxide, which has been implicated in the pathophysiology of a variety of diseases. In particular, a decrease in electrons transfer in the respiratory chain induces further production of ROS. In respiratory chain, CoQ_{10} plays a crucial role in cellular metabolism, acting as the electron carrier between complexes I and II and the complex III of the mitochondrial respiratory chain; and regulates uncoupling proteins, the transition pore, β-oxidation of fatty acids, and nucleotide pathway (Turunen *et al.* 2004). CoQ_{10} deficiency has been associated to a variety of human disorders, some of them caused by a direct defect of CoQ_{10} biosynthesis genes or as a secondary event (Quinzii *et al.* 2007; DiMauro 2008). CoQ_{10} deficiency has been suggested as mitochondrial dysfunction marker (Haas *et al.* 2008), so the lack of CoQ_{10} may cause human diseases by one or multiple processes, including reduced respiratory chain activity; induced by enhanced ROS production or increased ROS susceptibility, or both.

To this respect, mitochondrial dysfunction has been related with the pathogenic mechanism of numerous diseases and, interestingly, morphological and numerical changes of mitochondria have been showed in skeletal muscle from FM patients (Park *et al.* 2000; Sprott *et al.* 2004). In a previous study, we showed low levels of CoQ_{10} and high levels of ROS in blood mononuclear cells of FM patients (Yunus *et al.* 1988). It has been also published that fibroblasts of some patients with CoQ_{10} deficiency syndrome show a higher production of ROS in mitochondria (Quinzii *et al.* 2008). Recently, CoQ_{10} deficiency has been observed in plasma from ME/CFS patients (Maes *et al.* 2009), and biochemical dysfunction in metabolism of ATP and oxidative phosphorylation, showing an implication of mitochondrial dysfunction in the pathogenesis of ME/CFS, similar to FM (Myhill *et al.* 2009).

It should be known that, in general, there is a positive correlation between the content of CoQ_{10} in mononuclear cells and skeletal muscle (Land *et al.* 2007; Duncan *et al.* 2005), so mitochondrial dysfunction can be present in these tissues at the same time. To this respect, mitochondria has been identified as therapeutic targets in *in vitro* studies and in animal models of Parkinson's disease, Huntington's disease, amyotrophic lateral sclerosis, and Alzheimer's disease (Chaturvedi and Beal 2008), therefore, mitochondrial-targeted antioxidants, including mitochondrial CoQ_{10}, may play an important role in modulating ROS-induced mitochondria.

We have also demonstrated an important decrement of ROS production in mitochondria after treating blood mononuclear cells of FM patient with CoQ_{10}. In a previous pilot study it has been reported beneficial effects of CoQ_{10} administration to FM patients, although this could be also due to the presence of *Gingko biloba* extract, used in combination with CoQ_{10} (Lister 2002). These results suggest that ROS production in mitochondria may be involved in oxidative stress, and CoQ_{10} deficiency and mitochondrial dysfunction could be also involved in the pathophysiology of FM.

FUTURE PERSPECTIVES

In this article, we have reviewed the topic of oxidative stress in FM. Mitochondria are important producers of oxidative stress and they are involved in pathogenesis of many diseases. The use of cells from patient with FM provides a good model to study the pathophysiological mechanisms of this disease. The markers of oxidative stress commonly used on FM research have been observed in plasma, but we must consider that are cells where they are produced. Consequently, and knowing that there is a positive correlation between the content of CoQ_{10} in mononuclear cells, skeletal muscle and fibroblasts (but not in plasma) (Land *et al.* 2007; Duncan *et al.* 2005), we have used blood mononuclear cells from FM patient as a cell model of easy handling.

On the other hand, it has been postulated that alteration in serotonin metabolism are present in patients with FM (Alnigenis and Barland 2001). To this respect, a relationship has been demonstrated between mitochondrial function and 5HT receptor of serotonin showing that 5HT2BR activates both PI3K/Akt and ERK kinases and overexpression of 5HT2BR is associated with altered mitochondrial function (Nebigil *et al.* 2003). The observation of effects of mitochondrial dysfunction in 5HT receptor in FM could explain symptoms of depression, anxiety, insomnia, and somatic pains; suggesting novel therapeutic strategies about mitochondrial protection.

All these data support the idea that antioxidant therapy may be beneficial in FM patient. Nevertheless, although oxidative stress is accepted to be involved in the pathophysiology of FM, and the mitochondrial dysfunction could be involved in this disease, more studies

are necessary to elucidate the origin of this oxidative disorder and its role in the etiology of FM.

In conclusion, the hypothesis that mitochondrial dysfunction is the origin of oxidative stress in FM patients, could help to understand the complex pathophysiology of this disorder and may lead to development of new therapeutic strategies for prevention and treatment of this disease.

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