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Exercise training as a drug to treat age associated frailty

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ABSTRACT

Exercise causes an increase in the production of free radicals [1]. As a result of a hormetic mechanism antioxidant enzymes are synthesised and the cells are protected against further oxidative stress. Thus, exercise can be considered as an antioxidant [2]. Age-associated frailty is a major medical and social concern as it can easily lead to dependency.

In this review we describe that oxidative stress is associated with frailty and the mechanism by which exercise prevents age-associated frailty. We propose that individually tailored multicomponent exercise programmes are one of the best ways to prevent and to treat age-associated frailty.

1. Oxidative stress in exercise

Knowledge of the occurrence of free radicals in biological materials dates back to the 50's when Commoner and co-workers [3] reported that these radicals occurred in living matter. It was not, however, until the 80's when the first electron paramagnetic resonance measurements of free radicals during tetanic contraction were reported [4]. A critical paper in this field was published by Davies, Quintanila, Brooks, and Packer. These pioneers proposed that free radicals are produced in exercise in vivo [1]. This work was of outstanding importance in starting the whole field of free radical biology in exercise. Moreover, in that paper, it was first suggested that radicals could be signals to stimulate mitochondriogenesis associated with exercise. So two major ideas emerged, the first was that exercise could cause oxidative stress but, very importantly, the second was that radicals could act as signals to promote adaptation to exercise. Later on, we reported that exercise could only cause oxidative stress when it was exhaustive [5]. Therefore we proposed that exhaustion and not exercise was the source of oxidative stress and eventually damage associated with strenuous exercise. Over the next years, the idea that radicals act as signals became entrenched in biological thought and we finally proposed that exercise itself could be considered as an antioxidant, provided it is moderate, because it causes an upregulation of antioxidant enzymes that seriously increases the capacity of tissues to detoxify free radical species [2].

The whole field of exercise-induced oxidative stress was thoroughly reviewed by Powers and Jackson [6]. It is important, in a context of this review paper, to note that the idea that exercise training and hence adaptation to exercise would increase the defence of cells against stress had occurred during the 90's and early 2000s. For instance, Powers et al. reported that exercise training could increase superoxide dismutase in myocardium [7]. Moreover, Reid and co-workers [8] reported that free radicals are important in the development of muscle force and promotion of contractility in the unfatigued muscle.

Thus, during the last two decades, the idea that radicals act as signals to promote muscle contractility and increase muscle mass has been accepted by the scientific community. On the other side, the fact that inactivity can cause muscle atrophy is also very important. And the new ideas were that this atrophy could be due to the activation of ubiquitin ligases, many of which would be upregulated by the very presence of free radicals [9,10].

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The relatively recent interest in age-associated frailty, which is in a very high proportion the product of loss of muscle force as well as a loss of motor coordination, is relevant to the general scope that radicals can be important in determining muscle function. The interaction between frailty, exercise, and oxidative stress will be developed in the coming paragraphs of this review.

2. Free radicals and ageing – a brief summary

The free radical theory of ageing was first postulated in a general way by Rebecca Gerschman, an Argentinian investigator who was working in the 50's in the United States. She proposed that age-associated damage could be similar to radiation toxicity [11]. This paved the way for a more general postulation on the proper theory of ageing by Denham Harman who in 1956, proposed that "ageing and the degenerative diseases associated with it are attributed basically to the deleterious side attacks of free radicals on cell constituents and the connecting tissues" [12]. This was a hallmark in ageing research. The free radical theory of ageing has been subjected to critical tests and modifications on many occasions, and especially around the turn of the century. Many experiments have been performed that supported the theory but also very many supported the idea that the theory is no longer valid as it does not explain some experiments in which damage caused by free radicals is not always associated with ageing [13]. Many refinements of this theory have been postulated. One of the major experimental corollaries from this theory is that antioxidants should delay ageing and promote wellbeing. This proved to be incorrect. Meta-analysis very carefully performed on large numbers of persons who take antioxidants has shown that these do not protect against age-associated diseases and in fact that they do not prolong life [14–18]. Moreover, evidence from our own laboratory showed that antioxidants could prevent the onset of mitochondriogenesis associated with physical exercise and would be inadequate for training in young individuals and animals [19–21]. Although controversial [22,23], these findings were later confirmed and extended by Michael Ristow's group who showed that these antioxidants would not only impair the effects on the efficacy of training (as we had reported) but that they would also prevent some of the health effects associated with physical exercise [24]. These researchers coined the term mitohormesis [25]. To reconcile the pros and cons of the free radical theory of aging we proposed a modified, revised version of the theory: the cell signalling disruption theory of ageing. We suggested that, in aging, free radicals lose the capacity to be effective signals to control cell metabolism. This results in a lowering of homoeostatic capacity in the cell and therefore a lower "resilience" of the cells to tolerate stresses eventually resulting in lower capacity of the old organism to resist such stresses [13].

More recently, as will be apparent in the next paragraph, we have come up with the idea that probably, free radicals are more involved in the development of age-associated frailty than in ageing itself. There is a big difficulty in differentiating, at least in mammals, ageing with some measure of frailty. This is especially true at the very last stages of life. Our experiments, which will be described in the next section of this review, reveal that it is likely that oxidative stress is more associated with frailty than with ageing.

3. Oxidative stress and frailty

Frailty can be defined as a geriatric syndrome caused by a disorder of several interrelated physiological systems [26]. A main outcome of frailty is that it may lead to disability. The latter is a major source of distress to both the personal life of elderly people and to society as a whole. Disability causes a major burden on the economic programmes of nations and it is likely that the problem will become more and more difficult to solve.

In their article on "Frailty in the clinical setting" Rodriguez-Mañas and Fried state that the aim of health care has changed substantially because after centuries of trying to live longer, the time for living better has come [27].

Thus, research into frailty has become a major issue in basic biological research as well as in clinical practice [27]. The European Union has launched a major effort to promote research to treat frailty (JA-02-2015 Prevention of Frailty). Even though clinical interest in frailty has grown in recent years [27,28], to our knowledge, research in experimental animal models of frailty is very scarce. Only three models have been reported in the literature [29–31]. Thus, a major shortcoming in research into the biological basis of frailty is that we still lack a convenient animal model to study it. We will describe later on a model of frailty based on inactivity. As mentioned earlier, the free radical theory of aging stated that free radical associated damage could cause ageing [12]. Facts have disproven the general statement of the theory although restricted ones still hold true [32]. We asked whether frailty could be associated with oxidative stress. To that end, we measured oxidative stress in a population of elderly people (65–85) and determined lipid peroxidation (malondialdehyde levels) and protein oxidation [33]. We came to the rather surprising conclusion that oxidative stress is not strictly associated with ageing, but with frailty. Indeed, in the elderly persons from the Toledo cohort, we found that indices of oxidative stress were associated with the frailty status and not with the age of the persons [33]. Of course, persons in their eighties have more signs of oxidative stress in the blood plasma than persons in their twenties. But if we restrict ourselves to the geriatric age (65 years five or more) we do not find that oxidative stress is associated with age but rather with the frailty status. Vigorous old persons show fewer signs of oxidative stress than frail relatively young ones (i.e., around the age of 65). Only one publication had described the occurrence of oxidative stress associated with frailty [34], but the association of oxidative stress with frailty and not with age had not been described prior to our study [33]. The mechanisms by which frailty leads to oxidative stress are not fully understood. However, since the lack of frailty is usually associated with the capacity of performing exercise, the possibility remains that the defective regulation of mitochondriogenesis and of mitochondrial functions in general may be a possible explanation for the oxidative stress due to frailty. This will be described in the section below.

4. Exercise induced mitochondriogenesis is lost in ageing

The role of mitochondria in the process of ageing was underpinned by the work of Jaime Miquel. This researcher published that mitochondria are both origin and targets of free radicals that could cause damage in ageing [35]. In fact, we were first to prove that mitochondria were really involved in ageing by performing studies of mitochondria inside cells using both flow cytometry and a metabolic approach [36]. The doubt was whether mitochondria from old animals or persons were more fragile than those from young ones and whether mitochondrial dysfunction in ageing was derived from the fact that these organelles were damaged as they were being isolated from the organ. We showed that mitochondria were indeed damaged within cells of old animals [36]. But interestingly, the pioneer work of Davies and co-workers already indicated that free radicals could act as signals to stimulate mitochondriogenesis [1]. This is an important adaptation to physical exercise and one that is critical to maintain normal cell function.