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REVIEW

Exercise acts as a drug; the pharmacological benefits of exercise

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The beneficial effects of regular exercise for the promotion of health and cure of diseases have been clearly shown. In this review, we would like to postulate the idea that exercise can be considered as a drug. Exercise causes a myriad of beneficial effects for health, including the promotion of health and lifespan, and these are reviewed in the first section of this paper. Then we deal with the dosing of exercise. As with many drugs, dosing is extremely important to get the beneficial effects of exercise. To this end, the organism adapts to exercise. We review the molecular signalling pathways involved in these adaptations because understanding them is of great importance to be able to prescribe exercise in an appropriate manner. Special attention must be paid to the psychological effects of exercise. These are so powerful that we would like to propose that exercise may be considered as a psychoactive drug. In moderate doses, it causes very pronounced relaxing effects on the majority of the population, but some persons may even become addicted to exercise. Finally, there may be some contraindications to exercise that arise when people are severely ill, and these are described in the final section of the review. Our general conclusion is that exercise is so effective that it should be considered as a drug, but that more attention should be paid to the dosing and to individual variations between patients.

Abbreviations

ACSM, American College of Sports Medicine; ACTH, adrenocorticotropic hormone; AICAR, 5-aminoimidazole-4-carboxamide-1-β-D-ribofuranoside; AMPK, AMP-activated protein kinase; BDNF, brain-derived neurotrophic factor; CHD, coronary heart disease; GDNF, glial cell-derived neurotrophic factor; HIF-1, hypoxia-inducible factor 1; HSF, heat shock factor; HSP, heat shock protein; IGF, insulin growth factor; MET, metabolic equivalent (estimated oxygen cost of 3.5 $mL \cdot min^{-1} \cdot kg^{-1}$); MnSOD, mitochondrial superoxide dismutase; PGC-1α, PPAR-γ coactivator-1α; ROS, reactive oxygen species; SCD, sudden cardiac death; VO_2, oxygen consumption

Exercise, movement and health: definitions

Health promotion is the science and art of helping people change their lifestyle to move towards a state of optimal health (O'Donnell, 1986). The World Health Organization defines health as 'Physical, mental, and social well-being, not merely the absence of disease and infirmity'. Physical fitness is defined as the physiologic state of well-being that allows one to meet the demands of daily living (health-related physical fitness) or that provides the basis for sport performance (performance-related physical fitness), or both. Although we are aware that there is a clear difference between the terms physical activity ('any bodily movement') and exercise ('a subset of physical activity that is characterized by a planned and purposeful training') (Caspersen *et al.*, 1985), in this review, we are going to use these two concepts as synonymous because some of the studies to which we will refer use the terms interchangeably.

Historical background

The hypothesis that physical activity promotes health and longevity is not new. As far back as 2500 BC, in ancient China, records of organized exercise for health promotion

have been found (Lyons and RJja, 1978; Lee and Skerrett, 2001). In Greco-Roman times, 2500 years ago, Hippocrates (460–370 BC) and later Galen (AD 129–210) recognized the need to promote and prescribe exercise for health-related benefits and the need to provide general medical care for the athletic individual (Speed and Jaques, 2010). In this regard, the philosopher Plato (427–347 BC) said: 'Lack of activity destroys the good condition of every human being while movement and methodical physical exercise saves and preserves it' (Fox and Haskell, 1968).

Simple comparisons of men in different occupations provided the first empirical evidence that physical activity was associated with health. The first studies demonstrating a significant inverse relationship between physical activity and coronary heart disease (CHD) were those conducted by Morris *et al*. (1953b) in London early in the 1950s. These authors found that London bus conductors had only 73% the frequency of CHD that was found in the less active bus drivers. Their later comparison of London postmen and less active postal clerks produced much the same findings (Morris *et al*., 1953a). These seminal studies were followed by those of Paffenbarger and collaborators in the 1970s, assessing the increase in the relative risk of death from any cause and from specific diseases associated with physical inactivity (Paffenbarger and Hale, 1975; Paffenbarger *et al*., 1978).

Exercise is beneficial for your health

Exercise is one of the most frequently prescribed therapies both in health and disease. There is irrefutable evidence showing the beneficial effects of exercise both to prevent and to treat several diseases. Researchers have shown that both men and women who report increased levels of physical activity and fitness have reductions in relative risk of death (by about 20%–35%) (Blair *et al*., 1989; Macera *et al*., 2003).

Recent research suggests that modest increments in energy expenditure due to physical activity (~1000 kcal per week) or an increase in physical fitness of 1 MET (metabolic equivalent) is associated with lowering mortality by about 20% (Myers *et al*., 2004). Physically inactive middle-aged women (engaging in less than 1 h of exercise per week) experience a 52% increase in all-cause mortality, a doubling of cardiovascular-related mortality, and a 29% increase in cancer-related mortality when compared with physically active ones (Hu *et al*., 2004). Thus, there is clear evidence that regular physical activity produces significant health effects and reduces the risk of premature death from any cause and from cardiovascular disease in particular amongst asymptomatic men and women.

The benefits of physical activity are evident, not only in healthy persons but also in patients. Observational and randomized trials have shown that regular physical activity contributes to the treatment of several chronic diseases (Bouchard *et al*., 1994; Warburton *et al*., 2006a). There is evidence for prescribing exercise in the primary and secondary prevention of pulmonary and cardiovascular diseases (CHD, chronic obstructive pulmonary disease, hypertension, intermittent claudication); metabolic disorders (type 2 diabetes, dyslipaemia, obesity, insulin resistance); muscle, bone and joint diseases (rheumatoid arthritis, fibromyalgia, chronic fatigue syndrome, osteoporosis); cancer; and depression (Pedersen and Saltin, 2006; Warburton *et al*., 2006a). Even if exercise is an effective therapeutic agent for all of these diseases, as with any other medicine, the dosage (volume and intensity of the exercise), frequency of administration (sessions per week), type (aerobic vs. resistance exercise), systemic and psychoactive effects and contraindications and side effects of the exercise must be taken into account to achieve the best clinical outcome. For instance, both resistance and aerobic training have been shown to be of benefit for the control of diabetes; however, resistance training may have greater benefits for glycaemic control than aerobic training (Dunstan *et al*., 2005).

The dosage of exercise

Dosage is important in clinical medicine and all marketed drugs require data on their efficacy and safety (Lee, 2007). It is known that there is a minimum amount of physical activity for health benefits. These benefits increase with increasing the amount of exercise, but beyond a certain level, adverse effects outweigh benefits (Lee, 2007). Unlike chemical drugs, however, the minimum dose, dose response and maximum safe dose of physical activity are not well understood (Lee, 2007). There is a continuous debate on how much, what type, how often, what intensity and how lengthy physical activity should be. This is important for issuing public health recommendations (Blair *et al*., 2004). Summarizing available information across studies is difficult because investigators have measured exercise intensity in different ways and classified physical activity according to different dose schemes that are often difficult to compare (Lee, 2007). Over the years, various expert groups, based on the best evidence available, have postulated different physical activity recommendations and guidelines (see Table 1).

Intensity levels of physical activity can be expressed relative to oxygen consumption (VO_2) or to heart rate (Warburton *et al*., 2006b). Moderate-intensity activities are those in which heart rate and breathing are raised; but, still, it is possible to speak comfortably. This occurs around 4–6 METs and brisk walking at 3.0 mph (80.4 $m \cdot min^{-1}$) is one such activity. Vigorous-intensity activities are that in which heart rate is higher, breathing is heavier and conversation is harder (about 6–8 METs) (Warburton *et al*., 2006b), for instance jogging. It has been shown that exercising at even 50% of the recommended levels (72 min of moderate exercise a week) appears sufficient to provide some improvement in fitness. However, at this low exercise dosage, cardiovascular risk factors (blood pressure, lipid profile and weight) do not improve (Church *et al*., 2007). In fact, for many individuals, up to 60 min of daily physical activity are more appropriate if weight control is the primary goal (Lee, 2007). Thus, dose–response relations between physical activity and different health outcomes are different. The evaluation of the minimum amount of physical activity (lower dose) necessary to achieve its beneficial effects has been the object of intense research. Wen *et al*. (2011) have recently found that 15 min a day or 90 min a week of moderate-intensity exercise is of

Table 1
Historical evolution in physical activity recommendations and guidelines

	Physical activity recommendations			
	Intensity	Minutes	Frequency	Reference
1970s–1980s	Vigorous exercise (e.g. running)	20 min·day^{-1}	3 times·week^{-1}	(American College of Sports Medicine, 1978)
1990s	Moderate exercise (e.g. brisk walking)	30 min·day^{-1}	Most days of the week	(Pate *et al.*, 1995; Physical activity and cardiovascular health, 1996)
2000s	Moderate exercise	60 min·day^{-1}	3 times·week^{-1}	(Lee, 2007)
2010 (healthy adults ages 18–45)	Moderate exercise	30 min·day^{-1} (150 min week^{-1})	Most days of the week (5 days·week^{-1})	(O'Donovan *et al.*, 2010)
	Vigorous exercise	75 min·week^{-1}		(O'Donovan *et al.*, 2010)

benefit in terms of life expectancy, even for subjects with cardiovascular risks.

Exhaustive exercise and longevity

Although the health benefits of leisure-time physical activity are well documented, the association between vigorous exercise training and mortality or longevity of elite athletes is not fully understood (Teramoto and Bungum, 2010). For centuries, the general belief has been that exhaustive, competitive exercise is harmful and decreases life expectancy (Ruiz *et al.*, 2010). For instance, Moorstein (1968) stated that all members of the 1948 Harvard rowing crew had died early from cardiac diseases. In contrast, it has been shown that participation in endurance competitive sports increases life expectancy. It was found that the life expectancy of oarsmen was higher than that of their non-athletic controls (Hartley and Llewellyn, 1939; Prout, 1972). Karvonen and co-workers found that Finnish champion skiers (born between 1845 and 1910) lived 2.8–4.3 years longer than general male population in Finland. In contrast with most studies of that time, Polednak (1972) reported evidence against the beneficial effects of strenuous exercise. He found differences in longevity and cardiovascular mortality related to the extent of participation in college athletics. Moreover, in a recent animal study, it has been found that long-term vigorous endurance exercise training may in some cases promote adverse cardiac remodelling and produce a substrate for cardiac arrhythmias (Benito *et al.*, 2011). The incidence of sudden cardiac death (SCD) amongst young athletes (estimated to be 1–3 per 100 000 person-years) is higher than in non-athletes and may possibly still be underestimated (Drezner, 2008). However, it has been shown that the most common cause of SCD in young athletes is underlying inherited cardiac disease, such as cardiomyopathies, congenital coronary anomalies and ion channelopathies (Maron *et al.*, 2009). To clarify this apparent contradiction, we determined the longevity of the participants of the Tour de France and compared it with that of the general population born between 1892 and 1942. The Tour de France is amongst the most gruelling sport events in the world. We found an 11% increase in average longevity in Tour de France participants when compared with the general population (Sanchis-Gomar *et al.*, 2011b) (see Figure 1). Thus, the majority of data in human studies support the notion that prescription of regular, vigorous aerobic exercise might be a useful tool, with a dose–effect response to improve the overall health status and longevity of the general population (Ruiz *et al.*, 2010; Teramoto and Bungum, 2010). In our opinion, physicians, health professionals and general population should not be under the impression that strenuous exercise and/or high-level aerobic competitive sports are bad for one's health and shorten one's life. Thus, a dose–response relation appears to exist, such that people who have the highest levels of physical activity and fitness are at lowest risk of premature death (Warburton *et al.*, 2006a).

Training status is a very relevant factor in the prescription of the exercise 'dose'. Increasing the doses of exercise has positive consequences for health in trained individuals (Ruiz *et al.*, 2010; Sanchis-Gomar *et al.*, 2011b), whereas heavy physical exertion can trigger the onset of acute myocardial infarction, particularly in people who are habitually sedentary (Mittleman *et al.* 1993). Results from the same group showed that less active men participating in vigorous activity were more likely to have a myocardial infarction during exercise than the most active men (Thompson *et al.*, 2007).

In the pharmacological treatment of many conditions, physicians typically start with a dose of a drug believed to be the minimum effective dose. If the patient does not respond, this initial dose may then be titrated upwards to a maximum dose, beyond which the adverse effects of the drug are unacceptable for treatment (Lee, 2007). Thus, the intensity of aerobic training may be also titrated in healthy people (Warburton *et al.*, 2006b). Unfit people can get significant improvements in physical fitness with a low training intensity, while those with a higher fitness level need a greater level of exercise intensity to achieve further improvements in fitness (Shephard, 2001). Thus, these fit individuals who have met the physical activity levels recommended for all healthy adults for at least 6 months may obtain additional health benefits by engaging in 300 min or more of moderate-intensity aerobic activity per week, or 150 min or more of vigorous-intensity aerobic activity each week, or equivalent combinations of moderate- and vigorous-intensity aerobic activities (Lee and Skerrett, 2001; O'Donovan *et al.*, 2010). These relatively low doses are, obviously, not applicable to

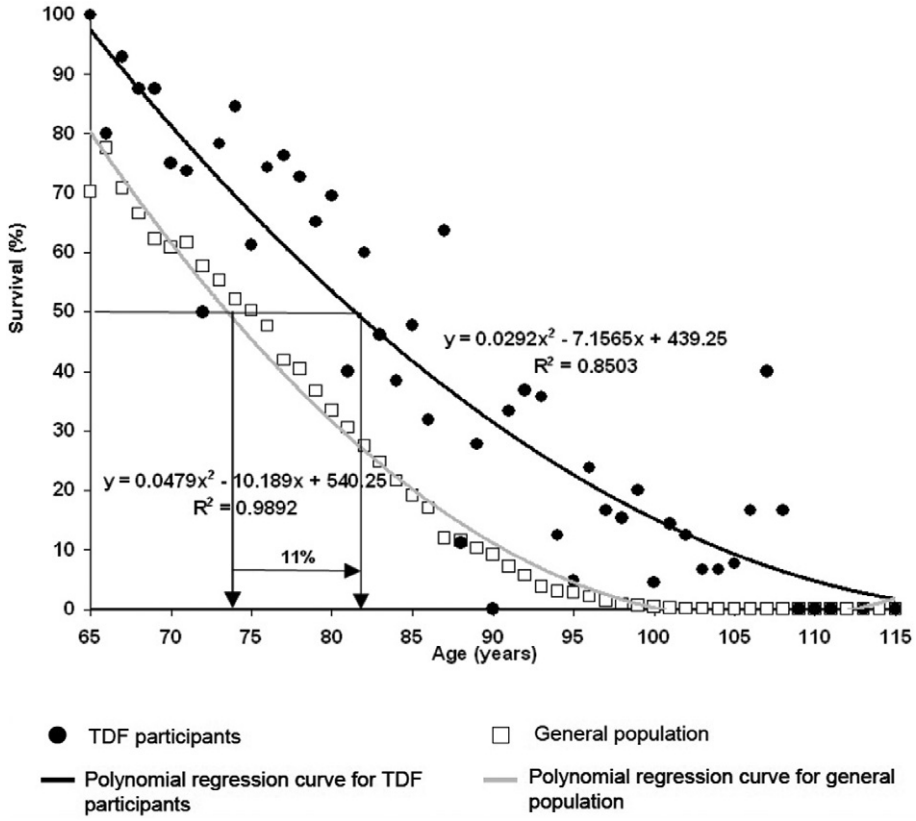

Figure 1

Percentage of survival related to age in Tour de France (TdF) participants and in the general population. Persons born between 1892 and 1942 have been studied. Average life span of Tour de France participants is higher ($P = 0.004$; 17.5%) than the general population of the same country in which the cyclists were born. The age at which 50% of the general population died was 73.5 years, compared with 81.5 years in Tour de France participants (i.e. 11% increase).

high level professional athletes who perform exercise at much higher doses.

The guidelines discussed above are generally appropriate for young to middle-aged adults. But, as with medicines, special considerations should be taken when prescribing exercise for people with special needs such as elderly, children, pregnant women, overweight or obese patients and patients with chronic diseases (Warburton *et al.*, 2006b). For instance, it has been shown that vigorous activities are not essential for the reduction of cardiovascular risk in men over 60. Regular physical activity is enough to achieve a significant decrease in mortality in this population. Thus, the greatest benefit to health is gained from sustained moderate exercise, above which there appears to be no further benefit to health in older men (Hakim *et al.*, 1998; Wannamethee *et al.*, 1998).

Regarding the 'dosage' of exercise, whether it should be performed in either one continuous or two or more accumulated bouts, the available evidence suggest that at least for fitness, accumulated and continuous patterns of exercise training of the same total duration confer similar benefits (Murphy *et al.*, 2009). For instance, it has been shown that five to eight 2 min bouts of stair climbing accumulated over the course of a day confer health benefits, including increases in cardiovascular fitness, compared with non-exercising controls (Boreham *et al.*, 2005).

Although physical activity is beneficial to health with or without weight loss, adults who find it difficult to maintain a normal weight and adults with increased risk of cardiovascular disease or type 2 diabetes, in particular, may benefit from going beyond the levels of activity recommended for all healthy adults and gradually progressing towards meeting the recommendations for conditioned individuals (O'Donovan *et al.*, 2010).

Systemic adaptations to exercise

The exercise-induced adaptations are especially evident in the cardiorespiratory and musculoskeletal systems, and body composition and metabolism (Warburton *et al.*, 2006a; Lee *et al.*, 2010). But the documented health benefits of exercise also include diminished symptoms of depression and anxiety (Kujala, 2011).

Skeletal muscle is the main target of exercise training. Modifications in skeletal muscle are crucial for enhancing endurance and metabolic efficiency (Matsakas and Narkar, 2010). Muscle fibres are commonly classified as type I slow-twitch or oxidative fibres, with a high mitochondrial content, and type II fast-twitch or glycolytic fibres, which have fewer mitochondria. Endurance exercise induces an increase in

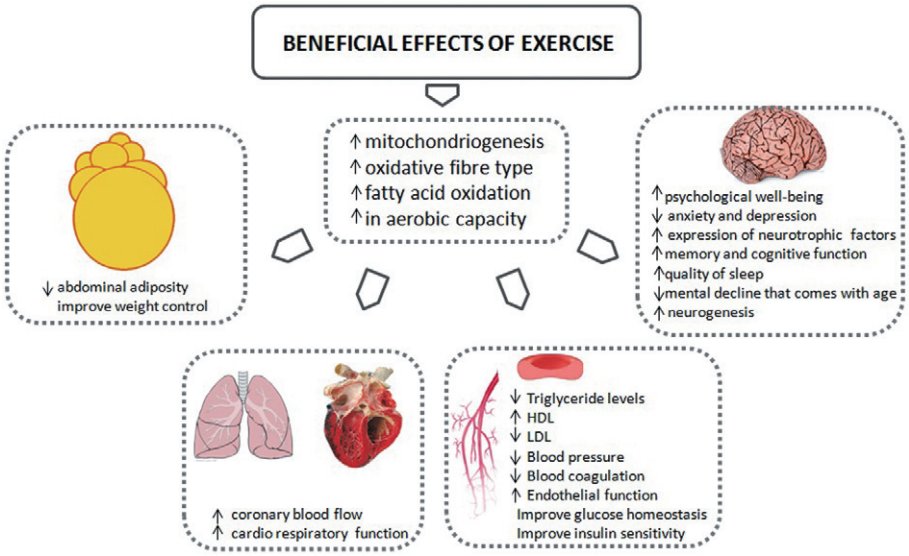

Figure 2
Health benefits of exercise in tissues and organs.

mitochondriogenesis, a shift in fibre distribution from glycolytic to oxidative and an increase in fatty acid oxidation that ultimately leads to an increase in aerobic capacity and retards diseases such as obesity, type 2 diabetes and cardiovascular diseases (Holloszy and Coyle, 1984; Mootha *et al.*, 2003).

It has been shown that regular exercise can reduce abdominal adiposity and improve weight control (Warburton *et al.*, 2006a), enhance lipoprotein profiles (e.g. reduce triglyceride levels, increase high density lipoprotein and decrease low-density lipoprotein levels), improve glucose homeostasis and insulin sensitivity, reduce blood pressure, improve autonomic tone, reduce systemic inflammation; decrease blood coagulation, improve coronary blood flow, augment cardiac function and enhance endothelial function (Warburton *et al.*, 2006a).

Regular physical activity is also associated with improved psychological well-being (e.g. through reduced stress, anxiety and depression) (Dunn *et al.*, 2001). The beneficial effects of exercise on cognitive function are well known (Neeper *et al.*, 1995). The mechanism behind this is not fully understood, but it seems to be associated with an increased expression of neurotrophic factors in some brain areas. Increased expression of these factors is related to better memory and improved cognitive function. Brain-derived neurotrophic factor (BDNF) can enhance the survival and differentiation of neurons, and voluntary exercise has been shown to increase it (Neeper *et al.*, 1996). Psychological well-being is particularly important for the prevention and management of cardiovascular disease, but it also has important implications for the prevention and management of other chronic diseases such as diabetes, osteoporosis, hypertension, obesity, cancer and depression (Warburton *et al.*, 2006a). It has been shown that physical activity results in specific adaptations that affect individual states in all of these diseases. For instance, adaptations that affect glucose homeostasis, in type 2 diabetes, are of great importance. Several changes occur as a result of regular physical activity, including increased glycogen synthase and hexokinase activities, increased mRNA and protein expression of the glucose transporter GLUT-4 and improved muscle capillary density (resulting improved glucose delivery to the muscle) (Mandroukas *et al.*, 1984).

Exercise causes a significant reduction in cancer rates (specifically colon and breast cancer) (Shephard and Futcher, 1997; Pedersen and Saltin, 2006). Possible explanations include reductions in fat stores, increased energy expenditure offsetting a high fat diet, activity-related changes in sex hormone levels, immune function, insulin and insulin-like growth factors, free radical generation and direct effects on the tumour cell biology (Westerlind, 2003).

The majority of the proposed mechanisms have been discussed in the context of chronic adaptations by regular physical activity. However, it has been shown that isolated exercise sessions (separate doses of exercise) also elicit transient, but still beneficial, changes in risk factors for chronic diseases (Thompson *et al.*, 2001). Many of the training adaptations derive from a single exercise bout that elicits cellular changes at the gene level leading to cumulative effects of training. The acute effect of exercise results in transient reductions in triglyceride levels, increases in HDL cholesterol level, decreases in blood pressure, reductions in insulin resistance and improvements in glucose control (Thompson *et al.*, 2001). These acute changes underpin the important role that individual exercise sessions have on health status. Thus, single doses of exercise have also a relevant impact on health. Figure 2 summarizes the favourable effects of exercise.

Signalling pathways regulated by exercise in skeletal muscle

The regulation of the cellular functions with exercise are dependent on many stimuli: alterations in metabolite con-

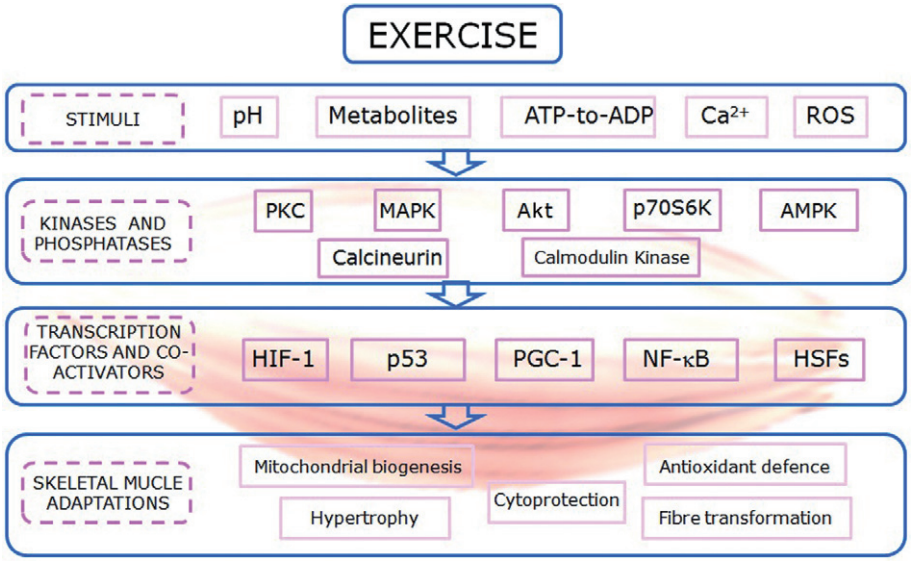

Figure 3
A summary of the signalling pathways regulated by exercise in skeletal muscle.

centrations, a shift in the ATP : ADP ratio, changes in the intracellular concentration of Ca^{2+}, in the intracellular pH, and activations of the oxidative stress-sensitive signalling pathways (Sakamoto and Goodyear, 2002; Ji *et al.*, 2004). To elucidate the molecular signalling mechanisms that enable skeletal muscle to respond to the contractile stimulus and that mediate the adaptations to exercise is of great importance (Sakamoto and Goodyear, 2002). It has been clearly established that physical exercise can activate MAPK signalling, including the ERK1/2 (Goodyear *et al.*, 1996), p38 (Gomez-Cabrera *et al.*, 2005) and JNK pathways (Goodyear *et al.*, 1996). It can also increase the activity of the AMP-activated protein kinase (AMPK), Akt and the p70 S6 kinase (Sakamoto and Goodyear, 2002). In skeletal muscle Ca^{2+}signalling is extensive. In addition to triggering muscle contraction through the troponin system, Ca^{2+} is also involved in the regulation of relevant intracellular proteins such as PKC, calcineurin and calmodulin kinase that mediate cellular signal transduction (Berchtold *et al.*, 2000).

More recently, it has been shown, that low-to-moderate levels of reactive oxygen species (ROS) play multiple regulatory roles in cells such as the control of gene expression, regulation of cell signalling pathways and modulation of skeletal muscle force production (Reid, 2001) (see Figure 3).

ROS and exercise: training as an antioxidant intervention

The role of ROS in the exercise-induced adaptations in skeletal muscle has been extensively studied (Salminen and Vihko, 1983; Gomez-Cabrera *et al.*, 2008b). The idea of the deleterious effects of ROS has been firmly entrenched in the minds of scientists during the last 30 years. However, there is growing evidence that the continued presence of low concentrations of free radicals is, in fact, able to induce the expression of antioxidant enzymes and other defence mechanisms. In this scenario, radicals may be seen as beneficial as they act as signals to enhance defences rather than deleterious as they are when cells are exposed to high levels of these radicals. Animals frequently exposed to chronic exercise have shown less oxidative damage after exhaustive exercise than untrained ones (Salminen and Vihko, 1983). This is largely due to the up-regulation of endogenous antioxidant enzymes such as glutathione peroxidase, mitochondrial superoxide dismutase (MnSOD) and γ-glutamylcysteine synthetase (Salminen and Vihko, 1983). A major conclusion that can be drawn from these results is that exercise itself acts as an antioxidant, because training increases the expression of antioxidant enzymes (Gomez-Cabrera *et al.*, 2008b). Subsequently, we and others have shown that antioxidant supplements prevent the induction of mitochondrial biogenesis, molecular regulators of insulin sensitivity and endogenous antioxidant defence by physical exercise (Gomez-Cabrera *et al.*, 2008a; Ristow *et al.*, 2009). Thus, ROS act as signals in exercise because decreasing their formation prevents activation of important signalling pathways, which cause useful adaptations in cells.

Because of the widespread implications of ROS in almost all important biological functions, it is difficult to define all the pathways and gene targets that are affected by redox signalling during exercise. The following are some of the most relevant signalling pathways modulated by exercise: the PPAR-γ coactivator-1α and β (PGC-1α and PGC-1β) (Gomez-Cabrera *et al.*, 2008a; Ristow *et al.*, 2009), p53 (Borras *et al.*, 2011), hypoxia-inducible factor 1 (HIF-1) (Huang *et al.*, 1996), heat shock factor (HSF) (Palomero *et al.*, 2008), NF-κB and MAPK signalling pathways (Ji *et al.*, 2004; Gomez-Cabrera *et al.*, 2005). Several important adaptations in skeletal muscle such as mitochondrial biogenesis, antioxidant defence, hypertrophy, cytoprotection and fibre transforma-

tion are regulated primarily by these pathways. Thus, its regulation should be tightly controlled (Gomez-Cabrera *et al.*, 2009) (see Figure 3).

Exercise, a psychoactive drug

The effects of exercise training on brain function have received much attention. In the early '80s, exercise was shown to increase β-endorphin in peripheral blood in humans (Bortz *et al.*, 1981; Carr *et al.*, 1981). Elevated serum β-endorphin concentrations induced by exercise have since been linked to a variety of psychological and physiological changes, including mood state changes and 'exercise-induced euphoria', altered pain perception and responses to numerous stress hormones (growth hormone, ACTH, prolactin, catecholamines and cortisol) (Harber and Sutton, 1984).

Exercise training can favourably influence cognitive function (Dishman *et al.*, 2006; Vaynman and Gomez-Pinilla, 2006). Exercise improves learning and memory (van Praag *et al.*, 1999), improves the quality of sleep, counteracts the mental decline that comes with age (Laurin *et al.*, 2001) and facilitates functional recovery from brain injury (Grealy *et al.*, 1999) and depression (Siuciak *et al.*, 1996; Shirayama *et al.*, 2002). Exercise is a very powerful stimulus to the induction of neurogenesis in the adult dentate gyrus (van Praag *et al.*, 1999) that can contribute to remodelling hippocampal synaptic circuits and to enhance cognitive function.

Exercise training can also mitigate the consequences of acute exposure to different types of psychological stress (Dishman *et al.*, 2006) and exercise-induced alterations in the 5-hydroxytryptaminergic and the noradrenergic systems can explain these responses (Dishman *et al.*, 2006). Most of the positive effects of exercise, as mentioned previously, have been related to the induction, in different brain areas, of neurotrophic proteins, including BDNF, glial cell-derived neurotrophic factor (GDNF) and insulin growth factor (IGF). Whether brain metabolic responses to acute physical activity extend beyond regions specifically involved with motor, sensory or cardiovascular autonomic control is not as yet clear (Dishman *et al.*, 2006). Transient increases in local cerebral glucose use and in cerebral blood flow have been reported in the different brain areas in response to acute strenuous treadmill running in rats and in humans (Vissing *et al.*, 1996). Also, the discharge rate of a select pool of hippocampal pyramidal cells increased as running velocity increased (Czurko *et al.*, 1999). Moreover, exercise increased metabolic capacity in the motor cortex and striatum (McCloskey *et al.*, 2001).

The psychoactive effects of exercise that we have just mentioned are not free from risks. Pathological patterns of behaviour in gym clients have been reported (Lejoyeux *et al.*, 2008). As observed in patients with eating disorders, active individuals usually worry about their body shape, put special attention on their eating patterns, show exercise addiction and have a perfectionism personality trait (Freimuth *et al.*, 2011). This body image disorder has been addressed as reverse anorexia, vigorexia or muscle dysmorphia (Lejoyeux *et al.*, 2008). Based on a review of a wide range of studies on exercise addiction, it has been estimated that its prevalence in the general population is close to 3%. Amongst certain groups such as ultra-marathon runners, body builders and sport science students, the percentage is even higher (Freimuth *et al.*, 2011; Sussman and Sussman, 2011).

Contraindications for exercise

The purpose of this section is to discuss why under some circumstances physical exercise does not increase the quality of life.

Although both the heart and the lung benefit significantly from physical activity, there are some contraindications when exercise is performed by patients suffering from heart and pulmonary diseases. Pedersen and Saltin (2006) reviewed the possible contraindications of exercise in most of the diseases in which exercise have shown beneficial effects. For instance in patients with CHD, exercise is contraindicated until the condition has been stable for at least 5 days; dyspnea at rest, aortic stenosis, pericarditis, myocarditis, endocarditis, fever and severe hypertension all are contraindications to exercise (Pedersen and Saltin, 2006). Black *et al.* (1975) were amongst the first to find that strenuous exercise can cause acute injury to coronary plaques, leading to occlusion of coronary arteries. However, years later, it was found that although the risk of primary cardiac arrest was transiently increased during a *single* bout of vigorous exercise, *habitual* vigorous exercise was associated with an overall decrease in this risk (Siscovick *et al.*, 1984; Albert *et al.*, 2000). There are no absolute contraindications to very moderate exercise in chronic obstructive pulmonary disease patients (Pedersen and Saltin, 2006). However, in patients with asthma, a pause in training is recommended when an acute exacerbation occurs. In cases of infection, a pause in training is recommended until the patient has been asymptomatic for a day, where after training can be slowly resumed (Pedersen and Saltin, 2006).

Regarding muscle, bone and joint diseases, for instance, osteoarthritis and rheumatoid arthritis, exercise is contraindicated in cases of acute joint inflammation, if pain worsens after training and in cases of pericarditis and pleuritis (Pedersen and Saltin, 2006). The training of patients with osteoporosis should include activities with a low risk of falling (Pedersen and Saltin, 2006).

In cancer patients being treated with chemotherapy or radiotherapy, exercise is contraindicated when leukocyte concentrations fall below 0.5×10^9 cells L^{-1}, haemoglobin below 100 $g \cdot L^{-1}$, thrombocyte concentration below 20×10^9 cells L^{-1} and temperature above 38°C. Patients with bone metastases should not perform strength conditioning at high load. In cases of infection, a pause in training is recommended until the patient has been asymptomatic for a day, where after training can be slowly resumed (Pedersen and Saltin, 2006). A major concern is whether exercise training influences the anticancer effects of conventional cytotoxic therapy. The potential interaction between exercise and chemotherapy efficacy is biologically plausible. Indeed, earlier preclinical studies have reported both an inhibitory (Baracos, 1989) and augmentary (Thompson *et al.*, 1989) effect of endurance exercise training on mammary tumour growth and progression, although others have reported no association (Jones *et al.*, 2005).

In diabetic patients (both types I and II), exercise should be postponed if blood glucose is >2.5 g·L^{-1} together with ketonuria and >3.0 g·L^{-1} even without ketonuria, in both cases, before it is corrected. In patients with hypertension and active proliferative retinopathy, high-intensity training or training involving Valsalva-like manoeuvres should be avoided. Patients with neuropathy and incipient foot ulcers should refrain from activities entailing the bearing of the patient's own body weight.

In metabolic syndrome-related disorders, such as insulin resistance, dyslipaemia and obesity, there are no general contraindications; but training should take into account any comorbidities (Pedersen and Saltin, 2006). Finally, hypertensive patients with a blood pressure >180/105 should begin pharmacotherapy before regular physical activity is initiated (relative contraindication) (Pescatello *et al.*, 2004). There is no evidence for an enhanced risk of sudden death or stroke in physically active persons with hypertension (Tipton, 1999). The American College of Sports Medicine (ACSM) recommends caution when performing very intensive dynamic exercise or strength conditioning with very heavy weights. Patients with left-sided cardiac hypertrophy should be particularly cautious about heavy strength conditioning. Patients with CHD should refrain from short intensive exercise situations.

It is well known that eccentric muscle contractions cause structural damage to muscle cells or inflammatory reactions within the muscles, as shown by an increase in the plasma activity of cytosolic enzymes and sarcolemma and Z-line disruption (Armstrong *et al.*, 1983). The severity of the damage and the extent of discomfort are exacerbated over time and can last for several days. The damaging effects of eccentric contractions can affect subsequent exercise sessions due to residual muscle pain, restriction of movement and reduced capacity to exercise at an intensity that may be beneficial for the exerciser (Howatson and van Someren, 2008). Thus, caution should be paid in exercise programs which include eccentric contractions especially in recreational or old practitioners.

Exercise mimetics

Despite the clear evidence showing the powerful influence of exercise on health, physical inactivity remains a pressing public health issue. Technology and economic incentives tend to discourage activity: technology by reducing the energy needed for activities of daily living and economics by paying more for sedentary than for physically active work (Haskell *et al.*, 2007). Moreover, endurance exercise can also be unapproachable for most people in whom it might be impractical because of physical limitations or, as mentioned in the previous section, side effects. This fact stimulates the search for exercise mimetics (or 'exercise pills') that mimic exercise and, therefore, it has been the focus of important research over the past decades (Goodyear, 2008).

As mentioned in a previous section, exercise improves performance by activating several pathways that induce genetic changes, particularly in skeletal muscle, to increase aerobic metabolism and vascularisation, to ultimately enhance performance (Narkar *et al.*, 2011). AMPK is activated by exercise and is essential for the exercise-mediated switch to aerobic myofibres in skeletal muscle (Wojtaszewski *et al.*, 2000). AMPK stimulates catabolic and suppresses anabolic pathways in an effort to restore cellular ATP levels and is activated robustly in skeletal muscle by acute as well as by chronic exercise (Winder *et al.*, 2006; Matsakas and Narkar, 2010). Recently, it was reported that 5-aminoimidazole-4-carboxamide-1-β-D-ribofuranoside (AICAR) can mimic the effects of exercise by increasing GLUT-4 protein, hexokinase activity, resting glycogen content and muscle mitochondria (Narkar *et al.*, 2008). Mitochondrial biogenesis is activated by AMPK (Jorgensen *et al.*, 2007). This may be explained because AMPK is present in a transcriptional complex with PPAR-δ, where it can potentiate receptor activity via direct protein–protein interaction and/or by phosphorylating and activating coactivators such as PGC-1α (Jager *et al.*, 2007). Puigserver *et al.* (1998) identified PGC-1α as the master regulator of mitochondriogenesis and fuel homeostasis in mammalian tissues and Koves *et al.* (2005) observed that PGC-1α mediates metabolic remodelling of skeletal myocytes, mimics exercise and reverses lipid-induced mitochondrial inefficiency. Thus, exercise training and oxidative fibre type are associated with increased mRNA expression of PGC-1α (Lin *et al.*, 2002). Over-expression of PGC-1α in mice induces dramatic changes in skeletal muscle such as increased mitochondrial biogenesis and fibre remodelling (Lin *et al.*, 2005). Moreover, PGC-1α may be activated by the Ca^{2+}-signalling pathway involving both calcineurin and Ca^{2+}/calmodulin-dependent kinase and by p38 MAPK (Schiaffino *et al.*, 2007).

Recently, we have found an age-associated lack of reactivity of PGC-1α in response to exercise (Derbré *et al.*, 2012), as aged rats had the same response as mice with genetic deletion (knockout) of PGC-1α. Our results highlight the role of PGC-1α in the loss of mitochondriogenesis associated with aging and point to this important transcriptional co-activator as a target for pharmacological interventions to prevent age-associated sarcopenia (Derbré *et al.*, 2012). Modulation of PGC-1α levels in skeletal muscle is crucial for the prevention and treatment of age-related disorders (Sandri *et al.*, 2006). Accordingly, we recently proposed several pharmacological, non-hormonal, interventions to prevent the loss of muscle mass and sarcopenia such as PGC-1α activators, angiotensin II receptor antagonists and allopurinol (Sanchis-Gomar *et al.*, 2011a).

On the other hand, activation or over-expression of the transcription factor PPAR-δ in muscle also results in an increase in mitochondrial biogenesis and in the proportion of oxidative muscle fibres (Narkar *et al.*, 2008). This results in increased running endurance and protection against diet-induced obesity and type 2 diabetes. The contrary is also true: muscle-specific knockout of PPAR-δ results in an age-dependent loss of oxidative muscle fibres, running endurance and insulin sensitivity (Schuler *et al.*, 2006). Thus, several potent and selective PPAR-δ agonists such as GW1516 have been also identified and proposed as mimetic drugs for endurance exercise (Narkar *et al.*, 2008).

Resveratrol has also been considered as an exercise mimetic. High doses of resveratrol improve endurance (Lagouge *et al.*, 2006). The deacetylase enzyme Sir2 and its mammalian homologue SIRT1 have been identified as its putative primary targets. Resveratrol also activates AMPK in

cells in culture, and it has been proposed for the prevention of mitochondrial dysfunction (Ungvari *et al.*, 2011) and of the wasting disorders associated with mechanical unloading (Momken *et al.*, 2011).

Remodelling of skeletal muscle by exercise is extremely complex. Many targets are available to mimic muscle adaptations induced by exercise. However, exercise is linked to other multiple physiological adaptations that affect the vast majority of organs. It seems premature to conclude that all these molecules or substances are mimetics of exercise until the effects in other organs have been fully investigated. Applicability of these compounds at this point in time is limited. Studies aimed to find potential drugs that mimic exercise are now being performed.

Concluding remarks

Exercise is so beneficial for health that it should be considered as a drug. As for any other drug, dosing is very important. Otherwise, unfavourable side effects may occur. Some of the favourable effects of exercise apply to the general population. Prominent amongst these are its role in prevention of many diseases and in the promotion of healthy longevity (see Figure 2). But exercise can also be considered as treatment of established diseases. These include commonly occurring conditions such as depression, diabetes or cardiovascular diseases.

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Conflict of interest

The authors declare that no conflict of interest exists.

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