

Review

Exercise as a Time-conditioning Effector in Chronic Disease: a Complementary Treatment Strategy

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Exercise has been widely believed to be a preventive and therapeutic aid in the treatment of various pathophysiological conditions such as cardiovascular disease and cancer. A common problem associated with such pathologies is cachexia, characterized by progressive weight loss and depletion of lean and fat body mass, and is linked to poor prognosis. As this syndrome comprises changes in many physiological systems, it is tempting to assume that the modulation of the psychoneuroimmunoendocrine axis could attenuate or even prevent cachexia progression in cancer patients. Cancer cachexia is characterized by a disruption in the rhythmic secretion of melatonin, an important time-conditioning effector. This hormone, secreted by the pineal gland, transmits circadian and seasonal information to all organs and cells of the body, synchronizing the organism with the photoperiod. Considering that exercise modulates the immune response through at least two different mechanisms—metabolic and neuroendocrine—we propose that the adoption of a regular exercise program as a complementary strategy in the treatment of cancer patients, with the exercise bouts regularly performed at the same time of the day, will ameliorate cachexia symptoms and increase survival and quality of life.

Keywords: exercise – time-conditioning effector – neuroimmunoendocrine system – glutamine – cachexia

Introduction

In many chronic diseases, such as cancer and chronic heart failure, patients die as a direct consequence of cachexia, a profound metabolic process characterized by the breakdown of skeletal muscle and deleterious, chaotic abnormalities in fat and carbohydrate metabolism (1). This syndrome is accompanied by changes in the neuroimmunoendocrine axis, as reviewed by Langstein and Norton (2) and Langhans (3). Physical exercise is one of the strategies adopted to counteract protein wasting during chronic diseases (4). In addition to the positive impact of exercise on protein metabolism, we propose that exercise acts as a ‘time-conditioning effector’ which regulates the neuroimmunoendocrine axis, increases survival and improves quality of life.

Exercise or regular physical activity has been widely adopted as a preventive or therapeutic aid in the treatment of numerous physiopathological conditions, including cardiovascular diseases (5) and some aspects of senescence (6). The

immense potential of exercise in various conditions seems to be correlated to the fact that it promotes adaptations in all the systems of the organism. This concept about the beneficial effects of exercise on human health is quite recent. In the past, physicians traditionally advised patients with chronic diseases, such as cardiovascular disorders, to avoid physical activity. However, the investigation of cardiac rehabilitation in the 1960s showed the benefits of early mobilization after myocardial infarction, which led to the development of cardiac rehabilitation programs based on exercise (7–9). In fact, these studies served as a starting point for research on the effects of exercise on other systems and pathophysiological processes such as immune response, cancer and inflammation.

As evidence supporting cardiac rehabilitation programs is available, we have started developing a scientific basis for the use of exercise as an adjuvant therapy for cancer patients. In fact, exercise has been used to improve shoulder mobility after breast cancer surgery (10), to help maintain the energy balance during adjuvant chemotherapy (4,11) and to improve the quality of life of cancer survivors (12,13). Leung *et al.* (14) showed that serum obtained from patients who had undergone exercise programs had reduced LNCaP prostate

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cancer cell growth by 27%, through an increase in cellular p53 protein content. Despite these emerging results, the present exercise programs are neither well defined nor included in the list of possible interventions for management of cancer symptoms.

Exercise and the Immune System

During the last two decades, a great effort has been made to understand the mechanisms that underlie the relationship between exercise and the immune system, as a second step in the study of the effects of physical activity on health. In fact, physical fatigue, caused by exercise or manual work, has long been considered a factor affecting susceptibility to illness. A study carried out in the earlier part of the previous century linked physical fatigue with increased susceptibility to poliomyelitis (15). Several studies provide epidemiological evidence that supports the anecdotal belief that regular exercise increases resistance to infections such as common cold whereas intense training is associated with increased upper respiratory tract infections (16–18). The positive effect of exercise on other diseases has also been acknowledged, and there is increasing evidence that physical activity, as a lifestyle, offers protection against malignancy (19).

This dual effect of exercise on the immune system led a group of scientists (20) to postulate a *J*-shaped curve to better express this relationship. Their results indicate that moderate intensity exercise lowers the incidence of infections while intense exercise increases it. Therefore, the present study aids to investigate the underlying mechanisms of such a relationship. Two principal research approaches have emerged in trying to establish a link between exercise and the immune system—a metabolic approach that involves glutamine metabolism (21), and another that considers changes in the neuroendocrine milieu as the mechanism for immunomodulation (22).

Glutamine Hypothesis

Glutamine is a 'conditionally essential' amino acid, which comprises 20% of the total plasma amino acids, and is actively produced in different organs—liver, kidneys, lungs and skeletal muscle (23)—under different pathophysiological conditions. Skeletal muscle is a major glutamine producer, and can release the amino acid into the bloodstream at a high rate (24,25). During the 1980s, Professor Eric Newsholme, at the University of Oxford, demonstrated that rapidly dividing cells, such as lymphocytes, as well as macrophages, both immune cells possessing a high secretory activity, utilize high rates of glutamine even when quiescent (26–28). It was also demonstrated that the glutamine pathway in both cell types is under external regulation, partly because of the supply of glutamine itself (26,27,29). Glutamine, when supplied to the immune cells in the proper concentration (30,31), allows lymphocytes to proliferate, killer cells to respond to lymphokines, and immune cells to produce cytokines. It also reg-

ulates macrophage function. The demand of the skeletal muscle and other organs for glutamine during intense exhaustive exercise, or after surgery, trauma, burns and sepsis, is such that the immune system may be forced into a glutamine debt, which temporarily affects its function (32–34).

Poortmans *et al.* (35) and Decombaz *et al.* (36) reported that a biphasic response of plasma glutamine concentration is present during exercise. A short-term exercise results in an increase in plasma glutamine concentration (27,35,37), while its concentration may decrease by as much as 25%, after a full marathon (21). Rennie *et al.* (38) demonstrated that athletes who ran on a treadmill at 50% of the maximal oxygen uptake showed increased glutaminemia during the first three hours of running, followed by a 17% decrease below pre-exercise levels after 3.75 h. This reduction in plasma glutamine concentration was also observed in overtrained athletes, who showed an unexplained decreased performance associated with higher incidence of upper respiratory tract infections (39,40).

Castell *et al.*, who studied more than 350 runners, reported that plasma glutamine concentration also falls after a marathon. They observed a 15% decrease in the amino acid concentration, 15 min after the end of the race, and an additional 15% decrease within the next hours, from 669 to 533 $\mu\text{mol/l}$ (21). The magnitude and the duration of lowered plasma glutamine vary considerably with the type of sport studied and the intensity of the exercise bout. Walsh *et al.* (41) observed a reduction in plasma amino acid concentration 5 h after an exhaustive cycling protocol while Rhodes *et al.* recorded the same observation in triathletes, 2 h after prolonged exercise. In our laboratory we found a reduction of 25% in plasma glutamine concentration after an Olympic triathlon, in well-trained, top-ranking athletes (42). A similar change was observed in athletes after 12 bouts of a 20-min cycling protocol (20-min rest period between two bouts) at 95% of the maximum oxygen uptake (43). It is interesting to note that the group that received carbohydrate supplementation, in the latter experiment, did not show any change in plasma glutamine concentration (43). The same observation was recorded by Lehman *et al.* (44) and Castell (29) after ultramarathons, during which the runners stopped routinely for 15 min and ingested food and drinks *ad libitum*.

The decrease observed in glutaminemia correlates with increased symptoms of upper respiratory tract infections (21,42), suggesting that immunodepression may occur in some athletes due to stress induced by prolonged, exhaustive exercise and competition. Some of the factors that might render athletes more vulnerable to opportunistic viruses or bacterial agents, as proposed by Castell (21), are a higher training mileage, additional stress (the mental stress of competition more than doubled the risk of getting an upper respiratory tract infection), a low body mass, bypassing the nasal filter mechanism (during exercise, athletes breathe through the mouth rather than through the nose, impairing the pro-

tective effects of mucosal secretions) and a decrease in environmental temperature.

Immune Changes after Exercise

The most common changes in immune cell function after strenuous exercise comprise decreased neutrophil activity, impaired antibody synthesis, decreased immunoglobulin levels in blood and saliva, decreased cytolytic activity of natural killer (NK) cells, lower circulating T lymphocyte number for 3–4 h after exercise, a reduction in the proliferative ability of lymphocytes in response to mitogens, and profound changes in the profile of cytokines produced after exercise, including a 100-fold increase in interleukin-6 production, and an augmented production of anti-inflammatory mediators (21,22).

These changes are transient, and most of them return to the basal level a few hours after exercise. In general, however, there are some long-term changes in the immune response of athletes. The adaptive immune system (resting state) seems to be largely unaffected by intensive and prolonged exercise training (45,46). The innate immune system appears to respond differently to the chronic stress of intensive exercise, with NK cell activity tending to be enhanced while neutrophil function is suppressed (47–50). However, the clinical significance of such changes remains to be elucidated.

How to Deal with Changes in Plasma Glutamine?

While considering the glutamine hypothesis, it is quite tempting to speculate that maintaining the plasma glutamine concentration within the normal range (found at rest) will restore the immune changes observed after strenuous exercise. Castell *et al.* (51,52) supplemented athletes with 7 or 5 g of glutamine per day and found only a slight and transient increase in plasma amino acid levels, which was, nevertheless, enough to decrease the incidence of upper respiratory tract infections (URTI) (53) as well as to prevent the changes in the CD4 : CD8 ratio found in the athletes of the placebo group (52). Our own studies (42) showed a similar magnitude of decrease in the incidence of infections in triathletes, in a group of athletes supplemented for 1 month with branched chain amino acids—precursors for glutamine synthesis. The supplementation protocol was efficient in maintaining the plasma glutamine levels after an Olympic triathlon within the same range as that found at rest. The maintenance of plasma glutamine levels was paralleled by an augmented production of IL-1, IL-2, tumor necrosis factor α (TNF- α), and interferon γ (IFN- γ), with changes in the balance between Th1: Th2 type immune response. Another study on athletes reported a reduction in IL-4 production in the supplemented group after a 30-km run (54), reinforcing the potential change in the type of immune response presented by the athletes who received branched chain amino acids as precursors for glutamine synthesis, and its diversion towards a Th1 type response, which promotes cellular immunity (55).

Therefore, it may be possible that the supplementation of glutamine or branched chain amino acids to athletes engaged in long-distance high-intensity exhaustive exercise might increase glutamine availability for the immune system at a critical period when athletes are vulnerable to opportunistic infections. On the other hand, moderate intensity exercise will warrant constant plasma glutamine concentration, which could be beneficial to the integrity of the immune response during wasting conditions such as cancer cachexia.

The 'Open Window' Hypothesis

The second hypothesis that attempts to explain the relationship between exercise and the immune system is based on the changes observed in the neuroendocrine system, and is known as the 'open window' hypothesis (22). During exercise, there is a marked increase in the plasma levels of adrenaline, noradrenaline, growth hormone and cortisol. Depending on the exercise intensity and duration, the profile of secretion of these hormones and their clearance rates are substantially modified (22,56). Adrenaline, and to a lesser degree noradrenaline, seem to be responsible for the acute effects of exercise on lymphocyte dynamics and lymphocyte function (57) and NK cell activity (22). Increase in growth hormone and catecholamine levels mediates the acute effects on neutrophils whereas cortisol exerts its effects within a time lag of at least 2 h, depending on the exercise duration and intensity, and therefore may help to maintain lymphopenia and neutrocytosis only after long-term exercise (18,58). The role of β -endorphins is less clear, but possibly linked to the immediate recruitment of NK cells in the blood (22).

As shown by several authors (43,54,59), exhaustive exercise induces a drift towards a Th1 type immune response associated with the production of glucocorticoids. Considering that glucocorticoids suppress the production of TNF- α , IFN- γ and IL-2 (60,61), which are important regulators of the Th1 type immune response, and that humoral immunity decreases during exhaustion, we can accept this as an important mechanism to explain exercise-induced immunodepression. Another interesting aspect is the effect of catecholamines in shifting the immune response towards a Th2-mediated humoral immunity. This effect could counteract the immunodepression related to exhaustion immediately after an acute bout of exercise, thereby maintaining the homeostasis of the immune response in such conditions. In fact, this could be linked to the 'stress-immune paradox' (62). Dhabbar *et al.* observed an enhancement in delayed type hypersensitivity response after acute stress. However, their studies demonstrated that the immune response should be enhanced, and not depressed, to protect the host during acute physical and/or psychological stress (62–64). If the physical exercise or psychological stress is above the adaptive capacity of the organism, over a long period of time, the effect will be deleterious (62,65).

The 'stress-immune paradox' could be correlated with the 'Cognitive Activation Theory of Stress', postulated by

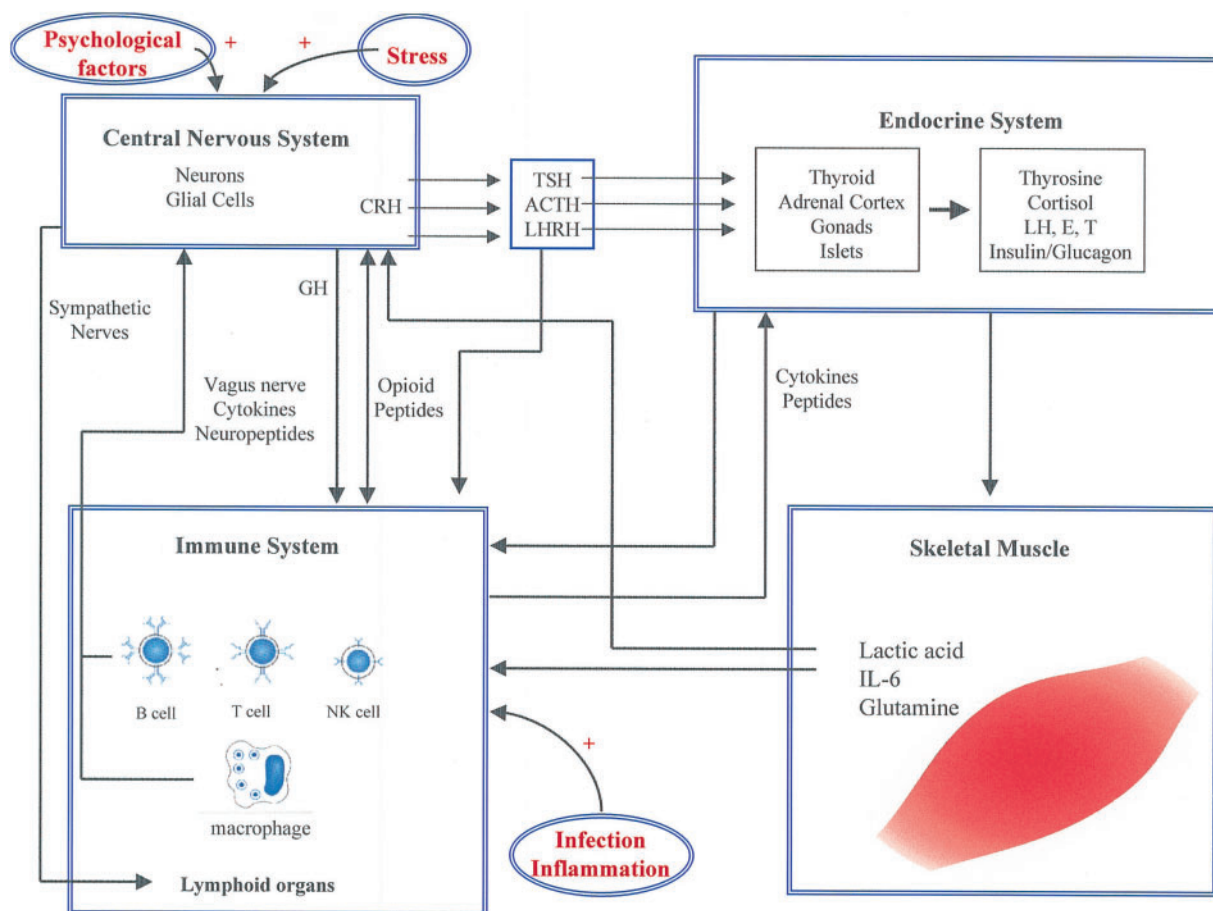


Figure 1. Interconnections among the nervous, immune, endocrine and muscular systems. These interactions involve the actions of small molecules such as neuropeptides and cytokines, hormone secretion, nervous activation and opioid peptides. ACTH, adrenocorticotropic hormone; CRH, corticotropin releasing hormone; E, estrogen; T, testosterone; TSH, thyroid-stimulating hormone; GH, growth hormone; IL-6, interleukin 6; LH, luteinizing hormone; LHRH, luteinizing hormone-releasing hormone.

Eriksen *et al.* (66) as a reformulation of the stress theory, within a homeostatic and physiological framework. According to this theory, the phases of the response are interpreted as an alarm occurring within a complex cognitive network, with feedback and control loops. One important consequence of this approach, at least for the model that correlates immunological changes and exercise through a neuroendocrine mechanism, is that the response is dynamic and develops over time. This time element must be taken into account as the stress response develops in phases. A better understanding of these phases is crucial to predict the pathophysiological consequences of the relationships between the stressor and the observed physiological response. As postulated by Eriksen *et al.* (66), subjects with efficient coping show the fast- and short-lasting catecholamines response while subjects with high defense mechanisms (related to stimulus expectancies) may show more signs of prolonged activation. Non-coping individuals show a sustained general activation, which may develop into somatic disease or illness.

Therefore, many metabolic and hormonal changes observed during cachexia could be counteracted by those induced by regular exercise, known to promote changes that

can be sustained for more than 24 h in the hormonal profile of athletes and also to positively modulate the immune response.

Integrating the Systems: a Psychoneuroimmunoendocrine System

Based on previous studies (67–70), we can hypothesize the existence of a neuroimmunoendocrine system that communicates through peptides, monoamines, glucocorticoids, free radicals, cytokines and opioids. Furthermore, neuropeptides found in the central nervous system, which show several immunomodulatory properties, are also expressed by immune cells (71,72). Another interesting point that reinforces the existence of such an integrative axis is the presence of ‘receptors’ of various neurohormones and hypothalamic releasing factors in leukocytes (67,68,70,73,74). Many authors, on the other hand, have postulated the existence of a psychoneuroimmunologic axis that (69,75) integrates the central nervous system, behavior and the immune system. As the nervous and the immune system actively interact with the endocrine system, we can acknowledge a psychoneuro-

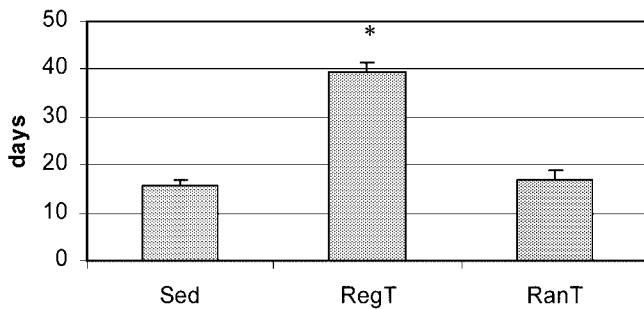


Figure 2. Life span of Walker-256 tumor-bearing rats trained for 8 weeks, 5 days a week, 3 h after the beginning of the dark period, at 60% maximum oxygen consumption (RegT), and that of tumor-bearing rats that followed the same training protocol, but exercised randomly throughout the day (RanT), compared with that showed by sedentary tumor-bearing animals (Sed). There were 25 animals/group, and the protocol described by Bacurau *et al.* (107) was followed. * $P < 0.05$ for comparison with Sed group.

immunoendocrine system. This system is the key to understanding various mechanisms, which are still primarily a patchwork of loosely linked observations, and thereby provide novel but fundamentally unsubstantiated treatments for disorders such as cancer, as proposed by Schleifer (75).

In the early 1980s, traditional immunologists and other scientists and physicians reviewed the proposal of this integrative system as an attempt to legitimize alternative medicine, and maintained that there was no correlation between psychosocial factors and survival in cancer patients (76,77). However, over the last decade, evidence showing that psychological stress modulates the immune system has been accumulated. In fact, it seems that chronic stress, such as marital problems, work-related stress or bereavement, has a suppressive effect on the parameters of immune response (69), including a reduction in the number of T and B lymphocytes, decreased proliferative response to mitogens and decreased NK activity, leading to increased susceptibility to infections and worsening of existing diseases such as cancer. On the other hand, it seems that acute stress, such as examination stress or experimentally induced stress, has a positive impact on immune parameters (69,78–82).

Considering the information presented in the previous paragraph, it seems quite impossible to avoid changing the terms 'chronic stress' and 'acute stress' to 'chronic exhaustive exercise' and 'acute exercise'. The assumption that exercise may be acting on a psychoneuroimmunoendocrine system opens multiple possibilities of using exercise as a therapy: preventing and/or reducing the incidence of chronic diseases, acting as a coadjuvant in the treatment of Alzheimer's disease (83), sub-acute low back pain (84), rheumatoid arthritis (85), fibromyalgia syndrome (86), cancer (87), chronic heart failure (88) and HIV-associated depression (89), among others.

Therefore, considering that an organism functions in an integrative manner, we can accept the proposal made by Professor Newsholme and integrate the skeletal muscle in our psychoneuroimmunoendocrine axis (Fig. 1) because glutamine seems to be essential for immune cells and its synthesis

is controlled by hormones (90). In fact, when investigating the relationship between glutamine and the immune system during exercise, we tested the immune response of athletes subjected to 12 bouts of indoor cycling, 20 min each, with 20 min interval, at 95% of the maximal oxygen consumption. We observed that the athletes who received carbohydrate supplementation during the trial showed a blunted response of cortisol during exercise and were able to maintain plasma glutamine levels within the normal range (43). After exercise, the proliferative response of lymphocytes to mitogens as well as the production of IL-1, IL-2, IL-4 and TNF- α were restored to the pre-exercise levels, indicating that both hypotheses—glutamine and 'open window'—cannot be excluded.

Exercise as a 'Zeitgeber'

In the past few years, the studies carried out in our laboratory provided evidence that led us to evaluate the possible effect of exercise as a 'Zeitgeber' or a time-conditioning effector. In mammals, the pineal gland transduces photoperiodic information to the neuroendocrine axis through nocturnal melatonin secretion (91). This hormonal message plays a key role in the biorhythm regulation, acting as a 'Zeitgeber', adjusting the internal clock to a 24-h cycle based on dark and light periods (91,92). Cachexia is a metabolic syndrome that occurs in about 80% of all advanced cancer patients and is associated with a decreased survival time (93,94). It is defined as 'a wasting syndrome involving loss of muscle and fat directly caused by tumor factors or indirectly caused by an aberrant host response to tumor presence', characterized by breakdown of skeletal muscle and harmful, chaotic abnormalities in fat and carbohydrate metabolism, despite adequate nutritional intake (1,95,96). These changes in energy metabolism are mediated by factors such as cytokines, serotonin, lactate, ketone bodies, glucocorticoids and thyroid hormones (97,98). The net metabolic result is increased basal energy expenditure that reflects a global change in energy use, associated with wasting of energy reserves combined with anorexia, which significantly reduces caloric intake (99). Considering that melatonin transmits circadian and seasonal information to all organs and cells of the body, thereby synchronizing the physiological processes and metabolism including energy metabolism (100) with the daily and annual photoperiod variations, it seems quite reasonable to assume that changes in its profile would lead to a loss of metabolic control that facilitates the initiation of cachexia-related changes. In fact, Bartsch *et al.* (101) showed a tumor-dependent depression of serum melatonin in patients with prostate or breast cancer. However, according to Bartsch and Bartsch (102) it is unclear whether the plasma melatonin depletion in cancer patients is due to peripheral metabolic processes or a reduced production by the pineal gland. Therefore, considering the possible link between melatonin and cancer cachexia, we showed that the administration of a daily dose of melatonin to Walker-256 tumor-bearing rats extended the life span of the animals by approximately 100% (103). This

result indicates that the rhythm of melatonin or its production may be impaired in our model, as previously described for other types of cancer (101,104).

To better understand what happens to melatonin rhythm during cachexia, we determined the 24-h profile of melatonin production in tumor-bearing rats during cachexia development. Ferreira *et al.* (105) showed that during Walker-256 tumor progression, the animals showed profound changes in the profile of melatonin secretion, with changes in the secretory profile of the amine as well as in the total amount of its secretion and in the response of the pineal gland to noradrenaline stimulation. It is interesting to note that the total amount of melatonin produced increased during cancer cachexia, but the profile of production during the dark period was profoundly changed. In fact, we observed a dramatic alteration on day 7 after tumor implantation, when the first signs of cachexia could be observed in the tumor-bearing rats (106). We also detected the highest melatonin production on day 7. On the day 14, the melatonin secretory profile was different from that observed in control rats, but the total amount of melatonin secreted during the night decreased. The change in the total amount and in the profile of melatonin production by the pineal gland of tumor-bearing rats could be involved in cancer cachexia progression, leading to a disruption in metabolism.

We also demonstrated that a regular exercise program prolongs the life span of Walker-256 tumor-bearing rats (107). The animals were trained for 1 h every day, starting always at the same hour during the dark period. Interestingly, we found that the moderate intensity protocol (60% maximal oxygen uptake) and the high-intensity protocol (85% maximal oxygen uptake) provoked the same effect, increasing the rats' life span if the training sessions were carried out at the same hour during the day. If the daily exercise bout was performed randomly through the day, the increase in life span was abolished (Fig. 2). Therefore, it seems quite reasonable to assume that a possible mechanism to explain the effects of exercise upon cancer cachexia could be related to its ability to act as a 'time-conditioning effector', assuming the previous function of melatonin. In fact, Baehr *et al.* (108) showed that exercise can phase-shift the circadian rhythms of young adults if performed at the right time of the day. The literature provides evidence of many other time markers that may partially replace melatonin in entraining the organism, such as food-anticipatory activity (109), exogenous corticosteroids (110) or even a carbohydrate-rich meal (111). On the other hand, a loss in melatonin secretory pattern is observed during ageing (112) and some pathologies such as chronic fatigue syndrome (113), in which the prescription of a regular training program restores the sleep pattern and general feeling of wellness (6,113). The potential role of exercise as a time-conditioning effector in different pathophysiological conditions needs to be further evaluated. The fact that a regular exercise program could postpone cell death by cancer cachexia assumes even more importance if we consider the premise of Zajicek (114) that the treatment of cancer patients is based on the false

premise that the tumor is the only threat to the patient. Thus, exercise would be an important complementary and alternative strategy for the treatment of cachexia.

Therefore, taking into account that physical exercise affects all tissues and systems in the human body, interacting and modulating the psychoneuroimmunoendocrine system, that changes in the equilibrium of such a system during chronic diseases such as cancer and chronic heart failure lead to cachexia, and that during cachexia there is a loss of control of the internal rhythm through rhythmic melatonin production by the pineal gland, it seems that a regular exercise program could be a useful and low-cost intervention to reduce cachexia-related mortality as well as serving as a complementary strategy for improving the quality of life of cancer survivors and reducing costs of the public health system.

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