Medical Hypotheses 72 (2009) 527–532

Contents lists available at ScienceDirect

Medical Hypotheses

journal homepage: www.elsevier.com/locate/mehy

Hormesis, allostatic buffering capacity and physiological mechanism of physical activity: A new theoretic framework

Guolin Li [a,1,*], Hong He [a,b,1]

[a] The Key Laboratory of Protein Chemistry and Developmental Biology of Ministry of Education, College of Life Sciences, Hunan Normal University, No. 177, Lushan Road, Changsha, Hunan 410081, PR China

[b] College of Physical Sciences, Hunan Normal University, Changsha, Hunan 410081, PR China

ARTICLE INFO

Article history:
Received 3 December 2008
Accepted 7 December 2008

SUMMARY

Despite great progress made in sports medicine, the physiological mechanism of moderate physical activity-induced physical fitness remains only partly understood. Combined with the hormetic characteristic of physical activity and property of allostasis, we first propose the hormesis induced allostatic buffering capacity enhancement as a physiological mechanism to explain the moderate physical activity-induced physical fitness. As stressful stimulus, physical activity can induce several stresses in the host, including eustress ('good stress') and distress ('bad stress'), which may have both positive and negative effects. Too little or too much physical activities will introduce too weak eustress or too strong distress and result in allostasis load through weakening allostatic buffering capacity or damaging allostatic buffering capacity respectively. However, moderate physical activities will introduce eustress and contribute to the hormesis induced allostatic buffering capacity enhancement, which benefits organism.

Introduction

Evidence from different ages, genders and races has revealed that the change in physical activity is the primary determinant of physical fitness, and exercise capacity and physical fitness are inversely correlated with the all-cause mortality in individuals with or without cardiovascular disease. However, the physiological mechanism of physical activity-induced physical fitness remains only partly understood. The anti-stress training, or termed as "hormesis" as integrated by Calabrese and others [1], in botanies cast meaningful light on it.

In plant physiology, a common treatment to minimize the harm of plant to withstand stress conditions is hormesis, that is, placing the plant in a moderate stress condition and triggering its own defense mechanisms to improve resistance to the stress [2,3]. For example, a simple and effective method to cultivate drought-resistant rice cultivars is anti-drought training, that is, by drought stress during the early growth stage, to stimulate the rice to gain an induced drought-resistance [4,5].

Besides botany, there are a large number of results showing that the hormesis also existed in yeast, nematodes, fruit flies, mammalian, and even human beings [6,7]. Probably, the hormesis of organism triggered induced-resistance, in a sense, represents the molecular memory of stress factors, which serves as an important index of biological organisms different from non-biological organisms at the molecular level.

Could the hormesis also apply to physical activity? What's the physiological mechanism of physical activity-induced physical fitness? To answer these questions, the first and foremost riddle to solve is whether physical activity itself can be recognized as a stressful stimulus.

Physical activity, stress and hormesis

Simple muscle contraction can lead to the formation of various reactive oxygen species (ROS), such as hydroxyl radicals produced in contracting skeletal muscle of cats [8], superoxide released by diaphragm myocytes into the interstitium and surrounding medium [9]. During physical activity, a series of stresses, including oxidative stress, ischemic/reperfusion stress and many other stresses [10,11], would result mainly from energy metabolism and energy demand. Intense and prolonged physical activity has been shown to induce a complex stress response, which involves reactions on the cardiovascular, metabolic, hormonal, and immunological levels [11,12]. Therefore, the physical activity could be recognized as a stressful stimulus.

Hormesis is characterized with the basic characteristics of biphasic dose-response, which is low dose stimulation and high dose inhibition [1,6,13], and now often used refers to the beneficial effects of low doses of potentially harmful substances [1,6,13]. Considering that moderate physical activity does assist in maintaining physical fitness, promoting physiological well-being and strengthening the immune system, while prolonged and intense physical

* Corresponding author. Tel./fax: +86 731 8872786.
E-mail address: hnsdlgl@hunnu.edu.cn (G. Li).

[1] These two authors contributed equal to this paper.

0306-9877/$ - see front matter © 2009 Elsevier Ltd. All rights reserved.
doi:10.1016/j.mehy.2008.12.037

activity can be harmful [14,15], which is a typical biphasic dose-response, it is reasonable to presume the action model of moderate physical activity is stressful stimulus induced hormesis. For this reason, Radak and others extended the hormesis theory to explain the physical activity-induced adaptation, mainly from the perspective of oxidative stress-related [16].

Physical activity and ABC

Allostasis and ABC

About 20 years ago, Sterling and Eyer coined allostasis from the Greek 'Allo' meaning 'variable', and 'stasis' meaning 'stable'. Thus allostasis means 'remaining stable by being variable' [17], that is, maintaining stable through multi-point. Since in organisms, especially higher animals, the stability of internal milieu is associated with many rhythms, such as daily rhythm of body temperature, daily rhythmic secretion of serotonin, melatonin, adrenocorticotropic hormone (ACTH) and other hormones and many other rhythms, it is reasonable to think allostasis as a more accurate concept of homeostasis (remaining stable by staying the same).

Based on the multi-point property of allostasis, we could image the allostatic system as a special 'buffering system': it has a basal level and certain buffering capacity that could maintain dynamic stability (Fig. 1A). Therefore, we coined the term of 'allostatic buffering capacity (ABC)' with five components: that is, basal level, peak level, buffering range, increase rate and recovery rate, to give a good picture of the capacity of allostatic system to maintain dynamic stability (Fig. 1).

The action model of physical activity to ABC

Different physical activities play different roles in ABC. According to the difference of intensity, three situations are associated with the role of physical activity to ABC.

The first is moderate physical activity-induced ABC enhancement (Fig. 1C). It has been widely accepted in sports medicine that moderate physical activity can improve the allostasis of heart, lung and many organs. Take heart rate, the simplest parameter of heart function, as an example. In comparison to untrained people, well-trained people generally have lower basal heart rate, and when they participate in the same intensity of physical activity, the heart rates of well-trained people will increase more slowly [18] and can arrive at higher peak heart rate (more close to the predicted maximum heart rate) depending on the intensity of physical activity. After the cessation of physical activity, their heart rates recover to the basal rate more rapidly [19,20], which from the point of allostasis is moderate activity enhanced all five components of ABC (Fig. 1C).

The second is inadequate physical activity weakened ABC (Fig. 1B). As we have known, aging is often defined as a process of age-related loss in the capacity of maintaining allostasis [21]. Evidences also show that inadequate stimuli induce inadequate signals output from the nervous system or neuroendocrine system, and inadequate signals input is one of the important causes of amyotrophy [22]. It may be the reason that persons of sedentary lifestyles or seldom participating in physical activity usually show an age-related weakening in ABC and have higher basal heart rate, lower peak rate, narrower buffering range, more rapidly increasing

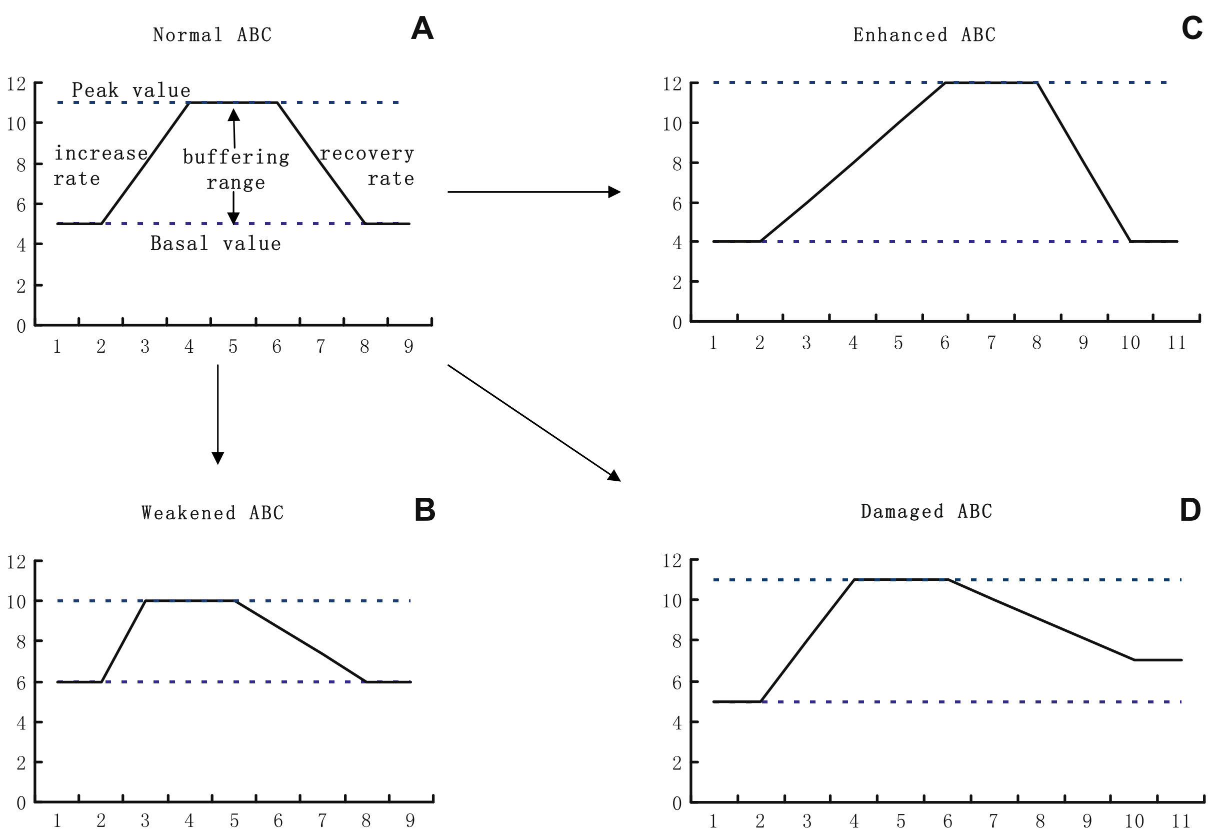

Fig. 1. The action model of physical activity to ABC. (A) illustrates the normal ABC constituted with basal level, peak level, buffering range (the range between basal and peak level), increase rate and recovery rate. The allostasis can maintain dynamic stability in the buffering range with normal rate when responses to certain stressful stimulus and can recover to the basal level after the cessation of stressful stimulus. The remaining panels (B, C and D) illustrate the three changes of ABC resulting from different lifestyles respectively: inadequate physical activity weakened ABC (B), moderate physical activity enhanced ABC (C) and intense and prolonged physical activity damaged ABC (D).

rate and more slowly recovery rate. This process can be defined as 'allostasis load' according to the opinion of McEwen [23,24].

The third is intense and prolonged physical activity breaks the ABC, and the special characteristic of it is, if not lacking, at least difficult to recover to basal level (Fig. 1D). It can also be defined as 'allostasis load' [23,24]. For instance, intense and prolonged physical activity could induce sympathetic and HPA-axis activity maintain in a higher level, resulting in weight loss, amenorrhea, and the often-related condition of anorexia nervosa [25].

Examples and performances of physical activity to ABC

Oxidative stress

The best-studied example of physical activity and ABC is oxidative stress. The oxidative stress was classically defined as an imbalance between the production of oxidations and the occurrence of cell antioxidant defenses by Helmut Sies in 1985 [26], and as a disruption of redox signaling and control by Dean P. Jones in 2006 [27]. However, with the advance in the concepts of allostasis [17] and allostasis load [23], we would prefer to consider it as a disturbing status of redox allostasis.

As reviewed elsewhere [28–30], physical activity, especially intense and prolonged physical activity, can cause a marked increase in the ROS and reactive nitrogen species (RNS) mainly from mitochondria, nonphagocytic NAD(P)H oxidase (NOX), xanthine oxidase or phagocytes. ROS and RNS, at high concentrations are hazardous for living organisms and damage all major cellular constituents, including proteins, lipids and nucleic acids, and result in oxidative stress, while at moderate concentrations play an important role as regulatory mediators in signaling processes and as initiators in reestablishing "redox allostasis" [31–33].

Regular moderate physical activity can promote mitochondrial biogenesis and enhance muscle oxidative capacity [34–36], and the molecular signals that drive mitochondrial biogenesis as a component of myofiber adaptation to increased muscle usage are mainly the increased ROS and RNS, such as hydrogen peroxide (H_2O_2) and nitric oxide (NO) [34,35,37]. In addition, regular physical activity can decrease ROS production through reducing the electronic leakage with more well-regulated mitochondrial electron-transport chain [38] and higher pool of functional mitochondria [39], which is critical to delay the onset and progressive course of age-related diseases [40]. Based on these, it is clear that regular moderate physical activity can enhance the redox ABC from lowering the basal level and increasing the oxidative buffering range.

Though the effects of regular physical activity on the total radical trapping antioxidant potential (TRAP), catalase (CAT) activity and glutathione peroxidase (GPX) activity have been inconsistent and controversial, in particular Sharpe and others have illustrated that regular physical activity cannot directly increase the TRAP in serum as index by the concentrations of urate, protein thiols, ascorbate, alpha tocopherol and bilirubin [41], the superoxide dismutase (SOD) activity has consistently been shown to increase with physical activity in an intensity-dependent manner [42]. In addition, ample evidences have indicated that regular physical activity can increase the activity of proteasome complex, which increase the degradation and turnover rate of oxidative modified proteins [43,44].

In short, in comparison with sedentary, regular physical activity can enhance the redox ABC that: (a) is from lowering the basal ROS level through reducing ROS production, decreasing resting respiration rate and reestablishing redox allostasis, (b) is from increasing the peak level and oxidative buffering range by promoting mitochondrial biogenesis, and (c) is from decreasing the oxidative stress rate and increasing recovery rate by reestablishing redox allostasis and enhancing antioxidant defensive system and damage repair system. In contrast, intense and prolonged physical activity may damage redox ABC.

Cardiorespiratory system

Many factors attribute to exercise capacity, and the function of cardiorespiratory system, especially the delivery of oxygen to muscles is the determinant factor [45,46]. Therefore, the direct effect of physical activity on exercise capacity, in fact, is the effect on cardiorespiratory system.

As addressed above, the physical activities have typical hormetic effects on the heart rate profile, and the beneficial effect of moderate physical activity on heart rate profile is typical mild stressful stimuli induced ABC enhancement. Though arguments still exist whether heart rate can be served as a predictor of cardiorespiratory-related mortality [47,48] and present results only support it to predict mortality from the heart rate recovery after treadmill exercise testing [49,50], numerous investigations have established a strong association between the heart rate profile and the cardiovascular functions and exercise capacity [51,52].

Beside the heart rate profile, though other adaptations of exercise capacity-related have not been fully studied from all five components of ABC, they show an obvious hormetic effect on physical activities. Physical inactivity or sedentariness is associated with low cardiorespiratory fitness and increased prevalence of CVD risk factors [53]. Moderate physical activity can not only improve cardiorespiratory fitness in a strong dose-dependent fashion [51,54], promote angiogenesis through overexpression of angiogenic factors [55], promote vasodilatation by increasing basal production of nitric oxide [56], prevent from age-related decline in oxygen delivery capacity of red blood cell [57], and lower basal resting heart rate and blood pressure through reducing sympathetic activity and/or increasing parasympathetic tonus [58], but also reduce the morbidity and mortality of cardiovascular diseases, such as heart failure [59], coronary heart disease (CHD) [60,61] and hypertension [62]. In contrast, intense and prolonged physical activity, such as marathon, may result in some damage to cardiorespiratory systems, including hypertension, endothelial dysfunction, coronary artery disease [63], intestinal ischemia [10], and exacerbating brain damage caused by in vitro ischemia, oxygen and glucose deprivation [64,65]. Thus, Blair research group has suggested that physical activity status is the determinant factor and is primarily responsible for cardiorespiratory fitness [51,66], and more detailed investigations are needed to be conducted from all five components of ABC to disclose the more detailed mechanism of physical activities to cardiorespiratory fitness.

Immune system

The immune system is a remarkably effective allostatic buffering system that the body healthy and protects the body from potential threats by recognizing and responding to molecular antigens and non-living antigens [11]. According to stress-immunology, stress can induce antigen-specific cell-mediated immunity [67] and induce a long-lasting increase in immunologic memory [68], which may serve as an early warning signal and help prepare the immune system for potential threats [69].

Physical activity, as a type of stressful stimulus, can introduce several threats to the allostasis of the host, which may mimic as antigens and stimulate several immune responses. Some of the immune responses may benefit immune function; some may not, depending on the intensity and amount of physical activity. Moderate physical activity is the most important strategy to enhance immune ABC and offset age-related decline in immune function in the elderly [70], whereas intense and prolonged physical activity can result in immune dysfunction [71].

Evidences from epidemiology or susceptibility to infection suggest that the physical activity plays hormetic role on immune system. For example, Nieman models the relationship between physical activity and the resistance to upper respiratory tract infection (URTI) as a "J"-shape curve [72]. Research data also shows that

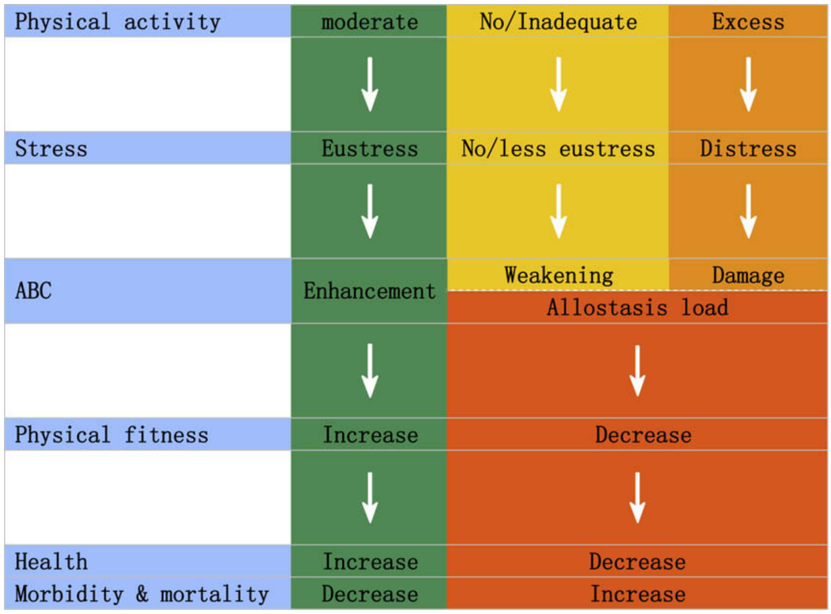

Fig. 2. The framework of physical activity acting on physical fitness and health. Physical activity is a stressful stimulus. Different amounts of physical activity can induce different effects on the host. Moderate physical activity may introduce eustress and result in ABC enhancing, physical fitness increasing, health improving and morbidity and mortality reducing in sequence (green column). In contrast, inadequate or excessive physical activity will lead to allostasis load through inadequate eustress induced ABC weakening (yellow column) or distress induced ABC damage (orange column), respectively, and subsequently threatens physical fitness and health (red column). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

regular moderate physical activity can accelerate wound healing [73], increase resistance to influenza virus [74], reduce inappropriate inflammation [73,75] and decrease incidence of infection [76], whereas high intensity or long duration of physical activity can suppress immune function and increase susceptibility to infections [76,77].

Recent studies have demonstrated that the alterations in immune allostatic parameters may account for the hormetic effect of physical activity on immune system. Moderate physical activity can induce mild stress, which can enhance immune surveillance and vigilance [78], mainly through changing proportional distribution of lymphocyte subpopulations and increasing natural killer (NK) cell cytotoxicity, circulatory lymphocyte counts and functions, and immunoglobulins [76,78]. It is a typical hormesis induced immune ABC enhancement. In contrast, intense and prolonged physical activity may suppress the functions of all immune cells and increase in plasma cytokines and stress hormones [77,79–81], such as suppressing the chemotaxis of neutrophil [80] and the mitochondrial energy status of peripheral blood leucocytes [81], increasing in the rate of leucocytes apoptosis [79] and suppressing the NK cell function and IgA output [77].

In sum, the effect of physical activity on the immune system is a typical hormetic process. In comparison to a sedentary lifestyle, regular moderate physical activity can induce immune ABC enhance and arouse its surveillance and vigilance, whereas intense and prolonged physical activity may result in immune ABC damage and immune system dysfunctions.

Whole-body

Studies in asymptomatic populations have revealed that physical activity can promote exercise capacity and physical fitness, and subsequently reduce all-cause mortality and make assurance of survival and longevity [20]. In fact, this process is an ABC enhancement by increasing resistance to the stress stimuli of physical activity and by reinforcing the capacity to deal with the stress stimuli, if we regard the whole body of human as a buffering system. That is to say, the health benefits of physical activity are achieved by enhancing ABC.

Conclusion and perspectives

The available data strongly indicates that physical activity plays an important role in physical fitness. Considering the hormetic characteristic of physical activity and property of allostasis, we first propose that the physiological mechanism of moderate physical activity-induced physical fitness is a 'hormesis induced ABC enhancement'. It will serve as a framework for organizing the current understanding of the physical activity into a unifying and testable concept.

Hormesis is a biphasic dose-response phenomenon primarily found in toxicology, and now is often used to refer to the beneficial effects of low dose stressful stimulus and has been widely extended to many fields [1,6,13]. However, how do low dose stressful stimuli benefit organisms? Or what's the physiological process of hormesis? It still is a Pandora's Box. At the same time, since Sterling and Eyer coined the concept of allostasis to discourse the stability of internal milieu, McEwen has defined the harmful effects of stressful stimuli as allostasis load and established the action models [23,24], while there is lacking action models to describe the beneficial effects of low dose stressful stimuli. The hormesis induced ABC enhancement discoursed in this paper can complete another piece of the jigsaw puzzle of allostasis and serve as a physiological process of hormesis.

As stressful stimulus, physical activity can induce several stresses in the host, including eustress ('good stress') and distress ('bad stress') [7], which may have both positive and negative effects. Too little or too much physical activities will introduce too weak eustress or too strong distress and result in allostasis load through weakening ABC or damaging ABC respectively. However, moderate physical activities will introduce eustress and contribute to the hormesis induced ABC enhancement, which benefits organism (Fig. 2).

Although the amount of evidence supporting the concept that physical activity is one of the most important steps to improve physical fitness, the change in allostasis and the detailed physiological process of physical fitness induced by moderate physical activity have seldom been reported. The lack of logical hypothesis may be responsible for it. Based on available evidences, we find the model of stress induced ABC change is useful to explain the physiological process of physical activities, and the hormesis induced ABC enhancement may serve as the physiological mechanism of the moderate physical activity-induced physical fitness. According to this hypothesis, it is reasonable to consider that the effects of physical activities on different systems may owe to the changes either in one or some or all of the five components of the allostatic buffering system, which is necessary for further investigations to focus on, aiming to demonstrate the basic principle of physical activity.

Acknowledgements

We are very grateful to Dr. Dazhong Yin for his constructive suggestions during preparation of the paper and Ms. Stephani Cramer for her careful reading of this review in draft form. This work has been supported by National 863 Grants of China (2008AA02Z411), National Science Funds of China (30800207), Hunan Province Grants (06FJ3001) and Hunan Normal University Doctorial Funds (53112-1392).

References

[1] Calabrese EJ, Bachmann KA, Bailer AJ, Bolger PM, Borak J, Cai L, et al. Biological stress response terminology: integrating the concepts of adaptive response and preconditioning stress within a hormetic dose-response framework. Toxicol Appl Pharmacol 2007;222:122–8.
[2] Schulze ED, Beck E, Muller-Hohenstein K. Stress physiology. Plant ecology, vol. 1. Berlin: Springer; 2005.
[3] Taiz L, Zeiger E. Stress physiology. Plant physiology, vol. 3. Sunderland, MA: Sinauer Associates, Inc.; 2002.
[4] Boonjung H, Fukai S. Effects of soil water deficit at different growth stages on rice growth and yield under upland conditions. 1. Growth during drought. Field Crops Res 1996;48:37–45.
[5] Fukai S, Cooper M. Development of drought-resistant cultivars using physiomorphological traits in rice. Field Crops Res 1995;40:67–86.
[6] Le Bourg E, Rattan SIS. Mild stress and healthy aging: applying hormesis in aging research and interventions. Dordrecht: Springer; 2008.
[7] Moberg GP, Mench JA. The biology of animal stress: basic principles and implications for animal welfare (Cabi Publishing): basic principles and implications for animal welfare. New York: CABI Publishing; 2000.
[8] O'Neill CA, Stebbins CL, Bonigut S, Halliwell B, Longhurst JC. Production of hydroxyl radicals in contracting skeletal muscle of cats. J Appl Physiol 1996;81:1197–206.
[9] Reid MB, Shoji T, Moody MR, Entman ML. Reactive oxygen in skeletal muscle. II. Extracellular release of free radicals. J Appl Physiol 1992;73:1805–9.
[10] Moses FM. Exercise-associated intestinal ischemia. Curr Sports Med Rep 2005;4:91–5.
[11] Kindt TJ, Osborne BA, Goldsby RA. Kuby immunology. In: Freeman WH, editor. New York; 2006.
[12] Hoffman-Goetz L, Pedersen BK. Exercise and the immune system: a model of the stress response? Immunol Today 1994;15:382–7.
[13] Mattson MP. Hormesis defined. Ageing Res Rev 2008;7:1–7.
[14] Suitor CW, Kraak VI. Adequacy of evidence for physical activity guidelines development: workshop summary. Washington: National Academy Press; 2007.
[15] Warburton DE, Katzmarzyk PT, Rhodes RE, Shephard RJ. Evidence-informed physical activity guidelines for Canadian adults. Can J Public Health 2007;98(Suppl. 2):S16–68.
[16] Radak Z, Chung HY, Goto S. Exercise and hormesis: oxidative stress-related adaptation for successful aging. Biogerontology 2005;6:71–5.
[17] Sterling P, Eyer J, Fisher S, Reason J. Allostasis: a new paradigm to explain arousal pathology. Handbook of life stress cognition and health. New York: John Wiley and Sons; 1988.
[18] Jakicic JM, Marcus BH, Gallagher KI, Napolitano M, Lang W. Effect of exercise duration and intensity on weight loss in overweight, sedentary women: a randomized trial. J Am Med Assoc 2003;290:1323–30.
[19] Imai K, Sato H, Hori M, Kusuoka H, Ozaki H, Yokoyama H, et al. Vagally mediated heart rate recovery after exercise is accelerated in athletes but blunted in patients with chronic heart failure. J Am Coll Cardiol 1994;24: 1529–35.
[20] Myers J, Hadley D, Oswald U, Bruner K, Kottman W, Hsu L, et al. Effects of exercise training on heart rate recovery in patients with chronic heart failure. Am Heart J 2007;153:1056–63.
[21] Vijg J. Introduction: the coming of age of the genome. Aging of the genome: the dual role of DNA in life and death, vol. 1. New York: Oxford University Press; 2007.
[22] McArdle WD, Katch FI, Katch VL. Exercise physiology: energy, nutrition, and human performance. Philadelphia: Lippincott Williams and Wilkins; 2006.
[23] McEwen BS. Protective and damaging effects of stress mediators. N Engl J Med 1998;338:171–9.
[24] McEwen BS, Stellar E. Stress and the individual. Mechanisms leading to disease. Arch Intern Med 1993;153:2093–101.
[25] Boyar RM, Hellman LD, Roffwarg H, Katz J, Zumoff B, O'Connor J, et al. Cortisol secretion and metabolism in anorexia nervosa. N Engl J Med 1977;296:190–3.
[26] Sies H. Oxidative stress: introductory remarks. Oxidative stress. Lodon: Academic Press; 1985.
[27] Jones DP. Redefining oxidative stress. Antioxid Redox Signal 2006;8:1865–79.
[28] Allen DG, Lamb GD, Westerblad H. Skeletal muscle fatigue: cellular mechanisms. Physiol Rev 2008;88:287–332.
[29] Jackson MJ. Free radicals generated by contracting muscle: by-products of metabolism or key regulators of muscle function? Free Radic Biol Med 2008;44:132–41.
[30] Sachdev S, Davies KJ. Production, detection, and adaptive responses to free radicals in exercise. Free Radic Biol Med 2008;44:215–23.
[31] Droge W. Free radicals in the physiological control of cell function. Physiol Rev 2002;82:47–95.
[32] Jackson MJ. Reactive oxygen species and redox-regulation of skeletal muscle adaptations to exercise. Philos Trans R Soc Lond B Biol Sci 2005;360:2285–91.
[33] Rhee SG. Cell signaling. H_2O_2, a necessary evil for cell signaling. Science 2006;312:1882–3.
[34] Davies KJ, Packer L, Brooks GA. Biochemical adaptation of mitochondria, muscle, and whole-animal respiration to endurance training. Arch Biochem Biophys 1981;209:539–54.
[35] Irrcher I, Adhihetty PJ, Joseph AM, Ljubicic V, Hood DA. Regulation of mitochondrial biogenesis in muscle by endurance exercise. Sports Med 2003;33:783–93.
[36] Menshikova EV, Ritov VB, Ferrell RE, Azuma K, Goodpaster BH, Kelley DE. Characteristics of skeletal muscle mitochondrial biogenesis induced by moderate-intensity exercise and weight loss in obesity. J Appl Physiol 2007;103:21–7.
[37] Nisoli E, Clementi E, Paolucci C, Cozzi V, Tonello C, Sciorati C, et al. Mitochondrial biogenesis in mammals: the role of endogenous nitric oxide. Science 2003;299:896–9.
[38] Starnes JW, Barnes BD, Olsen ME. Exercise training decreases rat heart mitochondria free radical generation but does not prevent Ca^{2+}-induced dysfunction. J Appl Physiol 2007;102:1793–8.
[39] Guarente L. Mitochondria – a nexus for aging, calorie restriction, and sirtuins? Cell 2008;132:171–6.
[40] Wallace DC. A mitochondrial paradigm of metabolic and degenerative diseases, aging, and cancer: a dawn for evolutionary medicine. Annu Rev Genet 2005;39:359–407.
[41] Sharpe PC, Duly EB, MacAuley D, McCrum EE, Mulholland C, Stott G, et al. Total radical trapping antioxidant potential (TRAP) and exercise. QJM 1996;89:223–8.
[42] Ji LL. Modulation of skeletal muscle antioxidant defense by exercise: role of redox signaling. Free Radic Biol Med 2008;44:142–52.
[43] Radak Z, Kumagai S, Taylor AW, Naito H, Goto S. Effects of exercise on brain function: role of free radicals. Appl Physiol Nutr Metab 2007;32: 942–6.
[44] Wakshlag JJ, Kallfelz FA, Barr SC, Ordway G, Haley NJ, Flaherty CE, et al. Effects of exercise on canine skeletal muscle proteolysis: an investigation of the ubiquitin–proteasome pathway and other metabolic markers. Vet Ther 2002;3:215–25.
[45] Jones NL, Killian KJ. Exercise limitation in health and disease. N Engl J Med 2000;343:632–41.
[46] Mortensen SP, Damsgaard R, Dawson EA, Secher NH, Gonzalez-Alonso J. Restrictions in systemic and locomotor skeletal muscle perfusion, oxygen supply and VO_2 during high-intensity whole-body exercise in humans. J Physiol 2008;586:2621–35.
[47] Gaibazzi N. Heart rate recovery after exercise is not demonstrated as a predictor of mortality: maybe after treadmill-exercise. J Am Coll Cardiol 2004;43:925.
[48] Gaibazzi N, Petrucci N, Ziacchi V. One-minute heart rate recovery after cycloergometer exercise testing as a predictor of mortality in a large cohort of exercise test candidates: substantial differences with the treadmill-derived parameter. Ital Heart J 2004;5:183–8.
[49] Cole CR, Blackstone EH, Pashkow FJ, Snader CE, Lauer MS. Heart-rate recovery immediately after exercise as a predictor of mortality. N Engl J Med 1999;341:1351–7.
[50] Nishime EO, Cole CR, Blackstone EH, Pashkow FJ, Lauer MS. Heart rate recovery and treadmill exercise score as predictors of mortality in patients referred for exercise ECG. J Am Med Assoc 2000;284:1392–8.
[51] Church TS, Earnest CP, Skinner JS, Blair SN. Effects of different doses of physical activity on cardiorespiratory fitness among sedentary, overweight or obese postmenopausal women with elevated blood pressure: a randomized controlled trial. J Am Med Assoc 2007;297:2081–91.

[52] Myers J, Prakash M, Froelicher V, Do D, Partington S, Atwood JE. Exercise capacity and mortality among men referred for exercise testing. N Engl J Med 2002;346:793–801.
[53] Carnethon MR, Gulati M, Greenland P. Prevalence and cardiovascular disease correlates of low cardiorespiratory fitness in adolescents and adults. J Am Med Assoc 2005;294:2981–8.
[54] Lee IM. Dose-response relation between physical activity and fitness: even a little is good; more is better. J Am Med Assoc 2007;297:2137–9.
[55] Ding YH, Luan XD, Li J, Rafols JA, Guthinkonda M, Diaz FG, et al. Exercise-induced overexpression of angiogenic factors and reduction of ischemia/reperfusion injury in stroke. Curr Neurovasc Res 2004;1: 411–20.
[56] Maeda S, Tanabe T, Otsuki T, Sugawara J, Iemitsu M, Miyauchi T, et al. Moderate regular exercise increases basal production of nitric oxide in elderly women. Hypertens Res 2004;27:947–53.
[57] Kasch FW, Boyer JL, Schmidt PK, Wells RH, Wallace JP, Verity LS, et al. Ageing of the cardiovascular system during 33 years of aerobic exercise. Age Ageing 1999;28:531–6.
[58] Zanesco A, Antunes E. Effects of exercise training on the cardiovascular system: pharmacological approaches. Pharmacol Ther 2007;114:307–17.
[59] Dracup K, Baker DW, Dunbar SB, Dacey RA, Brooks NH, Johnson JC, et al. Management of heart failure. II. Counseling, education, and lifestyle modifications. J Am Med Assoc 1994;272:1442–6.
[60] Lee IM, Rexrode KM, Cook NR, Manson JE, Buring JE. Physical activity coronary heart disease in women: is "no pain no gain" passe? J Am Med Assoc 2001;285:1447–54.
[61] Leon AS, Connett J, Jacobs Jr DR. Leisure-time physical activity levels and risk of coronary heart disease and death. The multiple risk factor intervention trial. J Am Med Assoc 1987;258:2388–95.
[62] Stewart KJ. Exercise training and the cardiovascular consequences of type 2 diabetes and hypertension: plausible mechanisms for improving cardiovascular health. J Am Med Assoc 2002;288:1622–31.
[63] Goel R, Majeed F, Vogel R, Corretti MC, Weir M, Mangano C, et al. Exercise-induced hypertension, endothelial dysfunction, and coronary artery disease in a marathon runner. Am J Cardiol 2007;99:743–4.
[64] Cechetti F, Rhod A, Simao F, Santin K, Salbego C, Netto CA, et al. Effect of treadmill exercise on cell damage in rat hippocampal slices submitted to oxygen and glucose deprivation. Brain Res 2007;1157:121–5.
[65] Scopel D, Fochesatto C, Cimarosti H, Rabbo M, Belló Klein A, Salbego C, et al. Exercise intensity influences cell injury in rat hippocampal slices exposed to oxygen and glucose deprivation. Brain Res Bull 2006;71:155–9.
[66] Blair SN, Kohl III HW, Barlow CE, Paffenbarger Jr RS, Gibbons LW, Macera CA. Changes in physical fitness and all-cause mortality. A prospective study of healthy and unhealthy men. J Am Med Assoc 1995;273:1093–8.
[67] Dhabhar FS, McEwen BS. Stress-induced enhancement of antigen-specific cell-mediated immunity. J Immunol 1996;156:2608–15.
[68] Dhabhar FS, Viswanathan K. Short-term stress experienced at time of immunization induces a long-lasting increase in immunologic memory. Am J Physiol Regul Integr Comp Physiol 2005;289:R738–44.
[69] Dhabhar FS, McEwen BS. Enhancing versus suppressive effects of stress hormones on skin immune function. Proc Natl Acad Sci USA 1999;96:1059–64.
[70] Friedrich MJ. Exercise may boost aging immune system. J Am Med Assoc 2008;299:160–1.
[71] Brolinson PG, Elliott D. Exercise and the immune system. Clin Sports Med 2007;26:311–9.
[72] Nieman DC. Exercise, infection, and immunity. Int J Sports Med 1994;15(Suppl. 3):S131–41.
[73] Keylock KT, Vieira VJ, Wallig MA, DiPietro LA, Schrementi M, Woods JA. Exercise accelerates cutaneous wound healing and decreases wound inflammation in aged mice. Am J Physiol Regul Integr Comp Physiol 2008;294:R179–84.
[74] Lowder T, Padgett DA, Woods JA. Moderate exercise protects mice from death due to influenza virus. Brain Behav Immun 2005;19:377–80.
[75] Lowder T, Padgett DA, Woods JA. Moderate exercise early after influenza virus infection reduces the Th1 inflammatory response in lungs of mice. Exerc Immunol Rev 2006;12:97–111.
[76] Gleeson M. Immune function in sport and exercise. J Appl Physiol 2007;103:693–9.
[77] Nieman DC. Marathon training and immune function. Sports Med 2007;37:412–5.
[78] Kruger K, Mooren FC. T cell homing and exercise. Exerc Immunol Rev 2007;13:37–54.
[79] Donovan DC, Jackson CA, Colahan PT, Norton NN, Clapper JL, Moore JN, et al. Assessment of exercise-induced alterations in neutrophil function in horses. Am J Vet Res 2007;68:1198–204.
[80] Gavrieli R, shlagi-Amiri T, Eliakim A, Nemet D, Zigel L, Berger-Achituv S, et al. The effect of aerobic exercise on neutrophil functions. Med Sci Sports Exerc 2008;12.
[81] Tuan TC, Hsu TG, Fong MC, Hsu CF, Tsai KK, Lee CY, et al. Deleterious effects of short-term, high-intensity exercise on immune function: evidence from leucocyte mitochondrial alterations and apoptosis. Br J Sports Med 2008;42:11–5.