

Exercise Physiology and Its Effect on Body Systems

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Abstract: Exercise produces significant increases in the body's demand for energy compared to its resting state. While at rest, the autonomic nervous system tends to favor a parasympathetic tone, which reduces the respiratory and heart rate. The sympathetic nervous system is activated during exercise, resulting in an integrated response that helps maintain an appropriate level of homeostasis to meet the increased demand in cellular metabolism.

Keywords: Exercise, Physiology, Body Systems.

Introduction:

Exercise is a skeletal muscle voluntary action for recreational, sporting, or occupational activities (1). It is also defined as a planned, structured, and repetitive physical activity aimed at improving or maintaining one or more components of physical fitness (2).

In general, physical exercises are grouped into three types, depending on the overall effect they have on the human body:

Aerobic exercise: The American College of Sports Medicine (ACSM) defines aerobic exercise as any activity that uses large muscle groups, can be maintained continuously and is rhythmic in nature and causes the body to use more oxygen than it would while resting (3). The goal of aerobic exercise is to increase cardiovascular endurance. Examples of aerobic exercise include running, cycling, swimming, brisk walking, skipping rope, rowing, hiking, dancing, playing tennis, continuous training, and long-distance running (4). Aerobic exercise consists of any form of physical activity that involves predominantly aerobic metabolism to generate adenosine triphosphate (ATP) from oxidative phosphorylation (i.e. brisk walking, jogging, swimming, cycling) (5).

Anaerobic exercise: Anaerobic exercise has been defined by the ACSM as intense physical activity of very short duration, fueled by the energy sources within the contracting muscles and independent of the use of inhaled oxygen as an energy source (6).

Anaerobic exercise, which includes strength and resistance training, can firm, strengthen, and increase muscle mass, as well as improve bone density, balance, and coordination. Examples of strength exercises are push-ups, pull-ups, lunges, squats, bench press (7).

➤ **Flexibility exercises:**

Flexibility exercise training programs are those involving movements of a joint or a series of joints, through complete range of motion, thus targeting major muscle-tendon units (8).

Another classification:

Physical exercise can be divided into two modes. One mode is open-skill exercise (OSE), which requires players to react in dynamic, unpredictable, and externally paced environments (e.g., basketball, football and tennis) (9). This exercise mode is accompanied by greater cognitive and executive loadings (10). The second mode is closed-skill exercise (CSE), which involves a relatively consistent, controllable, and self-adjustable environment (11), OSEs are predominantly perceptual and externally paced. In contrast, CSEs (e.g., running, swimming, cycling, golf, or archery) are performed in a relatively stable and predictable environment in which

motor movements follow set patterns, CSE skills tend to be self-paced, as there are fewer cognitive demands and decision-making requirements (12).

Furthermore, sports are classified by the level of intensity (low, medium, or high) of dynamic and static exercise required to perform that sport during competition (13). “Dynamic” refers to endurance-type activities requiring regular contraction of large muscle groups and characterized by the relative percentage of maximal aerobic power (maximal oxygen uptake) required to perform that activity. “Static” refers to the strength type activities requiring sustained muscle contractions performed to overcome resistance and can be characterized by the relative percentage of a maximal voluntary contraction (14).

Metabolism of physical exercise:

Physical activity is defined as any body movement resulting from the contraction of skeletal muscle that raises energy expenditure above the resting metabolic rate of ~ 3.5 mL O₂/min/kg, or 1 metabolic equivalent (15). Physical activity/exercise requires a concomitant increase in pulmonary oxygen uptake, circulatory oxygen transport, and oxygen utilization at the cellular level, which is required to support the higher metabolic demands of the body (16).

For muscles to contract, the body must hydrolyze adenosine triphosphate (ATP) to yield energy. The ways muscles maintain ATP levels is contingent upon the conditions of the body. Muscles can utilize glucose or glycogen in both aerobic or anaerobic manners. The glycolytic energy system tends to lead to lactate accumulation and subsequent pH decrease in muscle tissue, especially in the anaerobic setting (17).

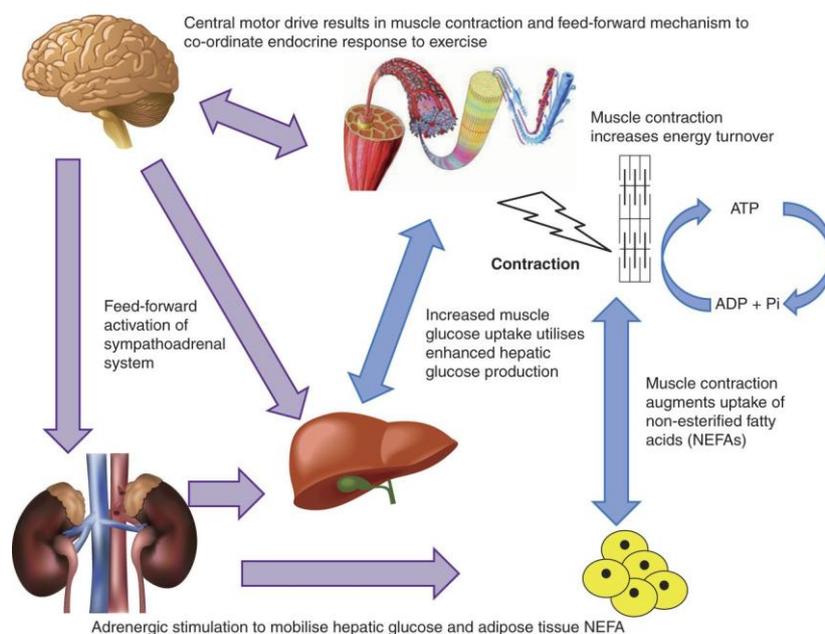


Fig 1: The activation of the CNS to initiate muscle contraction leads to an integrated response from the sympathoadrenal, cardiovascular, hepatic and adipocyte systems to mobilize and deliver oxygen and substrate to maintain energy turnover (18).

Benefits and importance of PE:

According to 2020 World Health Organization (WHO) guidelines, it is stated that 150–300 min of moderate intensity, or 75–150 min of vigorous-intensity physical activity, or some equivalent combination of moderate intensity and vigorous-intensity aerobic physical activity should be undertaken per week (19).

Exercise has demonstrated many health benefits including:

➤ Benefits of exercise in tissue regeneration:

Importantly, Adult cardiomyocytes physiologically increased in both size and proliferation rate in response to exercise in mouse models. Meanwhile, it has been identified that endurance exercise increases birth

of new cardiomyocytes in adult mice (~4.6-fold) based on incorporation of ¹⁵N-thymidine by multi-isotope imaging mass spectrometry (20). Therefore, exercise training provides a new intervention for enhancing the proliferation of cardiomyocyte. Also, exercise induces physiological hypertrophy of left ventricle and reduction of myocardial infarction area by promoting the proliferation of cardiomyocytes (21).

It has been uncovered that moderate exercise training enhances muscle regeneration after injury, as skeletal muscle mass recovery after extensive injury can be improved by contractile activity. In general, it has been widely convinced that the local adaptations of endurance exercise in skeletal muscle mostly focus on increased mitochondrial biogenesis and capillary density, which aids in the body's ability to transport and use oxygen to generate energy and therefore delay the onset of muscle fatigue during prolonged aerobic performance (22). In addition, it has been also shown that endurance exercise training promotes maintenance of muscle mass and recovery after injury (23). While in rat models of notexin-induced soleus muscle degeneration, running exercise ensured the full recovery of muscle mass and muscle cross sectional area during muscle regeneration, and made muscle recovery much faster than sedentary group (24).

It has been confirmed that the hippocampus contains neural stem and progenitor cells that continue to generate new neurons, called adult hippocampal neurogenesis (AHN), which almost continues across the lifespan, though declining with aging (25). Voluntary exercise promotes hippocampal neurogenesis and prevents age-related decline in cell-proliferation in this brain structure (26). Furthermore, it has also been revealed that exercise induces volumetric retention in the left hippocampus in humans, implying endurance exercise interventions are useful for preventing age-related hippocampal deterioration (27).

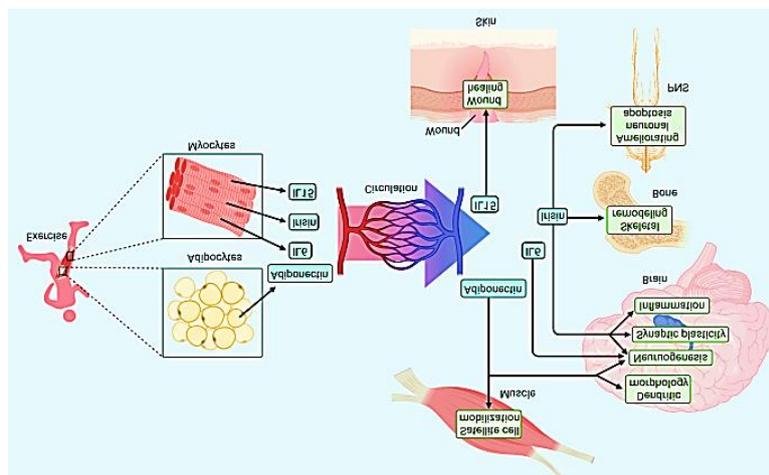


Fig 2 A: Benefits of exercise-induced tissue regeneration (21).

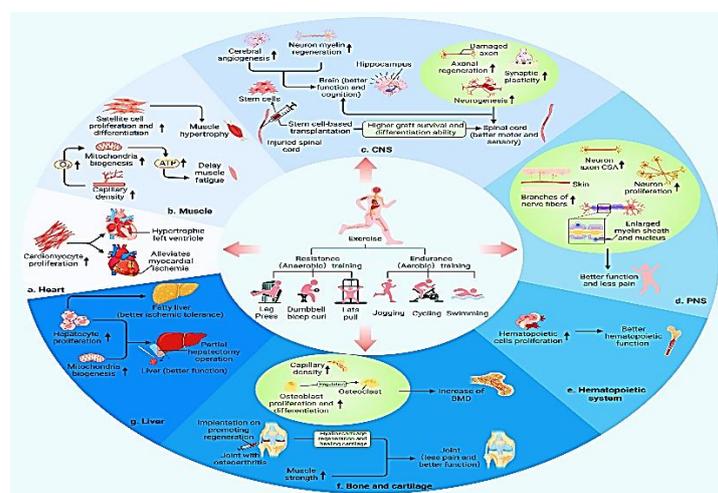


Fig 2 B: Benefits of exercise-induced tissue regeneration (21).

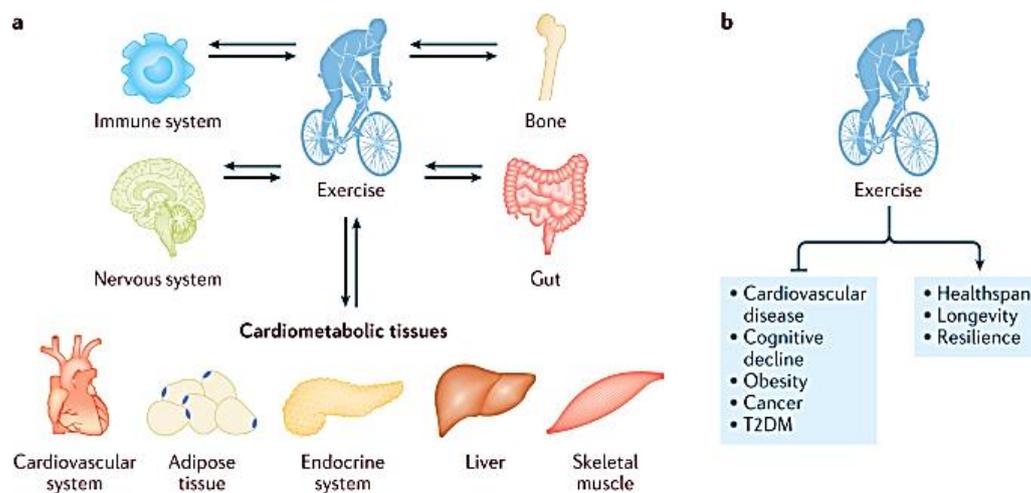
Exercise physiology and its effect on body systems:

Fig 3: The systemic effects of exercise. a: Organs and tissues that can serve as source of exerkinines and that are directly affected by exercise. B: Exercise results in profound health benefits, including reductions in the presence or severity of certain diseases, as well as increases in health span, longevity and resilience. T2DM, type 2 diabetes mellitus (28)

Exercise physiology is the study of how the body's functions are altered when we are physically active, since exercise presents a challenge to homeostasis. Physical exercise induces a coordinated response of multiple organ systems (29)

Exercise represents a major challenge to whole-body homeostasis, and in an attempt to meet this challenge, myriad acute and adaptive responses take place at the cellular and systemic levels that function to minimize these widespread disruptions (30).

The study of exercise and sport physiology involves learning the concepts associated with two distinct exercise patterns. how the body responds to the acute stress of a single bout of exercise or physical activity such as running on a treadmill for an hour or lifting weights, and how the body adapts to the chronic stress of repeated bouts of exercise sometimes referred to as chronic adaptation or training effects (13).

➤ **Cardiovascular system:**

When exercise is initiated, there is a parallel activation of the motor cortex and the cardiovascular control centres of the medulla. Thus, at the same time muscles are being stimulated to contract, a coordinated autonomic response is initiated in the medulla, a phenomenon referred to as central command. The autonomic response is composed of an immediate withdrawal of parasympathetic outflow to the heart followed by increased sympathetic activation of the heart and blood vessels (31). The net result is an immediate rise in HR, which contributes to the rise in cardiac output which increases from ~5 L/min at rest to ~25 L/min during maximal exercise, a fivefold change (32). Stroke volume also increases during exercise. Neural mechanisms responsible for these adjustments include central command, the exercise pressor reflex, and arterial and cardiopulmonary baroreflexes (33).

The circulatory system plays a critical role in maintaining homeostasis during exercise. Exercise training induces vascular adaptations to several tissues (34). These adaptations are mediated through increased expression of vascular endothelial nitric oxide synthase (eNOS). Exercise increases the intensity of physiological shear stress, inducing the shear stress-dependent activity of c-Src (non-receptor tyrosine kinase) in endothelial cells and increasing expression of eNOS (35). In the vascular endothelium, eNOS catalyzes the production of nitric oxide (NO) which causes vasodilation, inhibits platelet aggregation and prevents leukocyte adhesion to vessel walls, thus reducing the onset of atherosclerosis, thrombosis, ischemia, or other cardiac events (36). It has been hypothesized that the increase in NO production after exercise upregulates pro-angiogenic factors, particularly vascular endothelial growth factor (VEGF) (37). In the heart, the increase in vascularization protects against vascular stress and reduces the likelihood of a cardiac disease (38).

Cardiovascular adaptations which occur over days and months include increases in maximal cardiac output (Q max) due to large increase in stroke volume, which results from two factors. End-diastolic volume increases with training because blood volume increases, and venous return is more efficient. In addition, end-systolic volume is reduced with training because the stronger myocardium produces a stronger contraction, ejecting more blood. Resting heart rate can be reduced to 50 beats/min or less(13).

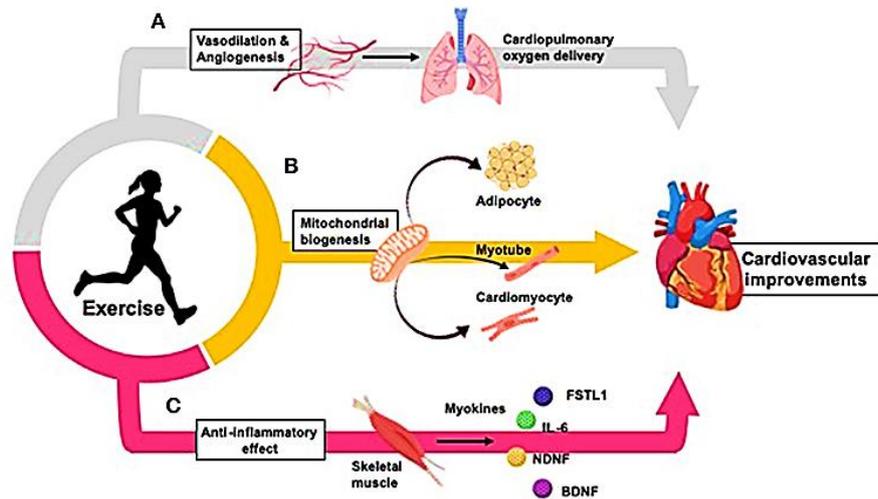


Fig 4: Exercise improves cardiovascular health by inducing changes in oxygen delivery, vasculature, peripheral tissues, and inflammation (39). (A) Exercise improves oxygen delivery throughout the body through promotion of vasodilation and angiogenesis (34). (B) Exercise increases mitochondrial biogenesis in adipocytes (40), skeletal muscle myotubes (41), and cardiomyocytes (42). (C) Exercise causes a long-term anti-inflammatory effect “which is inversely related to the increased inflammation typically seen in CVD and obesity” (43). Myokines released from skeletal muscle during physical exercise partially mediate these anti-inflammatory effects and promote inter-tissue cross talk to mediate further cardiovascular benefits (44).

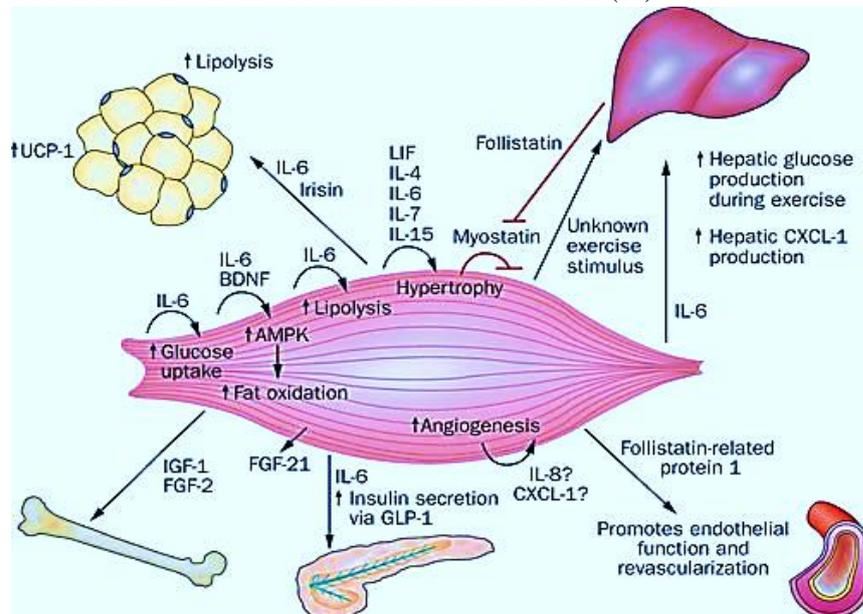


Fig 5: Skeletal muscle is a secretory organ (45)

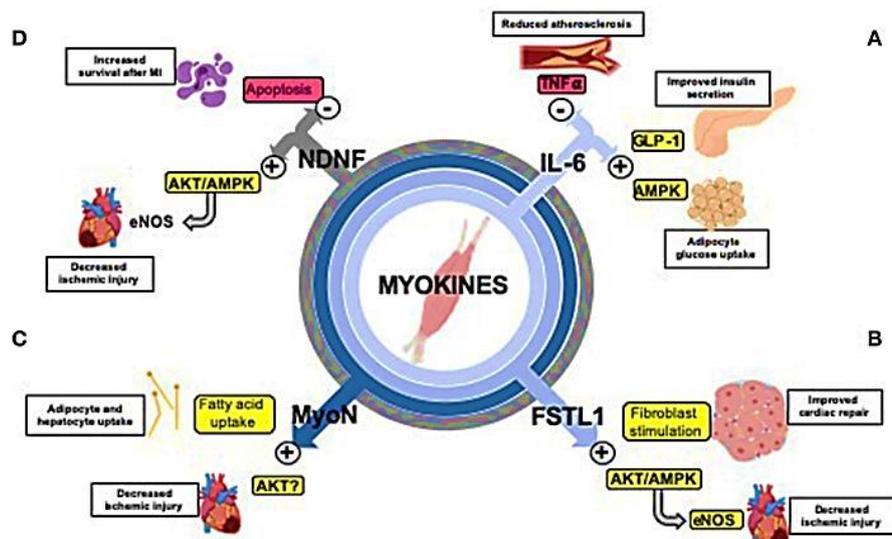


Fig. 6: Exercise-induced myokines mediate organ cross-talk and improve cardiometabolic health (39). (A) The myokine IL-6 inhibits TNF- α (46), reducing inflammation and protecting against the formation of atherosclerosis (47); stimulates GLP-1 secretion causing improved insulin secretion (48); increases lipolysis and fatty acid oxidation in adipose tissue (49) and increases glucose uptake through the AMPK signaling pathway (50). (B) Follistatin related protein 1(Fstl1) decreases ischemic injury size through activation of the Akt/AMPK pathway (activating eNOS and enhancing revascularization) (51) and early fibroblast stimulation (which aids in repair after ischemia-reperfusion) (52). (C) Myonectin (MyoN) increases fatty acid uptake in adipocytes and hepatocytes (53), and promotes protects against ischemic injury in the heart, possibly through Akt activation (54). (D) Neuron-derived neurotrophic factor (NDNF) improves survival after myocardial infarction (MI) by reducing apoptosis (55) through stimulation of the Akt/AMPK/eNOS pathway (enhancing revascularization) (56).

To accommodate the increased metabolic activity in skeletal muscle, the circulatory system must properly control the transport of oxygen (O₂) and carbon dioxide (CO₂), as well as help to buffer the pH level of active tissues (57). This action is accomplished by increasing cardiac output (increased heart rate and stroke volume) and modulating microvascular circulation. Also, the action of local vaso-mediator s such as NO from endothelial cells helps to ensure adequate blood flow (4).

Blood flow is preferentially shunted away from the gastrointestinal and renal systems toward active muscles through selective constriction and dilation of capillary beds. This increased skeletal muscle blood flow provides O₂ while facilitating the removal of CO₂ (58). The increased metabolic activity increases CO₂ concentrations and shifts the pH to the left, which further facilities red blood cells (RBCs) to extract CO₂ and release O₂ (59).

On a mechanical level, RBCs that have been in circulation for a long time tend to be less compliant than younger RBCs, meaning that during exercise, older RBCs can be haemolysed intravascularly when passing through capillaries in contracted muscles. This activity leads to an average decrease in RBC age since the younger RBCs have more favourable rheological properties (60).

Younger RBCs also have increased oxygen release compared to older RBCs. Exercise increases erythropoietin levels, which causes an increase in RBC production. Both previous factors improve the oxygen supply during exercise. Over time, vascularization in muscles also improves, further improving gas exchange and metabolic capacity (17).

➤ Nervous system:

A growing body of research has investigated the relationship between physical activity and cognition with an eye towards understanding how societal trends for sedentary behaviour might negatively impact not only physical health, but cognitive health and function as well (61).

Regular physical exercise has the potential to improve several aspects of cognitive function over a lifetime, including attention, processing speed, working memory, and executive function (62). This has been attributed to enhanced cerebral blood flow, oxygen and nutrient delivery to neurons and clearance of metabolic waste (63). Another plausible mechanism for the protective effect of exercise on neuron survival and enhanced cognitive function is through the induction of neurotrophins including brain-derived neurotrophic factor (BDNF) Which is expressed extensively throughout cortical and subcortical regions such as midbrain, cerebellum and striatum, its levels are highest in the hippocampus (64).

BDNF is a member of the neurotrophin family of factors that supports neural survival, growth, and synaptic plasticity and that is highly concentrated in the hippocampus (65). BDNF has a key role in neurogenesis and supports neural stem cells through tropomyosin receptor kinase B (TrkB) activation (66).

Aerobic exercise has been shown to increase neurogenesis in the rat and mouse dentate gyrus (67) and the rat hypothalamus (68). It also increases brain volume in older adults (69).

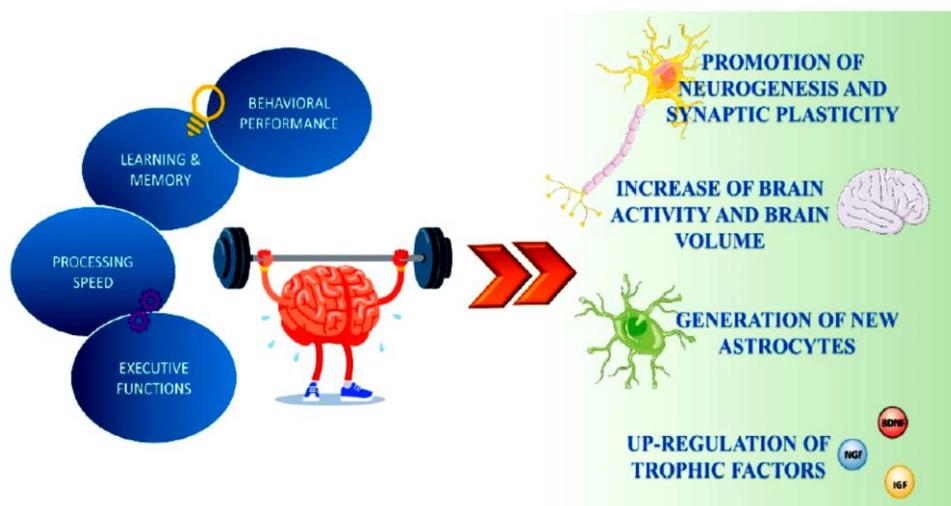


Fig 7: Exercise-mediated effects on brain functions. Exercise enhances cognitive performance by promoting neuronal plasticity, neurogenesis, and astrogenesis, and the production and release of neurotrophic factors (70).

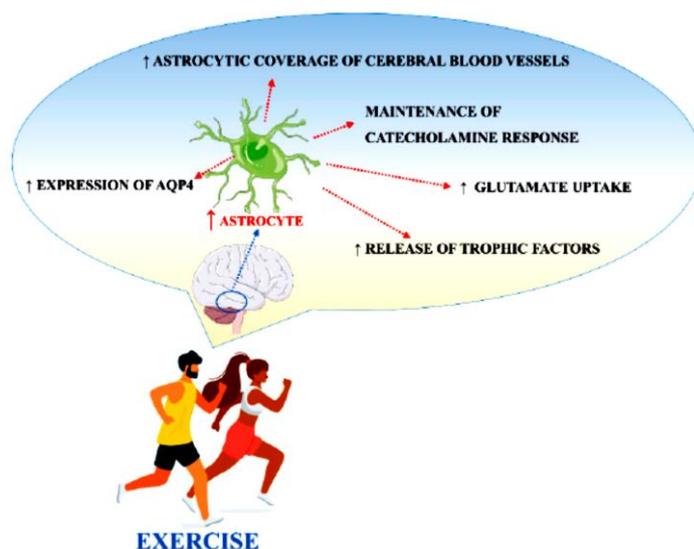


Fig 8: Main processes involved in exercise-induced modulation of astrocyte activities

➤ **Musculoskeletal System:**

Resistance and endurance exercise training have been shown to improve muscle mass and strength, and improve performance capacity (71). Resistance exercise results in a mild stimulation in rates of muscle protein breakdown but a greater stimulation of the rates of muscle protein synthesis (72). The biological basis of exercise-induced phenotypic changes in skeletal muscle is that exercise stimulates repeated increases in mRNA expression resulting in enhanced translation of the protein and ultimately adaptive changes in muscle protein content (73).

Bouts of exercise rapidly sensitize skeletal muscle to hormones and nutrients. A single (or 'acute') exercise session directly increases skeletal muscle transport of amino acids (74) and glucose (75). These effects appear somewhat specific to the contracted musculature, and they enhance postprandial muscle protein synthesis (76) and insulin-stimulated glucose disposal (77) in the recovery period after exercise. Consistent exercise training (over weeks, months and years) further augments skeletal muscle mass (78), peripheral insulin-sensitivity(79), maximal oxygen consumption (VO_{2max}) and strength (80).

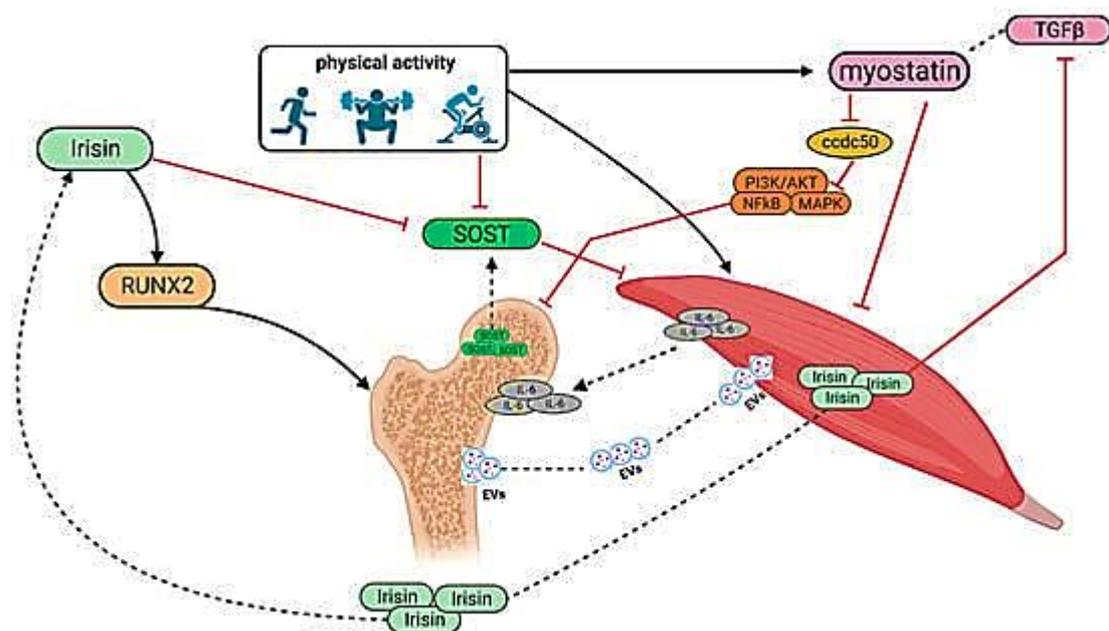
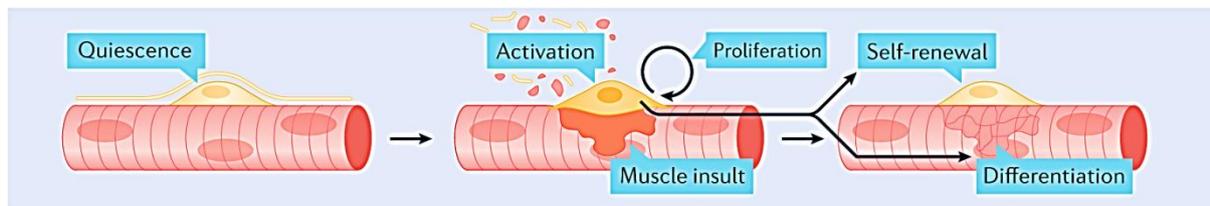


Fig 9: Physical activity stimulates the production and secretion of myokines such as irisin, IL-6 and myostatin which affect bone and muscle homeostasis. In particular, myostatin and irisin have an opposite action in bone–muscle metabolism: physical activity primarily stimulates the release of myostatin, which is part of the TGFβ-superfamily, induces osteoclastogenesis downregulating *Ccdc50* and protein degradation in skeletal muscle; subsequently, physical activity promotes the release of irisin which stimulates osteogenic and skeletal differentiation, inhibiting TGFβ-signaling and the *SOST* gene; the latter is also inhibited by the effect of physical activity. The production of IL-6 induced by physical activity promotes the differentiation of satellite cells and osteoblast differentiation. Extracellular vesicles mediated the bone and muscle crosstalk as well (81).

- **Role of Satellite cells:**

Satellite cells are myogenic stem cells located surrounding myofibers between the sarcolemma and basal lamina, which contribute to muscle growth and repair by a quick fusion of their nuclei into the cytoplasm of myofibers (82). Normally, in resting skeletal muscles, satellite cells are believed generally to be in a non-proliferative, quiescent state. Quiescent satellite cells can be identified using electron microscopy, Paired box transcription factor 7 (*Pax7*) is a commonly used biomarker to identify satellite cells in muscle tissues in animal and human models (83). While several studies have demonstrated increases in *Pax7* cell content in exercised human skeletal muscle (84).



c Transcriptional and post-transcriptional regulation

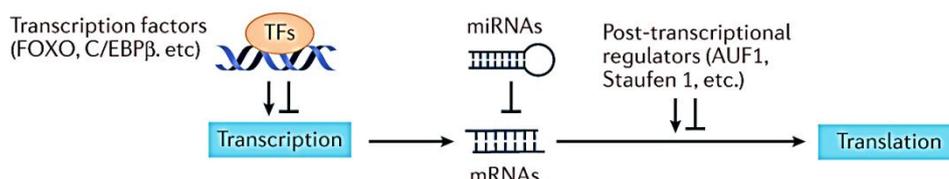


Fig 10: basic mechanisms controlling satellite cell quiescence and activation (85)

➤ **Respiratory System:**

The onset of exercise is accompanied by an immediate increase in ventilation which is proportional to the increase in CO₂ production (\dot{V}_{CO_2}) and O₂ consumption (\dot{V}_{O_2}) (86). In fact, like the heart rate response, immediately before exercise begins, ventilation increases, this increase obviously cannot be due to anything resulting from the exercise. Therefore, it is most likely due to stimulation from the cerebral cortex resulting from anticipation of the ensuing exercise bout (87).

Because of its rapid onset, this initial respiratory adjustment to the demands of exercise is undoubtedly neural in nature, mediated by respiratory control centers in the brain (central command), This neural response is probably responsible for the initial actions of the various physiological systems (88).

The respiratory system works in junction with the cardiovascular system. The pulmonary circuit receives almost all of the cardiac output. In response to the increased cardiac output, perfusion increases in the apex of each lung, increasing the available surface area for gas exchange (decreased alveolar dead space) (13). Recently, it is proved that Performing standard and defined exercise exercises for patients with the new coronavirus improves the physical activity and respiratory function of patients of COVID-19 (89)

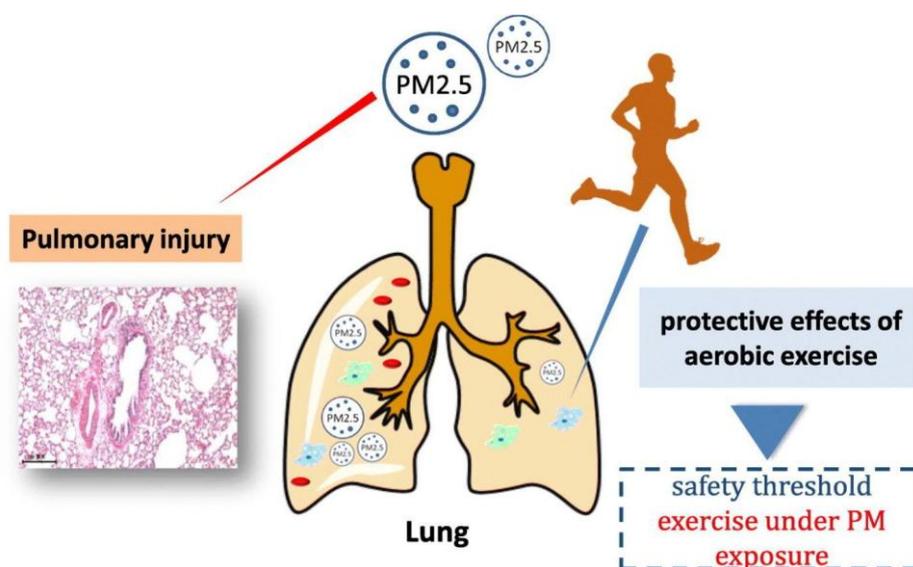


Fig 11: Effect of aerobic exercise and different levels of fine particulate matter (PM_{2.5}) on pulmonary response in Wistar rats (90)

➤ **Endocrine System:**

The hormonal changes to exercise occur for various physiological reasons: (a) to induce cardiovascular adjustments, (b) to activate energy production pathways and mobilize energy substrates, (c) to facilitate maintenance of adequate hydration, and (d) to some extent as part of stress reactivity (91).

Plasma levels of cortisol, epinephrine, norepinephrine, and dopamine increase with maximal exercise and return to baseline after rest. The increase in levels is consistent with the increase in the sympathetic nervous system activation of the body (59).

Growth hormone is released by the pituitary gland to enhance bone and tissue growth. Insulin sensitivity increases after long-term exercise. Testosterone levels also increase, leading to enhanced growth, libido, and mood (29).

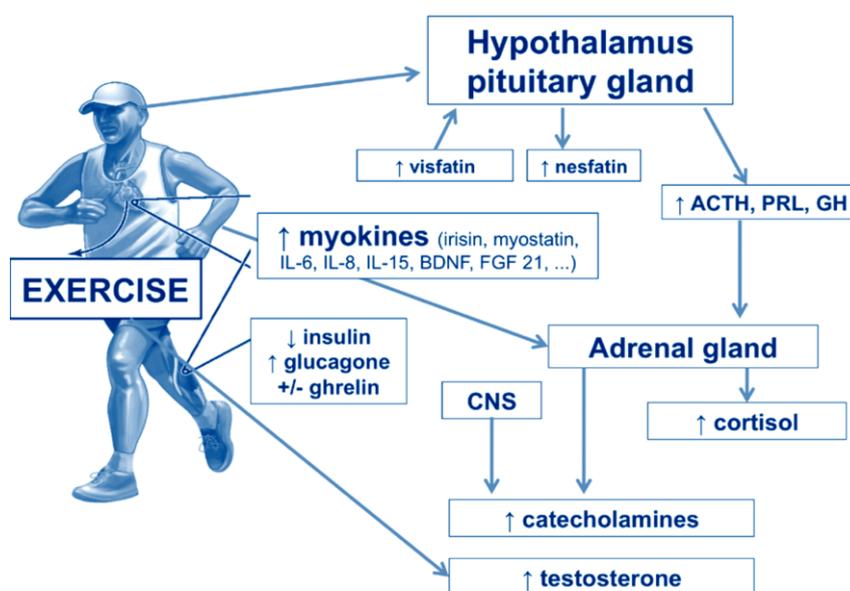


Fig. 12: Exercise induces a rise in many hormones and peptides. ACTH - adrenocorticotrophic hormone; GH - growth hormone; PRL - prolactin; CNS - central nervous system; IL - interleukin; BDNF - brain-derived neurotrophic hormone; FGF 21 - fibroblast growth factor 21- (92)

➤ **Anti-Inflammatory effects of exercise:**

Clinical studies demonstrated that persistent systemic inflammation is a common feature in many neurological disorders, including depression, Alzheimer's Disease (AD), Parkinson's Disease (PD), and Huntington's disease (HD) (93). Chronic systemic inflammation predisposes individuals to insulin resistance, endothelial cell dysfunction, and atherosclerosis and exacerbates neuroinflammation, thereby contributing to neuropathological changes in the brain (94).

The direct effect of exercise on inflammation can be varied depending on the different pathophysiological conditions of individuals, since both proinflammatory cytokines and anti-inflammatory cytokines were increased immediately in the circulation after exercise (95). Although there was previously a concern that exercise might aggravate symptoms of diseases like traumatic brain injury (TBI), stroke, and multiple sclerosis by exaggerating inflammation (96), exercise has now been suggested as a protective intervention to improve symptoms and reduce overall inflammatory conditions of those diseases if performed during the appropriate time.

Animal studies demonstrated that exercise could directly improve the immune condition of the brain by increasing the levels of IL-10 in the hippocampus of aged rats (97), and by reducing the levels of IL-1 β in the brain of a β -amyloid-induced mouse model of AD (98). Furthermore, physical exercise has also been shown to prevent brain inflammation in stroke (99).

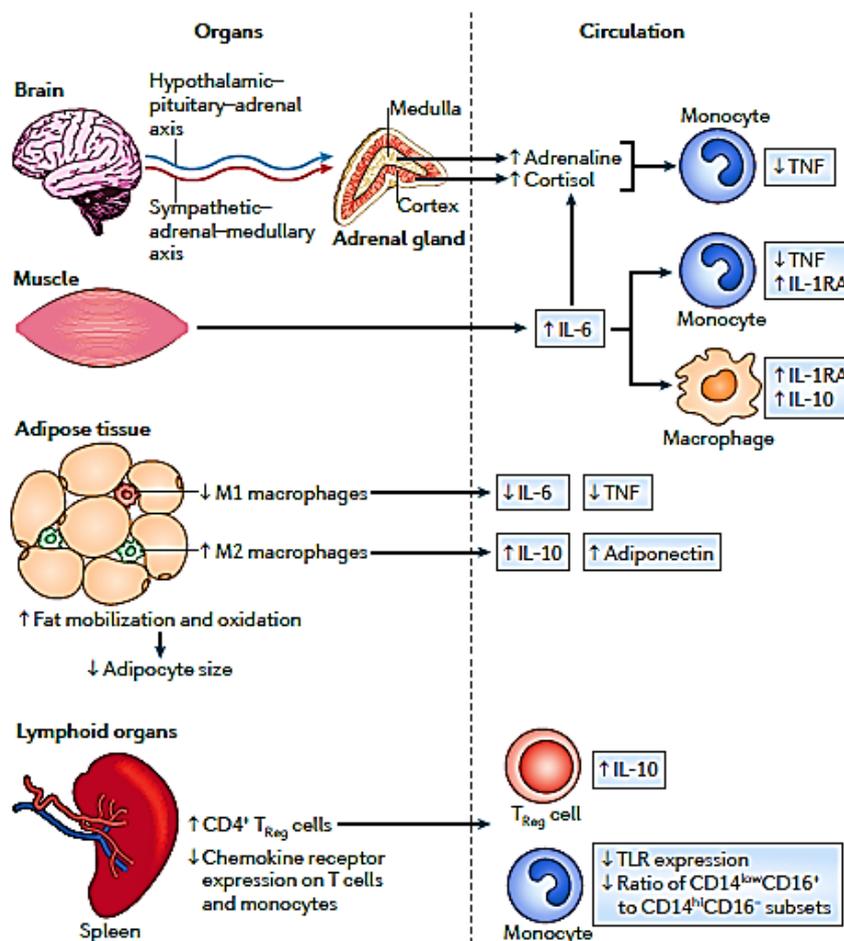


Fig 13: Potential mechanisms contributing to the anti-inflammatory effects of exercise (100).

References:

- [1] Hawley, J. A., Hargreaves, M., Joyner, M. J., & Zierath, J. R. (2014). Integrative biology of exercise. *Cell*, 159(4), 738-749.
- [2] Dasso, N. A. (2019). How is exercise different from physical activity? A concept analysis. In *Nursing forum* (Vol. 54, No. 1, pp. 45-52).
- [3] Patel, J. G., & Bhise, A. R. (2017). Effect of aerobic exercise on cancer-related fatigue. *Indian journal of palliative care*, 23(4), 355.
- [4] Sharples, A., Wackerhage, H., & Morton, J. (Eds.). (2022). *Molecular exercise physiology: an introduction*. Taylor & Francis.
- [5] Saghiv, M.S., Sagiv, M.S. (2020). Oxygen Uptake and Anaerobic Performances. In: *Basic Exercise Physiology*. Springer, Cham. https://doi.org/10.1007/978-3-030-48806-2_3
- [6] American College of Sports Medicine. (2013). *ACSM's guidelines for exercise testing and prescription*. Lippincott Williams & Wilkins.
- [7] Cheung, Stephen S., & Ainslie, Philip N. (2022). *Advanced environmental exercise physiology*. Human Kinetics.
- [8] Kim, K. B., Kim, K., Kim, C., Kang, S. J., Kim, H. J., Yoon, S., & Shin, Y. A. (2019). Effects of exercise on the body composition and lipid profile of individuals with obesity: a systematic review and meta-analysis. *Journal of obesity & metabolic syndrome*, 28(4), 278.

- [9] Wang, C. H., Chang, C. C., Liang, Y. M., Shih, C. M., Chiu, W. S., Tseng, P., ... & Juan, C. H. (2013). Open vs. closed skill sports and the modulation of inhibitory control. *PloS one*, 8(2), e55773.
- [10] Tsai, Chia-Liang, Pan, C. Y., Chen, F. C., & Tseng, Y. T. (2017). Open-and closed-skill exercise interventions produce different neurocognitive effects on executive functions in the elderly: a 6-month randomized, controlled trial. *Frontiers in aging neuroscience*, 9, 294.
- [11] Voss, Michelle W., Kramer, A. F., Basak, C., Prakash, R. S., & Roberts, B. (2010). Are expert athletes 'expert' in the cognitive laboratory? A meta-analytic review of cognition and sport expertise. *Applied cognitive psychology*, 24(6), 812-826.
- [12] Qian Gu, Q., Zou, L., Loprinzi, P. D., Quan, M., & Huang, T. (2019). Effects of open versus closed skill exercise on cognitive function: a systematic review. *Frontiers in psychology*, 10, 467457.
- [13] Kenney, W. L., Wilmore, J. H., & Costill, D. L. (2022). *Physiology of sport and exercise*. Human kinetics.
- [14] Johnson, J., & Mathew, P. (2023) Effectiveness of Aerobic Exercise on Peak Expiratory Flow Rate, Exercise Capacity and Quality of Life in Post COVID-19 Patients.
- [15] Caspersen, C. J., Powell, K. E., & Christenson, G. M. (1985). Physical activity, exercise, and physical fitness: definitions and distinctions for health-related research. *Public health reports*, 100(2), 126.
- [16] Martinez, Matthew W., Kim, J. H., Shah, A. B., Phelan, D., Emery, M. S., Wasfy, M. M., ... & Levine, B. D. (2021). Exercise-induced cardiovascular adaptations and approach to exercise and cardiovascular disease: JACC state-of-the-art review. *Journal of the American College of Cardiology*, 78(14), 1453-1470.
- [17] Margaritelis, V. Paschalis, Paschalis, V., Theodorou, A. A., Kyparos, A., & Nikolaidis, M. G. (2020). Redox basis of exercise physiology. *Redox biology*, 35, 101499.
- [18] Ball, Derek (2015). Metabolic and endocrine response to exercise: sympathoadrenal integration with skeletal muscle. *Journal of Endocrinology*, 224(2), R79-R95.
- [19] Bull, F. C., Al-Ansari, S. S., Biddle, S., Borodulin, K., Buman, M. P., Cardon, G., ... & Willumsen, J. F. (2020). World Health Organization 2020 guidelines on physical activity and sedentary behaviour. *British journal of sports medicine*, 54(24), 1451-1462.
- [20] Vujic, A., Lerchenmüller, C., Wu, T. D., Guillemier, C., Rabolli, C. P., Gonzalez, E., ... & Rosenzweig, A. (2018). Exercise induces new cardiomyocyte generation in the adult mammalian heart. *Nature communications*, 9(1), 1659.
- [21] Chen, H., Chen, C., Spanos, M., Li, G., Lu, R., Bei, Y., & Xiao, J. (2022). Exercise training maintains cardiovascular health: signaling pathways involved and potential therapeutics. *Signal Transduction and Targeted Therapy*, 7(1), 306.
- [22] Joyner, M. J., & Edward F. Coyle (2008). Endurance exercise performance: the physiology of champions. *The Journal of physiology*, 586(1), 35-44.
- [23] Qaisar, R., Bhaskaran, S., & Van Remmen, H. (2016). Muscle fiber type diversification during exercise and regeneration. *Free Radical Biology and Medicine*, 98, 56-67.
- [24] Koulmann, N., Richard-Bulteau, H., Crassous, B., Serrurier, B., Padeloup, M., Bigard, X., & Banzet, S. (2017). Physical exercise during muscle regeneration improves recovery of the slow/oxidative phenotype. *Muscle & Nerve*, 55(1), 91-100.
- [25] Moreno-Villanueva, M., Kramer, A., Hammes, T., Venegas-Carro, M., Thumm, P., Bürkle, A., & Gruber, M. (2019). Influence of acute exercise on DNA repair and PARP activity before and after irradiation in lymphocytes from trained and untrained individuals. *International Journal of Molecular Sciences*, 20(12), 2999.

- [26] Nam, S. M., Kim, J. W., Yoo, D. Y., Choi, J. H., Kim, W., Jung, H. Y., ... & Yoon, Y. S. (2013). Effects of treadmill exercise on neural stem cells, cell proliferation, and neuroblast differentiation in the subgranular zone of the dentate gyrus in cyclooxygenase-2 knockout mice. *Neurochemical research*, 38, 2559-2569.
- [27] Firth, J., Stubbs, B., Vancampfort, D., Schuch, F., Lagopoulos, J., Rosenbaum, S., & Ward, P. B. (2018). Effect of aerobic exercise on hippocampal volume in humans: a systematic review and meta-analysis. *Neuroimage*, 166, 230-238.
- [28] Chow L S., Gerszten R E., Taylor J M., Pedersen B K. van Praag H Trappe S. Febbraio M A et al. (2022) Exerkines in health, resilience and disease. *Nature Review | Endocrinology*, 18 , 2022, 273
- [29] Pedersen, B. K. (2019). Physical activity and muscle–brain crosstalk. *Nature Reviews Endocrinology*, 15(7), 383-392.
- [30] Egan, B., & Sharples, A. P. (2023). Molecular responses to acute exercise and their relevance for adaptations in skeletal muscle to exercise training. *Physiological Reviews*, 103(3), 2057-2170.
- [31] Maciel, B. C., Gallo Jr, L., JA, M. N., Lima Filho, E. C., & Martins, L. E. (1986). Autonomic nervous control of the heart rate during dynamic exercise in normal man. *Clinical Science (London, England: 1979)*, 71(4), 457-460.
- [32] Kanstrup, I. L., & Ekblom, B. J. O. R. N. (1978). Influence of age and physical activity on central hemodynamics and lung function in active adults. *Journal of Applied Physiology*, 45(5), 709-717.
- [33] Grotle, A. K., Langlo, J. V., Holsbrekken, E., Stone, A. J., Tanaka, H., & Fadel, P. J. (2023). Age-related alterations in the cardiovascular responses to acute exercise in males and females: role of the exercise pressor reflex. *Frontiers in Physiology*, 14, 1287392.
- [34] Olver, T. D., Ferguson, B. S., & Laughlin, M. H. (2015). Molecular mechanisms for exercise training-induced changes in vascular structure and function: skeletal muscle, cardiac muscle, and the brain. *Progress in molecular biology and translational science*, 135, 227-257.
- [35] Calvert, J. W., Condit, M. E., Aragón, J. P., Nicholson, C. K., Moody, B. F., Hood, R. L., ... & Lefer, D. J. (2011). Exercise protects against myocardial ischemia–reperfusion injury via stimulation of β 3-adrenergic receptors and increased nitric oxide signaling: role of nitrite and nitrosothiols. *Circulation research*, 108(12), 1448-1458.
- [36] Verhaar, M. C., Westerweel, P. E., Van Zonneveld, A. J., & Rabelink, T. J. (2004). Free radical production by dysfunctional eNOS. *Heart*, 90(5), 494-495.
- [37] Prior, B. M., Yang, H. T., & Terjung, R. L. (2004). What makes vessels grow with exercise training?. *Journal of applied physiology*, 97(3), 1119-1128.
- [38] Fiuza-Luces, C., Garatachea, N., Berger, N. A., & Lucia, A. (2013). Exercise is the real polypill. *Physiology*, 28(5), 330-358.
- [39] Pinckard K, Baskin KK and Stanford KI (2019) Effects of Exercise to Improve Cardiovascular Health. *Front. Cardiovasc. Med.* 6:69. doi: 10.3389/fcvm.2019.00069
- [40] Stanford KI, Goodyear LJ. (2016) Exercise regulation of adipose tissue. *Adipocyte.* 5:153–62. doi: 10.1080/21623945.2016.1191307
- [41] Lundby C, Jacobs RA (2016). Adaptations of skeletal muscle mitochondria to exercise training. *Exp Physiol.* (2016) 101:17–22. doi: 10.1113/EP085319
- [42] Vega RB, Konhilas JP, Kelly DP, Leinwand LA. (2017) Molecular mechanisms underlying cardiac adaptation to exercise. *Cell Metab.* 25:1012–26. doi: 10.1016/j.cmet.2017.04.025
- [43] Kasapis C, Thompson PD. (2005) The effects of physical activity on serum C-reactive protein and inflammatory markers - A systematic review. *J Am Coll Cardiol.* 45:1563–9. doi: 10.1016/j.jacc.2004.12.077

- [44] Joki Y, Ohashi K, Yuasa D, Shibata R, Kataoka Y, Kambara T. (2015) Neuron-derived neurotrophic factor ameliorates adverse cardiac remodeling after experimental myocardial infarction. *Circ-Heart Fail.* 8:342–51. doi: 10.1161/CIRCHEARTFAILURE.114.001647
- [45] Pedersen BK, Febbraio MA. (2012) Muscles, exercise and obesity: skeletal muscle as a secretory organ. *Nat Rev Endocrinol.* 8:457–65. doi: 10.1038/nrendo.2012.49
- [46] Keller C, Hellsten Y, Steensberg A, Pedersen BK (2006). Differential regulation of IL-6 and TNF-alpha via calcineurin in human skeletal muscle cells. *Cytokine.* (2006) 36:141–7. 10.1016/j.cyto.2006.10.014.
- [47] Kleinbongard P, Heusch G, Schulz R (2010). TNFalpha in atherosclerosis, myocardial ischemia/reperfusion and heart failure. *Pharmacol Ther.* (2010) 127:295–314.
- [48] Ellingsgaard H, Hauselmann I, Schuler B, Habib AM, Baggio LL, Meier DT. (2011). Interleukin-6 enhances insulin secretion by increasing glucagon-like peptide-1 secretion from L cells and alpha cells. *Nat Med.* (2011) 17:1481–9. 10.1038/nm.2513
- [49] Van Hall G, Steensberg A, Sacchetti M, Fischer C, Keller C, Schjerling P (2003). Interleukin-6 stimulates lipolysis and fat oxidation in humans. *J Clin Endocrinol Metab.* (2003) 88:3005–3010.
- [50] Carey AL, Steinberg GR, Macaulay SL, Thomas WG, Holmes AG, Ramm G. Interleukin-6 increases insulin-stimulated glucose disposal in humans and glucose uptake and fatty acid oxidation in vitro via AMP-activated protein kinase. *Diabetes.* (2006) 55:2688–97. 10.2337/db05-1404
- [51] Slentz CA, Bateman LA, Willis LH, Granville EO, Piner LW, Samsa GP. . Effects of exercise training alone vs. a combined exercise and nutritional lifestyle intervention on glucose homeostasis in prediabetic individuals: a randomised controlled trial. *Diabetologia.* (2016) 59:2088–98. 10.1007/s00125-016-4051-z
- [52] Maruyama S, Nakamura K, Papanicolaou KN, Sano S, Shimizu I, Asami Y, et al. . Follistatin-like 1 promotes cardiac fibroblast activation and protects the heart from rupture. *EMBO Mol Med.* (2016) 8:949–66. 10.15252/emmm.201506151.
- [53] Nystoriak MA, Bhatnagar A. Cardiovascular Effects and Benefits of Exercise. *Front Cardiovasc Med.* (2018) 5:135. 10.3389/fcvm.2018.00135 –
- [54] Otaka N, Shibata R, Ohashi K, Uemura Y, Kambara T, Enomoto T. Myonectin is an exercise-induced myokine that protects the heart from ischemia-reperfusion injury. *Circ Res.* (2018) 123:1326–38. 10.1161/CIRCRESAHA.118.313777
- [55] Conn VS, Koopman RJ, Ruppert TM, Phillips LJ, Mehr DR, Hafdahl AR. Insulin sensitivity following exercise interventions: systematic review and meta-analysis of outcomes among healthy adults. *J Prim Care Community Health.* (2014) 5:211–22. 10.1177/2150131913520328
- [56] Ouchi N, Ohashi K, Shibata R, Murohara T. Protective roles of adipocytokines and myokines in cardiovascular disease. *Circ J.* (2016) 80:2073–80. 10.1253/circj.CJ-16-0663
- [57] Pedersen, B. K. (2019). The physiology of optimizing health with a focus on exercise as medicine. *Annual review of physiology*, 81(1), 607-627.
- [58] Patel, P. N., & Zwibel, H. (2021). Physiology, exercise. In StatPearls. StatPearls Publishing.
- [59] Chandrasekaran, B., & Fernandes, S. (2020). “Exercise with facemask; Are we handling a devil's sword?”—A physiological hypothesis. *Medical hypotheses*, 144, 110002.
- [60] Taylor, A. W. (Ed.). (2022). Physiology of exercise and healthy aging. *Human Kinetics*.
- [61] Matthew B. Pontifex, Amanda L. McGowan, Madison C. Chandler, Kathryn L. Gwizdala, Andrew C. Parks, Kimberly Fenn, Keita Kamijo, (2019) A primer on investigating the after effects of acute bouts of physical activity on cognition, *Psychology of Sport and Exercise*, Volume 40, Pages 1-22, ISSN 1469-0292, <https://doi.org/10.1016/j.psychsport.2018.08.015>. (<https://www.sciencedirect.com/science/article/pii/S1469029218301870>)
- [62] Zhu, H., Chen, A., Guo, W., Zhu, F., & Wang, B. (2020). Which Type of Exercise Is More Beneficial for Cognitive Function? A Meta-Analysis of the Effects of Open-Skill Exercise versus Closed-Skill

- Exercise among Children, Adults, and Elderly Populations. *Applied Sciences*, 10(8), 2737. <https://doi.org/10.3390/app10082737>
- [63] Holsinger, R. D. (2015). Translation of low-risk dementia-associated interventions into practice—a call to action. *Healthy Aging Research*, 4, 30.
- [64] Wang, R., & Holsinger, R. D. (2018). Exercise-induced brain-derived neurotrophic factor expression: Therapeutic implications for Alzheimer’s dementia. *Ageing research reviews*, 48, 109-121.
- [65] Leal, G., Bramham, C. R., & Duarte, C. B. (2017). BDNF and hippocampal synaptic plasticity. *Vitamins and hormones*, 104, 153-195.
- [66] Bath, K. G., Jing, D. Q., Dincheva, I., Neeb, C. C., Pattwell, S. S., Chao, M. V., ... & Ninan, I. (2012). BDNF Val66Met impairs fluoxetine-induced enhancement of adult hippocampus plasticity. *Neuropsychopharmacology*, 37(5), 1297-1304.
- [67] Nokia, M.S.; Lensu, S.; Ahtiainen, J.P.; Johansson, P.P.; Koch, L.G. (2016): Physical exercise increases adult hippocampal neurogenesis in male rats provided it is aerobic and sustained. *J. Physiol.* 594 (7), 1855–1873. <http://dx.doi.org/10.1113/JP271552>.
- [68] Niwa, A.; Nishibori, M.; Hamasaki, S.; Kobori, T.; Liu, K. (2016): Voluntary exercise induces neurogenesis in the hypothalamus and ependymal lining of the third ventricle. *Brain Struct. Func.* 221 (3), 1653–1666.
- [69] Erickson, M.W. Voss, R.S. Prakash, C. Basak, A. Szabo, L. Chaddock, J.S. Kim, S. Heo, H. Alves, S.M. White, T.R. Wojcicki, E. Mailey, V.J. Vieira, S.A. Martin, B.D. Pence, J.A. Woods, E. McAuley, & A.F. Kramer, (2011) Exercise training increases size of hippocampus and improves memory, *Proc. Natl. Acad. Sci. U.S.A.* 108 (7) 3017-3022, <https://doi.org/10.1073/pnas.1015950108> .
- [70] Maugeri, G.; D’Agata, V.; Magri, B.; Roggio, F.; Castorina, A.; Ravalli, S.; Di Rosa, M.; Musumeci, G. (2021) Neuroprotective Effects of Physical Activity via the Adaptation of Astrocytes. *Cells* , 10, 1542. <https://doi.org/10.3390/cells10061542>.
- [71] Leenders, M., Verdijk, L. B., Van der Hoeven, L., Van Kranenburg, J., Nilwik, R., Wodzig, W. K. W. H., Senden, J. M. G., Keizer, H. A., & Van Loon, L. J. C. (2013). Protein supplementation during resistance-type exercise training in the elderly. *Medicine & Science in Sports & Exercise*, 45(3), 542-552.
- [72] McGlory, C., Devries, M. C., & Phillips, S. M. (2017). Skeletal muscle and resistance exercise training; the role of protein synthesis in recovery and remodeling. *Journal of applied physiology*, 122(3), 541-548.
- [73] Figueiredo, Vandr e C., Caldow, M. K., Massie, V., Markworth, J. F., Cameron-Smith, D., & Blazevich, A. J. (2016). Impact of resistance exercise on ribosome biogenesis is acutely regulated by post-exercise recovery strategies. *American Journal of Physiology-Endocrinology and Metabolism*, 309(1), E72–E83.
- [74] Gommaar D’Hulst, Evi Masschelein, Katrien De Bock, 2022, Resistance exercise enhances long-term mTORC1 sensitivity to leucine, *Molecular Metabolism*, Volume 66, 101615, ISSN 2212-8778, <https://doi.org/10.1016/j.molmet.2022.101615>. (<https://www.sciencedirect.com/science/article/pii/S2212877822001843>)
- [75] Goodyear, L. J., Van Houten, D. R., Fronsoe, M. S., Rocchio, M. L., Dover, E. V., & Durstine, J. L. (1990). Immediate and delayed effects of marathon running on lipids and lipoproteins in women. *Medicine and Science in Sports and Exercise*, 22(5), 588-592.
- [76] Burd, N. A., West, D. W. D., Moore, D. R., Atherton, P. J., Staples, A. W., Prior, T., Tang, J. E., Rennie, M. J., Baker, S. K., & Phillips, S. M. (2011). Enhanced amino acid sensitivity of myofibrillar protein synthesis persists for up to 24 h after resistance exercise in young men. *Journal of Nutrition*, 141(4), 568–573. <https://doi.org/10.3945/jn.110.135038>

- [77] McConell, G. K., Wadley, G. D., Le Plastrier, K., & Linden, K. (2020). Skeletal muscle AMPK is not activated during 2 hours of moderate-intensity exercise at ~65% $\dot{V}O_2$ peak in endurance-trained men. *The Journal of Physiology*, 598(24), 5339–5353. <https://doi.org/10.1113/JP277619>
- [78] Hostrup, M., Reitelseder, S., Jessen, S., Kalsen, A., Nyberg, M., Egelund, J., ... & Bangsbo, J. (2018). Beta2-adrenoceptor agonist salbutamol increases protein turnover rates and alters signalling in skeletal muscle after resistance exercise in young men. *The Journal of physiology*, 596(17), 4121-4139.
- [79] Robinson, M. M., Dasari, S., Konopka, A. R., Johnson, M. L., Manjunatha, S., Ruiz Esponda, R., Carter, R. E., Lanza, I. R., & Nair, K. S. (2017). Enhanced protein translation underlies improved metabolic and physical adaptations to different exercise training modes in young and old humans. *Cell Metabolism*, 25(3), 581–592.
- [80] Hellsten, Y., & Nyberg, M. (2016). Cardiovascular adaptations to exercise training. *Comprehensive Physiology*, 6(1), 1–32. <https://doi.org/10.1002/cphy.c140061>
- [81] Dalle Carbonare, L.; Minoia, A.; Zouari, S.; Piritore, F.C.; Vareschi, A.; Romanelli, M.G.; Valenti, M.T. (2023) Crosstalk between Bone and Muscles during Physical Activity. *Cells* , 12, 2088. <https://doi.org/10.3390/cells12162088>.
- [82] Moss, F.P. and Leblond, C.P. (1971), Satellite cells as the source of nuclei in muscles of growing rats. *Anat. Rec.*, 170: 421-435. <https://doi.org/10.1002/ar.1091700405>
- [83] Relaix F., Didier Montarras, Stéphane Zaffran, Barbara Gayraud-Morel, Didier Rocancourt, Shahragim Tajbakhsh, Ahmed Mansouri, Ana Cumano, Margaret Buckingham; (2006) Pax3 and Pax7 have distinct and overlapping functions in adult muscle progenitor cells . *J Cell Biol* 2 January 2006; 172 (1): 91–102. doi: <https://doi.org/10.1083/jcb.200508044>
- [84] Nederveen, J. P., Joannisse, S., Snijders, T., Ivankovic, V., Baker, S. K., Phillips, S. M., and Parise, G. (2016) Skeletal muscle satellite cells are located at a closer proximity to capillaries in healthy young compared with older men. *Journal of Cachexia, Sarcopenia and Muscle*, 7: 547–554. doi: 10.1002/jcsm.12105.
- [85] Sousa-Victor P, García-Prat L and Muñoz-Cánoves P (2022). Control of satellite cell function in muscle regeneration and its disruption in ageing . *Nature*, review, (23). <https://doi.org/10.1038/s41580-021-00421-2>
- [86] Bruce, Richard M. (2017). The control of ventilation during exercise: a lesson in critical thinking. *Advances in physiology education*, 41(4), 539-547.
- [87] Tipton, M.J., Harper, A., Paton, J.F.R. and Costello, J.T. (2017), The human ventilatory response to stress: rate or depth?. *J Physiol*, 595: 5729-5752. <https://doi.org/10.1113/JP274596>
- [88] Turner, Duncan L.; (1991) Cardiovascular and Respiratory Control Mechanisms During Exercise: an Integrated View. *J Exp Biol* 1 October 1991; 160 (1): 309–340. doi: <https://doi.org/10.1242/jeb.160.1.309>
- [89] Mirenayat MS, Abedi M, Zahiri R, Fakharian A. (2025) The Effect of Exercise on Improving Respiratory Function and Physical Activity in Hospitalized Patients with COVID-19. *J Iran Med Council*. 2025;8(1):80-6.
- [90] Qin F, Xu M-X, Wang Z-W, Han Z-N, Dong Y-N, Zhao J-X. (2020) Effect of aerobic exercise and different levels of fine particulate matter (PM_{2.5}) on pulmonary response in Wistar rats. *Life Sciences*, (254) , 117355. <https://doi.org/10.1016/j.lfs.2020.117355>
- [91] Hackney, A., Kraemer, W., Hooper, D. (2016). Hormonal Changes Associated with Physical Activity and Exercise Training. In: Vaamonde, D., du Plessis, S., Agarwal, A. (eds) *Exercise and Human Reproduction*. Springer, New York, NY. https://doi.org/10.1007/978-1-4939-3402-7_8
- [92] Bajer B, Vlcek M, Galusova A, Imrich R, Penesova A:(2015) Exercise associated hormonal signals as powerful determinants of an effective fat mass loss. *Endocrine Regulations*, 49: 151–163.

- [93] Liang, Z.; Zhao, Y.; Ruan, L.; Zhu, L. Jin, K.; Zhuge, Q.; Su, D.; Zhao, Y. (2017): Impact of aging immune system on neurodegeneration and potential immunotherapies. *Progress in Neurobiology*. 157. 10.1016/j.pneurobio.2017.07.006
- [94] Perry, V.H. (2010): Contribution of systemic inflammation to chronic neurodegeneration. *Acta Neuropathol.*; 120:277–86.
- [95] Cotman, C.W.; Berchtold, N.C.; Christie, L.A. (2007): Exercise builds brain health: key roles of growth factor cascades and inflammation. *Trends Neurosci.*;30:464–72.
- [96] Pandy, Li, F., J. T., Ding, J. N., Peng, C., Li, X., Shen, J., ... Geng, X. (2017). Exercise rehabilitation immediately following ischemic stroke exacerbates inflammatory injury. *Neurological Research*, 39(6), 530–537. <https://doi.org/10.1080/01616412.2017.1315882>
- [97] Gomes da Silva, S.; Simões, P.S.; Mortara, R.A.; Scorza, F.A.; Cavalheiro, E.A.; da Graça Naffah-Mazzacoratti, M.; Arida, R.M.(2013): Exercise-induced hippocampal anti-inflammatory response in aged rats. *J Neuroinflammation*. May 10;10:61. doi: 10.1186/1742-2094-10-61. PMID: 23663962; PMCID:PMC3657539
- [98] Souza, L. C.; Filho, C. B.; Goes, A. T.; Fabbro, L. D.; de Gomes, M. G.; Savegnago, L.; Oliveira, M. S.;Jesse, C. R. (2013): Neuroprotective effect of physical exercise in a mouse model of Alzheimer's disease induced by β -amyloid₁₋₄₀ peptide. *Neurotoxicity research*, 24(2), 148–163. <https://doi.org/10.1007/s12640-012-9373-0>
- [99] Curry, A.; Guo, M.; Patel, R.; Liebelt, B.; Sprague, S.; Lai, Q.; Zwagerman, N.; Cao, F. X.; Jimenez, D.; Ding, Y. (2010). Exercise pre-conditioning reduces brain inflammation in stroke via tumor necrosis factor-alpha, extracellular signal-regulated kinase 1/2 and matrix metalloproteinase-9 activity. *Neurological research*, 32(7), 756–762. <https://doi.org/10.1179/174313209X459101>
- [100] Gleeson M, Bishop N C., Stensel DJ., Lindley M R., Mastana S S. and Nimmo M A. (2011) The anti-inflammatory effects of exercise: mechanisms and implications for the prevention and treatment of disease. *Nature Reviews | Immunology*, 2011, 11: 607-615.