Journal of Ageing and Restorative Medicine
JARM, 2(3): 104-111
www.scitcentral.com

ISSN: 2637-7403

Review Article: Open Access

Exercise-Induced Epigenetic Modifications for Beneficial Health Manifestations

Trevor Archer[1*] and Rita Businaro[2]

*[*1]Department of Psychology, Box 500, SE-450 30 Gothenburg, Sweden*

[2]Department of Medico-Surgical Sciences, Sapienza University of Rome.

Received May 13, 2019; Accepted May 28, 2019; Published July 11, 2019

ABSTRACT

In the wake of multiple observations arising from diverse corners of physiological and molecular genetics, the onslaught of epigenetic changes, gene x environment interaction, under current appearances requires rendition for purposes of displaying both performance augmentation, amelioration of structural-functional impairment and the promotion of resilience manifested by the lasting health benefits that arise from regular and consistent physical exercise. The notion that individuals, who maintain an exercise habit that is pursued with regularity, incorporating appropriate combinations of endurance and resistance, will present lower levels of "epigenetic ageing", experience lesser metabolic disorders and express higher levels of longevity. The relationships and outcomes of the exercise influences upon epigenetic mechanisms are viewed from several angles, including: diet-exercise interactions, cognitive progression, maintenance and sustainability and cholinergic detriment over the very young, young, mature and aged, i.e. the complete lifespan. Although the numerous health advantages granted by regular physical exercise remain unequivocal it appears to be case that a plethora of the molecular and tissue adaptations will confer heritable health implications, hopefully positive, for future generations.

Keywords: Physical exercise, Gene, Environment, Epigenetic, Methylation, Histone, Diet, Cognition, Cholinergic, Performance, Health

INTRODUCTION

Independent of gender differences the relative roles of individuals in health, function and performance are determined by physiological, adaptive and psychobiological factors underlying physical exercise propensities [1]. Endurance and resistance exercises both exert their respective or similar influences upon human skeletal muscle epigenome and subsequent gene expressions across genders [2], whether or not the presence of gender variations may be construed to be real or apparent [3]. For example, analyzing osteocalcin, in the forms of total osteocalcin, under-carboxylated osteocalcin and carboxylated osteocalcin, the physiological functional responses to different types of acute and/or chronic exercise appears to be regulated by bone-related gene variants [4]. Among laboratory mice, higher levels of muscular strength, running ability, power and economy and exercise-induced thermoregulatory control was greater among the males in comparison with the female mice while it seems pro-estrus and estrus disturbed the running economy and exercise-induced thermoregulation of the latter [5]. The timing of exercise episodes in relation to food intake and meal times and early-late phases of rest/sleep, on one hand, and the active phase, on the other, may present an important determinant of health efficacy. Thus, it has been observed that the time of day presents a critical factor that amplifies the salutary influences of exercise on both metabolic pathways within skeletal muscle and systemic energy homeostasis [6].

Healthy lifestyles are composed typically of enduring physical fitness and strength, regular exercise, adaptive resilience-producing behavioral modification, dietary selection and restriction and the reduction of stress at several levels. The influence of acute aerobic exercise and the supplementation of omega-3 polyunsaturated fatty acids and extra virgin olive oil on global and gene-specific DNA methylation and DNMT mRNA expression in leukocytes of

Corresponding author: Trevor Archer, University of Gothenburg, Department of Psychology, Box 500, SE-450 30 Gothenburg, Sweden, E-mail: trevor.archer@psy.gu.se

Citation: Archer T & Businaro R. (2019) Exercise-Induced Epigenetic Modifications for Beneficial Health Manifestations. J Ageing Restor Med, 2(3): 104-111.

disease-free individuals, trained male cyclists, was studied [7]. Exercise provoked a global hypomethylation alongside hypomethylation and elevated mRNA expression of global and gene-specific DNA methylation with links between the latter methylation and exercise performance. There was an interaction between supplement and trial for a single CpG of interleukin-6 indicating enhanced DNA methylation following omega-3 polyunsaturated fatty acid and lowered methylation following extra virgin olive oil. Global and gene-specific DNA methylations were associated with markers of inflammation and oxidative stress. Extra virgin olive oil supplementation reduced DNMT1 mRNA expression compared to omega-3 polyunsaturated fatty acid supplementation whereas; DNMT3a and DNMT3b mRNA expression were lowered following exercise thereby presenting its role on methylation. Older adults were subjected to a one-year training program consisting of total, light, and moderate-to-vigorous exercise measuring Body mass index and waist circumference and increases in all three types of exercise were obtained accompanied by related reduction in Body mass index and waist circumference although Age, sex, education level and Body mass index did not moderate the effectiveness of the exercise intervention [8].

Despite the relative paucity of human studies displaying interrelationships between the epigenetic associations of regular physical exercise, movement interventions designed for long-term usage implement the requirement of environmentally-based stimuli to promote epigenetic adaptations. From certain quarters, there is forthcoming evidence indicating the influence of environmentally-induced modifications to epigenetic changes that culminate in health and disease transformation across multiple generations. Environmental pollutants, such as benzo[a]pyrene and dioxin and others are associated with changes in DNA methylation, an epigenetic change that is associated with disease progression [9-11]. Contrastingly, reductions in global DNA methylation among older Swedish individuals were associated with applications of physical exercise [12]. Furthermore, among individuals either presenting or not presenting Type II diabetes, exercise induced genome-wide changes in DNA methylation in human adipose tissue thereby potentially affecting adipocyte metabolism. The necessity of lifestyle improvement, such as exercise training and dietary selection-restriction, obtains ever-increasing attention which leads to favorable, heritable epigenetic modifications that augment transcriptional programmes protective of disease, including metabolic dysfunction, heart disease and cancer [13].

DIET-EXERCISE INTERACTIONS

Although conclusions concerning exercise effects upon epigenetic modifications are still relatively premature, physical activity-dietary manipulations are being selected may quantify those changes occurring among individuals particularly with immune system inflammaging. Physical exercise offers an epigenetic propensity that holds benefits with several health domains [14-16]. Definitions of exercise may vary widely yet all should include the movements of skeletal muscle and greater-or-lesser energy expenditure, both during every day-life events or the use of regular schedules through prearranged, deliberate and repetitive activities and movements together with both 'grassroots' sports and competitive sporting events [17,18]. Both animal laboratory models and preclinical-clinical studies have demonstrated that regular, chronic exercise, independent of type, instigates major improvements in brain-body energy metabolism concurrent with providing antidepressant, anxiolytic, antioxidant and neuroprotective functions in neuropathology [19]. The implications of epigenetics for development, adaptation and health may be associated with DNA methylation whereby hypermethylation relates to the silencing of genes essential for cellular functioning during homeostasis and disease conditions whereas demethylation induces gene transcription and activation [20-22]. Notably, preclinical and clinical studies the epigenetic-modulating effects of exercise [23,24]. In a study assessing phosphocreatine recovery rate after ten weeks of aerobic training, it was observed that non-responders (to the training schedule) reduced whereas responders elevated the phosphocreatine recovery rate due to training [25]. Furthermore, in the former non-responders, insulin sensitivity failed to improve and glycemic control deteriorated whereas among the latter insulin sensitivity and VO_2 peak (improved by ~12%) improved in both groups. Both groups were distinguished by distinct pre-training molecular (DNA methylation, RNA expression) patterns in muscle tissue, as well as in primary skeletal muscle cells. Among non-responders' pre-training enrichment analyses identified elevations in glutathione regulation, insulin signaling and mitochondrial metabolism, reflected in vivo by higher pre-training phosphocreatine recovery rate and insulin sensitivity among these participants. The authors concluded that distinct basal myocellular epigenomic profiles in muscle tissue defined particular individuals presenting type II diabetes thereby implying the variable outcomes of exercise training schedules.

COGNITIVE PROGRESSION

In addition to constituting a serious risk factor for several metabolic conditions, sarcopenia and osteopenia, obesity is increasingly linked with deficits in cognition and memory, dementia development, lower cognitive performance, reduced and/or altered white matter concentrations and intensity linked to inflammation, brain atrophy and increased risk of Alzheimer's disease [26-31]. Patients presenting amnestic mild cognitive impairment, as assessed by the Mini-Mental State Examination and Montreal Cognitive Assessment scores, showed related normal weight obesity with related expressions of genes in peripheral blood mononuclear cells and metabolic health deviations [32].

Amongst the necessary lifestyle alterations required to combat obesity and accompanying health hazards, dietary restrictions through reduced caloric intake, a sufficiency of protein intake and significantly enhanced physical exercise, particularly among the ageing episodes have been recommended for prevention and intervention of the obese condition and linked metabolic disorders and preservation of neuroimmune functioning [33-37]. The Physical Activity Guidelines for Americans has recommended 150-300 min/week of moderate-intensity aerobic activity or 75 min/week of vigorous-intensity aerobic activity [38]. For adults presenting chronic ailments involving cancer, osteoarthritis, hypertension, multiple sclerosis, diabetes type-II and dementia, although, unfortunately, the necessity for muscle-strengthening resistance exercise of varying intensities seems neglected. Both cardiovascular and metabolic together with co-morbid conditions, e.g. HIV, have been alleviated by exercise [39,40] and over the broad lifespan, i.e., from children to older adults [41-44].

The disorder-alleviating effects of physical exercise upon impairments of cognitive functioning, obesity and several other chronically debilitating conditions have been expressed from analyses of the biochemical-endocrinological pathways involved with a view towards elucidating mechanistic entities [45-47]. Epigenetic processes occur as natural mechanistic forces and, although essential to development and adaptation, may induce detrimental alterations under adverse environmental conditions through modifications at transcriptional and/or post-transcriptional levels involving several other processes that collectively regulate gene activity and eventual chemical modifications of individual DNA [48-50]. Through these processes, the dynamic regulation of gene expression occurs as riposte to environmental stimuli without alteration to the primary DNA sequence [51] and is often marked by changes to histone status [52]. Epigenetic pertains to regulatory processes influencing gene expression without altering the DNA-sequence [53]. For example, microRNAs may modulate gene expression through regulation of transcriptional and posttranscriptional of target genes thereby regulating almost every cellular and developmental process subject environment influence, including the regulation of instinct immune responses and inflammation [54]. Both epigenetic and biochemical mechanisms have been described to outline the role of exercise regularity in preventing, improving and provision of resilience to obesity-metabolic disease states, impaired cognition and dementia and dysfunctional immune defense systems [55-56]. Moderate regular exercise is associated with the reduction of pro-inflammatory cytokines and the enhancement of anti-inflammatory cytokines [57], whereas this capacity, present in the wild-type, was lost among the adiponectin knockout mice [58]. Physical exercise-induced epigenetic modifications modulate inflammation and cancer mechanisms, the essential and hyperactive functioning of the immune defense systems, the loss of integrity and dysfunctionality of brain and CNS regional probity and pathology involved in normal/abnormal ageing [59].

MAINTENANCE AND SUSTAINABILITY

Physical exercise may function as an epigenetic modulator for the maintenance and preservation of whole body and brain health and integrity [60-62]. In rodent laboratory models, both single exercise sessions and repeated, chronic bouts of exercise using treadmill running set-ups have been found to alter the DNA methylation status in rat brains during different stages of neurodevelopment thereby modulating and regulating the gene expression of several genes implicated in cognition, brain plasticity and disorder states [64-66]. Among mouse sires (i.e., fathers) assigned to exercise assess, as compared with the sedentary sires, there were markedly higher levels of brain-derived neurotrophic factor (BDNF) that were related to enhanced levels of spatial cognitive performance [67,68], for related clinical effects, using aerobic and aquatic exercise, with different types of improvement). Paternal exercise, consisting of treadmill running, five consecutive days/week for eight weeks (at a duration of twenty min/day)induced reductions of their offspring's' relative levels of gonadal fat weight and a lower percentage of global hippocampal DNA methylation compared to the offspring of sedentary sires [69], thereby indicating interference of male physical activity at the time of conception on adiposity and hippocampal epigenetic reprogramming of the male offspring; this outcome strengthens the notion that exercise is not injurious to the descendant's, offspring's, development therewith presenting benefits to include the practice of physical exercise in a healthier lifestyle of the parents. Additionally, exercise-induced up-regulation of plasticity-promoting genes, e.g. BDNF, ensued, as exercise outcome, through hippocampal DNA demethylation and histone hyperacetylation among rodents [70-72]. In a study assessing the role of paternal exercise, treadmill running 20 min/day 5 times/week over 22 weeks, on learning and memory, neuroplasticity and hippocampal DNA methylation among the male offspring, there were marked improvements in spatial learning and marked reductions of hippocampal global DNA methylation levels of offspring to exercised sires compared with sedentary sires [73]. Exercise did not alter the global DNA methylation of the paternal sperm. There appears to be an association between paternal preconception exercise-habit and cognitive capacity, possibly linked to hippocampal epigenetic programming among the male offspring. Finally, C57BL/6 4 week old male mice received a high-fat diet or control (normal) diet whereas age-matched female mice received only the control diet and were assigned to two groups: (i) swimming-trained (continuous swimming protocol over 10 weeks, before and during gestation), and (ii) non-trained and were allowed to mate at 12 weeks of age mice (father and mother mice, respectively) [74]. High-fat diet fathers showed obesity with elevated total cholesterol,

triglycerides and glucose intolerance concurrent with offspring of high-fat diet fathers and non-trained mothers expressing hyperglycemia, glucose intolerance and higher levels of total cholesterol and triglycerides. Contrastingly, offspring of high-fat fathers and swimming trained mothers expressed a bio-profile similar to the offspring of control diet fathers and non-trained mothers.

CHOLINERGIC DETRIMENT

An evolutionarily-constrained period of individual neurodevelopment, such as adolescent, features both brain and body progression, adaptively or mal-adaptively directed in the transitional process from an immature, primitive organ to the sophisticated mature product that ought to be fully functional, in particular the cholinergic forebrain pathway of the basal forebrain [75-77]. Chronic or semi-chronic ethanol intake among adolescents and young adults, expressed in different forms of binge-drinking, often with the outcome of Alcohol use disorder diagnosis, accompanies the neuropathological structural-functional disturbances arising in the basal forebrain [78-80]. Laboratory studies have indicated reduced populations of choline acetyl transferase-immunoreactive cholinergic neurons in adolescent animal basal forebrain areas that persisted into the adult animal [81], together with nicotinergic gene associations with alcohol abuse disorder [82]. Adolescent intermittent ethanol has been linked to pathology through neuroimmune activation [83]. Thus, it was observed that the adolescent intermittent ethanol-induced (postnatal days 25 to 55) rats there was disruption/loss of cholinergic neuron biomarkers, including choline acetyl transferase, tropomyosin receptor kinase, p75 neurotrophin receptor, cholinergic neuron shrinkage and the increased expression of the neuroimmune biomarker, nuclear factor kappa-light-chain-enhancer of activated B cells p65 that controls DNA transcription, cytokine production and cell survival that was reversed by voluntary physical exercise regime (cage-contained running wheels) from postnatal day 56 to 95 [84,85]. The authors postulated that the decreased expression of cholinergic neuron biomarkers that was persistent following the adolescent intermittent ethanol was the outcome of the loss of the cholinergic neuron phenotype through an epigenetic mechanism arising from DNA methylation and histone3 lysine 9 dimethylation at promotor regions of choline acetyl transferase and histone 3 lysine 9 dimethylation, an epigenetic associated markedly with transcriptional repression, of which alterations, including neuroimmune signalling and cognitive deficits at adult ages, were reversed by the wheel-running exercise.

CONCLUSION

Training endeavors encompassing a variety of physical exercise regimes and/or programs present challenges to whole-body and selective regional homeostasis continually, that through the combined biological and psychophysiological pressures of hormesis and resilience coerce avenues towards the augmentation of necessary performance with accompanying health benefits. The concurrent adaptations to schedules of exercise training are prompted by levels of complexity that are embedded within the interplay of both environmental and genetic forces. Epigenetic factors regulate gene expression perpetually as defined by tissue-specific conscription and duress thereby constituting the links between the individual genotype and the surrounding physical-chemical environment. Further to these pressures of regular and sustained exercise, the burgeoning occurrence of epigenetic factors are emanating to induce potential and authentic biomarkers that eventually ought to be capable of predicting the mandatory responses to exercise training.

REFERENCES

1. Canan BD, Haizlip KM, Xu Y, Monasky MM, Hiranandani N, et al. (2016) Effect of exercise training and myocardial infarction on force development and contractile kinetics in isolated canine myocardium. J Appl Physio 120: 817-824.
2. Ling C, Rönn T (2019) Epigenetics in human obesity and type 2 diabetes. Cell Metab 29: 1028-1044.
3. Landen S, Voisin S, Craig JM, McGee SL, Lamon S, et al. (2019) Genetic and epigenetic sex-specific adaptations to endurance exercise. Epigenetics, pp: 1-13.
4. Hiam D, Voisin S, Yan X, Landen S, Jacques M, et al. (2019) The association between bone mineral density gene variants and osteocalcin at baseline and in response to exercise: The Gene SMART study. Bone 123: 23-27.
5. Aguiar AS Jr, Speck AE, Amaral IM, Canas PM, Cunha RA (2018) The exercise sex gap and the impact of the estrous cycle on exercise performance in mice. Sci Rep 8: 10742.
6. Sato S, Basse AL, Schönke M, Chen S, Samad M, et al. (2019) Time of exercise specifies the impact on muscle metabolic pathways and systemic energy homeostasis. Cell Metab 4131: 30183-30184.
7. Hunter DJ, James L, Hussey B, Wadley AJ, Lindley MR, et al. (2019) Impact of aerobic exercise and fatty acid supplementation on global and gene-specific DNA methylation. Epigenetics 14: 294-309.
8. Schröder H, Cárdenas-Fuentes G, Martínez-González MA, Corella D, Vioque J, et al. (2018) Effectiveness of the physical activity intervention program in the PREDIMED-Plus study: A randomized controlled trial. Int J BehavNutr Phys Act 15: 110.
9. Lind L, Penell J, Luttropp K, Nordfors L, Syvänen AC, et al. (2013) Global DNA hypermethylation is associated with high serum levels of persistent organic

pollutants in an elderly population. Environ Int 59: 456-461.

10. Zhang CM, Sun ZX, Wang ZL, Chen JS, Chang Z, et al. (2019) Abnormal methylation of spermatozoa induced by benzo(a)pyrene in rats. Hum Exp Toxicol.
11. Zhang W, Yang J, Lv Y, Li S, Qiang M (2019b) Paternal benzo[a]pyrene exposure alters the sperm DNA methylation levels of imprinting genes in F0 generation mice and their unexposed F1-2 male offspring. Chemosphere 228: 586-594.
12. Luttropp K, Nordfors L, Ekström TJ, Lind L (2013) Physical activity is associated with decreased global DNA methylation in Swedish older individuals. Scand J Clin Lab Invest 73: 184-185.
13. Denham J (2018) Exercise and epigenetic inheritance of disease risk. Acta Physiol (Oxf) 222.
14. Archer T (2014) Physical exercise intervention in autoimmune disease. Autoimmune Diseases and Therapeutic Approaches 2.
15. Archer T, Garcia D (2014) Physical exercise influences academic performance and well-being in children and adolescents. Int J Sch Cogn Psychol 1: 2-3.
16. Archer T, Kostrzewa RM (2012) Physical exercise alleviates ADHD symptoms: Regional deficits and development trajectory. Neurotox Res 21: 195-209.
17. Barone R, Marino Gammazza A, Casarrubea M, De Martino L, Marino Gammazza M, et al. (2018) European week of sport: Innovative initiative of European Commission that inspires children to be active. J Sports Med Phys Fitness
18. Mika A, Macaluso F, Barone R, Di Felice V, Sledzinski T (2019) effect of exercise on fatty acid metabolism and adipokine secretion in adipose tissue. Front Physiol 10: 26.
19. de Oliveira Bristot VJ, de Bem Alves AC, Cardoso LR, da Luz Scheffer D, Aguiar AS Jr (2019) The role of PGC-1α/UCP2 signaling in the beneficial effects of physical exercise on the brain. Front Neurosci 13: 292.
20. Fernandes V, Sharma D, Vaidya S, Pa S, Guan Y, et al. (2018) Cellular and molecular mechanisms driving neuropathic pain: Recent advancements and challenges. Expert Opin Ther Targets 22: 131-142.
21. Myte R, Sundkvist A, Van Guelpen B, Harlid S (2019) Circulating levels of inflammatory markers and DNA methylation, an analysis of repeated samples from a population based cohort. Epigenetics, pp: 1-11.
22. Young C, Campolonghi S, Ponsonby S, Dawson SL, O'Neil A, et al. (2019) Supporting engagement, adherence and behavior change in online dietary interventions. J Nutr Educ Behav 4046: 30132-30140.
23. Denham J, Gray AJ, Scott-Hamilton J, Hagstrom AD, Murphy AJ (2018) Small non-coding RNAs are altered by short-term sprint interval training in men. Physiol Rep 6: e13653.
24. Fernandes J, Vieira AS, Kramer-Soares JC, Da Silva EA, Lee KS, et al. (2018) Hippocampal microRNA-mRNA regulatory network is affected by physical exercise. Expert Opin Ther Targets 22: 131-142.
25. Stephens NA, Brouwers B, Eroshkin AM, Yi F, Cornnell HH, et al. (2019) Exercise response variations in skeletal muscle PCr recovery rate and insulin sensitivity relate to muscle epigenomic profiles in individuals with type 2 diabetes. Diabetes Care 41: 2245-2254.
26. Barros L, Eichwald T, Solano AF, Scheffer D, da Silva RA, et al. (2019) Epigenetic modifications induced by exercise: Drug-free intervention to improve cognitive deficits associated with obesity. Physiol Behav 204: 309-323.
27. Chang EH, Chavan SS, Pavlov VA (2019) Cholinergic control of inflammation, metabolic dysfunction and cognitive impairment in obesity-associated disorders: Mechanisms and novel therapeutic opportunities. Front Neurosci 13: 263.
28. Dekkers IA, Jansen PR, Lamb HJ (2019) Obesity, brain volume and white matter microstructure at MRI: A cross-sectional UK Biobank study. Radiology 181012.
29. Grillo CA, Woodruff J, Macht VA, Reagan LP (2019) Insulin resistance and hippocampal dysfunction: Disentangling peripheral and brain causes from consequences. Exp Neurol 4886: 30693-30699.
30. Lampe L, Zhang R, Beyer F, Huhn S, Kharabian Masouleh S, et al. (2019) Visceral obesity relates to deep white matter hyperintensities via inflammation. Ann Neurol 85: 194-203.
31. Rochoy M, Rivas V, Chazard E, Decarpentry E, Saudemont G, et al. (2019) Factors associated with Alzheimer's disease: An overview of reviews. J Prev Alzheimers Dis 6: 121-134.
32. Zhang S, Zhao M, Wang F, Liu J, Zheng H, et al. (2019) Relationship between normal weight obesity and mild cognitive impairment is reflected in cognitive-related genes in human peripheral blood mononuclear cells. Psychogeriatrics.
33. Archer T, Fredriksson A, Schütz E, Kostrzewa RM (2011) Influence of physical exercise on neuroimmunological functioning and health: Aging and stress. Neurotox Res 20: 69-83.

34. Archer T, Kostrzewa RM (2016) Exercise and nutritional benefits in PD: Rodent models and clinical settings. Curr Top Behav Neurosci 29: 333-351.

35. Strasser B (2013) Physical activity in obesity and metabolic syndrome. Ann N Y Acad Sci 1281: 141-159.

36. Strasser B, Volaklis K, Fuchs D, Burtscher M (2018) Role of dietary protein and muscular fitness on longevity and aging. Aging Dis 9: 119-132.

37. Valdiglesias V, Sánchez-Flores M, Maseda A, Lorenzo-López L, Marcos-Pérez D, et al. (2017) Immune biomarkers in older adults: Role of physical activity. J Toxicol Environ Health A 80: 605-620.

38. (2018) US Department of Health and Human Services.

39. Fofonka A, Bock PM, Casali KR, da Silveira AD, da Rosa FM, et al. (2018) Impact of treatment with glibenclamide or vildagliptin on glucose variability after aerobic exercise in type 2 diabetes: A randomized controlled trial. Diabetes Res Clin Pract 143:184-193.

40. Guariglia DA, Pedro RE, Deminice R, Rosa FT, Peres SB, et al. (2018) Effect of combined training on body composition and metabolic variables in people living with HIV: A randomized clinical trial. Cytokine 111: 505-510.

41. Esteban-Cornejo I, Rodriguez-Ayllon M, Verdejo-Roman J, Cadenas-Sanchez C, Mora-Gonzalez J, et al. (2019) Physical fitness, white matter volume and academic performance in children: Findings from the active brains and FITKids2 projects. Front Psychol 10: 208.

42. Pentikainen H, Savonen K, Ngandu T, Solomon A, Komulainen P, et al. (2019) Cardiorespiratory fitness and cognition: Longitudinal associations in the FINGER study. J Alzheimers Dis 68: 961-968.

43. Singh AS, Saliasi E, van den Berg V, Uijtdewilligen L, de Groot RHM, et al. (2019) Effects of physical activity interventions on cognitive and academic performance in children and adolescents: A novel combination of a systematic review and recommendations from an expert panel. Br J Sports Med 53: 640-647.

44. Tari AR, Norevik CS, Scrimgeour NR, Kobro-Flatmoen A, Storm-Mathisen J, et al. (2019) Are the neuroprotective effects of exercise training systemically mediated? Prog Cardiovasc Dis 62: 94-101.

45. Minakaki G, Canneva F, Chevessier F, Bode F, Menges S, et al. (2019) Treadmill exercise intervention improves gait and postural control in alpha-synuclein mouse models without inducing cerebral autophagy. Behav Brain Res 363: 199-215.

46. Stavres J, Fischer SM, McDaniel J (2019) Exaggerated post exercise hypotension following concentric but not eccentric resistance exercise: Implications for metabolism. Eur J Sport Sci 1: 11.

47. Yoo SZ, No MH, Heo JW, Park DH, Kang JH, et al. (2019) Effects of acute exercise on mitochondrial function, dynamics and mitophagy in rat cardiac and skeletal muscles. Int Neurourol J 23: S22-31.

48. Andersen GB, Tost J (2018) A summary of the biological processes, disease-associated changes and clinical applications of DNA methylation. Methods Mol Biol 1708: 3-30.

49. Francaux M, Deldicque L (2019) Exercise and the control of muscle mass in human. Pflugers Arch 471: 397-411.

50. Kerr AG, Sinha I, Dadvar S, Arner P, Dahlman I (2019) Epigenetic regulation of diabetogenic adipose morphology. Mol Metab 8778: 30344-30348.

51. Morgan CP, Chan JC, Bale TL (2019) Driving the next generation: Paternal lifetime experiences transmitted via extracellular vesicles and their small RNA cargo. Biol Psychiatry 85: 164-171.

52. Hou H, Zhao L, Zheng X, Gautam M, Yue M, et al. (2019) Dynamic changes in histone modification are associated with upregulation of Hsf and rRNA genes during heat stress in maize seedlings. Protoplasma, pp: 1-12.

53. Donohoe DR, Bultman SJ (2012) Metaboloepigenetics: Inter-relationships between energy metabolism and epigenetic control of gene expression. J Cell Physiol 227: 3169-3177.

54. Shafabakhsh R, Aghadavod E, Mobini M, Heidari-Soureshjani R, Asemi Z (2019) Association between microRNAs expression and signaling pathways of inflammatory markers in diabetic retinopathy. J Cell Physiol 234: 7781-7787.

55. Abreu CC, Fernandes TN, Henrique EP, Pereira PDC, Marques SB, et al. (2019) Small-scale environmental enrichment and exercise enhance learning and spatial memory of *Carassius auratus* and increase cell proliferation in the telencephalon: An exploratory study. Braz J Med Biol Res 52: e8026.

56. Archer T, Lindahl M (2018) Physical exercise to determine resilience: Hormesic processes arising from physiologic perturbation. J Public Health Gen Med 1: 1-10.

57. Cabral-Santos C, de Lima Junior EA, Fernandes IMDC, Pinto RZ, Rosa-Neto JC, et al. (2019) Interleukin-10 responses from acute exercise in healthy subjects: A systematic review. J Cell Physiol 234: 9956-9965.

58. Diniz TA, Aquino Júnior JCJ, Mosele FC, Cabral-Santos C, Lima Junior EA, et al. (2019) Exercise-

induced AMPK activation and IL-6 muscle production are disturbed in adiponectin knockout mice. Cytokine 119: 71-80.

59. Ferioli M, Zauli G, Martelli AM, Vitale M, McCubrey JA, et al. (2018) Impact of physical exercise in cancer survivors during and after antineoplastic treatments. Oncotarget 9: 14005-14034.

60. Ferioli M, Zauli G, Maiorano P, Milani D, Mirandola P, et al. (2019) Role of physical exercise in the regulation of epigenetic mechanisms in inflammation, cancer, neurodegenerative diseases and aging process. J Cell Physiol 234: 14852-14864.

61. de Farias CAC, Gualdi LP, da Silva SB, Parreira VF, Montemezzo D, et al. (2019) Effects of different modalities of inspiratory muscle training as an add-on to conventional treatment of patients with chronic obstructive pulmonary disease (COPD): Study protocol for a randomized controlled trial. Trials 20: 231.

62. Minuzzi LG, Kuga GK, Breda L, Gaspar RC, Muñoz VR, et al. (2019) Short-term resistance training increases APPL1 content in the liver and the insulin sensitivity of mice fed a long-term high-fat diet. Exp Clin Endocrinol Diabetes.

63. Xavier R, Sánchez C, Paulucio D, da Silva IM, Velasque R, et al. (2019) A multidimensional approach to assessing anthropometric and aerobic fitness profiles of elite Brazilian endurance athletes and military personnel. Mil Med pii: usz003.

64. Fernandes J, Arida RM, Gomez-Pinilla F (2017) Physical exercise as an epigenetic modulator of brain plasticity and cognition. Neurosci Biobehav Rev 80: 443-456.

65. Hall JM, Gomez-Pinilla F, Savage LM (2018) Nerve growth factor is responsible for exercise-induced recovery of septohippocampal cholinergic structure and function. Front Neurosci 12: 773.

66. Spindler C, Segabinazi E, Meireles ALF, Piazza FV, Mega F, et al. (2019) Paternal physical exercise modulates global DNA methylation status in the hippocampus of male rat offspring. Neural Regen Res 14: 491-500.

67. Yang SY, Shan CL, Qing H, Wang W, Zhu Y, et al. (2015) The effects of aerobic exercise on cognitive function of Alzheimer's disease patients. CNS Neurol Disord Drug Targets 14: 1292-1297.

68. Zhang Y, Wang YZ, Huang LP, Bai B, Zhou S, et al. (2016) Aquatic therapy improves outcomes for sub-acute stroke patients by enhancing muscular strength of paretic lower limbs without increasing spasticity: A randomized controlled trial. Am J Phys Med Rehabil 95: 840-849.

69. Mega F, de Meireles ALF, Piazza FV, Spindler C, Segabinazi E, et al. (2018) Paternal physical exercise demethylates the hippocampal DNA of male pups without modifying the cognitive and physical development. Behav Brain Res 348: 1-8.

70. Inoue T, Ninuma S, Hayashi M, Okuda A, Asaka T, et al. (2018) Effects of long-term exercise and low-level inhibition of GABAergic synapses on motor control and the expression of BDNF in the motor related cortex. Neurol Res 40: 18-25.

71. Maejima H, Kanemura N, Kokubun T, Murata K, Takayanagi K (2018a) Exercise enhances cognitive function and neurotrophin expression in the hippocampus accompanied by changes in epigenetic programming in senescence-accelerated mice. Neurosci Lett 665: 67-73.

72. Maejima H, Ninuma S, Okuda A, Inoue T, Hayashi M (2018b) Exercise and low-level GABAA receptor inhibition modulate locomotor activity and the expression of BDNF accompanied by changes in epigenetic regulation in the hippocampus. Neurosci Lett 685: 18-23.

73. Spindler C, Segabinazi E, Meireles ALF, Piazza FV, Mega F, et al. (2019) Paternal physical exercise modulates global DNA methylation status in the hippocampus of male rat offspring. Neural Regen Res 14: 491-500.

74. Tarevnic R, Ornellas F, Mandarim-de-Lacerda CA, Aguila MB (2018) Beneficial effects of maternal swimming during pregnancy on offspring metabolism when the father is obese. J Dev Orig Health Dis, pp: 1-5.

75. Blake MG, Boccia MM (2017) Basal fore-brain cholinergic system and memory. Curr Top Behav Neurosci 37: 253-273.

76. Lee HW, Yang SH, Kim JY, Kim H (2019) The role of the medial habenula cholinergic system in addiction and emotion-associated behaviors. Front Psychiatry 10: 100.

77. Lehner KR, Silverman HA, Addorisio ME, Roy A, Al-Onaizi MA, et al. (2019) Fore-brain cholinergic signaling regulates innate immune responses and inflammation. Front Immunol 10: 585.

78. Cheng H, Kellar D, Lake A, Finn P, Rebec GV, et al. (2018) Effects of alcohol cues on MRS glutamate levels in the anterior cingulate. Alcohol Alcohol 53: 209-215.

79. Rivas-GrajalesAM, Sawyer KS, Karmacharya S, Papadimitriou G, Camprodon JA, et al. (2018) Sexually dimorphic structural abnormalities in major connections of the medial forebrain bundle in alcoholism. Neuroimage Clin 19: 98-105.

80. Vetreno RP, Crews FT (2018) Adolescent binge ethanol-induced loss of basal forebrain cholinergic neurons and neuroimmune activation are prevented by exercise and indomethacin. PLoS One 13: e0204500.

81. Vetreno RP, Broadwater M, Liu W, Spear LP, Crews FT (2014) Adolescent, but not adult, binge ethanol exposure leads to persistent global reductions of choline acetyl transferase expressing neurons in brain. PLoS One 9: e113421.

82. Zuo L, Tan Y, Li CR, Wang Z, Wang K, et al. (2016) Associations of rare nicotinic cholinergic receptor gene variants to nicotine and alcohol dependence. Am J Med Genet B Neuropsychiatr Genet 171: 1057-1071.

83. Harwani SC, Ratcliff J, Sutterwala FS, Ballas ZK, Meyerholz DK, et al. (2016) Nicotine mediates CD161a+ renal macrophage infiltration and premature hypertension in the spontaneously hypertensive rat. Circ Res 119: 1101-1115.

84. Vetreno RP, Lawrimore CJ, Rowsey PJ, Crews FT (2018) Persistent adult neuroimmune activation and loss of hippocampal neurogenesis following adolescent ethanol exposure: Blockade by exercise and the anti-inflammatory drug indomethacin. Front Neurosci 12: 200.

85. Vetreno RP, Bohnsack JP, Kusumo H, Liu W, Pandey SC, et al. (2019) Neuroimmune and epigenetic involvement in adolescent binge ethanol-induced loss of basal forebrain cholinergic neurons: Restoration with voluntary exercise. Addict Biol.