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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.

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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

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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.

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