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The flip side of Cell Talk in Exercise: Cell Noise

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Abstract

The article makes an effort to study, assess, and bring additional depth to the concept of cell talk, crosstalk, and cell noise -highlighting molecular-level occurrences such as signaling activity that affect different metabolic processes, gene expression, and protein synthesis. It also establishes the idea of "cell noise," or "dysregulated cell signaling," which is defined as cell activity that may worsen or result in cellular injury, oxidative stress, and inflammation. There is abundant evidence that consistent, lifelong exercise extends lifespan and delays the onset of chronic illnesses like cardiovascular disease, diabetes, cancer, hypertension, obesity, depression, and osteoporosis. The aforementioned highlights the need for metered or regulated physical training that takes into account genetic and environmental variances among individuals. Everyone is advised to engage in structured, well-chosen workouts that will promote longevity of life and result in the human body functioning at its best.

Keywords: Cell Talk in Exercise, Cell Noise

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Introduction

Many see exercise as an elixir of some sort; it plays a vital role in achieving physical and mental well-being thus ensuring a major component of the World Health Organization's definition of health is achieved. The World Health Organization (WHO) defines health as 'Physical, mental, and social well-being, not merely the absence of disease and infirmity'. Exercise on the other hand is said to be a subset of physical activity that is characterized by planned and purposeful training. Several studies have demonstrated the importance of exercise in promoting health and well-being and its advantages for a variety of physiological systems. Exercise is known to activate a sophisticated network of signalling channels at the cellular level that control metabolism, gene expression, and protein synthesis. Recent studies have also revealed the potential drawback of this complex signalling network, which we have termed "cell noise." (*Radak & Zhao, 2013)*. Cell noise is the term for excessive or dysregulated cell signalling, which can interfere with normal biological processes and may harm patient outcomes.

Although normal physiological processes may require some degree of cell signalling, overstimulating signalling pathways can cause tissue damage, inflammation, and cellular stress. Inadequate recuperation time in between exercises, high-intensity exercise, and chronic activity are a few causes of this excessive signalling. Reactive oxygen species (ROS) generation during exercise is one of the mechanisms driving cell noise. Although excessive ROS production can cause oxidative stress which harms cellular components like proteins, lipids, and DNA, ROS are recognized to serve a critical function in controlling cell signaling pathways *(Peake, Suzuki,& Hordern, 2015).* This can then set off a chain of events that disturb regular cellular processes and cause harm to health in general. Recent research has uncovered a probable connection between cell noise and fatigue, delayed onset of muscle soreness (DOMS) and exercise-induced muscle injury.

It may be possible to create exercise programs that maximize health benefits while limiting the danger of unfavourable effects by understanding the mechanisms underlying these effects. *(Powers & Jackson, 2008*). The idea of cell noise in exercise, its possible health effects, and the state of the research in this field will all be covered in this article. To improve exercise-induced signalling and achieve better health outcomes, we will also talk about ways to reduce cell noise.

Anthropological issues in exercise

Exercise has long had a very important place in the study of human societies, culture, and their development. The anthropological evolution of the human race is not left out. However, *Duda & Allison (1990),* in their article ''Cross-cultural analysis in exercise and sport psychology: A void in the field'' lamented the dearth of studies in the field of sports and exercise particularly as it relates to race and ethnicity. They observed that children of the black race and Hispanics were believed to have better motor skills and could easily thrive in sporting activities, they also observed a higher incidence of obesity and decreased activity amongst female adults of the black race in comparison to their Caucasian counterparts, and all these findings they ascribed to the cultural differences between them. An earlier article by Williams D (1976) examined dance as a form of exercise in Ghana and described dance not only as an act of exercise but an action in a complex multi-dimensional space. He stated that dance was also a communication with the physical and metaphysical and was associated with economic gains, physical healings, roles in society, and the transmission of such roles. Thus, dances are very important to any enquiry into human actions.

Often however, 'common' spoken language or 'ordinary' speech is not sufficiently sophisticated to express all the relational elements of that space. Delvin a skeletal biologist and evolutionary anthropologist forayed into the field of cell communication, in his article "Estrogen, exercise, and the skeleton" published in the journal *Evolutionary Anthropology (Delvin,2011).* He considered exercise induced modelling of bones and referred to results in an in vitro experiment showing that estrogen up-regulates transcription of ERα, increasing mechano-sensitivity and activating osteogenic signalling cascades in osteoblasts. He stated that in mice, estrogen receptors are required for osteogenic responses to loading; in sheep, exogenous estradiol up-regulates exercise induced bone formation, but has little effect in the absence of strain. In humans, skeletal adaptation to loads is greatest before and during puberty, and becomes significantly impaired following menopause, suggesting that estrogen affects bone strain thresholds. On the other hand, when the ovaries were removed, there was no significant influence on the mechano- sensitivity of bones thus resulting to his conclusion that there is no simple relationship between estrogen, strain and bone growth and that the effects of estrogen might be time bound and more important during intervals when it is rapidly rising or falling between puberty and menopause.

The aforementioned studies establish the fact that exercise transcends the physical, mental, metaphysical, spiritual and cross-cultural space, thus buttressing the need to evaluate its scientific basis at the cellular and molecular level.

BENEFITS OF EXERCISE

Exercise & metabolism

Exercise is said to have a profound effect on muscle growth, though this is dependent on the balance between protein synthesis and breakdown. Resistance exercise improves muscle protein balance but in the absence of adequate intake of protein, there would be a negative protein balance (Tipton & Wolfe 2001). Novel evidence from systematic review and meta-analysis has shown that supervised, long-term, moderate to moderately vigorous intensity exercise training, in the absence of therapeutic weight loss, improves the dyslipidaemic profile by raising high density lipoprotein-cholesterol and lowering triglycerides in overweight and obese adults with characteristics of the metabolic syndrome. Lifestyle interventions, including exercise and dietary-induced weight loss may improve insulin resistance and glucose tolerance in obesity states and are highly effective in preventing or delaying the onset of type 2 diabetes in individuals with impaired glucose regulation. Randomised controlled trial evidence also indicates that exercise training decreases blood pressure in overweight/obese individuals with high normal blood pressure and hypertension *(Carroll & Dudfield,2004*).

Physical exercise elicits potent anti-inflammatory effects that are likely to account for many of the salutary actions of regular exercise on chronic metabolic diseases. The WHO has estimated that in excess of 1 billion people worldwide are overweight, with 300 million defined as being clinically obese. Obesity is associated with the development of a cluster of chronic metabolic diseases such as insulin resistance, type 2 diabetes, atherosclerosis, non-alcoholic liver disease, hypertension, and some forms of cancer *(Lancaster & Febbraio 2014*). Studies have shown that cytokines and other peptides that are produced, expressed, and released by muscle fibers and exert

either paracrine or endocrine effects should be classified as "myokines." Since the discovery of interleukin-6 (IL-6) release from contracting skeletal muscle, evidence has accumulated that supports an effect of IL-6 on metabolism. We therefore agree that muscle-derived IL-6 fulfils the criteria of an exercise factor and that such classes of cytokines should be named "myokines."

Interestingly, recent research demonstrates that skeletal muscles can produce and express cytokines belonging to distinctly different families (Pederson *et al*, 2007). Thus, skeletal muscle has the capacity to express several myokines. To date the list includes IL-6, IL-8, and IL-15, and contractile activity plays a role in regulating the expression of these cytokines in skeletal muscle (*Schnyder et al, 2015).* Evidence exists that IL-6 and IL-8 are regulated by concentric muscle contractions, both at the mRNA and the protein level, and recently it has been shown that strength training regulates the expression of IL-15. A bout of exercise provokes the appearance of several cytokines in the circulation, including IL-6, IL-1 receptor antagonist (IL-1ra), IL-8, and IL-10, whereas tumour necrosis factor-α (TNF-α) is only stimulated by very intense exercise *(Nielson & Pederson, 2007).*

Therapeutic effects of exercise

In both health and disease, exercise is one of the most commonly recommended treatments. There is indisputable proof that exercise has positive health impacts for both treating and preventing several ailments. Studies have found that the relative risk of death is decreased (by roughly 20%–35%) for both men and women who report higher levels of fitness and physical activity *(Macera et al, 2003*). When compared to physically active middle-aged women, physically inactive middle-aged women experience a 52% increase in all-cause death, a doubling of cardiovascular-related mortality, and a 29% increase in cancer-related mortality *(Hu et al., 2004)*. Hence, there is ample proof that regular exercise improves health and lowers the risk of early mortality from all causes, particularly cardiovascular disease in asymptomatic men and women. The primary and secondary prevention of pulmonary and cardiovascular diseases (CHD, chronic obstructive pulmonary disease, hypertension, intermittent claudication), metabolic disorders (type 2 diabetes, dyslipidaemia, obesity, insulin resistance), muscle, bone, and joint problems (rheumatoid arthritis, fibromyalgia, chronic fatigue syndrome, osteoporosis), cancer, and depression can all benefit from exercise prescription (*Pedersen and Saltin, 2006*).

Even if exercise were a curative treatment for each of these conditions, the best clinical outcome would still depend on the dosage (volume and intensity of the exercise), frequency of administration (sessions per week), type (aerobic vs. resistance exercise), systemic and psychoactive effects, as well as contraindications and side effects of the exercise. For instance, there is evidence that both resistance and aerobic exercise are beneficial for the management of diabetes; however, resistance exercise may be more advantageous for glycaemic control than aerobic exercise (*Dunstan et al., 2005*). There is a minimal level of physical exercise necessary for good health. With increased activity, these advantages grow, but when it exceeds a certain level the negative effects, outweigh the benefits. Unlike pharmacological medications, it is not well known what the lowest and maximum safe doses of physical activity are *(Lee, 2007*). How much, what kind, how often, what intensity, and how long physical activity should last are all topics of ongoing discussion.

Cons of exercise

Regular exercise is beneficial to our health. However unaccustomed or exhaustive exercise can result in detrimental health effects such as muscle damage, inflammation and oxidative stress. Specifically, repetitive muscle contraction involves accumulation of reactive oxygen species (ROS) *(Zuo et al., 2015*). Muscle damage implies the extracellular efflux of myocellular proteins, the loss of skeletal muscle function (i.e force and range of motion decrease), and the development of muscle soreness that usually occurs several days after the exercise bout hence the name 'delayed onset muscle soreness' (*Clarkson et al., 2002*). The acute muscle response to exercise consists of micro destruction and disarrangement of myofibrils and cytoskeletal structures, a condition known as 'exercise induced muscle damage' *(peak et al., 1985*). It occurs primarily from the performance of unaccustomed exercise, and its severity is modulated by exercise intensity, duration, and, most notably, the type of muscle contraction *(Clarkson et al., 1992).*

The most interesting insight into the acute response of the skeletal muscle to exercise were obtained through another indirect marker of muscle damage; the increased circulating levels of skeletal muscle protein most commonly investigated to assess exercise induced muscle damage *(Pereira et al., 2014).* Conversely, in vitro studies have suggested that intensity related tendon cell deformation stimulates anabolic cellular and molecular adaptive responses *(Lavagino et al., 2003).* It has been observed that an increase mechanical strain induces a loss of collagen crips and an increase in fibers recruitment *(Hansen et al., 2002),* that likely result to increased cell deformation *(Amoczky et al., 2002).* Therefore, it has been suggested that the initial, acute reaction to exercise is net loss of collagen.

Cardiac muscle contraction is a complex process in which cardiomyocyte stimulation occurs as a result of cell membrane depolarization and subsequent increase in intracellular Ca^{2+} level, coupled with the generation of mechanical force. The key role in the regulation of muscle contraction belongs to one of the components of thin filament troponin complex. This protein consists of three subunits, troponin C (TnC), which binds Ca^{2+}, troponin I (TnI), which inhibits the ATPase activity of actomyosin complex, and troponin T (TnT), which interacts with tropomyosin *(Bhavsar et al., 1991).* Transient increase of cardiac troponin (cTn) concentrations may occur in a variety of circumstances, reflecting acute myocardial injury, in general, short term cTn elevation has been considered to reflect harmful pathophysiological processes. One notable exception has been the rise in cTn concentration observed after endurance exercise in presumably healthy individuals, which has commonly been considered a benign phenomenon (*Merghani et al., 2017).*

The clear cardiovascular health benefits of endurance exercise, the high frequency of cTn elevation after endurance exercise, and the lack of symptoms or imaging evidence suggesting acute cardiovascular disease. However, the theory has been challenged by recent observations a higher prevalence of atherosclerotic plaques in former athletes than in control subjects, suggesting that endurance exercise over years may be associated with atherogenesis, higher cTnI concentration after exercise among marathon runners with cardiovascular magnetic resonance evidence of myocardial scar *Möhlenkamp et al., (2014),* and an exaggerated and prolonged cTnI response after a bicycle race among participants with occult obstructive atherosclerotic coronary artery disease *(Kleiven et al 2019).*

Cumulating evidence has shown that intense exercise has adverse effects on different aspects of health. For example, heavy physical activity can trigger an acute myocardial infarction *Mittleman et al., (1993)* and increase the occurrence of premature ventricular depolarization, which have been associated with a long-term increase in the risk of cardiovascular death *(Jouven et al., 2000).* A high percentage of apoptosis of lymphocytes has been shown to be induced by intense treadmill exercise, which may in part account for exercise induced lymphocytopenia and reduced immunity *(Mars et al., 1998).* Moreover, it has also been shown that intense exercise induces cellular and circulating oxidative stress and free radical production (*Alessio et al., 1993).* Kong *et al* have shown that leucocyte mitochondrial trans membrane potential (MTP), a marker of the energy and redox status of cells, declined significantly after exhaustive aerobic exercise, and this appeared to have a temporal relationship with intravascular oxidative stress and increased propensity for apoptosis *(Kong et al., 2002).*

Exercise induced asthma (EIA) is a condition in which vigorous physical activity trigger acute airways narrowing in person with increased airway activity. 'Hyperosmolality theory' suggests that air movement through the airway results in relatively drying of the airway and leads to hypertonicity of the surface cells of the airways. This in turn, is believed to trigger pro inflammatory mediators' cascade of event that results in bronchospasm. Risk factors for the development of EIA include; environmental factors e.g, chlorination in pools, insecticides and pesticides used to maintain playing field, fertilizer and herbicide used to maintain playing field, decreased temperature and humidity of inspired air *(Egyptian journal of chest diseases 2012).* The female athlete triad (FAT) is an intertwined relationship between energy availability (EA), bone health, and menstrual dysfunction that can be observed in physicaly active girls and women *(Otis et al, 1997).*

Exercise and bio-macromolecules

Biological macromolecules are very large biological molecules like proteins, carbohydrates, lipids and nucleic acids; which are composed of thousands of covalently bonded atoms. They are polymers of smaller molecules called monomers. General speaking, macromolecules fall into 3 categories of; Biopolymers (nucleic acids, proteins, and carbohydrates), Large non-polymeric molecules (lipids) Synthetic fibers and experimental materials (carbon nanotubes)

Synthetic macromolecules e.g., synthetic polymers (plastics, synthetic fibers, and synthetic rubber), graphene, and carbon nanotubes are not biological molecules. *(kumar et al, 2016).* Living things depend on three essential biopolymers for their biological functions: DNA, RNA and proteins, which are all linear, unbranched structure and are hence, known as linear biopolymers. This includes the DNA and the RNA both formed from nucleotides, and protein also formed from amino acids (*Berg et al, 2010).* Carbohydrates serve a major role of contracting skeletal muscles during exercise. This use of carbohydrates during physical activity plays important role in carbohydrate metabolism. In recent times, with increasing sedentary lifestyle of humans and easy accessibility to modern high-energy food and drinks leading to excessive intake of carbohydrates, it has led to metabolic diseases like type-2 diabetes, a complex endocrine disorder characterized by abnormally high concentrations of circulating glucose.

Exercise has beneficial effects to help control impaired glucose homeostasis with metabolic disease, and is a well-established tool to prevent and combat type-2 diabetes (*Marni & Patricia, 2014).* It is now well established that there are different proximal signalling pathways that mediate the effects of exercise on glucose uptake, and these distinct mechanisms are consistent with the ability of exercise to increase glucose uptake in the face of insulin resistance in people with type 2 diabetes. *(Berg et al, 2010*). It is an established fact that elevated blood cholesterol level is a coronary artery disease (CAD) risk factor. Blood Total Cholesterol (TC) level is the major risk factor of CAD and efforts for effective management of blood TC levels have permeated the public health landscape. The American Heart Association (AHA) after establishing an inverse relationship between increased levels of physical activity and cardiovascular mortality, labelled inactivity as a CAD risk factor. (*Girdon et al, 2014).*

Lowering serum cholesterol can reduce the risk of coronary heart disease which currently is achieved by drug treatment. With the high limitation of drug treatment, exercise becomes a viable resort for individuals with dyslipidaemia as it improves lipids profile. Therefore, exercise affects profiles of low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, triglycerides and new lipids and lipoproteins such as non-high-density lipoprotein cholesterol, and postprandial lipoprotein. It is an undisputed fact that regular exercise increases protein needs, causing the rate of protein synthesis to increase. There are also changes in protein metabolism that are associated with many of the various phases of amino acid utilization and protein anabolism. Other factors that affect protein profile are diet composition, total energy intake, exercise intensity, duration and training, ambient temperature, gender and age. Epigenetic change in DNA during exercise brings about many health benefits. Exercise increases alanine output from skeletal muscle.

Evidence of in vitro study suggest that the branched-chain amino acids (glucose-alanine cycle) are the most important energy contributors during exercise. That is, protein/amino acids, under some conditions, contribute significantly to total exercise calories being burnt *(Marni & Patricia, 2014)*. Regular physical exercise has been shown to be one of the most important lifestyles influences on improving functional performance, decreasing morbidity and all causes of mortality among older people. It is a documented finding that physical exercise increases antioxidant activity and decreases lipid peroxidation levels thereby inducing protective effects against DNA damage in lymphocytes. DNA is the molecular instruction manual found in all cells, some sections are genes, which are instructions for building proteins, while others are enhancers that regulate genes. Therefore, exercise in essence rewires the enhancers in regions of our DNA that are known to be associated with the risk to develop disease. *(Kristine et al, 2021).*

As mentioned earlier, exercise through its improvement of antioxidant activity, induces protective effects against DNA damage in lymphocytes. Scientists have shown how exercise remodels DNA in skeletal muscle, so that new signals are established to keep the body healthy. (*Shchesno, 1990).*

Genetics and exercise

The overall interaction between genes and exercise may suggest that exercise has a beneficial effect in increasing the expression of genes that alleviate certain disease processes. On the other hand,certain genetic preponderances may result in the resistance to such benefits. The same set of genes may affect exercise behaviour and health outcomes. First of all, underlying genetic factors that have a positive influence on both traits may contribute to the association between regular exercise behaviour and health outcomes. This implies that the genetic variation that results in, for instance, lowered risk for blood pressure or depression may also affect voluntary exercise behaviour. Genetic pleiotropy refers to the phenomenon wherein a small amount of biological variation affects several complex traits at the organ and behavioural levels. This phenomenon can mimic the causal effects of exercise and, as a result, overestimate the positive effects of exercise if it is present in a time-lagged form, where genetic effects on exercise behaviour occur before effects of the same genes on health at a later time point.

Secondly, even when standardized training regimens are used, the size of the effects of exercise are not uniform across all participants, even when causal effects of exercise are established in experimental training research. Some individuals will react quite favourably, while others won't react at all or might even react negatively. Exercise effects are better characterized as gene-by-exercise interaction if these individual variations in the favourable training effects result from the genetic variance between the trainees *(De Geaus & De Moor, 2008).*

A growing body of research indicates that aerobic exercise is an effective treatment for enhancing brain function and that this benefit is partially mediated by upregulating brain derived neurotrophic factor (BDNF) by boosting the expression of the BDNF gene. Hence, taking advantage of the rises in BDNF brought on by aerobic exercise may be able to promote motor learning-related neuroplasticity for stroke recovery. Yet, the fundamental mechanisms that fuel neuroplasticity, such as BDNF signalling, rely on the expression of genes.

Hence, a genetic variance may influence a person's reaction to motor rehabilitation training, aerobic exercise training, and total motor recovery following a stroke *(Mang et al, 2013).* Insulin resistance and improper blood glucose regulation are two features of type 2 diabetes mellitus (T2D). The condition is also accompanied by impaired glycogen synthesis, dysfunctional mitochondria, and ectopic lipid build-up. Obesity and a lack of physical activity are two major risk factors in the development of T2D, even though regular exercise might prevent or delay the start of the disease. It has been established that between 15–20% of people do not experience an improvement in their insulin sensitivity, muscle mitochondrial density, or glucose homeostasis despite receiving a supervised aerobic training protocol (*Stephen & Sparks, 2015).*

Cell Talk & Cross Talk in exercise

Cell signalling is a fundamental process that occurs in all living organisms. It involves a complex series of molecular interactions that allow cells to communicate with each other and coordinate various physiological processes. This results in cell talk and crosstalk in various organs and systems.

The Brain

The majority of the 1.36 kg weight of the brain is blood. Although the brain only makes up 2% of the total body weight, it consumes 25% of the oxygen used by the entire body and 15% of the heart's daily 2000 L of blood flow *(Xing et al, 2017*). It is an organ that controls bodily processes and also represents the neuronal underpinnings of higher mental processes like consciousness, the spirit, language, learning, memory, and intellect. According to research in cognitive psychology, the brain may adapt its shape and function to environmental changes and exercise. Exercise training, in particular, is vital for the brain's evolution *(Raichlen & Alexander,2017*). Exercise can enhance synaptic plasticity and function, promoting the health of the hippocampus and cerebral cortex neural network *(Li et al, 2019*). It is well-known that exercise can slow cognitive aging and ward off mental disease. The nutrients necessary to maintain the form and function of nerve fibers and synaptic connections must be provided by neurotrophic factors such as brain-derived neurotrophic factor (BDNF) and nerve growth factor (NGF) (*Ivanov, 2014).*

By considerably increasing the amount of grey and white matter in the brain, aerobic exercise is thought to slow down cognitive aging. It has been established that physical activity can induce FNDC5 expression in skeletal muscle, which is then released into circulation with the Irisin variant. Peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC-1α), a metabolic regulatory molecule in skeletal muscle, is also a key player in the mechanism by which exercise may slow brain aging and improve cognitive function. PGC-1α promotes FNDC5 expression upregulation, then via the blood-brain barrier, FNDC5 penetrates the hippocampus, encouraging the expression of BDNF in the dentate nucleus of the hippocampus, which is in charge of learning and memory (Wrann et al, 2013). Several molecules have also demonstrated the ability to enhance brain activity. Cathepsin B (CSTB) can cross the blood-brain barrier and enter the brain increasing BDNF expressions and stimulating the formation of the hippocampus neuron (Moon et al,2016). Depression is reportedly made worse by elevated circulating levels of stress-induced uridine. PGC-1α levels in skeletal muscle rise during exercise, which then upregulates the production of the kynurenine aminotransferase (KAT) enzyme. Uridine could be quickly converted to uric acid by the KAT enzyme, which leads to the induction of a protective mechanism by preventing elevated uridine levels in the blood *(Schlittler, et al., 2016*).

Heart and skeletal muscle

It is well-known that people with cardiovascular problems benefit from physical activity. Increased mitochondrial biogenesis, improved endothelial function, and greater metabolic enzyme activation in both skeletal muscle and cardiac muscle are all indicators of the advantages of physical activity *(Fan & Xu, 2020).* In order to regulate metabolism, hypertrophy, angiogenesis, and neuronal regeneration in skeletal muscle and myocardium during endurance exercise, miRNAs are thought to be crucial mediators for communication between the two tissues. Certain miRNAs, like miR-1 (downregulated), miR-27a (upregulated), and miR-126 (upregulated), were consistently expressed in both skeletal muscle and myocardium following exercise, despite the fact that the mechanism by which skeletal muscle releases miRNAs is yet unknown.

It has been demonstrated that overexpressing miR-1 inhibits the IGF-1 signalling pathway, which causes muscular atrophy (*Wang, 2013*). Exercise, on the other hand, has been shown to simultaneously lower the expression of miR-1 while upregulating the induction of miR-222 in skeletal muscle and myocardium, resulting in physiological cardiac hypertrophy and eventually averting cardiovascular illnesses. Exercise-induced physiological cardiac hypertrophy requires the induction of miR-222 in the heart *(silva et al, 2012*). Functional overload in muscle caused miR-1 and miR-133a expressions to be downregulated among the myomiRs. To boost the expression of

muscle growth genes including IGF-1, HGF, c-Met, LIF, and SRF, and avoid skeletal muscle morphological abnormalities, miR-1 and miR-133a may be downregulated. The one that gets greater attention is IGF-1, which is a potential miR-1 target and helps to promote skeletal muscle growth.

Moreover, exercise training was found to lower miR-1 levels in the heart, which may aid in cardio-protection by reducing myocardial apoptosis (*Lenk et al, 2012).* Other organs are impacted by skeletal muscle through physical exercise. Exercise is known to cause the release of numerous signalling molecules and hormones from the musculoskeletal system, including growth factors, cytokines, and leptin (*Tagliaferri et al,2015*). By way of the endocrine system, these signaling molecules and hormones exert their effect on the motor, metabolic, and growth functions of skeletal muscle in addition to other peripheral tissues and organs. Inter-organ communication networks have extensively investigated skeletal muscle as an endocrine organ (*Hoffmann, & Weigert 2017).* Exercise causes the release of signaling molecules in the skeletal muscle, which then activate cellular signaling pathways and alter the cellular processes of target organs, resulting in cross-talk between the skeletal muscle and other organs.

Exercise can increase the release of metabolites from muscle cells, which can serve as a channel for organs to communicate with one another. For instance, increased PGC1α expression in myocytes triggers the intermediate -aminoisobutyric acid product (BAIBA), which modifies the metabolic cross-talk between the liver and fat.

THE GUT

One of the most crucial parts of the human body for digestion is the gastrointestinal tract (GIT). Exercise, certain diseases, and environmental changes can all affect how well the digestive system functions. The GIT microbiota controls metabolic processes throughout the body and physiological processes in the gastrointestinal tract *(Valle et al, 2018*). The makeup of the gut microbiota is said to be influenced by exercise. Existing evidence shows that athletes' gut flora is more varied when compared to non-athletes. For instance, compared to non-athletes, the athlete's stomach had much more members of the *Akkermansiaceae* bacterial family (*Clarke et al, 2014*). The *akkermansiaceae* family is negatively associated with metabolic diseases and obesity. In exercise-induced mice, *Enterococcus faecium* in the Lactobacillales order grew by 24 times, but c11-k211 in the Erysipelotrichales order declined by 361 times (*Choi et al, 2013).* The findings from these studies suggest that exercise can alter the intestinal microenvironment. Disorders of the intestinal flora are linked to immune-related illnesses like diabetes and obesity. Through interactions with the immune system, intestinal flora also fosters intestinal mucosal immunity, which may be a crucial defense mechanism for the body against pathogen invasion.

Pattern recognition receptors (PRR) and receptors with a nucleotide-binding oligomerization domain (NOD) like receptor (NLR) enable the innate immune system to identify and distinguish infections from non-pathogenic substances. According to research, the MAMP pathway in the gut microbiota controls the production of toll-like receptors (TLRs), which in turn activates the NF-B pathway and T cells (*Rescigno,2014).* Intestinal flora also produces significant signaling molecules called short-chain fatty acids (SCFAs). It has been reported that the protein-linked receptors Gpr41 and Gpr43, whose ligands are propionic acid and acetic acid, are extensively expressed in the small intestine and colon. Moreover, Gpr43 is strongly expressed in neutrophils and eosinophils, which are stimulated by SCFAs and hence help to lessen inflammatory response (Li et al., 2014). SCFAs may also inhibit leukocyte movement and cause lymphocyte, macrophage, and neutrophil death. Moreover, SCFAs were linked to decreased synthesis of chemokines and monocyte/macrophage recruitment as well as reduced stimulus-induced adhesion molecule expression, demonstrating the anti-inflammatory action of microbial by-products *(Bermon et al, 2015).*

The vagus afferent receptors of the enteric nervous system can be activated by a variety of metabolites and signalling molecules, such as SCFAs, that are generated by gut microbes *(Forsythe, Bienenstock, & Kunze, 2014).* These signals, which the nucleus solitarius transmits to other projection regions, are vital for mood and behavior *(Fan & Xu, 2020*). As a result, essential variables in fostering the growth of the brain and metabolism include exercise and gut microbiota (*Lim & Kwak, 2019*).

Liver, Pancreas & Metabolism

The liver is responsible for glucose metabolism, glycogen synthesis, and storage. The regulation of plasma glucose levels and glucose metabolism depend on insulin. Insulin sensitivity is a vital factor in the efficient utilization of glucose. Insulin resistance (IR) and problems with glucose metabolism can be brought on by obesity, aging, and unhealthy lifestyles *(Perry & Shulman 2013*). It is possible to reduce IR brought on by non-alcoholic fatty liver disease (NAFLD) and obesity by maintaining the liver's optimal physiological activity (*Kurauti et al 2016).* Most frequently, peripheral IR is associated with chronic disorders such as obesity, NAFLD, Type 2 diabetes (T2DM),

and others. This results in Lipid deposition in the liver and skeletal muscle (*Tsuzuki et al 2017*). Moreover, IR lowers the absorption and utilization of glucose. The liver then stores too much glucose in the form of triglycerides (TG).

The liver releases additional TG into the blood with a resultant increase in the level of TG in the peripheral circulation. Free fatty acids (FFA), are released into the blood during activated lipolysis. The liver generates TG when there is an excessive amount of circulating FFA. Increased oxidative stress and worsened IR are consequences of elevated lipid levels in the liver and peripheral circulation as well as excessive lipid deposition. Such a vicious loop impairs the liver's regular function and also causes the metabolic disorder to worsen *(Fan & Xu 2020).* Long-term exercise improved IR, lowered liver CLK2 levels, and reduced liver fat deposition in obese mice fed a high-fat diet for 16 weeks (*Munoz et al 2018*). Rats subjected to intermittent hypoxia were able to boost their systemic insulin sensitivity and activate AKT phosphorylation in the liver with high-intensity treadmill exercise *(Pauly et al 2017*). A high-fat diet-induced weight gain in mice was reduced by moderate exercise over a 24-week period, which was also associated with improvements in glucose tolerance, IR, hepatic steatosis, and p62 protein levels (*Wang, Zeng & Gu 2017).*

Additional research showed that ten weeks of exercise training could increase glucose tolerance and heat shock protein 72 (HSP72) levels in the liver and gastrocnemius muscle while lowering TG levels and FFA levels in obese adult rats (*Tsuzuki et al 2017).* Exercise training can also lower levels of CD36 and fatty acid transporter 4 (FATP4) in the liver, which inhibits the absorption of fatty acids into liver cells, as well as the build-up of diacylglycerol and total cholesterol (TC) in the liver of mice on high-fat *diets (Jordy et al 2015).* Aerobic exercise also enhanced blood fat metabolism in T2DM mice models and reduced oxidative stress markers, IR, and plasma glucose levels. This effect is linked to the downregulation of Toll-like receptor 4 *(Fan & Xu 2020*). By overexpressing and activating the AMPK1/2 signalling, endurance exercise training dramatically lowers the levels of TG and FFA in the liver of T2DM mice (*Yi et al., 2013*).

Moreover, voluntary exercise can increase glucose uptake by phosphorylating AMPK, AKT, and glycogen synthetic kinase 3 (GSK3) and suppressors-of-cytokine-signaling 3 (SOCS3), reducing TG levels in the liver and preventing fatty liver caused by obesity *(Kang, Kim,& Shin 2013).* Macrophage migration inhibitory factor (MIF), which is known to encourage intracellular lipid oxidation in cellular immunology, was discovered to increase MIF expression and prevent liver steatosis after four weeks of exercise training via phosphorylating AMPK and ACC in the liver (*Moon et al,. 2013).*

Studies have shown that in people with T2D, exercise enhances pancreatic-cell insulin secretory function (*Solomon et al., 2010).* Exercise-conditioned antecubital venous sera were shown to prevent proinflammatory cytokine-induced INS-1 and islet cell apoptosis, indicating that humoral mediators released into the systemic circulation after exercise prevents cell death brought on by T1D-like (IL-1 and IFN-) proinflammatory conditions (*Christenson et a.,l 2015).* According to a study by Azar and colleagues published in 2020, there is a connection between exercise and cell cycle proteins, HDL cholesterol, LDL cholesterol, and apoptosis in germ cells of rats given high-fat diets and subjected to exercise and their sedentary counterparts. When compared to the sedentary group, the trained rats showed a substantial rise in blood HDL cholesterol, testosterone, Cyclin D1, and Cdk4 expressions while a significant decrease in LDL cholesterol, P21 expression, DNA fragmentation, and apoptotic cell number (*Azar et al., 2020*).

Cell noise in Exercise

Cell noise, often referred to as excessive cell signalling, is a condition that happens when the body's cells receive an excessive amount of signalling input during exercise. Cellular damage, oxidative stress, and inflammation are a few adverse health outcomes that might result from this. Cytokines, growth factors, and hormones are just a few of the signalling molecules the body makes while exercising to help control numerous physiological processes. For instance, cellular elements like DNA, proteins, and lipids can be harmed by excessive exercise-induced oxidative stress, which can result in abnormal signalling and cellular malfunction. This is similar to how acute exercise-related chronic inflammation can impair normal signalling pathways, cause cellular damage, and perpetuate oxidative stress. Overtraining, inadequate diet or a lack of recuperation time are a few examples of the things that can cause excessive signalling. Inflammation and cellular damage may arise as a result, which may hasten the onset of chronic diseases.

According to one study, excessive cell signalling may contribute to the onset of insulin resistance, a condition in which the body's cells become less receptive to insulin and are more likely to develop type 2 diabetes and high blood sugar levels *(Henstridge et al., 2020*). Another study hypothesized that excessive cell signalling-induced chronic inflammation may be a factor in the development of cardiovascular disease (*Libby, 2019).*

Cardiovascular risk

Cardiovascular disease (CVD), the world's leading cause of death, has been linked to excessive cell noise during exercise. The "athlete's heart" phenomenon, in particular, has been linked to a paradoxical rise in CVD risk following long-term endurance training. Chronic exercise causes anatomical and functional changes in the heart, including thickened left ventricular walls and impaired diastolic function, which are the hallmarks of this syndrome. While these adaptations may at first have a positive impact on cardiovascular health, some athletes may experience an increased risk of arrhythmias, myocardial fibrosis, and sudden cardiac death as a result of them.

Female Athletes Triad

Due to the existence of the female athlete triad (FAT), female athletes are especially vulnerable to the harmful consequences of excessive exercise-induced cell noise. Disordered eating, amenorrhea (the lack of menstrual cycles), and osteoporosis (Bone loss) are the three interconnected symptoms of this illness. The urge to maintain a slim body for aesthetic or performance purposes is one psychological component that is hypothesized to contribute to FAT. Other variables include genetic, environmental, and genetic-environmental interactions. A disordered diet and poor energy levels can result in hormone imbalances and menstrual cycle disturbances, which can then lower bone density and increase the risk of stress fractures. Infertility, osteoporosis, and cardiovascular disease are just a few of the major long-term health effects that the FAT can have (*Birch, 2009).*

Male Athletes Triad

Male athletes can encounter the male athlete triad (MAT), a disease that is comparable to the FAT but less well-known. This disorder includes hypogonadism (reduced testosterone levels), decreased bone density, and limited energy availability. Similar to the FAT, it is believed that the MAT is brought on by a confluence of genetic, environmental, and psychological elements, such as the stress of maintaining a lean physique and achieving high levels of performance. The MAT can result in several medical issues, such as a loss of muscle mass and strength, an increased risk of stress fractures, and hormonal abnormalities that can aggravate cardiovascular disease (*Tenforde et al, 2016).*

It is crucial to adhere to suitable training procedures, which include allowing for enough rest and recuperation time, eating a balanced and nutrient-dense diet, and controlling stress levels, to prevent excessive cell signalling while exercising. Including foods rich in antioxidants and supplements, such as curcumin and omega-3 fatty acids, may assist to lessen inflammation and oxidative stress. Exercise-related cell noise can have a significant impact on one's health and performance, especially for athletes who engage in frequent, intense activity. In particular in female athletes with FAT and male athletes with MAT, excessive cell signalling can impede regular physiological functions and raise the risk of cardiovascular disease. To prevent or lessen the detrimental effects of excessive exercise-induced cell noise, athletes and their coaches must be aware of the hazards involved and take appropriate precautions, such as keeping a balanced and healthy diet.

Conclusion and future perspectives

Several chronic diseases can be prevented and treated with the help of exercise. As the idea that "exercise is medicine" continues to be incorporated into clinical settings, the integrative responses to exercise should undoubtedly draw a great degree of interest given its whole-body, health-promoting character. Regular physical activity is crucial for the body, and based on its many health advantages, we can conclude with confidence that it supports multiple biological systems that are linked to a lower risk of chronic disease and early death. For instance, regular exercise has been proven to enhance lipid lipoprotein profiles, reduce abdominal adiposity, and improve weight management (e.g., through reduced triglyceride levels, increased high-density lipoprotein [HDL] cholesterol levels, and decreased low-density lipoprotein [LDL]-to-HDL ratios).

Exercise is recognized to be more damaging when performed incorrectly or excessively, much like the adage goes, "Too much of everything is bad." Exercise's detrimental consequences are typically felt when a moderate or low-intensity workout is performed for a longer amount of time, when the recuperation period is cut short, and when athletes adopt poor eating habits. To individualize the dose as part of a future treatment plan, it is important to conduct extensive research on exercise to determine the average dose needed to obtain the physiological advantages of exercise while considering genetic variances.

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