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REVIEW ARTICLE: NEURO - ENDOCRINE - IMMUNE CROSS TALK IN EXERCISE

Debolina Kumar[1], Rahul Mazumder[2], Shreya Chakraborty[3], Haimanti Goswami[*4]

[1]Assistant Professor, Department of Optometry, School of Health Sciences, The Neotia University, Sarisha, Diamond Harbour Road, 24 Parganas (South), West Bengal - 743368
[2]State Aided College Teacher II, Kolkata Metropolitan College, Kolkata - 700006
[3]Assistant Professor, Department of Optometry, Arka Jain University, Jharkhand - 832108
[4*]Assistant Professor & HOD, Department of Physiotherapy, School of Health Sciences, The Neotia University, Sarisha, Diamond Harbour Road, 24 Parganas (South), West Bengal - 743368
***Corresponding Author:** Dr. Haimanti Goswami, Email: haimanti.goswami@tnu.in

ABSTRACT:
Neuro - endocrine - immune cross talk, both individually as well as in coordinated fashion regulate all major physiological and psychological functioning to maintain the overall homeostasis. This highly coordinated, synchronized, feedback based, integrated multimodal signalling system is the key to survival. The highly adaptive neuro - endocrine - immune response is pertinent in synchronizing various physiological & psychological responses against stressor induced insults that challenges the resting, baseline thresholds to regain homeostasis. With the onset of exercise, a potent physiological as well as psychological stressor, the entire neuro – endocrine - immune regulation system, owing to its highly adaptive and accommodative nature, rearranges the thresholds to achieve the new, improved homeostatic set point. The integrated, multidirectional network of neural, endocrine and immune systems is vital for the successful and effective encounter against the multifactorial, multimodal aspects of physical activities including exercise & training induced challenges.
The neuro - endocrine - immune cross talk system comprises 3 major components - the neural component includes hypothalamus, limbic system, cerebral cortex, medulla, pons, with the most important coordination maintained by the hypothalamus; the endocrine component includes the 3 major axes viz., HPA (hypothalamo - pituitary - adrenal); HPT (hypothalamo - pituitary - thyroid) & HPG (hypothalamo - pituitary - gonadal) axes; the immune component mostly includes the T, B & NK cells.
With the revelation of newer aspects of the multifactorial multimodal pattern of physical activities including exercise, training along with the recent developments of molecular endocrinology, the highly dynamic regulatory response to exercise induced stress needs to be constantly assessed. This review is an attempt to it.

KEYWORDS: Neuroendocrine-Immune Crosstalk; Exercise Stress; Homeostasis; HPA Axis; Immunomodulation; Physiological Adaptation.

INTRODUCTION

Endocrine system is a complex network of endocrine glands that secretes hormones - chemical messengers, directly into bloodstream. Hormones regulate the chemical signalling system, based on highly specific feedback regulation system. Endocrine system acts along with the nervous system – the electrical signalling system. The neuro-endocrine signalling / communication system is key to survival.
The neuro-endocrine feedback system as well as signals helps body to respond against all internal and external stimuli and provides the essential adaptive mechanism to survive.
The critical interplay of neuro - endocrine and immune systems helps the body to react against the physiological & / or psychological stress (stimuli / challenges) that disrupt the overall homeostasis.
Stress within the physiological & / psychological limits is indeed beneficial; it elevates the threshold level, acts as the primary mediator between stress and bodily adaptation; pushes the individual out of the comfort zone and motivates to achieve the goal. Exercise and physical activity is a prime example of physiological as well as psychological stress that drives the individual for achieving an elevated, improved benchmark.

STRESS CLASSIFICATION

In exercise physiology, stress can be categorized in many ways:
Depending on duration, stress 2 types: acute & chronic.

1. **Acute stress:** The immediate, short-term disruption caused by a single bout of exercise.
2. **Chronic stress:** The long-term effects of physical stress over weeks or months of training.

In terms of intensity, stress is of 3 types: mild, moderate & severe.

- **Mild stress:** the threshold from normal homeostasis is slightly changed, which is usually insignificant in making any impact.
- **Moderate stress:** optimum stress that elevates the threshold level upto highest beneficial physiological and psychological limits to achieve optimum positive impact.
- **Severe stress:** beyond optimum stress, which actually damages body & mind; could be fatal in extreme level.

ROLE OF ENDOCRINE GLANDS IN EXERCISE

A significant no of endocrine glands with their vast, diverse hormone profile play significant role in exercise and training. The hormonal engagement and outcome varies with the type of exercise & / training related stress.

Mostly, hormones regulate the energy balance, nutritional management required for the expected positive outcome.

Endocrine Gland	**Hormones**	**Key role in Exercise**
Pituitary	Growth Hormone (GH)	promotes muscle growth, tissue repair, carbohydrate & lipid catabolism to provide energy
Adrenal Medulla	Adrenaline & Noradrenaline	triggers "fight-or-flight" response; regulates carbohydrate & lipid catabolism to provide energy; regulates cardiovascular & respiratory functions to improve oxygen rich blood supply
Adrenal Cortex	Cortisol	mobilizes fuel sources (fat & carbohydrate) during prolonged stress; maintains overall anti stress response to prevent over stress
Thyroid	Thyroid hormones (T3 &T4)	regulates carbohydrate & lipid catabolism to provide energy; regulates cardiovascular & respiratory functions to improve oxygen rich blood supply; regulates homeothermy
Pancreas	Insulin & Glucagon	regulates blood sugar levels to ensure energy supply
Gonads	Testosterone & / Estrogen	Aids in muscle building, bone density, long-term tissue recovery

NEURO - ENDOCRINE RESPONSE TO ACUTE EXERCISE STRESS

Sympatho - Adrenomedulary System (SAM)

The instant or acute response to stress, especially during exercise & / training involves the sympathetic - adrenal response using the Hormonal Exercise Response Model (HERM) framework. With the onset of physical activity for exercise, the sympathetic nervous system starts releasing adrenaline & nor adrenaline. This triggers the motivation feelings in the individual and the person feels inspired for further continuation of exercise. This triggers the classic "fight-or-flight" response and results into:

1. **Cardiovascular changes:** all cardiovascular parameters including heart (pulse) rate, stroke volume, cardiac output, force of cardiac contraction, blood pressure etc increase significantly while opening as well as escalated functioning of vascular anastomoses, vasodilatation; significant decrease in peripheral vascular resistance, followed by escalated venous return – all contribute to enhance CV functions to ensure greater blood supply, especially relocation of blood as per need.
2. **Respiratory changes:** in coordination with CV changes, the respiratory system also undergoes significant modifications including increased respiratory (breathing) rate, tidal volume, ventilation perfusion ratio, bronchodilation, gas (both O2 & CO2) exchange – all that result into increased supply of oxygen to ensure oxidative metabolism and also, removal of excess CO2 to prevent metabolic and respiratory acidosis.
3. **Metabolic changes:** the neuro - endocrine response through the sympathetic - adrenal system results into elevated catabolism of carbohydrates & lipids to ensure uninterrupted energy supply. The instant, rapid catabolism of carbohydrates including Glycogenolysis, Glycolysis, TCA cycle along with lipid catabolism including Lipolysis, Neoglucogenesis of fatty acids and glycerol into glucose, followed by Glycolysis & TCA cycle – all ensure enhanced oxidative metabolism to provide greater energy supply required to continue extra muscular activities during physical activities & / exercise.

Role Of Pancreas

Fuel / energy management is vital for physical activities, where endocrine pancreas plays a very important role.; 3 pancreatic hormones – especially, glucagon & insulin along with pancreatic polypeptide play significant role in energy management during rest as well as exercise. The synergistic balanced actions of both glucagon & insulin help maintaining carbohydrates including Glycogenesis, Glycogenolysis, Glycolysis, TCA cycle along with lipid catabolism including Lipogenesis, Lipolysis, Neoglucogenesis of fatty acids and glycerol into glucose, followed by Glycolysis & TCA cycle. Pancreatic polypeptide regulates insulin actions.

Role of Cortisol / Hypothalamo - Pituitary - Adrenal (HPA Axis)

As exercise more than 20 - 30-minutes & / or with extremely high intensity exercise, triggers the HPA axis to stimulates cortisol release from adrenal cortex.

Cortisol, the main component of glucocorticoids, is termed as the anti-stress hormone. It mimics the carbohydrate & lipid metabolizing roles of adrenaline and pancreatic hormones. It also executes its vital anti-inflammatory role to prevent micro-tears in muscle tissue during hard work & protect from release of anti - inflammatory molecules. The anti - inflammatory actions of cortisol modulates immune cell trafficking and provides a permissive environment for muscle repair and protein remodelling after exercise. However, prolonged excess cortisol can deplete protein storage in muscles to replenish energy deficit.

Cortisol & Neuro-Immuno-Metabolic (NIM) Axis

Neuro-Immuno-Metabolic (NIM) axis - the framework that renders exercise as a systemic "energy challenge" that triggers a coordinated recalibration. NIM axis includes: (1) Metabolic Signalling: Lactate, ketone bodies, and the PGC-1α-mediated kynurenine detoxification pathway act as systemic signallers; (2) Immune Regulation: Exercise drives a shift from pro-inflammatory surveillance to "repair-oriented inflammation" rather than binary M1/M2 phenotypes; and (3) Gut-Brain Integration: Gut metabolites (e.g., indoles, SCFAs) regulate central immune tolerance via AhR signalling. Furthermore, we delineate the mechanistic specificity of aerobic, resistance, and high-intensity interval training (HIIT).
Cortisol integrates all these metabolic signals (like lactate; myokines including IL-6, BDNF, and PGC-1α pathways) to transition immune responses from chronic low-grade inflammation toward tissue repair and metabolic resilience.

Role of Thyroid Hormones

Thyroid hormones, both T3& T4 are instrumental to energy balance. Both T3 & T4 regulate basal metabolic rate (BMR), body temperature, cardio vascular and respiratory functions to regulate oxygen consumption and energy use; monitor metabolic activities in a similar fashion with adrenaline, cortisol, pancreatic hormones – all these ensure sufficient energy balance and cellular turnover.

Role of GI (Gastro – Intestinal) Hormones

GI system shares a complex, bi-directional relationship with exercise. Gut-derived hormones play a vital role in regulating appetite, energy balance, and metabolism during and after physical activity, forming a key part of the gut–brain axis. Hormones including GLP (Glucagon like polypeptide) - 1, Ghrelin, Polypeptide YY, cholecystokinin (CCK) modulate appetite, energy balance, and metabolism

Role of Endocrine Adipose tissue

Adipose tissue exerts a vital significant endocrine actions over skeletal muscles to regulate physical activities, exercise & training. Multiple hormones including Leptin, Adipokines, Lipokines are secreted from the Adipose tissue that integrate with liver, brain & skeletal muscle resulting in a complex, multimodal regulation over physical activities.

Role of Endocrine Bones

Bones function as active endocrine organs that both respond to and secrete hormones during physical activity and exercise training. By secreting osteocalcin (OCN), IGF (Insulin like Growth Factor) 1, Sclerostin etc, bones maintain its regulation over physical activity.

Role of Anabolic Hormones

These hormones primarily secreted from various endocrine organs and contribute to the tissue growth, repair related functions post exercise; include:

Growth Hormone (GH)

Growth Hormone (GH) acts as a powerful counter-weight to cortisol. It stimulates protein synthesis, helps repair damaged muscle fibres, strengthens bones, and regulates metabolism to ensure sufficient energy supply

Testosterone

Testosterone - the primary male sex hormone, plays a massive role in the long-term athletic adaptations observed in physical education students. It regulates:

i. Protein Synthesis and Breakdown - stimulates muscle protein synthesis (anabolic effect) and inhibit protein degradation (anti-catabolic effect), driving muscle hypertrophy and repair.

ii. Satellite Cell Activation - triggers the proliferation and fusion of satellite cells, which are essential for rebuilding and enlarging muscle fibers after mechanical stress.

iii. Metabolic Support - helps regulate body composition by favouring fat utilization, reducing visceral adipose tissue, and supporting strength and power output.

Estrogen

Estrogen influences multiple physiological systems that dictate strength, endurance, and injury risk:

i. Cardiovascular & Oxygen Delivery (VO2 max) - higher estrogen levels (around ovulation) are associated with optimized oxygen uptake (VO_2 max) and more effective oxygen circulation, supporting high-intensity aerobic exercise like running, cycling, and swimming, while lower estrogen phases (early follicular phase or post-menopause) can reduce peak oxygen efficiency.

ii. Muscle Mass, Strength & Repair - estrogen maintains muscle stem cells (satellite cells), supports muscle protein synthesis, enhances mitochondrial function, and regulates myosin performance. Declining or low estrogen (during postpartum, perimenopause, or menopause) can lead to reduced lean muscle mass, slower muscle regeneration, and a higher risk of atrophy.

iii. Connective Tissue and Joint/ACL Safety - estrogen affects collagen synthesis and structural integrity in tendons, ligaments, and cartilage. Fluctuations or lower estrogen periods (like the early menstrual cycle) can alter joint laxity and increase the risk of injuries such as anterior cruciate ligament (ACL) tears during high-impact or quick-cutting sports.

iv. Substrate Metabolism - estrogen influences how the body utilizes glycogen and fat during exercise, sparing muscle glycogen by promoting lipid oxidation under certain endurance conditions.

v. Protective Role - 17β-estradiol exerts membrane-bound and nuclear anti-inflammatory and antioxidant effects. Female athletes often exhibit modulated HPA-axis and antibody (B lymphocyte) responses compared to males undergoing identical physical challenges.

NEURAL REGULATION OF PHYSICAL ACTIVITY, EXERCISE, TRAINING

Neural regulation during exercise involves a tightly coordinated interplay between the central nervous system (CNS), the autonomic nervous system (ANS), and peripheral feedback loops to match cardiovascular, respiratory, and muscular demands in real time

Neural regulation is mediated in the following way:

i. Central Command - feedforward signal from higher brain centers sends motor signals to skeletal muscles and cardiorespiratory control centers in the brainstem, that initiates the immediate pre-exercise onset increase in heart rate and respiratory drive via parasympathetic withdrawal

ii. Exercise Pressor Reflex (EPR) - feedback mechanism originating from the contracting skeletal muscles. Group III (mechanoreceptive) and Group IV (metaboreceptive) nerve fibers detect mechanical deformation and chemical by products, like metabolites, sending afferent signals back to the CNS to further tune blood pressure and cardiac output

iii. Autonomic Nervous System (ANS) Adjustments - driven by a shift toward sympathetic activation and parasympathetic (vagal) withdrawal. It increases heart rate, enhances myocardial contractility, induces vasoconstriction in non-active visceral areas, and directs blood flow to working muscles

iv. Arterial Baroreflex & Chemoreflex: These reflexes modulate blood pressure and gas exchange, interacting dynamically with central command and the exercise pressor reflex to prevent excessive pressure spikes while maintaining vital organ perfusion

v. Brain-Derived Neurotrophic Factor (BDNF) and Neuroplasticity: Beyond acute systemic regulation, regular physical activity stimulates long-term neuroplastic adaptations, increases BDNF expression, promotes hippocampal neurogenesis, and refines emotional and stress-regulation circuits through the muscle-brain axis

NEURO IMMUNE REGULATION

Neuroendocrine-Immune Crosstalk Mechanisms

The functional communication between the brain, endocrine glands, and immune cells relies on shared molecular receptors and anatomical linkages:

Adrenergic Receptors on Leukocytes - B-cells, T-cells, and macrophages express β_2-adrenergic receptors. Catecholamines binding to these receptors directly regulate cellular trafficking, cytokine expression, and lymphocyte proliferation rates.

Cholinergic Anti-Inflammatory Pathway - vagal nerve stimulation (parasympathetic activation) releases acetylcholine, which binds to α7-nicotinic acetylcholine receptors (α7nAChRs) on tissue macrophages, actively inhibiting the nuclear factor kappa B (NF-κB) pathway and dampening the local release of pro-inflammatory cytokines.

Glucocorticoid Receptor Sensitivity - cortisol acts on glucocorticoid receptors across immune cell populations, tuning the intensity and resolution phases of post-exercise inflammation.

METABOLIC-IMMUNE CROSS-REGULATION MECHANISMS

Systemic metabolic changes during and after exercise modulate immune cell activation. They also affect differentiation and trafficking of these cells. These changes in turn impact neuro-immune interactions. Metabolic reprogramming of immune cells is characterized by shifts in glycolytic and oxidative phosphorylation pathways. This reprogramming is essential for their functional adaptation. It promotes the release of anti-inflammatory cytokines such as interleukin-10, that can cross the BBB (blood brain barrier) or signal via peripheral nerves to modulate CNS inflammation.

CHRONIC STRESS & OVERTRAINING SYNDROME

Overtraining Syndrome (OTS) develops when physical stress of training outweighs the body's capacity to recover. It is fundamentally an endocrine system failure, which results in chronic hypercortisolemia. This results into suppressed sex hormone activities, immune functions and disrupted sleep. Eventually these lead to neuroendocrine hypo activity, I.e., reduced ACTH and cortisol responses, chronically suppressed immune competence, elevated upper-respiratory tract infection (URTI) susceptibility, and psychological burnout.

SUMMARY & CONCLUSION

The neuro - endocrine - immune cross talk is indispensable for survival. This system helps the body to survive against the challenges from the insult induced by the most effective stressor – physical activity, exercise & training. A synergistic action of this system helps to

train smarter, optimize the recovery and achieve sustainable health and performance goals, thus improving the quality of life.

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