Perspective Article

A Mechanistic Model for Yoga as a Preventive and Therapeutic Modality

Abstract

Yoga is an ancient Indian technique of healthy living. Numerous studies have corroborated yoga's beneficial effects, including a favorable influence on autonomic function and negative emotions. Extensive research in the last few decades has revealed the critical role that yoga can play in eradicating stress. This has laid to the foundation for a scientific understanding of pathophysiological changes attributed to stress, particularly at the molecular and genetic levels. This primarily has helped understand the epigenetic and genetic mechanism at play to induce and alleviate stress, particularly those related to emotional aberrations. As research has indicated, negative emotions are translated into vascular inflammation appropriately accentuated by a sympathetic predominant autonomic function. This cascade is bolstered by multiple factors, including activation of "stressor" genes and elaborating hormones, including steroids with sometimes nocuous consequences, particularly when chronic. Yoga has been categorically found to have inhibited each and every one of these baneful effects of stress. In fact, it also changes the neuronal circuits that potentiate such a plethora of pathological changes. This, in turn, has accentuated yoga's relevance as a powerful preventive intervention in noncommunicable diseases (NCD). NCDs, including heart disease, stroke, and rheumatological disorders, are essentially inflammatory diseases that perpetuate inflammation in different beds like vascular or joint spaces. The precise mechanism by which yoga induces such beneficial changes is yet to be delineated. However, a cornucopia of pointers indicates that neural, endocrine, immunological, cellular, genetic, and epigenetic mechanisms are at play. This article attempts to cobble together newfangled research to delineate a medical model for this 5000-year-old practice from India. This is imperative, as a mechanistic model of this ancient-but-complex system would enable a more comprehensive understanding of its mechanism and reveal its yet-undiscovered positive health effects.

Keywords: *Inflammation, mechanism, noncommunicable diseases, yoga*

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Introduction

Yoga is a 5000-year-old Indian technique of healthy living that comprises the practices of asana (structured physical exercises), pranayama (breathing techniques), dharana (mindfulness), and dhyana (meditation). Yoga is known to be a powerful preventive intervention in many conditions and noncommunicable diseases (NCD), including heart disease, cancer, and rheumatological disorders not only to ameliorate risk but also to modify neurohormonal causes that potentiate the inflammation that results in disease.

Extensive research in the last few decades has revealed the critical role that yoga can play to eradicate stress, laying the foundation for a scientific understanding that stress-induced diseases can be alleviated or eliminated with a yogic lifestyle. The precise mechanism by which yoga induces such beneficial changes is yet to be delineated. However, a plethora of pointers indicates that neural, endocrine, immunological, cellular, genetic, and epigenetic mechanisms are at play.[1]

The beneficial effects of yoga include a wide spectrum of NCD. Cardiovascular disease is the number-one killer worldwide: Its fatality rate is double that of cancer, the second-largest killer. Coronary artery disease, heart failure, and atrial fibrillation are becoming increasingly prevalent, thanks to sedentary lifestyles, unhealthy eating habits, and stress.[2]

Here, we explore existing research to delineate a medical model for this ancient-but-complex practice from India. A medical model of yoga would enable a more comprehensive understanding of its mechanisms and may reveal its yet-undiscovered positive health effects.

How to cite this article: Basu-Ray I. A mechanistic model for yoga as a preventive and therapeutic modality. Int J Yoga 2021;14:152-7.

Submitted: 11-Dec-2020 **Revised:** 06-Jan-2021
Accepted: 28-Feb-2021 **Published:** 10-May-2021

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Access this article online

Website: www.ijoy.org.in

DOI: 10.4103/ijoy.IJOY_136_20

Quick Response Code:

The Brain

The use of functional magnetic resonance imaging, computed tomography, and radioactive targeting to discern neuronal activity, neurotransmitter concentration, blood flow, and other physiological correlates have revealed much about yoga's effect on the brain. The practice of yoga has been correlated with greater cortical thickness and gray-matter concentration in brain areas associated with arousal, mood, memory, and cognition and with functional attenuation of areas related to negative emotional processing, including the amygdala.[3-5] Changes in brain chemistry and selective neuronal firing elevate mood by enhancing release of neurotransmitters such as serotonin and norepinephrine. Decreased stimulation of brain basal areas associated with negative emotions and stress may moderate activation of the hypothalamic-pituitary-adrenal (HPA) axis, which fosters sympathetic discharges that release a cascade of hormones that initiate the "fight-or-flight" response.

The increased somatic sympathetic tone associated with these responses results in numerous aberrant pathological effects, including vascular inflammation that leads to cardiovascular disease, dangerous arrhythmias, and sudden cardiac death. In fact, all chronic stress is associated with this response and portends cardiovascular disease. Direct damage to the heart also has been reported,[6] along with angina and other forms of chest pain[7] and coronary artery spasm, which decreases nutritional flow to the cardiac musculature.[8]

Among yoga practitioners, electroencephalographic brain-wave recordings indicate increased theta and alpha frequency ranges. A global increase in alpha activity is known to increase feelings of calm and positive affect, thereby attenuating anxiety. Higher-frequency gamma activation (>30 Hz) also has been reported, particularly in long-term meditation practitioners.[9] Gamma frequency appears to be associated with various cognitive functions and may facilitate the neural mechanisms underlying attention.[9-11]

Yoga and meditation appear to influence the medulla oblongata, a brain-stem structure that contains a central vagal relay station with thousands of neurons. This neuronal station is instrumental in regulating heart rate and respiration and is modulated by the parasympathetic discharges seen in long-term yoga practitioners,[4] although details about relevant neural pathways remain to be delineated. Yoga elevates mammalian target of rapamycin (mTOR) signaling, which promotes the synthesis of proteins necessary for synapse formation and maturation; mTOR-dependent translational cascade may be the final pathway representing neurogenesis and neuroplasticity.[12,13]

Yoga also influences the sirtuin-1 signaling pathway.[12] Potential molecular mechanisms for enhancing neuroplasticity and alleviating depression by increasing sirtuin-1 include promotion of mTOR signaling, reduction of methylation in brain-derived neurotrophic factor (BDNF) transcription, and regulation of circadian rhythm by inhibiting CLOCK protein, a histone acetyltransferase.[12,14]

The Autonomic Nervous System

The fight-or-flight mechanism is a primal behavior pattern that enables humans to deal with emergencies and stress caused by anxiety, depression, or difficult situations such as economic downturns and pandemics. However, the fight-or-flight response is severely detrimental to cardiovascular health, particularly when protracted due to emotional instigation. Accentuated sympathetic nervous system (SNS) activity unleashed by psychological stress [Figure 1] can induce and propagate heart failure, leading to end-stage heart disease and death. High SNS activity increases heart rate and is believed to be the cause of refractory hypertension, wherein a patient's blood pressure is not amenable to medical therapy. Atrial fibrillation and ventricular tachycardia, both associated with considerable morbidity and mortality, are induced and sustained by an activated SNS.[15,16] Sudden cardiac death is a syndrome of ventricular tachycardia and ventricular fibrillation that can be induced by a sympathetic surge;[17] it is responsible for half of all heart disease deaths. The parasympathetic nervous system (PNS) also is essential for regulating heart

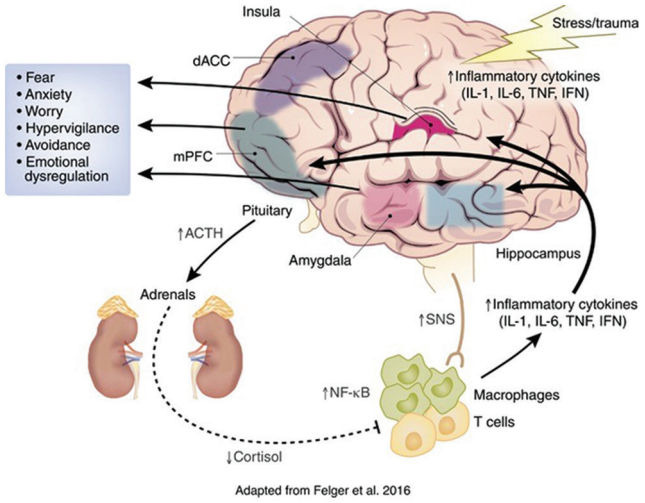

Figure 1: Mechanisms and consequences of inflammation in fear-and anxiety-based disorders. Exposure to acute stressors in individuals with anxiety may facilitate increased immune activity in both the periphery and the central nervous system via stress and trauma effects on neuroendocrine systems and the SNS. Overactivity of the SNS and decreased activity of the PNS promote proinflammatory cytokine release. Suppressed ability of glucocorticoids to inhibit inflammatory processes in these chronic stress states also contributes to a proinflammatory state that can influence neurotransmitter systems, neurocircuitry, and affective behavior. Cytokines may contribute to the maintenance of anxiety by affecting the activity and connections of related brain regions, including the amygdala, hippocampus, insula, mPFC, and the anterior cingulate (ACC). SNS: Sympathetic nervous system, PNS: Parasympathetic nervous system, mPFC: Medial prefrontal cortex. Reprinted by permission from Springer Nature: Neuropsychopharmacology 42 (1):254-270 (Inflammation in fear-and anxiety-based disorders: PTSD, GAD, and beyond. Michopoulos V, Powers A, Gillespie CF, Ressler KJ, Jovanovic T), Copyright (2017)

rate variability.[18] The SNS works in conjunction with the HPA axis to switch on the inflammatory cascade. Although new methods for attenuating sympathetic overactivity are being tested, most are experimental and come at considerable cost.

In contrast, yoga's beneficial effect in accentuating the PNS over the SNS has long been known.[19] Pranayam, an ancient breathing exercise inherent to yoga practice, regulates the PNS.[20] By effectively attenuating SNS overactivity, yoga reduces heart rate and achieves a better quality of life for patients with atrial fibrillation.[21,22] Yoga has been shown to help patients with discrete SNS overactivity that results in poorly controlled hypertension. Yoga reduces wear and tear on the body produced by chronic stress[23] by lessening sympathetic overactivity and improving parasympathetic tone, as evidenced by oxygen consumption level, heart rate, and the high-frequency component of heart rate variability.[24]

Psychological Effects

Various clinical trials indicate that yoga may play a significant role in defusing aberrant psychological states, such as anxiety, depression, despair, and anger, that foster cardiac changes leading to heart failure.[25] In times of stress, yoga helps its practitioners to develop a positive attitude, to become more self-aware, and to cope more effectively. Asana, pranayama, and meditation techniques enhance calm, mindfulness, and self-control.[26] Hatha yoga (which includes only postures, with little-to-no meditation) hastens recovery from stress by regulating autonomic balance, homeostasis, and the HPA axis.[27]

Endocrine Effects

Acute glucocorticosteroid (GCS) elevation is a survival mechanism that underlies the fight-or-flight response. However, chronic GCS elevation is counterproductive and may produce a plethora of cardiovascular pathologies, including endothelial dysfunction and vascular inflammation that accelerates the development of atherosclerosis, leading to stroke, myocardial infarction, and peripheral arterial disease. Chronic stress perpetuates GCS elevation, which triggers the inflammatory cascade by activating the nuclear factor (NF)κB pathway.

Glucocorticoid modulation occurs through the HPA axis [Figure 2].[28] Growing evidence suggests that yoga acts on the HPA axis to decrease GCS and increase GCS receptors, thereby reversing or even preventing the deleterious effects of chronic stress, cardiovascular disease, and aging.[29]

Cellular Effects

Yoga positively affects the immune system and inflammation pathways. By increasing the number and activity of natural-killer cells, yoga enhances the cell-mediated cytotoxicity of invading infectious organisms. Yoga practice is also associated with improvement in salivary cortisol levels, CD3 + and CD4 + cell counts, and immunoglobulin (Ig) A, a dominant factor in innate immunity.[30] Yoga increases IgA levels, thus preventing invasive organisms from gaining entry, and decreases cortisol, thus amplifying the body's ability to fight infection.

Multiple studies have documented yoga's beneficial role in attenuating the immunological dysfunction that causes overproduction of powerful proinflammatory cytokines and chemokines.[31] Yoga practice can downregulate an array of initiators and modulators of chronic inflammation, including interleukin (IL)-6, IL-1β, and tumor necrosis factor (TNF)-α [Figure 3]. Breast cancer patients who practiced yoga had a significant reduction in IL-6 after 3 months, compared with nonyoga controls, and this reduction was even more pronounced when the amount of yoga practice was increased, suggesting a dose-response effect.[32]

Markers for cellular recovery are higher in yoga practitioners. Mind-body interventions such as yoga improve mitochondrial integrity, as evident from increased cyclo-oxygenase activity, which helps to reduce supraphysiological free-radical levels during oxidative phosphorylation, thereby handling the oxidative milieu in a favorable way and preventing endothelial dysfunction, cardiovascular disease, and premature inflammation-related aging.[33]

Genetic Effects

When stress activates the SNS, nuclear factor-κB (NF-κB) is produced. Stress is translated into inflammation by NF-κB acting to change the expression of genes that code for inflammatory cytokines [Figure 2].[34] Yoga and other mind-body interventions directly inhibit the NF-κB pathway, thereby reducing the expression of inflammatory genes.[13]

Epigenetic alterations are an important mechanism of the favorable genetic modification achieved by yoga practitioners. Yoga decreases methylation of the *BDNF* gene, augmenting its activity and in turn enhancing neuroplasticity and cortical growth. Meditation has also been associated with significant reduction in methylation of the glucocorticoid-receptor gene and thus is related to a decrease in cortisol activity and stress levels. Global modification of histones (H4ac and H3K4 me3) and the silencing of several histone deacetylase genes (*HDAC* 2, 3, and 9) have been noted in practitioners of yoga and meditation.[13,35]

Telomerase activity has been widely discussed in mind-body intervention studies, as it is associated with premature aging and inflammation. However, results from these studies have been mixed, and most were short-term observational studies that failed to show reasonable improvement in

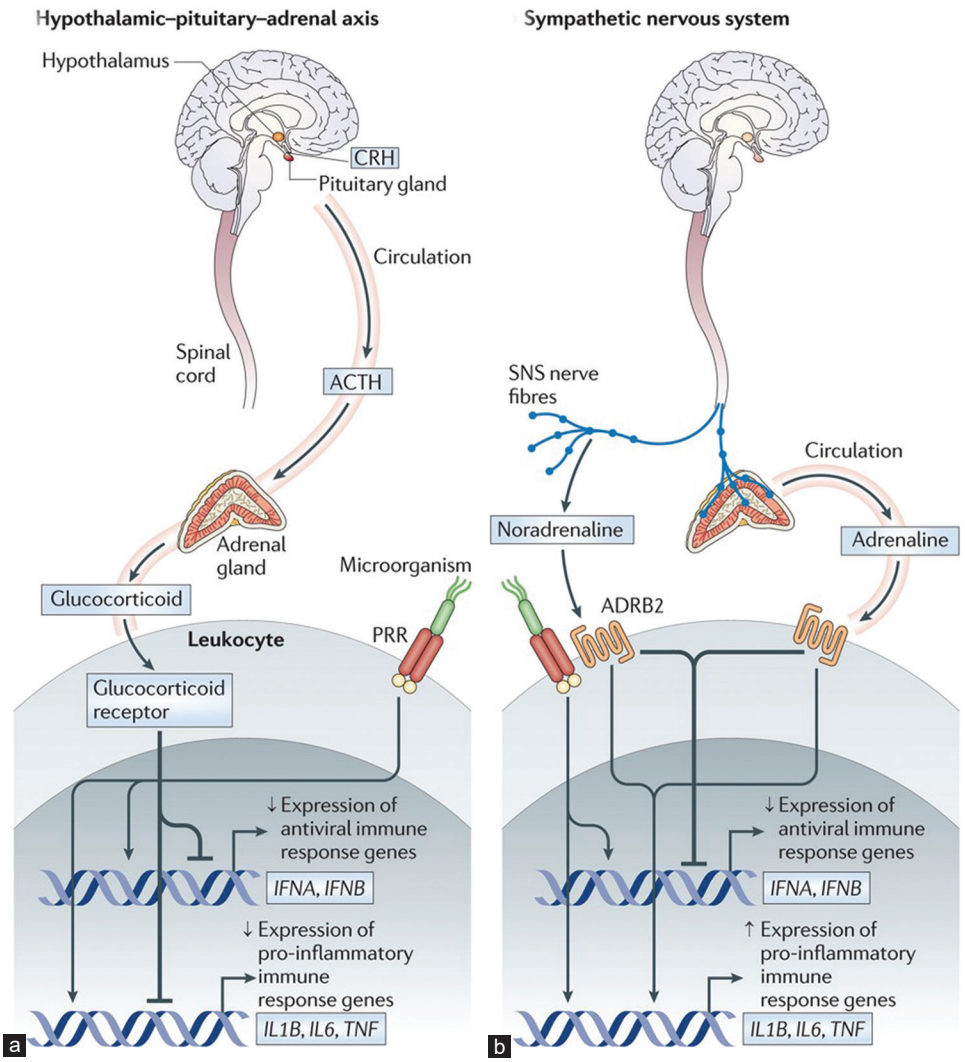

Figure 2: Central nervous system regulation of innate immune response gene programs. (a) The HPA axis distributes glucocorticoid hormones through the blood to regulate gene expression in virtually every cell of the body. Hormone activation of the glucocorticoid receptor in leukocytes results in profound suppression of both pro-inflammatory gene networks (for example, NF-κB-mediated transcription of proinflammatory cytokine genes, such as *IL1β*, *IL6* and *TNF*) and antiviral gene programs (for example, IRF-mediated transcription of type I interferon (IFN) genes, such as *IFNA* and *IFNB*). Activation of cytokine receptors in the hypothalamus triggers the production of glucocorticoids by the HPA axis. This constitutes the body's primary systemic mechanism for negative feedback control of pro-inflammatory gene expression triggered by microbial pattern recognition receptors (PRRs). (b) During fight-or-flight responses and acute injury, nerve fibers from the sympathetic nervous system (SNS) release the neurotransmitter noradrenaline into primary and secondary lymphoid organs, all other major organ systems (including the vasculature and perivascular tissues) and many peripheral tissues in which pro-inflammatory reactions occur. SNS nerve fibers can also stimulate the adrenal glands to release stored adrenaline into the systemic circulation. Both of these neuromediators regulate vascular function and stimulate leukocyte adrenergic receptors (for example, ADRB2) to activate transcription factors such as CREB and GATA family factors. SNS-induced transcriptional alterations can modulate hematopoiesis, redeploy leukocytes between tissue and blood, and repress IRF-mediated antiviral immune response gene programs while enhancing many NF-κB-mediated proinflammatory programs. ACTH: Adrenocorticotropic hormone; ADRB2: β2-adrenergic receptor, CRH: Corticotropin-releasing hormone, HPA: Hypothalamic–pituitary–adrenal, IL: Interleukin, IRF: Interferon regulatory factor, NF-κB: Nuclear factor-κB, TNF: Tumor necrosis factor[28]

telomerase activity. One study in hypertensive individuals did suggest that a combination of lifestyle modification techniques improves telomere maintenance.[36] Nonetheless, many more randomized trials are required to have a clearer understanding of yoga's role in this regard.

Yoga has been credited with dampening the activation of conserved transcriptional response to adversity (CTRA),[13] the primary characteristic of which is the upregulation of proinflammatory genes that produce major inflammation at the cellular level. Whereas acute inflammation is a short-lived, adaptive response that increases the activity of the immune system to fight injury or infection, chronic inflammation is maladaptive because it persists when no actual threat to the body exists.[14] Chronic inflammation is associated with increased risk for certain cancers, degenerative diseases, neurodegenerative diseases, cardiovascular diseases, and psychiatric illness. The secondary characteristic of CTRA is the downregulation of antiviral and antibody-related genes, which is associated with susceptibility to viral infections. As a result, CTRA

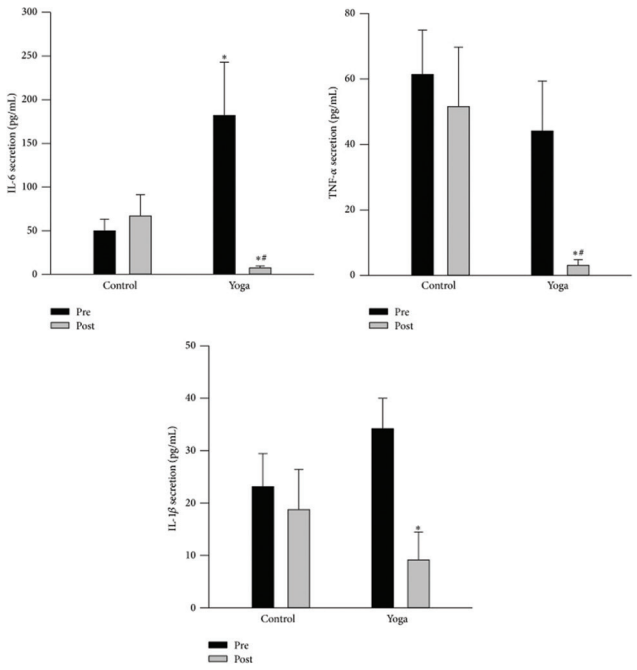

Figure 3: Reduced secretion of IL-6, TNF-α, and IL-1β from cultured whole blood *ex vivo* after yoga training. Whole blood was collected from 15 healthy participants at baseline and after yoga. Collected blood was diluted and cultured in 24-well plates under identical culture conditions. Supernatants were centrifuged and collected at 24 h for the measurement of IL-6, TNF-α, and IL-1β secretion via ELISA. Significant reduction in IL-6, TNF-α, and IL-1β secretion was seen after yoga, compared with the pre-yoga condition. Data are presented as mean + SEM *$P < 0.05$ versus preyoga training condition within the same treatment; #$P < 0.05$ versus control group at baseline level. IL: Interleukin, TNF: Tumor necrosis factor, SEM: Standard error of the mean. From Figure 3: Chen N, Xia X, Qin L, Luo L, Han S, Wang G, *et al*. Effects of 8-week Hatha yoga training on metabolic and inflammatory markers in healthy, female Chinese subjects: a randomized clinical trial. Biomed Res Int. 2016;2016:5387258. doi: https://doi. org/10.1155/2016/5387258, licensed under Creative Commons license CC BY 4.0

is considered a molecular signature of chronic stress. Yoga has been conclusively documented to lessen chronic stress, thus preventing the widespread activation of a pathophysiological state that garners chronic inflammation perpetuated by CTRA activation. Blocking activation of the CTRA genes has been suggested as a prime mechanism of yoga's anti-inflammatory effects.

Conclusions

Yoga is associated with numerous beneficial effects. It reduces inflammation by inhibiting the NF-κB pathway, moderating epigenetic alteration, and preserving telomerase length, which in turn reduces GCS level and increases glucocorticoid receptor sensitivity. Yoga augments neuroplasticity by promoting the mTOR pathway and enhancing gene expressions for BDNF, leading to increased cortical thickness in parts of the brain related to mood, awareness, and cognition. Yoga also depresses SNS activity and improves PNS activity, which is relevant to battling stress and maintaining a healthy cardiovascular profile. This appropriately may attenuate the initiation and perpetuation of multiple cardiovascular pathologies. Yoga has been found to reduce oxidative stress and prevent endothelial dysfunction, thus preventing premature atherosclerosis and coronary artery disease.

Yoga's role in reducing arrhythmia burden in atrial fibrillation by inducing PNS activity and reversing atrial remodeling has been described in multiple studies. Newer studies in yoga practitioners that explore proteomic and genomic sequencing, along with advanced neural imaging, will lead us further toward deciphering the yet-unretrieved mechanism of brain-heart axis that mediates aberrant cardiovascular pathophysiology.

Even more important, during the current pandemic and time of social isolation, yoga fills the need of the hour as a low-investment, readily available, and effective therapeutic alternative, from both the individual and public health perspectives.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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