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ORIGINAL RESEARCH

The Effects of Stress and Meditation on the Immune System, Human Microbiota, and Epigenetics

Ayman Mukerji Househam, MS; Christine Tara Peterson, PhD; Paul J. Mills, PhD; Deepak Chopra, MD

ABSTRACT

Context • Globally, more than 25% of individuals are affected by anxiety and depression disorders. Meditation is gaining popularity in clinical settings and its treatment efficacy is being studied for a wide array of psychological and physiological ailments. An exploration of stress physiology is an essential precursor to delineation of the mechanisms underlying the beneficial effects of meditation practices.

Objective • The review outlines a model of interconnected physiological processes that might support the continued inclusion and expansion of meditation in the treatment of diverse medical conditions and to investigate the role that gut microbiota may play in realizing well-being through meditation.

Design • The authors conducted a scientific literature database search with the goal of reviewing the link between stress management techniques and human microbiota. Their goal was also to identify the extent of underlying epigenetic reactions in these processes. The review was completed in approximately 2 y. Databases searched included Medline via PubMed and Ovid, PsycINFO via Ovid, Spinet, ProQuest Central, SAGE Research Methods Online, CINAHL Plus with Full Text, Science Direct, Springer Link, and Wiley Online Library. Keywords searched included, but were not limited to, *stress*, *meditation*, *mindfulness*, *immune system*, *HPA axis*, *sympathetic nervous system*, *parasympathetic nervous system*, *microbiota*, *microbiome*, *gut-barrier function*, *leaky gut*, *vagus nerve*, *psychoneuroimmunology*, *epigenetic*, and *NF-κB*.

Setting • The study took place at New York University (New York, NY, USA), the University of California, San Diego (La Jolla, CA, USA), and the Chopra Foundation (Carlsbad, CA, USA).

Results • Psychological stress typically triggers a fight-or-flight response, prompting corticotropin-releasing hormone and catecholamine production in various parts of the body, which ultimately disturbs the microbiota. In the absence of stress, a healthy microbiota produces short-chain fatty acids that exert anti-inflammatory and antitumor effects. During stress, an altered gut microbial population affects the regulation of neurotransmitters mediated by the microbiome and gut barrier function. Meditation helps regulate the stress response, thereby suppressing chronic inflammation states and maintaining a healthy gut-barrier function.

Conclusions • The current research team recommends the integration of meditation into conventional health care and wellness models. Concurrently, studies to explore the effects of meditation on human microbiota are warranted. (*Adv Mind Body Med.* 2017;31(4):10-25.)

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The Buddha taught followers how to end suffering (ie, *dukkha*) and to rise above the inevitable experience of illness, aging, and death. A positive or even neutral mindset (ie, *sukha*) is the prescription to overcome suffering.

The undeniable truths that bewildered the Buddha still exist. The world has made apparent progress, yet life has become increasingly overwhelming. Globally, more than 25% of individuals are affected by anxiety and depression disorders.[1] Anxiety-related disorders are now the predominant cause of mental illness, affecting 18% of the US population.[2]

Perhaps the art and science of happiness has been overlooked in the process of realizing material potential. A revisiting of the ancient teachings of happiness is thus warranted. However, revisiting them through philosophy alone would have a finite reach in this age of scientific reason. Fortunately, with practitioners now empowered by an understanding of stress physiology, the teachings may be interpreted in terms of the underlying science.

The mental state of equanimity that can be achieved through the practice of meditation is, in part, characterized by an absence of stress. Meditation is gaining popularity in clinical settings, and its treatment efficacy is being studied for a wide array of psychological and physiological ailments, including psychiatric disorders, cardiovascular diseases, dermatological conditions, gastrointestinal dysfunction, and musculoskeletal disorders. This interest necessitates further investigation into the underlying mechanisms of its therapeutic value.

Therefore, exploration of stress physiology is an essential precursor to delineation of the mechanisms underlying the beneficial effects of meditation practices. Stress physiology includes processes across the autonomic nervous system, the immune system, and the gut microbiota.

In the current review, the research team outlines a model of interconnected physiological processes that might support the continued inclusion and expansion of meditation in the treatment of diverse medical conditions. It discusses the role of physiological systems in the context of *dukkha* and *sukha*, with the intention of providing a novel framework in which to understand and conceptualize the beneficial effects of meditation practices.

The current research team hypothesized a significant role for the gut microbiota in realizing well-being through meditation. In describing this process model, the research team has underscored the profundity of the effects of these states by highlighting their epigenetic nature. Ultimately, the review highlights the potential avenues of meditation research and encourages the integration of meditation as a treatment modality in conventional medicine.

METHODS

Procedures

The review took place across 3 locations: New York University (New York, NY, USA), the University of California, San Diego (La Jolla, CA, USA), and the Chopra Foundation (Carlsbad, CA, USA). The goal was to identify details of the stress pathway consisting of the hypothalamic–pituitary–adrenal (HPA) axis, the autonomic nervous system, human microbiota (ie, especially the widely studied gut microbiota), and epigenetics. The review consists of studies reflecting the processes underlying the state of stress and the state devoid of stress. Therefore, the study aimed to examine more than 400 scientific papers and book chapters across the fields of neuroendocrinology, nervous system, human microbiota, immunology, mind-body medicine, and epigenetics. Databases searched include Medline via PubMed and Ovid, PsycINFO via Ovid, Spinet, ProQuest Central, SAGE Research Methods Online, CINAHL Plus with Full Text, Science Direct, Springer Link, and Wiley Online Library. Keywords searched included, but were not limited to, *stress*, *meditation*, *mindfulness*, *immune system*, *HPA axis*, *sympathetic nervous system*, *parasympathetic nervous system*, *microbiota*, *microbiome*, *gut barrier function*, *leaky gut*, *vagus nerve*, *psychoneuroimmunology*, *epigenetic*, and *NF-κB*. The number of citations was then narrowed to 144. The selection criterion was primarily to cite multiple studies that have been conducted in each of the aforementioned fields of discipline to support the theoretical arguments in this review. All members of the research team reviewed the articles and resulting analyses. Each team member vetted and signed off on the appropriateness of including the articles within this review.

RESULTS

Stress may be viewed as an actual or perceived challenge to physiological equilibrium.[3] *Dukkha* is a psychological state that triggers a physiological stress response, (ie, *dukkha* is psychological stress and s*ukha* is a psychological state of ease that is devoid of stress).

The interplay of physiological pillars shapes the cycle of *sukha* and *dukkha*, namely (1) the sympathetic nervous system (SNS) and the parasympathetic nervous system (PSNS) regulate the involuntary processes of the body, such as respiration, with the SNS initiating the fight-or-flight response in times of stress, and the PSNS restoring a resting state; (2) the neuroendocrine organs of the HPA axis also regulate the stress response, enabling the start, continuation, and end of the stress management process and maintaining physiological balance (ie, homeostasis); (3) the lymphoid organs of the immune system produce and activate an army of cells and a cascade of chemical reactions, ultimately neutralizing or destroying pathogens; and (4) the microbiota, a collection of 100 trillion microbes prevalent in the parts of the body that interface with the external environment (eg, the gut) and prompts chemical reactions in the body in response to environmental changes.

Dukkha hijacks the body's stress management machinery (Figure 1) and triggers a fight-or-flight response. The state of mental balance in *sukha* leads to homeostasis.

Stress Appraisal

Some form of somatosensory stimulus often initiates what is ultimately perceived as a stressor. Upon detection, the stimulus is analyzed to determine whether any action should

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Figure 1. Stress Management Process

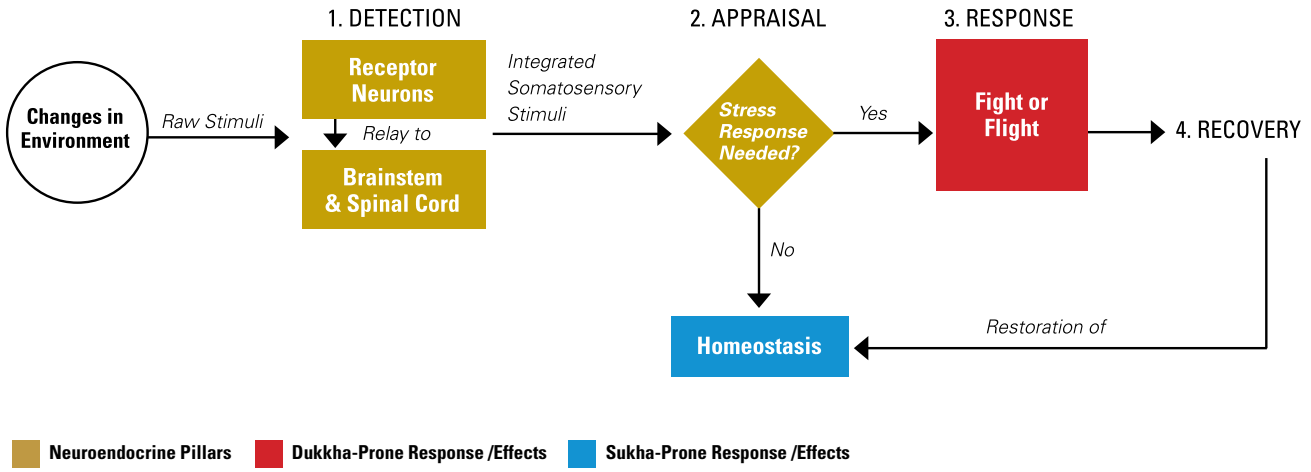
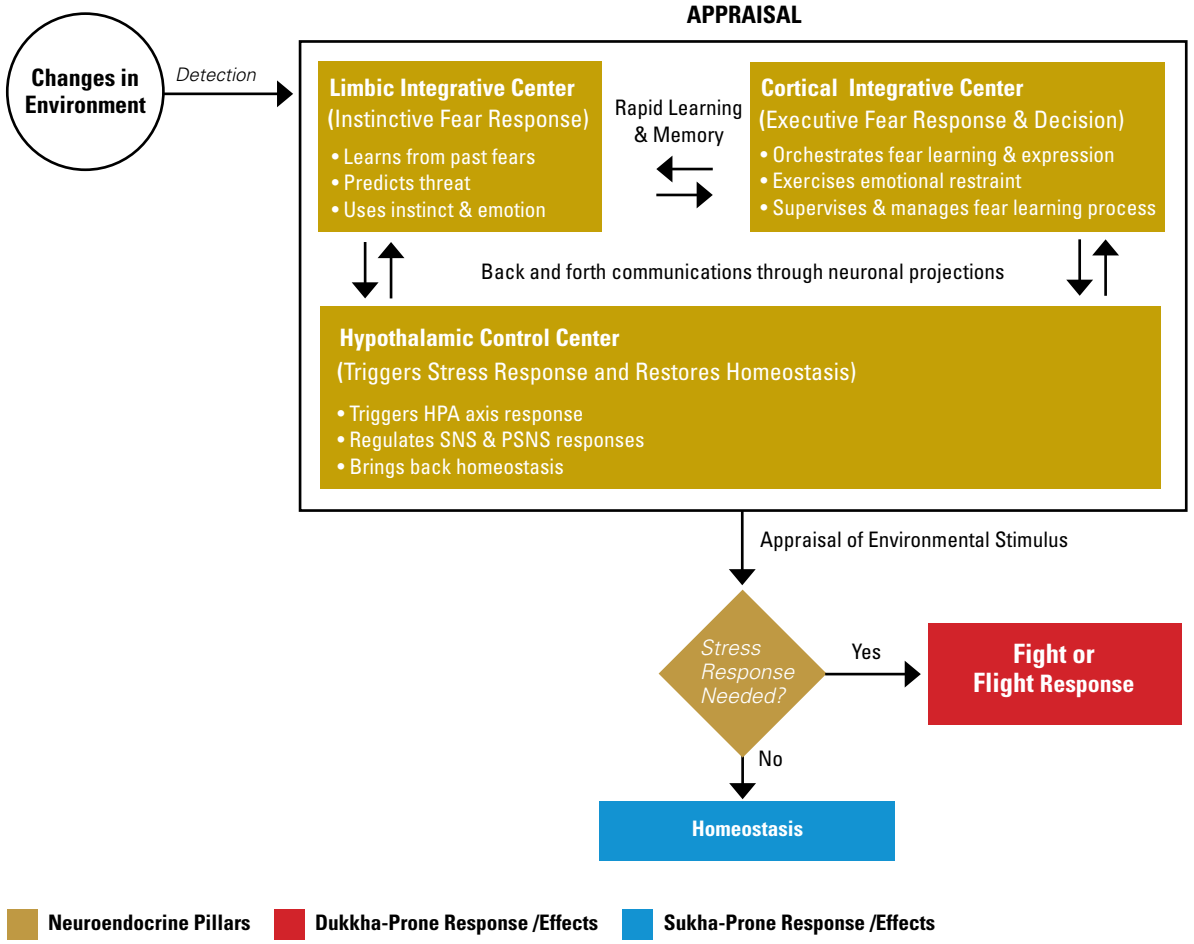


Figure 2. Stress Appraisal Phase



Abbreviations: HPA, hypothalamic-pituitary-adrenal; SNS, sympathetic nervous system; PSNS, parasympathetic nervous system.

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be taken. Interestingly, this stress appraisal process may be affected by judgment. The limbic system, cerebral cortex, and hypothalamus integrate and analyze raw environmental stimuli (Figure 2).[4]

Limbic Integrative Center. The limbic system is responsible for the instinctual fear response. A conditioned fear response originates when it identifies an event as a threat based on past memories. *Dukkha* could trigger this fear response. The limbic system includes the amygdala, hippocampus, thalamus, hypothalamus, basal ganglia, and cingulate gyrus.

The hippocampus helps individuals to remember the context of past events that were perceived as fearful, and the hippocampus-lateral-septum pathway helps them associate the context with an appropriate stress response.[5,6] The midline thalamus plays a role in predicting a threat based on past experiences.[7] The amygdala, which is activated in emotional responses, acts as a switch for the stress alarm system and initiates sympathetic and HPA responses.[8,9] The amygdala is the seat of the instinctual fear response and does not necessarily thoroughly appraise the threat.[10]

In summary, the limbic integrative center is where the threat level of an event is judged based on primal instincts and a subjective version of past memories; thus, it is possibly prone to emotional bias and judgment errors.

Cortical Integrative Center. The cerebral cortex supervises and facilitates limbic fear processing. The structures of the limbic and cortical integrative centers have intricate connectivity, supporting their close alliance.[11] The medial prefrontal cortex (mPFC) regulates the emotional response and plays an integral role in decision making.[12] Interestingly, the infralimbic cortex in the mPFC is part of a circuit that determines whether a stressor is under control.[4,11,13-15] It helps humans learn to control overreactions during times of danger.[16] In general, the cerebral cortex has the power to override emotional responses.[17] In contrast, a misguided cortical integrative center has the power to trigger false alarms.

Hypothalamic Control Center. The hypothalamic stress control center consists of the hypothalamic paraventricular nucleus (PVN), which is heavily innervated with afferents from the limbic and cortical integrative centers. It integrates and translates these inputs into a net excitatory or inhibitory response. If the response is excitatory, a series of stress-related regulatory hormones are secreted.[18,19]

Parvocellular neurons of the PVN release corticotropin-releasing hormone (CRH), triggering an HPA axis response. The parvocellular neurons project both to the SNS (eg, the parabrachial nucleus) and to the PSNS (eg, the dorsal nucleus of the vagus nerve), thereby exerting regulatory control over both.[18] In addition, the PVN's magnocellular neurons release oxytocin and arginine vasopressin (AVP). Oxytocin downregulates stress responses.[20] Among its other functions, AVP plays a crucial role in reducing the stress response of the HPA axis through a negative feedback mechanism,[21] toward the conclusion of a stressful event.

In summary, the hypothalamic stress control center integrates information from the limbic and cerebral cortices, promotes a fight-or-flight response if necessary, and regulates the neuroendocrine pillars (ie, the HPA, SNS and PSNS) of the cycle of *sukha*, (ie, homeostasis) and *dukkha* (ie, suffering). Ironically, these inputs can carry a faulty interpretation of upstream signals, thus resulting in an erroneous fight-or-flight response.

Stress Response

A phased fight-or-flight response initiates (1) an immediate induction of sympathetic hormones; (2) a longer lasting, intermediate effect facilitated by the SNS; and (3) a prolonged effect induced by the HPA axis.[22]

Immediate Stress Response. The immediate effects, which last for 2 to 3 seconds, provide urgent physical responses, such as sweating, rapid heart rate, and muscle tension. To enable a rapid response, the inputs of this phase are based on a quick assessment of the triggering event. This relatively hardwired response pathway originates in sympathetic premotor neurons of the brainstem and hypothalamus.[23,24] The brainstem receives somatosensory stimuli and mediates arousal.[25] It quickly detects danger.[8] The brainstem is implicated in instinctual primitive responses that are not muddled by subjective interpretation.[26] Therefore, this pathway is not biased by judgment.

The second branch of sympathetic premotor neurons originates in hypothalamic regions (eg, the PVN) and receives enough information about the somatosensory trigger and the psychological interpretation to offer an immediate threat assessment.[27,28] However, a quick assessment, instead of a complete analysis, can lead to a false alarm, as follows: (1) the sympathetic premotor neuronal pathway projects to sympathetic preganglionic neurons, which innervates the sympathetic ganglia with cholinergic projections (ie, secreting neurotransmitter acetylcholine [ACh])[22] and (2) the postganglionic neurons emerge from those projections and innervate the internal organs, directly injecting catecholamines and immediately eliciting the physical stress response.[22,29] However, a prolonged stress response is needed to ward off a potential danger effectively.

Intermediate Stress Response. The chromaffin cells of the adrenal medulla have the same embryological origin as the sympathetic ganglia and, thus, are innervated by cholinergic sympathetic preganglionic nerves.[29,30] When stimulated, these cells release catecholamines directly into circulation. It takes longer for the neurotransmitters to travel to effector organs than those being directly delivered by hardwired sympathetic nerves. However, the effects of the intermediate stress response last longer (ie, 20 to 30 seconds) than the immediate effects and are more global.[22]

Prolonged Stress Response. After stress stimuli are fully analyzed, the hypothalamic control center secretes CRH and AVP into the hypophyseal blood vessels that connect the hypothalamus to the anterior pituitary gland. These hormones stimulate the anterior pituitary gland to produce

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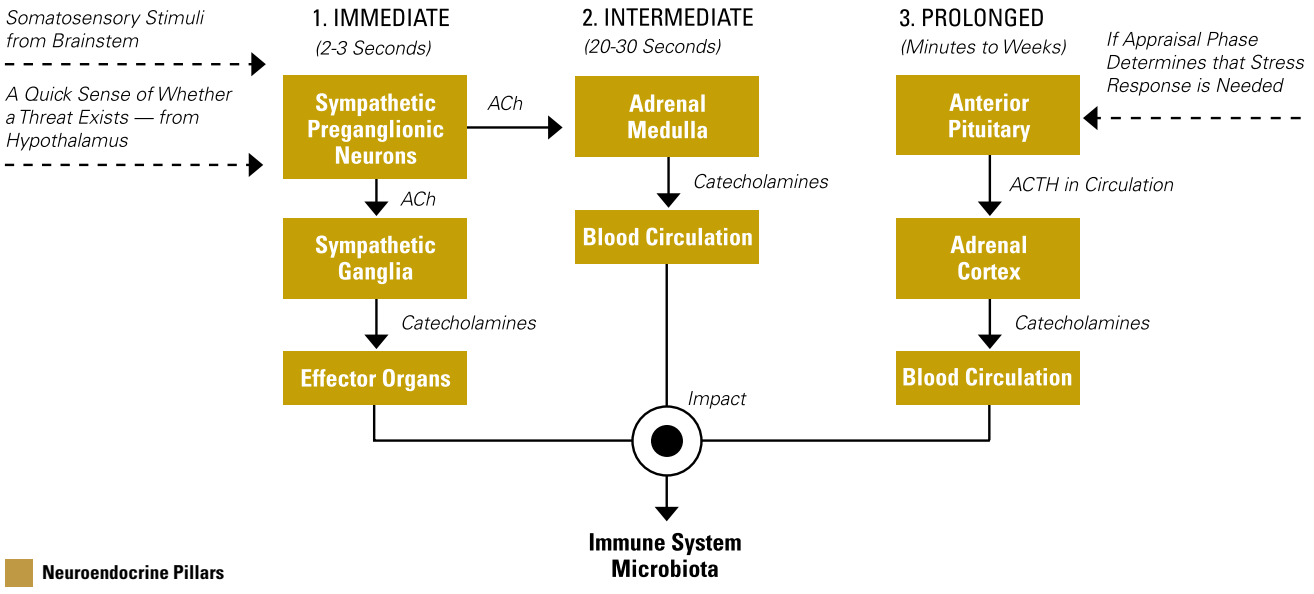
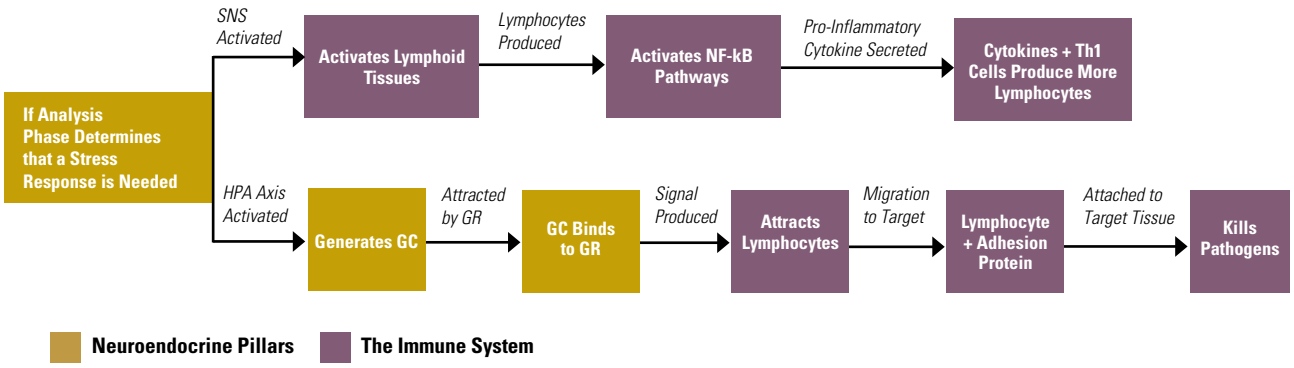
Figure 3. Stress Response Phase



Abbreviations: ACh, acetylcholine; ACTH, adrenocorticotropic hormone.

Figure 4. Immune Response to Stress



Abbreviations: SNS, sympathetic nervous system; NF-κB, nuclear factor kappa-light-chain-enhancer of activated B cells; Th1, T-helper1; HPA, hypothalamic-pituitary-adrenal; GR, glucocorticoid receptors; GC, glucocorticoid.

and secrete adrenocorticotropic hormone (ACTH) into the general circulation. ACTH induces glucocorticoid (GC) synthesis and release from the adrenal cortex.

GC mediates the stress management process by regulating metabolic, cardiovascular, and immunological activities. It stimulates the adrenal medulla to produce an increased amount of epinephrine for the sympathetic response[31] and to restore homeostasis after stress subsides.[27] Depending on the nature of the stressor, these effects may persist from minutes to weeks.

In summary, the hypothalamic control center initiates the HPA axis response, thereby generating potent steroids that remain active until the body recovers from stress. Thus, a fight-or-flight response triggered by judgment errors has harsh results. The processes underlying the immediate, intermediate, and prolonged stress responses are shown in Figure 3. The overall stress response has an expansive effect. The HPA axis also stimulates an immune response.

Immune Response to *Dukkha*

From an evolutionary perspective, a fight-or-flight response serves as a survival mechanism against physical injury or pathogenic invasion and infection. An immune response helps to prevent infection. Thus, in part, an immune reaction in stress offers an evolutionary advantage to humans.[32] However, *dukkha* can trigger a fight-or-flight response, including the accompanying immune response and inflammation, as elaborated in Figure 4.[32]

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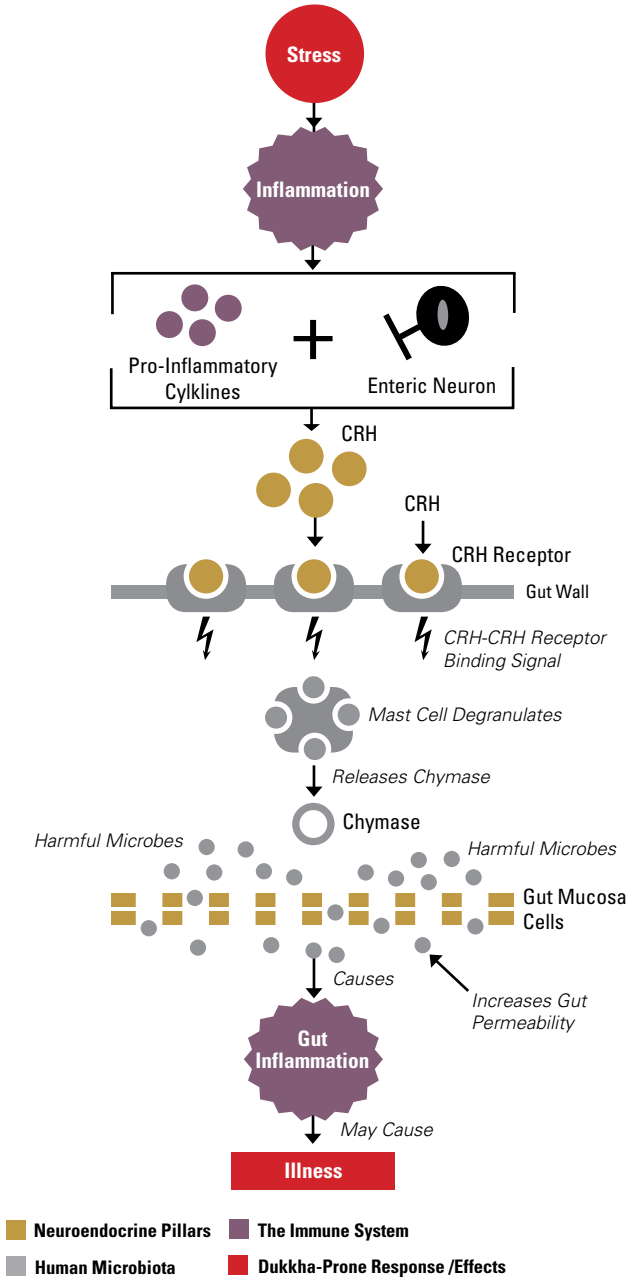
Figure 5. Gut Microbial Response to Stress, the CRH Pathway



Abbreviations: CRH, corticotropin-releasing hormone.

Catecholaminergic varicosities of postganglionic neurons innervate the lymphoid organs where lymphocytes are formed, matured, and activated.[33,34] During stress, sympathetic nerves release catecholamines that bind to the adrenergic receptors expressed on lymphoid tissues,[35] which then signal and regulate the activity of lymphocytes.[36] During stress, an altered gut microbial population affects the regulation of neurotransmitters mediated by the microbiome and gut barrier function, which will be discussed in the following section.[37]

The signals generated by B- and T-lymphocytes trigger the partial degradation of p100 protein that leads to the release of p52/relB proteins, which are the precursors of the transcription factor *nuclear factor kappa-light-chain-enhancer of activated B cells* (NF-κB) protein complex.[38] When NF-κB is expressed and activated, a cascade of signaling events leads to the production of proinflammatory cytokines. These cytokines induce the maturation and activation of both B and T cells, which upregulate the NF-κB pathways, thus intensifying a self-perpetuating proinflammatory cycle.[38-40] T-helper 1 (T_h1) cells, a T-cell subtype, play a key role in this proinflammatory phase of the immune response, which is known as a T_h1 response.

The HPA axis is activated during stress and produces GC molecules that bind to glucocorticoid receptors (GRs) located on target tissues. GRs signal lymphocytes to move toward effector sites.[41] Concurrently, the NF-κB pathway induces the transcription of adhesion proteins expressed on endothelial tissues at effector sites, which instruct lymphocytes to persist locally.[42,43]

Gut Microbial Response to *Dukkha*

Lymphoid tissues generate disease-fighting immune cells. Some are located near places where the body interfaces with the external environment. Environmental microbes are also picked up at these interfaces. Therefore, the microbiota, including gut microbes, is in close proximity to lymphoid tissues and engages in active bidirectional communication with the immune system. An immune response thus affects gut microbes and vice versa (Figure 5).

Gut Microbial CRH Pathway in *Dukkha*. Inflammation resulting from stress affects various parts of the body, including the gut. Proinflammatory cytokines interact with enteric nerves to stimulate the secretion of CRH locally.[44] CRH binds to CRH receptors found on the gut epithelium. Mast cells are found near these receptors and offer immune protection. Upon CRH receptor binding, the receptor signals mast cells to degranulate.[45]

A healthy gut wall selectively allows specific molecules (eg, nutrients) in while it keeps others (eg, pathogens) out. Tight junction protein (TJP) prevents permeability via the paracellular route between epithelial cells. Mast cell degranulation prompts the release of chymase, which is thought to degrade the cellular matrix including TJP, resulting in increased gut-barrier permeability.[46]

A permeable gut epithelium exposes the underlying immune system to bacterial and food-derived antigens that induce inflammation. Sustained inflammation due to leaky gut perturbs the balance of the gut microbiota and leads to dysbiosis that can feature an increased abundance of pathogenic organisms with the capacity to breach the epithelium, gain access to immune-sensitive compartments, and proliferate systemically via the bloodstream. The cell wall of Gram-negative bacteria contains lipopolysaccharide (LPS). Acute-phase LPS-binding protein binds with LPS and subsequently forms a ternary complex with cluster of

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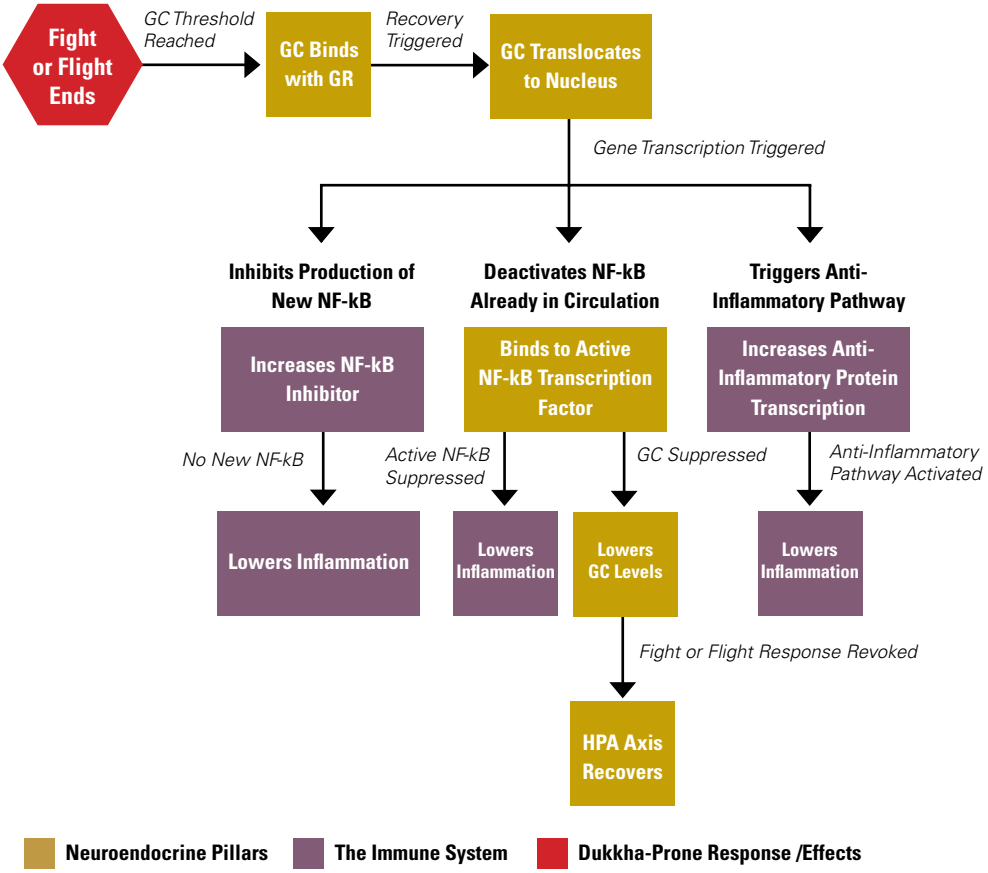
Figure 6. HPA Axis in Recovery Phase



Abbreviations: HPA, hypothalamic-pituitary-adrenal; GC, glucocorticoid; GR, glucocorticoid receptors; NF-κB, nuclear factor kappa-light-chain-enhancer of activated B cells.

differentiation 14 (CD14) protein. This action allows LPS to bind its receptor complex, which consists of toll-like receptor 4 (TLR4) proteins and myeloid differentiation protein 2 (MD-2).[47]

The LPS-MD-2 binding triggers TLR4 oligomerization, signaling the recruitment of the adaptor proteins (1) myeloid differentiation primary response gene88 (MyD88), (2) toll/interleukin (IL) 1 receptor (IL-1R) domain-containing adaptor (TIRAP), (3) TIR-domain-containing adaptor-inducing interferon-β (TRIF), (4) TRIF-related adaptor molecule (TRAM), and (5) sterile A and HEAT-Armadillo Motifs (SARM).[48]

TIRAP activates a MyD88-dependent inflammatory pathway, generating NF-κB and proinflammatory cytokines.[49,50] TRAM activates TRIF, which leads to the production of NF-κB and type 1 interferons. The MyD88 pathway recruits IL-1R-associated kinase-4 (IRAK-4) enzyme, which increases the stability of tumor necrosis factor alpha (TNF-α) mRNA. An activated TNF-α promotes inflammation and vasodilation of the intestinal endothelium, prompting an efflux of leukocytes.[51,52] In summary, adaptor-protein recruitment triggers an immune response in local lymphoid tissues,[53-55] thus increasing systemic inflammation.

Gut Microbial Zonulin Pathway in *Dukkha*. Systemic inflammation and exaggerated pathogenic stimulation often accompany anxiety and depression.[56-58] The resulting MyD88-dependent inflammatory pathway leads to the upregulation of zonulin, a scaffolding protein. Under normal circumstances, zonulin binds TJP to the gut epithelial cytoskeleton[59]; however, its upregulation leads to actin-microfilament polymerization and results in TJP disassembly.[56]

The microbiota is greatly affected by conditions of reduced gut-barrier function. A healthy microbiota has a diversity of species and functions. However, when gut-barrier activity is reduced, a shift occurs toward a less diverse microbial population.[60] The host's genetic predisposition plays a role in determining the microbial species that are more likely to bloom.[61] Moreover, as one microbial species often cross-feeds on the byproducts generated by another, new sets of intermicrobial relationships emerge.[62] These effects collectively affect processes, including biochemical, physical, and ecological processes within each gut microbial community, thus disturbing their equilibrium.[63]

Stress Recovery

Restoration of the HPA Axis. The fight-or-flight response is meant to be short lived. In a healthy organism, its effects tend to dampen appropriately. The GR detects when GC plasma levels reach a threshold and starts revoking the fight-or-flight response.[64] The bound receptor then

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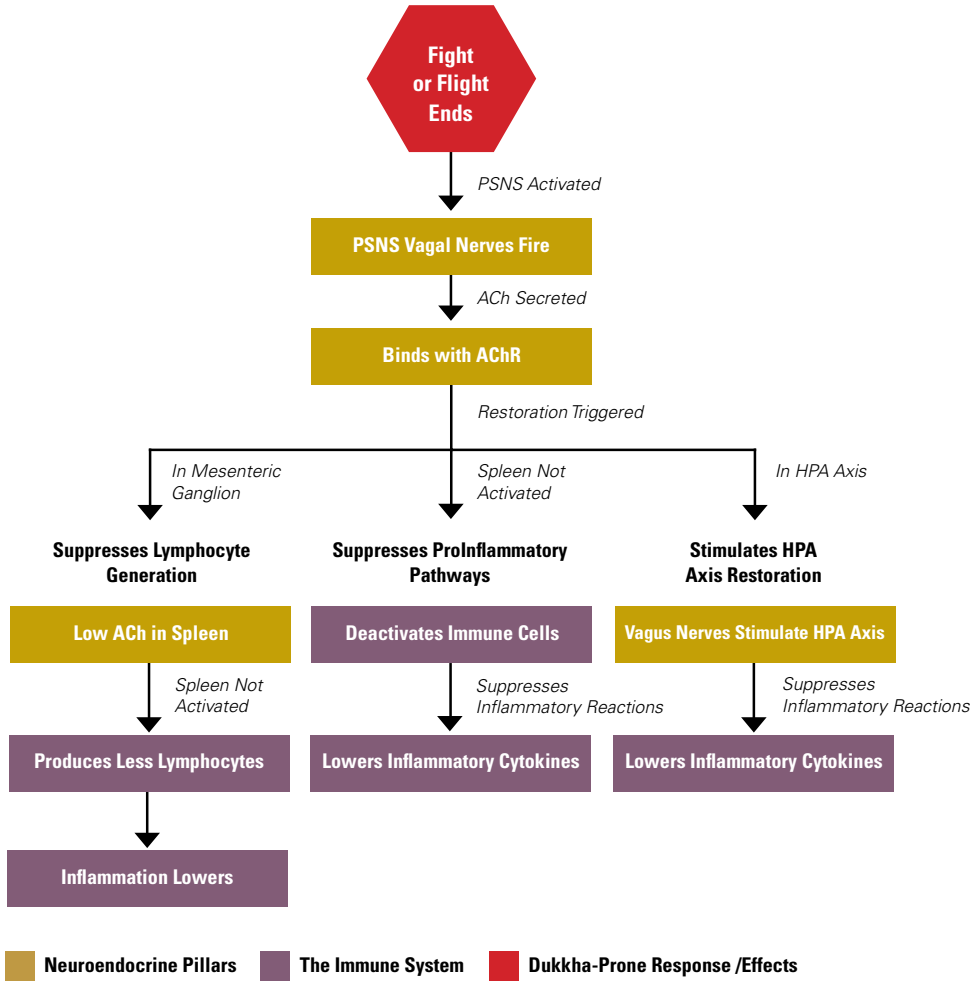
Figure 7. PSNS in Recovery Phase



Abbreviations: PSNS, parasympathetic nervous system; ACh, acetylcholine; AChr, ACh receptor; adrenocorticotropic hormone; HPA, hypothalamic-pituitary-adrenal.

translocates to the nucleus and thereafter triggers the transcriptional activities to initiate restoration (Figure 6).

GC induces transcription of the NF-κB inhibitor protein (ie, inhibitor of κB [IκB]), thereby downregulating the inflammatory NF-κB cascade.[65] GC retracts NF-κB that was already released.[66] GC and NF-κB transcription factor proteins bind to each other to create a mutual suppression.[67] Moreover, GC promotes the transcription of anti-inflammatory proteins.[67,68] Collectively, these processes terminate the inflammation that was triggered by a fight-or-flight response.

Restoration of the PSNS. Signaled by the negative feedback from the HPA axis, the PSNS takes an active role in restoring homeostasis. Its effects are communicated via the vagus nerve, which innervates many internal organs, including lymphoid organs. The main neurotransmitter in the PSNS is ACh. ACh binds to ACh receptor (AChR) and triggers a cascade of reactions that reduce inflammation.

Vagal innervations at the celiac-superior mesenteric ganglion modulate the adrenergic input to the spleen via the splenic nerve. Toward the resolution of a fight-or-flight response, vagal ACh suppresses adrenergic stimulation of the spleen, thereby stifling the production of immune cells.[69] Moreover, it binds to AChR found on immune cells to suppress the NF-κB pathway and the subsequent production of proinflammatory cytokines.[69,70] Furthermore, vagal afferents stimulate the anti-inflammatory pathway of the HPA axis, thus reinforcing its restorative function (Figure 7).[70]

Restoration of the Immune System. The pathogen-detecting, major histocompatibility complex (MHC) is upregulated on cell surfaces during a stressful event.[71] Circulating catecholamines reach a threshold level, signaling that pathogens have been eliminated. Cell surfaces thus downregulate MHC expression.[72] MHC modulates T-cell receptor signaling and, therefore, the resulting immune response. Downregulated MHC induces a weaker T-cell-receptor signal.[72] An attenuated signal serves as a trigger for the restorative T-helper 2 (T_h2) cell pathway,[32,73,74-75] which

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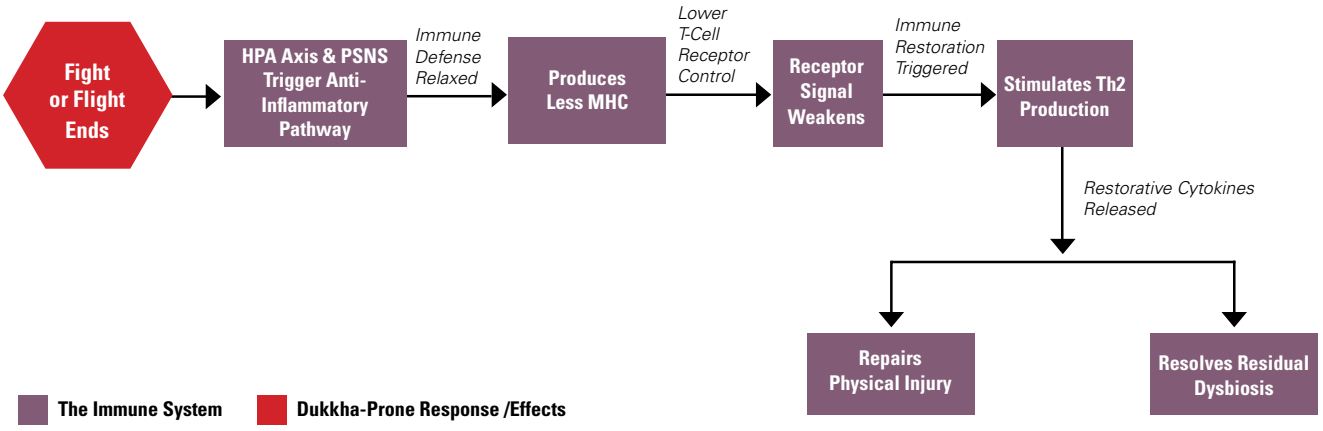
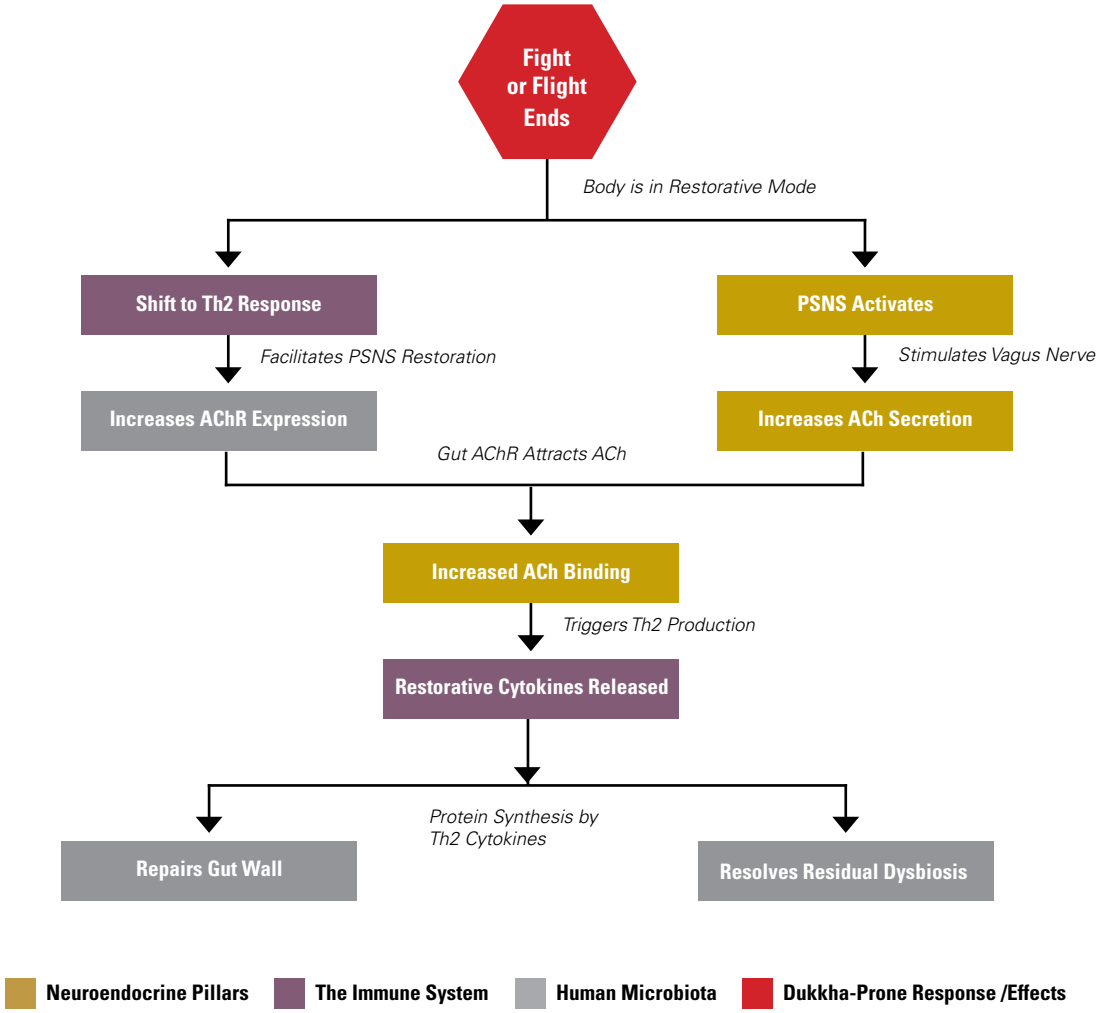
Figure 8. Immune System in Recovery Phase



Abbreviations: HPA, hypothalamic-pituitary-adrenal; PSNS, parasympathetic nervous system; MHC, major histocompatibility complex; Th2, T-helper 2.

Figure 9. Gut Microbes in Recovery Phase



Abbreviations: Th2, T-helper 2; PSNS, parasympathetic nervous system; AChR, ACh receptor; ACh, acetylcholine.

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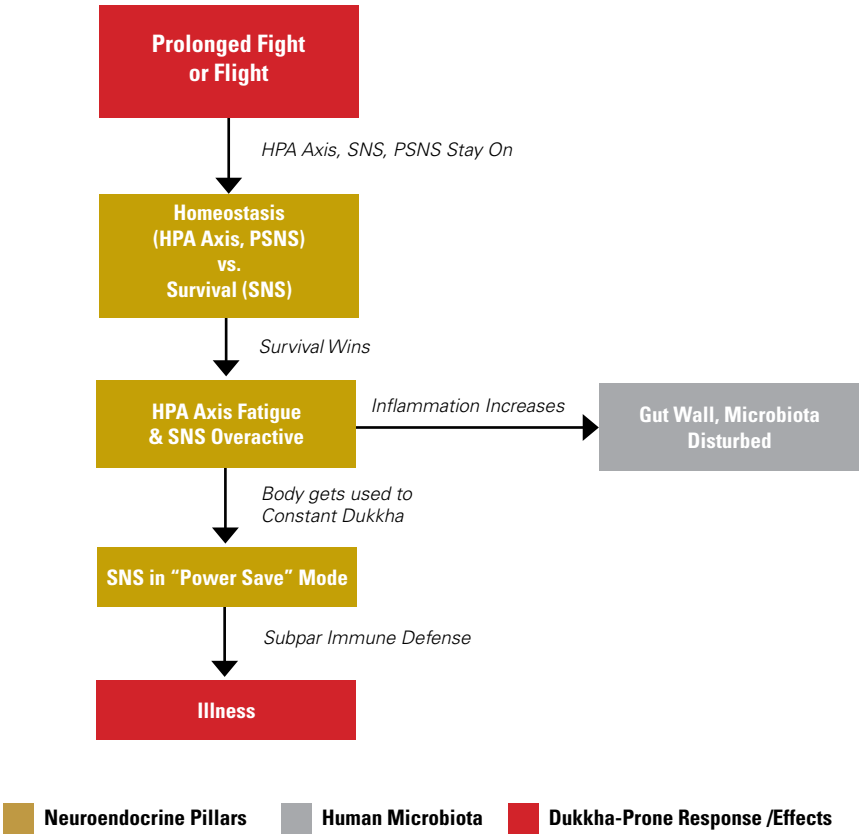
Figure 10. Stress Can Become Chronic



Abbreviations: HPA, hypothalamic-pituitary-adrenal; SNS, sympathetic nervous system; PSNS, parasympathetic nervous system.

ultimately releases cytokines that promote recovery from inflammation.[76] Cytokines IL-4 and IL-13 induce expression of proteins required for wound repair.[76] IL-4, IL-5, IL-10, and IL-13 activate macrophage scavenger cells to clear any persistent pathogens (Figure 8).[76]

Restoration of Microbial Health. The shift from the T_h1 to the T_h2 immune response upregulates nicotinic AChR on the gut epithelial surface, which is also heavily innervated by vagal ACh afferents, thereby upregulating ACh-AChR binding on the epithelium, ultimately to trigger anti-inflammatory responses (Figure 9).[77]

Chronic *Dukkha* or Suffering

The HPA axis restores homeostasis by lowering inflammation that accompanies a fight-or-flight response. However, the proinflammatory SNS continues to be activated by psychological stress. Thus, 2 opposing forces emerge during chronic stress. The SNS offers the more urgent protection from physical distress. Ultimately, survival is chosen over homeostasis (Figure 10).[78]

The HPA axis adapts to chronic stress. GC-GR binding normally signals homeostasis, but the HPA axis may become GR-resistant during chronic stress.[79] The GR facilitates a healthy immune response.[43] Thus, a blunted GR-sensitivity leads to weak immune responses, suppresses proinflammatory responses, and prevents T_h1 cytokine levels from reaching the levels necessary for disease fighting.[75,80] Natural killer cells that normally prevent tumors and microbial infections are less cytotoxic than T_h1-cells, which may explain, at least in part, the observed susceptibility to cancer during chronic stress.[81,82]

The PSNS attenuates vagal ACh-signaling, and the SNS remains activated.[83] Sympathetic overactivation promotes excessive catecholamine production.[84] A constantly stimulated SNS induces a steady production of cytokines, such as interferon gamma (IFN-γ). IFN-γ encourages TJP uptake from the gut epithelium to form vesicles, thus disturbing the integrity of the gut epithelial barrier.[85] IFN-γ also triggers the NF-κB pathway within the gut.[86]

Catecholaminergic receptors reuptake and store excess extracellular catecholamines. In chronic stress, the receptors desensitize themselves to prevent excessive catecholaminergic reuptake.[87-89] The stored catecholamines are eventually depleted. Because catecholamines are crucial for essential physiological functions, such as maintaining a normal heart rate, the adrenal medulla increases catecholamine production during chronic stress.[90] Prolonged stress can create a predictable, maladaptive pattern in which the SNS remains activated but slightly attenuated.[90]

Epigenetics of *Dukkha* and *Sukha*

The illness- and health-inducing effects of *dukkha* and *sukha*, respectively, can become epigenetically imprinted.

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Genetic modifications that occur throughout a lifetime are called epigenetics and can be inherited by future generations.[91]

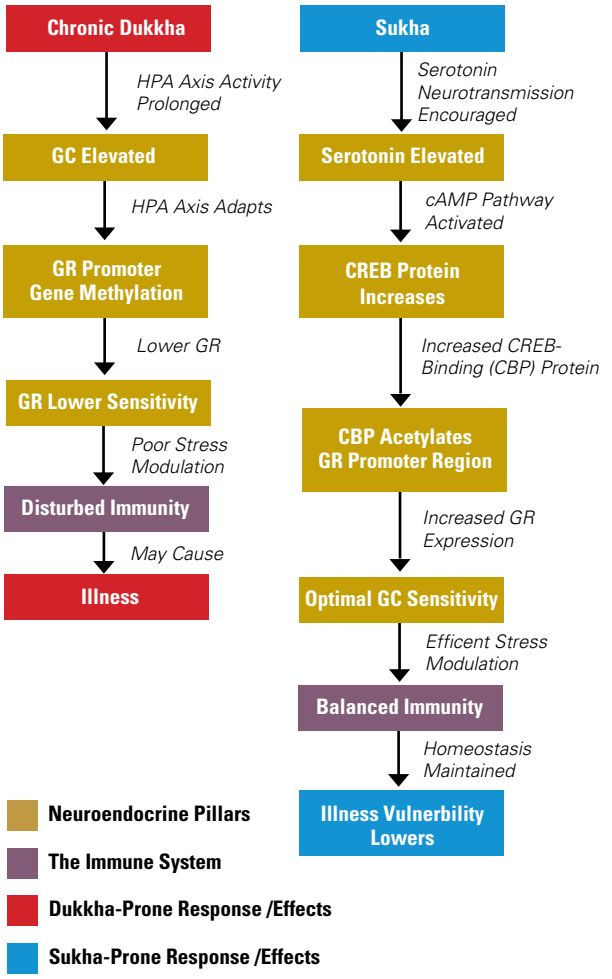
An epigenetic change does not alter the structure of deoxyribonucleic acid (DNA); it instead increases or decreases the rate of gene expression, through modifications of acetylation, deacetylation, messenger ribonucleic acid (mRNA), and microRNA (miRNA).[92] Acetylation loosens the histone protein that packages the DNA strand, thus opening up the DNA to be transcribed. Deacetylation by histone deacetylase (HDAC) causes the histone to wrap more tightly around the DNA, thus preventing the gene from being easily expressed. Methylation adds a methyl group to genes and typically silences gene expression. In addition, after a gene is expressed, mRNA decays. Modifications to mRNA can trigger early mRNA that suppresses gene expression. Finally, miRNA binds with target mRNA to regulate its translation. When an epigenetic modification occurs repeatedly, an epigenetic memory is formed, which is interpreted as a survival necessity and often is transmitted to offspring.[91,93]

During the cycle of *sukha* and *dukkha*, the body's physiological pillars undergo epigenetic modifications that result in a decrease or increase in inflammatory gene expression.[94]

Epigenetic Reactions of the HPA Axis. In chronic stress, methylation of GR promoter genes is upregulated, which results in suppression of the GR expression and, therefore, the GC signaling that follows GC-GR binding.[95,96]

Pleasant experiences or *sukha* promote serotonin production, which is associated with cyclic adenosine monophosphate (cAMP) activation. The cAMP pathway facilitates cellular communication. An activated cAMP pathway results in increased production of the cAMP-response element-binding (CREB) protein, which recruits the CREB-binding protein (CBP). CBP acetylates promoter regions of GR genes, ultimately to upregulate the number of GRs during *sukha* (Figure 11).[95]

Figure 11. Epigenetic Changes of HPA Axis in *Dukkha* & *Sukha*



Abbreviations: HPA, hypothalamic-pituitary-adrenal; GC, glucocorticoid; GR, glucocorticoid receptors; CREB, cyclic adenosine monophosphate (cAMP) response element-binding protein; CBP, CREB-binding protein.

Epigenetic Reactions of the SNS and PSNS. In chronic *dukkha*, the SNS ultimately adapts by silencing its reuptake transporter genes through methylation (Figure 12).[97]

The PSNS helps restore homeostasis primarily through ACh. *Dukkha* and *sukha* both exert epigenetic effects on ACh neurotransmission. Because excessive ACh accumulation is toxic, acetylcholinesterase (AChE) clears ACh postneurotransmission through deactivation.[98,99] *Dukkha* downregulates acetylation and upregulates methylation of the promoter gene for AChE and thus represses AChE expression.[99] Therefore, ACh is not effectively cleared during *dukkha*. PSNS neurotransmission is dependent on the presence of synaptic ACh. During *dukkha*, high levels of ACh accumulate; PSNS neurotransmission is interrupted; and the restoration of homeostasis becomes challenging.

In *sukha*, a normally functioning PSNS activates the AChR alpha-7 nicotinic acetylcholine receptors, initiating production of microRNA miR-124, which induces an anti-inflammatory response (Figure 13).[100,101]

Epigenetic Reactions of the Immune System. In *sukha*, a healthy balance between the T_h1 response and the T_h2 response is maintained via epigenetic regulation. Both T_h1 and T_h2 cells differentiate from naive T cells after being stimulated by IFN-γ and IL-4, respectively. During a T_h1 response in *sukha*, IFN-γ is acetylated, resulting in subsequent IFN-γ expression. DNA methylation is subsequently downregulated at the IFN-γ promoter region of T_h1 cells, stimulating T_h1 cell development. Concurrently, T_h2-stimulating IL-4 expression is silenced through methylation.[102] During a T_h2 response in *sukha*, acetylation of the IL-4 gene leads to IL-4 expression, promoting T_h2 proliferation. Meanwhile, IFN-γ is silenced through methylation, suppressing the T_h1 response.[34]

In *dukkha*, a timely shift from a T_h1 to a T_h2 response does not occur due to underlying epigenetic reactions, which can lead to immune dysfunction.[103]

Epigenetic Reactions of Gut Microbiota. The human microbiota is a potent agent of epigenetic modification. In

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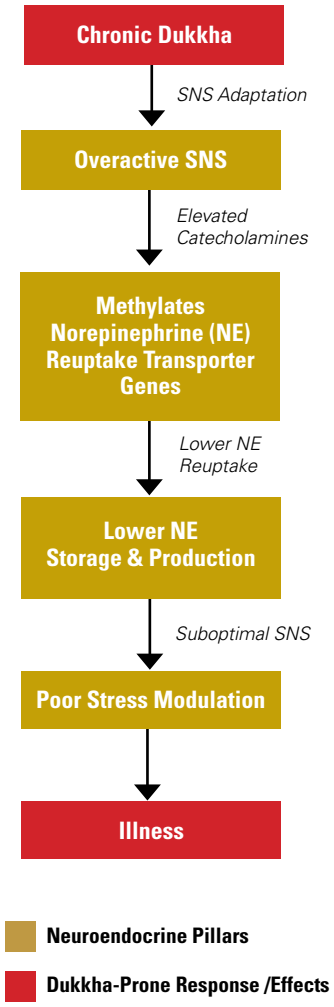
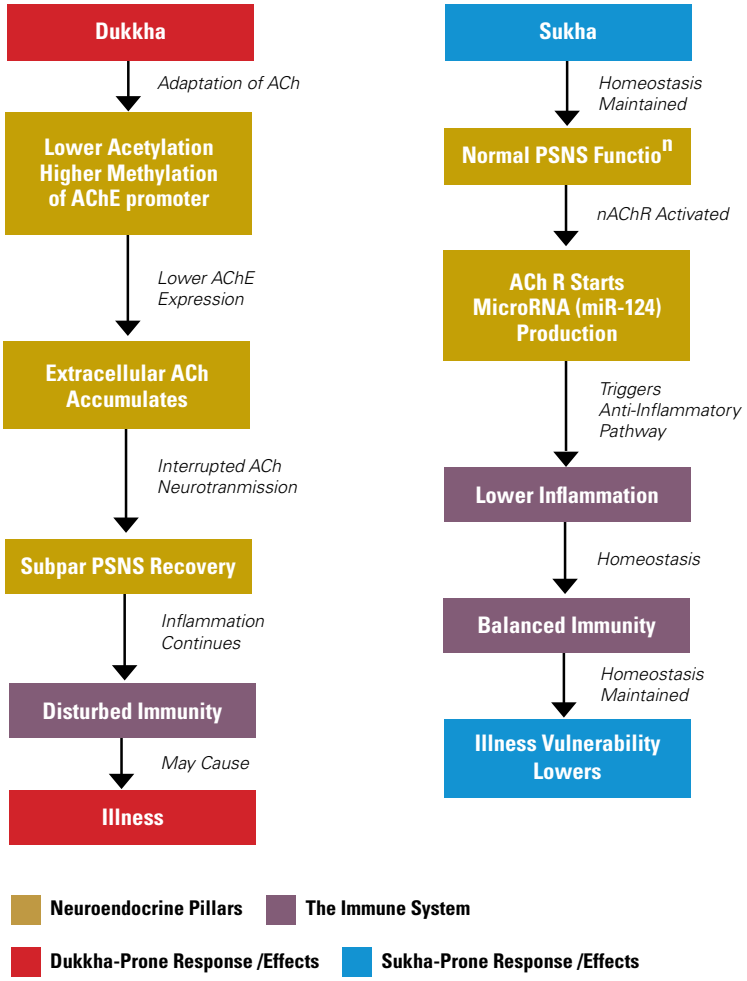
Figure 12. Epigenetic Changes of the SNS in *Dukkha*



Abbreviation: SNS, sympathetic nervous system.

Figure 13. Epigenetic Changes of the PSNS in *Dukkha* and *Sukha*



Abbreviations: PSNS, parasympathetic nervous system; ACh, acetylcholine; AChE, acetylcholinesterase; nAChR, nicotinic acetylcholine receptor; AChR, ACh receptor.

dukkha, an imbalanced or dysbiotic structure of the microbial population can develop. Microbes undergo DNA mutation, adjusting to this change. The new genes are passed on to the next generation of microbes in as little as 20 minutes.[104] This exceptionally fast evolution signals the rest of the body to adapt. Meanwhile, inflammatory microbes continue displacing beneficial microbes.[105]

In *sukha*, the microbiota preserves well-being through a multitude of epigenetic effects, such as its anti-inflammatory and antiproliferative benefits and improved barrier function. In healthy individuals, the gut microbiota produces short-chain fatty acids (SCFAs), such as butyrate, in abundance.[106,107]

Butyrate, a potent HDAC inhibitor, promotes acetylation and thus gene expression through several mechanisms. The metabolic products propionate, lactate, and pyruvate are HDAC-inhibitory as well but to a lesser degree than butyrate, with propionate being the most potent HDAC inhibitor of the 3 products.[108] This HDAC-inhibitory property often leads these metabolic products to hyperacetylate histones that ultimately exert beneficial effects on health.

For example, butyrate uses its acetylation properties to put a brake on the NF-κB pathway. This pathway employs cytochrome c oxidase 2 (COX2) to generate inflammatory cytokines. A set of proteins keeps the COX2 mRNA stable. Butyrate is hypothesized to acetylate these proteins, thus destabilizing COX2 mRNA and downregulating its proinflammatory pathway.[109] In addition, butyrate modulates the immune system by inhibiting HDAC classes I and IIa.

HDAC classes I and IIa suppress regulatory T-cell (Treg) proliferation. Therefore, their inhibition leads to Treg proliferation and, thus, downregulation of effector T-cell functions.[110] Another study found that the copious amount of butyrate produced in *sukha* hyperacetylates pyruvate dehydrogenase kinase (PDK) histones, thereby upregulating PDK expression, which inhibits the pyruvate dehydrogenase complex (PDC).[106,107,111]

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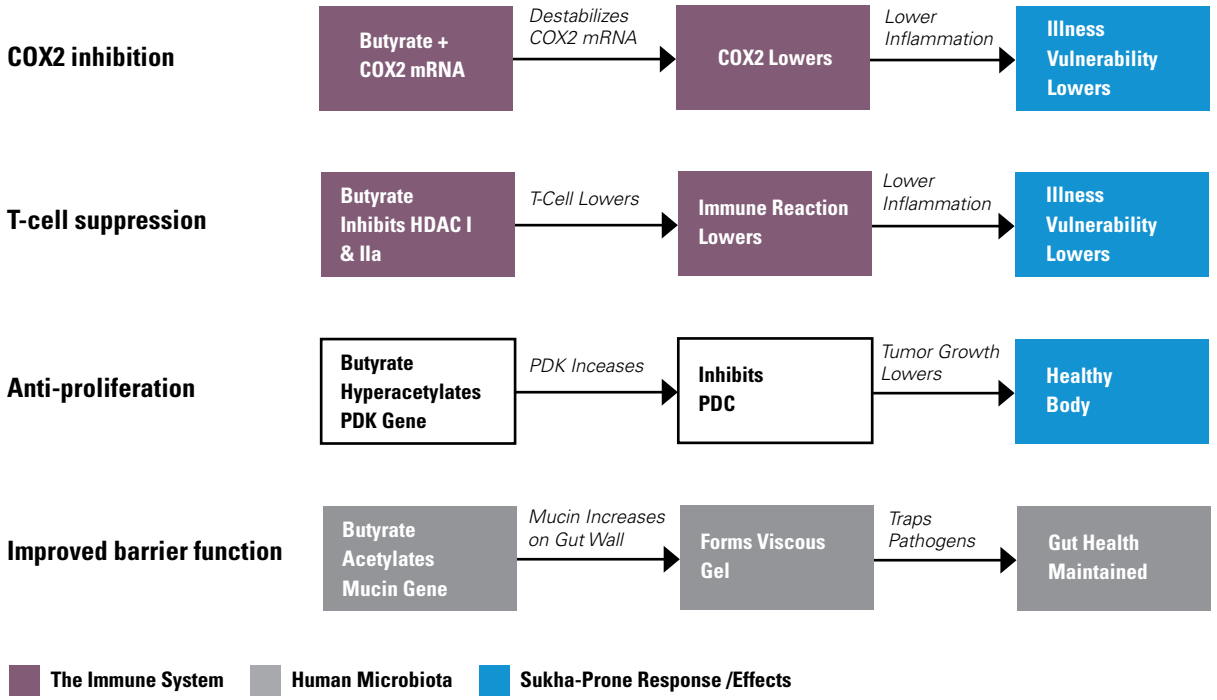
Figure 14. Butyrate-induced Epigenetic Changes in *Sukha*



Abbreviations: COX2, cytochrome c oxidase 2; HDAC, histone deacetylase; PDK, pyruvate dehydrogenase kinase; PDC, pyruvate dehydrogenase complex.

PDC helps divert pyruvate to the mitochondrial oxidative pathway as a source of energy for tumor growth.[111] Therefore, through PDC inhibition, butyrate may arrest tumor survival and growth.

In a final example, the acetylative properties of the ample butyrate and propionate in *sukha* promote the barrier function by upregulating mucin expression.[112,113] Mucin, a protein found in the epithelial layer, forms viscous gels to trap pathogens and promotes gut-barrier function. Moreover, the SCFAs produced in the gut are speculated to influence miRNA acetylation and methylation patterns.[114,115] These miRNAs, in turn, regulate intestinal barrier functions and immune defense (Figure 14).[115,116]

Due to the pervasiveness and system-wide effects of human microbiota, these epigenetic effects are not limited to the gut. Moreover, microbes communicate with the body via the general circulation by triggering immune pathways.[53,54,117] Therefore, their epigenetic effects may also be systemic.

Meditation to End Chronic *Dukkha*

Meditation, a common technique to calm the mind, exerts marked physiological influence and ultimately reduces the effects of *dukkha*.

Effects on the HPA Axis. On average, meditators exhibit lower levels of cortisol compared to nonmeditators.[118-121] Interestingly, some studies reported elevated levels of plasma cortisol following meditation, which also correlated with an increase in positive affect.[122,123] Although seemingly counterintuitive, meditation is speculated to have a regulatory effect on plasma cortisol. In 2 groups of participants with higher and lower than normal baseline cortisol levels, a normalizing effect was observed.[123,124]

Effects on the SNS and the PSNS. Meditators tend to have a lower heart rate, blood pressure, respiratory rate, and oxygen metabolism.[120,121,125-127] In addition, increased heart-rate variability is observed during meditation, which is often associated with activation of the anterior cingulate cortex (ACC).[128-130] The engagement of attention and working memory during meditation can be attributed to ACC activation, which in turn exerts autonomic control over cardiac functions.[129,130] Interestingly, greater coactivation of the SNS and PSNS in cardiac function is observed in meditators, which represents a mechanism that promotes healthier cardiac function by regulating ventricular contractility and heart rate.[130-132]

Effects on the Immune System. IL-6 and C-reactive protein—both biomarkers of inflammation—are reduced after meditation, and the magnitude of the reduction correlates with the amount of meditation experience.[124] Meditators also produce an increased antibody response compared to nonmeditators following flu vaccine administration.[133,134]

The biological mechanisms underlying the beneficial effects of meditation on the immune system are being investigated currently. Receptor-interacting serine-threonine kinase 2 (RIPK2), which promotes generation of NF-κB,[135] is downregulated in meditators.[136] COX2 genes are also

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downregulated in meditators.[136] NF-κB employs COX2 to generate inflammatory cytokines; thus, COX2 inhibition reduces inflammation. Among differentially expressed inflammatory pathways, NF-κB is observed as being frequently affected in mind-body practices.[137,138]

Interestingly, meditation upregulates HDAC inhibition,[136] and the degrees of RIPK2 and COX2 downregulation in meditators are correlated with the level of HDAC inhibition.[136] However, the cause of these positive changes is yet to be determined.

Effects on the Gut Microbiota. Meditation practice improves the symptoms of functional gastrointestinal disorders, such as irritable bowel syndrome.[139-142] Changes in the structure of the microbial population of the gut are thought to underlie both physiological and psychological symptoms of such disorders.[143] A healthy microbiota, on the other hand, promotes homeostasis and a robust immune system.[144] Although the effects of meditation on the microbiome have yet to be established, it would not be surprising that the microbiome, at least in part, mediates some of the beneficial effects of meditation on such disorders.

DISCUSSION

Psychological stress often triggers a fight-or-flight response, prompting CRH production in various parts of the body, including the gut where more than 100 trillion microbes reside.[144] Stress-induced factors such as CRH disturb the microbiota. In the absence of stress, a healthy microbiota produces SCFAs that exert anti-inflammatory and antitumor effects, potentially through such mechanisms as HDAC inhibition and NF-κB suppression. Interestingly, meditation induces epigenetic changes that mirror these latter effects, which include upregulated histone deacetylase inhibitors (HDACi) and downregulated inflammatory NF-κB.

The current research team speculates that meditation helps regulate the stress response, thereby suppressing inflammation and maintaining healthy gut-barrier function. In addition, the team hypothesizes that the microbiota then generates healthy amounts of HDAC inhibitory SCFAs, which can contribute to the HDAC inhibition and downregulation of NF-κB that has been observed in contemplative practices.[136,137] Although the biological mechanisms of meditation are still being fully elucidated, its salutary effects are evident.

CONCLUSIONS

The current research team recommends the integration of meditation into conventional health care and wellness models. Concurrently, further studies to explore the effects of meditation on human microbiota are warranted.

ACKNOWLEDGEMENTS

The research team thanks Victor Hewitt for the illustrations that he provided.

AUTHOR DISCLOSURE STATEMENT

Paul J. Mills is director of research at the Chopra Foundation. Deepak Chopra is the cofounder of the Chopra Center for Wellbeing and the Chopra Foundation and Christine Tara Peterson (CTP) is a postdoctoral fellow at the University of California, San Diego, and CTP is partially funded by the Chopra Foundation.

REFERENCES

1. World Health Organization (WHO). *Health Topics, Noncommunicable Diseases, Mental Health, Data and Statistics*. Geneva, Switzerland: WHO; 2013.
2. Anxiety and Depression Association of America (ADAA). Press room: Facts and statistics. ADAA Web site. https://adaa.org/about-adaa/press-room/facts-statistics. Published 2013. Accessed November 16, 2017.
3. Chrousos GP. Stress and disorders of the stress system. *Nat Rev Endocrinol.* 2009;5(7):374-381.
4. Kvetnansky R, Esther SL, Palkovits M. Catecholaminergic systems in stress: Structural and molecular genetic approaches. *Physiol Rev.* 2009;89(2):535-606.
5. Phillips RG, LeDoux JE. Differential contribution of amygdala and hippocampus to cued and contextual fear conditioning. *Behav Neurosci.* 1992;106(2):274-285.
6. Reis DG, Scopinho AA, Guimaraes FS, et al. Involvement of the lateral septal area in the expression of fear conditioning to context. *Learn Mem.* 2010;17(3):134-138.
7. McNally GP, Johansen JP, Blair HT. Placing prediction into the fear circuit. *Trends Neurosci.* 2011;34(6):283-292.
8. Shin LM, Liberzon I. The neurocircuitry of fear, stress, and anxiety disorders. *Neuropsychopharmacology.* 2010;35(1):169-191.
9. Ressler KJ. Amygdala activity, fear, and anxiety: Modulation by stress. *Biol Psychiatry.* 2010;67(12):1117-1119.
10. Liddell BJ, Brown KJ, Kemp AH, et al. A direct brainstem–amygdala–cortical 'alarm'system for subliminal signals of fear. *Neuroimage.* 2005;24(1):235-243.
11. Diorio D, Viau V, Meaney MJ. The role of the medial prefrontal cortex (cingulate gyrus) in the regulation of hypothalamic-pituitary-adrenal responses to stress. *J Neurosci.* 1993;13(9):3839-3847.
12. Euston DR, Gruber AJ, McNaughton BL. The role of medial prefrontal cortex in memory and decision making. *Neuron.* 2012;76(6):1057-1070.
13. Arco AD, Mora F. Neurotransmitters and prefrontal cortex–limbic system interactions: Implications for plasticity and psychiatric disorders. *J Neural Transm.* 2009;116:941-952.
14. Cechetto DF. Cortical control of the autonomic nervous system. *Exp Physiol.* 2014;99(2):326-331.
15. Müller-Ribeiro FC, Zaretsky DV, Zaretskaia MV, Santos RA, DiMicco JA, Fontes MA. Contribution of infralimbic cortex in the cardiovascular response to acute stress. *Am J Physiol Regul Integr Comp Physiol.* 2012;303(6):R639-R650.
16. Barker JM, Taylor JR, Chandler LJ. A unifying model of the role of the infralimbic cortex in extinction and habits. *Learn Mem.* 2014;21(9):441-448.
17. Dalgleish T. The emotional brain. *Nat Rev Neurosci.* 2004;5(7):583-589.
18. Swanson LW, Sawchenko PE. Paraventricular nucleus: A site for the integration of neuroendocrine and autonomic mechanisms. *Neuroendocrinology.* 1980;31(6):410-417.
19. Ferguson AV, Latchford KJ, Samson WK. The paraventricular nucleus of the hypothalamus: A potential target for integrative treatment of autonomic dysfunction. *Expert Opin Ther Targets.* 2008;12(6):717-727.
20. Neumann ID, Wigger A, Torner L, et al. Brain oxytocin inhibits basal and stress-induced activity of the hypothalamo-pituitary-adrenal axis in male and female rats: Partial action within the paraventricular nucleus. *J Neuroendocrinol.* 2000;12(3):235-244.
21. Scott LV, Dinan TG. Vasopressin and the regulation of hypothalamic-pituitary-adrenal axis function: Implications for the pathophysiology of depression. *Life Sci.* 1998;62(22):1985-1998.
22. Seaward BL. *Managing Stress: Principles and Strategies for Health and Well-Being.* 7th ed. Burlington, MA: Jones and Bartlett Publishers; 2011.
23. Nakamura K, Matsumura K, Hubschle T, et al. Identification of sympathetic premotor neurons in medullary raphe regions mediating fever and other thermoregulatory functions. *J Neurosci.* 2004;24(23):5370-5380.
24. Carrive P, Gorissen M. Premotor sympathetic neurons of conditioned fear in the rat. *Euro J Neurosci.* 2008;28:428-446.
25. Ziegler DR, Herman JP. Neurocircuitry of stress integration: Anatomical pathways regulating the hypothalamo-pituitary-adrenocortical axis of the rat. *Integr Comp Biol.* 2002;42(3):541-551.
26. MacLean PD. *The Triune Brain in Evolution: Role in Paleocerebral Functions*. Berlin, Germany: Springer Science & Business Media; 1990.
27. Nussey SS, Whitehead SA. *Endocrinology: An Integrated Approach*. Boca Raton, FL: CRC Press; 2013.
28. Loewy AD. Forebrain nuclei involved in autonomic control. *Prog Brain Res.* 1990;87:253-268.
29. Gilbey MP, Spyer KM. Essential organization of the sympathetic nervous system. *Baillieres Clin Endocrinol Metab.* 1993;7(2):259-278.
30. Elenkov IJ, Wilder RL, Chrousos GP, et al. The sympathetic nerve—an integrative interface between two supersystems: The brain and the immune system. *Pharmacol Rev.* 2000;52(4):595-638.
31. Wurtman RJ, Axelrod J. Control of enzymatic synthesis of adrenaline in the adrenal medulla by adrenal cortical steroids. *J Biol Chem.* 1966;241(10):2301-2305.
32. Sainz B, Loutsch JM, Marquart ME, et al. Stress-associated immunomodulation and herpes simplex virus infections. *Med Hypotheses.* 2001;56(3):348-356.
33. Hori T, Katafuchi T, Take S, et al. The autonomic nervous system as a communication channel between the brain and the immune system. *T Neuroimmunomodulation.* 1995;2(4):203-215.

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34. Nance DM, Sanders VM. Autonomic innervation and regulation of the immune system (1987-2007). *Brain Behav Immun.* 2007;21(6):736-745.
35. Maestroni GJ, Conti A. Modulation of hematopoiesis via alpha 1-adrenergic receptors on bone marrow cells. *Exp Hematol.* 1994;22(3):313-320.
36. Bellinger DL, Lorton D. Autonomic regulation of cellular immune function. *Auton Neurosci.* May 2014;182:15-41.
37. Sampson TR, Mazmanian SK. Control of brain development, function, and behavior by the microbiome. *Cell Host Microbe.* 2015;17(5):565-576.
38. Weil R, Israël A. T-cell-receptor-and B-cell-receptor-mediated activation of NF-κB in lymphocytes. *Curr Opin Immunol.* 2004;16(3):374-381.
39. Gerondakis S, Siebenlist U. Roles of the NF-kappaB pathway in lymphocyte development and function. *Cold Spring Harb Perspect Biol.* 2010;2(5):a000182.
40. Schmitz ML, Bacher S, Dienz O. NF-kappaB activation pathways induced by T cell costimulation. *FASEB J.* 2003;17(15):2187-2193.
41. Dhabhar FS, Malarkey WB, Neri E, et al. Stress-induced redistribution of immune cells—From barracks to boulevards to battlefields: A tale of three hormones–Curt Richter Award Winner. *Psychoneuroendocrinology.* 2012;37(9):1345-1368.
42. Danese S, Dejana E, Fiocchi C. Immune regulation by microvascular endothelial cells: Directing innate and adaptive immunity, coagulation, and inflammation. *J Immunol.* 2007;178(10):6017-6022.
43. Springer TA. Adhesion receptors of the immune system. *Nature.* 1990;346(6283):425-434.
44. Saunders PR, Santos J, Hanssen NP, et al. Physical and psychological stress in rats enhances colonic epithelial permeability via peripheral CRH. *Digest Dis Sci.* 2002;47(1):208-215.
45. Santos J, Saunders PR, Hanssen NP, et al. Corticotropin-releasing hormone mimics stress-induced colonic epithelial pathophysiology in the rat. *Am J Physiol.* 1999;277(2 Pt 1):G391-G399.
46. Groschwitz KR, Ahrens R, Osterfeld H, et al. Mast cells regulate homeostatic intestinal epithelial migration and barrier function by a chymase/Mcpt4-dependent mechanism. *Proc Natl Acad Sci U S A.* 2009;106(52):22381-22386.
47. Palsson-McDermott EM, O'Neill LA. Signal transduction by the lipopolysaccharide receptor, Toll-like receptor-4. *Immunology.* 2004;113(2):153-162.
48. Saitoh SI, Akashi S, Yamada T, et al. Ligand-dependent Toll-like receptor 4 (TLR4)-oligomerization is directly linked with TLR4-signaling. *J Endotoxin Res.* 2004;10(4):257-260.
49. Xu Y, Tao X, Shen B, et al. Structural basis for signal transduction by the Toll/interleukin-1 receptor domains. *Nature.* 2000;408(6808):111-115.
50. Lu YC, Yeh WC, Ohashi PS. LPS/TLR4 signal transduction pathway. *Cytokine.* 2008;42(2):145-151.
51. Parameswaran N, Patial S. Tumor necrosis factor-alpha signaling in macrophages. *Crit Rev Eukaryot Gene Expr.* 2010;20(2):87-103.
52. Bende RJ, van Maldegem F, van Noesel CJ. Chronic inflammatory disease, lymphoid tissue neogenesis and extranodal marginal zone B-cell lymphomas. *Haematologica.* 2009;94(8):1109-1123.
53. Brodsky IE, Medzhitov R. Targeting of immune signalling networks by bacterial pathogens. *Nat Cell Biol.* 2009;11(5):521-526.
54. Perdigon G, Maldonado Galdeano C, Valdez JC, et al. Interaction of lactic acid bacteria with the gut immune system. *Eur J Clin Nutr.* 2002;56(Suppl 4):S21-S26.
55. Artis D. Epithelial-cell recognition of commensal bacteria and maintenance of immune homeostasis in the gut. *Nat Rev Immunol.* 2008;8(6):411-420.
56. Fasano A. Physiological, pathological, and therapeutic implications of zonulin-mediated intestinal barrier modulation: Living life on the edge of the wall. *Am J Pathol.* 2008;173(5):1243-1252.
57. Dinan TG, Stanton C, Cryan JF. Psychobiotics: A novel class of psychotropic. *Biol Psychiatry.* 2013;74(10):720-726.
58. de Punder K, Pruimboom L. Stress induces endotoxemia and low-grade inflammation by increasing barrier permeability. *Front Immunol.* 2015;6(223):223.
59. Bauer H, Zweimueller-Mayer J, Steinbacher P, et al. The dual role of zonula occludens (ZO) proteins. *J Biomed Biotechnol.* 2010;2010:402593.
60. Manichanh C, Borruel N, Casellas F, et al. The gut microbiota in IBD. *Nat Rev Gastroenterol Hepatol.* 2012;9(10):599-608.
61. Backhed F, Ley RE, Sonnenburg JL, et al. Host-bacterial mutualism in the human Intestine. *Science.* 2005;307(5717):1915-1920.
62. Glenn GR, Roberfroid MB. Dietary modulation of the human colonic microbiota: introducing the concept of prebiotics. *J Nutr.* 1995;125:1401-1412.
63. Merritt J, Kuehn S. When communities collide. *eLife.* 2016;5:e18753.
64. Alkadhi K. Brain physiology and pathophysiology in mental stress. *ISRN Physiol.* 2013;2013:1-23.
65. Almawi WY, Melemedjian OK. Molecular mechanisms of glucocorticoid antiproliferative effects: Antagonism of transcription factor activity by glucocorticoid receptor. *J Leukoc Biol.* 2002;71(1):9-15.
66. Scheinman RI, Cogswell PC, Lofquist AK, et al. Role of transcriptional activation of IκBα in mediation of immunosuppression by glucocorticoids. *Science.* 1995;270(5234):283-286.
67. Barnes PJ. Anti-inflammatory actions of glucocorticoids: Molecular mechanisms. *Clin Sci (Lond).* 1998;94(6):557-572.
68. Yang N, Ray DW, Matthews LC. Current concepts in glucocorticoid resistance. *Steroids.* 2012;77(11):1041-1049.
69. Van Der Zanden EP, Boeckxstaens GE, De Jonge WJ. The vagus nerve as a modulator of intestinal inflammation. *Neurogastroenterol Motility.* 2009;21(1):6-17.
70. Borovikova LV, Ivanova S, Zhang M, et al. Vagus nerve stimulation attenuates the systemic inflammatory response to endotoxin. *Nature.* 2000;405(6785):458-462.
71. Anton LC, Yewdell JW. Translating DRiPs: MHC class I immunosurveillance of pathogens and tumors. *J Leukoc Biol.* 2014;95(4):551-562.
72. Corse E, Gottschalk RA, Allison JP. Strength of TCR-peptide/MHC interactions and in vivo T cell responses. *J Immunol.* 2011;186(9):5039-5045.
73. Paul WE, Zhu J. How are TH2-type immune responses initiated and amplified? *Nat Rev Immunol.* 2010;10(4):225-235.
74. Elenkov IJ. Glucocorticoids and the Th1/Th2 balance. *Ann N Y Acad Sci.* 2004;1024(1):138-146.
75. Elenkov IJ, Chrousos GP. Stress hormones, proinflammatory and antiinflammatory cytokines, and autoimmunity. *Ann N Y Acad Sci.* 2002;966(1):290-303.
76. Allen JE, Wynn TA. Evolution of Th2 immunity: A rapid repair response to tissue destructive pathogens. *PLoS Pathog.* 2011;7(5):e1002003.
77. Matteoli G, Boeckxstaens GE. The vagal innervation of the gut and immune homeostasis. *Gut.* 2013;62(8):1214-1222.
78. Rohleder N. Acute and chronic stress induced changes in sensitivity of peripheral inflammatory pathways to the signals of multiple stress systems–2011 Curt Richter Award Winner. *Psychoneuroendocrinology.* 2012;37(3):307-316.
79. Cohen S, Janicki-Deverts D, Doyle WJ, et al. Chronic stress, glucocorticoid receptor resistance, inflammation, and disease risk. *Proc Natl Acad Sci U S A.* 2012;109(16):5995-5999.
80. Elenkov IJ, Iezzoni DG, Daly A, et al. Cytokine dysregulation, inflammation and well-being. *Neuroimmunomodulation.* 2005;12(5):255-269.
81. Sklar LS, Anisman H. Stress and cancer. *Psychol Bull.* 1981;89(3):369-406.
82. Schedlowski M, Jacobs R, Stratmann G, et al. Changes of natural killer cells during acute psychological stress. *J Clin Immunol.* 1993;13(2):119-126.
83. Huston JM, Tracey KJ. The pulse of inflammation: Heart rate variability, the cholinergic anti-inflammatory pathway and implications for therapy. *J Intern Med.* 2011;269(1):45-53.
84. Adameova A, Abdellatif Y, Dhalla NS. Role of the excessive amounts of circulating catecholamines and glucocorticoids in stress-induced heart disease. *Can J Physiol Pharmacol.* 2009;87(7):493-514.
85. Al-Sadi R, Boivin M, Ma T. Mechanism of cytokine modulation of epithelial tight junction barrier. *Front Biosci (Landmark Ed).* 2009;14(2765):2765-2778.
86. Boivin MA, Roy PK, Bradley A, et al. Mechanism of interferon-gamma-induced increase in T84 intestinal epithelial tight junction. *J Interferon Cytokine Res.* 2009;29(1):45-54.
87. Peroutka SJ. Migraine: A chronic sympathetic nervous system disorder. *Headache.* 2004;44(1):53-64.
88. Schildkraut JJ. The catecholamine hypothesis of affective disorders: A review of supporting evidence. *Am J Psychiatry.* 1965;122(5):509-522.
89. Yirmiya R, Goshen I, Bajayo A, et al. Depression induces bone loss through stimulation of the sympathetic nervous system. *Proceed Nat Acad Sci.* 2006;103(45):16876-16881.
90. McCarty R, Horwatt K, Konarska M. Chronic stress and sympathetic-adrenal medullary responsiveness. *Soc Sci Med.* 1988;26(3):333-341.
91. Heard E, Martienssen RA. Transgenerational epigenetic inheritance: Myths and mechanisms. *Cell.* 2014;157(1):95-109.
92. Andoh A, Tsujikawa T, Fujiyama Y. Role of dietary fiber and short-chain fatty acids in the colon. *Curr Pharm Des.* 2003;9(4):347-358.
93. Blum R. Stepping inside the realm of epigenetic modifiers. *Biomol Concepts.* 2015;6(2):119-136.
94. Zhou Y, Schmitz KM, Mayer C, et al. Reversible acetylation of the chromatin remodelling complex NoRC is required for non-coding RNA-dependent silencing. *Nature Cell Biol.* 2009;11(8):1010-1016.
95. Weaver IC. Epigenetic effects of glucocorticoids. *Seminar Fetal Neonat Med.* 2009;14(3):143-150.
96. Gudsnuk K, Champagne FA. Epigenetic influence of stress and the social environment. *ILAR J.* 2012;53(3-4):279-288.
97. Esler M, Eikelis N, Schlaich M, et al. Human sympathetic nerve biology: Parallel influences of stress and epigenetics in essential hypertension and panic disorder. *Ann N Y Acad Sci.* 2008;1148(1):338-348.
98. Pandit V, Seshadri S, Rao SN, et al. A case of organophosphate poisoning presenting with seizure and unavailable history of parenteral suicide attempt. *J Emerg Trauma Shock.* 2011;4(1):132-134.
99. Sailaja BS, Cohen-Carmon D, Zimmerman G, et al. Stress-induced epigenetic transcriptional memory of acetylcholinesterase by HDAC4. *Proc Natl Acad Sci U S A.* 2012;109(52):E3687-3695.
100. Ulloa L. The cholinergic anti-inflammatory pathway meets microRNA. *Cell Res.* 2013;23(11):1249-1250.
101. Cairo S, Buendia MA. How transient becomes stable: An epigenetic switch linking liver inflammation and tumorigenesis. *J Hepatol.* 2012;57(4):910-912.
102. Sanders VM. Epigenetic regulation of Th1 and Th2 cell development. *Brain Behav Immun.* 2006;20(4):317-324.
103. Glaser R, Kiecolt-Glaser JK. Stress-induced immune dysfunction: Implications for health. *Nat Rev Immunol.* 2005;5(3):243-251.

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104. Powell EO. Growth rate and generation time of bacteria, with special reference to continuous culture. *J Gen Microbiol.* 1956;15(3):492-511.
105. Reid G, Younes JA, Van der Mei HC, et al. Microbiota restoration: Natural and supplemented recovery of human microbial communities. *Nat Rev Microbiol.* 2011;9(1):27-38.
106. Brown CT, Davis-Richardson AG, Giongo A, et al. Gut microbiome metagenomics analysis suggests a functional model for the development of autoimmunity for type 1 diabetes. *PLoS One.* 2011;6(10):e25792.
107. Kinross JM, Darzi AW, Nicholson JK. Gut microbiome-host interactions in health and disease. *Genome Med.* 2011;3(3):14.
108. Schilderink R, Verseijden C, de Jonge WJ. Dietary inhibitors of histone deacetylases in intestinal immunity and homeostasis. *Front Immunol.* 2013;4(226):226.
109. Tong X, Yin L, Giardina C. Butyrate suppresses Cox-2 activation in colon cancer cells through HDAC inhibition. *Biochem Biophys Res Commun.* 2004;317(2):463-471.
110. Furusawa Y, Obata Y, Fukuda S, et al. Commensal microbe-derived butyrate induces the differentiation of colonic regulatory T cells. *Nature.* 2013;504(7480):446-450.
111. Blouin JM, Penot G, Collinet M, et al. Butyrate elicits a metabolic switch in human colon cancer cells by targeting the pyruvate dehydrogenase complex. *Int J Cancer.* 2011;128(11):2591-2601.
112. Hatayama H, Iwashita J, Kuwajima A. The short chain fatty acid, butyrate, stimulates MUC2 mucin production in the human colon cancer cell line, LS174T. *Biochem Biophys Res Commun.* 2007;356(3):599-603.
113. Corfield AP, Myerscough N, Longman R, et al. Mucins and mucosal protection in the gastrointestinal tract: New prospects for mucins in the pathology of gastrointestinal disease. *Gut.* 2000;47(4):589-594.
114. Hu S, Dong TS, Dalal SR, et al. The microbe-derived short chain fatty acid butyrate targets miRNA-dependent p21 gene expression in human colon cancer. *PLoS One.* 2011;6(1):e16221.
115. Runtsch MC, Round JL, O'Connell RM. MicroRNAs and the regulation of intestinal homeostasis. *Front Genet.* 2014;5:347.
116. Masotti A. Interplays between gut microbiota and gene expression regulation by miRNAs. *Front Cell Inf Microbio.* 2012;2:137.
117. Banks WA, Lynch JL, Price TO. *Cytokines and the Blood-Brain Barrier: The Neuroimmunological Basis of Behavior and Mental Disorders.* New York, NY: Springer; 2009.
118. John S, Verma S, Khanna G. The effect of mindfulness meditation on HPA-Axis in pre-competition stress in sports performance of elite shooters. *Nat J Integr Res Med.* 2011;2(3):15-21.
119. Walton KG, Pugh ND, Gelderloos P, et al. Stress reduction and preventing hypertension: Preliminary support for a psychoneuroendocrine mechanism. *J Altern Complement Med.* 1995;1(3):263-283.
120. Sudsuang R, Chentanez V, Veluvan K. Effect of Buddhist meditation on serum cortisol and total protein levels, blood pressure, pulse rate, lung volume and reaction time. *Physiol Behav.* 1991;50(3):543-548.
121. Jevning R, Wilson A, Davidson J. Adrenocortical activity during meditation. *Horm Behav.* 1978;10(1):54-60.
122. Harte JL, Eifert GH, Smith R. The effects of running and meditation on beta-endorphin, corticotropin-releasing hormone and cortisol in plasma, and on mood. *Biol Psychol.* 1995;40(3):251-265.
123. Carlson LE, Speca M, Patel KD, et al. Mindfulness-based stress reduction in relation to quality of life, mood, symptoms of stress and levels of cortisol, dehydroepiandrosterone sulfate (DHEAS) and melatonin in breast and prostate cancer outpatients. *Psychoneuroendocrinology.* 2004;29(4):448-474.
124. Pace TW, Negi LT, Adame DD, et al. Effect of compassion meditation on neuroendocrine, innate immune and behavioral responses to psychosocial stress. *Psychoneuroendocrinology.* 2009;34(1):87-98.
125. Barnes VA, Davis HC, Murzynowski JB, et al. Impact of meditation on resting and ambulatory blood pressure and heart rate in youth. *Psychosom Med.* 2004;66(6):909-914.
126. Jevning R, Wallace RK, Beidebach M. The physiology of meditation: A review. A wakeful hypometabolic integrated response. *Neurosci Biobehav Rev.* 1992;16(3):415-424.
127. Travis F. Autonomic and EEG patterns distinguish transcending from other experiences during Transcendental Meditation practice. *Int J Psychophysiol.* 2001;42(1):1-9.
128. Kox M, Stoffels M, Smeekens SP, et al. The influence of concentration/meditation on autonomic nervous system activity and the innate immune response: A case study. *Psychosom Med.* 2012;74(5):489-494.
129. Kubota Y, Sato W, Toichi M, et al. Frontal midline theta rhythm is correlated with cardiac autonomic activities during the performance of an attention demanding meditation procedure. *Cogn Brain Res.* 2001;11(2):281-287.
130. Tang Y-Y, Ma Y, Fan Y, et al. Central and autonomic nervous system interaction is altered by short-term meditation. *Proceed Nat Acad Sci.* 2009;106(22):8865-8870.
131. Paton JF, Boscan P, Pickering AE, et al. The yin and yang of cardiac autonomic control: Vago-sympathetic interactions revisited. *Brain Res Brain Res Rev.* 2005;49(3):555-565.
132. Uijtdehaage SH, Thayer JF. Accentuated antagonism in the control of human heart rate. *Clin Auton Res.* 2000;10(3):107-110.
133. Davidson RJ, Kabat-Zinn J, Schumacher J, et al. Alterations in brain and immune function produced by mindfulness meditation. *Psychosom Med.* 2003;65(4):564-570.
134. Morgan N, Irwin MR, Chung M, et al. The effects of mind-body therapies on the immune system: Meta-analysis. *PLoS One.* 2014;9(7):e100903.
135. Yin L, Laevsky G, Giardina C. Butyrate suppression of colonocyte NF-κB activation and cellular proteasome activity. *J Biol Chem.* 2001;276(48):44641-44646.
136. Kaliman P, Alvarez-Lopez MJ, Cosin-Tomas M, et al. Rapid changes in histone deacetylases and inflammatory gene expression in expert meditators. *Psychoneuroendocrinology.* February 2014;40:96-107.
137. Bhasin MK, Dusek JA, Chang BH, et al. Relaxation response induces temporal transcriptome changes in energy metabolism, insulin secretion and inflammatory pathways. *PLoS One.* 2013;8(5):e62817.
138. Kuo B, Bhasin M, Jacquart J, et al. Genomic and clinical effects associated with a relaxation response mind-body intervention in patients with irritable bowel syndrome and inflammatory bowel disease. *PLoS One.* 2015;10(4):e0123861.
139. Aucoin M, Lalonde-Parsi M-J, Cooley K. Mindfulness-based therapies in the treatment of functional gastrointestinal disorders: A meta-analysis. *Evid Based Complement Alternat Med.* 2014;2014:140724.
140. Schoultz M, Atherton IM, Hubbard G, et al. The use of mindfulness-based cognitive therapy for improving quality of life for inflammatory bowel disease patients: Study protocol for a pilot randomised controlled trial with embedded process evaluation. *Trials.* 2013;14(1):431.
141. Schoultz M, Atherton I, Watson A. PWE-057 Mindfulness based cognitive therapy for inflammatory bowel disease: The results from a pilot randomised control trial. *Gut.* 2015;64(Suppl 1):A236-A237.
142. Schoultz M, Macaden L, Hubbard G. Participants' perspectives on mindfulness-based cognitive therapy for inflammatory bowel disease: A qualitative study nested within a pilot randomised controlled trial. *Pilot Feasibil Stud.* 2016;2(1):3.
143. Cryan JF, Dinan TG. Mind-altering microorganisms: The impact of the gut microbiota on brain and behaviour. *Nat Rev Neurosci.* 2012;13(10):701-712.
144. Kamada N, Seo S-U, Chen GY, et al. Role of the gut microbiota in immunity and inflammatory disease. *Nat Rev Immunol.* 2013;13(5):321-335.