Mechanisms of Yogic Practices in Health, Aging, and Disease

Viktoriya Kuntsevich, PhD,1 William C. Bushell, PhD,2 and Neil D. Theise, MD1

1Beth Israel Medical Center of Albert Einstein College of Medicine, New York, NY
2Massachusetts Institute of Technology, Anthropology Program, Cambridge, MA; Tibet House US, New York, NY

OUTLINE

TRANSDUCTION PATHWAYS OF YOGIC PRACTICES

Humoral Signaling
Nervous System Activity
Cell Trafficking
Bioelectromagnetism

TOWARD A CHANGING PARADIGM FOR INVESTIGATION

CONCLUSION

ABSTRACT

Mechanisms underlying the modulating effects of yogic cognitive-behavioral practices (eg, meditation, yoga asanas, pranayama breathing, caloric restriction) on human physiology can be classified into 4 transduction pathways: humoral factors, nervous system activity, cell trafficking, and bioelectromagnetism. Here we give examples of these transduction pathways and how, through them, yogic practices might optimize health, delay aging, and ameliorate chronic illness and stress from disability. We also recognize that most studies of these mechanisms remain embedded in a reductionist paradigm, investigating small numbers of elements of only 1 or 2 pathways. Moreover, often, subjects are not long-term practitioners, but recently trained. The models generated from such data are, in turn, often limited, top-down, without the explanatory power to describe beneficial effects of long-term practice or to provide foundations for comparing one practice to another. More flexible and useful models require a systems-biology approach to gathering and analysis of data. Such a paradigm is needed to fully appreciate the deeper mechanisms underlying the ability of yogic practice to optimize health, delay aging, and speed efficient recovery from injury or disease. In this regard, 3 different, not necessarily competing, hypotheses are presented to guide design of future investigations, namely, that yogic practices may: (1) promote restoration of physiologic setpoints to normal after derangements secondary to disease or injury, (2) promote homeostatic negative feedback loops over nonhomeostatic positive feedback loops in molecular and cellular interactions, and (3) quench abnormal “noise” in cellular and molecular signaling networks arising from environmental or internal stresses.

Key Words: circadian, cytokine, inflammation, integrative medicine, meditation, melatonin, pranayama, vagus nerve, yoga.

Imagination is more important than knowledge. For while knowledge defines all we currently know and understand, imagination points to all we might yet discover and create. —Albert Einstein

Practitioners of cognitive-behavioral practices (CBPs) of diverse “yogic” traditions, such as yoga asana, meditation, pranayama breathing, and caloric restriction, have made claims regarding their benefits for optimization of health, protection from injury, rejuvenation, and increased life expectancy. It should be kept in mind that although we use the term “yogic,” typically indicating derivation from practices historically traced to south Asia, variations of such practices are found in many cultures and traditions around the world, some of which may represent importation
from that region whereas others are independent developments. However, contemporary research of such practices, which we will discuss in this speculative review, is most often focused on practices from specifically Asian yogic traditions.

**TRANSDUCTION PATHWAYS OF YOGIC PRACTICES**

Exploration of such physiology-modulating effects of yogic CBPs on health and longevity suggests 4 possible transduction pathways of such global/systemic interventions into site-specific, local effects: humoral factors, nervous system activity, cell trafficking, and bioelectromagnetism (Figure 1).

1 In this article, we will give some recent examples of each of these pathways and point to the often tight interconnections between pathways. However, we also recognize that such examples are simply demonstrations of end effects, but do not really reach to the core of “what yogic practices do” in the process of improving systemic regulation or “restoring balance” to the system. Indeed, most of these investigations, although of great significance, remain in the realm of reductive science. Though an important first step in the exploration of the modulating effects of yogic CBPs, they are incomplete, largely focused on a small number of physiologic events in recently trained practitioners. The leap to a systems-analytic approach is necessary for a comprehensive understanding of the mechanisms whereby yogic CBPs influence, optimize, or restore human physiology.

*A comprehensive understanding of the mechanisms whereby yogic cognitive-behavioral practices (CBPs) influence, optimize, or restore human physiology requires a leap to a systems-analytic approach. Within this framework, explorations suggest 4 possible transduction pathways of global/systemic yogic interventions into site-specific, local effects: humoral factors, nervous system activity, cell trafficking, and bioelectromagnetism.*

Thus, we will follow these specific examples of each transduction pathway and their interconnectedness, with a presentation of speculative hypotheses that we hope will lead to more detailed and useful explanations of these intriguing and perhaps (literally) vital effects, including optimization of health,
delayed aging, and amelioration of chronic illness and of stress from disability.

**Humoral Signaling**

Circulating signaling molecules, including hormones, neurotransmitters, growth factors, and the network of cytokines, chemokines, and adipokines (CCA network) link all of the cells and tissues of the body, in health or disease. Although many of these have organ-specific names based on how they were first discovered (eg, hepatocyte growth factor, erythropoietin), they are now recognized as being systemic signaling pathways shared by most, if not all, organs. Thus, if any CBP intervention can modulate these humoral networks on physiological levels, it will have systemwide effects. The largest body of investigation documenting physiologic effects of yogic CBPs, perhaps in part because of the ease of serum sampling and testing, involves such circulating molecules.

A prime example is melatonin. Liou *et al.* have shown, by functional magnetic resonance imaging, that the Chinese meditative practice of “quiet sitting” (similar to mindfulness and Zen “just sitting” meditations) leads to pineal gland activation. It has also been shown that meditation acutely increases circulating melatonin levels in the hours after a period of meditation. In fact, in older adults serum melatonin is significantly elevated toward youthful levels by yoga asana practice, different forms of meditation, and pranayama breathing, both in response to individual sessions of practice (∼1 hour) and also as a sustained baseline elevation in long-term practitioners (this is an uncommon study inclusive of long-term practitioners).

Melatonin is most commonly associated with its role in maintenance of circadian rhythms (to which we will return), but a large body of evidence shows that the molecule has a far wider variety of important physiologic effects. A detailed review of these studies is beyond the scope of this article, and has been extensively covered elsewhere. However, it is worth noting that, being small and amphophilic, the molecule distributes throughout all tissue compartments and fluids and can be found in greatest subcellular concentrations in mitochondria. Its potential impact on perhaps every tissue is therefore profound, leading some to consider it a “master regulatory molecule” not only for the circadian clock, but for other physiologic processes as well.

Melatonin promotes survival and/or regeneration in the liver, skin, hair, bone, hematopoiesis, brain, eyes, heart, gastrointestinal (GI) tract, endothelium, neuroendocrine-reproductive axis, and muscle. It has been shown to protect healthy tissues from a range of offending agents (toxins, radiation, caloric and mechanical insult) through antioxidant, antiapoptotic, and other mechanisms to stimulate regeneration in healthy tissues. It selectively and differentially induces apoptosis in malignant cells (and tissues with other pathologies), including in the breast, lungs, stomach, endometrium, ovaries, cervix, prostate, GI tract, and bone marrow.

Pierpoli and colleagues found that both chronic melatonin administration and cross-transplantation of pineal glands from young to old mice lead to a broad range of apparent aging-delaying and/or aging-reversing effects in behavior and physical appearance. Of course, therefore, if yogic CBPs increase pineal activation and circulating melatonin levels, the same beneficial effects found by Pierpoli are likely to result without the need for ingestion of exogenous compound.

Melatonin is not the only humoral signaling molecule that is so affected by yogic CBPs. Dehydroepiandrosterone (DHEA), increasingly known as a cytoprotective, pleiotropic, “ubiquitous” antiaging steroid, has also recently been found to stimulate stem/progenitor cell–based regenerative effects in the brain. The salubrious effects of caloric restriction are attributed, in part, to the maintenance of more youthful levels of DHEA and melatonin, whereas meditation has been found in some studies to increase circulating DHEA to levels more typical of individuals 5–10 years younger on average.

Some forms of meditation have also been found to enhance activity of the growth hormone/insulin-like growth factor-I (GH/IGF-1) axis, which is claimed to account for >80% of postnatal growth, and recently enhancement of activity in this axis has been found to promote stem and progenitor cell activation, proliferation, and mobilization. Arginine vasopressin (AVP), circulating levels of which are increased during meditation by approximately 5–7 orders of magnitude, has been found to significantly increase myogenesis and may also play a trophic role in both the peripheral nervous system and the central nervous system (CNS), where it is known to enhance learning and memory through up-regulation of other growth factors. Constitutive nitric oxide may also crucially contribute to beneficial therapeutic, regenerative effects in a diverse range of pathologies and exert a “global healing effect” and has been shown to be modulated through Zen meditation practices.

Another very important player in humoral signaling is the CCA network, which is involved in
immune reactions of different kinds and magnitude. These reactions are not instantaneous, but take time to occur and propagate through the network and likewise take time to resolve. For example, it takes 1.5–2 hours for the monocytes in a human body to respond to lipopolysaccharide injection. Thus, the resources of this network mobilize in well-defined units over time: increasing concentrations of proinflammatory molecules are followed by increased synthesis of anti-inflammatory molecules to balance the response and eventually resolve the reactive change once the challenge has passed.

However, if not resolved, increased concentrations of proinflammatory and anti-inflammatory molecules are sustained in nonhomeostatic states of imbalance. Evidence suggests that yogic CBPs may inhibit production of such states of imbalance or facilitate resolution back to homeostasis. Indeed, several randomized clinical trials have shown that such CBPs can decrease inflammation (and, not incidentally, thereby improve quality of life and other important, vital parameters in different diseases).

Randomized clinical trials in which New York Heart Association Class I-III heart failure patients were randomized to yoga treatment or standard medical therapy revealed that an 8-week regimen of yoga in addition to standard medical therapy improved exercise tolerance and positively affected levels of inflammatory markers in patients with chronic heart failure. There were statistically significant reductions in serum levels of interleukin-6 (IL-6) and C-reactive protein (CRP) in the yoga-treatment group, and there was also a trend toward improvements in quality of life. Likewise, application of cognitive-behavioral therapy and mindfulness meditation for pain in patients with rheumatoid arthritis promotes actual decrease in mitogen-stimulated levels of IL-6, along with improvement in self-reported pain control and in coping efficacy.

In another example we find evidence that emphasizes not only the utility of a yogic intervention for optimizing health, but confirms that the most benefit is through long-term practice rather than the more commonly studied acute training. As such, it may be seen as a personalized, preventive therapy and of particular import for our contemporary society. Namely, the study at the Institute for Behavioral Medicine Research at The Ohio State University was aimed to investigate the mechanisms underlying hatha yoga’s potential stress-reduction benefits. It included 50 healthy women (mean age 41.32 years; range, 30–65 years), 25 novices, and 25 experts (at least 2 years of practice). The results were remarkable: although novices and experts did not differ on key dimensions, including age, abdominal adiposity, and cardiorespiratory fitness, novices’ serum IL-6 levels were 41% higher than those of experts across sessions, and the odds of a novice having detectable CRP were 4.75x those of an expert. Thus, in this setting, it is long-term practice, not an acute intervention, that results in beneficial physiologic changes.

Although data about possible connections between CBPs and the CCA network are limited in both numbers of actual randomized trials and in the sets of molecules those trials investigate, it is important to recognize the complexity and diversity of CCA network functions for explanations of possible mechanisms through which CBPs can impact on site-specific molecular and cellular events in the body as well as systemic improvements in aging and/or illness.

Thus, cytokines, chemokines, and adipokines function not only as proinflammatory and anti-inflammatory agents, but also as neurotransmitters, immunosensors and signaling agents. Advances in modern molecular biology, genetics, immunology, and biomedical engineering provide abundant data demonstrating that the immune system is a sophisticated sensory organ capable of detecting and sorting global/systemic information and translating this information into modulations of tissue with site-specific, local effects the way other sensory organs use their own biological mechanisms for detection and sorting of input signals from the environment and then translate these into perception.

In addition to positive selection driving the evolution of cell-to-cell communicators in the mammalian immune system (like gamma chain receptor interleukins IL-2, IL-4, IL-7, IL-9, IL-15, and IL-21), regulation of CCA network takes place on multiple levels of the organism: intracellular and intercellular interactions within specific tissues, between organ systems, and in maintenance of the biological clock. This immune-modulatory network tightly connects all aspects of the body, providing a special biochemical language for bi-directional communications in different situations. For example, members of the tumor necrosis factor and tumor necrosis factor receptor–associated factors family serve as signaling molecules for numbers of physiological processes including adaptive immunity, innate immunity, bone metabolism, and the development of several tissues such as lymph nodes, mammary glands, skin, and the CNS.

Moreover, the CCA network is involved in sleep regulation, which brings us back around, of course, to melatonin physiology. The CCA network and circadian rhythms modulated, in part, by melatonin are intimately linked. So, not only the median levels
of members of the CCA network are important, but circadian variations of their concentrations probably play essential roles in maintenance of normal homeostasis and immune response.45–50 This reciprocal relationship is demonstrated by the strong association between circadian melatonin production, activation/expression of clock genes (\textit{CRY1} and \textit{PER1}),40 and adjustments in the immune system parameters.44 This multilevel physiological rhythmicity depends on, but is not limited by, internal biological clocks and external factors like day/night and seasonal periodicity and is frequently altered during senescence12 and in different disorders such as cerebrovascular stroke,43 acute myocardial infarction,44 and major depressive disorder.45

This brief and limited overview might suggest a working hypothesis that yogic CBPs activate the pineal gland, in turn leading to increased levels of circulating melatonin, in turn leading to changes in CCA network signaling. However, such a unidirectional, hierarchical cascade is unlikely. Feedback loops help all members of these interlocked systems to communicate and influence each other. Thus, we have a glimpse of how application of a systems-biologic approach to their understanding will provide for more nuanced understandings. Collaborators from Rutgers University and the University of Medicine and Dentistry, New Jersey-Robert Wood Johnson Medical School, responding to that broadened perspective, have thus developed a mathematical model of the interplay between inflammation and circadian rhythms, based on the hypothesis that these diurnal rhythms are entrained by the cyclic production of the hormones cortisol and melatonin, as stimulated by the central clock in the suprachiasmatic nucleus.46

**Nervous System Activity**

A second transduction pathway involves both CNS activity and signaling by peripheral nerves. Impact of yogic CBPs on CNS activity is, again, beyond the scope of this article (and the expertise of its authors), but has been well summarized elsewhere, in particular for impacts made by meditative practice.47,48 Here we will for the most part focus on exploring how yogic CBPs can influence human physiology through peripheral nervous system activity.

For example, vagal tone, most often assessed through measurements of heart rate variability (HRV), can be modulated by acupuncture49,50; transdental, Zen and other meditation practices44,51–54; and yogic breathing.24,49,53–57 Intriguingly, Peressutti et al. found that not only could Zen meditation alter HRV, but it did so in proportion to the level of experience of the meditator.58 Influences of such CBP on well-being may be more profound and far-reaching than changes in HRV. Tracey and colleagues have demonstrated that the efferent aspects of the vagal nerve complex play a crucial role in modulating the body’s inflammatory response to infectious disease, other forms of physical insult, and psychosocial stress by modulating nuclear factor-kappa B (NF-kappa B)—a key regulator of, among many other pathways, the CCA network—though acetylcholine binding to the alpha-7 nicotinic receptors on activated macrophages and other cytokine-producing cells.59–61

In another example, Brown and Gerbarg describe yogic breathing practices, variously including aspects of slow breathing, laryngeal contraction, inspiration against airway resistance, prolonged expiration against airway resistance, and breathholding, and how these affect physiologic responses to stress as well as maintenance of stabilization of baseline functioning. They do so through mechanisms involving both afferent vagal activity (altering CNS behaviors) and efferent vagal activity, as well as through decreased chemoreflex sensitivity and improved baroreflex sensitivity.49,50,56 Again, as with topics described above, a detailed review of these findings is beyond the scope of this article, but one may summarize a large body of experimental literature by indicating that vagal nerve afferents synapse in the medulla on the nucleus tractus solitarius, which in turn communicates via the parabrachial nucleus to the thalamic nuclei (leading to modulatory effects on frontal and parietal occipital cortices) and the limbic system. Through the limbic system, directly or indirectly through other centers, neuroendocrine outputs are then modulated, including reduction of cortisol and increases in AVP, oxytocin, and prolactin.

These last links in the chain of Brown and Gerbarg’s neurophysiologic model of pranayama are yet another indication of the interconnectedness of these transduction pathways for the impact of yogic CBPs on physiologic functions. Along these lines, we note that the neuroendocrine and immune systems produce a common set of peptide and nonpeptide neurotransmitters and cytokines that act on a common repertoire of receptors in the 2 systems. This complete biochemical information circuit between neurons and immune cells allows the immune system to function as a sensory organ,62 providing an evidence of interconnection of 2 transduction pathways: humoral factors and nerve signaling. For example, it has been recently reported that oxytocin, a primitive neurohypophyseal hormone considered a modulator of lactation and social bonding, is a direct regulator of bone mass.63 Additionally, depending on

DOI:10.1002/MSJ
diet composition, certain cytokines are expressed in the hypothalamus, contributing to the activation of intracellular inflammatory signal transduction, and calorie restriction may provide neuroprotection to the aging brain by preserving DNA-repair enzymes in their intact form and/or up-regulating specific antiapoptotic proteins involved in neuronal cell death.

**Cell Trafficking**

We have already noted above that Tracey’s work indicates the possibilities for vagal innervation of circulating immunocytes, such as macrophages, through stimulation of nicotinic receptors on their surface. This brings us to the third transduction pathway of cell trafficking. The field of psychoneuroimmunology, for which Tracey’s efforts represent an important component, details how circulating cells such as macrophages and lymphocytes are not independent of external or internal environmental influences and their activities are mediated through CNS and peripheral nervous system actions. As yogic CBPs can effect CNS and at least vagal functioning, so may they in turn effect mobilization, activation states, and cell production.

There is comparatively little data demonstrating effects of yogic CBPs on immunocyte trafficking, however. Two recent examples are fairly typical and straightforward. Kochupillai et al. show that cancer patients taught yogic breathing practices increased natural killer cells significantly \( P < 0.001 \) at 12 and 24 weeks of the practice compared with baseline, and the increase in natural killer (NK) cells at 24 weeks was significant \( P < 0.05 \) compared with controls. Witek-Janusek and colleagues studied women recently diagnosed with breast cancer who were enrolled in a mindfulness-based stress reduction (MBSR) program. These patients, over time, re-established their homeostatic NK cell activity and cytokine levels. In contrast, breast cancer patients in the non-MBSR control group exhibited continued reductions in NK cell activity and interferon-gamma production, with increased production of cytokines IL-4, IL-6 (proinflammatory), and IL-10 (anti-inflammatory).

That immunocytes traffic through the body as part of immune system defense is obvious, though the diversity of effects ranges far beyond the most traditionally studied antimicrobial or antitumor defenses. Immunocytes are increasingly recognized for their importance in promoting cell repopulation, revascularization, and modulation of scar formation. In our own work and that of other colleagues with expertise in a variety of organs, the role of circulating stem/progenitor cells has been a central focus, with marrow-derived, hematopoietic, and mesenchymal cells traveling throughout the body to contribute to repair at sites of injury. One possible route for such an effect (and yet another indication of how intimately interconnected are all these “separate” transduction pathways) is that the CNS can directly modulate hematopoietic stem cell activity in the marrow. We speculate that these signals may be influenced by yogic practices as well.

Indeed, sites of injury themselves produce humoral signals that further influence cell trafficking. Intriguingly, the work of Ellen Heber-Katz of the Wistar Institute, showing scarless healing in mixed lymphocyte reaction mice mediated by circulating monocytes homing to sites of wounding, raises questions about well-documented bloodless and scarless healing in response to acute piercing and cutting in rituals performed during profound meditative and trance-induced mental states.

**Bioelectromagnetism**

This area is the most difficult to conceptualize, in that the scientific as well as daily languages available for its description are profoundly limited. However, for the purposes of these efforts, we will focus on electrical conductivity reflective of ionic or electron flux. Obviously, some aspects of electrical flux in the body are also mediated by nerves, but there is electrical conduction through all tissues and it plays significant roles in diverse cellular-level and tissue-level processes.

An interesting example is that of skin, in which electrical conduction plays a critical role in tissue repair and regeneration, with specific gene expression playing a (necessary) role in these basic wound-healing mechanisms. There is a normal, actively maintained voltage drop from the epidermal basement membrane to the skin surface. Disruption of epidermis by wounding shifts the gradient toward the wound. Ex vivo studies of cultured squamous cells showed that the direction of this gradient guides cell migration into the wound, and ex vivo and in vivo studies demonstrated that increasing the strength of local electrical fields in the range of the endogenous wound electrical field enhanced healing. Finally, these investigators showed that such enhancement was abolished by disruption of genetic pathways encoding for phosphatidylinositol-3-OH kinase-gamma.

When combined with research that shows acupuncture or application of “energy” by Chi...
masters can increase skin conductivity or that maintenance of different meditative absorptive states can do likewise,77–79 the possibility that yogic practices might directly impact on rate of at least cutaneous wound healing may be significant.74 However, as stated, this represents a considerably understudied area.

TOWARD A CHANGING PARADIGM
FOR INVESTIGATION

Although these examples demonstrate impacts on various signaling pathways, sometimes in great detail and sometimes with obvious potential to maximize repair after injury, improve restoration of normal baselines following physiologic stress, and even promote rejuvenation in the face of aging, they do not actually answer the question of how alteration of pathways leads to systemic improvements. Indeed, most studies to date remain locked in a reductionist paradigm of investigation, focused on very small numbers of possible effects with very little to suggest a holistic consideration of the body as an extraordinarily complex system of interacting parts, a whole that is far beyond explanations supplied by assembled pieces. Thus, as we suggested in discussing of melatonin and its role in transducing effects of yogic CBPs, although the data support the notion of a hierarchical, top-down flow of effects, in fact this would be an oversimplification that misses the greater, complex interweaving of possibilities. In the discussion of the impact on CNS behavior and subsequent modulation of cortisol, oxytocin, prolactin, and AVP, might it not also impact on the pineal gland and on melatonin production? Thus, with consideration of that possibility alone, the hope for a unidirectional, hierarchical mode explanation of physiologic effects of yogic CBPs crumbles.

We suggest, as have others,51 that a systems approach would be not only beneficial, but necessary for a full understanding of these issues. The work of Scheff et al., noted earlier, producing mathematical models for the relationships of circadian rhythms and CCA network signaling, is an example of this methodology for understanding complex biological systems and the impacts of interventions on their behaviors. The data necessary for such model-building would ideally be derived, of course, from high-throughput, real-time analyses of such domains as functional genomics, proteomics, and metabolomics. It is in the changing patterns of the whole system that the profoundest understanding of yogic mechanisms will be reached. It is also with such an approach that we are more likely to understand and appreciate the benefits of their consistent, long-term practice rather than their acutely applied, therapeutic use. After all, it is unlikely that long-term use is simply going to achieve the summation of cumulative, single "doses." On that basis, we propose 3 possible conceptual ways of considering this larger question of mechanism that implies the need for different kinds of investigations than are currently typical, investigations that pursue an understanding of how the biological system of the body, as a whole, is modulated by yogic CBPs (Figure 1).

The first relates to the fact that in response to stress, resulting in or arising from aging, disease, injury, or disability, there are changes to physiologic setpoints. Biological systems are rarely if ever truly stable. Rather, they self-regulate within a homeostatic range. Disturbances of the normal, baseline state of the organism may result in alterations of the setpoints that define and bound such homeostatic control. Normal body temperature, for example, follows a circadian rhythm. In response to viral infection, fever may be an appropriate response in which the setpoints for homeostatic control are shifted upward to facilitate antiviral responses; however, circadian rhythms are maintained, only the setpoints for temperature control for the organism have changed. Thus, we propose that yogic practices may help to restore physiologic setpoints to normal.

We propose that yogic practices may help to restore physiologic setpoints to normal.

Additional hypotheses follow upon consideration that bodies represent examples of complex adaptive systems; ie, they are emergent, self-organized structures arising from the interactions of their component cellular and molecular parts. As we have discussed in greater detail elsewhere, the cells and molecules of the body give rise to the development of the body over time (from embryo to fetus to postnatal life) and also to its nature at any given moment within its lifespan.52,80–82 They do so because they fulfill certain criteria: they are sufficiently numerous; all elements within the system are responding only to local signals, without global sensing; there is an overall balance of negative over positive feedback loops; and there is quenched disorder in the system. These last 2 criteria suggest additional hypotheses.

The need for an overall balance of negative, or homeostatic, feedback loops for adaptive stability of a living system is fairly self-evident. Complexity theory

DOI:10.1002/MSJ
describes that self-organization can still occur with a balance of positive feedback loops, but rather than being adaptive, these forms of self-organization are energy expending and self-limiting. Tornadoes and hurricanes are examples; cancer would be another, more germane to this current context. The emergence of cancer may be thought of as the gradual dominance of positive feedback signaling between cancer cells and normal cells/matrix that leads to the expanding, energy-expending, ultimately self-limiting growth of malignancy. Thus, we hypothesize that yogic CBPs may inhibit emergence of positive feedback loops or enhance homeostatic negative feedback.

**Yogic CBPs may inhibit emergence of positive feedback loops or enhance homeostatic negative feedback.**

The oncostatic properties of melatonin or the inhibition of NF-kappaB in macrophages by vagal stimulation are examples of suppressive control of positive feedbacks. Likewise, pranayama enhancements of baroreflexes and increasing numbers of circulating natural killer cells in breast cancer patients after mindfulness meditation may be demonstrations of enhanced negative, homeostatic feedback loops.

The presence of quenched disorder in complex systems is important, because without it there would be no ability for the system to explore adaptive responses to a changing environment. Too little disorder in the system and there would be no opportunity for the system to change, leading to eventual collapse. On the other hand, too much disorder and the system will not be able to respond efficiently to the challenge of a changing environment, also leading to collapse. Sufficiently large increases in disorder cannot be overcome by yogic CBPs (or any other intervention, for that matter). However, subtly increased “noise” in the system that is not immediately fatal may be a way of conceiving some aspects of aging, chronic disease, injury, and disability.

For example, a majority of molecules in the CCA network are present in very small serum/plasma concentrations, only several picograms per milliliter; thus, seemingly negligible variations might have dramatic impact on function. For example, whereas normal serum albumin level is 30–50 g/L, serum levels of one of the most studied proinflammatory cytokines, IL-6, are approximately 1 pg/mL, or 0.000000000001 g/L (reported values of IL-6 may vary depending on measurement methods). The importance of such pg/mL values can be illustrated, for example, by the results of the study of a possible connection of serum IL-6 level and the development of disability in persons aged 71 years or older, where even after adjustments for multiple confounders there was strong nonlinear association between the increased risk of mobility/disability and IL-6 concentration, with the risk rising rapidly beyond plasma levels of only 2.5 pg/mL. Additionally, every particular change should be relatively big in order to be noticeable and, therefore, the system as a whole should be relatively free of “noise” to notice subtle but important changes. There should also be sufficient numbers of active receptors to identify such subtle changes and initiate proper response.

Thus, low-level, disordered signaling, promoted through aging, disability, or disease, may swamp the delicate signaling required for maintenance of health and optimization of the organism. Chronic infections, dysregulated gene activation in aged cells, and exposures to intermittent or persistent environmental stresses are examples of challenges to the system that might not decisively interfere with functioning, but will lead to sufficient, random fluctuations or “noise,” such that normative, homeostatic signaling is impaired. Therefore, a third proposal is that “noise” in the signaling networks may interfere with physiologic homeostasis and that yogic CBPs may assist in quenching such disorder.

**“Noise” in the signaling networks may interfere with physiologic homeostasis and yogic (CBPs) may assist in quenching such disorder.**

CONCLUSION

It would be disingenuous at this point in time for a critic or skeptic to declare that there is insufficient evidence with regard to the possible beneficial effects of various yogic practices for optimization of health, delay of senescence, and promotion of recovery from disease or injury. As we found it necessary to repeat in several sections of this article, the truly extensive nature of the data in support of these possibilities makes it impossible to contain within a single, short review such as this. Indeed, consideration of a comprehensive textbook may be the next step in moving this field of investigation forward.

However, review of the abundant data available allows for certain principles to emerge with some degree of clarity. First, the physiologic effects of yogic
CBPs can be described as modulating physiologic systems through 4 transduction pathways: humoral signaling, nervous system activity, cell trafficking, and bioelectromagnetism. Some of these (humoral signaling) have been extensively studied, others (cell trafficking and bioelectromagnetism) have not. Clearly, there is much work to be done in all these areas.

At the same time, there is enough data to know that studies of a traditional nature will only yield very limited windows on the mechanisms whereby yogic CBPs can benefit practitioners. After all, it becomes very quickly clear that behaviors within one transduction pathway will rapidly propagate through and effect others, the web of interactions becoming rapidly too complex to contain within a simple framework. Moreover, the overwhelming numbers of studies are of short-term duration in subjects who have only recently been taught the intervention.

Furthermore, the models of such mechanisms derived from such narrowly focused studies have relatively little explanatory power. The example we gave of melatonin physiology is emblematic: yogic practices can activate the pineal gland, presumably leading to the confirmed increases in circulating melatonin, which in turn leads to tissue-protective effects through its antioxidant and oncostatic actions. However, could one not simply take a little bit of melatonin at bedtime and achieve these same effects? But the actions of yogic practices are more subtle and are not strictly dose dependent; practitioners readily claim that long-term practice promotes greater benefits than could be explained by simple, repeated “dosing” of an intervention. Where is there room in the reductionist approach to begin to assess the effects of long-term practice?

To address these possibilities, a systems-biology approach must be applied to the study of the physiologic effects of yogic CBPs. In doing so, we will develop a richer set of concepts to understand these practices, particularly as they deepen in long-term practice; a new set of hypotheses to guide more subtle (and more ambitious) study designs; and the possibility of devising ways to directly compare one practice to another.

We suggest 3 such hypotheses, in part based on our understanding of the body as a complex adaptive system, namely that yogic practices may: (1) promote restoration of physiologic setpoints to normal after derangements secondary to disease or injury, (2) promote homeostatic negative feedback loops over nonhomeostatic positive feedback loops in molecular and cellular interactions, and (3) quench abnormal “noise” in cellular and molecular signaling networks arising from environmental or internal stresses. These hypotheses are not in opposition and may all function in parallel or in series in different circumstances and at different times. They are also merely the first 3 that we have imagined—there may indeed be many more. We offer these as places to start.

DISCLOSURES
Potential conflict of interest: Nothing to report.

REFERENCES


DOI:10.1002/MSJ