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The dynamic range of biologic functions and variation of many environmental cues may be declining in the modern age: implications for diseases and therapeutics

Anthony J. Yun[a,*], Kimberly A. Bazar[b], Anthony Gerber[c], Patrick Y. Lee[a], Stephanie M. Daniel[d]

[a] *Department of Radiology, Stanford University, 470 University Avenue, Palo Alto, CA 94301, USA*
[b] *Department of Dermatology, San Mateo Medical Center, 222 West 39th Avenue, San Mateo, CA 94403, USA*
[c] *Cardiovascular Research Institute (CVRI), Box 0130, University of California, San Francisco, San Francisco, CA 94143, USA*
[d] *University of California, San Francisco, San Francisco, CA 94143, USA*

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Summary We hypothesize that declining dynamic range and variation of environmental cues may contribute to health dysfunctions, and that judicious expansion of biologic dynamic ranges may be beneficial. Three disparate examples involving the endocrine, autonomic, and musculoskeletal systems are discussed. Daytime sheltering, optical shading, and nighttime use of artificial light may reduce circadian luminal variation. The resulting melatonin alterations may contribute to systemic dysfunctions. Loss of temporal variation of other hormones may contribute to biologic dysfunctions, especially those involving the hypothalamic–pituitary axis. Reduced variation of physical exertion, environmental stressors, and thermal gradients that characterize modern lifestyles may reduce the autonomic dynamic range resulting in lowered heart rate variability and a myriad of systemic dysfunctions. The health benefits of activities such as exercise, meditation, acupuncture, coitus, and laughter may operate through increasing autonomic variability. Reduced physical exertion also accounts for declining dynamic range of musculoskeletal function. The resulting muscle atrophy, fat infiltration, and sarcomere shortening may not only have deleterious local effects, but may also be involved in systemic metabolic dysfunctions such as insulin resistance. The extent to which our endogenous systems rely on environmental variation for self-tuning and the impact that under-utilization of compensatory mechanisms has on biologic function are not well understood. Modern therapeutic approaches generally result in reversion to the mean of physiologic functions and may buffer against variation. For example, beta-blockers are given to reduce adrenergic excess, insulin to treat insulin insufficiency, serotonin-reuptake inhibitors for depression, and refractive lenses for myopia. By undermining the demand for native compensatory functions, such therapeutic strategies may actually impair future ability to respond to biologic disequilibria. Generalizing from these

* Corresponding author. Tel.: +1 650 387 6667; fax: +1 650 325 5028.
E-mail address: ayun@stanford.edu (A.J. Yun).

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observations, we anticipate benefits of therapeutic and lifestyle approaches that expand, rather than reduce, the dynamic range of many biologic experiences.

Hypothesis

The perceived dynamic range and variation of many environmental features may be narrowing due to human interventions. However, it is not well understood to what extent our endogenous systems rely on environmental variation for self-tuning and what the impact under-utilization of compensatory mechanisms has on biologic function. We hypothesize that reduced dynamic range and variation of environmental cues may contribute to the formation of diseases, and that judicious expansion of biologic dynamic range may offer health benefits.

Loss of environmental variation and biologic dysfunction

Circadian variation of light

Natural light is one of the most profound environmental cues in nature. Karl von Frisch [1] first demonstrated that honeybees use location and changes in sun position for navigation. Pigeons and other birds use sun position, sun movement, and photoperiod variation for navigation and migration [2,3]. Many species rely on photoperiod variation to time developmental changes, mating, and foraging [3—6]. Many of these functions have been shown to operate through melatonin [4—6], an indolamine hormone predominantly secreted by the pineal gland in inverse relationship to photoperiod exposure. Melatonin release fluctuates in well-characterized circadian and seasonal patterns [7].

The influence of light on biologic functions in humans is not fully understood, but recent research points to a potentially significant role. As one of the master clocks in the body, melatonin secretion, mediated by photoperiod variations, regulates temporal variation of many core systems in the body including the autonomic, endocrine, and immune systems [5,8]. Melatonin dysfunctions have been implicated in a wide range of diseases involving these systems [9]. Light exposure is thought to regulate pineal function primarily through circadian retinal photoreceptors [10], most likely involving ganglion cells [11] and the suprachiasmatic nucleus [12]. Melatonin regulation through pathways independent of ocular photoexposure such as skin photoexposure has also been speculated [13], and bilirubin absorption of light is also thought to play a role in circadian entrainment [14]. Skin exposure to light also modulates the immune system [15].

In this context, the changing pattern of light exposure associated with modern lifestyles may be an under-recognized source of biologic dysfunction. In general, attributes of modern lifestyle, such as indoor vocations, daytime sheltering, eyeglasses that shade light, and nighttime use of artificial light may narrow the dynamic range of circadian light exposure. As a result, modern humans may experience less luminal contrast between daytime and nighttime compared to our biologic predecessors, and duration of light exposure per day may be longer. Evidence suggests that biologic dysfunctions may occur as a result. For instance, poor daytime lighting conditions in institutionalized elderly patients, as well as increased nighttime light exposure, have been implicated in melatonin dysfunction and sleep disorders [16]. Conversely, daytime luminescence therapy, which negatively regulates daytime melatonin, improves nighttime sleep, suggesting a possible rebound elevation of nocturnal melatonin function [16,17].

The loss of temporal variation of many hypothalamic-pituitary hormones is often associated with biologic dysfunction [18]. Given the central role that melatonin function plays in the regulation of other hormones [19], the melatonin dysfunction induced by changes in light patterns may contribute towards many other systemic dysfunctions. For example, melatonin dysfunction is known to impair the regulation of sex hormones and may contribute to precocious or delayed puberty [20]. Additional studies are warranted to fully understand the downstream health consequences that result from the dampened dynamic range of light exposure.

Variability of autonomic balance

Variation of input stressors to the autonomic system may be essential for maintaining the dynamic range of the autonomic system. Heart rate variability (HRV), a measure of dynamic range of autonomic function, can decline under various circumstances and lead to an increased risk of cardiac events and mortality [21]. High HRV connotes robust strength of the sympathetic and

parasympathetic response systems, as the interaction between these systems determines HRV [22]. Input variables that can produce a decline in HRV include aging, chronic stress, and lack of exercise [23,24].

We see the loss of variation of stressor inputs as a major source of autonomic dysfunction and dampened HRV. It is intuitively appealing to speculate that everyday lives of our biologic predecessors may have been characterized by a substantially greater variation of stressors due to predatory forces and unpredictability of the environment. These stressors were probably acute in nature and spaced by stress-free periods. Modern humans have substantially altered their own environment such that acute stressors and environmental uncertainties including predation may have declined while background chronic stressors such as traffic, smog, and high-density living have emerged. The dynamic range of other input variables for autonomic function may have declined during the modern age. For instance, our predecessors likely experienced substantial circadian and seasonal variation of temperature. Cooler temperature elicits thermogenesis and shivering while warmer temperature elicits sweating and other cooling mechanisms. The autonomic system plays a substantial role in these processes [25,26]. Technological innovations such as heating and cooling systems, as well as the emergence of apparel, have dramatically narrowed the range of thermal experience among modern humans. Although these systems provide comfort, it is unclear to what extent they undermine long-term health by removing a fluctuating input signal to the autonomic system and by under-utilizing compensatory mechanisms. Another example of an input variable whose dynamic range may be declining is hydration status. Degree of hydration is a significant input variable for various metabolic functions and regulates autonomic function through the modulation of baroreceptors [27,28]. Our predecessors likely had less predictable access to hydration sources compared to modern humans who generally have ready access to potable water. The dynamic range of water accessibility has arguably lessened, and variation of hydration status has likely decreased as a result. These and other mechanisms by which the autonomic system was periodically challenged may be disappearing as a byproduct of modernization.

Declining variation of physical exertion during the modern age may negatively impact health by promoting autonomic dysfunction. Intermittent physical exertion was likely an intrinsic part of everyday life among our biologic predecessors, and the modern reduction of physical exertion has been directly linked to reduced HRV, increased autonomic dysfunction, and many systemic illnesses [21]. While exercise may increase HRV through pathways independent of sympathetic stimulation, the evidence generally supports the assertion that exercise-associated intermittent sympathetic challenge is a key determinant of high HRV [22,29,30]. Even a single episode of sub-maximal exercise can increase HRV and promote vagal function [30]. The reduced dynamic range of exertion may be a key component of the output dysfunctions related to the autonomic and metabolic systems. Our hypothesis suggests that exercise regimens that emphasize variation of speed, power, and type may produce the optimal, non-linear input pattern of signals for the autonomic system and generate robust improvements in HRV. The benefits of intermittent exercise may also be related to the variation of dynamic blood flow to muscle, which may be a key part of maintaining normal endothelial function [31].

In addition to exercise, hot—cold baths, meditation, acupuncture, caffeine, alcohol, mood variation, stress variation, coitus, poetry reading, rhythmic breathing, crying, and laughter are among the many activities that may offer health benefits by challenging the autonomic system and expanding its dynamic range [32,33]. Laughter has been called ''the best medicine'' and the enhancement of HRV through intermittent acceleration of heart rate and respiration represents a plausible mechanism by which health benefits may accrue [32,33].

Muscle stretching

In addition to dampening the dynamic range of the autonomic system, reduced physical exertion during modernity may also impair health by narrowing the kinesiologic range of the musculoskeletal system. It is well known that the range of motion (ROM) of many joints declines during aging [34]. The ROM of the jaw decreases with aging, independent of temporomandibular joint dysfunction [35]. The hip joint also demonstrates reduced ROM with advancing age [36].

While the decline of ROM may be a consequence of the aging process, the loss of ROM due to modern lifestyle changes may also be a contributing cause of some of the systemic dysfunctions seen with aging [34]. Skeletal muscle exhibits tremendous plasticity, and even temporary immobilization in a shortened position can result in muscle fiber atrophy, proliferation of connective tissue, reduction in the

number of serial sarcomeres, alterations in gene transcription, and a reduction in ROM [37–39]. In addition to the musculoskeletal under-use associated with modern lifestyles, another potential cause of reduction in the dynamic range of joint mobility may be unbalanced weight training and repetitive positions, which may create unequal strength among agonist/antagonist muscle groups [40].

Whatever its inciting cause, reduced ROM elicits secondary changes, such as muscle atrophy, fatty deposition, and inhibition of protein synthesis, which may promote systemic disturbances [39,41,42]. For instance, conversion of muscle, a large consumer of insulin and glucose, to adipose tissue can have undesirable metabolic consequences such as increased insulin resistance [43]. Indeed, computed tomographic evaluation of muscle composition suggests that fat content within muscles, which increases with aging, under-use, and decreased ROM [37–39,44], correlates strongly with systemic insulin resistance [45]. These concepts may help elucidate the unexplained improvement of diabetes among patients who participate in yoga [46], a form of exercise focused on muscle stretching. Sarcopenia could be an indicator of catabolic state, and may participate in the pathogenesis of many other systemic dysfunctions [47]. It appears that musculoskeletal dysfunction such as atrophy, loss of strength, imbalance, and joint pain associated with under-use or misuse may be independent contributing factors in the pathogenesis of osteoarthritis, which has traditionally been thought to result from accumulated structural damage [48]. Perhaps autonomic dysfunction also contributes to arthritis, especially the inflammatory joint diseases. Confirmatory studies are required to determine if yoga and other activities that involve stretching or increasing ROM of joints may offer systemic health benefits.

Implications

We hypothesize that reduced dynamic range of various environmental signals may be a byproduct of modernization and that these changes may represent under-recognized sources of biologic dysfunction. In this paper we offer three examples of this phenomenon involving systems as diverse as the endocrine, autonomic, and musculoskeletal systems. Empiric observation suggests that the perceived variation of many other environmental features may be potentially diminishing in modern times. For example, the foraging behaviors of many species follow circadian patterns and alternate between states of hunger and satiety, which are intertwined by a complex network of gut–brain hormones that also modulate metabolic function in reciprocal fashion [49]. It is unknown whether modern feeding patterns which reduce the dynamic range of hunger–satiety cycles, such as the extreme example of continuous 24-h feeding in the intensive care unit, are contributing to metabolic dysfunctions. Furthermore, while industrialization of the food industry has diversified the modern diet in some ways, nutrition may actually be becoming more homogeneous as processed foods become more ubiquitous. The hyper-hygiene obsession of modern life may reduce the infectious disease burden, but the potential negative impact of dampening the immune dynamic range by reducing variability of infectious cues is unknown. Other potential cues whose dynamic range may be narrowing from the human perception perspective may include olfactory signals, auditory signals, convection currents, degree of weight-bearing, visual distances, and pain. The extent to which the narrowing of these environmental features may be contributing to biologic dysfunctions warrants additional investigation. We anticipate potential benefits from therapeutic and lifestyle approaches that expand, rather than reduce, the dynamic range of many biologic experiences.

Ironically, many current therapeutic approaches generally result in reversion to the mean of physiologic functions and may buffer against natural variations. For example, beta-blockers are given for adrenergic excess, serotonin reuptake inhibitors for serotonin pathway deficits, refractive lenses for myopia, and insulin for insulin insufficiency [24]. These approaches, augmenting a deficit and blocking an overactive pathway, may not only narrow the system dynamic range, but may also induce tachyphylaxis [24]. Perhaps a paradoxical approach which expands the biologic dynamic range and relies on compensatory mechanisms, rather than drug effects, may be useful in the treatment of diseases [24]. The ideal solution may involve asynchronous or alternating administration of drugs that have opposing mechanisms to widen the dynamic range and strengthen compensatory mechanisms in both directions. Thoughtful integration into native chronobiologic patterns may be necessary. The goal is to enable eventual withdrawal of all drugs while restoring the normal dynamic range of physiologic functions.

Beyond individuals, the dynamic range of parameters at the population level may also be changing during modern times. Since the advent of mass

transportation, a global melting pot has emerged and the variation of human genotypes and phenotypes may be declining. Modern trends in agriculture have narrowed the genotypic variation of many plant species. Whereas speciation enables greater genotype variation in a population over time through reproductive isolation, extinction of species (de-speciation) that occurs as humans overrun natural habitats may be contributing to an earth-wide loss of genotypic dynamic range. Advances in telecommunications have enabled unprecedented sharing of knowledge, but the collective dynamic range of esoteric ideas and skills that had accrued over thousands of years of human evolution may be declining with the emergence of a global information consensus.

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