Paradoxical strategy for treating chronic diseases where the therapeutic effect is derived from compensatory response rather than drug effect

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Summary Reversing chronic conditions remains an elusive goal of medicine. The modern medical paradigm based on blocking overactive pathways or augmenting deficient pathways offers symptomatic benefit, but tolerance to therapy can develop and treatment cessation can produce rebound symptoms due to compensatory mechanisms. We propose a paradoxical strategy for treating chronic conditions based on harnessing compensatory mechanisms for therapeutic benefit. Many current drugs may be repurposed for a paradoxical indication where the therapeutic effect is derived from compensatory response, rather than drug effect. For example, although exercise is associated with acute adrenergia, paradoxical downregulation of baseline sympathovagal ratio occurs as a remodeling response. For conditions that manifest chronic sympathetic bias such as cardiovascular diseases, judicious administration of adrenergic agonists may induce compensatory downregulation of baseline sympathovagal ratio. The concept may generalize to many other diseases, especially those involving pathways which exhibit strong homeostatic tendencies such as the neurologic, immune, and endocrine systems. Careful consideration of chronobiologic features is necessary to optimize dosing strategies for modulating compensatory responses, and eccentric dosing schedules, shorter-acting formulations, or pulsatile delivery may be desirable in some cases. To what extent the effect of desensitization to current therapy is mistaken for disease progression in conditions such as diabetes, myopia, depression, and hypertension warrants investigation. The merits of combining behavioral and drug therapies such as diet-insulin therapy for diabetes and exercise-\textsuperscript{b} blockade for cardiovascular disease should be revisited since there is a risk for exacerbating the underlying dysfunction. The reduced dynamic range of various environmental experiences and the tendency to revert to the mean through medical intervention, thermoregulation, and other modern lifestyle changes may play under-recognized roles in human diseases. Perhaps alternating agonists and antagonist may exercise the entire dynamic range of pathways and improve health.

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Hypothesis

Reversing chronic conditions remains an elusive goal of medicine. The modern medical paradigm based on blocking overactive pathways or aug-
menting deficient pathways offers symptomatic benefit, but tolerance to therapy can develop and treatment cessation can produce rebound symptoms due to compensatory mechanisms. Tolerance is defined as either a situation requiring dose escalation to maintain the therapeutic effect or a decreasing response to repeat similar dosing. A classic example is the use of β-blockers for hypertension, in which abnormally high sympathovagal ratio represents one of the therapeutic targets. With time, chronic sympathetic blockade with β-blockers may induce compensatory elevation of sympathovagal ratio, thereby creating higher dosing requirements and the potential for rebound hypertension upon cessation [1,2].

We propose a paradoxical strategy for treating chronic conditions based on harnessing compensatory mechanisms for therapeutic benefit. Our counterintuitive paradigm suggests that many current drugs may be repurposed for their paradoxical indication where the therapeutic effect is derived from the compensatory response they provoke, rather than the drug effect. For the purposes of discussion, we specifically focus on the potential use of sympathetic agonists for the treatment of diseases involving chronic sympathetic bias. The concepts of this specific case may generalize to many other areas of medicine.

Evidence

Autonomic dysfunction and diseases

Separately identifiable named medical conditions number in the thousands. However, the constitutional symptoms that manifest them are relatively few in number and typically involve the autonomic system [3]. Many diseases, including the compendium of conditions associated with aging, are associated with end-organ dysfunctions compatible with sympathetic bias [4]. Why adrenergic behavior emerges among end-organs is unknown, but withdrawal of central autonomic regulation leading to unmasking of intrinsic sympathetic bias in end-organs is one hypothesis [4]. Early evidence suggests that autonomic nerves may regress [4], relinquishing their regulatory hegemony over target organs [5]. Indeed, parasympathetic [5] and sympathetic receptor hypersensitivity [6–13] are common features of many diseases, especially those associated with aging, and may reflect upregulation of postsynaptic autonomic receptors in target organs as a compensatory adaptation to lost signal input. The autonomic receptor hypersensitivity during aging and disease and the dysfunctional behavior of target organs that ensues are not unlike those seen in denervation injury [8,9]. Thus, the hyperadrenergic behavior of target organs during aging may reflect a regression to their intrinsic state after emancipation from central regulation. The hyperadrenergic behavior of all transplanted organs, which are initially electrically isolated from host autonomic regulation, supports this view [4]. From a teleologic perspective, it is intuitively appealing to speculate that target organ functions were acquired during evolution in their "agonal" state, with the central nervous system generally playing an inhibitory role. It is widely known that central nervous injury often manifests as peripheral hyperexcitation. Integrating these ideas, we postulate that regression of central autonomic control and simultaneous unmasking of end-organ hyperadrenergia accompanied by compensatory upregulation of autonomic receptors are emergent properties of many diseases, particularly those associated with aging.

Current treatment paradigms may need to be revisited in light of this framework. The important role of sympathetic overactivity in diseases is increasingly becoming recognized in many conditions including hypertension, acute coronary syndrome, and congestive heart failure. The dominant trend today in the treatment of such conditions is adrenergic blockade, typically with a β-blocker. β-Blockers have been shown to provide substantial clinical benefit in a number of large randomized clinical trials [14]. However, tolerance to therapy requiring dose escalation develops over time and patients can become refractory [15]. Furthermore, rebound hyperadrenergia occurs upon cessation of therapy [1,2]. These phenomena suggest that adrenergic blockade is far from the ideal solution.

Tolerance and rebound associated with β-blocker use suggest a compensatory host response. Drug holiday between doses of β-blockers can re sensitize patients to therapy in systemic hypertension and ocular hypertension [16–18]. The elements of the compensatory response are not fully understood, but increased sensitivity of the adrenergic pathway with or without downregulation of the parasympathetic pathway are likely culprits. The data supporting this view is somewhat controversial. While most authors have observed increased adrenergic sensitivity in response to β-blocker therapy [2], some have noted adrenergic downregulation after chronic exposure to β-blockers [19]. The discrepancy could be attributed to many factors including specific drug used and the chronobi-
ology of dose administration. Overall, while β-blockers provide objective clinical benefit in many diseases, they appear to elicit a compensatory response that may potentially exacerbate the underlying cause of the disease by further enhancing adrenergic hypersensitivity [2].

Paradoxical use of adrenergic agonists for chronic sympathetic bias

We propose a paradoxical idea that judicious administration of sympathetic agonists may be useful in the treatment of conditions that manifest chronic sympathetic bias. The experimental pharmacologic evidence supporting our proposal is scant. How can we justify augmenting the sympathetic pathway when hyperadrenergia is the problem we are trying to correct? The justification lies in the recognition that chronic sympathetic bias in many diseases may be an intrinsic end-organ phenomenon accompanied by sympathetic receptor hypersensitivity [4,5]. Whereas β-blockers may induce further compensatory increase in chronic adrenergic hypersensitivity, β-agonists may induce a compensatory decrease in chronic adrenergic hypersensitivity and a compensatory increase in vagal function.

An intriguing piece of evidence is the additional benefit of administering a β-agonist during holiday periods between timolol doses in the treatment of ocular hypertension [17,18]. That such β-agonist administration augments the benefit of β-blockade could be attributed to the promotion of a compensatory vagal response by the β-agonist. Another interesting piece of evidence is the unexplained down-regulation of airway inflammation by the chronic administration of a long-acting β-agonist [20]. The pro-inflammatory effects of adrenergia are well-described elsewhere and aging is generally accompanied by both phenomena [4,21,22]. How can we reconcile these last two statements? The answer may lie in a subtle but important distinction between these scenarios. The chronic sympathetic bias of aging may be a post-synaptic, intrinsic end-organ phenomenon. One such end-organ system is the lymphoid system. The adrenergic behavior of the lymphoid system is the production of T helper (Th)2 pro-inflammatory cytokines [4,21,22]. The chronic administration of β-agonists, on the other hand, can be seen as a central pre-synaptic phenomenon. As such, chronic β-agonist administration may induce compensatory downregulation of the post-synaptic adrenergic receptor population and function in the end-organs. The decreased inflammation seen in chronic β-agonist administra-

tion may reflect the anti-adrenergic (or pro-vagal) remodeling of the lymphoid system.

Evidence from exercise

The best supporting evidence for our paradigm comes from exercise. It is well-documented that enhanced efferent vagal activity increases heart rate variability (HRV) whereas sympathetic stimulation decreases HRV [23], and low HRV is associated with an increased risk of cardiac events and mortality [24,25]. Extensive evidence indicates that exercise strengthens vagal tone and increases HRV [26–28], suggesting that repeat sympathetic challenge may enable vagal rehabilitation and reduce sympathovagal ratio. Even a single episode of submaximal exercise appears to increase HRV and promote parasympathetic function [27]. While the possibility that exercise may lower sympathovagal ratio through pathways independent of the sympathetic stimulation cannot be excluded, the evidence supports the hypothesis that sympathetic activity of exercise may induce compensatory downregulation of baseline post-synaptic end-organ adrenergic function and relative upregulation of vagal function. Exercise exemplifies our biologic rehabilitation hypothesis, and we propose that the autonomic remodeling response to exercise may be similarly elicited by judicious therapeutic administration of agents that promote adrenergia to treat chronic disorders of sympathetic bias.

Potential safety issues related to acutely promoting adrenergia must be addressed [29]. Acute adrenergia plays a role in the precipitation of cardiovascular events including sudden death [29,30], especially in patients who have chronic sympathetic bias. Substantial controversy exists as to whether the use of β-agonists in asthma is independently associated with an increased risk of death [31,32]. To be safe, however, we believe that initiating therapy with a low dose of short-acting sympathetic agonists, then gradually building up the dose in crescendo fashion, may be prudent. The rationale is similar to starting with low-level exercise before advancing to more ambitious exertion in patients with a high-risk cardiovascular profile.

Our hypothesis has implications for the question of whether additional cardioprotective benefits accrue to patients who exercise while taking β-blockers [33,34]. Patients on β-blockers initially cannot raise their adrenergic response sufficiently to meet the cardiovascular demands during exercise and may fatigue quickly [35], an effect that can be reversed with atropine [36]. Patients in this group
usually report improved tolerability to exercise over time as their body accommodates. It is plausible that accommodation occurs as a result of sympathetic upregulation to compensate for an insufficient adrenergic response during exercise. Confirming this view is the evidence that baseline serum norepinephrine levels may increase after initiating metoprolol in exercising patients [37], perhaps indicating sympathetic compensation to chronic blockade. Sympathetic compensation may also explain why the theoretical risk of administering β-blockers to asthmatic patients remains unsubstantiated empirically [38]. Chronic β-blocker use is associated with impotence, anxiety, worsening diabetes, and insomnia, which may be paradoxical indicators of vagal withdrawal and adrenergic excess [39–41]. Furthermore, exercising patients who are on β-blockers tend to have markedly elevated levels of natriuretic peptides as compared to those not on β-blockers [42]. The authors of the study concluded that the higher levels of natriuretic peptides constitute a protective mechanism [42], but the findings could also be interpreted as a signal that additional adrenergic stress may be present in the cardiovascular system. If this line of thinking holds, then withdrawing β-blockers from regularly exercising patients may unmask sympathetic hypersensitivity that had further increased in compensation during β-blockade. Health hazards of sympathetic overactivity are increasingly being elucidated [3], and ironically, β-blockers and exercise, which independently promote vagal tone, may exacerbate sympathetic hypersensitivity and pose greater health risks when combined in the same patient. Importantly, exercise-related ischemia in patients on β-blockers is a strong predictor of eventual fatal cardiovascular events [43].

**Other conditions associated with compensatory response to therapy**

The concepts discussed in previous sections may generalize to many other areas of medicine. The opportunity is particularly intriguing in systems which exhibit substantial tolerance and tachyphylaxis during therapy. For reasons that are unclear, there is an interesting pattern among psychototropic medications to induce tolerance, and drug holidays are frequently required to counter compensatory mechanisms and reestablish sensitivity. Tolerance to baclofen occurs in the treatment for spasticity [44–46] and is thought to be related to a persistent occupation of γ-aminobutyric acid (GABA)B receptors by baclofen resulting in a decreased receptor population [45,47,48], reduced sensitivity [48], or impaired interaction with other receptor systems [49]. Drug holiday appears to resensitize such patients [50]. Other examples where drug holiday has shown benefit include opioids for pain [51–54], L-dopa and bromocriptine for Parkinson’s disease [55–59], selective serotonin reuptake inhibitors (SSRIs) for depression [60], haloperidol and chlorprozamine for schizophrenia [61,62], nitrates for hypertension [1,2,63–65], and anti-epileptic drugs for seizures [66], and tandospirone for the treatment of Machado-Joseph disease [67]. Immune and endocrine disorders also often exhibit strong compensatory responses, and drug holidays or pulsed dosing strategies, which generally involve high doses given in short bursts, are sometimes used to counter these effects [68]. Examples include prednisone, growth-hormone releasing hormone (GHRH), erythropoietin, and estrogen therapies [69–79]. Pulsed prednisone is used for various immune and oncologic disorders and may offer a superior efficacy or a decreased side effect profile compared to conventional administration [72–79]. Pulsed estrogen is used to mitigate the side-effects related to hormone replacement therapy [69,70]. Pulsed administration mirrors endogenous chronobiologic patterns that characterize many natural cellular and organismal functions. Examples include cyclical pulsatile secretion of insulin [80,81] and various hypothalamic hormones [82,83]. The importance of temporal resolution is reflected in the observation that pulsed administration can produce interesting, somewhat unexpected effects. For instance, pulsed estrogen has been proposed to reduce undesirable hormonal stimulation of breast and uterine tissue [69], but interestingly, such pulsing appears to increase stimulation of breast cancer cells [84]. Pulsed administration has been proposed to reduce bone demineralization associated with glucocorticoids, but substantial bone demineralization [73] and insulin resistance [74] still occur in these patients. Pulsed GHRH, which is thought to promote growth, can actually reduce growth rate in chickens [85]. Continuous parathyroid hormone (PTH) exposure, which occurs in conditions such as hyperparathyroidism, stimulates osteoclast formation and bone death while intermittent PTH stimulates osteoblast activity and bone growth. These findings suggest that careful considerations of chronobiologic dimensions to therapy are in order.

The differential response to acute and chronic therapy is similar to the paradoxical responses to acute and chronic endogenous stimuli. For instance, the immune response to sepsis behaves in opposing patterns during the acute phase, which
is associated with upregulation of tumor necrosis factor (TNF-α), interleukin (IL)-1, IL-6, and interferon-γ [86], and the chronic phase, which is associated with downregulation of immune function [87]. The hypothalamic-pituitary (HP) axis also shows differential response to acute versus chronic stress. The acute HP neuroendocrine response consists of activated anterior pituitary function with increased levels of hormones such as thyrotropin-releasing hormone, gonadotropin releasing hormone, and growth hormone releasing peptide [88] whereas chronic stress uniformly reduces pulsatile secretion of anterior pituitary hormones [88–90]. Notably, endocrine dysfunctions with the loss of hypothalamic feedback control, loss of pulsatility, HP axis downregulation, target-organ receptor downregulation, desensitization, and hormone resistance characterize not only sepsis but also menopause, aging, and death [86–95]. Simply replacing a deficient hormone may not only fail to correct the problem, but may even cause deleterious effects [89]. Rehabilitating these pathways by restoring various HP and target organ functions to the proper temporal pattern and pulsatility represents a potentially exciting area of future research.

Chronic diseases which exhibit strong compensatory tendencies are compelling candidates for our paradoxical treatment model. Drugs which have the opposite function to current therapies may be tested for their ability to rally the compensatory response for therapeutic purposes. In most cases, the empirical pharmacologic evidence to support our hypothesis is very difficult to find, in part due to the counterintuitive nature of the idea. Further understanding of the temporal dimensions of physiology, cell biology, and molecular biology may yield new clues to the pathogenesis of diseases and treatment methodologies.

**Embodiments**

The concept of temporarily exacerbating an underlying dysfunction to ameliorate it long-term raises safety issues which must be addressed. The benefits of such a strategy must be weighed against the risk posed by compounding the underlying dysfunction. As is the case with exercise, however, short challenges in escalating doses can probably safely induce a paradoxical effect in the long term. Short-acting formulation, pulsed administration, and intermittent dosing may offer a better risk–benefit profile compared to chronic, long-acting dosing when it comes to paradoxical therapeutic strategies. The exact temporal pattern of administration and withdrawal is likely to be critical, and the optimum pulsatility of administration as well as dose escalation and weaning tactics remain to be explored. For instance, the regular daily use of long-acting β-agonists has been shown to induce more compensatory tolerance than intermittent dosing [96]. Regular administration patterns should be compared with irregularly irregular patterns of pulses as to which can produce more robust and durable compensatory rehabilitation of a dysfunctional pathway. The latter eccentric pattern may be more successful in producing a balanced compensatory response. Sometimes, the ideal target for a compensatory response induction may reside in remote parts of the biologic feedback loop. For instance, using a therapeutic strategy to negatively regulate the feedback loop at the hypothalamic level may produce an augmented effector response such as enhanced end-organ endocrine or autonomic output. Targeting such upstream centers of pathway regulation may be particularly desirable since the resulting compensatory output is more likely to exhibit a natural pulsatility and temporal profile. Another potential variation on the theme is alternating administrations of agonists and antagonists to fully exercise the entire dynamic range of the compensatory mechanism. The ideal parameters likely will vary by drug, the pathway being rehabilitated, and the individual patient, and will need to be determined by future research.

Given the potential need for more frequent dosing and possibly a more irregular pattern of dosing, patient compliance may emerge as an issue and may necessitate the development of novel drug-delivery methodologies. For instance, patches, depots, pumps, and automated drug delivery devices that can deliver drugs in selected patterns may be useful. In addition to varying the dosing schedule, it may be useful to vary the drug amount over time and to tailor the therapy to changing conditions. Closed-loop drug delivery systems that use software to adapt to measurable host parameters intelligently would provide additional advantages. For instance, a drug delivery device that can deliver a tailored dose of an appropriate β-agonist in response to a diagnostic measure of HRV may be useful.

**Implications**

The concept of rehabilitating diseased pathways by harnessing intrinsic compensatory mechanisms may represent a fundamental paradigm shift in modern therapeutics. Many current drugs may be
The dynamic range of various environmental experiences has substantially dampened in modern times due to medical intervention, technologic innovation, and ecological changes. Reduced day-night light variation due to indoor living and electricity, reduced thermal range due to heat and air conditioning systems, reduced hunger-satiety oscillations from snacking and 24 h tube feeds, reduced visual focal length variation due to emergence of books and computers are among the countless environmental features that have narrowed in dynamic range during modern times. To what extent the loss of dynamic range of physiologic functions plays a role in the pathogenesis and progression of diseases warrants further investigation. Perhaps the effect of desensitization to current therapy is mistaken for disease progression in conditions such as hypertension, depression, myopia, and diabetes. For example, SSRIs are widely used to treat depression, but biologic dependence is common and careful weaning is required to avoid discontinuation syndrome (DS), which is characterized by rebound depression, dizziness, and gastrointestinal disturbances [101–103]. Even patients remaining on therapy are at a risk for increased risk of suicide [104]. Could depression instead be treated with judicious administration of serotonin pathway antagonists? Earlier we discussed the possibility that combining exercise and β-blocker therapy may worsen adrenergic hypersensitivity and tachyphylaxis by inducing compensatory upregulation of the sympathetic system to meet the cardiovascular demands of exercise in a β-blocked state. Applying the same theory, does acute grief after tragedy adaptively upregulate the serotonin pathway and elevate baseline degree of happiness, and if so, does SSRI administration during tragedy undermine the compensatory benefits of acute grief and possibly further dampen baseline serotonin function? Are current diabetic management strategies inducing downregulation of β-cell function, which can be mistaken for disease progression? Does combining exercise with insulin therapy offset the compensatory response and possibly reduce baseline insulin sensitivity? Instead, could insulin antagonists be used to resensitize patients to insulin and treat diabetes?

The health merits of alternative medical practices, particularly those that expand the dynamic range of environmental experiences, can be reconsidered in light of our hypothesis. Hot sauna, sometimes alternating with cold baths, is a popular activity among Norwegian and other populations. Since thermal gradients, hot or cold, can acutely activate sympathetic activity [91,105], it is plausible that saunas and cold baths can "exercise" the autonomic system and strengthen it. Similarly, the benefits of acupuncture, meditation, yoga, and herbal therapies may in part be mediated through exercising the autonomic system. While chronic stress has many untoward health implications, popular activities that create an acute "adrenaline rush" including riding roller-coasters, watching horror movies, laughter, gambling [106], and ingesting caffeine may have beneficial health con-
sequences that remain to be explored. There may be a similar natural resonance to hunger—satiety oscillations, light—dark exposures, heat—cold variations, and sleep—wake cycles that optimally exercise various pathways. Yet there is a modern tendency to use technology to restore equilibrium, thereby reducing the dynamic range of biologic experience and possibly undermining the ability to respond to environmental disequilibria in the future. Modern medicine is largely built on this paradigm of pharmacologic reversion to the mean. The resulting tolerance to therapy that requires dose escalation and physiologic dependence do not serve as disincentives for drug companies. Patient compliance issues have led to a trend favoring extended-release formulations over short-acting formulations, but the resulting chronic intervention may be inconsistent with the subtle chronobiologic features of pathways and may even exacerbate the underlying system dysregulation. Our hypothesis portends a different trend in pharmacology: the development of drugs that require more innovative dosing, increase sensitization over time enabling dose reduction, and may cure the underlying chronic condition. Many current drugs may be repurposed for a paradoxical indication, possibly using shorter acting formulations that have previously been shunned due to patient compliance issues. Future research is needed to validate these and many other potential applications of our strategy.

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