Interacting Mediators of Allostasis and Allostatic Load: Towards an Understanding of Resilience in Aging

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Individual differences in the aging process can be conceptualized as an accumulation of wear and tear of daily experiences and major life stressors that interact with the genetic constitution and predisposing early life experiences. The neuroendocrine system, autonomic nervous system, and immune system are mediators of adaptation to challenges of daily life, referred to as *allostasis*, meaning "maintaining stability through change." Physiological mediators such as adrenalin from the adrenal medulla, glucocorticoids from the adrenal cortex, and cytokines from cells of the immune system act upon receptors in various tissues and organs to produce effects that are adaptive in the short run but can be damaging if the mediators are not shut off when no longer needed. When release of the mediators is not efficiently terminated, their effects on target cells are prolonged, leading to other consequences that may include receptor desensitization and tissue damage. This process has been named "allostatic load," and it refers to the price the tissue or organ pays for an overactive or inefficiently managed allostatic response. Therefore, allostatic load refers to the "cost" of adaptation. This article discusses the mediators of allostasis and their contributions to allostatic load as well as their role in resilience of the aging organism to stressful experiences.

THE NEUROENDOCRINE system, autonomic nervous system, and immune system are mediators of adaptation to challenges of daily life, referred to as *allostasis*, meaning "maintaining stability through change".[1] Physiological mediators such as adrenalin from the adrenal medulla, glucocorticoids from the adrenal cortex, and cytokines from cells of the immune system act upon receptors in various tissues and organs to produce effects that are adaptive in the short run but can be damaging if the mediators are not shut off when no longer needed. When release of the mediators is not efficiently terminated, their effects on target cells are prolonged, leading to other consequences that may include receptor desensitization and tissue damage. This process has been named "allostatic load,"[2,3] and it refers to the price the tissue or organ pays for an overactive or inefficiently managed allostatic response. Therefore, allostatic load refers to the "cost" of adaptation and it is prominent in the aging process.

Allostasis represents the integrated output of interacting physiological systems, such as, but not confined to, the HPA axis and autonomic nervous system. An allostatic state reflects a response pattern in which these systems are overactive and/or dysregulated. The overactivity and dysregulation may be manifested during the normal course of daily activities or as a result of stressful events, and may be exacerbated by genetic risk factors for hypertension and diabetes, as well as by early life events that make the physiological response systems particularly vulnerable to dysregulation or overactivity. Thus allostatic states and allostatic load represent the final common path that reflects contributions of genetic risk factors, early developmental influences, the diurnal rhythm, life style factors and stressors.

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Individual differences in the aging process can be conceptualized as an accumulation of wear and tear of daily experiences and major life stressors that interact with the genetic constitution and predisposing early life experiences.[4-6] Here we briefly describe the most easily measured and widely acting mediators of allostasis and indicate some of their connections to the pathophysiological secondary outcome measures of allostatic load. Four allostasis mediators will be considered briefly below: glucocorticoids, dehydroepiandrosterone (DHEA), catecholamines, and cytokines. They each have many effects on a variety of body systems and their production and actions are interconnected with each other. Moreover, along with other hormones and tissue mediators, they confer on the body a considerable capacity for resilience in the face of chronic stress.

GLUCOCORTICOIDS

Glucocorticoids are among the most versatile of hormones, having important regulatory effects on the cardiovascular system, the regulation of fluid volume and response to hemorrhage, immunity and inflammation, metabolism, brain function, and reproduction.[7] Virtually every tissue in the body has intracellular glucocorticoid receptors, and some of the key effects are highlighted below.

For *cardiovascular function*, the predominant effect of glucocorticoids is to permissively enhance cardiovascular function during times of acute stress, in part by enhancing sensitivity to catecholamines.

For control of *fluid volume*, glucocorticoids suppress the local edema that occurs in response to a hemorrhagic stressor, thus inhibiting potential damage from an overly exuberant response to damage.

In the case of *inflammation and immunity*, glucocorticoids are well known to suppress inflammation and the acute phase response to an infection, keeping these responses under control to minimize damage that they might inflict if overactive. At the same time, glucocorticoids enhance initial mobilization of immune cells to sites of infection and shape the nature of the immune response, favoring for example humoral over cellular immunity. Finally, however, glucocorticoids ultimately contain all types of immune responses, which is why they are useful in

the treatment of autoimmune disorders and reducing rejection of organ transplants.

In the sphere of *metabolism*, glucocorticoids promote appetite and food-seeking behaviors and they are classically described as promoting lipolysis, proteolysis, and gluconeogenesis (hence, their name). At the same time, they generally work in opposition to insulin, an anabolic hormone, except under the allostatic state of chronic glucocorticoid elevation, in which case they act to promote hepatic glycogen deposition and lipogenesis (that leads to fat deposition, especially in the abdomen, as in Cushing's disease at the expense of muscle protein loss), while raising insulin levels and impairing insulin actions on their receptors. The extreme consequence of this progression is type 2 diabetes, culminating in exhaustion of insulin production.

In the *central nervous system*, glucocorticoids inhibit glucose transport into brain cells and oppose the glucose-uptake promoting effects of catecholamines that act by increasing cardiovascular activity and enhancing cerebral blood flow. As noted above, however, glucocorticoids increase appetite for food and work in opposition to the anorectic effects of stress-activated release of brain corticotropin-releasing factor (CRF), the neuropeptide that also directs corticotropin (ACTH) release from the pituitary. Finally, as discussed earlier herein, glucocorticoids also biphasically modulate memory formation, with basal levels enhancing formation of memories of emotionally charged events and stress levels suppressing memory. Moreover, over long time periods involving repeated stress, glucocorticoids participate in a mechanism that causes atrophy of neural structures subserving memory.

With respect to *reproduction*, glucocorticoids participate in mechanisms found in many species that inhibit reproduction, and this can be rationalized as a logical contribution to the response to stress that operates to delay reproduction to a more auspicious time.

In conclusion, glucocorticoids fulfill the criterion of an allostatic mediator that can be measured noninvasively in human subjects and which gives useful information about a wide range of normal and pathophysiological conditions. As noted several times in this review, chronic elevations of glucocorticoids participate in a host of conditions that fall into the category of allostatic load, such as hypertension, abdominal obesity, bone mineral loss, loss of muscle mass, suppression of immune responses, memory impairment, and atrophy of brain structures like the hippocampus. Further, chronic insufficiency of glucocorticoids contributes to increased inflammatory and autoimmune responses and contributes to conditions of imbalance of cytokines and pain mechanisms in fibromyalgia and chronic fatigue syndrome (CFS). In addition, there are important interactions of glucocorticoids with other primary mediators that are described below.

DEHYDROEPIANDROSTERONE

DHEA is an adrenal steroid that has a number of effects that can be described as "functional antagonism" of the actions of glucocorticoids.[8-10] "Functional antagonism" refers to the fact that DHEA does not directly interact with the glucocorticoid receptor, and, in fact, there is no known receptor for DHEA in any tissue, which presents a considerable disadvantage for investigations of this interesting steroid.

The antagonistic effects of DHEA are most clearly demonstrated in terms of its ability to counteract the weight-inducing actions of elevated glucocorticoids in the Zucker rat.[10] DHEA treatment also counteracts the actions of glucocorticoids to inhibit memory and primed-burst potentiation,[11] a form of long-term potentiation. Bone mineral loss is correlated with reduced production of DHEA as a result of glucocorticoid therapy for autoimmune and inflammatory disorders,[12,13] which has led to the suggestion that DHEA should be supplemented in individuals receiving glucocorticoid treatment for autommune and inflammatory disorders.[13]

DHEA produces functional antagonism of glucocorticoid actions on a number of immune parameters. It antagonizes the thymolytic actions of glucocorticoids,[14] as well as the suppression of inflammatory cytokine production and cellular and humoral immune responses.[9] DHEA is also thought to function as more than an anti-glucocorticoid in preserving immune function, for example, after a thermal injury.[15]

Glucocorticoid actions in relation to obesity may be related, at least in part, to the ability of glucocorticoids to increase glucose uptake in cultured cells.[16] In principle, this action might work in opposition to glucocorticoid-induced insulin resistance. It is interesting to note that DHEA administration also antagonizes oxidative damage in brain, kidney, and liver produced by acute hyperglycemia.[17]

In the brain, interactions of DHEA with neurotransmitter systems such as serotonin, gamma amino butyric acid (GABA), excitatory amino acids, and dopamine are implicated in the actions in the central nervous system, although, again, the cellular and molecular details of these interactions are not clear.[18] One of the reported actions of DHEA is to reduce depressive symptomatology, particularly in depressed elderly.[19] In addition, DHEA, which declines with increasing age and has memory-enhancing effects in aging rodents, has been implicated as a possible neuroprotective agent in aging, even though it does not appear to directly improve cognition in human subjects.[8] However, the data thus far collected do not strongly support this hypothesis, although it is still tempting to speculate that DHEA antagonizes and moderates the allostatic load produced by chronic elevation of glucocorticoids. In that connection, the mood-elevating actions attributed to DHEA may be related either to glucocorticoid antagonism or to the actions related to neurotransmitter systems such as serotonin.

Despite of the many caveats, and based on the functional antagonism of some glucocorticoid actions, the level of DHEA relative to glucocorticoids, both of which can be assessed in blood samples, is a potentially useful measure of the possible amelioration of pathophysiological glucocorticoid actions in relation to allostatic load. It is important to remember that low levels of DHEA are indicative of a higher potency of glucocorticoids.

CATECHOLAMINES

The other major mediators of allostasis besides glucocorticoids are the circulating catecholamines, which have effects that in some cases synergize with and, in other cases, oppose

the actions of glucocorticoids. Glucocorticoids potentiate the actions of catecholamines while at the same time containing their release, and, in the adrenal medulla, glucocorticoids promote epinephrine synthesis by regulating the key enzyme, phenylethanolamine N methyl transferase (PNMT).[7,20] At the same time, catecholamines help maintain normal hypothalamo-pituitary-adrenal axis (HPA) function, since adrenergic input to the adrenal cortex facilitates ACTH-induced steroidogenesis.[21]

One of the most important distinctions is between norepinephrine release by the dispersed sympathetic nerves and epinephrine release by the adrenal medulla.[21,22] For example, in girls with CFS, morning resting epinephrine levels are elevated, whereas norepinephrine levels are not, compared to age-matched controls.[23] Whereas norepinephrine release is particularly important for the discrete regulation of blood vessel constriction and blood flow, redistribution and influencing a host of organs such as the heart, spleen, and pancreas, epinephrine release is important for skeletal muscles that do not have extensive sympathetic innervation. One of the important actions of epinephrine in muscle is to retard the degradation of proteins, working against the catabolic actions of glucocorticoids.[21] Epinephrine release is also more closely related to emotional distress, whereas norepinephrine release is more related to physical exertion.

Some of the other major effects of catecholamines are considered below in relation to the same processes that were discussed above for glucocorticoids.[21,22]

For *cardiovascular function*, the sympathetic nervous system maintains adequate cerebral blood flow in the transition from lying to standing and helps maintain blood flow during upright physical activity. Adrenal medullary epinephrine is also released during daily physical activity and this may be relevant to the normal metabolic activity of skeletal musculature, involving regulation of muscle glycogen stores and protecting muscle protein from degradation. In congestive heart failure, there is increased cardiac sympathetic activity in the face of declining sensitivity of the heart to the catecholamines.[22]

For control of *fluid volume*, both extreme underfilling and overfilling of the heart increase cardiac sympathetic activity, whereas hypernatremia causes inhibition of sympathetic activity and promotes natriuresis. Hyponatremia, on the other hand, increases sympathetic activity and promotes activity of the vasopressin and renin-angiotensin systems and aldosterone secretion that increase water and sodium retention.

In the case of *inflammation and immunity*, circulating catecholamines are involved in the mobilization and redistribution of immune cells in the body during stress and after a specific immune challenge, as is the case in delayed-type hypersensitivity.[24,25] Catecholamines may also be involved in suppressing immune function in the spleen under stressful conditions,[26] since the spleen receives heavy sympathetic innervation[27] and is relatively protected from access to circulating endogenous glucocorticoids.[24] In general, enhancing sympathetic tone decreases both T-cell and natural killer (NK) cell functions but not the proliferation of splenic B cells.[25] In contrast, chemical sympathectomy, while having varying results, does seem to increase the severity of autoimmune disorders.[25]

With respect to *metabolism*, catecholamines promote mobilization of fuel stores at a time of stress and act synergistically with glucocorticoids to increased glycogenolysis, gluconeogenesis and lipolysis, but exert opposing effects on protein catabolism, as noted above. One important aspect is regulation of *body temperature*.[22] Epinephrine levels are also positively related to serum levels of high-density lipoprotein (HDL)-cholesterol and negatively related to triglycerides. However, perturbing the balance of activity of various mediators of metabolism and body weight regulation can lead to well-known metabolic disorders such as type 2 diabetes and obesity. For example, there is evidence that deficiency of leptin or leptin receptors decreases adrenal medullary epinephrine release, and, furthermore, that a developmental impairment in epinephrine production may contribute to the insulin resistance syndrome. At the same time, increased sympathetic activation and norepinephrine release is elevated in hypertensive individuals and also related to higher levels of insulin, and there are indications that insulin further increases sympathetic activity in a vicious cycle.[28] Thus the origins of type 2 diabetes may be related, on the one hand, to a deficient leptin system with decreased adrenal medullary activity and, on the other hand, to an activated sympathetic nervous system with elevated levels of norepinephrine and glucocorticoids, both of which contribute to insulin resistance and hyperglycemia.[29]

In the *central nervous system*, catecholamines are associated with attention, vigilance, and arousal mechanisms[20] and with the formation of memories related to strong emotions, as discussed earlier.

In conclusion, epinephrine and norepinephrine are two, somewhat independent, indices of adrenal medullary and sympathetic neural activity that are related to changes in emotional state, physical activity, metabolism and body temperature, cardiac function, and fluid and electrolyte balance. Elevated levels of catecholamines, particularly during the night when sympathetic activity is normally decreased, are indicative of an allostatic state that may contribute to allostatic load. Separate measurements of norepinephrine and epinephrine and their metabolites in blood and urine are therefore useful indices of potentially abnormal allostatic states.

CYTOKINES

Cytokines are a diverse group of molecules that were first identified in relation to the acute-phase response and the subsequent activation of immune responses to a pathogen or other immunogenic agent. Inflammatory cytokines include interleukin (IL)-1, IL-2, IL-6, tumor necrosis factors (TNFs), fibroblast growth factors, and interferons, whereas the anti-inflammatory cytokines, so named because they inhibit inflammatory cytokine production, include IL-4 and IL-10. These cytokines are produced locally by immune cells but are also produced by diverse organs such as the brain and the liver.[30,31] As a result of their local production, cytokines enter the circulation and can be detected in plasma samples. Circulating levels of a number of inflammatory cytokines are elevated in relation to viral and other infections and contribute to the feeling of being sick as well as the associated sleepiness, with both direct and indirect effects on the central nervous system.[30,31] Circulating cytokines appear to have a limited access to the brain and also to induce a signal via the vagal system that induces the brain to express increased levels of its own inflammatory cytokines.[30,31]

Inflammatory autoimmune diseases such as multiple sclerosis, rheumatoid arthritis and type 1 diabetes reflect an allostatic state that consists of at least 3 principal causes: genetic risk factors such as those related to different major histocompatibility complex (MHC) alleles, factors that contribute to the development of tolerance to self-antigens or to antigens associated with food or other common agents, molecular mimicry between antigens on bacteria and self-antigens, and the hormonal milieu that regulates adaptive immune responses.[25] Besides sex hormones, the relative insufficiency of glucocorticoids in the Lewis, compared to the Fischer rat, is often cited as an example of this latter influence and, as noted above, represents one type of allostatic state in which other agents that are normally counter-regulated by glucocorticoids, such as inflammatory cytokines, may achieve the upper hand in pathophysiological conditions.[25]

There is also evidence that cytokines are involved in the regulation of normal sleep, independently of their ability to induce fever.[31,32] There is evidence for normal fluctuations in plasma levels of IL-1, IL-6, and TNF in relation to the diurnal cycle and sleep deprivation, whereas the story as far as circulating levels of interferons and fibroblast growth factors and normal sleep is less clear.[31] The anti-inflammatory cytokines, IL-10 and IL-4, have been shown to inhibit sleep in rats, but there is a paucity of data on their involvement in normal sleep-wake cycles.[31]

Conditions such as allergies and exercise of an intensity that promotes muscle proteolysis tend to increase the production of cytokines that can be detected in blood.[32-35] CFS and fibromyalgia are related conditions that appear to represent an allostatic state in which there is dysregulation of cytokine production, as well as a somewhat deficient level of circulating glucocorticoids that have counter-regulatory effects on cytokine production.[32-36] There is evidence that both mild exercise and allergies will exacerbate symptoms of CFS and fibromylagia.[32,34,35,37] In addition, viral infections are often reported as either precipitating or exacerbating CFS.[32]

Along with the symptoms of CFS and fibromyalgia, there are frequently reported signs of an allostatic state featuring elevated levels of certain inflammatory cytokines.[23,32,34,45,37,38] It is interesting to note that the balance of inflammatory to anti-inflammatory cytokines may be affected in CFS sufferers, as shown by a deficient counter-regulatory effect of both glucocorticoids and catecholamines on the balance between these 2 antagonistic types of cytokines in young women suffering from CFS.[23] Furthermore, as predicted from what we know of the linkage between peripheral and central nervous system cytokines, changes in circulating levels of inflammatory cyokines may signal increases in brain production of these same cytokines. Judging from recent work on a mouse model of CFS, these elevations may be more relevant than serum levels themselves to the symptoms of CFS and fibromyalgia.[40] In this connection, hyperalgesia and perception of chronic pain has been associated with increased levels of TNF-α in the hippocampus and other brain regions in a rodent model in which the TNF-α appears to reduce the release of norepinephrine.[41-43]

In conclusion, the measurement of circulating levels of inflammatory and anti-inflammatory cytokines, as well as circulating glucocorticoids, DHEA, and catecholamines, provides clues as to the existence of allostatic states reflecting an imbalance of various regulators of inflammation and adaptive immunity. Given the generally suppressive effects of glucocorticoids on inflammatory cytokine production,[24] cytokine levels should generally move in the opposite direction from glucocorticoid levels. One problem associated with the measurement of all of these markers is that their plasma levels may be very much related to the acute state of other processes related to such factors as recent exercise, allergies, sleep deprivation, and persistence of viral or other infections that exacerbate the existing allostatic state.[23,32,34,35,37,38] Thus the collection of body fluids for their measurement should be conducted under well-controlled conditions with some information as to the general state of health of the subjects.

CENTRAL ROLE OF THE BRAIN

The brain is the master controller of the mediators noted above and is also a target of these systems, subject to both protection and damage. Allostasis also applies not only to circulating hormones but also to organs and tissues of the body. In the nervous system, neurotransmitters are released by neuronal activity, and they produce effects locally to either propagate or inhibit further neural activity. Neurotransmitters and hormones are usually released during a discrete period of activation and then are shut off, and the mediators themselves are removed from the synaptic cleft by reuptake or metabolism in order not to prolong their effects. When that does not happen, however, there is allostatic load and the brain is at increased risk for damage.[44]

The processes of allostasis and allostatic load have been described and measured for metabolic and cardiovascular changes that are associated with obesity, type 2 diabetes, and cardiovascular disease.[45] However, the same type of elevated and prolonged secretion of glucocorticoids during aging has also been associated with impairment of cognitive function in rodents[46-48] and in humans.[49-51] Moreover, the endogenous excitatory amino acid neurotransmitters appear to play a major role in these changes,[48] even though they are also an essential part of normal synaptic neurotransmission and plasticity. Their actions lead to the formation of excess free radicals that can damage nerve cells, leading to the search for agents that can interfere with free radical production or enhance free radical quenching. The “glucocorticoid cascade hypothesis” of aging[48,52-54] is an example of a theory of aging that emphasizes the pivotal nature of aging of key brain structures such as the hippocampus, a brain region involved in key aspects of episodic, declarative, spatial, and contextual memory and also in regulation of autonomic, neuroendocrine, and immune responses. Agents that are protective against accelerated aging should be judged for their ability to protect key brain structures such as the hippocampus from the effects of a variety of insults, many of which involve excitotoxicity and damage from reactive oxygen species and free radicals. The glucocorticoid cascade hypothesis of aging is a prime example of allostatic load since it recognizes a feed-forward mechanism that gradually wears down a key brain structure, the hippocampus, while the gradually dysregulated HPA axis promotes pathophysiology in tissues and organs throughout out the body. In spite of its

vulnerability to allostatic load, the brain retains considerable resilience in the face of challenges to adapt through allostasis. Studies on the hippocampus reveal a number of types of structural plasticity, ranging from neurogenesis in the dentate gyrus to remodeling of dendrites to the formation and replacment of synapses.[55] These changes, along with compensatory neurochemical and neuroendocrine responses, provide the brain with a considerable amount of resilience. In psychiatric illnesses such as depression and the endocrine imbalance associated with Cushing's disease, there is evidence for remodeling of brain structures such as hippocampus and amygdala with some indications that the remodeling may be a reversible process.[56] The capacity of neurons in the brain to grow or shrink and the ability of some brain regions to replace neurons during adult life provide the brain with a capacity to respond to chronic stress and other challenges with a degree of resilience. For example, exercise has been shown to enhance neurogenesis in the hippocampal formation in an animal model,[57] and exercise is an effective antidepressant,[58] as well as being able to enhance executive function, a function associated with the prefrontal cortex.[59] A variety of hormonal mediators are implicated in these types of resilience including neurotrophins like neurotrophin 3 (NT-3) and brain-derived neurotrophic factor (BDNF)[60,61] and circulating hormones like insulin-like growth factor-1 (IGF-1).[62-64]

CONCLUSIONS

Allostatic states and the cumulative wear and tear (allostatic load) that the body experiences as a result of daily life experiences, differences in individual life style, major life events, and socioeconomic status is a highly individual matter, dependent on genotype, early experience, and the types of experiences throughout life. Initial attempts to measure allostatic states and allostatic load have been successful enough to encourage further development of methods for measuring biological parameters in order to predict later vulnerability for disease. The use of such measures to assess "predisease pathways"[5] offers hope of encouraging early interventions to delay or prevent diseases later in life.

The only way that assessment of predisease pathways is possible is through new knowledge pertaining to mechanisms leading to diseases that increase in prevalence with age. We strongly suspect that the mediators of allostasis discussed in this article play a role in determining the rate of brain and body aging and that they do so in part by exacerbating processes involving the generation of excess free radicals that cause damage to tissues and organs, including cardiac smooth muscle cells and brain cells. Yet, at the same time, there are natural processes and agents such as neurotrophins and IGF-1 that have neuro- and cardioprotective effects and enhance allostasis while minimizing allostatic load. Moreover, the brain and body have the capacity for considerable resilience in the face of stressful challenges, and we need to appreciate more the ways in which this resilience can be harnessed to improve individual trajectories of aging.

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