Allostasis and allostatic load: expanding the discourse on stress and cardiovascular disease

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Aim. The aim of this discursive paper is to introduce allostasis and allostatic load, which are relatively new concepts proposed to explain physiological responses to stress, and to suggest ways in which allostasis theory can be applied to the development of clinical interventions to increase resilience for producing better health outcome.

Background. Common explanations of stress have failed adequately to explicate its association with health and chronic illness. Allostasis is the extension of the concept of homeostasis and represents the adaptation process of the complex physiological system to physical, psychosocial and environmental challenges or stress. Allostatic load is the long-term result of failed adaptation or allostasis, resulting in pathology and chronic illness.

Discussion. The concepts of allostasis and allostatic load introduced the idea that external challenges initiate allostasis and chronic stress causes allostatic load that can be measured with multiple biomarkers. Finding from several studies suggests that higher allostatic load is associated with worse health outcomes. Resilience represents successful allostasis and strategies can be implemented to enhance resilience and thereby improve health outcomes.

Conclusions. This theoretical model provides a comprehensive explanation of the human body’s adaptation processes in response to stress and the results of failed adaptation over time. In addition, combining the concepts of allostasis and resilience may help us to understand and implement clinical strategies better to reduce or prevent the debilitating physiological and psychological effects of chronic stress and chronic illness.

Relevance to clinical practice. Clinical practice should be based on a solid theoretical foundation to improve health outcomes. Strategies to manage stress and increase resilience along with clinical interventions to manage the physiological responses to chronic stress are necessary to assist in preventing and controlling the detrimental effects of chronic disease on human life.

Key words: allostasis, allostatic load, cardiovascular disease, nursing, resilience, stress

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Introduction

The impact of chronic illness such as cardiovascular disease on individuals and families and the burden on the nation’s health care cost have made prevention and management increasingly important healthcare issues. Cardiovascular disease in particular is the most frequent cause of death in the United States today (Rosamond et al. 2007). Although stress has been linked to cardiovascular disease (Armario et al. 2003, Uchiyama et al. 2005, Guimont et al. 2006), most studies of their relationships have failed to explain the mechanism by which stress influences health. Common environmental, psychological, and physiological explanations of stress and health including factors such as poverty, perceptions and genetics have not clarified the complex process of adaptation or maladaptation to stress. The word ‘stress’ has become a very ambiguous and oversimplified term that is often used to explain both events (stressor) or individual response to various life challenges (McEwen 2002, McEwen & Wingfield 2003). For clarity, in this manuscript, stress refers to events or stressors that are threatening to an individual and that evoke behavioural and physiological responses (McEwen 2002, McEwen & Wingfield 2003). The actual response to stress is captured in the process of allostasis which is described in this study.

Aims

The aims of this paper are to expand the discourse on the concepts of allostasis and allostatic load as a framework for explaining the physiological responses to stress leading to cardiovascular disease and other chronic illnesses. Further, we will suggest ways in which allostasis theory can be applied to the development of clinical interventions to improve health outcomes particularly related to stress and cardiovascular disease.

Background

Cardiovascular disease

According to heart disease and stroke statistics of American Heart Association, 36.3% (871 517) of all deaths (2 398 000) in 2004 were from cardiovascular disease including hypertension, coronary heart disease, heart failure, stroke and congenital cardiovascular defects (Rosamond et al. 2007). Hypertension in particular is an important risk factor for cardiovascular morbidity due to its contributions to abnormalities of the arteries such as increasing vessel stiffness and abnormal thickening of the heart muscle (Wallace et al. 2007). About 72 million people (nearly one in three adults) age 20 and older in the United States have hypertension (Rosamond et al. 2007). Although there are many risk factors linked to cardiovascular disease including aging, obesity, genetic factors and sedentary lifestyle, little is understood about the specific mechanisms leading to cardiovascular disease. Using cardiovascular disease as an exemplar of chronic disease, we will discuss how stress and the concepts of allostasis and allostatic load may explain its development.

Differentiating allostasis, homeostasis and allostatic load

Allostasis and allostatic load are relatively new concepts, which are proposed to explain the physiological responses to stress (McEwen 2003). Sterling and Eyer (1988) introduced allostasis, which means literally to remain stable during change. Allostasis is the extension of the concept of homeostasis and represents the adaptation process of complex physiological systems to physical, psychosocial and environmental challenges (Karlamangla et al. 2002, McEwen 2002). With homeostasis, the internal environment of the organism is maintained relatively steady by homeostatic regulation (Cannon 1932). However, many physiologic responses including hormones, temperature, and blood pressure always vary in response to perceived challenges (Sterling & Eyer 1988). Allostasis is an active regulatory process that continuously evaluates physiological needs and adapts to those needs (Karlamangla et al. 2002). Therefore, allostasis takes into account normal variations in a dynamic biological system (Carlson & Chamberlain 2005).

Although the concept of allostasis seems very similar to homeostasis, it places emphasis on the flexible adaptation process to changing environments or stressful challenges. With homeostasis, the feedback mechanism aims to reduce variability and maintain constancy in the system (Carlson & Chamberlain 2005). However in allostasis, more variability is favourable because it means that the internal environment has the capacity to adapt to various environmental challenges to support the body system (Carlson & Chamberlain 2005).

Allostatic load refers to the state in which the normal allostatic processes wear out or fail to disengage or shut off and therefore, the physiological systems are not able to adapt (Seeman et al. 2004). Frequent or chronic challenges produce dysregulation of several major physiological systems, including the hypothalamic–pituitary–adrenal (HPA) axis, the sympathetic nervous system and the immune system (Schulkin 2004).
McEwen (2002) introduced four response patterns to environmental challenges representing allostatic load. In the first pattern, there are repeated insults leading to allostasis over time. In the second response pattern, the organism is not able to habituate to stressful stimuli. Thirdly, there is a response pattern in which the physiologic systems remain at heightened levels of activation without sufficient recovery. Lastly the primary adaptation mechanisms are inadequate to meet the challenge which results in the activation of compensatory mechanisms (McEwen 2002). These four types of over actively or inefficiently managed allostatic responses may occur alone or in combination ultimately resulting in chronic illness.

Methods

This discursive paper reviews current literature related to allostatic and allostatic load as a framework for explaining the relationship between chronic stress and chronic illness in general with a focus on cardiovascular disease in particular. Literature searches were performed using PubMed and CINAHL databases to identify peer reviewed manuscripts that addressed physiological responses to stress and its associations with chronic diseases. Keywords included allostatic, allostatic load, homeostasis, stress responses, resilience, cardiovascular disease, hypertension and blood pressure. Papers reviewed were written in English and primarily limited to those published with the last 10 years.

Discussion

The stress response and allostatic load

This concept of allostatic load might better explain how chronic stress contributes to illness and disease. According to McEwen (1998), the brain is the most important organ for determining what is perceived as stressful. The perceptions of the brain are influenced by individual differences including genes, one’s experiences, early development and learned behaviours. Perceived stress initiates the person’s physiologic and behavioural responses, and the physiologic responses lead to allostasis in various systems including the sympathetic-adrenal medullary system, the hypothalamic pituitary adrenal cortical axis, and cardiovascular, metabolic, neural, endocrine, and immune systems. Repeated and cumulative allostasis over time causes allostatic load, and this overexpose to neural, endocrine, and immune stress mediators results in various organ diseases (McEwen 1998, 2006). For example, blood pressure (one allostatic biomarker) is continuously rising and falling during the day according to physical and emotional status (Sterling & Eyer 1988). However, repeated elevated blood pressure (allostatic load) may increase atherosclerotic plaques and stiffness of large arteries leading to greater risk for cardiovascular disease (McEwen 2002, Manuck et al. 1995).

Carlson and Chamberlain (2005) suggested that the theory of allostatic load could provide a new theoretical orientation for understanding the role of stress in health disparities. African Americans have higher rates of hypertension and cardiovascular disease, and health disparities in African Americans cannot be adequately explained by genetics or socioeconomic status alone (Smedley et al. 2003, Brown 2004). Racial discrimination, a looming overt and covert experience that has been reported by African Americans throughout the generations, has been linked with hypertension and cardiovascular disease (Krieger 1990, Krieger & Sidney 1996, Jones 2000, Harrell et al. 2003, Steffen et al. 2003, Ryan et al. 2006). Stress responses caused by perceived racism cause allostatic that involves the sympathetic nervous system and HPA cortical axis. The stress responses from racial discrimination are life-long and cumulative leading to continuously elevated cortisol levels which is detrimental to the Hippocampus in charge of mediating the negative feedback process with glucocorticoid receptors. Damage to the Hippocampus causes failure of the HPA (allostatic load) resulting in adverse physiological responses including increased heart rate, elevated BP, and altered cortisol level (Al’Absi et al. 1997, McEwen & Wingfield 2003). Allostatic load may better explain how repeated perceptions and experiences of racial discrimination can be linked to poorer health in this ethnic minority group (Carlson & Chamberlain 2005).

Although cardiovascular diseases are good examples of allostatic and allostatic load, these concepts are not limited to cardiovascular responses but involve whole brain and body (Sterling & Eyer 1988). Every system involves allostatic response with acute challenge and if these acute responses last over time, allostatic load may occur. In other words, physiologic mediators including adrenaline, glucocorticoids, and cytokines work on various organs as adaptive responses to stress (Kiecolt-Glaser et al. 2003, McEwen 2004, Schulkin 2004). If these mediators are continuously elevated without efficient shutting off, they would cause tissue damage or receptor desensitisation as allostatic load. Suppressed immune function (by glucocorticoids), atherosclerosis and obesity (by cytokines), and anxious depression showing atrophy of nerve cells in the brain (by cortisol) can be examples of chronic illnesses associated with allostatic load (McEwen 2004, Schulkin 2004).
Operationalisation of allostatic load in research

The numbers and types of physiologic indicators used to measure allostatic load vary across research studies. In the first edited volume to focus on allostasis, Schulkin (2004) introduced glucocorticoids, dehydroepiandrosterone (DHEA), catecholamines, and cytokines as the four most common allostatic mediators. Schulkin (2004) provided detail explanations of how each indicator have many effects on a variety of body systems, and how their production and actions are interconnected. In the MacArthur Successful Aging Study, Seeman et al. (2001) tested the construct validity of allostatic load with 1189 subjects. Ten physiologic indicators [systolic blood pressure, diastolic blood pressure, waist-hip ratio, high-density lipoprotein (HDL) cholesterol, total/HDL cholesterol ratio, glycosylated haemoglobin, urinary cortisol, urinary norepinephrine, urinary epinephrine, and serum dihydroepiandrosterone sulphate (DHEA-S)] were selected as primary and secondary mediators of allostatic load. To derive the allostatic load score, they calculated the number of physiologic indicators that belong to the highest risk quartile. Although the risk range of each physiologic indicator was not clinically significant, the integrated scores lead to a meaningful allostatic load. The baseline allostatic load score had significant correlations with mortality, incidence of cardiovascular disease, changes in physical functioning, and changes in cognitive functioning 7 years later. This finding suggests that higher allostatic load is associated with worse health outcomes (Seeman et al. 2001). Seeman et al. (2004) tried to explain the socioeconomic status differences in mortality with a cumulative measure of biological dysregulation (the allostatic load). Compared with their previous study, six additional biological components including albumin, interleukin-6, C-reactive protein, peak flow (a measure of lung function), fibrinogen, creatinine clearance (a measure of renal function) were added. Although the cause of death and decreased physical and cognitive functioning were not investigated in these studies, they found that 35.4% of the difference in mortality risk between subjects with higher vs. lower educational attainment was explained by the cumulative index of biological risk. Before controlling for the measure of allostatic load, baseline morbidity mediated only 10.4% of the educational differential. Evans (2003) used six physiological dysregulation indexes including systolic blood pressure, diastolic blood pressure, urine cortisol, epinephrine, norepinephrine and body mass index to measure allostatic load. Findings showed that cumulative risk factors including physical (crowding defined as number of people per room, noise, housing problems) and psychosocial aspects (family separation, family turmoil, violence), and personal characteristics (income-to-needs ratio, single parent, maternal high school drop out) were associated with heightened cardiovascular and neuroendocrine responses, increased deposition of body fat, and a higher summary index of total allostatic load.

Three analytical strategies can be used to calculate allostatic load scores for individuals: (i) summation of the number of biomarkers in the risk zone; (ii) weighted summation of standardised biomarker scores (through canonical correlation), and (iii) recursive partitioning of persons into empirically determined classifications of allostatic load (Schulkin 2004).

The concept of allostasis and allostatic load introduced the interesting notion that stress (external challenge) initiates strain on multiple biological systems including organs and tissues, and chronic stress (cumulative risk factors) leads to accumulative physiological wear and tear that can be measured with multiple biomarkers. Although this theoretical model provides a better explanation for the human body’s adaptation process to stress and the development of chronic illness, biomarkers used in research to measure allostatic load so far tend to be tied to indicators of cardiovascular disease. As allostatic load is explained mainly based on the sympathetic nervous system, HPA axis, and immune systems, physiological parameters used to measure allostatic load mainly consists of hormones (glucocorticoids such as cortisol) and catecholamines (adrenaline and noradrenaline), which modulate cardiovascular function. Other biological parameters are also highly related to cardiovascular risk factors. The summation of these biological parameters would predict the prevalence of cardiovascular disease and mortality. Therefore, the next agenda in developing this theory is to find valid biomarkers to explain the allostatic load of various systems and to verify their prediction of associated chronic diseases through population-based research.

Allostasis and resilience to the effects of chronic stress

Why do some people who experience chronic stress become sick and others do not under similar degree and types of stress? In other words, why are some people resilient and others vulnerable to chronic stress? To better answer these questions, allostasis theory must proceed from the level of description of various health-related phenomena to the level of reduction and control of disease development and progression. Researchers should focus on explaining the differences in people’s vulnerability to disease and illness and on ways to increase individual capacity to adapt or adjust in a healthy manner to various strengths or kinds of stress. Better mechanisms for delaying, easing, or preventing allostatic load
by identifying the causes of differences in individual capacity are required. This necessitates a broader understanding and application of allostasis.

Allostasis is tied to the central nervous system (Schulkin 2004). The brain perceives stress and produces behavioural responses and physiologic responses to the stress. These responses depend on interpretations by the brain (McEwen 2002). Individual difference in the interpretation of the brain produces different behavioural and physiologic responses that can be measured through the functioning of various physiologic systems. The hippocampus located in the temporal lobe of brain plays an important role in memorising and interpreting circumstances and regulating the primary stress mediators for an allostatic state (Sapolsky 2003). That is, the memory of previous stress influences the ability to anticipate the needed physiological adaptation (Carlson & Chamberlain 2005). This explains why vulnerability of many body systems to stress is influenced by experiences from earlier in life (McEwen 2002).

The brain is not only the organ which produce behavioural and physiological responses after receiving stress but is also a target organ of stress. The hippocampus, amygdale and prefrontal cortex are known to undergo stress-induced structural remodeling (McEwen 2007). According to recent research, as with cells in other human parts, neurons in brain continuously grow and die (Eriksson 2003, Rossini et al. 2007). Komitova et al. (2006) defined this balance between neurogenesis and atrophic processes as neuroplasticity. Therefore, if the rate of neurogenesis drops and constant cell death occurs, the brain can shrink (Komitova et al. 2006). The hippocampus has been known to shrink under stressful events exhibiting cells shrinkage and a decrease in total number of cells (Duman & Monteggia 2006). The shrinkage of the hippocampus has also been shown in various mental illnesses including schizophrenia and severe depression (Rossi et al. 1994, Duman & Monteggia 2006). However, there is the recent evidence that this shrinkage is reversible (Malberg 2004, Perera et al. 2007). Cortisol may be correlated with the size of hippocampus (Lupien et al. 1998). Sapolsky (2003) explained that severe and prolonged stress can impair hippocampal dependent learning and plasticity and that mild and transient stress can facilitate such plasticity. Neuroplasticity may be facilitated to increase the capacity of hippocampus in mediating stress response (Sapolsky 2003). The fact that the brain can reshape itself with new life experience gives hope that through a facilitated environment, resilience can be enhanced and physiologic outcomes may be changed.

Resilience as defined by Fossion and Linkowski (2007) is the ability to successfully adapt and function proficiently when faced with traumatic circumstances. McEwen (2002) states that ‘resilience is an example of successful allostasis in which wear and tear is minimised, and the brain retains considerable resilience in the face of stress’. A resilient organism with the ability to adapt to challenging environments will be able to minimise physiological damage (Carlson & Chamberlain 2005). Dyer and McGuinness (1996) define resilience as the ability to bounce back from adverse situations and go on. Resilience has been associated with positive outcomes even in situations that could produce pathological conditions (Masten & Coatsworth 1998, Luthar et al. 2000).

The concept of resilience can be explained by using the example of the elasticity of a rubber band. The rubber band can be stretched to a certain point and then released to return to its original size. Firstly, if a rubber band is stretched many times, over time the rubber band will eventually loose its elasticity and not return to its original size even though it was used in the appropriate way. Secondly, if the rubber band is consistently used with relatively excessive strength, with time it will lose its elasticity or break. Thirdly, if the rubber band is stretched too much at once, the rubber band may break. Lastly, sometimes there are rubber bands that have an original defect whereby some part is thinner and weaker than other parts. These rubber bands have a greater possibility of being broken than others even with a smaller amount of tension. These four states of the rubber band are analogous to the four response patterns related to allostatic load that were discussed earlier. Resilience can be considered as the capacity in which allostatic biomarkers in response to stress can still be considered normal. That is, the person who has a larger adaptive capacity (more resilience) would have more resistance to allostatic converting to the allostatic load than the person who has a relatively small adaptive capacity as illustrated in the rubber band example.

Many recent studies indicate that behavioural or clinical interventions and timely management can increase resilience. Foe example, Lee et al. (2007) demonstrated the effectiveness of a social intervention program that was conducted to build the perception and practices of resilience among children and youth in Hong Kong Special Administrative Region. Koller and Lisboa (2007) presented studies conducted in different parts of Brazil emphasising the resilience process in children, youth and families of different at-risk conditions. Kumpfer and Summerhayes (2006) discussed a prevention intervention to increase resilience in high-risk children and adolescents. Many studies to increase resilience have been conducted with children or youth because their early life experiences are considered one of the most important predictors of resilience. These early life experiences are also believed to be significant contributors to allostatic and allostatic load. Schulkin (2004)
stated that genetic risk factors, early developmental influences, the diurnal rhythm, lifestyle factors and life stresses contribute to allostatic states and allostatic load.

Although much literature on resilience is available, we found no empirical evidence that explain its relationship to health with physiological pathways. The connection of allostatic and resilience could help to explain how resilience might delay or prevent various chronic illnesses.

Rutter (2007) emphasised that research conducted to identify the causal process of resilience must include physiological pathways and the neuroendocrine system as well as compensatory neural adaptations. Allostasis theory is a good theoretical framework on which the mechanism of resilience can be explained particularly if resilience increases the capacity of the hippocampus to withstand physiological, psychosocial, and environmental challenges that contribute to chronic illness. Furthermore, based on this framework social and behavioural intervention programs to reduce chronic stress and increase brain resilience and overall health can be developed.

Relevance to clinical practice

Clinical practice should be based on a solid theoretical foundation to improve health outcomes. Strategies to manage chronic stress, increase resilience and to treat the physiologic responses to chronic stress are required. A major goal of practitioners should be to reduce the psychological and resulting physiological burden of chronic stress through social, behavioural and therapeutic interventions (McEwen 2007). As chronic stress disrupts brain function, it can also impair individuals’ coping and self-regulation abilities. Strategies must be implemented to enhance coping and adaptation (Compas 2006, McEwen 2007).

Other interventions to manage stress and allostatic load include helping individuals to change behaviours or lifestyles that are not conducive to health, improve sleep, enhance social networks, increase self-esteem and promote physical activity which is associated with improved cardiovascular function, memory and mood. Pharmacological agents (e.g. anti-depressants, anti-hypertensive, sleep medications and anti-inflammatory agents) may be necessary to address physiological manifestations of allostatic load (McEwen 2007). Practitioners should advocate for more research on ways to improve resilience in the presence of chronic stress (McEwen 2003) and on how resilience impacts allostatic and allostatic load. Research should continue to identify and test bio-makers suggestive of allostatic load so that strategies can be implemented early to prevent or delay the detrimental effects of chronic stress-related diseases on human life.

Conclusion

Stress responses are multi-faceteted; however, the brain determines or interprets what is stressful (McEwen 2007). Chronic stress interferes with the functions of the brain and can lead to psychological dysfunction (e.g. depression, distress and worry) and physiological dysfunction (e.g. hypertension, impaired glucose tolerance and chronic fatigue) (Compas 2006). Allostasis and allostatic load help to expand the discourse on the mechanism where by stress contributes to cardiovascular disease and other chronic illnesses associated with neuroendocrine, autonomic nervous system and immune system dysfunctions.

Allostasis theory starts at the microcellular level (homeostasis), includes the physiological and behaviour responses to various challenges, and addresses the epidemiologic level such as the prevalence of cardiovascular disease and mortality. Even more exciting, combing the concepts of allostatic and resilience may help us to understand and better implement strategies to reduce or prevent the debilitating physiological and psychological effects of chronic stress.

Contributions

Study design: JL, DB; data collection and analysis: JL, DB; manuscript preparation: JL, DB.

References


