Biological Basis of Allostatic Load and its Measurement

Burton Singer, Princeton University & University of Wisconsin - Madison

Introduction

Allostasis is a term that has come into increasing use in both social and biological sciences to describe the active process through which systems of the body adapt to challenges. ***Allostatic Load*** is a term that refers to the inevitable wear and tear on body systems from adaptively responding to challenges by events in daily life as well as repeated major stressors. These terms emphasize five aspects of adaptation and pathophysiology that are often overlooked in conventional thinking about 'stress'. (1) allostasis and allostatic load reflect, respectively, the response to and the cumulative effects of experiences in daily life that involve ordinary events as well as major challenges; (2) there are multiple mediators of allostasis , which have a biphasic role in both adaptation and damage, depending on the dose and time course over which they are produced; (3) these mediators have concurrent influences on multiple body systems, from brain to cardiovascular , metabolic and immune systems; (4) the nervous system is the master regulator of behavioral and physiological responses to daily experiences as well as a changing environment and major stressors; and (5) the brain is a key target of events and has the capacity to change structurally and functionally in response to experiences (McEwen, 2007).

Moving from the above intuitive ideas to operationalization of allostatic load has been difficult in the sense that the small number of biomarkers – usually less than 15 – that have been employed in any one empirical study do not, by any means, come close to providing a comprehensive measure of dysregulation in the whole organism. For example, measurement of immune system responses usually involves a few cytokines, C-reactive protein, and fibrinogen, while any one or more of the unmeasured cytokines may actually reflect the organism's response to challenge. A way forward, beyond the highly coarse-grained set of system parameters currently in use, is to focus attention on metabolic systems where NMR spectroscopy and mass spectrometry provide a more comprehensive measurement technology.

Rationale for operationalization of allostatic load via metabolic systems

Complex organisms (e.g. mammals) possess multiple cellular, tissue, and organismal mechanisms that provide for adaptability and facilitate management of localized and systemic perturbations of physiology and metabolism. The term ***robustness*** has been defined for biological systems (Kitano, 2007) as a property that allows a system to maintain its ***functions*** in the face of internal and external perturbations. In any disease state there is some loss of allostatic control that usually results in non-normative, or disordered, metabolic behavior. System recovery depends on the capacity to adapt and reestablish allostatic control. Dysregulation, disease processes and underlying robustness must be understood in the context of the ***global*** system, in which diverse cellular

metabolic networks interact cooperatively to maintain the functional integrity of the whole organism (Nicholson, 2006).

We focus attention on metabolic networks, as they are constructed out of communicating sets of small molecules that represent minimal ingredients for maintaining the functional integrity of living organisms. In humans, more manifest indications of dysregulation, such as prolonged elevation of cytokines, hyper- or hypo-cortisolism, symptoms of depression and schizophrenia, persistent elevated blood pressure, etc. reflect, at a deeper level, non-normative, or disordered, behavior of metabolic networks.

Considerable research under the umbrella of systems biology attempts to acquire comprehensive information on metabolic processes, such as topologies of metabolic networks, flux distributions, metabolite concentrations and enzyme catalytic properties. This activity is focused on understanding metabolic behavior of individual cell types, where all the required parameters can be measured directly. However, disease – or more generally, dysregulation – processes involve multiple cell types interacting in both space and time. Cell-based metabolic failure models cannot capture this complexity, and we are rather far from having whole-organism models incorporating detailed information on the ***simultaneous and sequential*** action of, and interaction between, metabolic networks in multiple types of cells.

What is feasible is the consideration of metabolic linkages of a disparate nature that are dispersed through the medium of extracellular fluids such as blood plasma and lymph, but are also removed through multiple discrete secretory and excretory drains on the metabolite pool such as urine, bile, and sweat. Sampling these fluids gives many clues as to what is happening in the integrated system. It is difficult to map the metabolite signature in these fluids to specific pathway activity -- but see studies of liver toxins as a generic case of doing just this (Veselkov et al., 2008) -- because analytic data represent the weighted average of the whole system. However, such measurements provide a means of studying the whole system's responses collectively. They facilitate the introduction of summary measures of system function – and malfunction – that can be viewed as operationalizations of the idea of allostatic load.

Operationalizing allostatic load via trajectories of metabolite concentrations.

Let C_{i0} denote the within-normal range concentration of metabolite i for a given individual. This value can be a mean of concentrations for an individual within the normal range. It will serve as a baseline value for comparison with measured values that may be either inside or outside the normal range. Let $C_i(t)$ denote the measured concentration of metabolite i at time t. Then calculate $x_i(t) = \log(C_i(t)/C_{i0})$ for all measured metabolites. This can be a set of roughly 1000 metabolites, but possibly more depending on resolution of the extant technology. Now construct the histograms of x_i values for each value of t, and set $p_j(t)$ = proportion of metabolites with $x_i(t)$ in bin j of the histogram. This defines a surface of histograms indexed by t. Then define ***metabolic entropy*** via

$$S_m(t) = \sum_j p_j(t) \log p_j(t)$$

where the summation is over bins in the histogram. The entropy measure has a standard interpretation as a measure of system disorder (Haynie, 2008), and it is thereby a plausible candidate for use in scoring allostatic load. Let S* denote metabolic entropy when the organism has all metabolites in normal range. Under the assumption that $S^* > 0$, a highly plausible situation, we introduce the ratio $\rho(t) = [S_m(t)/S^*]$. Then we set a threshold value c such that if $\rho(t) > c$, we say that the organism is showing signs of metabolic dysregulation, or disorder, at time t. It also indicates that the organism is doing work to restore metabolic networks to normal operating conditions. This can be interpreted as a cost paid by the organism at time t for adapting to challenges that raised or lowered concentrations of some metabolites outside of normal ranges. Formally, we introduce the function

$$\rho^*(t) = \rho(t) \text{ if } \rho(t) > c$$
$$0 \text{ otherwise}$$

With these ingredients at hand, we define allostatic load over the time interval $[T_1, T_2]$ as

$$A[T_1, T_2] = \int \rho^*(t)\, dt\ ,$$

where the integral is taken over the interval $[T_1, T_2]$. This expression quantifies the idea of cumulation of dysregulation over a defined time interval.

Implementation of a close approximation to this formulation is given in Veselkov et al. (2008), where metabolic entropy is used to assess the consequences, over time, of liver toxin administration in rats. Recent evidence identifying alterations in energy metabolism in schizophrenia (Khaitovich, 2008), and in identifying metabolic signatures over time in a restraint stress model in rats (Teague et al., 2007), imply that the above formulation of allostatic load can be utilized to measure overall system dysregulation in response to a diversity of challenges.

Allostatic Load assessed via concentrations of large molecules and other physiological measures

The operationalizations of allostatic load in current use (Seeman et al., 2001; Karlamangla et al., 2004) are based on assessments of elevated levels of inflammatory cytokines, overnight urinary cortisol, overnight urinary catecholamines, glycosylated hemoglobin, and the ratio of total to HDL cholesterol. Depressed levels of DHEA-S and HDL cholesterol are also included in the scoring of allostatic load, along with BMI and waist-hip ratio. The studies that use these measures on human populations are frequently based on single point-in-time assessments. Justification of high risk levels of combinations of this set of biomarkers in a single individual as a signature of a process of cumulation of dysregulation across one or several physiological systems is based on appeal to a large literature of specialized studies of responses to stressful experience. However, there is a pressing need for longitudinal appraisals of the above battery of

biomarkers and their incorporation into allostatic load scores in order to acquire a stronger empirical justification for the cumulation interpretation of extant measures. Finally, it would be of great value to obtain metabolic profiles on the same set of individuals that are assessed for the above set of biomarkers to facilitate identification of more comprehensive biological signatures of psychosocial experience and to move toward effective clinical use of allostatic load measures.

References

Haynie DT. (2008), *Biological Thermodynamics, 2nd Edition*, Cambridge, UK: Cambridge University Press

Karlamangla A, Singer BH, Williams DR, Schwartz JE, Matthews KA, Kiefe CI, Seeman TE. (2004), Impact of socioeconomic status on longitudinal accumulation of cardiovascular risk in young adults: The CARDIA study. *Social Science and Medicine*, 60: 999 – 1015

Khaitovich P, Lockstone HE, Wayland MT, Tsang TM, Jayatilaka SD, Guo, AJ, Zhou J, Somel M, Harris LW, Holmes E, Pääbo S, Bahn S. (2008), Metabolic changes in schizophrenia and human brain evolution, *Genome Biology*, 9: R124.1 – 124.11

Kitano H. (2007), Towards a theory of biological robustness. *Molecular Systems Biology*, 3:137; doi:10.1038/msb4100179

McEwen B. (2007), Physiology and Neurobiology of Stress and Adaptation: Central Role of the Brain. *Physiological Reviews*, 87: 873 – 904

Nicholson JK (2006), Global Systems Biology, personalized medicine and molecular epidemiology. *Molecular Systems Biology*, 52; doi:10.1038/msb4100095

Seeman TE, McEwen BS, Rowe JW, Singer BH. (2001), Allostatic load as a marker of cumulative biological risk: MacArthur studies of successful aging. *Proceedings of National Academy of Sciences*, 98(8): 4770 – 4775

Teague CR. Dhabhar FS, Barton RH, Beckwith-Hall B, Powell J, Cobain M, Singer B, McEwen BS, Lindon JC, Nicholson JK, Holmes E. (2006), Metabonomic Studies on the Physiological Effects of Acute and Chronic Psychological Stress in Sprague-Dawley Rats. *Journal of Proteome Research*, 6: 2080 – 2093.

Veselkov KA, Pahamov VI, Lindon JC, Volynkin V, Crockford D, Osipenko GS, Davies DB, Barton R, Bank J-K, Holmes E, Nicholson JK. (2008) A metabolic entropy approach to model experimental patho-physiological states. *Nature Biotechnology* (in press).