Neuroscience and Biobehavioral Reviews 86 (2018) 12–20

Contents lists available at ScienceDirect

Neuroscience and Biobehavioral Reviews

journal homepage: www.elsevier.com/locate/neubiorev

# Stress, autonomic imbalance, and the prediction of metabolic risk: A model and a proposal for research

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ARTICLE INFO

*Keywords:*
Stress
Autonomic imbalance
Metabolic disorders
Prevention

ABSTRACT

*Background:* Devising novel prevention strategies for metabolic disorders will depend in part on the careful elucidation of the common pathways for developing metabolic risks. The neurovisceral integration model has proposed that autonomic imbalance plays an important role in the pathway from acute and chronic stress to cardiovascular disease. Though generally overlooked by clinicians, autonomic imbalance (sympathetic overactivity and/or parasympathetic underactivity) can be measured and modified by methods that are available in primary care.

*Method:* This review applies the neurovisceral integration concept to the clinical setting by proposing that autonomic imbalance plays a primary role in the development of metabolic risks. We present a testable model, a systematic review of the evidence in support of autonomic imbalance as a predictor for metabolic risks, and specific approaches to test this model as a guide to future research on the role of stress in metabolic disorders.

*Conclusions:* We propose that autonomic imbalance deserves consideration by researchers, clinicians, and policymakers as a target for early interventions to prevent metabolic disorders.

## 1. Introduction

In spite of great strides in the treatment of heart disease and diabetes globally over the last 50 years, in the United States we have made little progress in the prevention of these disorders (http://www.cdc.gov/heartdisease/facts.htmhttp://www.cdc.gov/heartdisease/facts.htm). On the contrary, the dramatic recent rise in rates for two major cardiovascular risk factors, obesity and diabetes (http://www.cdc.gov/diabetes/data/statistics/2014statisticsreport.htmlhttp://www.cdc.gov/diabetes/data/statistics/2014statisticsreport.html), remind us that good treatment for heart disease, diabetes, and obesity have not been not good enough to reduce the burden of these illnesses. We now face in the US both an economic and clinical imperative for a shift from fee-for-service to population-based care that will demand and reward effective prevention strategies for our high cost epidemics.

Devising novel prevention strategies for metabolic disorders will depend in part on the careful elucidation of the common pathways for developing metabolic risks. Heart disease, diabetes, and obesity—three of our most costly epidemics—share a common but rarely treated mechanism, sustained autonomic imbalance (sympathetic overactivity and/or parasympathetic underactivity). Though ignored by most clinicians, autonomic imbalance is associated with all eight major cardiovascular risk factors, including obesity and diabetes (Thayer and Yamamoto Brosschot, 2009). Autonomic imbalance is also a common feature of the biology of acute and chronic stress (Jarczok et al., 2013; Thayer and Lane, 2000; Beauchaine and Thayer, 2015). And several studies have found that autonomic imbalance may predict the development of metabolic risks and metabolic disorders (Licht et al., 2013; Liao et al., 1996; Singh et al., 1998; Schroeder et al., 2003; Wulsin et al., 2016; Schroeder et al., 2005; Wulsin et al., 2015). Autonomic imbalance can be measured and treated by a variety of methods often used in primary care settings, making autonomic imbalance a potential target for preventive interventions for heart disease, diabetes, obesity, and metabolic risks in general.

Though public health experts generally acknowledge in vague terms the importance of psychosocial factors, the most common models for predicting metabolic outcomes, such as the Framingham Heart Index, PROCAM, and SCORE (Schuster et al., 2016; Bitton and Gaziano, 2010), have ignored the contributions of chronic stress, in part because of the difficulties of operationalizing the concept of stress in clinical settings.

In this review we will use the term “stress” or “stressor” to refer to the stimulus that elicits the stress response. Acute or brief stressors

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https://doi.org/10.1016/j.neubiorev.2017.12.010
Received 24 July 2017; Received in revised form 7 November 2017; Accepted 19 December 2017
Available online 23 December 2017
0149-7634/ Published by Elsevier Ltd.

usually last seconds or minutes and don't recur, but since chronic illness is most affected by repetitive, episodic, or persistent stressors that last hours, days, or many months, we will usually be discussing these patterns of chronic stress, unless otherwise specified. It is also important to distinguish between exposures to stressful events or stimuli, the person's appraisal of the severity of the stressor, and the person's biological and behavioral responses to the stressor.

Recent advances in stress research clarify some of the conceptual and measurement issues related to the role of chronic stress in the prediction of metabolic disorders. In particular, chronic stress has been shown to contribute to the pathophysiology of metabolic syndrome and metabolic disorders (Brindley, 1995; Peeke and Chrousos, 1995; Chandola et al., 2006). The Whitehall II study (Chandola et al., 2008; Brunner et al., 2002) found a dose-response relationship between the severity of chronic stress, measured by self-reported work stress at four phases between 1985 and 99, and the severity of metabolic syndrome. Employees with chronic work stress had more than double the chance of developing metabolic syndrome (OR = 2.25, 95% CI 1.31–3.85), while controlling for other risk factors, providing "evidence for the biological plausibility of psychosocial stress mechanisms linking stressors from everyday life with heart disease."

McEwen has spearheaded one of the most comprehensive efforts to operationalize the relationship of stress to the risk for physical illness through the concept of allostatic load (McEwen, 1998) (see also http://www.macses.ucsf.edu/research/allostatic/http://www.macses.ucsf.edu/research/allostatic/). A substantial number of reports have found that allostatic load is associated with a past history of chronic stress and it predicts a range of poor clinical outcomes (Seeman et al., 1997; Wegman and Stetler, 2009; Thomas et al., 2008; Alastalo et al., 2009; Tyrka et al., 2010; Kananen et al., 2010). However, most operational definitions of allostatic load do not include the common measures of autonomic imbalance, such as resting heart rate or heart rate variability.

Three examples from clinical epidemiology illustrate the need to operationalize the role of stress in metabolic risk in order to better understand the options for more effective prevention.

1) By what mechanism could adverse childhood events lead to the early development of cardiovascular risk factors (Felitti et al., 1998; Dong et al., 2004)? Experts have proposed that trauma during critical developmental stages fosters a pattern of excessive sympathetic activity or low vagal tone, accelerating the onset of cardiovascular risk factors (von Kanel et al., 2001; Harris and Matthews, 2004; Porges, 2011; van der Kolk, 2014). Two recent meta-analyses (Bartoli et al., 2013; Rosenbaum et al., 2015) have found that people with post-traumatic stress disorder have an increased risk for metabolic syndrome and cardiovascular disease. The startle responses, overreactivity, and slow recovery typical of triggered flashbacks and nightmares in people with PTSD reflect one expression of autonomic imbalance. The authors of the second review (Rosenbaum et al., 2015) note (p 931): "emerging evidence suggests that both [PTSD and metabolic syndrome] share pathophysiological features, including hypothalamic-pituitary-adrenal (HPA) and sympathoadrenomedullary dysfunction, inflammation, common genetic links and epigenetic interactions."
2) How does severe mental illness subtract 20–30 years of life from its victims (Colton and Manderscheid, 2006; Saha et al., 2007)? The chronic sympathetic activity and low vagal tone associated with schizophrenia, bipolar disorder, and severe depression may play a major role in the observed high rates of early onset heart disease, diabetes, and obesity associated with chronic severe mental illness (Beauchaine and Thayer, 2015; Scott et al., 2008; Scott et al., 2016; Rottenberg et al., 2014).
3) By what pathways does depression accelerate the onset and progression of diabetes (Katon et al., 2004; Mezuk et al., 2008)? Evidence suggests that dysregulation of the sympathetic and parasympathetic systems during major depressive episodes plays a role in the relationship between clinical depression and the increased risk for insulin resistance, followed by the development and progression of type II diabetes (Thorp and Schlaich, 2015; Lansdown and Rees, 2012; Pavlov and Tracey, 2012).

Building on the neurovisceral integration model (Thayer and Lane, 2000; Thayer and Lane, 2009; Williams et al., 2015; Smith et al., 2017), this review proposes that one feature of the biology of chronic and episodic stress, sustained autonomic imbalance, plays a central role among the multiple factors that contribute to the process of developing metabolic risks. The concept of sustained autonomic imbalance offers one modifiable mechanism for operationalizing the noxious physiologic impact of chronic and episodic stress on metabolic risks.

More specifically, this review proposes that risk for metabolic disorders begins with the appraisal of threat and the cortical activation of the stress response over extended periods of time. The cortical control of heart rate via the vagus nerve and the sympathetic chain, to cite just one example articulated by the neurovisceral integration model, extends to other major organs involved in the stress response, such as the gut, lungs, endocrine glands, and the immune system. Autonomic imbalance is a key pathway in this model between cortical appraisal of threat and each type of organ dysregulation. Persistent dysregulation of these organ systems through episodic or persistent stress leads to multisystem organ dysregulation and later diseases, such as adult onset diabetes and coronary heart disease. This model justifies treatments that approach visceral regulation through retraining the brain and the autonomic nervous system.

## 2. Autonomic imbalance

The autonomic nervous system in humans and animals has evolved through a dynamic balance between its sympathetic and its parasympathetic branches, as described by Porges in Chapter 2 of *The Polyvagal Theory* (Porges, 2011). Most of our organs are dually innervated by sympathetic and parasympathetic nerves (with the notable exception of the vasculature and the immune system organs such as the spleen, which lack parasympathetic nerve fibers), and our endocrine system circulates a blend of sympathetic (epinephrine, norepinephrine) and parasympathetic (acetylcholine) hormones. The sympathetic branch is generally associated with energy mobilization and the parasympathetic branch with vegetative and restorative functions, although in any given organ system the two branches may function in an antagonistic (such as the iris), complementary (the salivary glands), or cooperative (genitals) relationship. Within any individual the balance between the two branches is set by genes and modified by circadian rhythms and environmental stress and aging. Evolutionary pressures in humans have resulted in a system that seeks to minimize energy requirements through patterns of dynamic variability, as opposed to static regularity or rigidity (Thayer and Yamamoto Brosschot, 2009; Kok et al., 2013; van der Kolk, 2014).

Loss of dynamic variability in the autonomic nervous system, during which one branch dominates over the other for extended periods of time and across multiple environmental demands, is associated with illness and eventually chronic disease (Malliani and Montano, 2004; Brook and Julius, 2000). This state of dysregulation can be achieved by excessive sympathetic activation, too little parasympathetic activation, or some combination of both. Two measures of autonomic imbalance, persistent high resting heart rates and low heart rate variability, have been associated with the later development of a variety of cardiovascular diseases, such as coronary heart disease (Thayer and Lane, 2007), Takotsubo's cardiomyopathy (Akashi et al., 2008), atrial fibrillation (Thrall et al., 2007), and with all-cause mortality(Tsuji et al., 1996).

Slow recovery after a stressor, as reflected in long intervals required to recover to baseline heart rates after exercise or mental stress, is generally regarded as a stronger indicator of autonomic imbalance than