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Review article

Developmental origins of cardiovascular disease: Impact of early life stress in humans and rodents

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ABSTRACT

The Developmental Origins of Health and Disease (DOHaD) hypothesizes that environmental insults during childhood programs the individual to develop chronic disease in adulthood. Emerging epidemiological data strongly supports that early life stress (ELS) given by the exposure to adverse childhood experiences is regarded as an independent risk factor capable of predicting future risk of cardiovascular disease. Experimental animal models utilizing chronic behavioral stress during postnatal life, specifically maternal separation (MatSep) provides a suitable tool to elucidate molecular mechanisms by which ELS increases the risk to develop cardiovascular disease, including hypertension. The purpose of this review is to highlight current epidemiological studies linking ELS to the development of cardiovascular disease and to discuss the potential molecular mechanisms identified from animal studies. Overall, this review reveals the need for future investigations to further clarify the molecular mechanisms of ELS in order to develop more personalized therapeutics to mitigate the long-term consequences of chronic behavioral stress including cardiovascular and heart disease in adulthood.

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1. Introduction

Early life stress (ELS) is known to increase the risk of psychiatric disorders and health risk behaviors including smoking, overeating, and substance abuse (Danese et al., 2009; Dong et al., 2004; Freedman et al., 2007). In the last two decades a growing number of clinical studies demonstrated that exposure to ELS serves as an independent risk factor for the development of chronic disease. Therefore, ELS has been proven as a robust predictor of the risk for ischemic heart disease, cardiovascular disease, stroke, respiratory disease, diabetes and cancer (Alastalo et al., 2013; Joung et al., 2014; Low et al., 2009; Murgatroyd and Spengler, 2011; Parrish et al., 2013; Romans et al., 2002; Slopen et al., 2012; Su et al., 2015; Vaiserman, 2014; Weder et al., 2014; Yang et al., 2013).

Although it is well known that exposure to ELS influences the biological responsiveness to future stress, the physiological and molecular mechanisms are not completely understood. There is substantial evidence that stress delivered by parents and other caregivers can affect a child's developing brain architecture and chemistry increasing the susceptibility to stress-related disorders later in life (Carroll et al., 2013; Furukawa et al., 1999). This finding has been mirrored in animal models as well (Caldji et al., 1998; McEwen et al., 2015; Sapolsky and Meaney, 1986; Weaver et al., 2004). Stress responses include activation of a variety of hormonal and neurochemical systems across the body. In this regard, the hypothalamic- pituitary-adrenocortical (HPA) system and the sympathetic nervous system (SNS) have received special attention. In addition, it has been shown that several vasoactive peptides such as vasopressin, endothelin-1 and angiotensin II are released secondary to behavioral stimuli, exerting amplificatory effects in cardiovascular reactivity (Aguilera and Rabadan-Diehl, 2000; Loria et al., 2010b; Mangiafico et al., 2002; Mayorov, 2011; Spieker et al., 2002; Treiber et al., 2000). Cardiovascular reactivity reflects an enhanced response in blood pressure, heart rate or other hemodynamic parameters to secondary stressors (Manuck and Krantz, 1985). Importantly, it has been shown that individuals showing exaggerated cardiovascular responses linked to acute and/or chronic behavioral stress may be at higher risk for the development of cardiovascular disease including hypertension and coronary artery disease than those individuals that do not display this positive correlation. (Beutel et al., 2014; Carroll et al., 2013; Ginty et al., 2016; Spartano et al., 2014). Moreover, the impaired post-stress recovery of blood pressure has been shown blunted in patients with a history of ELS (Evans et al., 2013).

In this review, we will provide an overview of epidemiological data linking ELS to the development of cardiovascular disease. Also, we will discuss the use of animal models as a tool to mimic the effects of ELS on key components of the cardiovascular regulation in order to analyze the underlying molecular mechanisms leading to chronic disease.

2. From allostasis to toxic stress

Not all stress is harmful. In a child, when the stress response is activated in the context of a supportive psychosocial environment (e.g. supportive relationship with parents), these physiological effects are balanced and return to basal levels (National Scientific Council on the Developing Child, 2004). As a result of this adaptive process, there is a development of healthy stress response or even resilience to stress (Daskalakis et al., 2013; Smith and Carlson, 1997; Steptoe et al., 2009). Traumatic events can also be tolerable, or even beneficial, depending on the duration, intensity, and timing of the stressful experience, as well as its context (Shonkoff and Garner, 2012). Since a child's ability to cope with stress in the early years has consequences for physical and mental health throughout life, understanding the origin and complexity of different types of stress responses to early adverse experiences can help us make better conclusions about the type of interventions needed to potentially reduce the risk for later negative physiological outcomes in each patient.

In animal models, positive experiences after weaning, such as being exposed to an environment rich in opportunities for exploration and social play have been shown to compensate to some degree for the negative behavioral consequences of prenatal stress and postnatal neglect (Reynolds et al., 2010; Zanca et al., 2015). This compensation involves adaptive changes in both the architecture and the chemistry of the developing brain. However, the brain is not infinitely plastic. Some stress-related effects (e.g., reduced glucocorticoid (GR) in the hippocampus) may lead to permanent changes in the adult phenotype (Filipović et al., 2005). For instance, chronic stress can increase anxiety and decrease memory and cognitive flexibility (Marin et al., 2011). From the point of view of therapeutic approaches, it is promising that these changes in neuronal circuitry are reversible in a healthy, resilient brain (Russo et al., 2012).

Allostasis refers to the body's response to toxic stress such as loud noise, hostility, fatigue, isolation, hunger, and threats to safety (Sterling and Eyer, 1981). Allostatic load is the "wear and tear on the body" and results when these allostatic systems including the HPA axis, metabolic pathways, and immune system are hyperactivated after a stressful event. The concept of allostatic load has been described to explain these adverse health outcomes in adulthood. The autonomic nervous system and HPA axis lead to adaptation, coined as "allostasis" by Sterling and Eyer when the body responds to stress (Sterling and Eyer, 1981); however, these responses to stress can have long-term deleterious effects on the body (McEwen, 1998). The hippocampus plays a key role in perception of stress or the level of allostatic load that an individual will experience (McEwen, 1998). According to the allostatic load hypothesis, ELS induce biological changes that modify the maturation of allostatic systems. Frequent or chronic activation of allostatic systems may cause allostatic overload, thereby resulting in chronic disease later in life (Katz et al., 2012; Misra et al., 2013).

Yet, when the environmental insults overwhelm the individual's capacity to adapt to the stressor, it becomes harmful and toxic. Toxic stress is defined as "the excessive or prolonged activation of physiologic stress response systems in the absence of buffering protection afforded by stable responsive relationships (Shonkoff and Garner, 2012). " It has been shown that toxic stress can disrupt the developing brain, thereby influencing health outcomes decades later (McEwen, 2006). Examples of toxic stress include significant adversity such as poverty, abuse, neglect, neighborhood violence, or the substance abuse or mental illness of a caregiver. Table 1 shows the findings from a large number of cohort studies that were able to identify biomarkers associated with higher cardiovascular risk in response to the exposure to different sources of ELS. Overall, the intensity, length and number of adverse factors seem to have an additive effect in the physiological outcomes analyzed and certainly predict an enhanced risk to develop cardiovascular disease during the adult life (Dong et al., 2004; Felitti et al., 1998).

3. Early life stress and cardiovascular disease: what the cohort studies revealed

Numerous clinical studies link ELS to a broad range of negative health outcomes. The association between ELS and psychosis, depression, anxiety, and attempted suicide are typically studied. However, more recent attention has been brought to ELS as an independent risk factor for hypertension, obesity, substance abuse, smoking as well, which are major contributors in the development

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