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.

Keywords

early life stress; adverse childhood experiences; cardiovascular risk; hypertension; maternal separation

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 & 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., 2014a; Carrol 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 (Filipovi 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 of cardiovascular disease (CVD) and type 2 diabetes (Brent and Silverstein, 2013; Luecken, 1998; Varese et al., 2012).

A seminal paper from Dong et al. first described the relationship between ELS, given by exposure to adverse childhood experiences (ACEs). Dong's group reported a dose-response relationship of ACEs to ischemic heart disease (Dong et al., 2004). In addition, children raised in low socioeconomic status households under stressful conditions have developed elevated blood pressure over time and increased vascular reactivity to stress (Carroll et al., 2013). In the Bogalusa Heart and other studies, those individuals with the greatest trajectory of blood pressure increase during childhood and adolescence had severalfold higher prevalence of hypertension and increased mortality as adults (Oikonen et al., 2011). Further evidence has been provided by a natural human event involving Finnish children separated from their parents during World War II revealed that those children separated at ages 4–7 years had systolic blood pressure approximately 9 mmHg higher as adults than non-separated individuals while those separated at different ages did not have significant difference in systolic blood pressure. Notably, Woodall and Matthews have reported that boys aged 8–17 (but not girls) from unsupportive families have stronger heart rate responses during a series of laboratory stressors (Matthews et al., 1990).

More recently, findings from the Georgia Stress and Heart (GSH) study revealed that individuals who were exposed to multiple ACEs display a greater increase in blood pressure levels in young adulthood compared to control individuals in a 23-year follow up period (Su et al., 2015). This effect was present independent of BMI and the authors suggest that increased levels of endothelin-1 (Su et al., 2014) may be a potential mechanism linking ELS and the development of stress-induced elevations in blood pressure.

In a situation of extreme adversity, starvation plays a detrimental role in terms of programming for adult disease. Several epidemiological reports following birth cohorts exposed to famine (Dutch 1944–1945; Ukraine 1932–1933; Chinese Famine 1959–1961) reveal that exposure to starvation conditions in early life induce metabolic disease in adulthood including a cluster of metabolic syndrome biomarkers such as dyslipidemia, hypertension, obesity, type 2 diabetes, and cardiovascular morbidity (Vaiserman, 2014), all risks factor for coronary artery disease. In sum, these studies (also see Table 1) show that there is a highly sensitive window of life to induce permanent changes in the cardiovascular system (Anda et al., 2009; Miller et al., 2011).

4. Maternal Separation as an animal model to mimic childhood adversity

There is growing evidence of comorbidities for anxiety, depression and CVD (Davidson, 2012; Glassman, 2007; Halaris, 2009; Huffman et al., 2013; Ruo et al., 2003), challenging the current research community to provide animal models in order to investigate the mechanisms by which behavioral stress during the developmental stages of life influences adult cardiovascular function. Multiple models of perinatal programming have shown to induce a significant increase in blood pressure in the offspring. These models include restraint stress during gestation days 15 to 21, maternal protein deprivation, and glucocorticoid exposure via dexamethasone administration during gestation (Harris and Seckl, 2011; Igosheva et al., 2004; Mizuno et al., 2013). However, maternal separation (MatSep) and similar models of chronic behavioral stress seem to induce a "first hit" effect that does not change the baseline cardiovascular parameters in young adult rodents, but primes the physiological systems to overreact in response to a secondary stressor or "second hit."(Ho et al., 2016; Loria et al., 2010b; Sanders and Anticevic, 2007).

MatSep is a well-established model of ELS in which neonatal pups are separated from their mothers for 3 hours a day from postnatal day 2 to 14 (Lehmann et al., 2000; Lippmann et al., 2007; Loria et al., 2010b).

Originally, MatSep has been widely used in the psycho-neuroendocrinology field to assess its long lasting effects on behavioral responses. These results demonstrated that animals exposed to MatSep develop depressive-like behavior and anxiety in adult life.

MatSep has been most widely performed in rats and mice, but also different species including non-human primates, rabbits, pigs, guinea-pig, birds (see review Loria et al., 2013). The variety of species, length of separation protocol and the period of life for the analysis of the outcomes (e.g. juvenile vs. adult) have resulted in numerous derangements described in the literature. However, rodents are the most consistently used models perhaps due to their similar responses to stress in comparison to humans as well as availability, cost-effectiveness and the possibility for genetic manipulation in the investigation of basic molecular mechanisms. Previously, we have reported impaired blood pressure regulation in rats exposed to 3 hours of maternal separation daily from postnatal day 2–14 (Loria et al., 2013a). Within a murine model, MatSep with early weaning consists of separating the litters for 4 hours per day during postnatal days 2–5 followed by 8 hours per day from postnatal day 6–16 with weaning at day 17 induces vascular endothelial dysfunction and superoxide production thus increasing cardiovascular risk (Ho et al., 2016).

MatSep in rodents is ideally suited to model ELS in humans because of the strong parallels in long-term neuronal and cardiovascular outcomes. For instance, many symptomatic characteristics associated with the consequences of emotional trauma have been shown to impact the cardiovascular system of rodents in a similar fashion to the observed in adult humans (Beutel et al., 2014; Loria et al., 2013a; Mascitelli et al., 2006; Rahman et al., 2013; Sanders and Anticevic, 2007). Rodent models mimic the behavioral outcome of ELS in humans such as anxiety and depression (Heim and Binder, 2012; Schmidt et al., 2011; Uchida et al., 2010). Similar to humans, rodents exposed to MatSep have increased risk of

developing hypertension and cardiovascular pathologies in adulthood (Loria et al., 2013a; Loria et al., 2010b). Interestingly, MatSep in mouse has been a useful paradigm to model childhood neglect as well (Fabricius et al., 2008; George et al., 2010).

Nevertheless, a number of concerns were raised denoting some limitations of using MatSep as a model of ELS including: 1) there is a mismatch of environment and developmental period between humans and rodents since the postnatal life in mice aligns with the third trimester in humans; conversely, this mismatch provides a useful experimental model to perform interventions avoiding *in utero* manipulation, 2) emotional stress in humans is often self-perpetuated from an initial stressor, whereas in other animal species, stressors are often acute and non-self-perpetuated, thus allowing the researcher to evaluate the effect of stress in the absence of self-perpetuation and 3) there is remarkable consensus of effect across a variety of different MatSep protocols, but the development of a standardized protocol (e.g. time and length of separation) would help move the field forward.

Given that MatSep enhances the correlation between stress-induced cardiovascular outcomes, the use of an adequate protocol and species to study the molecular mechanisms by which ELS enhances adult cardiovascular disease risk can be proposed taking into account the nature of the phenotypic outcomes of interest.

5. Mechanisms contributing to ELS-induced cardiovascular dysfunction

5.1. The central nervous system (CNS)

The brain processes environmental input from emotional, sexual and physical abuse, neglect or illness differently at critical ages (Cirulli et al., 2009; Furukawa et al., 1999). It is well-accepted that ELS has detrimental effects on adult health, especially when experienced through critical "windows of plasticity." During development, the timing of ELS can be harming if occurring when neural system differentiation and synapses are being formed and reinforced (Gershon and High, 2015). When children experience toxic stress, their cortisol levels remain elevated for prolonged periods of time. Both animal and human studies show that long-term elevations in cortisol levels can alter the function of a number of neural systems, suppress the immune response, and even change the architectural regions in the brain that are essential for processes such as learning and memory (Kumari et al., 2013; Pervanidou and Chrousos, 2011).

One mediator of neural function and plasticity is the brain derived neurotrophic factor (BDNF). It has been hypothesized that BDNF is a candidate molecule through which early life experiences persistently modify brain structure and function (Branchi et al., 2004). BDNF is active within the hippocampus, cortex, and basal forebrain and is important for cognitive function, energy homeostasis, long term memory and neurogenesis (Marosi and Mattson, 2014). While MatSep decreased BDNF decreased in hippocampus and striatum, it increased in ventral tegmental area. Unlike, cAMP response element binding protein (CREB) and fosB were unchanged in all brain regions from animals exposed to MatSep.

Recent Imaging studies on adults with a history of childhood stress revealed a significant impact in the frontal cortex, corpus callosum, amygdala, locus coeruleus, hippocampus,

HPA axis and cerebellum (Brietzke et al., 2012; Hanson et al., 2015; Reynolds, 2013). As such, adults with a history of childhood adversity also have reduced hippocampus and prefrontal cortex volumes (Danese et al., 2009; McEwen et al., 2015).

It is important to discuss that in some condition, ELS during early stages of life exerts profound effects to impart resilience to later psycho-physiological dysfunction. A review of Dr. Meaney's work (Roth and David Sweatt, 2011) has described the molecular changes in the brain following high-quality maternal care that provided resilience to stress later in life. These adaptations were attributable to increased hippocampal glucocorticoid receptor (GR) expression, increased expression of transcription factor NGFI-A decreased hypothalamic corticotropin releasing factor (CRF) expression leading to enhanced glucocorticoid feedback sensitivity. This data further enforces that the quality of social support is the key event to determine exposure to or protection to secondary behavioral stressors (Ozbay et al., 2008; Smith and Carlson, 1997).

C57BL/6 inbred mice have been noted for resiliency to early environmental stressors (Anisman, 2001; Shanks et al., 1990). Selection for low or high care C57BL/6 mothers also has a minimal impact on offspring behavior and stress response (Pedersen et al., 2011). These studies suggest that alternative more severe models of ELS, beyond three hours, combined with early weaning are necessary to induce the ELS-like phenotype in mice (George et al., 2010; Ho et al., 2016).

5.2. The Hypothalamic-Pituitary-Adrenal (HPA) Axis

An important role of the hypothalamic-pituitary-adrenal (HPA) axis response is regulation of many biological systems in the body to allow an individual to adapt to its environment and promote survival (Munck et al., 1984). Glucocorticoid secretion improves cardiovascular tone, suppresses immune function, and mobilizes energy stores to enable the individual to cope with its environment including stressors. However, prolonged exposure to elevated glucocorticoids has deleterious effects to many organ systems within the body including the central nervous system, immune system, and regulation of blood pressure (McCormick and Mathews, 2007; Woolley et al., 1990).

Through the actions of glucocorticoid hormone signaling in the brain, the HPA axis is involved in programming responses to future challenges, thereby influencing how an individual will respond to stressors in adulthood. Glucocorticoid secretion, which occurs with levels peaking in the morning and declining throughout the day in a diurnal pattern, are involved in the suppression of their own release through fast (seconds), delayed (minutes to hours), and slow (hours to days) negative feedback systems that inhibit the release of adrenocorticotrophin hormone (ACTH) (Dallman et al., 1987; Keller-Wood and Dallman, 1984). The hippocampal subiculum transsynaptically inhibits the HPA axis by way of the bed nucleus. Experimentally, it was shown that (1) HPA-inhibitory influences of medial prefrontal cortex (mPFC) and hippocampal formation (HF), are additive and (2) anterior bed nucleus of the stria terminali (aBST) plays a more substantial inhibitory role over stress-induced HPA responses than ventral subiculum (Cullinan et al., 1993; Radley and Sawchenko, 2011). The hippocampus itself can become more damaged with increased exposure to stress (Brown et al., 1999), thus perpetuating this loss in feedback inhibition to

the HPA axis. Electrical stimulation of the hippocampus has been shown to have an inhibitory effect on the HPA axis by reducing glucocorticoid levels (Herman et al., 2003). Lesion studies indicate that a damaged hippocampus prolongs HPA axis responses to acute stress (Herman et al., 1998) most likely through a genomic mechanism.

Hyporesponsive period in rodents—Early postnatal life is a sensitive period and there is a distinct pattern of HPA axis activity during early development that was first described in rodents. HPA axis activity maintains stable with low circulating glucocorticoids levels during the stress hyporesponsive period (SHRP) which corresponds to postnatal days 1–10 in mice and postnatal days 3–14 in rats (Sapolsky and Meaney, 1986; Schmidt et al., 2005; Stanton et al., 1988).

Prolonged maternal separation implemented during the SHRP causes neonates to display elevated basal and stress-induced levels of glucocorticoids, thus making the HPA axis hyper-responsive to future stressors. Chronic stress exposure during this period can have a long-lasting impact on the HPA axis (Gunnar and Quevedo, 2007). Long-lasting alterations in the HPA axis induced by ELS in rodents have been linked to epigenetic modifications in regulatory regions of stress-related genes as described above. Specifically, impairment of mother-infant interactions during the postnatal period has been shown to upregulate hippocampal glucocorticoids receptor (GR) and to increase hypothalamic corticotropin-releasing factor (CRF), corticosterone, and ACTH levels (Korosi et al., 2010; Lehmann et al., 2000; Lippmann et al., 2007; Nishi et al., 2013)

Corticosterone levels and ACTH suppression—A key physiological response to stress involves the increased secretion of glucocorticoids. A major role of glucocorticoids is to regulate glucose mobilization during stressful periods as part of the adaptive response to stress. However, the adaptive responses to stress through glucocorticoids can become harmful when its threshold is exceeded. Excessive glucocorticoids lead to hyperlipidemia, hypertension and vasoconstriction, thus increasing the risk for cardiovascular events including myocardial infarction, stroke, and heart failure. MatSep has been shown to increase plasma corticosterone release and elevate Neuronal Growth Factor levels in the hippocampus, which can affect the development and maturation of specific organs that regulate blood pressure control including the heart, vasculature, kidney, and brain (Igosheva et al., 2004), suggesting that ELS presents the capability to exert programming effects.

To measure HPA activity, human populations often undergo a dexamethasone suppression test followed by a low dose ACTH stimulation test to examine pituitary and adrenal gland function by measuring urinary levels of cortisol. ELS is associated with persistent changes in HPA axis function, with ELS-exposed adults often exhibiting a flattened cortisol circadian rhythm and both hypo- and hyper-responsiveness to future stressors (Miller et al., 2013). A recent study examining the relationship between the HPA axis and cardiovascular risk factors in obese children revealed a positive association between systolic blood pressure and ACTH and cortisol levels (Prodam et al., 2013) thereby the risk for cardiovascular disease.

The mechanisms by which glucocorticoids and a dysfunctional HPA axis mediate the development of hypertension during postnatal life are still unclear. Numerous studies have

demonstrated that acute or chronic exposure of the fetus to elevated maternal glucocorticoids during pregnancy programs the offspring for hypertension and cardiovascular disease (Moritz et al., 2003) (Ortiz et al., 2003, 2001). Additionally, glucocorticoids directly regulate blood pressure by increasing sodium and calcium intake within the vascular smooth muscle (Kornel et al., 1993) and by increasing vascular responsive to Ang II (Provencher et al., 1995) and noradrenaline (Bian et al., 1992). Nonetheless, few studies have addressed the long-term consequences of the exposure to elevated corticosterone levels during postnatal life using animal models. The glucocorticoid-induced changes in both central and peripheral sites of cardiovascular control may be reflected in enhanced cardiovascular responses to acute stress seen in MatSep mice (Pote et al., 2013) and rats (Loria et al., 2010b). Meaney's group has demonstrated that offspring exposed to less maternal care display elevated glucocorticoid responses to stress (Weaver et al., 2004). On the other, it has been shown that foster litters during maternal separation can prevent the sensitization of the HPA axis (Huot et al., 2004). These findings support the implication of the HPA-programmed sensitivity on the correlation between ELS and heightened response to stressors.

5.3. The sympathetic nervous system (SNS)

Sympathetic activation is one of the fastest systems in response to stressors (Farah et al., 2004; Lee et al., 2004; Randall et al., 1994). Acute stressors induce neuro-humoral and vascular responses that lead to greater blood pressure reactivity to stress or to delayed post-stress blood pressure recovery (Chida and Steptoe, 2010; Gerin and Pickering, 1995). It has been shown that alteration in a single acute stress response event can predict future cardiovascular disease risk (Chen et al., 2007), such as stroke (Jern et al., 1989) and hypertension (Kohan and Padilla, 1994). Acute stress can trigger autonomic and neuroendocrine-mediated changes in cardiac contractility and peripheral vascular resistance (Reich et al., 1981) and involves vasoactive mediators such as plasma endothelin (ET-1) (Fujii et al., 2005; Kaehler et al., 2002), angiotensin II (Mayorov, 2011) and corticosterone (Taniyama and Griendling, 2003; Treiber et al., 2000).

While a large body of literature addresses the mechanisms by which SNS mediates the stress response, it is less frequent to find studies in animal models that have investigated the mechanisms underlying autonomic activation in response to emotional stress during postnatal life. The priming of the neuroendocrine responses to stress may have its origin in the brain as discussed above. In particular, we now know that early life abuse and neglect have adverse effects upon the developing brain and body that can result in poor self-control and emotional regulation, impaired cognitive development, and increased risk of cardiovascular, metabolic and immune system diseases (Boersma et al., 2014; Danese et al., 2009).

The neonatal rodent lacks the ability to produce sympathetic responses to hypoglycemia until the growth of the adrenal nerve supply has occurred. A surge in activity of postganglionic neurons occurs during the third postnatal week, which is associated with a profound elevation in the overall sympathetic hyperactivity and development of the baroreceptor regulation of sympathetic tone (Bartolome et al., 1980). However, it is possible that exposure to stressors early in this developmental queue accelerates a number of events,

exacerbating the sensitivity of blood pressure regulatory mechanism such as the baroreflex function.

Four structurally related proteins including NGF brain-derived neurotrophic factor (BDNF), neurotrophin-3 (NT3), NT4/5, and NT6 have been considered as the key mediators of the ELS-induced developmental changes in the autonomic responses (McEwen et al., 2015; Murgatroyd et al., 2009; Weder et al., 2014). Nonetheless, the consequences of emotional stress during the specific window of plasticity on the reset of the sensitivity of the autonomic system have an amplificatory effect at the end-organ level, which will be further highlighted in the sections below.

Heart—Myocardium growth during the early postnatal period must respond not only to the increasing demands of the rapidly growing animal but also to the relatively sudden changes in the patterns of blood flow and circulatory resistance occurring shortly after birth. Cardiac tissue, specifically cardiomyocytes, undergoes structural and functional physiological changes that may be altered by exposure to behavioral stress (Anversa et al., 1980). The effect of MatSep on heart function has been reported in different animal models. Using borderline hypertensive rats (BHR), the first generation offspring of spontaneously hypertensive and Wistar-Kyoto rats, it was shown that MatSep alters the cardiovascular stress response induced by 30 min of restraint stress (Sanders and Anticevic, 2007). Despite a similar mean arterial pressure response, rats exposed to MatSep showed exaggerated heart rate response compared to control counterparts. MatSep also increased the stress-induced Fos positive cells in the central nucleus of the amygdala (CeA), paraventricular nucleus of the hypothalamus (PVN), and the bed nucleus of the stria terminalis (BNST) (Sanders and Anticevic, 2007). These nuclei play an important role in integrating the physiological and behavioral response to stress. Thus, MatSep enhances the neuronal activation leading to an overactive autonomic system in response to stressful environmental cues.

Studies using Wistar rats reported that MatSep did not have a significant effect on the intermittent restraint stress (IRS)-induced acute modifications of cardiac sympathovagal balance (Trombini et al., 2012). Heart rate variability analysis has shown similar values as reported in non-MatSep rats. MatSep did not affect the autonomic blockade with scopolamine and atenolol, which suggests a normal cardiac pacemaker intrinsic activity. However, MatSep had a significant effect in cardiac parasympathetic drive following IRS (Trombini et al., 2012).

Taken together, these functional changes in the autonomic function of the heart have an effect on the cardiac structure involving cardiomyocyte hypertrophy, increased density of vascular structures, and myocardial fibrosis. Although these are considered mild functional and structural cardiac alterations, these changes confer increased susceptibility to the development of an exaggerated response to secondary stressors.

Vasculature—ET-1 is a 21-amino acid peptide characterized and purified from cultured endothelial cells (54). The actions of ET-1 are the result of activation of two receptor subtypes, ETA (located on vascular smooth muscle and mediates vasoconstriction) and ETB (predominantly expressed on the vascular endothelium) (Barton et al., 1998; D'Angelo et al.,

2005). Interestingly, both receptor subtypes are localized on sympathetic nerves (Milner et al., 2000). Studies have demonstrated a link between the ET-1 pathway and stress-induced raise in blood pressure in humans and rodents (D'Angelo et al., 2005; Kaehler et al., 2002; Spieker et al., 2002; Treiber et al., 2000). One potential link between ET-1 pathway and stress is given by the fact that exposure of vessels or cultured vascular smooth muscle cells from rat or rabbit to dexamethasone or cortisol resulted in concentration-dependent stimulation of endothelin release (Gómez-Guzmán et al., 2012; Intengan et al., 1998). Rats exposed to MatSep display acute stress-mediated ET release, indicating that alterations in the expression or function of the ET pathway may be implicated in the short- and/or long-term control of stress-induced responses. Specifically, MatSep exaggerates the acute blood pressure response to acute behavioral stress, which involves ET-1. In this regard, D'Angelo et al. (D'Angelo et al., 2005) suggested that there is a crosstalk between the ET-1 Type A (ETA) receptors and catecholamines in the terminal nerves, enhancing vasoconstriction. For instance, acute behavioral stress showed that the lack of ET-B receptor subtype in non-neuronal tissue, such as the vasculature, blunted the MatSep induced enhanced pressor response to stress that was observed in wild type MatSep rats (Loria et al., 2010a). Furthermore, in normotensive rats, endogenous ETA receptor activation attenuates the air jet stress-mediated pressor response (D'Angelo et al., 2005). This data suggests a cross-talk between the ETA receptor and the adrenergic pathway (Mangiafico et al., 2002). However, MatSep reduced both ETA and ETB receptors expression in the vasculature. Thus, reduced ET receptor expression, particularly ETA might lead to exaggerated activation of the adrenergic-mediated responses in MatSep rats.

Kidneys—The role of the SNS in the development of hypertension has been described in several experimental models such as spontaneously hypertensive rats (SHR) and Dahl salt-sensitive (DS) rats (D'Angelo et al., 2005; Mattson et al., 2004; Zicha et al., 2012). Additionally, kidneys play a critical role in the regulation of fluid homeostasis and chronic blood pressure control (Dahl and Heine, 1975; Navar, 1997). Renal denervation (DnX) is one of the most studied therapies for resistant hypertension (Esler et al., 2010; Osborn et al., 2005). In experimental models, Dr. Alexander's group showed that the exacerbated renal nerve activation plays a causal role in the early onset of hypertension in a model of intrauterine growth restriction (IUGR) (Alexander et al., 2005; Ojeda et al., 2007). Furthermore, Samuelsson et al show that sympathetic activation leads to hypertension in offspring from obese dams and is most likely derived from early exposure to energy-dense nutrients (Kirk et al., 2009; Samuelsson et al., 2013).

It has been reported that MatSep lowers the renal excretory capacity, or glomerular filtration rate (GFR) (Loria et al, 2013a). One of the mechanisms suggested involves an increased sympathetic outflow to the kidneys, since renal denervation normalized GFR in MatSep rats. Taken together, there is substantial evidence in the literature to support a profound effect of MatSep in the autonomic function. Thus, leading to exacerbated acute and chronic reactions to a wide range of environmental stressors, particularly the ones triggering blood pressure responsiveness. There is no proof of a direct sympathetic nerve activation involving baseline changes in HR and increased blood pressure due to exacerbated renal sodium retention.

Overall, MatSep seems to impair the blood pressure regulation required to face the adaptive response to stimuli when a secondary stressor challenges the cardiovascular system.

6. Perspectives for the study of ELS-induced cardiovascular dysfunction

6.1. The Renin-angiotensin-aldosterone system (RAAS)

Many investigations have shown that alterations in normal vasculature development are associated with changes in renal structure/function with a subsequent impact on blood pressure levels (Gomez and Norwood, 1995; Sequeira Lopez and Gomez, 2004). However, there is a gap in knowledge regarding the impact of behavioral stress early in life and the mechanisms underlying the programming of the adult vascular phenotype.

The RAAS plays an important role in the vasculogenesis and angiogenesis processes (Gomez and Norwood, 1995; Sequeira Lopez and Gomez, 2004; Shi and Clegg, 2009; Tufro et al., 1999). The literature has not directly addressed the effect of stress in modulating these mechanisms; however, several studies have shown that models with increased GC levels during perinatal life are frequently associated with increases in Ang II sensitivity later in life. For instance, maternal GC exposure in sheep (Moritz et al., 2003) and low protein exposure in rats (McMullen and Langley-Evans, 2005; Woods et al., 2004) have been shown to induce marked changes in the renal renin–angiotensin system (RAAS) in the fetus and the offspring, suggesting that this system is of importance in many species and models of fetal programming.

In addition to the effects in the vasculature, the RAAS has been described as a required factor for a normal renal structural and functional development (Guron and Friberg, 2000; Lasaitiene et al., 2003; Saez et al., 2007). It is well-known that AT1 receptor blockade impairs the nephron endowment and induces structural damage leading to the development of hypertension later in life. However, the effects of chronic stress during the late nephrogenic period have not been investigated. In Wistar Kyoto rats, MatSep lowers GFR in baseline conditions, although the histopathology of these animals is normal (Loria et al., 2013a, 2013b). However, chronic AngII administration exaggerates hypertension. In these conditions, the kidney but not the conductance vessels from the MatSep animals show vascular damage, suggesting that exposure to AngII most likely induces a renal-dependent hypertension. Thus, reduced renal filtration capacity is a potential mechanism by which MatSep impairs chronic blood pressure control. Since the vascular development is an event highly associated with the circulating and local levels of AngII and the expression of AT1 and AT2 receptors as well, further investigations to address the connections between stress and cardiovascular sensitivity to AngII are required.

6.2. The Inflammatory system

Humans exposed to ELS display a heightened inflammatory status that parallels what is observed in rodent models of ELS (Clarke et al., 2009; Danese et al., 2007; Slopen et al., 2012). Adults who reported experiences of childhood maltreatment demonstrated an attenuated HPA axis sensitivity in response to a psychosocial stress test (Heim et al., 2000). Since glucocorticoids exert an inhibitory influence on inflammation, it is possible that

maltreated children display increased levels of inflammation in adulthood through this mechanism. Furthermore, adults reporting ELS or ACEs have been shown to be at an increased risk of disease associated with an inflammatory origin (Dong et al., 2004; Felitti et al., 1998). The persistent activation of inflammatory pathways is proposed as one of the mechanisms by which ELSalter long-term cardiovascular status since inflammation is a central part of the stress response (Glaser and Kiecolt-Glaser, 2013). In the context of the "fight or flight" reaction, acute psychosocial stress can induce activation of the transcription nuclear factor κB (NFkB) and secretion of proinflammatory cytokines (Bierhaus et al., 2003; Maes et al., 1998). As such, through the production of proinflammatory cytokines, immune activation progressively stimulates the secretion of glucocorticoids (Flier, 1995). These events have been shown to induce hypertension and promote cardiovascular disease. Thus, ELS may disrupt the potentially adaptive response to stress. Animal models suggest that maternal care influences the development of the stress response (Caldji et al., 1998; Weaver et al., 2004) and may alter the long-term susceptibility to inflammation (Bailey and Coe, 1999).

The Dunedin Multidisciplinary Health and Development Study, one of the few prospective studies in a birth cohort followed to age 32 years revealed that maltreated children display a significant and graded increase in the risk for clinically relevant C-reactive protein levels 20 years later (Danese et al., 2007). This investigation also shows that more than 10% of cases of low-grade inflammation in the population may be secondary to adverse childhood experiences. The association between childhood adversity and adult inflammation also generalizes to fibrinogen and white blood cell count (Raposa et al., 2014).

Likewise, adult animals subjected to chronic stress show an inflammatory response in the hippocampus; which has been related to cognitive dysfunction and psychopathology. MatSep activates microglial cells and decreases astrocyte density in the hippocampus. A differential cytokine expression was observed in the hippocampus and the hypothalamus after MatSep and in response to an acute stressor. Also, MatSep induced an independent response of peripheral cytokines, where peripheral concentrations of IL-1β were decreased and IL-6 concentrations were increased after a single acute stress event in MatSep pups at postnatal day 15 (Roque et al., 2015). Taken together, this studies reveals that ELS is associated with persistent elevations in proinflammatory cytokines; however, future studies are needed to elucidate the molecular mechanisms.

6.3. Epigenetics

Developmental and behavioral neuroscience research continues to provide evidence that the epigenome remains sensitive to environmental influences. Epigenetics is the study of heritable, but modifiable, changes in gene expression, and permits an individual's biological systems to adapt to its environment by changing the methylation patterns (Berger et al., 2009). Epigenetic mechanisms mediate gene-environment interplay during the lifespan. Post-translational modifications of histones and DNA methylation have been intensely studied and the growing body of evidence indicates that changes in gene activity are a result of a variety of environmental factors including, toxins, stress, diet and behaviorally relevant stimuli (Gershon and High, 2015a; Vaiserman, 2014b; Yang et al., 2013).

Among the mechanisms that change the normal function of genes and/or neurons, changes in DNA methylation have been shown to play a critical role in the development of chronic disease in response to stress (Gershon and High, 2015; Murgatroyd and Spengler, 2011; Weder et al., 2014). Specifically, challenges during early neonatal life alter the gene promoter methylation and therefore directly or indirectly effect gene expression in a range of physiological processes (Gluckman et al., 2008). In rats, several models of fetal programming have extensively described these effects. Altered promoter methylation and gene expression have been shown in the hepatic GR and the peroxisome proliferator-activated receptor (PPAR-α), influencing carbohydrate and lipid metabolism (Burdge et al., 2008; Lillycrop et al., 2005). Other epigenetic changes have been observed in p53 of the kidney (Pham et al., 2003) and the angiotensin II type 1b receptor in the adrenal gland (Bogdarina et al., 2007) influencing renal apoptosis and pressor responses, respectively. These phenotypic effects may not manifest until later in life in response to inadequate nutritional factors such as a high fat diet (Gluckman et al., 2008).

Also, a significant attenuation of methylation at several CpG sites in the paraventricular nucleus (PVN) has been found even one year after exposure to MatSep in male mice (Kember et al., 2012). To test the hypothesis of correlation between rodent versus human ELS-induced epigenetic changes, a study of male suicide victims' hippocampi exhibited decreased levels of GR, which correlated with increased methylation in the Nr3c1 promoter, the human GR (McGowan et al., 2009) (Murgatroyd and Spengler, 2011). Taken together, these data indicate that ELS modify the epigenetic landscape at multiple levels, including the modification of key regulators of the stress and cardiovascular responses.

7. Summary

Among the numerous environmental factors that affect the programming of the cardiovascular system, chronic behavioral stress during early life emerges as an independent risk factor. A multi-organic response in adaptation to this first exposure to stress early in life induces long lasting effects on the responsiveness to secondary stimuli, increasing the risk to develop chronic disease (Figure 1). Focusing on the psychological and cardiovascular comorbidity, a compelling number of mechanisms triggered by stress have been shown to have a major impact in the neuroendocrine plasticity associated with the regulation of cardiovascular function. This review also reveals that there is a need for further investigation in the ELS-induced mechanisms underlying future risk of premature morbidity and mortality. In the quest to understand the systems and mechanisms involved with organ and tissue plasticity, it is important to consider these pathways to develop a more personalized pharmacotherapy to alleviate the long-term effects of ELS, including ACEs.

Benefits of early intervention, efforts to curb child psycho-emotional and physical abuse, could reduce hypertension and heart disease in the adult population (Alastalo et al., 2013; Gluckman et al., 2008; Lehman et al., 2009; Parrish et al., 2013). Yet, sensitivity of the developing brain provides an opportunity for improving outcomes, and this is leading to efforts to improve consistency of supportive parental care.

Acknowledgments

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Highlights

- Early life stress (ELS) can overwhelm an individual's capacity to adapt to a stressor, thus leading to harmful effects on the cardiovascular system in adulthood. Cohort studies have demonstrated a strong link between ELS experiences and cardiovascular disease.

- Toxic stress defined as "the excessive or prolonged activation of physiologic stress response systems in the absence of buffering protection afforded by stable responsive relationships" includes poverty, physical and sexual abuse, neglect, neighborhood violence, or the substance abuse or mental illness of a caregiver.

- Maternal separation (MatSep) is a well-established animal model of ELS and provides a paradigm to test the correlation between ELS and cardiovascular disease

- Among the mechanisms contributing to ELS-induced cardiovascular dysfunction, this review outlines the central nervous system (CNS); the Hypothalamic-Pituitary-Adrenal (HPA) axis; and the sympathetic nervous system (SNS), the renin-angiotensin-aldosterone system (RAAS) and the immune system.

- We conclude that ELS emerges as an independent risk factor for cardiovascular disease. This review reveals the need for further investigation in the ELS-induced mechanisms underlying future risk of premature CVD morbidity and mortality.
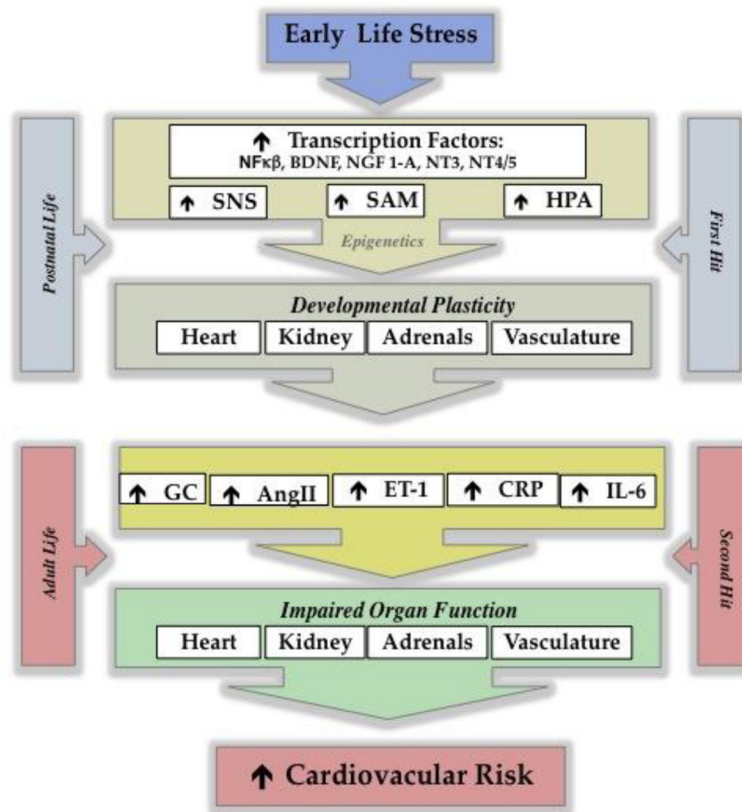
Figure 1.
Impact of ELS on the normal development of tissues and organs. During postnatal life, the exposure to a "first hit" influences the future sensitivity to a "second hit". As a result, several components of the cardiovascular system display an enhanced reactivity, leading to a greater risk to develop cardiovascular disease.

SNS=sympathetic nervous system; SAM=sympathomedullary pathway; HPA: Hypothalamic- Pituitary-Adrenal Axis; NF-KB: nuclear factor kappa-light-chain-enhancer of activated B cells BDNF:Brain-derived neurotrophic factor NGF 1-A: Nerve growth factor-induced protein A; NT3: neurotrophin-3 NT4/5: neurotrophin-4, neurotrophin-5, GC: glucocorticoid; AngII: angiotensin II; ET-1: endothelin-1; CRP: C-reactive protein; IL-6: interleukin-6

Table 1

Cohort studies exposed to different types of Adverse Childhood Experiences (ACEs) and their correlation with Cardiovascular Disease Risk.

Type of Adversity	Participants	Outcome	Reference
Childhood maltreatment (maternal rejection, physical abuse, harsh discipline, sexual abuse)	Members of the Dunedin Multidisciplinary Health and Development Study, age 32 (n=972)	• Elevated levels of cardiovascular risk clusters: overweight, high blood pressure, high cholesterol, and low VO2 max, high hsCRP • Higher smoking rates and sedentary lifestyle	(Danese et al., 2007)
Repeated sexual and/or physical abuse	Healthy women, age 18–45 with regular menses (n=49)	• Increased pituitary-adrenal and autonomic responses • Greater ACTH response to stress	(Heim et al., 2000)
Childhood Trauma Questionnaire including emotional, physical, and sexual abuse	~342 women from SWAN (Study of Women's Health Across the Nation	• Physical abuse but not sexual or emotional linked to development of metabolic syndrome including elevated blood pressure.	(Midei et al., 2013)
Physical abuse, sexual abuse, and childhood neglect	National Comorbidity Survey (n=5877)	• 3.7x likely to develop CVD • childhood neglect associated with diabetes	(Goodwin and Stein, 2004)
Physical and sexual abuse; neglect, parental death; divorce, family violence, family economic adversity	WHO World Mental Health Surveys (n=18,630)	• 3 or more ACEs associated with hypertension in adulthood	(Stein et al., 2010)
ACE questionnaire: childhood abuse, neglect, and household dysfunction	ACE study, n=9367 women, 7970 men	• Dose response relationship of ACEs to ischemic heart disease	(Dong et al., 2004)
Sexual abuse	Sexually abused females referred from CPS agencies in Washington, D.C. (n=84)	Significant increased risk for obesity by age 20–27 (43%)	(Noll et al., 2007)
7 Categories of ACE: psychological, physical, sexual, household dysfunction (substance abuse, mental illness, mother treated violently, criminal behavior)	13,494 adults completed questionnaire about ACE (the Adverse Childhood Experience Study)	• Strong dose response relationship between severity of abuse/ household dysfunction and risk factors for several chronic diseases including ischemic heart disease, cancer, chronic lung disease, and liver disease.	(Felitti et al., 1998)
Emotional neglect, physical neglect, household dysfunction, and abuse (similar to ACE Study)	1958 British Cohort (n=9310)	• Certain severe ACEs linked with increased BMI and waist circumference • Physical abuse had strongest link with obesity	(Thomas et al., 2008)
ACEs (with sexual and physical abuse omitted) including death of family member or pet, divorce, serious illness of family member, conflict between parents	1,234 middle school students from the Heart Behavioral and Environmental Assessment Team (HBEAT) Study	Those with >4 ACEs: • Increased BMI, • Increased resting heart rate • Increased waist circumference	(Pretty et al., 2013)

Type of Adversity	Participants	Outcome		Reference
Adapted questionnaire from ACE study (abuse, neglect, and household dysfunction)	The Georgia Stress and Heart Study (n=221)	•	Elevated levels of endothelin-1, higher total peripheral resistance index, diastolic blood pressure, and pulse wave velocity in healthy adolescents and young adults.	(Su et al., 2014)
Adapted questionnaire from ACE study (abuse, neglect, and household dysfunction)	The Georgia Stress and Heart Study (n=213 African Americans, n=181 European Americans)	•	Significant increase in BP levels in young adulthood due to multiple ACE exposure.	(Su et al., 2015)
Parental loss	N=88 adults with no current Axis I psychiatric disorder	•	Parental loss associated with increased cortisol responses.	(Tyrka et al., 2008)
Parental separation	1361 Finnish war evacuees	•	The separated subjects had significantly higher systolic blood pressure than non- separated controls.	(Alastalo et al., 2013)
Harsh family environments including low SES	Coronary Artery Risk Development in Young Adults N=2,738	•	Low SES and a harsh family environment predict increased blood pressure in adulthood.	(Lehman et al., 2009)
Parental divorce, death of a parent, parental incapacity through illness, serious debt, parental criminal behavior	Cohort members at the Royal Victoria Infirmary, Newcastle. N=412	3.2 % variation in carotid artery in men & 2.2% variation in females		(Lamont et al., 2000)
Holocaust exposure	70 European Jews born during 1940–1945	•	Prevalence of hypertension was elevated (62.9% vs 43%)	(Bercovich et al., 2014)