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Reduced left ventricular dimension and function following early life stress: A thrifty phenotype hypothesis engendering risk for mood and anxiety disorders

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ABSTRACT

Background: Early life stress (ELS) in macaques in the form of insecure maternal attachment putatively induces epigenetic adaptations resulting in a "thrifty phenotype" throughout the life cycle. For instance, ELS induces persistent increases in insulin resistance, hippocampal and corpus callosum atrophy and reduced "behavioral plasticity", which, taken together, engenders an increased risk for mood and anxiety disorders in humans but also a putative sparing of calories. Herein, we test the hypothesis whether a thrifty phenotype induced by ELS is peripherally evident as hypotrophy of cardiac structure and function, raising the possibility that certain mood disorders may represent maladaptive physiological and central thrift adaptations.

Methods: 14 adult bonnet macaques (6 males) exposed to the maternal variable foraging demand (VFD) model of ELS were compared to 20 non-VFD adult subjects (6 males). Left ventricle end-diastolic dimension (LVEDD), Left ventricle end-systolic dimension (LVESD) and stroke volume (SV) were calculated using echocardiography. Blood pressure and heart rate were measured only in females. Previously obtained neurobehavioral correlates available only in males were analyzed in the context of cardiac parameters.

Results: Reduced LVESD ($p < 0.05$) was observed when controlled for age, sex, body weight and crown-rump length whereas ejection fraction (EF) ($p = 0.037$) was greater in VFD-reared versus non-VFD subjects. Pulse pressure was lower in VFD versus non-VFD females ($p < 0.05$). Male timidity in response to a human intruder was associated with reduced LVEDD ($p < 0.05$).

Conclusions: ELS is associated with both structural and functional reductions of left ventricular measures, potentially implying a body-wide thrifty phenotype. Parallel "thrift" adaptations may occur in key brain areas following ELS and may play an unexplored role in mood and anxiety disorder susceptibility.

1. Introduction

Early-life exposure to stress is a well-known risk factor for psychiatric disorders later in life, including mood and anxiety disorders (Heim and Nemeroff, 2001). Exposure to stress during

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childhood has also been linked to a greater prevalence of cardiovascular risk factors, premature coronary artery disease and an increased risk for cardiovascular events in adulthood (Felitti et al., 1998). Specifically, preclinical (Loria et al., 2013) and human studies have shown higher rates of obesity (Alciati et al., 2013), smoking (Anda et al., 1999), diabetes (Kaufman et al., 2007), hypertension (Loria et al., 2010; Alastalo et al., 2013; Nuyt, 2008) and myocardial infarction (Dong et al., 2004) many years following exposure to early life stressors (Steptoe and Kivimäki, 2012). Stressors include separation from parents, parental death and other adverse experiences (Bercovich et al., 2014). While early adversity is a well-known cause of cardiomyopathy (Steptoe and Kivimäki, 2013), few studies have assessed the long term effects of ELS directly on cardiac structure and function (Carlier et al., 1988). Underdevelopment of cardiac structure and/or function may represent "thrift" oriented developmental programming, raising the possibility that neurotrophic compromise may be implicated as a strategy for saving energy.

Among the first clinical syndromes linking early life stress (ELS) to blunted somatic growth was psychosocial dwarfism (Money, 1977), a clinical entity observed in childhood caused by profound emotional deprivation or stress with an associated growth hormone deficiency (Albanese et al., 1994). Reversal of stunted growth occurred only with emotional normalization and not with nutritional provisions alone (Reinhart and Drash, 1969). Epigenetic studies in maltreated children examining genome-wide methylation differences (Weder et al., 2014) identified three genes relevant to the stress response, neural plasticity, and neural circuitry. In maltreated children, methylation of 32 of an identified 150 CpG sites located in these three genes specifically related to cardiac development (Weder et al., 2014).

The persistent disruption of central (Coplan et al., 1996) and peripheral (Kaufman et al., 2007) biological measures observed to date using our nonhuman primate model of ELS are accompanied by epigenetic effects at the serotonin transporter gene promoter region as well as genome-wide methylation effects (Kinnally et al., 2011).

We report on adult LV structure and function in an animal model of ELS, specifically bonnet macaques exposed to variable foraging demand (VFD), a paradigm in which infants are reared by mothers subjected to an experimentally-induced perception of food uncertainty without caloric deprivation (Rosenblum and Paully, 1984). VFD-reared subjects exhibit timidity (Jackowski et al., 2011) and loss of "behavioral plasticity" – a term applied to adaptive modifications of behavior (Molteni et al., 2004) – in response to a human intruder (Rosenblum et al., 2001). Moreover, VFD-reared macaques exhibit persistent elevations in cerebrospinal fluid (CSF) concentrations of corticotropin releasing-factor (CRF) (Coplan et al., 2005), high levels of which were found to predict components of the metabolic syndrome (Perera et al., 2011). Reductions in corpus callosum cross-sectional area are also observed (Jackowski et al., 2011) – the latter finding has been replicated in rhesus macaques (Sánchez et al., 1998) and young humans (Teicher et al., 2004) exposed to ELS. Should the latter parameters — "behavioral timidity", increased CSF CRF concentrations and reduced corpus callosum cross sectional area — be significantly related to cardiac parameters reflecting decreased dimension and function, preliminary support would be provided for the view that neurotrophic compromise may represent one consequence of thrift following early life stress.

Investigators have utilized nonhuman primates as models for human mood and anxiety disorders (Coplan et al., 2014). However, macaques are also remarkably similar anatomically to humans with regard to cardiovascular physiology and metabolism (Lazar et al., 2008; Haider et al., 1977; Vaitkevicius et al., 2001; Kaufman et al., 2005). Our group has used echocardiography to characterize left ventricular size and function in a laboratory colony of adult bonnet macaques and has reported reference values for LV systolic and diastolic dimension across the life span (Lazar et al., 2008). Furthermore, the very low incidence of atherosclerosis in chow-fed bonnet macaques provides an opportunity to study the relation between early life stress and cardiac structure and function in a model impervious to ischemic heart disease (Lazar et al., 2009).

Although infants reared by mothers exposed to VFD do not experience any lag in normative weight gain (Coplan et al., 1996), several lines of evidence, outlined below, suggest that body-wide adaptations shift the bonnet macaque's physiology towards an energetically "thrifty" mode across the life cycle. Hales and Barker first termed the "Thrifty Phenotype Hypothesis" to explain the origins of Type II Diabetes Mellitus as the consequence of long-term adaptations to early life caloric deprivation (Hales and Barker, 1992). However, recently the concept has been theorized as a programmatic reconfiguration following ELS leading to a '"Thrifty Psychiatric Phenotype" in which the convergence of caloric deprivation and early life emotional deprivation may engender an uncertainty of caloric access (Garcia-Rizo et al., 2015; Ockenburg et al., 2015). This view is supported by several lines of evidence in our early life stress model, including 1) persistent hypocortisolemia (Coplan et al., 1996) leading to reduced tissue catabolism for gluconeogenesis, 2) elevated concentrations of CSF CRF (Coplan et al., 1996), a stress neuropeptide with anorexogenic effects (Pelleymounter et al., 2000), 3) CRF inversely predicting the trophic signaling of GH in response to the GH secretagogue, clonidine (Coplan et al., 2000) and 4) insulin resistance and features of the metabolic syndrome (Kaufman et al., 2007). Based on these considerations and other putatively thrift-driven adaptations observed in VFD subjects such as decreased hippocampal volume (22), we hypothesized that LV cardiac dimension may be persistently "hypotrophic". Certainly, longstanding reductions in LV capacity would be consistent with a calorically thrifty adaptation. Our primary hypothesis was that VFD-rearing would lead to a persistent reduction in LV dimension, which would necessitate an increase either in ejection fraction (EF) or heart rate to maintain adequate stroke volume. In addition, evidence of a relationship between left ventricular dimension/function and previously obtained biobehavioral markers of affective dysregulation would support the hypothesis of wide-spread thrift adaptations following ELS. We therefore explored whether alterations in LV dimension/function would predict greater timidity in response to a human intruder, relative elevations of CSF CRF concentrations and relative reductions in corpus callosum white matter cross-sectional area.

2. Methods

2.1. Colony

Characteristics of the State University of New York Downstate Medical Center primate colony have been described previously (Kaufman et al., 2005). The colony consisted of laboratory-born and raised bonnet macaques (*Macaca radiata*) living either in social groups of 6–10 (females) or singly-housed adult males in full view of their peers maintained on standard commercial monkey chow who had been reared under social conditions until fully mature at which point injurious fights may occur. All procedures were performed in careful accordance with the Guide for the Care and Use of Laboratory Animals (https://www.aaalac.org/resources/theguide.cfm). The State University of New York Downstate Medical Center Institutional Animal Care and Use Committee (IACUC) approved the study.

Subjects: 34 adult bonnet macaques (22 female, 12 male) of

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