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Review

Developmental psychoneuroendocrine and psychoneuroimmune pathways from childhood adversity to disease

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ABSTRACT

Childhood adversity has been repeatedly and robustly linked to physical and mental illness across the lifespan. Yet, the biological pathways through which this occurs remain unclear. Functioning of the inflammatory arm of the immune system and the hypothalamic-pituitary-adrenal (HPA)-axis are both hypothesized pathways through which childhood adversity leads to disease. This review provides a novel developmental framework for examining the role of adversity type and timing in inflammatory and HPA-axis functioning. In particular, we identify elements of childhood adversity that are salient to the developing organism: physical threat, disrupted caregiving, and unpredictable environmental conditions. We propose that existing, well-characterized animal models may be useful in differentiating the effects of these adversity elements and review both the animal and human literature that supports these ideas. To support these hypotheses, we also provide a detailed description of the development and structure of both the HPA-axis and the inflammatory arm of the immune system, as well as recent methodological advances in their measurement. Recommendations for future basic, developmental, translational, and clinical research are discussed.

1. Introduction

Childhood adversity is a robust risk factor for mental and physical illness (Chapman et al., 2004; Felitti et al., 1998) as well as earlier mortality (Chen et al., 2016). Our understanding of *how* child adversity becomes embedded in biological systems to perpetuate this risk remains limited and would benefit from examination of the potentially distinct consequences of different forms of adversity within a sophisticated developmental framework. Childhood adversity is associated with alterations to the body's physiological stress response systems, including the hypothalamic-pituitary-adrenal axis (HPA-axis) (Gunnar and Quevedo, 2007; Heim and Nemeroff, 2001) and the inflammatory arm of the immune system (Carpenter et al., 2010; Danese et al., 2011; Danese et al., 2007; Slopen et al., 2013; Taylor et al., 2006). Intermediate phenotypes comprised of upregulations in these systems are thought to be central to the pathogenesis of stress-related illness (McEwen, 2013). In particular, the disease risk phenotype includes elevated glucocorticoids and inflammation, yet there are several physiological pathways through which this phenotype can emerge. Notably, the HPA-axis and inflammatory arm of the immune system respond and habituate differently to various types of stressors (Bowers et al., 2008; Kant et al., 1985; Kuhlman et al., 2014; Pacák, 1999; Pacák et al., 1998, 1995; Sheridan and McLaughlin, 2014; Weiner, 1992). Thus, it is possible that subtypes of childhood adversity have distinct physiological pathways that elucidate developmental origins of disease. An emerging literature also suggests childhood trauma exposure during specific phases of development is important to later neurobiological functioning (Andersen et al., 2008; Cowell et al., 2015; Gee and Casey, 2015; Kuhlman et al., 2015a,b), and is critical to our understanding of how biological systems develop under conditions of threat and adversity. To date, the association between adversity and health has predominantly been tested as a dose-response relationship (e.g., Anda et al., 2006; Chapman et al., 2007; Evans et al., 2013; Kessler et al., 2010). This approach limits what we know to the overlap between heterogeneous adversity exposure (See Fig. 1), and few studies have considered the role of timing, thus limiting our understanding in the context of human development. Clarifying these gaps in the literature has the potential to inform developmentally-sensitive prevention and intervention strategies that mitigate the negative health sequelae of child adversity exposure across the lifespan.

The purpose of this review is to propose a framework examining adversity type and timing as key distinctions to be made in the link

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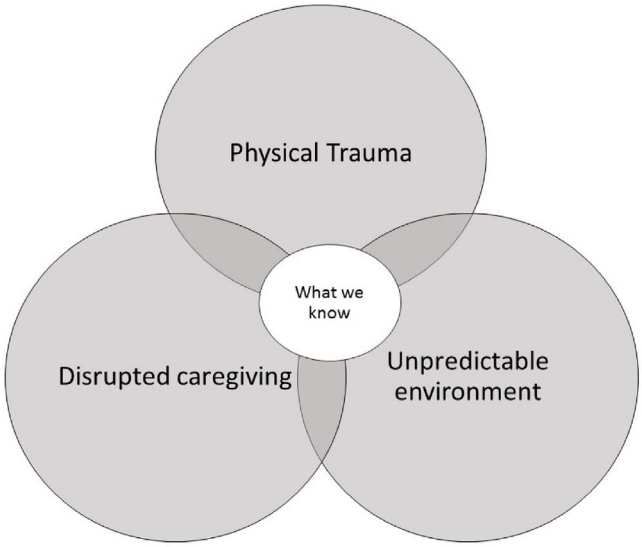

Fig. 1. Dose-response models of childhood adversity limit what we know.
Predominant dose-response models of childhood adversity exposure have limited our understanding of the peripheral biological consequences of childhood adversity to the overlap between different elements of stressful experiences.

between childhood adversity and lifespan health via alterations to HPA-axis and inflammatory processes during development. To do this, we first provide a basic conceptual framework for HPA-axis and inflammatory stress physiology and their measurement within psychology and psychiatry research. Comprehensive reviews of these systems can be found elsewhere (Black, 2002; Danese and Lewis, 2017; Irwin and Cole, 2011; Weiner, 1992). We then examine three commonly represented elements of adverse childhood experiences, the "biological salience" of these elements, and their potentially distinct physiological consequences. We define biological salience as the component of an adverse experience that is relevant to the organism's successful survival from or adaptation to that stressor. The biologically salient and distinguishable elements of adversity we identify are: physical trauma, disrupted caregiving, and unpredictable environment. The shortage of causal experimental models has been a barrier to understanding type and timing as important factors in physiological and health consequences that accompany childhood adversity exposure. For this reason we identify a candidate animal model that may provide a useful framework for examining health-relevant physiological consequences to each of these biologically salient elements of adversity. We then review the development of the HPA-axis and inflammatory systems with an emphasis on the limited research examining potential periods of sensitivity to adversity exposure. Finally, because translation of rodent models to human experience is inherently limited, we propose implications and future directions for both animal and human research to investigate the distinct physiological pathways from subtypes of childhood adversity to the intermediate phenotype associated with disease.

2. HPA-axis and inflammatory physiology: concepts and measurement

We focus on the associations between childhood adversity and two peripheral biological systems (HPA-axis and inflammation) that are linked to physical and mental health, have been linked to childhood adversity, can be measured non-invasively in pediatric populations, and can also be measured in ambulatory settings that demonstrate high ecological validity. Coordination of the sympathetic nervous system (SNS), HPA-axis, and the inflammatory arm of the immune system, particularly in response to acute stress, is essential to development, survival, and well-being (Gunnar and Quevedo, 2007; Chrousos, 1995; Gunnar and Quevedo, 2007,b; Lopez-Duran et al., 2009a,b). Under circumstances of acute threat, both the HPA-axis and immune system are activated. See Fig. 2 for an illustration of the coordinated HPA-axis and inflammatory response to stress.

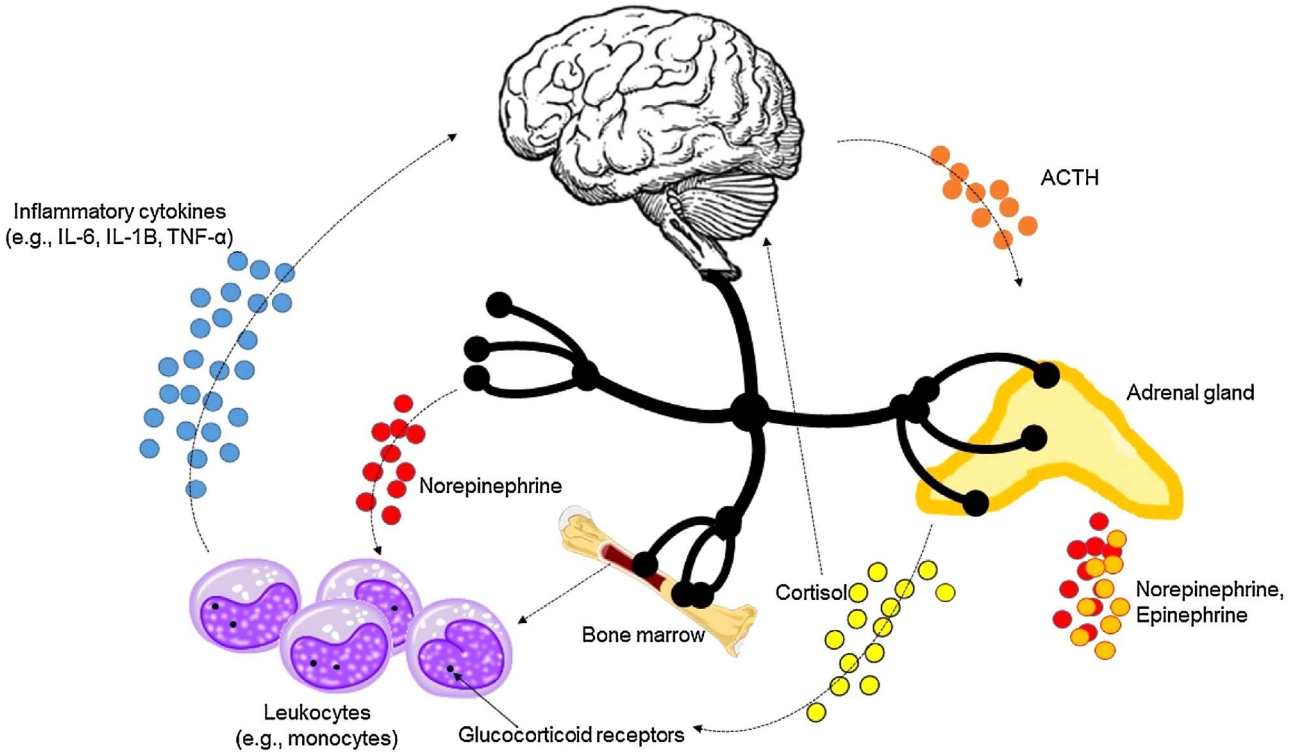

Fig. 2. Coordinated hypothalamic-pituitary-adrenal axis (HPA-axis) and inflammatory response to stress.