Neurotoxicology and Teratology xxx (xxxx) xxx–xxx

Contents lists available at ScienceDirect

Neurotoxicology and Teratology

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

Review article

Adaptation or pathology? The role of prenatal stressor type and intensity in the developmental programing of adult phenotype

Sophie St-Cyr[a], Patrick O. McGowan[a,b,c,*]

[a] Department of Biological Sciences and Center for Environmental Epigenetics and Development, Department of Cell and Systems Biology, University of Toronto, Scarborough Campus, 1265 Military Trail, Toronto, ON, Canada
[b] Department of Psychology, University of Toronto, Toronto, ON, Canada
[c] Department of Physiology, University of Toronto, Toronto, ON, Canada

ARTICLE INFO

Keywords:
Epigenetics
Prenatal stress
Predator threat
Hypothalamic-pituitary-adrenal axis
Developmental origins of health and disease
Predictive Adaptive Response

ABSTRACT

The mother is the major interface between the offspring and its prenatal environment. Prenatal toxins and stress-inducing physical agents are important factors programming the developmental trajectory of mammals that likely involve epigenetic modifications. However, prenatal stressors commonly-used in the laboratory (e.g. prenatal restraint stress and prenatal chronic variable stress) are typically administered at high intensities. These exposures typically lead to pathological phenotypes supporting the development origin of health and disease hypothesis. In this review, we compare the phenotypic outcomes of these commonly-used prenatal stressors to an ecologically-relevant, psychogenic stressor that has been present over evolutionary times, predator or predator cues presence. Prenatal stress by predator threat results in behavioral, physiological, endocrine, transcript abundance and epigenetic (DNA methylation) modifications. These phenotypic modifications are consistent with developmental forecasting according to the Predictive Adaptive Response hypothesis, yielding adaptive responses in environments where such predation stress is present. The evidence described in this review suggests that the type of prenatal stress agent and its intensity modifies the phenotype expressed, which can range from adaptive to pathological. Prenatal Bisphenol A exposure studies are presented as an example where graded intensities (concentrations) of prenatal toxin exposure can be compared directly. Finally, we emphasize the importance of studying both sexes in these studies, as sex differences appear to be a common feature of the response to prenatal stress.

1. Introduction

The mother constitutes the prenatal environment of her offspring and is the major interface between the fetus and the external environment. The mother's experiences during pregnancy are therefore significant factors that can modify the developmental health trajectory of her offspring. For example, information about the external environment can be transduced by changes in maternal physiology, including maternal levels of circulating glucocorticoids (Koehl et al., 1999; Morley-Fletcher et al., 2003). These early life factors play an important role in shaping the long-term phenotype of an individual (Kim et al., 2015; Kundakovic and Jaric, 2017; Love et al., 2013). It is well documented that multiple pharmacological substances (e.g. serotonin reuptake inhibitor antidepressants), diets (e.g. high-fat or low-protein diet), toxins (e.g. Bisphenol A [BPA], fungicide Vinclozolin), and physical stressors (e.g. prenatal restraint stress [PRS], prenatal chronic variable stress [PCVS]) exposure during the perinatal period leads to the expression of behaviors and associated neurophysiological changes characteristic of neuropsychiatric disorders (Clement et al., 2011; Erhuma et al., 2007; Kundakovic et al., 2013; Morley-Fletcher et al., 2003; Mueller and Bale, 2008; Pawluski et al., 2012; Sasaki et al., 2013).

Prenatal programming agents are typically examined in relation to their negative health impact or pathological outcome on offspring phenotype (Kim et al., 2015). However, their effects are often examined

Abbreviations: 11β-HSD, 11β-hydroxysteroid dehydrogenase; ACTH, adrenocorticotropic hormone; AVP, arginine vasopressin; BNST, bed nucleus of the stria terminalis; BPA, bisphenol A; CBG, corticosteroid-binding globulin; CORT, corticosterone; CRF, Corticotropin-Releasing Factor; CVS, chronic variable stress; DOHaD, Developmental Origin of Health and Disease; FKBP5, FK506 binding protein 5; GD, gestational day; HPA axis, Hypothalamic-pituitary adrenal axis; mPFC, medial prefrontal cortex; NR3C1, glucocorticoid receptor; PAR, Predictive Adaptive Response; PCVS, prenatal chronic variable stress; PN, postnatal day; PO, prenatal predator odor; PRS, prenatal restraint stress; POMC, proopiomelanonortin; PTSD, post-traumatic stress disorder; PVN, paraventricular nucleus of the hypothalamus; TMT, 2,3,5-trimethyl-3-thiazoline

* Corresponding author at: Department of Biological Sciences and Center for Environmental Epigenetics and Development, Department of Cell and Systems Biology, University of Toronto, Scarborough Campus, 1265 Military Trail, Toronto, ON M1C1A4, Canada.
E-mail address: patrick.mcgowan@utoronto.ca (P.O. McGowan).

https://doi.org/10.1016/j.ntt.2017.12.003
Received 9 August 2017; Received in revised form 25 October 2017; Accepted 4 December 2017

using agents that are administered at a high intensity or concentration in experimental settings, often outside of the normal physiological range or recommended doses. While this approach may be understandable and even preferable at an initial stage of research, there is evidence that those same stressors given within a physiological range or tolerable intensity can mediate different, potentially adaptive, long-term programming effects.

In this review, we will discuss the graded offspring phenotypic response that can be elicited by different stressor intensities or toxin concentrations. In some instances, the same toxin has been investigated at different concentrations. Evidence presented in this review suggests that the phenotypic response to prenatal stress is graded by its nature and is contingent upon the concentration or intensity of the insult.

We first present the hypotheses that have been suggested to explain the mechanisms by which the early life milieu can influence the development of long-term phenotypic changes followed by an overview of some targets of this early life programming. We then describe the phenotypic impacts to exposure to well-studied and commonly-used prenatal stressors, PRS and PCVS exposure. We then present a case study in which exposure to variable concentrations of prenatal BPA leads to differential offspring phenotype. Finally, we contrast the effects of exposure to a naturalistic prenatal stress, prenatal predator, to exposure to well-studied and commonly-used prenatal stressors. We suggest that high intensity prenatal stress typically leads to pathological outcomes while these effects could be adaptive under some circumstances when they are applied within a physiological range relevant to the animal's evolutionary history.

The naturalistic prenatal stressor presented here is predator cue exposure, with a particular emphasis on predator odors. In contrast to the commonly-used physical stressors, this type of stress elicits a robust innate response that does not habituate over a wide range of concentrations (Blanchard et al., 2003; Wallace and Rosen, 2000). Mild stressor effects can be potentiated in the case where it is novel, unpredictable, uncertain and uncontrollable (Cabib, 1997). Further, predator odors have been investigated as a repellent to protect crops against browsing damage (Apfelbach et al., 2005; Lindgren et al., 1995; Rosell, 2001; Sullivan et al., 1985). However, high intensities of this stressor have been associated in adult animals with symptoms associated with post-traumatic stress disorder (PTSD; Zoladz et al., 2008) but can lead to fetal resorption when presented to pregnant animals (St-Cyr and McGowan, 2015). Predation stress and predator cues are therefore ecologically- and evolutionary-relevant stressors to which prey species are sensitive, even at low intensities.

1.1. Description of the early life programming hypotheses

The ‘Thrifty phenotype’ hypothesis was proposed by Hales and Barker (1992). This hypothesis states that predisposition to type 2 diabetes is determined through the energetic availability during early human development. More broadly, energy restriction in utero leads to a growth restriction through an energy allocation trade-off in which vital organs development is prioritized over tissue development. This trade-off leads to an irreversible change in the developmental trajectory of the individual. This prenatal condition can be detected through low birth weight and, later, by raised blood pressure and increased insulin resistance in adulthood.

These long-term modifications linked to low birth weight were later described as the metabolic syndrome, including changes in growth, metabolism and vasculature. The original developmental origins of health and disease (DOHaD) hypothesis linked lower birth weight with a subsequent increase in the appearance of cardiovascular disease (hypertension) in adulthood (Barker et al., 1990, 1993). The DOHaD hypothesis has later suggested that early life energy deprivation modifies the life-long functional capacity of organs (e.g. liver). These changes during development predispose individuals to develop hypertension, insulin resistance and increased stress response (as detected through increased blood glucocorticoid and adrenocorticotropic hormone [ACTH]) (Hales and Barker, 2001; Phillips et al., 2000; Reynolds, 2001). The metabolic syndrome describes the impacts of early life events on the developmental trajectory of the individual, predicting inflammation and increased risk of developing obesity in preadolescent years (Gluckman and Hanson, 2006). Therefore, the DOHaD hypothesis can be described as prioritizing fetal growth when energy availability is scarce to maximize immediate survival at birth, with the consequence of decreased health later in life.

New evidence indicates that early energetic deprivation confers an advantage later in life by increasing energy conservation and reducing somatic growth in poor nutritional environments (Youngson and Whitelaw, 2008), which can confer increased longevity (Ozanne and Hales, 2004) in this type of environment. Incidentally, in human populations exposed to famine, a baby with increased birth weight raises 9-fold the risk of developing rickets, a disease associated to severe malnutrition (Chali et al., 1998). Larger babies are more likely to exceed the energetic resources provided by their mother, with a consequent net energetic insufficiency. These observations suggest that the thrifty phenotype could be adaptive in a deprived thrifty postnatal environment and maximize the immediate offspring fitness. Conversely, a thrifty phenotype would be inappropriate in an environment where energy is abundant and available and would induce obesity or insulin resistance. This observation introduced the concept of the importance of a similar and stable prenatal and postnatal environment for efficient maternal programming, through reliable maternal cues.

The Predictive Adaptive Response (PAR) hypothesis is an extension of the mismatch hypothesis proposed by Bateson and Gluckman (2011) stating that developmental forecasting determines the developmental trajectory of the individual. Cues from the early life would therefore influence the development of a phenotype appropriate to the predicted later life environment while maximizing the offspring fitness. However, a mismatch with the predicted environment would lead to adverse health and fitness effects. This hypothesis also predicts that developmental plasticity happens in response to an adaptive range of cues and signals, while producing non-adaptive outcomes in response to a novel or extreme insult (Bateson et al., 2014). Contrary to the DOHaD hypothesis, which produces two distinct phenotypes, the PAR hypothesis predicts graded phenotypic changes. Further, the PAR hypothesis explains the adverse effects described in the thrifty hypothesis as by-products of the evolutionary recent raise in human longevity and emergence of the westernized diet rich in carbohydrate and fat (Bateson et al., 2014), therefore increasing the probability of long-term mismatched environments. The major implication of this mismatch is that the ‘adaptive’ trade-off traits triggered prenatally by maternal cues leads to adverse outcomes in the long run.

Permanent programming of the fetus through maternal influence can happen through long-lasting epigenetic alterations of the fetus, a phenomenon called maternal programming. Epigenetic programming has been suggested to mediate offspring phenotypic plasticity described in the DOHaD and PAR hypotheses (Bateson et al., 2014; Gluckman and Hanson, 2006). Epigenetic inheritance could optimally transmit the PARs by propagating a well-adapted phenotype in a specific environment within a population until genetic fixation occurs (Bateson et al., 2014). Epigenetic inheritance would also allow species to survive short-term environmental challenges while preserving maximal genotypic variation. This topic will be addressed in Sections 4 to 7 in the context of naturalistic and commonly-used prenatal stressors.

2. Hypothalamic-pituitary adrenal axis

The endocrine response to stress is mediated through the HPA axis from minutes to hours following the stress onset via glucocorticoid signaling. Upon stress exposure, the Corticotropin-Releasing Factor (CRF) and arginine vasopressin (AVP) are released by the paraventricular nucleus of the hypothalamus (PVN) and, acting