Neuroscience and Biobehavioral Reviews 33 (2009) 191–203

Contents lists available at ScienceDirect

Neuroscience and Biobehavioral Reviews

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

Review

Long-term effects of prenatal stress: Changes in adult cardiovascular regulation and sensitivity to stress

Francesca Mastorci [a], Massimo Vicentini [a], Odile Viltart [b], Massimo Manghi [a], Gallia Graiani [c], Federico Quaini [c], Peter Meerlo [d], Eugene Nalivaiko [e], Stefania Maccari [f], Andrea Sgoifo [a,*]

[a] Stress Physiology Laboratory, Department of Evolutionary and Functional Biology, University of Parma, Via Usberti 11/a, 43100 Parma, Italy
[b] NeuroImmunoEndocrinology Laboratory, Pasteur Institute of Lille, France
[c] Department of Internal Medicine, University of Parma, Italy
[d] Department of Molecular Neurobiology, University of Groningen, Haren, The Netherlands
[e] Neurocardiology Laboratory, School of Biomedical Sciences, University of Newcastle, Australia
[f] Perinatal Stress Team, University of Lille 1, Villeneuve d'Ascq, France

ARTICLE INFO

Keywords:
Prenatal stress
Intrauterine growth restriction
Restraint
Radiotelemetry
Sympathetic and parasympathetic nervous system
Hypothalamic-pituitary-adrenocortical axis
Glucocorticoids
Renin–angiotensin system
Heart rate
Heart rate variability
Blood pressure
Circadian rhythms
Adrenals
Hypertension
Myocardial fibrosis

ABSTRACT

Prenatal environment exerts profound influences on the development of an organism and stressful events during pregnancy can bring about long-term physiological/behavioral alterations in the offspring. Epidemiological evidence points to a relationship between intrauterine growth restriction (IUGR), body weight at birth, and adult cardiovascular disease. Experimental research employed different models of IUGR, including altered maternal nutrition, exposure to elevated glucocorticoids, and reduced placental perfusion, all of which can program, when acting during sensitive temporal windows of foetal life, alterations in cardiovascular regulation and stress sensitivity. Original data are presented indicating that prenatal psychological stress (intermittent restraint) does not induce in the rat adult offspring changes of plasma corticosterone levels, cardiac autonomic modulation, and circadian rhythmicity of heart rate (HR), body temperature (*T*) and physical activity (Act) at rest. However, prenatally stressed rats – when further stimulated in adulthood – exhibit prolonged adrenocortical stress responsivity, disturbed circadian rhythmicity of HR, *T*, and Act, and increased adrenal weight. This evidence supports the idea that prenatal stress *per se* does not change dramatically a given structure or function, but it affects resilience and renders the animal more susceptible to pathophysiological outcomes when further insults occur during adulthood.

Contents

* Corresponding author. Tel.: +39 0521 905625; fax: +39 0521 905673.
E-mail address: andrea.sgoifo@unipr.it (A. Sgoifo).

0149-7634/$ – see front matter © 2008 Elsevier Ltd. All rights reserved.
doi:10.1016/j.neubiorev.2008.08.001

1. Introduction

Cardiovascular diseases such as hypertension and ischemic cardiomyopathy are the leading causes of death in western countries (Wilson et al., 1998). Smoking, exposure to tobacco smoke, lack of physical activity, obesity, high cholesterol or abnormal blood lipids, diabetes and emotional stress are well recognized risk factors for cardiovascular morbidity and mortality (Khot et al., 2003). Although it has been clearly shown that some individuals are genetically prone to develop cardiovascular diseases, genetic background does not seem to account for all pathophysiological outcomes. More recently, a growing body of literature underlined the role of an additional risk factor: prenatal programming. Programming results from adaptive changes in gene expression patterns that occur in response to stressors leading to altered growth of specific organs and systems during their most critical time of development (Barker, 1998b). Indeed, prenatal environment exerts profound influences on the development of an organism and stressful events during pregnancy can induce alterations in the foetal environment resulting in early and long-term structural and functional consequences (Maccari et al., 2003; Wadhwa et al., 2001; Weinstock, 1997, 2001). The nature and severity of prenatal stress effects seem to be influenced by the timing of the stressors intervening during gestation. In fact, a large number of scientific reports support the idea that prenatal development is characterized by sensitive periods or developmental windows when organisms are more vulnerable to stressors (Rice and Barone, 2000; Seckl, 1998; Symonds et al., 2007). Human studies reveal that offspring from mothers that suffered from adverse conditions during their first trimester display modest effects, while babies whose mothers were exposed to stress during the third trimester exhibit long-lasting consequences such as low birth weight, heart malformations, hearing loss, and skeletal abnormalities (Talge et al., 2007). In spite of the wealth of literature on the short- and long-term neuronal, neuroendocrine and behavioral consequences of prenatal stress in humans and animals, there is less information regarding the effects of stressors occurring during pregnancy on the adult cardiovascular system. Providing current update for this issue is the major aim of our review.

Firstly, we summarize the evidence for neuroendocrine and behavioral consequences of prenatal stressors, features which have been widely described in the literature; this part is deliberately concise and refers to the special issue "Prenatal programming of behaviour, physiology and cognition" (vol. 29, number 2, pp. 207–384, 2005) of Neuroscience & Biobehavioral Reviews for an exhaustive view on the topic. Then, the review briefly lists different animal models of prenatal stress, with special emphasis on those non-human primate and rodent models which have been used to study long-term cardiovascular implications. Afterwards, the effects of prenatal stress on cardiovascular function and structure are thoroughly reviewed, with reference to epidemiological evidence, the role of the sympathetic-adrenomedullary and renin–angiotensin systems, and the two major approaches to the study of the relationship between adverse prenatal environment and cardiovascular (patho)physiology. Finally, original experimental results from our laboratory are presented, where cardiac, autonomic, and neuroendocrine parameters were collected altogether, in adult rats born to mothers which were exposed to repeated restraint stress during pregnancy

2. Animal models of prenatal stress

Animal models have been widely used to investigate the relationship between adverse environment during foetal life and vulnerability to psychosomatic/psychological disorders in adulthood, as they offer the opportunity to separate the role of prenatal stress from other morbidity risk factors. In addition, animal models allow to focus on specific periods of pregnancy and to highlight the different impact of a stressor according to differences in foetal age.

2.1. Primate models

Although most prenatal stress studies have been conducted in rodents, non-human primate models are particularly valuable because of their slow-paced foetal growth rates, long gestations, enriched placental nourishment, and single births (Newell-Morris and Fahrenbruch, 1985). An example of prenatal manipulation in non-human primates involves removing pregnant monkeys from their cages and subsequently exposing them to uncontrollable noise burst. In a study by Clarke et al. (1994) on rhesus monkeys this manipulation was applied once per day, 5 days a week, for 25% of gestation period. Another type of prenatal stress manipulation in non-human primates involves injecting pregnant females with the synthetic glucocorticoid analog dexamethasone, usually during the fourth month postconception of their 5.5-month-long gestation (Coe and Lubach, 2005; Uno et al., 1990).

2.2. Rodent models

Among rodents, guinea pigs represent a valid animal model given that the landmarks of brain and neuroendocrine growth are well characterized in this species (Dobbing and Sands, 1970). They were used to explore the long-term brain, endocrine, autonomic, and behavioral effects in the offpsring born to pregnant females which were exposed to unstable social environment (Kaiser and Sachser, 1998), strobe light (Kapoor and Matthews, 2005), or synthetic glucocorticoids (Banjanin et al., 2004).