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Review article

Long-term consequences of prenatal stress and neurotoxicants exposure on neurodevelopment

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ABSTRACT

There is a large consensus that the prenatal environment determines the susceptibility to pathological conditions later in life. The hypothesis most widely accepted is that exposure to insults inducing adverse conditions *in-utero* may have negative effects on the development of target organs, disrupting homeostasis and increasing the risk of diseases at adulthood. Several models have been proposed to investigate the fetal origins of adult diseases, but although these approaches hold true for almost all diseases, particular attention has been focused on disorders related to the central nervous system, since the brain is particularly sensitive to alterations of the microenvironment during early development. Neurobiological disorders can be broadly divided into developmental, neurodegenerative and neuropsychiatric disorders. Even though most of these diseases share genetic risk factors, the onset of the disorders cannot be explained solely by inheritance. Therefore, current understanding presumes that the interactions of environmental input, may lead to different disorders. Among the insults that can play a direct or indirect role in the development of neurobiological disorders are stress, infections, drug abuse, and environmental contaminants. Our laboratories have been involved in the study of the neurobiological impact of gestational stress on the offspring (Dr. Antonelli's lab) and on the effect of gestational exposure to toxicants, mainly methyl mercury (MeHg) and perfluorinated compounds (PFCs) (Dr. Ceccatelli's lab). In this focused review, we will review the specialized literature but we will concentrate mostly on our own work on the long term neurodevelopmental consequences of gestational exposure to stress and neurotoxicants.

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1. Introduction

There is nowadays little doubt that early life exposure to a variety of environmental influences is critical for later susceptibility to diseases. Early life is often referred as both the gestational period, during which the fetus is exposed to different environmental constituents, as much as the postnatal period which is also crucial in rendering a susceptible individual. The hypothesis most widely accepted is that the exposure to different influences during *in-utero* and/or postnatal stages of life affects the development of target organs, disrupting the homeostasis and increasing the risk of adult diseases.

Several models have been proposed but most of them stem in Barker's hypothesis of Fetal Basis of Adult Diseases (FeBAD) based on their studies on adult cardiovascular diseases. Barker's hypothesis fits well with almost all diseases and it suggests that the fetus responds to the maternal health status and shows adaptive responses for survival. Later, Gluckman and Hanson suggested that the fetus predicts the extra-uterine environment according to intrauterine conditions, making changes for its better survival. This model was named PAR for Predictive Adaptive Response. An extension of these models was later introduced as the DOHaD (Developmental Origin of Health and Disease) by Gluckman postulating that the postnatal period of development also plays a role in health. A more elaborate vision of this model have been put forward by Van den Bergh who proposes the "Developmental Origins of Behavior, Health and Disease" (DOBHaD) hypothesis that integrates early brain and behavioral development with new insights from the field of epigenetics. The DOBHaD hypothesis opens new perspectives on the prevention of diseases by detecting them before they start to develop, based on the working hypothesis of Ben-Ari (2008), who proposes that early- and late-onset neurological disorders might be, in part, born at early developmental stages before symptoms appear. The core of this working hypothesis is that imaging or non-invasive recordings might unravel signatures of disorders to come, thereby permitting earlier diagnosis and potential treatment of neurological disorders. Therefore, Van den Bergh observes that rather than treating symptoms, there should be an initial appreciation of the disturbed intrinsic and extrinsic factors of the developmental process that will guide the understanding of the nature of the illness and its future treatment.

Lahiri and collaborators described a model termed LEARn (Latent Early life Associated Regulation) in which each of the environmental exposures are considered "hits" acting through induced latent epigenetic changes (Lahiri et al., 2009). According to this model, disorders develop according to an "n" number of hits. The first hit is the early environmental exposure that leads to epigenetic perturbations, and after a long latency period, a second trigger is necessary for the disease to develop.

The importance of these models is revealed by Hertzman (1999) who broadens the approach suggesting that early child development is also influenced by the socioeconomic and psychosocial environment of childhood that will eventually be linked to adult health status. This process has been termed "biological embedding" and has been more recently up-dated to include the epigenetic changes that occur early in life and affect behavior and physiology (Danese and McEwen, 2012; McEwen, 2015). Although these models hold true for almost all diseases, particular attention has been focused on disorders related to the central nervous system since brain sculpting is related to the conditioning of the host defense system that depends on communication with the developing brain (Hertzman, 1999).

The brain is particularly sensitive to alterations of the perinatal microenvironment during early development, although the consequences of prenatal damage may not necessarily be apparent until a critical age when neurodevelopmental defects may be unmasked or precipitated by a subsequent exposure to other insults.The development of the nervous system is a very complex process characterized by stages reached according to a tightly regulated program. Essential processes like cell proliferation, migration and differentiation occur at well-coordinated time points to ensure the establishment of normal brain structure and functions (Andersen, 2003). This arrangement of developmental processes results in different windows of susceptibility towards insults.

Neurobiological disorders can be broadly divided into:

a) Developmental disorders, such as autism spectrum and attention deficit disorders, usually manifested in childhood.
b) Neuropsychiatric disorders, such as bipolar disorder and schizophrenia, most typically appear in adolescence and early childhood.
c) Neurodegenerative disorders, such as Alzheimer's disease (AD), Parkinson's disease (PD) usually appear late in life and are characterized by progressive loss of synaptic markers eventually resulting in dementia.
d) Other disorders including major depressive disorders (MDD), substance abuse disorder and anxiety disorders, which onset present a broad range of age and lifestyle.

Most of these diseases share genetic risk factors but the onset of the disorders cannot be explained solely by inheritance. Therefore, current understanding presumes that the interactions of multiple agents, including environmental input, leads to a disorder.Among the different environmental agents that can play a direct or indirect role in the development of neurobiological disorders are food, metals, pesticides, stress, infections and drugs of abuse. A revision of these different agents and its influence on neurodegenerative disorders can be found in Modgil et al.(2014).

In this review, we will concentrate our efforts in reviewing the existing literature but mostly our own work on the long term neurobiological consequences of gestational exposure to stress and toxicants.

2. Prenatal exposure to stress

2.1. Stress definition and mechanisms

The concept of stress has been thoroughly revised in the literature since it was originally defined by Selye (1950) as the "non-specific response of the body to any noxious stimulus". Later,