



Review

Prenatal stress and the programming of the HPA axis

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ABSTRACT

There are several independent prospective studies showing that a wide variety of forms of prenatal stress can have long-term effects on the behavioural and cognitive outcome for the child. Animal studies have shown that prenatal stress, as well as affecting behaviour, can also reprogram the function of the HPA axis in the offspring. However, the effects on the HPA axis are very variable depending on the nature of the stress, its timing in gestation, the genetic strain of the animal, the sex and age of the offspring and whether basal or stimulated HPA axis responses are studied. There are also several recent studies showing long-term effects of prenatal stress on basal cortisol levels, or cortisol responses to stress, in humans. The designs of these studies differ considerably, many are small, and the effects on outcome are also varied. There is little evidence, so far, that altered function of the HPA axis in the child mediates the behavioural or cognitive alterations observed to be associated with prenatal stress.

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1. Introduction

Fetal programming describes the process whereby the development of a fetus is altered because of changes in its immediate environment. The effects can vary at different sensitive periods and can shape the structure and function of the brain and peripheral organ systems, with long-term or permanent effects on subsequent child and adult physiology, behaviour and health. Many studies in animals have shown that prenatal stress can have such programming effects on both neurodevelopment and the function of the hypothalamic-pituitary-adrenal (HPA) axis. In humans also there is an increasing number of prospective studies showing that various forms of prenatal stress are associated with a range of later behavioural and cognitive alterations in the child, and some limited evidence for associations with alterations in the HPA axis. It

has been suggested that these fetal adaptations may have been of evolutionary value, in order to confer characteristics in the offspring that were adaptive in the context of the stressful environments in which they were developing and presumably would subsequently live in (Viltart and Vanbesien-Mailliot, 2007). However, for humans in the modern world, there may often be a mismatch between characteristics of the early environment during development and subsequent environment during later stages of life. This, in turn, may result in maladaptive properties in the context of a different environment, with direct implications for increasing vulnerability for pathophysiological health outcomes (Gluckman et al., 2005).

2. Prenatal stress and programming the HPA axis-animal studies

It has been known for over five decades from animal studies that maternal stress during pregnancy can have a range of long-term effect on the offspring (Weinstock, 2001). These include

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learning deficits, more anxious behaviour, reduced attention, altered immune function, as well as altered cardiovascular responses to stress (Igosheva et al., 2007) and glucose intolerance (Lesage et al., 2004). These effects are clearly different in male and female offspring (Darnaudery and Maccari, 2008). With animals it is possible to cross-foster the prenatally stressed pups to control mothers after birth, or nursery rear in the case of monkeys (Schneider et al., 2002), and thus establish that the origin of these effects are prenatal rather than postnatal.

In the animal work much research has shown how prenatal stress can alter the function of the HPA axis in the offspring. These effects have been found in a range of species. Variation in the responsiveness of the HPA axis plays an adaptive role, and it is plausible that the prenatal reprogramming has evolutionary significance and is part of the predictive adaptive response (Love and Williams, 2008). Weinstock (2005, 2008) has reviewed this comprehensively for the rodent. She discusses the variability in results and the many parameters that may affect this: the nature and the timing of the stress exposure during pregnancy, the age of testing of the offspring, the genetic strain of rat or mouse used, the sex of the offspring, the time of day of testing the offspring HPA axis, and whether basal or stress-induced corticosterone levels were measured. Despite the variability many of the studies have found that prenatal stress did cause both an increase in basal levels and an increase in corticosterone response in the offspring. However, several others showed a decrease in the corticosterone stress response, and others still showed no change. She concludes that to have an effect the prenatal stress needs to be of sufficient intensity, be administered daily in the last week of gestation, and that female offspring are more sensitive than males. Different rat strains appear to respond in different ways. There has been little study of whether the changes in the function of the HPA axis underlie the behavioural changes induced by prenatal stress, although both have been shown to occur in the same model (Abe et al., 2007).

Animal studies have also identified brain structures altered by prenatal stress. For example, Coe et al. (2003), studying non-human primates, have shown that exposure to unpredictable noise, either early or late in pregnancy, resulted in reduced volume of the hippocampus in the offspring. This is a part of the brain that is important both for memory and the control of the HPA axis. In rodents prenatal stress has been shown to reduce the number of both glucocorticoid and mineralocorticoid receptors in the hippocampus (Henry et al., 1994). This could explain why the corticosterone response to a new stressor is both increased and prolonged: there is less feedback inhibition via corticosterone acting on its receptors.

Another finding in the animal research is that programming effects can last until the grandchild generation. In one experiment in which the pregnant female was treated with dexamethasone, reduced birthweight and glucose intolerance were transmitted to the second generation by both the first generation female and male offspring (Drake et al., 2005). This suggests the possibility that epigenetic changes can affect both oocyte and sperm.

Rodent experiments have shown that the effects of prenatal stress may be moderated and even reversed by positive postnatal rearing (Maccari et al., 1995). This indicates that although there can be persisting effects of prenatal stress, it is not inevitable, and that the period of sensitivity or programming extends beyond the prenatal period. Meaney and his group have shown how variation in the nature of maternal care can have long lasting effects on both the behaviour and function of the HPA axis of the offspring. Offspring of mothers showing more maternal care are both less anxious and have a less pronounced corticosterone response to a new stressor (Liu et al., 1997). This group is also uncovering some of the epigenetic changes in the brain, altered methylation in the

promoter region of the glucocorticoid receptor in the hippocampus, which underlie this (Weaver et al., 2004).

Although many of the same mechanisms may well occur in humans we need to be aware that there are obviously many physiological and other differences between humans and animal models. For example, rodents are born at a much less developed stage than humans. There are differences in the nature and regulation of maternal–placental–fetal neuroendocrine processes underlying development and birth across mammals, even between non-human primates and humans (Smith and Nicholson, 2007). Nevertheless, and despite the caveats about the animal findings cited above, animal experiments have provided strong evidence that prenatal stress can have long lasting and varied effects on the offspring, including the function of the HPA axis.

3. Prenatal stress: human studies

An immediate link between prenatal maternal mood and fetal behaviour is well established from 27 to 28 weeks of pregnancy onwards (Van Den Bergh et al., 2005). The mechanisms underlying this link are not known.

In the last 10 years several independent prospective studies have examined the longer lasting effects of prenatal stress, anxiety or depression on the behavioural, emotional and cognitive outcomes during childhood. Even though these studies used a wide range of different methods, both for measuring prenatal stress or anxiety, and for assessing the child, they all support a link between prenatal mood and changes in outcome that suggest changes in neurodevelopment (Van Den Bergh et al., 2005). Different studies have examined the child at different ages, from newborn to adolescence. The newborn studies show effects that must be independent of postnatal experience; those with adolescents show the persistence of impairment (Van Den Bergh et al., 2005). In several studies these findings have been shown to be independent of potential confounding factors such as smoking or poverty, and also maternal postnatal depression and anxiety. This adds support to the effect being due to the prenatal environment, rather than genetic transmission—although no evidence directly testing the genetic mediation hypothesis has yet been presented. The studies are mainly from European and North America; none are from developing countries or countries at war, where one might predict that the effects would be even more marked.

A wide range of different outcomes have been found to be affected by prenatal stress. The most consistent adverse outcome is in symptoms of attention deficit hyperactivity disorder (ADHD) (Rodriguez and Bohlin, 2005; Van Den Bergh and Marcoen, 2004) but an increase in anxiety is also often observed (Van Den Bergh and Marcoen, 2004). Other studies have shown an effect of prenatal stress or anxiety on the cognitive development of the child, as assessed by scores on the Bayley Mental developmental Index (MDI) (Huizink et al., 2003) or language development (Laplante et al., 2004).

A recent study has shown that prenatal maternal stress, due to exposure to a Canadian Ice storm, during the fetal period of fingerprint development, in the second trimester, resulted in greater dermatoglyphic asymmetry in their children, especially in the face of greater maternal distress (King et al., 2009). This asymmetric pattern is also found in subjects with schizophrenia. The finding is of particular interest as the fingerprint pattern develops at the same time as the hippocampus, and may be a physical marker for altered development of this region, which is important in both cognition, and feedback control of the function of the HPA axis (Cottrell and Seckl, 2009).

A recent MRI study has shown that high pregnancy-specific anxiety in mid-gestation, but not later, is associated with

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