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BRAIN RESEARCH REVIEWS

Review

Fetal programming of hypothalamic–pituitary–adrenal (HPA) axis function and behavior by synthetic glucocorticoids

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ABSTRACT

Reduced fetal growth has been closely associated with an increased risk for the development of chronic disease in later life. Accumulating evidence indicates that fetal exposure to excess glucocorticoids represents a critical mechanism underlying this association. Approximately 7% of pregnant women are at risk of preterm delivery and these women are routinely treated with synthetic glucocorticoids (sGC) between 24 and 34 of weeks gestation to improve neonatal outcome. Animal studies have demonstrated that maternally administered sGC crosses the placenta, affecting fetal hypothalamic–pituitary–adrenal (HPA) development, resulting in changes in HPA axis function that persist throughout life. These changes appear to be modulated at the level of glucocorticoid receptors (GR) and mineralocorticoid receptors (MR) in the brain and pituitary. As the HPA axis interacts with many other physiological pathways, the changes in endocrine function are also sex-specific and age-dependent. Alterations in behavior, particularly locomotion, in animals exposed to sGC *in utero* have also been demonstrated. Consistent with the finding in animal models, emerging human data are indicating attention deficit-hyperactivity disorder (ADHD)-like symptoms in children exposed to repeated courses of sGC *in utero*. This behavioral phenotype is likely linked to alterations in dopamine (DA) signaling, suggesting that sGC are able to permanently modify or 'program' this system. Finally, it is emerging that changes in HPA axis function and behavior following antenatal exposure to sGC are transgenerational and likely involve epigenetic mechanisms. A comprehensive understanding of the acute and long-term impact of sGC exposure *in utero* is necessary to begin to develop recommendations and treatment options for pregnant women at risk of preterm delivery.

Contents

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1. Introduction

The ability of the early environment to modify HPA axis function in adulthood was described nearly 50 years ago (Levine, 1957). However, more recent human epidemiological evidence indicating that the fetal and early postnatal environment can influence susceptibility to later disease has rejuvenated the field (Barker et al., 2002). Such observational studies have revealed that low birth weight and increased cortisol levels in adulthood are associated with an increased risk for the development of cardiovascular disease and its associated risk factors, including hypertension, in adult life (Kajantie et al., 2005; Syddall et al., 2005). More recently, human studies have shown an association between altered maternal physiology, such as increased salivary cortisol levels during pregnancy and an increased incidence of behavioral problems in during childhood (King and Laplante, 2005; Laplante et al., 2004; O'Connor et al., 2003). As a result of these associations, it has been proposed that exposure to excess glucocorticoids *in utero* acts to 'program' the fetal HPA axis, permanently altering basal and stress-induced HPA axis activity and regulation in offspring throughout life. Indeed, fetal exposure to excess glucocorticoids can occur via a number of mechanisms such as maternal stress and maternal treatment with synthetic glucocorticoids (sGC). In this review, we will focus on the longitudinal effects of antenatal exposure to sGC on HPA axis function and related behaviors in fetuses and offspring. This is of clinical importance given the widespread use of sGC to treat women at risk of preterm delivery and perinatal death (Joseph et al., 2007; Roberts and Dalziel, 2006). sGC are highly effective in maturing the fetal lung in premature infants and, in doing so, reduce the incidence of respiratory distress in the newborn. We will also consider exciting, and somewhat concerning, emerging evidence indicating that the effects of antenatal sGC exposure are transgenerational. While the present review is focused on HPA axis activity and behavior following antenatal exposure to sGC, it is important to note that sGC exposure also likely impacts fetal renal and hepatic development and that these effects may directly alter susceptibility to the development of disease in later life (Hoppe et al., 2007; Nyirenda et al., 1998).

2. Clinical significance of antenatal sGC exposure

Preterm delivery occurs in approximately 7% of pregnancies in North America and results in approximately 75% of all neonatal deaths. In such cases, antenatal sGC therapy, administered between 24 and 34 weeks gestation, is highly effective in reducing the frequency of respiratory complications and perinatal death (Anonymous, 1995). In 1994, the NIH endorsed the use of maternal sGC therapy during pregnancy; (Anonymous, 1995) a similar approach has been adopted around the world. Due to difficulty in predicting preterm birth, many women received repeat courses of sGC. Indeed, surveys revealed that repeated dosing had become common practice in the late 1990s, with some women receiving up to 11 repeat courses (Brocklehurst et al., 1999; Quinlivan et al., 1998). At the same time, data from animal studies were beginning to demonstrate long-term effects of fetal sGC exposure on endocrine function and behavior (Matthews, 2000; O'Regan et al., 2004; Owen et al., 2005; Smith et al., 2000). In 2000, an NIH consensus update conference recommended limiting multiple course sGC to ongoing clinical trials (Committee on Obstetric Practice, 2002). As a result, there has been a move away from multiple course therapy. However, large prospective trials comparing the efficacy and safety of single vs. multiple course therapy on neonatal outcome are being undertaken (e.g. Multiple Antenatal Corticosteroids, MACS, Toronto) or have been recently completed (Australian Collaborative Trial, ACTORDS). Importantly, the latter study reported that repeat course sGC improved short-term neonatal outcome compared to single course therapy and concluded that, pending long-term outcome results, the short-term benefits support the use of repeat doses of sGC (Crowther et al., 2006).

Long-term follow-up of children and adults following antenatal sGC exposure are now beginning to be reported. A follow-up study of 30-year-old men and women failed to identify overt neurological or physiological effects of a single course of sGC therapy in late gestation (Dalziel et al., 2005a,b). However, early markers of insulin resistance were associated with single course sGC exposure. A number of retrospective studies have