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Glucocorticoid programming of intrauterine development

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ABSTRACT

Glucocorticoids (GCs) are important environmental and maturational signals during intrauterine development. Toward term, the maturational rise in fetal glucocorticoid receptor concentrations decreases fetal growth and induces differentiation of key tissues essential for neonatal survival. When cortisol levels rise earlier in gestation as a result of suboptimal conditions for fetal growth, the switch from tissue accretion to differentiation is initiated prematurely, which alters the phenotype that develops from the genotype inherited at conception. Although this improves the chances of survival should delivery occur, it also has functional consequences for the offspring long after birth. Glucocorticoids are, therefore, also programming signals that permanently alter tissue structure and function during intrauterine development to optimize offspring fitness. However, if the postnatal environmental conditions differ from those signaled in utero, the phenotypical outcome of early-life glucocorticoid receptor overexposure may become maladaptive and lead to physiological dysfunction in the adult. This review focuses on the role of GCs in developmental programming, primarily in farm species. It examines the factors influencing GC bioavailability in utero and the effects that GCs have on the development of fetal tissues and organ systems, both at term and earlier in gestation. It also discusses the windows of susceptibility to GC overexposure in early life together with the molecular mechanisms and long-term consequences of GC programming with particular emphasis on the cardiovascular, metabolic, and endocrine phenotype of the offspring.

1. Introduction

Glucocorticoids (GCs) are important stress hormones in adult animals but have a wider range of functions in the fetus. In late gestation, they act as maturational signals that ensure the fetus is mature enough to survive the transition to extrauterine life at delivery [1]. Earlier in gestation, GCs can act as signals of suboptimal environmental conditions and modify fetal development in relation to the available resource for intrauterine growth. While improving the likelihood of survival both in utero and at birth, this early overexposure to GCs adapts the phenotype that develops from the genotype inherited at conception with lifelong functional consequences [2–11]. Glucocorticoids are, therefore, also programming signals that permanently alter tissue structure and function during intrauterine development to optimize offspring fitness [12,13]. Previous reviews of GC programming have tended to concentrate on the human implications and/or the experimental studies of short-lived, laboratory species such as mice, rats, and guinea pigs [2–9]. In contrast, this review examines the role of GCs in developmental programming with particular

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emphasis on the longer-lived farm species such as sheep, pigs, cattle, and horses.

2. Fetal GC exposure

There are a number of different mechanisms by which GC concentrations can rise in the fetal circulation (Fig. 1). For most of gestation, the primary source of cortisol in fetal ovine plasma is the mother [19]. Glucocorticoids cross the placenta readily by diffusion down a materno-fetal concentration gradient which exists in normal conditions in all species studied to date including pigs, cattle, sheep, pigs, and horses [1,3]. Consequently, increases in maternal GC concentrations induced by stressful conditions, such as isolation, transport, undernutrition, and housing conditions, can lead to raised concentrations in the fetus [20]. However, the degree of fetal overexposure to the higher maternal GC concentrations is minimized by the presence in the placenta of the enzyme, 11β-hydroxysteroid dehydrogenase type II (11βHSD2, Fig. 1). This isoform of the enzyme converts active GCs into their inactive keto-metabolites and, hence, acts as a barrier to transplacental GC transfer [14]. Among species, placental 11βHSD2 activity appears to be positively related to the magnitude of the materno-fetal GC gradient and is influenced by gestational age and a range of environmental factors including glucocorticoid receptor (GR) concentrations on both sides of the placenta (Fig. 1). In addition, in the hemochorial type of placenta, there are multidrug resistance transporters, which transfer xenobiotics such as synthetic GCs from the trophoblast cells back into the maternal circulation (Fig. 1). Abundance of these transporters is also regulated developmentally and by GCs but whether they are present in the epitheliochorial placenta of ruminants, pigs, and horses remains unknown [9]. Fetal GC concentrations can, therefore, be altered independently of maternal levels by manipulating the effectiveness of the placental barrier to materno-fetal GC transfer. Glucocorticoid programming in early- to mid-gestation, therefore, depends on the level of stress experienced by the mother during pregnancy, her hypothalamic-pituitary-adrenal (HPA) responses and ensuing cortisol concentration, and on the GC permeability of the placenta.

Later in gestation when the fetal HPA axis has developed functionally, fetal GC concentrations can also rise independently of maternal levels by direct cortisol secretion from the fetal adrenal glands (Fig. 1). This occurs via activation of the HPA axis in response to adverse intrauterine conditions such as hypoxia and hypoglycemia caused, for example, by cord occlusion, placental insufficiency, poor uterine perfusion, or maternal alterations in dietary composition or calorie intake [20]. Development of fetal HPA responsiveness to adverse stimuli varies in timing between species and with both early GC overexposure and repeated insults during late gestation [13,21]. Closer still to term, fetal cortisol concentrations rise naturally in the absence of adverse stimuli as part of the normal sequence of prepartum maturational events that ensure viability at birth ([1]; Fig. 2). The magnitude and timing of this normal prepartum cortisol surge also varies widely between species (Fig. 2) and can be activated earlier than normal by poor nutritional conditions either around the time of conception or during late gestation [1,18,22,24]. Its timing is also influenced by the number of fetuses in sheep [22]. In some species such as the horse, the main perinatal rise in cortisol concentrations occurs immediately after and not before birth [21,25]. The window of susceptibility to GC programming in late gestation will, therefore, vary with species in relation to environmental conditions in utero and the development and responsiveness of the fetal HPA axis.

Fetal GC overexposure can also occur as a result of clinical use of synthetic GRs such as dexamethasone and betamethasone during pregnancy. These drugs are 20 times

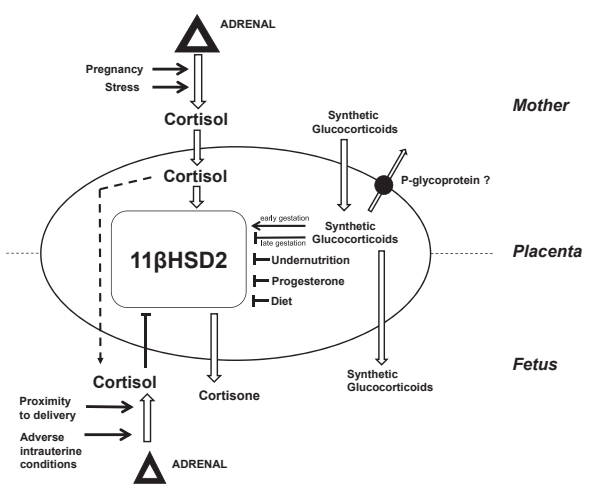

Fig. 1. Schematic diagram showing the sources of cortisol in the fetal circulation and the role of 11 beta-hydroxysteroid dehydrogenase as a placental barrier to materno-fetal cortisol transfer in sheep. Open arrows = major cortisol movements. Dashed arrow = minor cortisol movement. → Stimulatory effect. ⊣ Inhibitory effect. Data from references [14–18]. 11βHSD2, 11β-hydroxysteroid dehydrogenase type II.

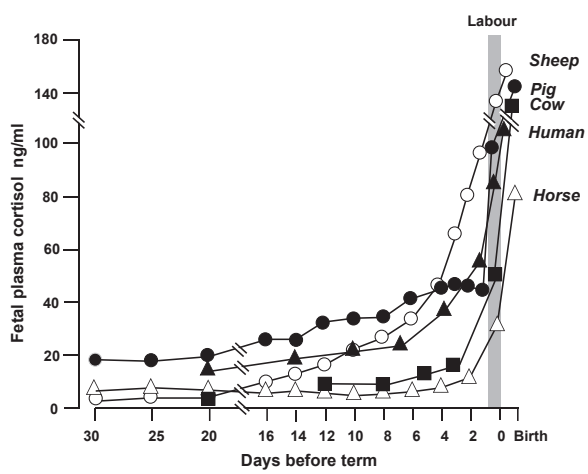

Fig. 2. Fetal cortisol concentrations with respect to proximity to delivery in different species. Length of pregnancy: pig 115 d (filled circles), sheep 145 d (open circles), humans 280 d (filled triangle), cow 280 d (filled squares), and horses (pony) 335 d (open triangles). Data from references [1,22,23].