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Review

Fetal programming of sexual development and reproductive function

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ABSTRACT

The recent growth of interest in developmental programming of physiological systems has generally focused on the cardiovascular system (especially hypertension) and predisposition to metabolic dysfunction (mainly obesity and diabetes). However, it is now clear that the full range of altered offspring phenotypes includes impaired reproductive function. In rats, sheep and nonhuman primates, reproductive capacity is altered by challenges experienced during critical periods of development. This review will examine available experimental evidence across commonly studied experimental species for developmental programming of female and male reproductive function throughout an individual's life-course. It is necessary to consider events that occur during fetal development, early neonatal life and prior to and during puberty, during active reproductive life and aging as reproductive performance declines.

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1. Introduction

Developmental programming can be defined as a response of the mammalian organism to a specific challenge during a critical developmental time window that alters the trajectory of development with persistent effects on offspring phenotype (Rabadan-Diehl and Nathanielsz, 2013).

The concept of developmental programming, or the developmental origins of adult disease phenotype, is not new. One of the first carefully controlled and well conducted experiments of developmental programming was the demonstration of the prevention of estrous cycles in the rat by early exposure of the female hypothalamus to androgens (Barraclough, 1961; Barraclough and Gorski, 1961; Gorski and Barraclough, 1963). These classical studies demonstrated that the normal female cyclic reproductive phenotype could be changed to the acyclic male phenotype by exposure to androgens at a critical period of neonatal development. This review aims to describe available evidence for programming at different levels of the female and male brain–hypothalamus–pituitary–gonad–target tissue axis and stimulate future research in this

Abbreviations: 11β-HSD2, 11β-hydroxysteroid dehydrogenase type 2; ACTH, adrenocorticotropic hormone; AR, androgen receptor; DES, diethylstilbestrol; ER, estrogen receptor; *FSH*, follicle-stimulating hormone; GnRH, gonadotropin-releasing hormone; GR, glucocorticoid receptor; HPA, hypothalamic–pituitary–adrenal; IUGR, intrauterine growth restriction; *LH*, luteinizing hormone; P450scc, P450 side chain cleavage; StAR, steroid acute regulatory protein; AMH, antimullerian hormone; DHT, dihydrotestosterone; PR, progesterone receptor.

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important area. We will consider models that inform about potential exposure and general mechanisms as well as differences across species.

The many developmental differences among species including duration of pregnancy, maturity at birth and susceptibility to a variety of environmental conditions, enable them to optimize reproduction, and hence species survival, in their particular environmental niche. However, due to the plasticity of development, distinctive windows of susceptibility to programming of reproductive tissues and organs by environmental influences occur across species (Goyal et al., 2003; Gunn et al., 1995; Guzman et al., 2006; Lummaa, 2003; Zambrano et al., 2005). Rodents are, in general, altricial species born after short pregnancies and requiring considerable maternal postnatal care to regulate basic functions such as maintenance of body temperature while they develop the ability to thermoregulate (Newkirk et al., 1995). However, this generalization does not apply universally to rodents. There are exceptions such as the guinea-pig which is born at a mature stage able to immediately eat solid food (Hunt et al., 1996). Precocial species, e.g. humans, nonhuman primates and sheep are more mature at birth. However, even in precocial species, not all physiological systems are equally mature at birth. The fetus is exposed to a very different endocrine milieu including placental hormones and maternal metabolites compared to the neonate. As a result, similar challenges to precocial and altricial species present different outcomes. For example, when comparing the critical period for windows for some tissues in rodents, sheep, human and nonhuman primates, the neonatal, suckling period in one species could be a critical window of development equivalent to the end of gestation in others (Dumesic et al., 1997; Foecking et al., 2005). Thus the study of the neonatal environment is as important as fetal life to synthesize available data on programming. Accordingly, different animal models exhibit advantages and disadvantages for translation to programming in humans. We will focus on studies in the rat, sheep and nonhuman primates.

There are also major differences between species in the nutritional burden the mother bears during pregnancy and lactation. Humans are monotocous species – meaning that women generally bear only one fetus. In contrast, rodents are polytocous species bearing large litters. Thus, even under optimal feeding conditions, the nutritional demands of pregnancy and lactation on the litter-bearing rodent mother is much greater than in mothers in monotocous species. In addition, differences exist in key metabolic pathways. For example, when evaluating nutritional effects on the one-carbon cycle and its role in gene methylation it should be noted that rodents are able to synthesize vitamin B12 while primates are not (Bailey and Ayling, 2009).

To optimize the various models it is important to evaluate the characteristics of the challenge, effects of window exposure and relevance to the specific species under study.

2. Developmental programming of the reproductive axis

The reproductive health of animals in adult life can be affected by several environmental influences acting at different stages of development, which are mediated by changes in the hypothalamic–pituitary–gonadal axis. Experimental data in human and laboratory animals indicate that several reproductive disorders are influenced by intrauterine factors and postnatal exposures (Davies and Norman, 2002). It has been well established that reproductive performance is susceptible to environmental factors in cattle in which nutritional restriction during early gestation results in heavier offspring at younger ages thereby increasing financial profits – but not necessarily the animal's long term health (Rhind et al., 2001). Girls born during or immediately after the Dutch Hunger Winter were IUGR. Although these women did not show fertility problems, their children were born with lower body weight and high perinatal mortality (Lumey and Stein, 1997; Lummaa, 2003; Stein et al., 1995).

Early experimental research on reproductive programming by nutrition performed during the 1970s (Allden, 1970; Doney et al., 1973; Gunn and Doney, 1973), described the effects of the maternal environment on offspring reproductive capacity. A wide range of stress challenges in either the prenatal or the postnatal environment has been used to induce developmental programming. We have classified the different models in three major groups: (1) glucocorticoid overexposure, (2) sex steroid exposure and (3) suboptimal nutrition.

2.1. Glucocorticoid over exposure

In several precocial species fetal circulating glucocorticoid levels increase in late gestation (Fowden et al., 1998). In sheep fetal cortisol has an important role in the induction of labor (Liggins, 1968, 1969). However, independent of effects on parturition, fetal glucocorticoids are crucial for maturation of structure and function of the lung (Surbek et al., 2012), intestine (Trahair and Sangild, 1997), and endocrine systems (Franko et al., 2007; Thomas et al., 1978). The magnitude and timing of this prenatal glucocorticoid surge varies between species (Fowden et al., 1998). However, early overexposure to glucocorticoids increases the risk of IUGR (Benediktsson et al., 1993; Sugden et al., 2001) and metabolic and cardiovascular disorders (Benediktsson et al., 1993; Lindsay et al., 1996; O'Regan et al., 2004; Seckl, 2004; Seckl et al., 1999; Sloboda et al., 2005). Placental 11β-hydroxysteroid dehydrogenase type 2 (11β-HSD2) acts as a partial but incomplete barrier to the passage of glucocorticoids from mother to fetus. (Benediktsson et al., 1993). Manipulation of pregnant rats with ACTH (Stylianopoulou, 1983), corticosterone, inhibitors of 11β-HSD2 or synthetic glucocorticoids (Smith and Waddell, 2000), increases fetal glucocorticoid exposure and modifies synthesis and secretion of fetal adrenal and gonadal steroids which then act at all levels of the fetal hypothalamus–pituitary gonadal and adrenal axes and other peripheral systems during pregnancy (Harvey and Chevins, 1987), heat restraint (Herrenkohl, 1979) and alteration of the light:dark cycle (Montano et al., 1991) have all been used as maternal stress challenges that increase corticosterone levels during pregnancy.

Glucocorticoids act on tissues including reproductive tissues by binding and activating the glucocorticoid receptor (GR). Chronic treatment of adult male rats with glucocorticoids suppresses GnRH mRNA levels, and decreases LH serum concentrations with no changes in LHβ gene expression. These data suggest that corticosterone exerts effects on LH release, either directly at the gonadotrope or indirectly through GnRH-mediated actions (Gore et al., 2006). Although over exposure to corticosteroids is a well-documented model in the field of developmental programming little is known about effects on reproductive function.

Exposure of newborn female mice to ACTH increases the length of estrous cycles (Politch and Herrenkohl, 1984) and over exposure to corticosteroids delays sexual maturation (Harvey and Chevins, 1987; Smith and Waddell, 2000) and diminishes fertility rate (Politch and Herrenkohl, 1979) (Table 1). Prenatal treatment with glucocorticoids causes the disappearance of sexual dimorphism of aromatase activity in the hypothalamic preoptic area of rat pups in early postnatal life (Reznikov et al., 2004). The critical period for sexual differentiation of the rodent brain extends from late fetal life (gestational days 14–21) through the first 2 weeks of postnatal life. There is a surge of testicular testosterone secretion on the 18th and 19th fetal days, which is essential for brain masculinization (Reznikov et al., 2004). Prenatal betamethasone exposure of male