Theriogenology xxx (2016) 1–9

Contents lists available at ScienceDirect

Theriogenology

journal homepage: www.theriojournal.com

Review

Prenatal programming of neuroendocrine reproductive function

Neil P. Evans*, Michelle Bellingham, Jane E. Robinson

Institute of Biodiversity Animal Health and Comparative Medicine, College of Medical Veterinary and Life Sciences, University of Glasgow, Glasgow, UK

Keywords:
Prenatal programming
Androgen
Stress
Nutrition
Environmental chemical
Sheep

A B S T R A C T

It is now well recognized that the gestational environment can have long-lasting effects not only on the life span and health span of an individual but also, through potential epigenetic changes, on future generations. This article reviews the "prenatal programming" of the neuroendocrine systems that regulate reproduction, with a specific focus on the lessons learned using ovine models. The review examines the critical roles played by steroids in normal reproductive development before considering the effects of prenatal exposure to exogenous steroid hormones including androgens and estrogens, the effects of maternal nutrition and stress during gestation, and the effects of exogenous chemicals such as alcohol and environment chemicals. In so doing, it becomes evident that, to maximize fitness, the regulation of reproduction has evolved to be responsive to many different internal and external cues and that the GnRH neurosecretory system expresses a degree of plasticity throughout life. During fetal life, however, the system is particularly sensitive to change and at this time, the GnRH neurosecretory system can be "shaped" both to achieve normal sexually differentiated function but also in ways that may adversely affect or even prevent "normal function". The exact mechanisms through which these programmed changes are brought about remain largely uncharacterized but are likely to differ depending on the factor, the timing of exposure to that factor, and the species. It would appear, however, that some afferent systems to the GnRH neurons such as kisspeptin, may be critical in this regard as it would appear to be sensitive to a wide variety of factors that can program reproductive function. Finally, it has been noted that the prenatal programming of neuroendocrine reproductive function can be associated with epigenetic changes, which would suggest that in addition to direct effects on the exposed offspring, prenatal programming could have transgenerational effects on reproductive potential.

1. Introduction

It is now well recognized that an animal's adult phenotype is the result of both genetic processes and the prenatal environment, which can be influenced by maternal conditions not only during pregnancy but also before conception. Although potentially an adaptive strategy, whether this is for the benefit of the fetus, to ensure that it is "matched" to its postnatal environment, or to maximize maternal fitness, is controversial. The concept that the gestational environment shapes offspring phenotype has been well described with regard to energy partitioning and/or metabolism and the resultant "thrifty phenotype" of offspring where maternal nutrition has been restricted [1]. Such "prenatal programming," is associated with functional changes in neural control systems and has been shown to be applicable to other physiological systems

* Corresponding author. Tel.: +44141 330 5795; fax: +441413305797.
E-mail address: Neil.Evans@glasgow.ac.uk (N.P. Evans).

http://dx.doi.org/10.1016/j.theriogenology.2016.04.047

including reproduction. Normal mammalian development is characterized by a series of "critical periods," during which the fetal environment can influence postnatal form and function, via plastic changes in neural and neuroendocrine systems. A classic example of developmental plasticity occurs during normal sexual differentiation of the neuroendocrine regulatory systems controlling mammalian reproduction. Normal sexual differentiation of the brain is regulated by testosterone, secreted by the testes, during the neonatal period in rodents but during the prenatal period in humans and sheep [2]. On conception, the resultant embryo is by default phenotypically female; however, under the direction of the SRY gene on the Y chromosome, the production of testosterone results in regression of the female genital tract and development of the male reproductive organs and the programming of a permanent "male" phenotype. This includes plastic changes at the level of the neuroendocrine hypothalamus, such that the male phenotype loses the ability of estradiol to induce a GnRH and/or LH surge (i.e., estradiol positive feedback), which is one of the defining features of female reproductive physiology among spontaneously ovulating mammals. Having established that the reproductive axis exhibits such a large degree of developmental plasticity, it is not surprising that additional developmental influences such as stress, nutrition, and toxins, can also affect reproductive development. In this article, we review the effects of androgens, nutrition, and toxins, including alcohol and environmental chemicals (ECs), and the effects of prenatal stress on reproduction with a focus on the neuroendocrine mechanisms that are implicated in the observed effects on phenotype and the results obtained from ovine models.

2. Plasticity is normal within the reproductive system

Normal reproductive function relies on the coordinated production of gametes and the expression of behavior to facilitate fertilization. These critical reproductive system functions are regulated by the delicately coordinated actions of steroid hormones synthesized in the male and female gonads. Gonadal steroid secretion is regulated by the pituitary gonadotrophins, LH, and FSH, the secretion of which is directed by the patterned release of the hypothalamic neuropeptide GnRH [3–6]. Changes in the patterns of GnRH secretion occur at key reproductive transitions, including puberty, the estrous and/or menstrual cycle, menopause, and the annual reproductive cycle in seasonal breeding animals. These changes in the pattern of GnRH secretion are associated with markers of neuronal plasticity and suggest that remodeling of GnRH neurons may occur at these times [7,8]. GnRH secretion, and therefore reproductive function, can also be influenced by internal factors, such as nutritional state, pregnancy, and stress. The ability of these diverse regulatory inputs to impact on the reproductive system occurs via a series of afferent neuronal inputs to the GnRH neurons, which collectively with the GnRH neurons are often referred to as the "GnRH neurosecretory system". Within rodents and sheep, GnRH neuronal cell bodies are predominantly located in the ventral preoptic area (POA) with a small additional population present in the mediobasal hypothalamus [9,10], [11] whereas in primates, guinea pigs, and rabbits, most GnRH cell bodies are located within the mediobasal hypothalamus. In each case, the axons of the GnRH neurons extend to the median eminence [12,13], and dendritic connections encompass additional brain areas including the POA and arcuate nucleus (ARC) where afferent systems such as noradrenaline [14], kisspeptin, dynorphin, neurokinin B (KNDy neurons) [15], gamma aminobutyric acid, neuropeptide Y, agouti related peptide, pro-opiomelanocortin [16], and cocaine- and amphetamine-regulated transcript are found, which are known to regulate GnRH release. Thus, plasticity within the reproductive system can occur through changes in neuronal connectivity within the GnRH neurosecretory system. The following section will summarize effects of some of the major factors known to program the reproductive neuroendocrine axis before birth.

3. Effects of prenatal exposure to exogenous steroid hormones

3.1. Androgens

Prenatal exposure to testosterone is a critical component of normal sexual differentiation in mammals. A number of animal models have been developed in which exogenous testosterone (or other androgens such as dihydrotestosterone) have been administered during gestation to examine the developmental effects of androgen exposure and the physiological mechanisms through which specific effects are mediated. This section of the review will concentrate on the substantial studies that have been conducted on the effects of prenatal testosterone exposure in the sheep and the developmental windows that are key to programming postnatal reproductive development. These studies show that exposure of female fetuses to concentrations of androgens similar to that observed in male fetuses between days 30 and 90 of a 147-day gestation results in complete virilization of the external genitalia, and the presence of internal male structures such as the bulbourethral glands. This exposure pattern also results in advanced puberty, altered estrous cyclicity [17,18] followed by anovulation during the second breeding season [17], and decreased primordial follicle number [17,19] but a multifollicular ovarian phenotype [19,20]. Although this treatment does not result in fetal exposure to pharmacologic concentrations of steroid hormones, the reproductive axis of male lambs born to testosterone treated ewes is also affected, specifically, they exhibit reduced scrotal circumference, higher numbers of sertoli cells [21], and reduced sperm count and motility [22]. Similar effects have been noted after *in utero* androgen exposure in other species including monkey [23–27] rat [28,29], and mouse [30].

3.1.1. Do prenatal androgens program the reproductive neuroendocrine system?

The neuroendocrine effects of gestational androgen exposure are perhaps the best characterized in the ovine model, with alterations being seen at all levels of the reproductive axis from the GnRH neurons and afferents to the level of the pituitary gland and the gonads. The