Molecular and Cellular Endocrinology 373 (2013) 2–7

Contents lists available at SciVerse ScienceDirect

Molecular and Cellular Endocrinology

journal homepage: www.elsevier.com/locate/mce

Review

Rodent models of polycystic ovary syndrome

Alan S. McNeilly *, W. Colin Duncan

MRC Centre for Reproductive Health, Queen's Medical Research Institute, University of Edinburgh, 47 Little France Crescent, Edinburgh EH16 4TJ, United Kingdom

ARTICLE INFO

Article history:
Available online 23 October 2012

Keywords:
Rat
Mouse
Ovaries
Pituitary
Metabolic syndrome

ABSTRACT

Rodents are clearly valuable models for assessing disruption of fertility. The effects of different steroid treatments at different stages of reproductive life through from fetal to adult have been assessed for effects on fertility, ovarian morphology, hypothalamic–pituitary function or metabolic consequences. The results show that steroid treatments do disrupt fertility in many cases, but the underlying mechanisms are complicated by the effects of the different treatments at multiple sites. As models for PCOS at the ovarian level however, there are a number of problems particularly related to the fact that rodents are multi-ovular species. Apart from an absence of ovulation and corpora lutea, many of the different steroid regimes result in an increase in large atretic, or cystic follicles that do not parallel PCOS in women. Indeed a number of treatments are given at times when they will cause disruption of the positive feedback effects of estradiol, thus blocking ovulation in adult life. The resulting ovarian morphology thus appears to be like that of PCOS but is in fact not a clear mimic. This review of the various studies highlights parallels and problems with the use of rodents to study the mechanisms underlying the development of PCOS in women.

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1. Introduction

There is a clear utility for the development of robust rodent models of human disease. Although PCOS does not occur naturally in rodents, and its genetic aetiology in women remains unknown, rat and mouse models of PCOS have been proposed. Three main modeling paradigms have been utilised. The first is developmental programming of polycystic ovaries using prenatal and/or neonatal steroid manipulation. This strategy recapitulates the prenatal androgenisation model of PCOS described in primates and sheep (Dumesic et al., 2007). The second is steroid manipulation of the pubertal or adult animal and the third is the assessment of knock-out or knock-in transgenic mouse models that have a polycystic ovary phenotype. These latter models have been comprehensively reviewed recently (Walters et al., 2008) and will not be discussed in any detail here. PCOS represents a phenotypic spectrum whose hallmarks include polyfollicular ovaries, hyperandrogenism and anovulation with an increased incidence of insulin resistance. Patterns of gonadotrophin secretion may vary and are not used in the diagnosis of PCOS. However FSH levels characteristically remain within the normal menstrual cycle range. In thin

* Corresponding author. Tel.: +44 0131 242 6162.
E-mail address: a.mcneilly@ed.ac.uk (A.S. McNeilly).

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http://dx.doi.org/10.1016/j.mce.2012.10.007

women with PCOS pulsatile LH secretion and serum LH are increased, while obese women with PCOS tend to have normal, or mildly raised, concentrations of LH (Pagán et al., 2006). While primate and ovine models have variously described the co-existence of these features, robust rodent models have proven more problematic.

One problem is the difference between the rodent ovary and that of mono-ovular species. As poly-ovular species with at least six ovulations in any normal oestrous cycle there are numerous large follicles present at any one time in the rat and mouse ovary. These preovulatory follicles are relatively healthy, growing and functionally normal and can be identified as such by analysis of apoptosis, atresia, and e.g. aromatase activity. Furthermore, corpora lutea (CLs) of the current oestrous cycle and those from the previous oestrous cycle that are undergoing luteolysis are also present and represent the dominant mass of the ovary. It is also clear that absence of ovulation, through any cause, in adult animals is easily recognised by the absence of CLs in the ovary and the presence of multiple antral follicles. Further complexity is added as stromal tissue is not of great abundance in the mouse and rat ovary in comparison with sheep, primate and human ovaries.

The nature of the polycystic ovary in rodents may not be like that in women. In women during the luteal phase of the normal menstrual cycle when plasma levels of FSH are low, or in women with hypogonadotrophic hypogonadism (e.g. Kallman's Syndrome) follicles are present up to around 5 mm in size, having proceed to grow to this size in the absence or presence of low FSH (Schoot et al., 1994; Jokubkiene et al., 2012). This phase of follicle growth has been termed the gonadotrophin-independent phase as, although gonadotrophins particularly FSH may influence the rate of follicle growth, they are not essential (Scaramuzzi et al., 2011). Further growth to preovulatory sized follicles of 18–20 mm in diameter is completely dependent on FSH and LH, the gonadotrophin dependent phase of follicle growth. In women with PCOS follicle growth is stalled in this gonadotrophin-dependent phase. Follicles range in size from 5 mm to 10 mm that is less than half the diameter of a preovulatory follicle. Indeed almost none of these stalled follicles are in fact cystic as they contain a healthy oocyte (Zhao et al., 2009) and can be rescued by exogenous FSH. Indeed ovarian hyperstimulation syndrome (OHSS) with development of multiple preovulatory follicles is a major risk in women with PCOS undergoing ovarian stimulation with gonadotrophins (Delvigne and Rozenberg, 2002). In contrast in a number of rodent models follicles are of a size equivalent to, or larger than, a preovulatory follicle and some or many, depending on the treatments and the windows of treatment, may indeed be atretic and cystic.

Women with PCOS have normal or slightly elevated serum estradiol concentrations. Some rodent models eliminate estrogens using letrozole, or in the case of the ArKO transgenic mouse have knocked out the aromatase gene, which results in increased endogenous androgen production by the ovaries. However, the lack of estrogens will increase preovulatory follicle number and inhibit ovulation by increased gonadotrophin drive to the ovaries while failing to trigger the preovulatory LH surge. This would give the impression of a polycystic ovary but its link to PCOS would be potentially misleading.

Primate and sheep models utilise prenatal exposure to androgens at a time of organ growth and maturation that includes the stage when primordial follicles are formed in the ovary (McNatty et al., 1995). Rodents are born at a less mature stage and this occurs in the neonatal rather than the prenatal period with different influences (McLaughlin and McIver, 2009). Thus exposure of rodents to androgens in fetal life may not be relevant to the potential of fetal androgens causing permanent changes in ovarian physiology in adult life as seen in the sheep and primate models. Few studies in rodents have sought to determine whether there is a window of exposure to androgens or other steroids during fetal or immediate postnatal life which results in an PCOS like effect in adult life. Indeed even this is problematic since there is potential for steroids given at this time to interfere with the normal development of positive estrogen feedback system in adult life, again leading to lack of ovulation with the apparent development of polycystic ovaries. Such abnormalities were described many years ago in the androgen and estrogen sterilised rats resulting from neonatal bolus steroid treatment (Chappel and Barraclough, 1976).

The programming of ovarian hyperandrogenism has not been robustly investigated in rodent models. No studies have assessed individual follicle androgen status, a common feature of increased androgen production in follicles from the ovaries of women with PCOS. Comparisons of gene or protein changes in whole ovaries is not possible in the presence of marked structural alterations. A further complication is that many of the studies have determined the effects of treatment on ovaries and/or pituitary gonadotrophin status without addressing any changes in metabolic function, or alternatively have concentrated on inducing a metabolic syndrome without formally assessing ovarian function.

Nevertheless within all the studies that have been undertaken some common outcomes are apparent. This brief review will address the issues raised above and seek to provide common themes that emerge from these studies. It will address the issue of steroid treatments that range from administration in adult life, fetal life, or a combination of both, with a few addressing the issue of fetal/neonatal programming. While most use testosterone as the androgenic steroid others have used DHEA and DHT and others still have used estrogens. On the metabolic side most have concentrated on treatment of pregnant mothers with glucocorticoids and the consequences on the offspring in adult life, but few if any have addressed issues of fertility.

Given all these caveats, the following sections will report the published results and should allow the reader to determine the utility and issues in the use of rodents as models of PCOS. They do however confirm the essential roles of androgens in normal ovarian biology.

2. Effects on ovarian and pituitary function

2.1. DHEA

Elevated levels of DHEA have been found in women with PCOS and the effects of DHEA on immature and adult female rats have been investigated. Levels of androstenedione, testosterone and DHEA achieved after injection are very high compared with normal levels (Anderson et al., 1997) and may compromise the results. In adult females treatment caused acyclicity, and the appearance of cystic and atretic follicles in the ovaries (Lee et al., 1991; Ward et al., 1978). This was associated with elevated prolactin and FSH but reduced LH levels in blood, indicating a disruption of pituitary function. Furthermore the treatments resulted in the appearance of ovaries with corpora lutea and either cystic or normal follicles, or no corpora lutea indicating a lack of ovulation with or without the presence of cystic follicles (Lee et al., 1991).

A similar effect on follicles in the ovary was seen after treatment of immature rats with DHEA from around day 22 of age for 7–21 days. Atretic follicles were associated with increased TUNEL, FasL and processed caspase 8, and MT1-MMP mRNA levels (Anderson and Lee, 1997; Honnma et al., 2006). Furthermore, DHEA treatment of immature prepubertal rats resulted in premature activation of meiosis in oocytes associated with the high levels of DHEA, testosterone and androstenedione in these animals (Anderson et al., 1997). All these studies have given long-term treatments at high doses, and examined the effects while