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Mini Review

Recent female mouse models displaying advanced reproductive aging

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Abstract

Reproductive senescence occurs in all female mammals with resultant changes in numerous body functional systems and several important features may be species-specific. Those features that appear to parallel human menopause and aging include general similarity of hormone profiles across the menopausal transition, progression to cycle termination through irregular cycles, declining fertility with age, disturbances in thermogenesis, age-related gains in body weight, fat distribution and disposition towards metabolic syndrome. Structural and hormonal changes in the brain and ovary play a critical role in determining the onset of reproductive senescence. The short life span of rodents such as mice (compared to humans) and the ability to generate specific and timed gene deletions, provide powerful experimental paradigms to understand the molecular and functional changes that precede and follow the loss of reproductive capacity. In theory, any manipulation that compromises ovarian function either partly or totally would impact reproductive events at various levels followed by other dysfunctions. In this article, we provide an overview of three mouse models for the study of female reproductive aging. They are derived from different strategies and their age related phenotypes have been characterized to varying degrees. The follitropin receptor knockout (FORKO) mouse, in its null and haploinsufficient state as well as the dioxin/aryl hydrocarbon receptor (AhR) knockout mouse, serve as two examples of single gene deletions. A third model, using administration of a chemical toxicant such as 4-vinylcyclohexene diepoxide (VCD) in the adult state, produces ovarian deficiencies accompanied by aging changes. These will serve as useful alternatives to previously used radical ovariectomy in young adults. It is anticipated that these new models and more that will be forthcoming will extend opportunities to understand reproductive aging and resolve controversies that abound on issues related to benefits and risks of hormone replacement therapy or other modalities for improving quality of life.

1. Concepts of reproductive aging

Reproductive aging in female mammals is characterized by a progressive decline in fertility attributed to the loss of follicles from the ovary and decrease in oocyte quality, age-related defects in the uterus, and changes in neuroendocrine axis. These events are noted both in women and rodents (Costoff and Mahesh, 1975; Faddy et al., 1983; vom Saal et al., 1994; Wise et al., 1999). Menopause is most evident in women as a cessation of cyclic menstruation that occurs at a mean age of about 51 years in developed countries. The actual end of ovarian activity is preceded by a period of irregular reproductive cycles of suboptimal fertility in both women and laboratory rodents (vom Saal et al., 1994). Although alterations in neuroendocrine and uterine factors could contribute to age related reduction in fertility, progressive depletion of the follicle pool is thought to be the major cause of permanent cessation of menstruation (vom Saal et al., 1994; Fitzgerald et al., 1998).

A hallmark of the postmenopausal period (meaning total exhaustion of ovarian follicular reserves) is certainly accompanied or preceded by the age-related changes in the hypothalamus and central nervous system (Wise et al., 1999; vom Saal et al., 1994). Data from rodent models (Wise et al., 1999) suggest that primary defects in the hypothalamus and pituitary during aging may affect reproductive decline; however, this remains as yet conjectural in humans (Fitzgerald et al., 1998). Neuroendocrine changes common to middle aged female rats and humans include elevated FSH, altered LH release (generally increased duration and decreased frequency of pulses) and increased variability in cycle length (Wise et al.,

Abbreviations: AhR, aryl hydrocarbon receptor; FORKO, follitropin receptor knockout; VCD, 4-vinylcyclohexene diepoxide.

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2002). A selective rise in circulating FSH that occurs as a first endocrine sign of reproductive aging is also associated with a decline in ovarian inhibin B production by granulosa cells of a few healthy antral follicles in the ovary (Te Velde et al., 1998). This period of dynamic changes in the hypothalamic–pituitary–ovarian axis that precede the final menses by several years is accompanied by an acceleration of follicle depletion.

Altered ovarian steroidogenesis associated with aging, brings about significant changes of uterine functions affecting implantation and reduced capability to sustain pregnancy (vom Saal et al., 1994). In several rodent species also litter size decreases with age, largely due to age-related defects in the uterine ability to support embryo implantation and growth (Thorneycroft and Soderwall, 1969; vom Saal et al., 1994; Finn, 2001). In humans, available reports have been inconsistent (Klein and Sauer, 2001). In addition, many uterine abnormalities such as leiomyomas or most commonly called fibroids that usually occur in many women also contribute to infertility and other health problems (Buttram and Reiter, 1981).

The time that is required for the follicle pool to deteriorate varies among women, indicating the effects of some genetic and environmental components. Among the factors that have been implicated in different rates of oocyte depletion are the size and pace at which the primordial follicles leave the resting pool and/or the events attributable to direct atresia (Fauser, 2000) such as autoimmune disease (Pal and Santoro, 2002), cigarette smoking (Sharara et al., 1994), and environmental contaminants (Gray and Ostby, 1995). Environmental toxicants such as 2,3,7,8-tetrachloro-dibenzo-*p*-dioxin (TCDD) accelerate the transition to reproductive senescence via activation of the aryl hydrocarbon pathway (Gray and Ostby, 1995).

Although laboratory rodents do not have menstrual cycles, unlike primates, they do generate mature eggs every week upon stimulation by FSH and experience age related decline in reproductive events. It has been shown that important commonalities in the hypothalamic control of ovarian function exist between primates and rodents (Wise et al., 1999). Herein, we present an overview of some potential mouse models that are utilized for studies of the reproductive aging process itself, not the underlying molecular and cellular processes created by radical ovariectomy. Among reproductive points generally applied to assess senescence in animal models we have chosen: (1) fertility (e.g. litter size, cycle patterns, duration and frequency); (2) reproductive tract morphology (e.g. oocyte numbers, uterine condition); (3) ovarian steroid (estradiol, testosterone, and progesterone) and inhibin production; and (4) neuroendocrine parameters (as reflected in plasma levels of FSH and LH). Thus, the purpose of this review is to present the potential advantages and disadvantages of the ovary-intact mouse models that are currently available for use in reproductive aging research and to evaluate which model(s) is most likely to come close to understanding the mechanism of menopause in women. None of the models that we discuss below have analyzed the full extent of changes that might occur in the hypothalamo–pitutary axis.

2. Genetic models

2.1. FORKO mice[1]

One of the principal hormonal signaling systems that play a key role in ovarian follicular development is the follicle stimulating hormone receptor (FSH-R). Recently mice lacking the *FSH-R gene* were engineered by homologous recombination (Dierich et al., 1998). Follitropin receptor knockout (FORKO) females are sterile due to anovulation and have atrophic ovaries unable to secrete E2 despite higher androgen levels (Danilovich et al., 2000). The condition of chronic E2 deficiency and hormonal imbalance in null female mutants from early development, leads to many age related changes that include obesity, skeletal abnormalities, cardiovascular disturbances and neural impairments. These prominent phenotypes are similar to those occurring during ageing in women (Danilovich et al., 2000, 2003a).

Although the FORKO mouse is an excellent ovary-intact model in which the effects of aging and hormonal deficiency could be separately investigated, this model as well as many other transgenic mouse models, suffer from one main drawback. FORKO mice are infertile and acyclic from the beginning. This phenomenon, similar to primary amenorrhea in women does not occur during normal reproductive aging. Thus, the null mutants cannot parallel exactly what happens in typical peri- and menopause-related conditions. Additionally, proper formation of germ cells is also disrupted in the absence of FSH-R signaling, as null mutants have fewer naked oocytes at postnatal day 2 (Balla et al., 2003) suggesting that the reproductive system might be affected during embryonic development or soon after birth. Additional studies are required to delineate these early alterations.

2.2. 'Menopause' mice

Unlike the null mouse, loss of a single FSH-R allele in heterozygous females, leads to less severe but time-dependent decline in reproductive functions. Such mutants, dubbed 'menopausal mice,' (Beckman, 2002) closely mimic reproductive failure in peri- and postmenopausal women. The reproductive capacity of heterozygous mice is compromised in two ways. In addition to reduction in litter size sired by 3-mo-old heterozygotes (Danilovich et al., 2000; Danilovich and Sairam, 2002), another indication of suppressed reproductive potential in heterozygous females, is the increased interval between mating and conception that progressively lengthens with each pregnancy. After about 6–8 births, the FSH-R heterozygous females can no longer conceive. By 7 months,

[1] As this article's main focus is on females, we have not dealt with here the gradual and age dependent decline in testosterone that occurs in null FORKO males and the associated effects on androgen dependent metabolic functions. As important as menopause is for women the study of more subtle but perceptible andropause in men (or the more recent terminologies such as ADAM-androgen deficiency in the aging male or PADAM- partial ADAM) also stands to gain from an examination of mouse models.