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Review article

Modeling menopause: The utility of rodents in translational behavioral endocrinology research☆

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ABSTRACT

The human menopause transition and aging are each associated with an increase in a variety of health risk factors including, but not limited to, cardiovascular disease, osteoporosis, cancer, diabetes, stroke, sexual dysfunction, affective disorders, sleep disturbances, and cognitive decline. It is challenging to systematically evaluate the biological underpinnings associated with the menopause transition in the human population. For this reason, rodent models have been invaluable tools for studying the impact of gonadal hormone fluctuations and eventual decline on a variety of body systems. While it is essential to keep in mind that some of the mechanisms associated with aging and the transition into a reproductively senescent state can differ when translating from one species to another, animal models provide researchers with opportunities to gain a fundamental understanding of the key elements underlying reproduction and aging processes, paving the way to explore novel pathways for intervention associated with known health risks. Here, we discuss the utility of several rodent models used in the laboratory for translational menopause research, examining the benefits and drawbacks in helping us to better understand aging and the menopause transition in women. The rodent models discussed are ovary-intact, ovariectomy, and 4-vinylcylohexene diepoxide for the menopause transition. We then describe how these models may be implemented in the laboratory, particularly in the context of cognition. Ultimately, we aim to use these animal models to elucidate novel perspectives and interventions for maintaining a high quality of life in women, and to potentially prevent or postpone the onset of negative health consequences associated with these significant life changes during aging.

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Abbreviations: HT, hormone therapy; VCD, 4-vinylcyclohexene diepoxide; WRAM, water radial-arm maze; DMS, delayed match-to-sample task.

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1. Introduction

Natural aging processes result in physiological changes in the brain and body of all organisms. In most mammalian species, females experience natural reproductive senescence in mid- to late- life. While the vast majority of species' lifespans do not far surpass their reproductive years, one clear exception to this common phenomenon is the human female, whose lifespan extends well beyond the reproductive life stage. For women, reproductive senescence typically occurs around the fifth decade of life, when their finite pool of immature ovarian follicles is depleted via a combination of ovulatory cycles and normal apoptosis (i.e., programmed cell death) called atresia. Menopause ensues when the menstrual cycle ceases due to anovulation, and is verified retrospectively after one year of amenorrhea [1,2]. Notably, menopause is not an abrupt event; indeed, the transition to menopause typically spans four to six years [3]. The onset of the menopause transition and subsequent post-reproductive life stage come with a variety of physiological, behavioral, and brain changes that can impact quality of life [4–6]. Many health risk factors change with aging and after menopause, including, but not limited to, an increased risk for cardiovascular disease, osteoporosis, cancer, weight gain, diabetes, stroke, sexual dysfunction, affective disorders, sleep disturbances, and cognitive decline [1,6,7].

Currently, the estimated average female lifespan worldwide is 70 years [8], and life expectancy is increasing, especially for women [9]. Given these numbers, the post-reproductive life stage now encompasses about a third of a woman's lifespan on average. Presently, about 14.88% of United States (U.S.) residents are over the age of 65 (of which about 56% are female) [8]. By 2030, as the "baby boomer" generation ages and life expectancy continues to increase, approximately one out of five people will be aged 65 and older in the U.S. [10,11]. With over 6,000 women projected to reach menopause each day in the U.S. alone [1], it is imperative that we understand the impact of natural and surgical gonadal hormone loss as women reach the post-reproductive life stage in order to inform researchers and clinicians about options for women to maintain a high quality of life across the entire lifespan.

Remarkable work has been accomplished in the realm of clinical research on women's health. Yet, the biological underpinnings of the menopause transition can be challenging to systematically evaluate in humans due to heterogeneous variations in many life factors, including age, parity, diet, socioeconomic status, environmental exposures, and genetic characteristics. This rich variability in humans can make it difficult to dissociate genetic and environmental factors while evaluating specific variables associated with aging and menopause. As such, animal models have been instrumental in evaluating gonadal hormone effects on various body systems and functions, including developmental and cognitive processes, while also providing a more homogeneous population to study in the laboratory compared to humans [12]. There are several well-characterized laboratory animal models used to evaluate the effects of gonadal hormones and aging, including non-human primates and rodents. Non-human primate models are especially insightful for translational research because of their genetic, physiological, behavioral, and reproductive system similarities to humans [13–16]; however, they are costly and often require many years of study to elucidate the impact of aging and reproductive senescence due to their increased longevity relative to rodents. Rodent models, especially laboratory rats and mice, are particularly useful because of their well-defined aging trajectories and thoroughly studied brain and reproductive systems, as well as their approximate two to three year lifespan [17]. This review focuses on these rodent models, comparing and contrasting the benefits and drawbacks of rodent models of reproductive senescence, and discussing the utility of the rodent model for translational menopause and aging research.

1.1. The human menopause transition

It is a well-accepted tenet that women are born with a finite pool of immature ovarian follicles. Histological follicle counts and mathematical models of ovarian follicle reserves estimate an average of 295,000 follicles per ovary at birth to 180,000 follicles per ovary at puberty; as the menopause transition approaches, estimates are reduced to between 100 and 1,000 immature follicles per ovary [18,19]. At puberty, the ovulatory cycle begins as a result of the maturation of the hypothalamic–pituitary–gonadal (HPG) feedback loop. Women experience regular ovulation, and therefore a consistent menstrual cycle, for about 40 years. Approximately 400 eggs are ovulated across a woman's reproductive life stage; the remainder – and vast majority – of ovarian follicles undergo atresia [20,21].

The female reproductive cycle involves an intricate feedback system between the brain, pituitary gland, and reproductive tract. The hypothalamus synthesizes and releases gonadotropin releasing hormone (GnRH) from GnRH neurons. GnRH signals the anterior pituitary gland to synthesize and secrete the gonadotropins follicle stimulating hormone (FSH) and luteinizing hormone (LH) into the general bloodstream. Immature ovarian follicles undergo various developmental stages over the course of several months and are classified by size and the different cell types that comprise the growing follicle (Fig. 1) [18,22]. Once the follicle pool depletes over time, menopause ensues. What initiates the transition to menopause, whether it is the declining follicle pool and/or brain changes resulting in dysregulation in the HPG axis, is a topic of debate. Phyllis Wise's elegant work in rodents and non-human primates suggests that the central nervous system is of chief importance for the onset of reproductive senescence and that, ultimately, a breakdown in communication between the brain and ovaries results in anovulatory cycles and eventual cessation of the menstrual cycle. This landmark research, discussed in Section 3.1, suggests that a complex set of changes in neuroendocrine and neurotransmitter signaling involving hypothalamic GnRH neurons and alterations in glutamatergic, GABAergic, and monoaminergic signaling, likely play roles in early stages of the transition to a reproductively senescent state for rodents, non-human primates, and women alike [23–28].

Around the onset of the menopause transition, women may opt to take hormone therapy (HT) to attenuate some of the neg-