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Research Report

An update on the cognitive impact of clinically-used hormone therapies in the female rat: Models, mazes, and mechanisms

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ABSTRACT

In women, ovarian hormone loss associated with menopause has been related to cognitive decline. Hormone therapy (HT) may ameliorate some of these changes. Understanding the cognitive impact of female steroids, including estrogens, progestogens, and androgens, is key to discovering treatments that promote brain health in women. The preclinical literature has presented elegant and methodical experiments allowing a better understanding of parameters driving the cognitive consequences of ovarian hormone loss and HT. Animal models have been a valuable tool in this regard, and will be vital to future discoveries. Here, we provide an update on the literature evaluating the impact of female steroid hormones on cognition, and the putative mechanisms mediating these effects. We focus on preclinical work that was done with an eye toward clinical realities. Parameters that govern the cognitive efficacy of HT, from what we know thus far, include but are not limited to: type, dose, duration, and route of HT, age at HT initiation, timing of HT relative to ovarian hormone loss, memory type examined, menopause history, and hormone receptor status. Researchers have identified intricate relationships between some of these factors by studying their individual effects on cognition. As of late, there is increased focus on studying interactions between these variables as well as multiple hormone types when administered concomitantly. This is key to translating preclinical data to the clinic, wherein women typically have concurrent exposure to endogenous ovarian hormones as well as exogenous combination HTs, which include both estrogens and progestins. Gains in understanding the parameters of HT effects on cognition provide exciting novel avenues that can inform clinical treatments, eventually expanding the window of opportunity to optimally enhance cognition and brain health in aging women.

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1. Ovarian hormones and cognition in the rodent: Historical context and clinical Implications

In 1927, A.S. Parkes published a monograph in The Proceedings of the Royal Society of Medicine entitled "Internal Secretions of the Ovary", in which it is stated that, "The solution of the type of problem found in studying the internal secretions of the ovary is most satisfactorily sought by experiment, and since the lower mammals have to be used for this type of work, it is on their reactions that our knowledge of ovarian activity mainly depends. At the same time, however, ovarian activity in the human subject must obey similar laws, and with the aid of clinical observations, experimental work on the lower mammals may be made to throw much light on the problems associated with the human species" (Parkes, 1927, page 45). It is notable that even now, some eight decades later, researchers studying "internal secretions of the ovary" employ similar tenets of utilizing rodent models to understand the multiple effects that these hormones have on body systems and functions. Today we typically refer to "internal secretions of the ovary" as ovarian steroid hormones. Early researchers seeking to learn the functions of the internal secretions of the ovary observed, via experimental evaluations, that the ovary is essential for development of accessory reproductive organs, the estrous cycle, sustaining pregnancy, and mammary gland development (Parkes and Bellerby, 1926). Other studies led to the discovery that these secretions are involved in more than reproductive-related morphology and function; they are also involved in reproductive behaviors (Beach, 1947). Subsequent research has now shown that gonadal steroids impact many non-reproductive actions and functions in the brain as well, including learning and memory, and several of its postulated mechanisms. For many researchers, the hope is to translate findings to a genuine clinical impact on women's health.

In animal models and humans, the female steroids estrogens, progestogens and androgens have each been shown to impact cognition. To evaluate the cognitive effects of female steroid hormones in humans, researchers have been creative in their assessments and have reported effects across menopause transition stages (Luetters et al., 2007), with sex-reassignment operations and concomitant sex hormone treatment (Gomez-Gil et al., 2009), and with hormone therapy (HT) before versus after surgery in surgically menopausal women (Sherwin, 2006). Animal models have been used to test the cognitive effects of steroid hormones. In animal models, the traditional procedure is to remove the major source of endogenous synthesis and release, the testes in the male (gonadectomy, or GDX) or the ovaries in the female (ovariectomy, or Ovx), then administer the exogenous steroid of question as a treatment regimen after surgery.

Notably, within the last decade, research in both the animal and human literature evaluating the potential influence of gonadal hormones on brain health and function during aging has increased in breadth and depth. Much of this elevated interest is largely because of the recent discussion and debate about whether HTs impact normal aging and/or Alzheimer's disease (AD). These reports include, but are not limited to: a meta-analysis showing that estrogen-containing HTs decreased the risk of AD by 29% (Yaffe et al., 1998); placebo-controlled studies showing estrogens enhanced memory or improved dementia scores in female AD patients (Asthana et al., 1999, 2001; Ohkura et al., 1994, 1995); a study showing that menopause exacerbated age-related cognitive changes in several domains, including visuospatial abilities (Halbreich et al., 1995); and then more recently, the outcome of the Women's Health Initiative (WHI) studies showing null or detrimental effects on cognition or dementia from the most commonly used HTs (for discussion, see Coker et al., 2010; Henderson, 2008; Maki and Henderson, 2012; Sherwin and Henry, 2008).

A major factor propelling research in women's health is that the life expectancy of women has significantly increased from an average of 54 years, to about 80 years (Singh et al., 1996). Since women are living longer, but age of spontaneous menopause has remained stable, women are now living approximately one-third of their lives in a hypo-estrogenic menopausal state (Amundsen and Diers, 1970, 1973; Sherwin, 2003). This realization has resulted in an increased interest in understanding the effects of ovarian hormone loss and subsequent HT administration. Emerging findings are now indicating that multiple parameters impact the extent, and even in some cases the direction, of cognitive effects of hormone loss and administration. Findings show the broad impact of gonadal hormone effects on brain functions such as learning and memory, and underscore the rich effects that ovarian hormones have on brain plasticity.

Here, we review recent findings on the impact of gonadal hormones during cognitive aging. We discuss this work in the context of landmark gonadal hormone-related discoveries that have provided the framework to guide a path to healthy cognitive aging. Evidence regarding hormone loss and parameters involving treatment optimization has emerged from both preclinical and clinical realms. Preclinical animal models have been widely used because they allow methodical experimental control of factors likely influencing outcome in clinical studies such as age, duration of hormone loss or treatment, specific type and dose of hormone manipulated, socioeconomic status, and education. Here, we review literature focusing on the female, spanning the activational effects of estrogens, progestogens, and androgens. We will discuss effects on cognition, brain health, and the neuromechanisms possibly mediating these effects. Further, because spatial cognition has been the focus of the majority of the preclinical research in this area, we will focus on spatial cognition, and review the memory types most commonly measured. We will discuss ovarian hormones, as well as synthetic and naturally-derived hormones included in various HT regimens. Ovarian hormones are endogenous and originating from the ovaries of the organism, and hormones from HTs are exogenous and originating from outside of the organism. Thus, the term "ovarian hormone" does not accurately encompass hormones that are exogenously administered and not released endogenously, such as many of those in HTs. For parsimonious discussion, we refer collectively to both endogenous ovarian-derived hormones from the subject, and administered HT hormones, as "female steroid" hormones. A summary of female steroid hormone exposure throughout the lifespan,