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Research Report

II. Cognitive performance of middle-aged female rats is influenced by capacity to metabolize progesterone in the prefrontal cortex and hippocampus

Jason J. Paris[a], Alicia A. Walf[d], Cheryl A. Frye[a,b,c,d,*]

[a]Department of Psychology, The University at Albany-SUNY, Albany, New York 12222, USA
[b]Department of Biological Science, The University at Albany-SUNY, Albany, New York 12222, USA
[c]Center for Neuroscience, The University at Albany-SUNY, Albany, New York 12222, USA
[d]Center for Life Sciences Research, The University at Albany-SUNY, Albany, New York 12222, USA

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ABSTRACT

Cognitive decline can occur with aging; however, some individuals experience less cognitive decline than do others. Secretion of ovarian hormones is reduced post-menopause and may contribute to cognitive function. The extent to which hormonal effects may be parsed out from other age-related factors to influence cognition is of interest. Middle-aged (12-month-old) female rats that were retired breeders were categorized as maintaining or declining reproductive function based upon their estrous cyclicity (regular 4–5 day cycles), fertility (> 60 % successful pregnancy), and fecundity (>10 pups/litter). Performance in object recognition, Y-maze, water maze, inhibitory avoidance, and contextual–cued fear conditioning was evaluated. Estradiol, progesterone (P_4), dihydroprogesterone, and 5α-pregnan-3α-ol-20-one (3α,5α-THP) were assessed in medial prefrontal cortex (mPFC) and hippocampus; corticosterone was assessed in plasma. Rats maintaining reproductive function performed significantly better on the object recognition, Y-maze, water maze, inhibitory avoidance, and cued fear conditioning tasks than did rats with declining reproductive function. Steroid concentrations varied greatly within groups. Higher levels of P_4 in mPFC and hippocampus were associated with better Y-maze performance. In mPFC, higher levels of P_4 were associated with poorer inhibitory avoidance performance; greater levels of 3α,5α-THP were associated with better object memory. Neither estradiol nor corticosterone levels significantly contributed to cognitive performance. Thus, the capacity for cortico-limbic P_4 utilization may influence cognitive performance in aging.

* *Corresponding author*. The University at Albany-SUNY, 1400 Washington Avenue, Life Sciences Research 1058, Albany, NY 12222, USA. Fax: +1 518 591 8848,
E-mail address: cafrye@albany.edu (C.A. Frye).

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1. Introduction

Cognitive decline, independent of dementia, can occur with aging; however, some individuals experience less cognitive decline than do others (Colsher and Wallace, 1991; Wilson et al., 2002). For example, some centenarians experience no measureable cognitive decline (Motta et al., 2008). Various factors, including neuronal loss (Schochet, 1998), decrements in cell signaling (Zoli et al., 1999), changes in survival processes at the cellular level (Johnson et al., 1999; Von Zglinicki et al., 2001; Xiong et al., 2002), and physical health may be contributors (Bergman et al., 2007). Similarly, physical and psychological factors experienced across the lifespan can impact other faculties, including affective status (Petkus et al., 2009). Thus, it is important to understand the neurobiological factors that underlie individual differences in aging.

Steroid hormones are involved in the function and maintenance of cognition, and other processes, and can be markedly influenced by age. Among women, the climacteric is associated with decline of ovarian steroids, including estradiol (E_2) and progestogens (progesterone and its metabolites), which may contribute to changes in cognitive function (Utian et al., 2008). However, cognitive decline also occurs with aging and the relative contribution of hormone decline versus other age-related processes is not well understood.

Steroid hormones are developmentally regulated and have pleiotropic effects to modulate a number of higher order processes across the lifespan. In particular, progestogens, such as progesterone (P_4) and/or its 5α-reduced metabolites, dihydroprogesterone (DHP) and 5α-pregnan-3α-ol-20-one (3α,5α-THP, a.k.a. allopregnanolone), are critical for the maintenance of pregnancy and throughout neurodevelopment (Albano et al, 1998; Edwards et al., 1980; Smitz et al., 1988; Tavaniotou et al., 2001). The enhancement of ovarian hormones, including E_2 and progestogens, characterizes the pubertal transition to young adulthood. In women, cyclical enhancements of E_2 and progestogens are associated with reduced anxiety (Le Mellédo and Baker, 2004). Similar effects occur concomitant with enhanced cognitive performance in female rodents (Archer, 1975; Gray and Levine, 1964; Johnston and File, 1991; Paris and Frye, 2008; Rhodes and Frye, 2004; Walf et al., 2009a). The hippocampus is an important target for progestogens' actions to reduce anxiety (Bitran et al., 1999; Frye et al., 2000) and, in addition to prefrontal cortex, to mediate cognition in rodents (Walf et al., 2006). Notably, the prefrontal cortex (Jutapakdeegul et al., 2010; Murmu et al., 2006) and hippocampus (Swaab et al., 2005; Schmitz et al., 2002) are sensitive structures to neurodegenerative effects of stress and neurological insults, which increase with age. Indeed, developmental stressors that promote neurodegeneration in prefrontal cortex and/or hippocampus are associated with reduced dendritic spine density and/or progestogen formation (Murmu et al., 2006; Paris and Frye, in press a,b). In rodents, administration of P_4 or 3α,5α-THP is neuroprotective and can promote synaptic connectivity in hippocampus (Brinton and Wang, 2006; Charalampopoulos et al., 2008; Djebaili et al., 2005; He et al., 2004a,b; Rhodes et al., 2004; Sayeed et al., 2005; Schumacher et al., 2007). Thus, ovarian steroids influence cognitive and affective processes and can have trophic/neuroprotective effects, which may play an important functional role in the aging brain.

Steroid-based interventions have been used to manage the sequelae of ovarian cessation due to natural, or surgical, menopause. Despite some evidence that hormone therapy may reduce cognitive deficits (Sherwin, 1988, 2007), such as the Cache County Study, which found E_2 to reduce the rate of cognitive decline (Carlson et al., 2001), results of clinical trials have not all consistently reported beneficial effects of ovarian steroids (Sherwin, 2007). In the Women's Health Initiative Memory Study (WHIMS), a number of factors may have belied potential beneficial effects of steroid-based treatments. For instance, most participants were over 60 years of age and were not put on hormone therapy until 10–20 years after menopause. Effects of E_2 and/or progestins may be more favorable when compromise is not already present, which implies that there may be a "window of opportunity" for beneficial effects of hormones. For example, preclinical studies demonstrate that aged rats only respond favorably to E_2-based treatments when E_2 is administered in temporal proximity to ovarian decline (Daniel and Bohacek, 2010; Gibbs and Gabor, 2003; Walf et al., 2009b). Given the considerable individual variability among women that experience age-related cognitive decline, it is critical to begin to parse out the contributions of aging-related changes versus hormone-related changes for these effects.

It is important to understand the effects and mechanisms by which steroid hormones may influence cognition. Among rodents, removal of the ovaries impairs performance in the object recognition task; administration of E_2 and/or P_4 reinstates high levels of performance, akin to that of natural steroid enhancement (Walf et al., 2006). Moreover, formation of neuroactive progestogens may be critical, given that systemic 3α,5α-THP is as efficacious as E_2 and/or P_4 administration, at enhancing object memory (Frye et al., 2007a; Walf et al., 2006). Indeed, parous rodents that are exposed to elevated levels of hormones for longer than are their nulliparous counterparts demonstrate life-long enhancements of cognitive and affective performance (Kinsley and Lambert, 2008; Lambert et al., 2005; Macbeth and Luine, 2010; Paris and Frye, 2008). Synthetic progestins that do not form natural P_4 metabolites fail to produce beneficial cognitive and/or neuroprotective effects (Greendale et al., 1998; Ciriza et al., 2006). As well, the neuroprotective effects of P_4 are diminished in rats that are 14–18 months old (Toung et al., 2004; Murphy et al., 2002), which implies the importance of changes in metabolic function with age. Thus, factors that promote formation of progestogen metabolites, such as 3α,5α-THP, may be key components in maintenance of higher-order function of the aging brain.

In the present investigation, we examined cognitive performance of 12-month-old female, retired breeder rats. In rodents, age-related cognitive impairments are consistently noted (Decker et al., 1988; Fischer et al., 1992; Frick et al., 1995, 2000) and have been observed as early as 11 months of age (Frick et al., 1995). Some of our 12-month-old rats were experiencing reproductive decline (based upon cyclicity, fertility, and fecundity—see methods for detailed characterization of reproductive status). Other 12-month-old rats,