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The role of testicular hormones and luteinizing hormone in spatial memory in adult male rats

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ABSTRACT

Attempts to determine the influence of testicular hormones on learning and memory in males have yielded contradictory results. The present studies examined whether testicular hormones are important for maximal levels of spatial memory in young adult male rats. To minimize any effect of stress, we used the Object Location Task which is a spatial working memory task that does not involve food or water deprivation or aversive stimuli for motivation. In Experiment 1 sham gonadectomized male rats demonstrated robust spatial memory, but gonadectomized males showed diminished spatial memory. In Experiment 2 subcutaneous testosterone (T) capsules restored spatial memory performance in gonadectomized male rats, while rats with blank capsules demonstrated compromised spatial memory. In Experiment 3, gonadectomized male rats implanted with blank capsules again showed compromised spatial memory, while those with T, dihydrotestosterone (DHT), or estradiol (E) capsules demonstrated robust spatial memory, indicating that T's effects may be mediated by its conversion to E or to DHT. Gonadectomized male rats injected with Antide, a gonadotropin-releasing hormone receptor antagonist which lowers luteinizing hormone levels, also demonstrated spatial memory, comparable to that shown by T-, E-, or DHT-treated males. These data indicate that testicular androgens are important for maximal levels of spatial working memory in male rats, that testosterone may be converted to E and/or DHT to exert its effects, and that some of the effects of these steroid hormones may occur via negative feedback effects on LH.

Introduction

For decades testicular hormones, primarily androgens, have been implicated in processes underlying learning and memory (Chambers, 1976; Janowsky, 2006; van Haaren et al., 1990). Several studies have identified androgen receptor mRNA and protein in various regions of the central nervous system in rodents and primates, including the hippocampus and cortex (Abdelgadir et al., 1999; Beyenburg et al., 2000; Choate et al., 1998; Kerr et al., 1995; Young and Chang, 1998), both of which subserve memory. Furthermore, androgens have been shown to influence spine formation in the hippocampus (Leranth et al., 2003), a process associated with memory formation (Leuner and Shors, 2004). Additionally it has been noted that testicular hormones in males can affect performance on a plethora of learning and memory tasks including those that measure active and passive avoidance (Edinger and Frye, 2007b; Frye et al., 2004; van Haaren et al., 1990), taste aversion learning (Chambers, 1976; Chambers et al., 1981), lever-press behavior (van Haaren et al., 1990) and novel object recognition (Aubele et al., 2008; Ceccarelli et al., 2001). These molecular, cellular, and behavioral observations have built a foundation for the hypothesis that testicular androgens can influence learning and memory in males.

One of the most reliable memory differences noted between males and females is that males generally have an advantage over females in tests of spatial memory, both in rodents (Jonasson, 2005) and in humans (Linn and Petersen, 1985; Voyer et al., 1995). Attempts to address the role of testicular androgens in spatial memory have yielded contradictory results, however. For example, gonadectomy only affects performance in some spatial memory tasks. Gonadectomy of male rats has been shown to have only a minimal effect on the acquisition of reference memory in the Morris water maze task or 8 arm radial maze (Isgor and Sengelaub, 1998; Sandstrom et al., 2006; Spritzer et al., 2008), but significantly impairs spatial working memory (i.e. task-specific memory) in an operant T-maze, a delayed matching-to-place water maze task, and radial arm maze (Daniel et al., 2003; Kritzer et al., 2001; Kritzer et al., 2007; Sandstrom et al., 2006; Spritzer et al., 2008).

Administration of exogenous testosterone (T) to male rodents has produced no effect, a decrease, or an increase in spatial memory.

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Studies that administered superphysiological levels of T to gonadally intact adult male rats found no effect or an impairment of performance in the Morris water maze (Clark et al., 1995; Goudsmit et al., 1990) and a radial arm maze task (Smith et al., 1996). When a high dose of T was injected into the hippocampus, it again impaired memory in the Morris water maze (Moradpour et al., 2006; Naghdi et al., 2001). Other studies have concluded that physiological levels of T improve spatial memory. Gonadectomized adult male rats were impaired in the Morris water maze and T-maze and had their performance rescued by supplemental, physiological levels of T (Kritzer et al., 2001; Sandstrom et al., 2006). Moreover, aged male rats treated with T performed better in the water radial arm maze compared to controls (Bimonte-Nelson et al., 2003).

In human males, there is a growing body of literature that supports the potential positive effect of physiological levels of testicular androgens on spatial memory. Although some studies have found no relationship between T and spatial ability or even a negative relationship (Gouchie and Kimura, 1991), a number of studies have found that T levels are positively correlated with performance on a variety of spatial tasks including route learning (Cherrier et al., 2001; Choi and Silverman, 2002) and maze navigation (Driscoll et al., 2005). Additionally, it is well established that androgen levels decrease with aging in men (Janowsky, 2006; Sherwin, 2003). T supplementation in elderly men improved spatial reasoning and memory (Cherrier et al., 2001; Janowsky et al., 1994). Moreover, men with Alzheimer's disease have lower androgen levels than controls (Holland et al., 2011), and show improved spatial memory following T treatment (Cherrier et al., 2005b).

Although T is the primary androgen released from the testes, it can be converted to either estradiol (E) (by the enzyme aromatase) to act at estrogen receptors, or to the nonaromatizable androgen dihydrotestosterone (DHT) (by the enzyme 5α-reductase), which binds to androgen receptors. Aromatase, estrogen receptors, and 5α-reductase have been detected in the hippocampus and other brain regions (Hojo et al., 2004; Loy et al., 1988; MacLusky et al., 1994; Pelletier et al., 1994). Thus, testosterone may exert its effects on spatial memory by working as either an androgen or an estrogen.

Some studies support the hypothesis that T can enhance memory in males via its estrogenic metabolites. For example, intrahippocampally-injected E enhanced spatial memory in intact male rats in a water maze (Packard et al., 1996). Consistent with this, mice lacking the gene that codes for aromatase demonstrated impaired spatial reference memory in the Y-maze (Martin et al., 2003). Moreover, subcutaneous E capsules enhanced spatial working memory in a maze task in young adult and aged male rats (Luine and Rodriguez, 1994). However, other studies have presented contrasting evidence. Administration of E to gonadectomized male rats had no effect on a delayed alternation task (Kritzer et al., 2007). E also impaired spatial memory performance in a water maze when it was injected into the hippocampus at high doses (Moradpour et al., 2006). Consistent with this, an aromatase inhibitor improved performance in the Morris water maze (Moradpour et al., 2006). Similarly, healthy, elderly men treated with either T alone or T with an aromatase inhibitor both demonstrated improved spatial memory compared to placebo-treated controls (Cherrier et al., 2005a).

There is evidence that DHT and possibly other reduced metabolites play a role in emotional memory (Edinger and Frye, 2007b; Frye et al., 2004), but it remains unclear whether or not they are important for spatial memory. In aged male rats, T improved working memory in a radial arm maze, and DHT-treated males generally scored between sham-treated and T-treated males (Bimonte-Nelson et al., 2003). Specifically, DHT-treated males showed a significant decrease in the number of working memory incorrect errors, similar to T-treated males, but DHT overall had only a small, usually nonsignificant, facilitatory effect on working memory in aged males.

Gonadal hormones can have indirect as well as direct actions on the brain. In males, gonadal hormones exert negative feedback effects keeping gonadotropin releasing hormone (GnRH) and Luteinizing Hormone (LH) levels low relative to those present in gonadectomized males. Recent work in female rats and mice has indicated that high levels of LH may have a detrimental effect on the hippocampus and spatial memory (Berry et al., 2008; Bryan et al., 2010; Casadesus et al., 2006; Casadesus et al., 2007; Ziegler and Thornton, 2010) but to our knowledge no research has yet been reported for male rodents. There are indications that high levels of LH may be harmful to the memory of human males as higher LH is correlated with poor memory recall in men (Hyde et al., 2010), and serum LH is significantly higher in individuals with Alzheimer's disease compared to age-matched controls (Bowen et al., 2000; Short et al., 2001).

Many factors may contribute to the conflicting effects of hormones that have been seen in previous studies. In addition to the type of hormone (e.g. T, DHT, or E) the level of hormone may be important; androgens may have differential effects depending on whether they are at physiological or superphysiological concentrations (Sandstrom et al., 2006). Moreover, the type of task and the type of spatial memory, be it spatial reference, or spatial working memory may be critical (Dohanich et al., 2009; Sandstrom et al., 2006). Most spatial memory tests require extensive training and rely upon food or water deprivation or an aversive stimulus (e.g. forced swimming in a pool of water) to motivate males to perform. It has been suggested that the behavioral effects of testicular hormones may differ whether the behavior is an aversively or positively motivated behavior (van Haaren et al., 1990) and there are known interactions between stress and gonadal hormones (Andreano and Cahill, 2009; Viau, 2002).

In the present studies we used the Object Location Memory Task (OLMT; Ennaceur et al., 1997), which is unencumbered by potential stress effects from food or water deprivation or aversive stimuli, to examine the effects of physiological levels of testicular hormones and luteinizing hormone on spatial memory in adult male rats. First, to test the hypothesis that testicular secretions contribute to spatial memory, gonadectomized and sham-gonadectomized adult male rats were compared in the OLMT. Secondly, to test the hypothesis that the deficits observed in gonadectomized rats were due to the absence of T from the testes, gonadectomized rats were implanted subcutaneously with blank capsules or capsules containing T and tested for spatial memory. Finally, to examine whether T's effect on spatial memory is mediated by its estrogenic or androgenic metabolites or by inhibition of high LH levels, gonadectomized males were tested for spatial memory after they were implanted with a capsule that contained either T, DHT, or E, or were injected with the LH-lowering compound Antide.

General methods

Animals

Adult male Sprague–Dawley rats, derived from the breeding of animals purchased from Hilltop Animal Laboratories, were weaned at four weeks of age and then housed in same-sex groups. After surgery, animals were housed in groups of 2–3 in 27.9 cm × 20 cm × 17.8 cm cages with ad libitum access to Purina Labdiet and water. All were kept on a 14 hour light: 10 hour dark cycle (7:00 pm lights off). The Oberlin College Institutional Animal Care and Use Committee approved all procedures.

Surgery and hormone implants

Rats were gonadectomized (GDX) or sham gonadectomized under anesthesia with 2–3% isoflurane, 1 l/min oxygen using aseptic technique. For gonadectomy a midline abdominal incision was made, testes were exposed, the vas deferens and accompanying blood vessels were ligated bilaterally and the testes were removed. The incised abdominal muscles were sutured together, and the skin incision was