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Short-term testosterone manipulations modulate visual recognition memory and some aspects of emotional reactivity in male rhesus monkeys

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ABSTRACT

The role of testosterone (T) in modulating cognitive function and emotion in men remains unclear. The paucity of animal studies has likely contributed to the slow progress in this area. In particular, studies in nonhuman primates have been lacking. Our laboratory has begun to address this issue by pharmacologically manipulating T levels in intact male rhesus monkeys, using blind, placebo-controlled, crossover designs. We previously found that T-suppressed monkeys receiving supraphysiological T for 4 weeks had lower visual recognition memory for long delays and enhanced attention to videos of negative social stimuli (Lacreuse et al., 2009, 2010) compared to when treated with oil. To further delineate the conditions under which T affects cognition and emotion, the present study focused on the short-term effects of physiological T. Six intact males were treated with the gonadotropin-releasing hormone antagonist degarelix (3 mg/kg) for 7 days and received one injection of T enanthate (5 mg/kg) followed by one injection of oil vehicle 7 days later ($n=3$), or the reverse treatment ($n=3$). Performance on two computerized tasks, the Delayed-non-matching-to-sample (DNMS) with random delays and the object-Delayed Recognition Span test (object-DRST) and one task of emotional reactivity, an approach/avoidance task of negative, familiar and novel objects, was examined at baseline and 3–5 days after treatment. DNMS performance was significantly better when monkeys were treated with T compared to oil, independently of the delay duration or the nature (emotional or neutral) of the stimuli. Performance on the object-DRST was unaffected. Interestingly, subtle changes in emotional reactivity were also observed: T administration was associated with fewer object contacts, especially on negative objects, without overt changes in anxious behaviors. These results may reflect increased vigilance and alertness with high T. Altogether, the data suggest that changes in general arousal may underlie the beneficial effects of T on DNMS performance. This hypothesis will require further study with objective measures of physiological arousal.

1. Introduction

Sex hormones have far-reaching effects on brain function and modulate several aspects of cognition [1,2] and emotion [3,4]. While considerable progress has been made towards understanding the neurocognitive and emotional effects of estrogens in females [5–10], much less research has been carried out to determine whether androgens have similar effects in males. Neurobiological and cellular data suggest that androgens have the same potential as estrogens to affect cognitive and affective processes: androgen receptors are present in brain areas important for cognition and emotion such as the hippocampus, prefrontal cortex and amygdala [11–13]. Secondly, androgens modulate synaptic plasticity in the hippocampus and frontal cortex [14–17]. Third, not unlike estradiol, androgens have a myriad of neuroprotective and neurotrophic effects [18].

Evidence for an effect of androgens, in particular testosterone (T) on cognitive function in men is mixed. While positive associations have consistently been observed between endogenous T and various tests of visuospatial ability in young men [19–28], inconsistent results have been provided regarding the cognitive effects of exogenous T. In one study in which T was administered for 8 weeks to both eugonadal and hypogonadal men [29], supraphysiological T was found to decrease spatial ability and increase verbal fluency. Two studies using pharmacological manipulations of T found no effect of T administration on executive function, memory, spatial cognition [30] or visuospatial ability [31]. In contrast, Cherrier et al. [32] reported that T depletion induced by a synthetic progestin was associated with a decline in verbal memory that was restored by T supplementation. Many more studies have been conducted in older men and the majority reported improvements in visuospatial ability, verbal memory, verbal fluency or working memory following T administration [29,33–39]. Yet, there are many inconsistencies, with other studies

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finding no effect [30,40–44] or even a negative effect of T on cognition [45].

Multiple factors may account for the differences across studies, including the variety of cognitive domains examined, differences in health status and demographic factors of the population studied and differences in the specific T regimen used (i.e., dose, duration, formulation). In addition, some of the cognitive effects of T may be mediated by changes in emotional states, but emotional variables have rarely been incorporated in the studies mentioned above. The development of a new paradigm for exogenous T administration in humans, which raises T levels for only a few hours, has allowed the investigation of the influence of T on human emotional processing [4]. These studies have repeatedly shown that T modulates anxiety, social vigilance and aggression [46]. Importantly, because of health risk posed by T administration in eugonadal men, these studies have been conducted in women. Thus, it remains unclear whether androgens have similar effects in men.

Studies in animal models may be best suited to examine the effects of T on cognition and emotion in the male. The male rhesus monkey is an excellent model for such investigations because the endocrine control of testicular function is, in many respects, similar in men and male macaques [47,48] and because rhesus monkeys share many cognitive, emotional and physiological characteristics with humans [49]. In previous studies in this model, we found that supraphysiological T administered for 4 weeks had a negative impact on visual recognition memory [50] and an enhancing effect on selective attention to threatening social stimuli [51]. The present study was conducted to further delineate the conditions under which T affects cognition and emotion in males, by using an acute T administration paradigm more directly comparable to that used in recent human studies [4]. Based on these data, we tested the hypothesis that short-term treatment (3–5 days) with a physiological dose of T would enhance cognitive function [52] and reduce anxiety [53]. Endogenous T was suppressed with a GnRh antagonist prior to T administration to avoid supraphysiological increases in T levels and prevent reciprocal actions of the environment on endogenous T levels. Monkeys were tested in two memory tasks and an approach/avoidance task 3–5 days after administration of a physiological dose of TE (5 mg/kg) or oil vehicle. We predicted that T would improve performance on the memory tasks and reduce anxiety in the approach/avoidance task.

2. Methods

2.1. Subjects

Six young (8 years old) male rhesus monkeys (*Macaca mulatta*) participated in the study. All monkeys were housed in stainless steel primate cages in the same room at constant 12:12 h lighting conditions. Four monkeys were singly housed and two monkeys were housed together. All but one male were surrogate peer-reared [54]. The monkeys were humanely treated in accordance with the standards of the PHS policy on Humane Care and Use of Laboratory Animals. The study was approved by the Institutional Animal Care and Use Committee of the University of Massachusetts. The monkeys were proficient with the touchscreen and had participated in several cognitive and emotional studies prior to the current experiment [50,51,55].

2.2. General procedure and treatments

The design of the study can be seen in Fig. 1. The experiment involved four week-long phases. The baseline phase (Week 1) was a period during which monkeys were tested on the battery of tasks in the absence of any drug treatment. The degarelix phase (degarelix only, Week 2) started 7 days after the onset of the baseline phase and involved the administration of degarelix (Ferring Pharmaceuticals, Inc.), a newly FDA approved GnRh antagonist for use in humans with advanced prostate cancer. Degarelix rapidly suppresses T as early as 3 days after administration in humans, without the T flare associated with GnRh agonists [56–59]. Degarelix was injected subcutaneously at a dose of 3 mg/kg which suppresses gonadal function for up to 16 weeks in male rhesus monkeys (Dr. Wolfgang Koechling, pers. comm.). The goal of the degarelix phase was to ensure suppression of gonadal hormone activity before the onset of treatment with TE and oil. Monkeys were not tested on the tasks during this phase. Seven days after the degarelix injection, 3 monkeys received one I.M. injection of TE (5 mg/kg) and 3 monkeys received one I.M. injection of oil vehicle. Seven days after receiving their first treatment, monkeys switched to the alternate treatment. TE administered at 5 mg/kg to adult male rhesus monkeys yields T levels that increase sharply after 24 h, peak on day 3 and decrease progressively afterwards [60]. The half-time of the TE terminal elimination phase has been shown to be 5 days in male rhesus monkeys [61]. The experimenters were blind to the treatment assignments. Monkeys performed the cognitive tasks 3 days per week (Monday–Wednesday, i.e., from days 3 to 5 post-treatment) on a computerized touchscreen system with a 17-inch color monitor that was rolled in front of their home cages. The emotional reactivity assessments were also performed 3 days per week in the home cage, several hours following the cognitive tests.

2.2.1. Delayed non matching to sample (DNMS)

The DNMS is a classic task of visual recognition memory, in which monkeys are required to discriminate a new from a previously seen stimulus after various delays. The task was created with custom-designed Java-based software. Monkeys had previously performed a version of the task with a 1 s delay [55]. The stimuli were 6 × 6 cm black and white images. The images were either social images, consisting of neutral and emotional (lipsmacks or threats) portraits of rhesus monkey faces, or nonsocial images, consisting of neutral (shoes, cage locks and lab wall fixtures) and emotional pictures of objects such as capture gloves and syringes (negative), or apples, bananas and grapes (positive). Animals were presented with 30 trials of the DNMS per testing day, consisting of 6 trials per delay. Images were drawn from a set of 288 images, 48 images for each emotion (negative, neutral, positive) in each category (social, nonsocial). Images were never repeated within a testing session (60 images), but were repeated twice on average during the experiment. The accuracy and response times (RT) were recorded. Monkeys performed the DNMS 3 days per week.

The task began with the presentation of a start button that the animals had to touch to begin the session. Then, one sample image was presented in the center of a black screen, which the animal was required to touch in order to proceed through the trial. Following a specific delay (0, 5, 10, 15 or 30 s, randomly selected) during which the screen was blanked, two images were presented side-by-side, centered on the y-axis of the screen. One image was the same as the sample image and one image was a novel image from the same category (Fig. 2). Animals were rewarded with a fruit-flavored 190 mg pellet (Test Diet, Inc) for touching the novel image. A touch on the image matching the sample or failure to respond within 60 s triggered a time-out of 15 s signaled by a green screen.

2.2.2. Object-Delayed Recognition Span Test

The object-DRST required subjects to select the new stimulus among an increasing array of stimuli appearing one at a time at different locations on the screen (Fig. 2). For this task, created with Java-based software, the screen was programmed to display 15 non-overlapping positions, arranged in a 3 × 5 matrix. The stimuli were clip-art images (randomly drawn at each testing session from a database of 1500 clip-art images), presented on a black background. On