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Testosterone may increase selective attention to threat in young male macaques

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ABSTRACT

Animal studies indicate that sex hormones have widespread effects on the brain, cognition and emotion, but findings in humans are inconsistent. Well-controlled studies in nonhuman primates are crucial to resolve these discrepancies. In this study, we examined the effects of testosterone (T) on emotion in male rhesus monkeys. Six young adult males were tested on two emotional tasks during three hormonal conditions in a crossover design: when intact at baseline and when pharmacologically hypogonadal with add-back of T or placebo. The emotional tasks were the Approach–Avoidance task, which tested behavioral responses to three categories of objects (familiar, novel, and negative) and a Social Playback task which tested behavioral responses to scenes of unfamiliar conspecifics engaged in three types of social activities (neutral, positive, or negative). Following a 4-week baseline period, monkeys were treated with Depot Lupron, 200 μg/kg before being randomly assigned to one of two treatment groups: Depot Lupron + Testosterone Enanthate (TE, 20 mg/kg) or Depot Lupron + oil vehicle. In each treatment group, monkeys received one injection of Lupron and one injection of TE or one injection of Lupron and one injection of oil at the onset of a 4-week testing period, before crossing over to the alternate treatment for an additional 4 weeks of testing. TE treatment had no effect on behavioral measures in the Approach–Avoidance task. For the Social Playback task, however, TE significantly increased watching time of video clips which depicted fights between unfamiliar conspecifics. The enhancing effect of T on watching time for negative social scenes is consistent with human data suggesting that T decreases aversion or facilitates approach to threatening social stimuli. Further studies are needed to understand the mechanisms by which T may mediate responsiveness to social threat in male primates.

Introduction

The neuroendocrine system plays an important role in modulating cognitive function, emotions, and social behavior in a range of mammals (Becker et al., 2002; Pfaff et al., 2002). In male humans and male macaques, androgens, particularly testosterone (T), affect sexual behavior (Gray et al., 2005; Wallen, 2001), social behavior (Czoty et al., 2009; Rose et al., 1971), selective aspects of cognition, such as verbal and working memory (Cherrier, 2009; Janowsky, 2006; Lacreuse et al., 2009), and emotional states (Schmidt et al., 2004; van Honk et al., 1999).

One aspect of behavior that has been consistently found to be modulated by T in these species is aggressive behavior. Many correlational studies in humans (Archer, 2006; Mazur and Booth, 1998; Rubinow and Schmidt, 1996) and rhesus monkeys (Higley et al., 1996; Rilling et al., 2004; Rose et al., 1971) have shown that higher endogenous T levels are associated with higher levels of aggressive behavior. Increases in aggressive behavior are also seen in rodent models treated with T (Melloni et al., 1997), in adolescent men taking supraphysiologic doses of anabolic steroids (Beaver et al., 2008) and in placebo-controlled studies of anabolic steroid use in adult men (Pope et al., 2000). In male humans and rhesus monkeys, T may be more associated with aggressive motives and competitiveness than with violence *per se* (Archer, 2006; Higley et al., 1996). For example, although rhesus monkeys with high T display increased rates of aggression, these behaviors are comprised of behavioral displays and gestures (e.g., stares, threats, displacements) used to maintain or ascertain dominance rather than overt aggressive interactions (Higley et al., 1996). Likewise, humans often use angry facial expressions as a means to assert dominance: increased staring duration is associated with dominant social status, while an averted gaze is generally a sign of submission (Mazur and Booth, 1998). In a series of studies, van Honk and colleagues demonstrated a link between T and attention to threatening faces in humans. In one study using a Stroop task with angry and neutral faces, men and women with higher T showed interference (increased attention toward the angry face), while those

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with lower T showed facilitation (attention away from the angry face; van Honk et al., 1999). These findings were replicated in a more recent study (Wirth and Schultheiss, 2007). Moreover, in a placebo-controlled study, women treated with T exhibited cardiac acceleration in response to angry faces, but not to neutral or happy faces, a finding interpreted as reflecting fearlessness and willingness to face challenge (van Honk et al., 2001). Overall, these findings suggest that T biases attention towards signals of dominant challenge, thereby promoting social aggression.

There is also considerable evidence for fear- and anxiety-reducing properties of T across a number of species, including rats (Bitran et al., 1993; Fernandez-Guasti and Martinez-Mota, 2005; Frye and Seliga, 2001; Toufexis et al., 2005; Viau, 2002), mice (Aikey et al., 2002), cattle (Boissy and Bouissou, 1994), ewes (Bouissou and Vandenheede, 1996), and humans (Hermans et al., 2006). In one study in women, T administration reduced the unconscious attentional bias to fearful faces (van Honk et al., 2005). In another study, T administration reduced fear-potentiated startle in women tested in a verbal threat of shock paradigm (Hermans et al., 2006). Although parallel studies have not been conducted in men due to health concerns associated with T administration, indirect evidence suggests that T may also reduce anxiety in men. For example, Almeida et al. (2004) noted increases in anxiety in men with prostate cancer chemically castrated for 36 weeks.

Overall, the data briefly reviewed here suggest that T may increase attention to threatening stimuli and may also reduce fear and anxiety. One interpretation of these findings is that these overlapping aggression-increasing and fear-reducing properties promote approach and attention towards threat signals, while simultaneously decreasing anxiety and aversion to threat signals (Wirth and Schultheiss, 2007). Yet, studies administering a comprehensive battery of tests to validate this hypothesis are lacking. In addition, because of health risks associated with T administration in eugonadal men (Liverman and Blazer, 2004), many human studies are correlational, or otherwise conducted in women (e.g., van Honk et al., 1999) or hypogonadal men (Janowsky, 2006), with a paucity of studies investigating the effects of T manipulations on emotions in healthy men (Schmidt et al., 2004; Young et al., 2010). Clearly, animal models are needed to fully understand the role of T in modulating emotions in males.

Because of their similarity to humans in terms of brain organization, reproductive endocrinology, and affective regulation (Kalin and Shelton, 2003; Suomi, 2006), rhesus monkeys are excellent models to conduct such investigations. Very few studies, however, have investigated the potential effects of T on emotional processing rhesus monkeys. A recent study in adolescent males found that intact rhesus monkeys were faster in retrieving a treat placed in front of a threatening facial expression than a neutral facial expression, while castrated males did not show differential responses according to the emotional valence of the pictures, suggesting that circulating T may modulate responses to social cues during adolescence (Richards et al., 2009).

In the present study, we manipulated T levels to examine the effects of relatively high *vs.* low T on emotional behavior in adult male rhesus monkeys. Monkeys were presented with two tasks designed to elicit emotional responses: an Approach–Avoidance task with familiar, novel, and negative objects and a Social Playback task that exposed monkeys to videos of unfamiliar conspecifics engaged in neutral, negative, or positive interactions. Based on the literature reviewed above, we hypothesized that when treated with T relative to placebo, monkeys would exhibit fewer anxious behaviors and be more prone to approach and attend to potentially threatening stimuli.

Methods

Subjects

Six young adult male rhesus monkeys (*Macaca mulatta*), 5–6 years old participated in the study. One monkey was mother-reared, 5 monkeys were nursery-reared according to the surrogate peer-rearing standards described by Ruppenthal (1979) and Shannon et al. (1998). In this protocol, infants are separated from their mothers at birth and reared in a nursery for the first 30 days, while given continuous access to an inanimate fleece-covered surrogate mother. After the first 30 days of life, they receive 2 hours of daily exposure to other infants of the same age. Unlike peer-reared monkeys, surrogate peer-reared monkeys show normal patterns of sexual and reproductive behaviors and species-typical patterns of social organization (Novak et al., 1992; Novak and Sackett, 2006).

The six monkeys were housed indoors within the same room at constant 12:12 h lighting conditions. Two monkeys were paired-housed and four monkeys were singly housed with full visual and auditory contact with their conspecifics. Cage sizes varied between $1.5 \times 0.76 \times 1.65$ m and $1.8 \times 0.66 \times 1.62$ m. The monkeys were not deprived of food or water and received their normal ration of monkey chow (at 0800 and 1300) and fresh fruits (at 1800) everyday, except on Fridays, when food was withheld until full recovery from anesthesia. The monkeys were given three tests of cognitive function during the experiment, several hours apart from the emotional tests (Lacreuse et al., 2009). 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.

Treatments, blood samples, and assays

The design of the study can be seen in Fig. 1. The experiment involved four 4-week phases. The baseline phase (conducted in November) was a period during which monkeys were tested on the battery of tasks in the absence of any drug treatment. The Lupron phase (Lupron Only) started 4 weeks after the onset of the baseline phase and involved the administration of leuprolide acetate, a long-acting gonadotropin-releasing hormone agonist that suppresses gonadal activity in humans (Bhasin et al., 2001) and nonhuman primates (Lacreuse et al., 2009; Wilson et al., 2004). Importantly, the drug initially induces a sharp rise in gonadal hormones and via negative feedback inhibits ovarian and testicular steroidogenesis. This effect is reversible upon discontinuation of the drug.

Depot Lupron was injected I.M. at a dose of 200 μg/kg, which successfully suppresses gonadal function for 1 month in male rhesus monkeys (Lacreuse et al., 2009). The goal of the Lupron Only phase was to ensure suppression of gonadal hormone activity before the onset of treatment with TE and oil. Monkeys were not tested on the battery

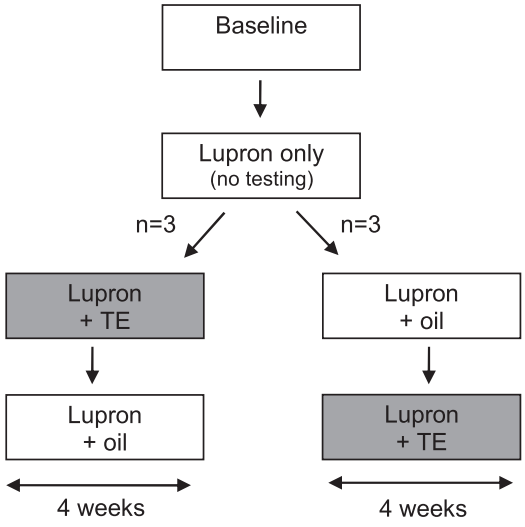

Fig. 1. Study design. Monkeys were not tested on the emotional tasks during the Lupron Only phase.