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Characterization of verbal and spatial memory changes from moderate to supraphysiological increases in serum testosterone in healthy older men

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Summary
Background: It has been suggested that cognitive changes in response to T supplementation may occur within an ideal range. The objective of this study was to compare the cognitive responses of older, eugonadal men in whom moderate or large increases in serum testosterone levels was induced by exogenous testosterone supplementation.
Design: Randomized, double-blind, placebo-controlled study with subsequent grouping of participants according to average increase in circulating T from baseline.
Setting: Community dwelling participants.
Participants: Fifty-seven healthy, eugonadal, community dwelling male volunteers, mean age 67 years (±11 years).
Interventions: Participants were randomized to receive weekly intramuscular (I.M.) injections of either 50, 100 or 300 mg T enanthate or placebo (saline) injection for 6 weeks. Cognitive evaluations using a battery of neuropsychological tests were conducted at baseline, weeks 3 and 6 of treatment and after 6 weeks of wash-out.
Main outcome measures: Performance on cognitive tests of verbal and spatial memory.
Results: Men with moderate increases in serum T and/or its metabolites demonstrated significant improvements in verbal and spatial memory. In contrast, men with large or low increases in circulating T levels, failed to demonstrate significant changes in memory.

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Conclusion: These results suggest that in healthy older men, beneficial changes in cognitive function induced by T supplementation are most evident with moderate changes in cognition from moderate to high T supplementation increases in T levels. Large or no to low increases in T levels do not appear to appreciably effect cognition.

1. Introduction

Age-related decline in testosterone (T) is associated with several physiologic changes including decreased muscle mass and strength, osteoporosis and reduced sexual activity (Matsumoto, 2002; Swerdloff and Wang, 1993). The age-related decline in T is also associated with a progressive decline in cognitive abilities. Several retrospective epidemiological studies have found declines in bioavailable or free testosterone to be associated with decrements in cognitive functioning (Barrett-Connor et al., 1999; Moffat et al., 2002; Yaffe et al., 2002).

Studies examining T supplementation in older men have found evidence for a beneficial effect on cognition (Cherrier et al., 2001, 2003, 2005; Gray et al., 2005; Janowsky et al., 1994, 2000; Kenny et al., 2002). In contrast, other studies have found no support for beneficial effects on cognition (Kenny et al., 2004; O'Connor et al., 2001; Sih et al., 1997; Wolf et al., 2000). It has been suggested that a positive relationship between testosterone and cognition may exhibit an inverted U shape dose–response, such that beneficial effects on cognition occur within a moderate dose range but not at high or low levels (Gouchie and Kimura, 1991; Hampson and Moffat, 1994; Hogervorst et al., 2005; Moffat and Hampson, 1996; Muller et al., 2005; Shute et al., 1983). In the present study, we directly examined the role of dose effects of T supplementation on cognition in a sample of healthy older men.

2. Methods

2.1. Participants

Participants were healthy older men between the ages of 50 and 90 mean age 67 years ($\pm$11 years) recruited from the community through flyers. The study protocol was approved by the University of Washington Institutional Review Board and approved informed consent procedures were followed. Participants underwent a screening visit to determine eligibility including a physical exam, psychiatric and laboratory evaluation to exclude any significant physical or medical illness. This included tests of liver function, hypertension, and prostate disease (prostate-specific antigen (PSA) level, and digital rectal exam (DRE)). Participants with abnormal findings were excluded from the study. Participants also underwent a cognitive screening examination consisting of the Mattis Dementia Rating Scale (DRS) to ensure that participants were within the normal range for their age (Folstein et al., 1975; Mattis, 1988). Participants with scores at or below the recommended cut-off score (DRS 130 or lower) were excluded from the study. Participants with a history of significant alcohol abuse, psychiatric illness, head injury with loss of consciousness greater than 1 h, or who were taking lupron, finasteride, spironolactone or cimetidine, testosterone or dutasteride were excluded. Participants with previous or current prostate cancer, elevated PSA levels, history of myocardial infarction, abnormal renal or hepatic disease, sleep apnea, previous T or other androgen treatment, or other gonadal endocrine disorders were also excluded.

2.2. Procedures

2.2.1. Study design

Participants who were not excluded from screening criteria, were randomly assigned to one of four treatment groups. Assignment for each consecutively enrolled participant was made by research pharmacists using a pre-determined assignment sheet that was created using a random number generator. Study personnel, investigators and subjects were blind to treatment condition.

Fifty-seven healthy older men who met screening criteria reported to the University of Washington General Clinical Research Unit or the Clinical Research Unit of the Veterans Administration Puget Sound Health Care System (VAPSHCS) and received weekly intramuscular (I.M.) gluteal injections of 50,100 or 300 mg testosterone enanthate (Delatestryl, Manufactured for BTG Pharmaceuticals Corporation by Bristol-Myers Squibb, Princeton, NJ 08543) or placebo (saline) for 6 weeks. Cognitive testing was conducted at baseline and repeated at weeks 3 and 6 of treatment and again after six weeks of no medication (washout). Blood samples were taken to measure serum testosterone and estradiol levels by IFMA and RIA (see below). Blood sampling and testing sessions occurred within 24–48 h following T or placebo injection to capture peak T levels. Therefore, cognitive performance results reflect the effects of peak T levels. Endogenous T levels measured at baseline, prior to the start of the study were in the slightly low to normal range (5.4–34 nmol/L) and were not significantly different between groups. PSA and hematocrit levels were measured at screening, week 4 of treatment and again at washout. Mean PSA level of 1.54 ($\pm$1.2) ng/ml for all participants at the start of the study was within normal limits (0–4 ng/ml). DRE was also conducted at screening and at the washout visit with no abnormal findings.

2.2.2. Neuropsychological test measures

The cognitive test battery included a measure of verbal and spatial memory. To help control for practice and learning effects, randomized, comparable versions of each test were