Monoamines and Neurosteroids in Sexual Function During Induced Hypogonadism in Healthy Men

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Context: Although the behavioral effects of high-dose androgen administration may involve alterations in serotonergic activity, few studies have investigated the impact of androgen withdrawal on the central nervous system in humans.

Objective: To examine the effects of pharmacologically induced hypogonadism on several cerebrospinal fluid (CSF) systems that could mediate the behavioral concomitants of hypogonadism.

Design: Double-blind assessment of the effects of the short-term induction of hypogonadism and subsequent replacement with testosterone and placebo in a crossover design.

Setting: National Institutes of Health, Bethesda, Md.

Participants: Twelve healthy male volunteers.

Interventions: We administered the gonadotropin-releasing hormone agonist leuprolide acetate (7.5 mg intramuscularly every 4 weeks) to the healthy male volunteers, creating a hypogonadal state, and then either replaced testosterone (200 mg intramuscularly) or administered a placebo every 2 weeks for 1 month.

Main Outcome Measures: Mood and behavioral symptoms were monitored with daily self-ratings, and lumbar punctures were performed during both hypogonadal (placebo) and testosterone-replaced conditions for CSF levels of steroids and monoamine metabolites.

Results: The CSF testosterone, dihydrotestosterone, and androsterone levels were significantly lower during hypogonadism (\(P=0.002, 0.04, \text{and } 0.046\), respectively), but no significant changes were observed in CSF measures of 5-hydroxyindoleacetic acid, homovanillic acid, dehydroepiandrosterone, or pregnenolone. Decreased sexual interest was observed during the hypogonadal state compared with both baseline and testosterone replacement (\(P=0.009\) and correlated significantly with CSF measures of androsterone during both hypogonadism and testosterone replacement (\(r=-0.76 \text{ and } -0.81\), respectively; \(P<0.01\)). Moreover, the change in severity of decreased sexual interest correlated significantly with the change in CSF androsterone levels between testosterone replacement and hypogonadism (\(r=-0.68; P<0.05\)). The CSF 5-hydroxyindoleacetic acid and homovanillic acid levels did not correlate significantly with any behavioral or CSF measure.

Conclusion: These data suggest that the neurosteroid androsterone contributes to the regulation of sexual function in men.

Arch Gen Psychiatry. 2006;63:450-456

Recently, there has been considerable interest in the behavioral effects of androgenic anabolic steroids, in large part due to the extent and consequences of androgenic anabolic steroid abuse among young men, the potential impact on mood and behavior of the age-related decline in androgen secretion, and the potential therapeutic use of androgen replacement in symptomatic aging men. Both increased and decreased androgen secretion have been observed to induce clinically significant mood and behavioral changes in some men. However, the effects observed are not uniform, and factors have not been identified that will predict which individuals will develop androgen-induced mood and behavioral disorders. Additionally, despite the well-described relationship between hypogonadism and loss of sexual function, the hormonal mediators of the reported loss of libido are not well described.

Several physiologic systems could mediate changes in mood associated with a change in androgen secretion, including the \(\gamma\)-aminobutyric acid (GABA) and serotonin systems, both of which are involved in the control of mood and behavior and are regulated by androgens. The animal literature has clearly documented the important regulatory effects on these systems of both increases and decreases in...
androgen secretion. Concerted changes in androgen and serotonin may underlie behavioral disorders in humans as well. For example, Virkkunen et al reported both lower 5-hydroxyindoleacetic acid (5-HIAA) and higher testosterone levels in the cerebrospinal fluid (CSF) of alcoholic, impulsive offenders with antisocial personality disorders compared with controls. In this study, although levels of both 5-HIAA (lower) and testosterone (higher) differed from controls in the group as a whole, higher CSF testosterone levels were associated with aggressive behavior, whereas lower 5-HIAA levels were associated with impulsive behavior. More recently, Daly et al observed that the androgenic anabolic steroid–induced hypogonadism and testosterone replacement. The next 18 mL was drawn in 3 aliquots (12, 3, and 3 mL) clinically significant mood and behavioral symptoms of moderate severity on the DRF during their 2-month screening phase. The protocol was reviewed and approved by the National Institute of Mental Health Intramural Research Board, and oral and written informed consent documents were obtained from all participants. Each of the men in the larger study was approached, and 12 agreed to participate in the lumbar puncture (LP) portion of the study. All of the men were paid for their participation in this protocol according to the guidelines of the National Institutes of Health Normal Volunteer Office.

PROCEDURE

This was a double-blind assessment of the effects of the short-term induction of hypogonadism and subsequent replacement with testosterone and placebo in a crossover design. After a 2-month screening phase, men received leuprolide acetate (7.5 mg intramuscularly) (Lupron; TAP Pharmaceuticals, Chicago, Ill) every 4 weeks for 3 months. Leuprolide alone was administered for the first 4 weeks. Once a consistent state of hypogonadism was achieved, participants continued to take leuprolide for an additional 8 weeks and received replacement therapy under double-blind, placebo-controlled conditions. Thus, all participants received, in addition to leuprolide, testosterone enanthate (200 mg intramuscularly every 2 weeks) or placebo (sesame oil, 1.5 mL intramuscularly every 2 weeks as color-matched vehicle) for 1 month (ie, 2 consecutive injections of each compound) and then crossed over to the other replacement. The order of replacement was randomly assigned and counterbalanced. Both subjects and raters were blind to the order of replacement. Blood samples were obtained at the time of the LP. Blood samples were centrifuged, aliquoted, and stored at −70°C until time of assay.

CSF MEASURES

All participants consumed a low-monoamine diet for 2 days before LP. The participants remained fasting from midnight. All LPs were conducted between 9:00 AM and 10:30 AM at the end of both the testosterone replacement and placebo phases. The LPs were performed with a sterile technique in the L4–L5 interspace with the participant in the lateral decubitus position. A total of 21 mL of CSF was collected from each participant. The first 3 mL collected was used for standard clinical studies. The next 18 mL was drawn in 3 aliquots (12, 3, and 3 mL). The first aliquot was subdivided into six 1-mL subaliquots and two 3-mL aliquots, to which 20 µL of 20% formic acid was added. The samples were placed on ice and stored at −70°C until assayed.

ASSAYS

The following CSF assays were performed: 5-HIAA, homovanillic acid (HVA), testosterone, dihydrotestosterone, androstenedione, DHEA, and pregnenolone. The CSF steroids and neurosteroids were analyzed by gas chromatography/electronic
To assess the severity of mood symptoms, the DRF was completed at baseline and during each hormonal condition. The DRF, a 6-point Likert-type scale, was modified to include the symptoms measured in this study and was completed nightly to represent a composite rating for the previous 12 hours; scores range from 1 (symptom not present) to 6 (symptom present in the extreme). The symptoms measured included the following: avoidance of social activity; loss of enjoyment or interest; impaired function at work or at home; irritability or anger; impaired concentration or distractibility; mood swings; feeling depressed, sad, low, or blue; anxiety or nervousness; decreased eating; increased eating; more sleep, naps, or lying in bed; low energy; loneliness or feeling rejected; being physically restless or agitated; feeling powerful, emotionally charged, or pumped up; increased sexual interest; decreased sexual interest; disturbed sleep; drinking of alcohol or use of nonprescribed drugs; impulse to hurt self; impulse to hurt someone else; acting on impulse to hurt someone; daytime hot flushes; and nighttime hot flushes. The mean DRF rating for the last 7 days of each hormonal condition was calculated for each symptom. Finally, during each biweekly clinic visit, the Beck Depression Inventory (BDI), a standardized measure of depression severity, was completed.

STATISTICAL ANALYSIS

Levels of both blood and CSF androgens and BDI and DRF symptom ratings were not normally distributed (ie, the standard deviation approximated the mean for several measures, and no values were negative numbers); consequently, all measures were compared across hormone conditions (hypogonadal vs testosterone replacement) by the Wilcoxon signed rank test.

Spearman correlation coefficients were used as a conservative measure because of the nonparametric nature of mood ratings and the skewed distribution of CSF measures. Correlations performed were those between CSF measures of steroids and monoamine metabolites and those between selected mood and behavioral symptoms and CSF measures. Spearman correlations were performed on the values for measures obtained during both the hypogonadal and testosterone-replaced conditions and on the difference in measures between these conditions. However, the latter correlations were limited to only those measures (either biological or behavioral) that significantly changed across hormone conditions (as demonstrated by the Wilcoxon signed rank test). Finally, Spearman correlation coefficients were calculated between levels of free and total testosterone in the blood and levels of testosterone in the CSF.

Plasma hormone levels (Table 1) showed significant changes between testosterone-replaced and hypogonadal conditions, with the hypogonadal state associated with significantly lower levels of total testosterone, free testosterone, dihydrotestosterone, and estradiol. Comparisons of the BDI scores and the DRF symptom scores across hormone conditions showed a significant increase (more symptomatic) in the following symptoms during the hypogonadal state compared with the testosterone-replaced condition: BDI scores (z = 2.4; P < .02), daytime hot flushes (z = 2.2; P < .03), nighttime hot flushes (z = 2.2; P = .03), and decreased sexual interest (z = 2.6; P = .009) (the symptom of increased sexual interest changed [decreased] but only at a trend level of significance [z = −2.0; P = .05]). The BDI scores during hypogonadism ranged from 0 to 14, but only 2 men had BDI scores of 7 or greater (values of 9 and 14). No other symptom rating scores significantly changed across hormone conditions. A similar pattern of symptom change was observed in a larger study of men participating in this protocol (many of whom did not undergo LP).

The CSF monoamine and neurosteroid levels are presented in Table 2. Significantly lower CSF levels of testosterone, androsterone, and dihydrotestosterone but not DHEA or pregnenolone were observed during hypogonadism compared with the testosterone-replaced condition. No significant differences in CSF measures of 5-HIAA or HVA were observed across hormonal conditions.

CORRELATIONS BETWEEN SYMPTOMS AND CSF MEASURES

The CSF levels of androsterone were correlated with the severity of decreased sexual interest during both hypogonadal and testosterone-replaced conditions (r = −.76, P < .01; and r = −.81, P < .001, respectively) (Table 3). Additionally, the change in CSF androsterone levels was correlated with the change in the severity of decreased sexual interest between testosterone-replaced and hypogonadal conditions (r = −.68; P < .05). Only a few addi-
tional symptom correlations were significant. During the hypogonadal state, values of CSF testosterone significantly correlated with BDI scores ($r = -0.72; P = .01$), as well as with both daytime and nighttime hot flushes ($r = -0.72$ and $-0.83$, respectively; $P < .01$). No other significant correlations were observed between those symptoms selected for showing a significant difference across hormone conditions and measures of CSF monoamines or neurosteroid levels.

**CORRELATIONS BETWEEN INDIVIDUAL CSF MEASURES**

The change in serum levels of free testosterone but not total testosterone correlated with the change in CSF testosterone ($r = 0.6; P < .05$); no significant correlations were observed, however, between these measures during either the hypogonadal or testosterone-replaced conditions.

**CORRELATIONS BETWEEN BLOOD HORMONE LEVELS AND CSF MEASURES**

The CSF measures of 5-HIAA and HVA were significantly correlated during both the leuprolide-induced hypogonadism ($r = 0.85; P < .01$) and testosterone-replaced conditions ($r = 0.87; P < .001$). Additionally, during the hypogonadal state, CSF measures of androsterone were correlated with both CSF 5-HIAA ($r = -0.60; P = .05$) and CSF DHEA ($r = -0.66; P < .05$). During testosterone replacement, there were no significant correlations other than that between 5-HIAA and HVA. However, across hormone conditions, a significant correlation

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**Table 2. Cerebrospinal Fluid Measures of Monoamine Metabolites and Neurosteroids in 12 Men During Leuprolide Acetate–Induced Hypogonadism and After Testosterone Replacement**

<table>
<thead>
<tr>
<th>Hormone</th>
<th>Hypogonadism</th>
<th>Testosterone Replaced</th>
<th>z Score†</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>5-HIAA, pmol/mL</td>
<td>149.1 (59.1)</td>
<td>137.3 (45.7)</td>
<td>-0.9</td>
<td>.39</td>
</tr>
<tr>
<td>HVA, pmol/mL</td>
<td>257.2 (105.5)</td>
<td>229.0 (78.2)</td>
<td>-0.9</td>
<td>.35</td>
</tr>
<tr>
<td>Testosterone, pg/mL</td>
<td>9.8 (4.8)</td>
<td>143.3 (63.9)</td>
<td>3.1</td>
<td>.002</td>
</tr>
<tr>
<td>Androsterone, pg/mL</td>
<td>20.8 (34.4)</td>
<td>41.1 (27.5)</td>
<td>2.1</td>
<td>.04</td>
</tr>
<tr>
<td>Dihydrotestosterone, pg/mL</td>
<td>0.3 (1.2)</td>
<td>3.7 (5.2)</td>
<td>2.0</td>
<td>.046</td>
</tr>
<tr>
<td>DHEA, pg/mL</td>
<td>328.5 (181.6)</td>
<td>366.0 (370.6)</td>
<td>0.0</td>
<td>&gt;.99</td>
</tr>
<tr>
<td>Pregnenolone, pg/mL</td>
<td>11.1 (8.4)</td>
<td>16.8 (15.1)</td>
<td>1.2</td>
<td>.24</td>
</tr>
</tbody>
</table>

**Table 3. Spearman Correlation Coefficients Between Cerebrospinal Fluid Measures of Neurosteroids and Symptom Ratings**

<table>
<thead>
<tr>
<th></th>
<th>Androsterone</th>
<th>Dihydrotestosterone</th>
<th>Testosterone</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypogonadism</td>
<td>1.00</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Androsterone</td>
<td>1.00</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dihydrotestosterone</td>
<td>0.60</td>
<td></td>
<td>0.40</td>
</tr>
<tr>
<td>Testosterone</td>
<td>0.01</td>
<td>0.10</td>
<td>1.00</td>
</tr>
<tr>
<td>Beck Depression Inventory</td>
<td>-0.12</td>
<td>-0.41</td>
<td>-0.72*</td>
</tr>
<tr>
<td>Hot flushes (day)</td>
<td>-0.24</td>
<td>-0.32</td>
<td>-0.79*</td>
</tr>
<tr>
<td>Hot flushes (night)</td>
<td>-0.28</td>
<td>-0.32</td>
<td>-0.83*</td>
</tr>
<tr>
<td>Decreased sexual interest</td>
<td>-0.76*</td>
<td>-0.50</td>
<td>-0.02</td>
</tr>
<tr>
<td>Testosterone replaced</td>
<td>1.00</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Androsterone</td>
<td>1.00</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dihydrotestosterone</td>
<td>0.36</td>
<td></td>
<td>1.00</td>
</tr>
<tr>
<td>Testosterone</td>
<td>0.60</td>
<td>0.40</td>
<td>1.00</td>
</tr>
<tr>
<td>Beck Depression Inventory</td>
<td>-0.11</td>
<td>-0.02</td>
<td>0.02</td>
</tr>
<tr>
<td>Hot flushes (day)</td>
<td>-0.08</td>
<td>0.49</td>
<td>0.08</td>
</tr>
<tr>
<td>Hot flushes (night)</td>
<td>-0.30</td>
<td>0.44</td>
<td>0.20</td>
</tr>
<tr>
<td>Decreased sexual interest</td>
<td>-0.81*</td>
<td>-0.26</td>
<td>-0.49</td>
</tr>
<tr>
<td>Change from hypogonadism to testosterone replaced</td>
<td>1.00</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Androsterone</td>
<td>1.00</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dihydrotestosterone</td>
<td>0.67*</td>
<td></td>
<td>1.00</td>
</tr>
<tr>
<td>Testosterone</td>
<td>0.15</td>
<td>0.27</td>
<td>1.00</td>
</tr>
<tr>
<td>Beck Depression Inventory</td>
<td>0.13</td>
<td>-0.08</td>
<td>0.30</td>
</tr>
<tr>
<td>Hot flushes (day)</td>
<td>0.04</td>
<td>0.22</td>
<td>0.31</td>
</tr>
<tr>
<td>Hot flushes (night)</td>
<td>0.14</td>
<td>0.27</td>
<td>0.22</td>
</tr>
<tr>
<td>Decreased sexual interest</td>
<td>-0.68*</td>
<td>-0.46</td>
<td>0.04</td>
</tr>
</tbody>
</table>

*P < .05.
was present between changes in CSF dihydrotestosterone and androsterone ($r=0.67; P<.05$).

**COMMENT**

This study yielded 2 main findings. First, the symptom of decreased sexual interest correlated significantly with CSF measures of androsterone. Thus, this novel hormone, whose affinity is low for the androgen receptor (AR) but high for the GABA<sub>A</sub> receptor, could mediate the effects of androgen on male sexual function. Second, during hypogonadism, changes in mood, sexual interest, and hot flushes were not correlated with CSF 5-HIAA or HVA. In contrast to previous studies in both animals and humans, levels of these monoamine metabolites did not significantly change during hypogonadism compared with testosterone replacement.

The short-term suppression of androgen secretion is associated with decreased libido and the development of hot flushes in most men and with changes in mood, energy level, and cognition in only some men. In a relatively small sample of men with leuprolide-induced hypogonadism, we observed that hypogonadism was associated with a significant decrease in sexual interest and an increase in both hot flushes (daytime and nighttime) and BDI scores (depression). These data are consistent with observations from the larger cohort of men, from which the men in this study were recruited. The symptom of decreased sexual interest did not correlate with CSF measures of testosterone, dihydrotestosterone, or DHEA, all of which are reported to increase sexual interest when administered to hypogonadal men. However, we observed that decreased sexual interest significantly correlated with CSF measures of androsterone. The correlations with CSF androsterone were observed during both the hypogonadal and testosterone-replaced conditions; in addition, the magnitude of the decrease in sexual interest correlated with the magnitude of the decrease in CSF androsterone levels across conditions. Thus, regardless of the hormonal state, the association between decreased sexual interest and CSF androsterone levels (but not other androgens measured) remained significant. Our findings, then, suggest that CSF androsterone contributes to the regulation of sexual interest in men.

The neurobiologic characteristics of sexual behavior are complex, involving multiple neuroanatomical regions (eg, limbic and prefrontal reward areas), neuroregulatory systems (eg, serotonin, dopamine, and nitric oxide), and the influence of numerous contextual variables (eg, past experience and environmental cues). Gonadal steroids are well-established neuromodulators and play an integral regulatory role in several aspects of sexual behavior. For example, in male sexual behavior, the AR and estrogen receptors α and β are implicated; however, the mechanisms involved are not fully documented. Additionally, sexual regulation in female rodents appears to involve neurosteroid metabolites of both progesterone and androgens, potentially acting through modulation of ligand-gated ion channels, mediating several important aspects of sexual behavior (eg, receptivity). Our findings with androsterone in men are not without precedent in studies of animal sexual behavior. Although less is known about the behavioral relevance of androsterone compared with other androgens, androsterone administration reverses castration-induced decreases in the sexual behavior of male zebra finches. However, these effects of androsterone are not observed in other species of birds or rodents. Finally, androsterone reduces anxiety in male mice during sexual encounters and therefore may indirectly modulate aspects of sexual behavior.

Androsterone (3α-hydroxy-5α-androstan-17-one) is a 17-ketosteroid metabolite of 3α-dihydrotestosterone, and like other gonadal steroids, androsterone may exert its effects on the central nervous system through several possible mechanisms. It is a weak androgen with a lower affinity for the AR than either of its precursors, dihydrotestosterone or testosterone. Androsterone and its sulfate are also potent neurosteroids and modulate activity at the GABA<sub>A</sub> receptor complex with an affinity comparable to the neurosteroid allopregnanolone. Androsterone increases GABA-activated chloride influx, with brain region-specific potentiation in the amygdala and hippocampus. Finally, androsterone may serve as a precursor for the production of 3α- and 3β-androstanediol, the latter compound being an active ligand at the estrogen receptor β receptor. Thus, androsterone has neuroregulatory potential and could regulate sexual function by its actions at the AR, the estrogen receptor, or the GABA<sub>A</sub> receptor complex. Recent studies of both estrogen receptor β and aromatase knockout mice have identified regulatory roles for both estradiol and its receptors in male sexual function. Two observations in this study suggest that androsterone’s effects on sexual function are more likely mediated through estrogen receptor than either AR or GABA<sub>A</sub> receptors. First, the lack of association between changes in sexual function and either testosterone or dihydrotestosterone is not consistent with an AR-mediated effect. Both testosterone and dihydrotestosterone are more potent agonists at the AR than androsterone, and if the effects on sexual function involved the AR, one would expect to observe greater effects on sexual function with changes in these more potent AR ligands. Second, no significant changes in anxiety accompanied the hypogonadism-related changes in either libido or androsterone levels, and therefore a role for GABA<sub>A</sub> action is unlikely.

The second finding of this study was the absence of evidence in humans that short-term induction of hypogonadism alters CSF monoamine activity. No significant changes in CSF monoamine levels were observed during hypogonadism compared with testosterone replacement, and no significant correlations were observed between CSF 5-HIAA and either CSF testosterone or behavioral symptoms. In fact, with the exception of a significant negative correlation between CSF androsterone and 5-HIAA, no significant correlations were observed between CSF levels of monoamines and those of testosterone, DHT, DHEA, or pregnenolone. Although CSF androgen levels significantly decreased during hypogonadism, we observed no decrease in 5-HIAA levels. The significant correlation...
between 5-HIAA and androsterone levels during hypo-
gonadism was negative, in a direction consistent with the
observations of Virkkunen et al.16 As a caveat, it is diffi-
cult to attribute physiologic significance to the correla-
tions between CSF measures of androsterone and 5-HIAA
or DHEA, since levels of neither 5-HIAA nor DHEA changed across hormonal conditions despite significant changes in androsterone. In contrast to the reported asso-
ciation of anabolic steroid–induced mood and behav-
ioral symptoms (activation) with increased CSF 5-HIAA
levels,17 we observed no correlation between androgen
withdrawal–related behavioral symptoms and measures of
CSF 5-HIAA or HVA. There are several possible rea-
sons for our inability to detect significant changes in CSF
monoamine activity during induced hypogonadism. First,
androgen withdrawal–related behavioral symptoms may
be mediated by systems distinct from those implicated in
the behavioral activation secondary to androgen ex-
cess (ie, serotonergic). Alternatively, CSF measures of
monoamine metabolites, which represent integrated mea-
sures of central monoamine activity, may not be suffi-
ciently sensitive to brain region–specific changes in mono-
amines occurring after a short-term change in endocrine
state or behavior. For example, in male rats gonadectomy
alters brain monoamine metabolism in a brain re-
gion–specific manner, increasing levels of HVA in the
hypothalamus and brainstem and levels of 5-HIAA in the
hypothalamus and striatum.68 Finally, it is possible that
our failure to observe significant correlations between CSF
5-HIAA and sexual behavior was due to the relatively low
levels of behavioral symptoms that were observed in our
sample.

Although not significantly correlated with sexual in-
terest, CSF levels of testosterone correlated with both hot
flush severity and BDI scores during the hypogonadal state,
when men were symptomatic. Hot flush severity ac-
counted for approximately 60% of the variance in BDI
scores in a stepwise linear regression; therefore, BDI scores
probably reflected hot-flush–related symptoms of dis-
turbed sleep or fatigue. The correlation between hot
flushes and testosterone suggests that testosterone may
be a direct thermoregulator or, alternatively, that testos-
terone levels reflect the amount of precursor available for
aromatization to estrogen.

Our data suggest that the effects of testosterone on
some aspects of sexual function are mediated by the neuro-
steroid metabolite of dihydrotestosterone, androste-
one. In contrast to the other androgens measured in this
study, CSF levels of androsterone alone correlated with
decreased libido during both hypogonadism and testos-
terone replacement; in addition, the change in andro-
sterone levels across hormone conditions was correlated
with the corresponding decrease in sexual interest. The
self-report rating scale that we used does not permit discri-
mination of changes in sexual behavior from changes in
cognition or perception. As a caveat, had we studied
a larger sample of men, it is possible that some of the cor-
relations between additional CSF measures and sym-
poms would have met statistical significance. Future stud-
ies using larger samples of men, a more comprehensive
measure of the components of sexual function, and pos-
sibly measures of performance may identify a more spe-
cific role of androsterone or its metabolites in male sexual
function. Finally, the failure to measure androsterone may
help explain the discrepant findings in the literature re-
garding the role of testosterone in sexual function in men.

Submitted for Publication: May 20, 2005; final revision
received September 28, 2005; accepted September 29, 2005.
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Funding/Support: This study was supported by the In-
tramural Research Programs of the National Institutes of
Health, National Institute of Mental Health, and National
Institute of Alcohol Abuse and Alcoholism, Bethesda, Md.

Acknowledgment: We acknowledge Markku Linnoila,
MD, PhD (in memoriam), for the monoamine metabo-
lite assays; Carolyn Gibson, BSc, for assistance with data
analysis; and Merry Danaceau, RN, MSNCS, for clinical
assistance.

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