

Cerebrospinal Fluid and Behavioral Changes After Methyltestosterone Administration

Preliminary Findings

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Background: Anabolic androgen steroid abuse is associated with multiple psychiatric symptoms and is a significant public health problem. The biological mechanisms underlying behavioral symptom development are poorly understood.

Subjects and Methods: We examined levels of monoamine metabolites, neurohormones, and neuropeptides in the cerebrospinal fluid (CSF) of 17 healthy men, at baseline and following 6 days of methyltestosterone (MT) administration (3 days of 40 mg/d, then 3 days of 240 mg/d). Subjects received MT or placebo in a fixed sequence, with neither subjects nor raters aware of the order. Potential relationships were examined between CSF measures, CSF MT levels, and behavioral changes measured on a visual analog scale.

Results: Following MT administration, levels of 3-methoxy-4-hydroxyphenylglycol (MHPG) were significantly lower (mean±SD, 103.8±47 vs 122.0±50.7 pmol/mL; $P<.01$), and 5-hydroxyindoleacetic acid (5-HIAA) levels were significantly higher (mean±SD,

104.7±31.3 vs 86.9±23.6 pmol/mL; $P<.01$). No significant MT-related changes were observed in CSF levels of corticotropin, norepinephrine, cortisol, arginine vasopressin, prolactin, corticotropin-releasing hormone, β -endorphin, and somatotropin release-inhibiting factor. Changes in CSF 5-HIAA significantly correlated with increases in "activation" symptoms (energy, sexual arousal, and diminished sleep) ($r=0.55$; $P=.02$). No significant correlation was observed between changes in CSF and plasma MT, CSF MHPG, and behavioral symptoms.

Conclusions: Short-term anabolic androgenic steroid use affects brain neurochemistry, increasing CSF 5-HIAA and decreasing MHPG. Changes in 5-HIAA levels caused by anabolic androgenic steroids are related to the behavioral changes we observed. In this small sample, we did not observe a significant relationship between behavioral measures and either dose of MT or CSF and plasma levels of MT.

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ANABOLIC ANDROGENIC steroid (AAS) abuse poses a significant public health problem and has been associated with a range of psychiatric symptoms, including psychosis,¹ irritability and aggression,² and major mood syndromes.³ In a previous study of normal men,⁴ we demonstrated that even short-term administration of the AAS methyltestosterone (MT) produced significant mood and behavioral symptoms. Two subsequent blind, placebo-controlled studies^{5,6} confirmed the ability of such steroids to induce mood and behavioral symptoms in both normal volunteers and AAS users. The mechanisms underlying the development of AAS-induced psychiatric symptoms remain largely undetermined.

Studies in animals and humans have implicated several neurochemical sys-

tems in the observed effects of AAS. For example, in rodents these steroids produce brain region-specific increases in β -endorphin⁷ and vasopressin,⁸ up-regulate glucocorticoid receptor immunoreactivity in the hippocampus,⁹ and bind the benzodiazepine binding site of the γ -aminobutyric acid type A receptor¹⁰; further, AAS-induced aggression can be modulated by manipulation of central serotonin function.^{11,12} In human beings, AAS administration may be accompanied by increases in plasma homovanillic acid (HVA). In addition, steroid abuse may be associated with hypomania, depression, and a dependent pattern of use.^{5,13} Previous studies examining cerebrospinal fluid (CSF) have yielded valuable information about the pathophysiology of such conditions, including the potential roles of somatotropin release-inhibiting factor (SRIF)¹⁴ and corticotropin-releasing hor-

SUBJECTS AND METHODS

Subject selection and protocol are as previously described⁴ and are summarized as follows. Twenty-three medication-free, healthy men between the ages of 18 and 42 years were recruited through advertisements in the hospital newsletter of the National Institutes of Health Clinical Center in Bethesda, Md. Three volunteers were excluded because of medical problems or a positive drug screen. The remaining 20 subjects had no significant history of psychiatric illness or AAS use and were free of any recent (past 2 years) history of alcohol or substance abuse. This was confirmed with a standardized psychiatric interview¹⁷ administered by a psychiatrist. After the subjects received a complete description of the study, written informed consent was obtained. The protocol was approved by the National Institute of Mental Health (NIMH) Institutional Review Board (Bethesda, Md).

Following a 2-day acclimatization period at an NIMH inpatient unit, all subjects received MT or placebo administered as 3 capsules, 3 times daily. These capsules were given in a fixed sequence with neither subjects nor raters aware of the order of administration. The following schedule was used for each subject: 3 days of placebo (baseline phase), 3 days of MT (low-dose phase; 40 mg/d), 3 days of MT (high-dose phase; 240 mg/d), and 3 more days of placebo (withdrawal phase). Subjects were informed that the purpose of the study was to understand possible behavioral reactions to AAS and were told that they would be asked questions regarding their mood and thinking on a daily basis.

CSF MEASURES

All subjects adhered to a low-monoamine diet beginning 2 days before the first lumbar puncture. Before the

procedure, subjects fasted for at least 9 hours and had continuous bed rest for a minimum of 1 hour, except for getting up once to void. Lumbar punctures were conducted between 9 AM and 10:30 AM on the final mornings of the baseline and high-dose phases. They were performed in the L4-5 interspace with the patient in the lateral decubitus position, using a sterile technique. Seventeen of the 20 subjects underwent successful CSF sampling in both phases. From each subject, 21 mL of CSF were collected. The first 3 mL were used for standard clinical studies, and the next 18 mL were drawn in 3 aliquots (12 mL, 3 mL, 3 mL). The first aliquot was subdivided into 1-mL subaliquots; the samples were placed on ice and stored at -70°C until assayed. The following CSF assays were performed: 3-methoxy-4-hydroxyphenylglycol (MHPG), 5-hydroxyindoleacetic acid (5-HIAA), HVA, norepinephrine, dopamine, β -endorphin, prolactin, adrenocorticotrophic hormone (ACTH), cortisol, CRH, SRIF, and arginine vasopressin (AVP). Cerebrospinal fluid measures and serum MT level assays were also performed on samples obtained during the high-dose phase.

BEHAVIORAL MEASURES

Visual analog scale ratings were completed 3 times per day (10 AM, 6 PM, and 10 PM) for a range of subjective behavioral measures. The reliability and validity of such analog scales in rating subjective feelings has been established.¹⁸ The highest rating recorded each day was selected and then averaged for the 3 days of that particular phase (ie, baseline or high-dose phase). The use of highest daily rating scores was chosen for several reasons. The low doses of AAS used in this study (compared with doses abused) gave rise to relatively modest mood changes. Additionally, mood symptoms

Continued on next page

mone (CRH) in affective disorders¹⁵ and of endorphins in addiction.¹⁶

In an effort to further identify possible mechanisms underlying observed behavioral changes, we performed CSF sampling in our previously described group⁴ at baseline and following 6 days of MT administration. A variety of CSF measures were obtained, including amine metabolites that reflect the activity of neural systems presumed to underlie affect and behavioral regulation, and neuropeptides and neurohormones that can cause behavioral disorders related to stress and addiction.

Two questions were posed in the investigation. First, during MT administration, are there alterations in CSF metabolites that have been observed to change either in animal studies of AAS effects or in clinical syndromes in humans (such as hypomania or aggression) that may be associated with AAS use? Second, are such metabolic changes (if any) correlated with the observed behavioral changes following AAS use?

RESULTS

Following MT administration, CSF MT levels ranged from 65 to 898 nmol/L (mean \pm SD, 232.7 ± 210.9 nmol/L). Serum MT levels ranged from 3 to 102 nmol/L (mean \pm SD,

20.5 ± 24.0 nmol/L). After MT administration, there was a significant increase (compared with baseline) in CSF levels of 5-HIAA ($t_{16}=3.3$, $P=.005$) (**Figure 1**) and a significant decrease in MHPG levels ($t_{16}=3.0$, $P=.009$) (**Figure 2**). After the Bonferroni adjustment, P values for changes in CSF 5-HIAA and MHPG remained significant or near significant at $P \leq .05$ and $P \leq .1$, respectively. Other CSF measures did not change significantly between the baseline and high-dose phases (**Table 2**). Changes in CSF 5-HIAA were not significantly correlated with changes in CSF MHPG ($r=0.21$, $P=.40$). Changes in CSF 5-HIAA were significantly correlated with changes in activation cluster scores ($r=0.55$, $P=.02$) (**Figure 3**); changes in aggressiveness ($r=-0.30$, $P=.21$) and cognitive ($r=0.18$, $P=.49$) cluster scores did not correlate significantly with changes in CSF 5-HIAA. Changes in MHPG did not significantly correlate with activation ($r=-0.09$, $P=.72$), aggressiveness ($r=0.03$, $P=.91$), or cognitive ($r=0.31$, $P=.22$) cluster score changes.

Cerebrospinal fluid and serum MT levels were significantly correlated ($r=0.77$, $P<.01$). Cerebrospinal fluid MT levels did not significantly correlate with aggressiveness ($r=-0.19$, $P=.47$), activation ($r=0.14$, $P=.61$), or cognitive ($r=-0.03$, $P=.91$) cluster score changes, nor did they correlate with changes in CSF 5-HIAA ($r=-0.12$,

occurring in response to AAS tend to be episodic. Consequently, the use of highest daily scores enhanced our ability to detect symptoms precipitated during the course of the study. Mood and behavioral ratings were measured during all 4 phases of the study (baseline, low-dose, high-dose, and withdrawal) and were reported in our previous article.⁴ The Bonferroni *t* test comparison of the withdrawal phase with the baseline phase demonstrated only 1 symptom, sexual arousal, to be significantly increased during withdrawal; in this article we confined our analysis to symptoms showing significant change during the high-dose phase. Use of this approach (examining the difference between baseline and high-dose scores) yielded 7 symptoms that changed during the high-dose phase ($P \leq .1$; **Table 1**). These symptoms fell within 3 previously observed⁴ behavioral symptom clusters: "activation" (energy, sexual arousal, and diminished sleep), "aggressiveness" (anger, violent feelings, and irritability), and "cognitive" (distractibility). Cluster scores were calculated by averaging the means from each contributory symptom. Cluster score changes, not individual symptom score variations, were correlated with CSF changes (to decrease the number of comparisons made). To reduce the possibility that a significant correlation would represent the effect of a single symptom, the symptom of forgetfulness was added to distractibility to create a cognitive cluster.

ASSAYS

The following assays were performed by the methods previously described: ACTH,¹⁹ CRH,²⁰ and β -endorphin²¹ were measured at Hazelton Laboratories in Vienna, Va, by radioimmunoassay, with intra-assay and interassay coefficients of variation of 9.4% (18.6%), 5.6% (12.7%), and 9.3% (6.7%), respectively. Cortisol and AVP^{22,23} were also measured by radioimmunoassay. Intra-assay and

interassay coefficients of variation were 1.8% (7.2%) and 9.8% (19.4%), respectively. Cerebrospinal fluid and serum MT measurements²⁴ were performed by Christiane Ayotte, PhD, at the Institute National de la Recherche Scientifique-Santé in Quebec City, Quebec, using gas chromatography and mass spectrometry. Cerebrospinal fluid SRIF assays²⁵ with modifications²⁶ were performed by the Behavioral Endocrinology Laboratory at the NIMH using radioimmunoassay. Catecholamine and monoamine metabolite measures were performed by the Laboratory of Clinical Science at the NIMH. Norepinephrine and dopamine were initially extracted by acid hydrolysis.²⁷ The metabolites 5-HIAA, MHPG, and HVA, and the extracted catecholamines, were measured using high-performance liquid chromatography with electrochemical detection.^{28,29} Assays for 5-HIAA, MHPG, HVA, dopamine, and norepinephrine were performed in 1 batch, with 4% to 6% intra-assay variation.

ANALYSIS OF DATA

All analyses were computed using the Systat 8.0 (Statistical Product and Service Solutions, Chicago, Ill) statistical package. Differences in CSF laboratory parameters between baseline and high-dose phases were analyzed using paired *t* tests; *P* values for paired *t* test scores examining differences in CSF measures were adjusted using the Bonferroni adjustment for multiple comparisons. Spearman rank correlation coefficients were calculated between behavioral cluster scores, CSF measures showing changes (Bonferroni adjustment, $P \leq .1$) during MT administration, CSF MT levels, and plasma MT levels. The α level of significance was $P \leq .05$ for analyses unless otherwise specified. Two-tailed *t* tests were used; data are presented as mean \pm SD.

Table 1. Effect of Methyltestosterone on Symptom Cluster Scores Between Baseline and High-Dose Phases*

Symptom Clusters	Baseline Rating, Mean (SD)	High-Dose Rating, Mean (SD)	Paired <i>t</i> Test†
Cognitive	4.6 (4.7)	9.3 (8.8)	$t = 2.3, P = .03$
Forgetfulness	3.8 (4.6)	7.2 (9.8)	$t = 1.56, P = .13$
Distractibility	5.4 (6.9)	11.4 (12.4)	$t = 2.69, P = .01$
Activation	24.8 (20.7)	31.5 (16.9)	$t = 4.2, P = .001$
Energy	37.5 (30.8)	42.0 (28.5)	$t = 2.24, P = .04$
Sexual arousal	27.3 (29.8)	35.3 (31.1)	$t = 4.09, P = .001$
Disturbed sleep	9.5 (11.4)	17.2 (16.8)	$t = 1.83, P = .08$
Aggressiveness	14.6 (9.9)	18.5 (12.3)	$t = 2.8, P = .01$
Anger	5.4 (8.9)	7.4 (11.6)	$t = 1.93, P = .07$
Violent feelings	23.9 (18.4)	27.1 (20.3)	$t = 2.0, P = .06$
Irritability	14.6 (12.5)	20.9 (19.8)	$t = 2.25, P = .04$

**N* = 20.

†*df* = 19.

$P = .65$) or CSF MHPG ($r = 0.08, P = .76$). In addition, plasma MT levels did not correlate significantly with aggressiveness ($r = -0.02, P = .93$), activation ($r = -0.07, P = .78$), or cognitive ($r = 0.35, P = .18$) cluster score changes, nor did they correlate with changes in CSF

5-HIAA ($r = 0.08, P = .76$) or CSF MHPG ($r = 0.16, P = .55$ levels).

COMMENT

To our knowledge, this is the first reported study examining CSF changes following AAS administration in human subjects and suggests a possible mechanism underlying AAS-induced alterations of mood and behavior. Most notably, CSF 5-HIAA increased and MHPG levels decreased following MT administration, and the changes observed in CSF 5-HIAA were significantly correlated with the changes seen in activation symptom cluster scores.

After oral MT administration, MT was present in both plasma and CSF, and levels were significantly correlated. A high CSF-to-plasma concentration gradient was observed; relative differences between CSF and plasma in amounts of binding proteins and solubility of MT may possibly have contributed to this gradient. The absence of correlation between CSF or plasma MT levels and either behavioral changes or CSF measure changes suggests that biological and behavioral responses to MT do not show a linear dose-response relationship. Hence, variability in the expression of

adverse behavioral symptoms is not attributable simply to differences in dose of MT or to plasma levels achieved. The finding of lowered CSF MHPG (albeit at a trend level of significance when the Bonferroni adjust-

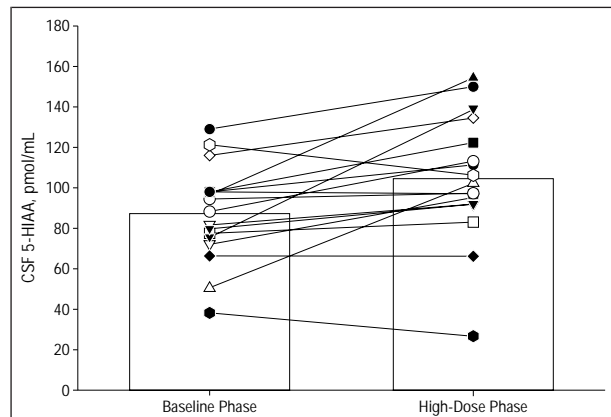


Figure 1. Methyltestosterone-induced changes in cerebrospinal fluid 5-hydroxyindoleacetic acid (CSF 5-HIAA) concentrations ($n = 17$). Treatment conditions resulted in a significant increase in CSF 5-HIAA ($t_{16} = 3.3, P = .005$).

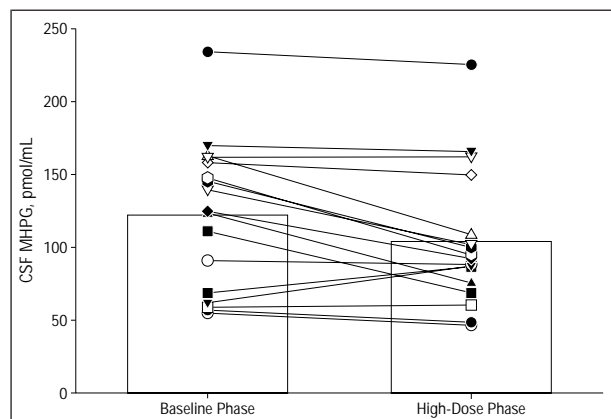


Figure 2. Methyltestosterone-induced changes in cerebrospinal fluid 3-methoxy-4-hydroxyphenylglycol (CSF MHPG) concentrations ($n = 17$). Treatment conditions resulted in a significant decrease in CSF MHPG ($t_{16} = 3.0, P = .009$).

ment was used) may reflect a decrease in norepinephrine clearance, a speculation consistent with the increase (however insignificant) in CSF norepinephrine and supported by data showing decreased metabolism of norepinephrine by monoamine oxidase and catechol-O-methyltransferase in rat adrenal glands after AAS administration.³⁰ Nevertheless, the absence of significant correlations between changes in MHPG and behavioral changes suggests a minimal role for noradrenergic changes in the development of behavioral symptoms.

Hypomaniac symptoms have been widely reported as occurring during AAS use,^{1,5,6} and the activation cluster, which comprised diminished sleep, increased energy, and increased sexual feelings, samples symptoms of hypomania. Our finding of a correlation between increases in CSF 5-HIAA and the development of activation symptoms is consistent with 2 studies, one showing higher levels of 5-HIAA in women with mania compared with controls,³¹ and another showing increased levels of CSF 5-HIAA during mania compared with recovery.³² However, other reports have shown

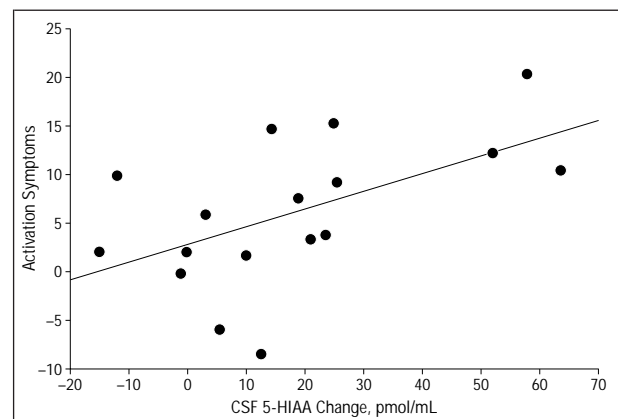


Figure 3. Correlation of changes in activation symptom cluster scores with changes in cerebrospinal fluid 5-hydroxyindoleacetic acid (CSF 5-HIAA) following methyltestosterone administration ($r = 0.55, P = .02$). Activation symptom cluster includes energy, sexual arousal, and diminished sleep.

Table 2. Effect of Methyltestosterone on Cerebrospinal Fluid Neuropeptide and Neurotransmitter Metabolite Levels*

Cerebrospinal Fluid Measure†	Baseline Levels, Mean (SD)	Levels After High-Dose Anabolic Androgen Steroid Administration,		Paired <i>t</i> Test‡
		Mean (SD)	Mean (SD)	
5-HIAA, pmol/mL	86.9 (23.6)	104.7 (31.3)		$t = -3.26, .005$
MHPG, pmol/mL	122.0 (50.7)	103.8 (47.0)		$t = 2.98, .009$
HVA, pmol/mL	174.1 (62.2)	187.3 (77.3)		$t = -0.82, .42$
Norepinephrine, pmol/mL	3.5 (4.1)	4.6 (3.9)		$t = -0.74, .47$
Dopamine, pmol/mL	3.1 (0.9)	2.9 (2.2)		$t = 0.17, .86§$
ACTH, pg/mL	26.4 (6.9)	25.5 (6.1)		$t = 0.76, .46$
AVP, pg/mL	2.6 (1.0)	2.3 (0.5)		$t = 0.94, .36§$
Cortisol, µg/dL	0.5 (0.1)	0.5 (0.1)		$t = 1.69, .11$
CRH, pg/mL	39.9 (13.8)	41.1 (14.4)		$t = -1.03, .32§$
Endorphin, pg/mL	20.5 (6.5)	20.3 (5.0)		$t = 0.13, .90$
Somatostatin, ng/L	70.8 (23.8)	74.3 (24.4)		$t = -1.1, .29$

* $N = 17$.

†5-HIAA indicates 5-hydroxyindoleacetic acid; MHPG, 3-methoxy-4-hydroxyphenylglycol; HVA, homovanillic acid; ACTH, adrenocorticotropic hormone; AVP, arginine vasopressin; CRH, corticotropin-releasing hormone.

‡Data are presented as *t* test score (*P* values); *df* = 16 unless otherwise indicated.

§*df* = 15.

CSF 5-HIAA to be decreased^{33,34} in patients with mania compared with control subjects, and to date no consistent abnormalities of CSF monoamine levels have been demonstrated in mania.

A large body of research has demonstrated an association between changes in serotonergic function and both aggressive feelings and behavior. Although not reaching statistical significance (perhaps because of a type II error), the direction of the relationship we observed (an association between lower 5-HIAA levels following AAS administration and aggressive feelings) is in keeping with most of these findings. Nevertheless, at least 5 studies have not shown an inverse relationship between CSF 5-HIAA and aggression: 3 reported no correlation between CSF 5-HIAA and aggressive feelings,³⁵⁻³⁷ and 2 showed a positive correlation.^{38,39} The exact nature of the relationship between aggression and serotonergic function remains undetermined.

This study has several limitations, including small sample size, absence of a true placebo group, and possible confounding by stress associated with the lumbar puncture and hospital confinement. The return of most symptoms to baseline by the end of the withdrawal period, however, suggests that they are not a result of prolonged hospitalization. Treatment limitations are notable; although the doses of steroids we administered may be comparable with those abused (63% of users in one study reported taking steroid doses of 1000 mg/wk or less³), many abusers use higher doses, and the duration of treatment we employed was short (cycles of steroid abuse commonly last 4-12 weeks⁴⁰). Additionally, the steroid-abusing athlete may constitute a different biological or biosocial group than healthy volunteers who have never used androgens. The effects of MT on 5-HIAA may be different in such groups compared with men who exhibit aggressive behavior.

Cerebrospinal fluid studies can provide neither identification nor neuroanatomical localization of neural subsystems underlying the changes in CSF monoamine metabolites observed in this study. Similarly, correlational studies cannot establish a causal relationship between the observed CSF and behavioral changes. However, short-term AAS use does have effects on brain metabolism that are reflected in CSF changes, including an increase in 5-HIAA and a decrease in MHPG. The effects of MT on CSF 5-HIAA are related to the behavioral changes observed but are unrelated to dose of MT or to CSF or plasma MT levels. These preliminary findings suggest that serotonergic function is altered with MT administration and that this change may be associated with some of the behavioral effects accompanying the use of AAS.

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