High-dose testosterone treatment reduces monoamine oxidase A levels in the human brain: A preliminary report

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A B S T R A C T

The sex hormones testosterone and estradiol influence brain structure and function and are implicated in the pathogenesis, prevalence and disease course of major depression. Recent research employing gender-affirming hormone treatment (GHT) of gender dysphoric individuals and utilizing positron emission tomography (PET) indicates increased serotonin transporter binding upon high-dosages of testosterone treatment. Here, we investigated the effects of GHT on levels of monoamine oxidase A (MAO-A), another key target of antidepressant treatment. Participants underwent PET with the radioligand [11C]harmine to assess cerebral MAO-A distribution volumes (V T) before and four months after initiation of GHT. By the time this study was terminated for technical reasons, 18 transgender individuals undergoing GHT (11 transmen, TM and 7 transwomen, TW) and 17 cisgender subjects had been assessed. Preliminary analysis of available data revealed statistically significant MAO-A V T reductions in TM under testosterone treatment in six of twelve a priori defined regions of interest (middle frontal cortex (−10%), anterior cingulate cortex (−9%), medial cingulate cortex (−10.5%), insula (−8%), amygdala (−9%) and hippocampus (−8.5%, all p<0.05)). MAO-A V T did not change in TW receiving estrogen treatment. Despite the limited sample size, pronounced MAO-A V T reduction could be observed, pointing towards a potential effect of testosterone. Considering MAO-A’s central role in regulation of serotonergic neurotransmission, changes to MAO-A V T should be further investigated as a possible mechanism by which testosterone mediates risk for, symptomatology of, and treatment response in affective disorders.

1. Introduction

Mental health disorders show clinical sex dichotomies that have been associated with differences in sex hormone levels: women are twice as likely to be diagnosed with major depressive disorder (MDD) (Kessler, 2003), have greater illness severity (Young et al., 1990) and possibly a differential response to serotonergic antidepressants (Sramek et al., 2016). Accumulating evidence from preclinical and clinical research illustrates substantial effects of sex hormones on serotonin neurotransmission (Spies et al., 2020). Positron emission tomography (PET) allows for human in vivo investigation of sex hormone related changes to serotonin proteins and function (Spies et al., 2020).

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Sex differences in serotonin markers provide indirect evidence for an influence of sex hormones, as has been shown for serotonin synthesis (Frey et al., 2010; Sakai et al., 2006; Chugani et al., 1998; Nishizawa et al., 1997) and reuptake (Erritzoe et al., 2010; Kranz et al., 2014a, 2014b), as well as 5-HT1A (Parsey et al., 2002; Jovanovic et al., 2008) and 5-HT4 receptor levels (Madsen et al., 2011). Other evidence comes from correlational studies linking sex hormone levels to serotonin protein levels, as is the case for the 5-HT1A (Lanzenberger et al., 2011; Witte et al., 2009; Stein et al., 2014) and 5-HT2A receptors (Froikjaer et al., 2010).

A more direct assessment is made possible by studies on serotonin markers during phases characterized by substantial changes in sex hormone levels. For example, monoamine oxidase A (MAO-A), which degrades serotonin and for which increased expression can be understood as an endophenotype of MDD (Meyer et al., 2006), was shown to be elevated in the early postpartum period (Sacher et al., 2010) and in postpartum depression (Sacher et al., 2015).

However, strongest evidence for an influence of sex hormones on human serotonin neurotransmission comes from treatment studies linking exogenous sex hormone administration to changes in serotonin markers. For example, hormone replacement therapy (HRT) in postmenopausal women has been shown to increase cortical 5-HT2A receptors (Moses et al., 2000; Moses-Kolko et al., 2003) and decrease serotonin transporter (5-HTT) levels (Jovanovic et al., 2015).

In this context, gender-affirming hormone treatment (GHT) in transgender individuals, which aims to adjust physical appearance in accordance with gender identity, provides a unique investigatory framework (Kranz et al., 2020). GHT in transmen (TM) i.e., assigned men at birth with male gender identity, allows for the investigation of long-term effects of high dosages of testosterone on the brain. Conversely, GHT in transwomen (TW), i.e., in assigned men at birth with female gender identity, provides information on the effects of high dosages of estradiol and anti-androgen treatment. Using this approach, we recently observed testosterone treatment related increases in 5-HTT levels in TM in several cortical and subcortical brain regions (Kranz et al., 2015). These effects are in line with preclinical studies showing increased SLC6A4 messenger RNA and 5-HTT protein expression upon testosterone exposure (McQueen et al., 1999).

However, membrane 5-HTT levels are usage dependent and positively related to synaptic serotonin levels (Ramamoorthy and Blakely, 1999). Hence, reduction in serotonin degradation and resulting increase in synaptic serotonin and serotonin reuptake via 5-HTT offers an alternative explanation to our previous PET findings (Kranz et al., 2015). Indeed, animal research supports this interpretation (Smith et al., 2004) whereas human research testing this hypothesis is lacking. Hence, we aimed to investigate the effects of GHT on MAO-A levels using PET. Based on animal research (Betha et al., 2015; Briggs and Briggs, 1972), we hypothesized that MAO-A V1 would be reduced both in TW and TM after four months of estrogen and testosterone treatment, respectively.

2. Methods and materials

2.1. Participants

Eighteen transgender individuals (11 TM and 7 TW) and 17 cis-gender controls (9 CW, 8 CM) participated in this study. Transgender participants reported gender dysphoria starting before or at puberty. Mean age was numerically larger in TW 33.4±13.3 (mean±SD) compared to TM 23.9±6.8 and cis-controls 26.8±7.7, but this difference was not statistically significant (p=0.05, ANOVA). Transgender individuals were included if they had a DSM-5 diagnosis of gender dysphoria (302.85), had no steroid hormone treatment within 6 months prior to inclusion, and were seeking GHT. As in our previous studies, e.g., (Kranz et al., 2014a, 2014b, 2018, 2017, 2015), transgender and control participants underwent a standard medical examination including ECG, physical examination and routine laboratory testing to rule out internal and neurological disorders. Further exclusion criteria were pregnancy (positive urine pregnancy test) or breastfeeding, other psychiatric comorbidities as determined by the Structured Clinical Interview for DSM-IV (SCID) as well as body dysmorphic disorder (DSM-5: 300.7). Current psychopharmacologic treatment, current substance abuse, as well as stainless steel grafts and other contradictions for MRI or PET were further exclusion criteria. All subjects provided written informed consent. The study was approved by the Ethics Committee of the Medical University of Vienna (1104/2015).

2.2. Study design and treatment protocol

The study was designed as a longitudinal mono-center study (ClinicalTrials.gov Identifier: NCT02715232). TM and TW underwent a baseline scan before start of GHT (PET 1) and a second scan four months (156.1±22.2 days) into GHT (PET 2). Cis-gender controls (CW, CM) underwent two scans with the time interval of 139–273 days between PET 1 and PET 2 to determine the test-retest variability of MAO-A V1. Baseline scans in TM and CW were performed irrespective of their menstrual cycle phase. GHT followed protocols routinely implemented at the Department of Obstetrics and Gynecology, Unit for Gender Identity Disorder at the Medical University of Vienna. GHT is based on estrogen, progesterone and testosterone administration and alters sex hormone levels in the direction of those of the desired gender. TM received 1000 mg testosterone undecanoate every 12 weeks (Nebido® 250 mg/ml, 4 ml vial, intramuscular). TW received daily 50 mg cyproterone acetate (Androcure® 50 mg tablet, oral). Additionally, TW over 40 years of age received daily doses of 100 μg estradiol (Estradot®/Estramon®, transdermal therapeutic system applied twice a week) while those less than 40 years of age received 4 mg/day estradiol hemihydrate (Estrofem® 2 mg, oral). Hamilton Depression rating scale (HDRS) was assessed by an experienced clinician at a screening as well as at a follow-up visit after PET 2.

2.3. Serum sampling

Blood samples were collected prior to PET scanning for transgender individuals at each visit. Plasma levels of estradiol (E2), testosterone (T) and progesterone (P) were determined using quantitative electrochemiluminescence immunoessay method (ECLIA) at the Department of Laboratory Medicine, Medical University of Vienna, Austria (http://www.kimcl.at).

2.4. Positron emission tomography

Synthesis and quality control of [11C]harnine, (7-[11C]methoxy-1-methyl-9H-pyrido[3,4-b]indole) was performed as published by our group by means of a GE TRACERlab FX C Pro module (Philippe et al., 2015). [11C]harnine was produced with a radiochemical purity of >95% and a radiochemical yield (end of synthesis) of 6.8±3.0 GBq/μmol and molar activity of 158.1±114.4 GBq/μmol. The molar activity at the time of administration was 105.1±91.1 GBq/μmol. All PET scans were performed in a GE Advance full-ring scanner (General Electric Medical Systems, Milwaukee, WI, USA) at the Department of Biomedical Imaging and Image-guided Therapy, Division of Nuclear Medicine, Medical University of Vienna as described previously (Baldinger-Melich et al., 2019; Spies et al., 2018; James et al., 2019). Briefly, a 5 min transmission scan was done using retractable 68Ga rod sources for tissue attenuation correction. Data acquisition started simultaneously with an intravenous bolus injection of [11C]harnine (4.6 MBq/kg body weight). PET scans were acquired in 3D mode with a total scanning time of 90 min, separated into 51 optimized time frames, a spatial resolution of 4.36 mm FWHM one cm next to the center of the field of view and reconstructed in 35 transaxial section volumes with an iterative filtered backprojection algorithm (128×128 matrix). Automatic arterial blood sampling was carried out continuously for the first 10 min at a rate of 4 ml/min (ALLOGG,
Mariefred, Sweden) and manually at 5, 6, 7, 8, 10, 20, 40, 60, and 80 min after \([1^{14}]\text{C}\) harmine injection (Ginovart et al., 2006). A gamma counter cross-calibrated to the PET system was used to obtain radioactivity concentrations in whole blood and plasma. Samples at 6, 7, and 8 min were used for individual cross-calibration between manual and automated blood sampling. Radioactive metabolites of the tracer were determined using high-performance liquid chromatography (HPLC) (Hilton et al., 2000).

2.5. Magnetic resonance imaging (MRI)

For co-registration of PET data in SPM12 (Wellcome Trust Center for Neuroimaging, London, United Kingdom; http://www.fil.ion.ucl.ac.uk/spm/), every participant underwent a T1-weighted structural MRI scan performed using a 3 Tesla PRISMA MR Scanner (Siemens Medical, Erlangen, Germany, MPRAGE sequence: TE/TR=2.19/2000 ms, flip angle=9°, 1×1 mm voxel size, 1 mm slice thickness, 256 slices).

2.6. Data preprocessing and MAO-A quantification

Quantification was carried out using PMOD 3.509 (PMOD Technologies Ltd., Zurich, Switzerland; www.pmod.com). By multiplication of fitted whole blood activity, plasma-to-whole blood ratio and the fraction of intact radioligand in the plasma, the final arterial input function (AIF) was obtained. Next, the Logan plot, using estimated AIF and the time activity curve of the thalamus as high uptake region, was used to quantify voxel-wise MAO-A total volume of distribution (\(V_T\)). Regional \(V_T\) were delineated by regions-of-interest (ROIs) from a modified AAL atlas (Savil et al., 2012), in combination with a delineation of the dorsal and median raphé nucleus in MNI space (Kranz et al., 2012). See Fig. 1 for analyzed ROIs. The primary endpoint of the analyses was MAO-A \(V_T\) in 12 ROIs, namely the middle frontal cortex, the insula, the anterior, middle, and posterior cingulate cortex, hippocampus, amygdala, caudate, putamen, thalamus, as well as dorsal and median raphé nucleus. ROI-selection was based on our previous study investigating the effects of GHT on 5-HTT (Kranz et al., 2015).

2.7. Statistics

Linear mixed model analysis was used. The global model included group (transgender, cis-controls), PET (PET 1, PET 2) and ROI (11 a-priori defined ROIs) as factors and MAO-A \(V_T\) as dependent variable. This was followed by post hoc models and pairwise comparisons. Multiple testing was corrected using Fisher least significant difference procedure in accordance with the closed test principle, i.e., post hoc models were declared nonsignificant if the comparison of interest in the global model (i.e., of the three-way interaction) was nonsignificant, but carried out without further correction in case of a significant \(p\) value in the global model. Likewise, linear mixed models were computed to assess treatment-induced changes in plasma hormone levels. Finally, associations between treatment-induced hormonal changes and changes in regional MAO-A \(V_T\) were calculated using correlation analysis. Here, the Bonferroni procedure was applied to prevent alpha inflation (twelve separate tests). SPSS version 24 for Windows (SPSS Inc., Chicago, Illinois; www.spss.com) was used for statistical analyses.

3. Results

Measurements were terminated prematurely (December 2019) due to irreversible damage of the PET scanner. By then, 52 scans suitable for quantitative analysis were available including 16 scans from TM, 10 scans from TW, 15 scans from CW and 11 scans from CM. At screening, HDRS was 3.89±5.56, 3.00±4.69, 0.00±0.00 and 0.63±0.44 in TM, TW, CM and CW, respectively. After PET2 HDRS was 4.00±5.57, 4.86±7.03, 0.20±0.45 and 0.38±1.06 (TM, TW, CM, and CW).

3.1. GHT effects on plasma hormone levels

As anticipated, testosterone plasma levels changed over time as a result of GHT in TM and TW compared to cis-controls, illustrated by a statistically significant group by time interaction effect \((F_{2,13}=172, p<0.001)\). Post hoc analysis revealed expected increase \((F_{1,5}=8, p=0.014)\) and decrease \((F_{1,6}=58, p<0.001\), see Fig. 2a and b, for means and SD, see Table 1\), in testosterone levels in TM upon testosterone treatment and TW upon anti-androgen treatment, respectively, whereas no change was observed in controls \((F_{1,24}=1, p=0.05)\). Conversely, estradiol treatment led to a numerical increase in plasma estradiol levels in TW towards female levels whereas levels declined in TM (see Table 1). However, these changes were not statistically significant. Similarly, there was no significant effect of GHT on progesterone levels, although values changed in the expected directions in TM and TW, see Table 1.

3.2. MAO-A \(V_T\) change in TM, TW and cis-controls

Investigating a change in MAO-A \(V_T\) in TM compared to cis-controls in the global model revealed a three-way interaction between group, PET and ROI \((F_{1,43}=2, p=0.043)\), in addition to a main effect of ROI \((F_{1,68}=171, p<0.001)\) and an interaction between group and PET \((F_{1,49}=10, p=0.002)\). Post hoc pairwise comparisons between PET 1 and PET 2 for each separate ROI in TM revealed significant reductions in middle frontal cortex \((-10\%, p=0.014)\), anterior cingulate cortex \((-9\%, p=0.028)\), medial cingulate cortex \((-10.5\%, p=0.001)\), insula \((8%, p=0.020)\), amygdala \((-9\%, p=0.017)\) and hippocampus \((-8.5\%, p=0.002)\), see Fig. 2c, for means and SD, see Table 2. To validate this effect, we performed additional Wilcoxon Signed Rank Tests given the small sample size. This analysis revealed significant MAO-A \(V_T\)
showing statistical significance, see supplement (Table S1). Based on previous literature associating affective symptoms (Meyer et al., 2006) with MAO-A, analyses were repeated including HDRS scores as covarates. This step rendered the three-way interaction between group, PET and ROI non-significant ($F_{11,41}=1.8, p=0.079$) but no significant interaction between ROI and PET ($F_{11,27}=1, p>0.05$). The main effect of PET indicated on average higher MAO-A $V_T$ at PET 2 compared to PET 1. However, exploratory post hoc pairwise comparisons between PET 1 and PET 2 showed no significant changes in separate ROIs except for the MRN ($p=0.026$), for means and SD, see Table 2.

### Table 1

|                      | TM     | TW     | PET 1  | PET 2  | PET 1  | PET 2  |
|----------------------|--------|--------|--------|--------|--------|--------|
| N                    |        |        |        |        |        |        |
| Testosterone (pg/ml)  | 10.9±1.6| 2.9±0.8* | 6.0±1.5| 0.2±0.2* |        |        |
| Estradiol (pg/ml)    | 107.7±58.9| 75.8±70.9| 34.2±7.3| 183.0±237.1|        |        |
| Progesterone (pg/ml) | 4.2±6.1 | 2.2±4.5 | 0.2±0.2 | 0.7±0.7 |        |        |

Finally, examining the test-retest variability of MAO-A $V_T$ in controls revealed a main effect of ROI ($F_{11,55}=105, p<0.001$) and a main effect of PET ($F_{1,32}=9, p=0.006$) but no significant interaction between ROI and PET ($F_{11,27}=1, p>0.05$). The main effect of PET indicated on average higher MAO-A $V_T$ at PET 2 compared to PET 1. However, exploratory post hoc pairwise comparisons between PET 1 and PET 2 showed no significant changes in separate ROIs except for the MRN ($p=0.026$), for means and SD, see Table 2.

#### 3.3. Association between testosterone increases and changes in MAO-A $V_T$ in TM

Correlation analysis revealed no statistically significant association between GHT induced increases in testosterone plasma levels and changes in MAO-A $V_T$ in any investigated ROI (all $p>0.05$, corrected).

### 4. Discussion

Utilization of GHT of transgender individuals as an investigatory framework (Kranz et al., 2018, 2017, 2015, 2020; Hahn et al., 2016; Seiger et al., 2016; Spies et al., 2016) has provided our lab the unique opportunity to study the long-term effects of high dosages of testosterone and estradiol on the living human brain. Effects on serotonin neurotransmission are of particular relevance given the neurotransmitter’s pathophysiological and therapeutic role in affective and anxiety disorders (Spies et al., 2015). Here we demonstrate MAO-A $V_T$ reduction in several cortical and subcortical limbic brain regions in TM receiving GHT, which may be suggestive of a suppressive effect of testosterone.

A negative effect of testosterone on MAO-A $V_T$ would be in line with previous animal data and human studies assessing plasma MAO activity. MAO-A suppression by testosterone was observed in the dorsal raphe nucleus of macaques (Beetha et al., 2015) while correlational research indicates a negative association between plasma testosterone...
concentration and plasma MAO activity in healthy men (Briggs and Briggs, 1972). However, the latter study also found a negative association between estradiol concentration and plasma MAO activity in healthy females (Briggs and Briggs, 1972) raising the possibility that testosterone exerts its suppressive effect on MAO activity via aromatization to estradiol, which is also supported by animal data (Bethea et al., 2015). Indeed, conversion to estradiol is proposed for many of testosterone’s actions, including its effect on 5-HTT expression, as suggested in our previous study (Kranz et al., 2015). The observed MAO-A V2015.5 decreases over time in twelve a priori regions of interest (ROI) in transmen (TM), transwomen (TW) and cis-gender controls. Values represent means±SD at baseline (PET 1) and four months after (PET 2) start of GHT. *indicates significant changes from PET 1 at p<0.05.

| Gender-affirming hormone treatment (GHT)-induced MAO-A V2015.5 | PET 1 | PET 2 | PET 1 | PET 2 |
|---------------------------------------------------------------|-------|-------|-------|-------|
| **N**                                                         | 10    | 6     | 6     | 4     |
| MFC                                                          | 15.1±2.2 | 13.7±1.7* | 13.1±2.7 | 13.1±1.7 |
| INS                                                          | 16.7±2.1 | 15.4±2.2* | 14.7±2.7 | 14.6±2.4 |
| ACC                                                          | 17.5±2.3 | 15.9±2.1* | 15.1±3.0 | 15.0±2.1 |
| MCC                                                          | 17.2±2.5 | 15.4±2.2* | 14.7±3.0 | 14.6±2.9 |
| PCC                                                          | 17.5±2.6 | 13.9±2.2 | 13.5±2.2 | 13.8±3.0 |
| HIP                                                          | 15.3±2.0 | 14.0±1.8* | 13.3±2.8 | 12.7±2.4 |
| AMY                                                          | 15.5±2.7 | 14.1±1.6* | 13.1±2.6 | 12.5±2.0 |
| CAUD                                                         | 15.5±2.2 | 14.4±1.8 | 14.3±2.4 | 14.3±3.0 |
| PUT                                                          | 15.8±2.4 | 15.0±2.0 | 14.5±2.4 | 14.7±3.1 |
| THAL                                                         | 22.5±3.1 | 20.7±2.6 | 19.2±3.7 | 19.4±3.0 |
| DRN                                                          | 19.8±2.6 | 17.5±2.4 | 16.7±3.1 | 16.8±2.6 |
| MRN                                                          | 14.9±2.4 | 13.8±2.0 | 13.7±2.9 | 12.8±1.9 |

Our study has several limitations, first and foremost its limited sample size. Results therefore remain preliminary and await further validation from replication studies in considerably larger samples. The small sample size in our study may also underlie the absence of a statistically significant correlation between GHT-induced testosterone plasma level changes and changes in MAO-A V2. In addition, we were not able to correct for smoking which (Fowler et al., 2008) has been associated with MAO-A including personality traits, particularly aggression (Soliman et al., 2011). Furthermore, we recognize that we are not able to address additional clinical and behavioral characteristics that have been associated with MAO-A including personality traits, particularly aggression (Soliman et al., 2011), nor MAO-A’s role in moderating the effects of childhood maltreatment (Ouellet-Morin et al., 2016). In addition, we were not able to correct for smoking which (Fowler et al., 1996; Leroy et al., 2009), together with nicotine-withdrawal, have been shown to impact on cerebral MAO-A (Bacher et al., 2011). Furthermore, because psychiatric comorbidities were excluded in our sample, caution is warranted when interpreting the observed effects of testosterone on MAO-A V2 as an underpinning for the hormone’s clinical effects in depression.
4.1. Conclusion

We observed regional MAO-A V_{f} reduction in TM under GHT, pointing towards a potential suppressive effect of long-term high-dosage testosterone treatment. These findings might in theory be interpreted in the context of MAO-A’s role within the serotonergic hypothesis of depression and testosterone's antidepressant properties. Further studies should investigate whether modulation of MAO-A may serve as a mechanism by which testosterone exerts its antidepressant effects.

CRediT authorship contribution statement

R. Lanzenberger (PI) and G.S. Kranz: planned and supervised the study. M. Spies, P.A. Handschuh and M.E. Konadu: recruited subjects and coordinated medical aspects. U. Kaufmann: performed GHT. M. Hacker and T. Traub-Weidinger: supervised PET measurements. V. Pichler, W. Wadsak, L. Nics, E. Klebermass, and M. Ozenli: were involved in radiolgand production and quality control. C. Vraka: performed metabolite measurement and analyses. H. Ibeschitz: performed PET measurements. M. Murgas and L. Rischka: supported technical aspects during the PET measurements and performed imaging data analyses. A. Hahn supervised PET data analysis. G.S. Kranz: performed statistical analyses. G.S. Kranz and M. Spies: wrote the manuscript, all authors edited the manuscript.

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Conflict of Interest

Without any relevance to this work, R. Lanzenberger received travel grants and/or conference speaker honoraria within the last three years from Bruker BioSpin MR, Heel, and support from Siemens Healthcare regarding clinical research using PET/CT. He is a shareholder of the start-up company BM Health GmbH since 2019. Without relevance to this work, W. Wadsak received within the last three years research grants from ITM Medical Isotopes GmbH (Munich, Germany) and Scintomics (Führungsklinik, Germany). He is a part-time employee of CBmed GmbH (Graz, Austria) and a co-founder of MINUTE medical GmbH (Vienna, Austria). G.S. Kranz received travel grants from Roche, AOP Orphan Pharmaceuticals and Pfizer. M. Spies received travel grants from Janssen and AOP Orphan Pharmaceuticals, speaker honoraria from Janssen and Astroplont, and workshop participation from Eli Lilly. All other authors report no potential conflict of interest regarding this publication.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.psyneuen.2021.105381.

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