European Neuropsychopharmacology (2013) **23**, 79–88

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REVIEW

Testosterone in the brain: Neuroimaging findings and the potential role for neuropsychopharmacology

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Received 25 January 2012; received in revised form 4 April 2012; accepted 16 April 2012

KEYWORDS
Testosterone;
Brain;
Neuroimaging;
Sex differences;
Androgen;
PET;
fMRI

Abstract
Testosterone plays a substantial role in a number of physiological processes in the brain. It is able to modulate the expression of certain genes by binding to androgen receptors. Acting via neurotransmitter receptors, testosterone shows the potential to mediate a non-genomic so-called ''neuroactive effect''. Various neurotransmitter systems are also influenced by the aromatized form of testosterone, estradiol. The following article summarizes the findings of preclinical and clinical neuroimaging studies including structural and functional magnetic resonance imaging (MRI/fMRI), voxel based morphometry (VBM), as well as pharmacological fMRI (phfMRI) and positron emission tomography (PET) regarding the effects of testosterone on the human brain. The impact of testosterone on the pathogenesis of psychiatric disorders and on sex-related prevalence differences have been supported by a wide range of clinical studies. An antidepressant effect of testosterone can be implicitly explained by its effects on the limbic system – especially amygdala, a major target in the treatment of depression – solidly demonstrated by a large body of neuroimaging findings.

1. Introduction

Testosterone plays a major role in a number of physiological processes. Alterations in plasma testosterone concentration and the hypothalamic-pituitary-gonadal axis (HPG) are also associated with psychiatric disorders including mood disorders, psychosis and aggression (Carre et al., 2011; Carre and Mehta, 2011; Popma et al., 2007; Talih et al., 2007; van Wingen et al., 2011). Testosterone has also been described as a biomarker for social and economic interactions as well as for status seeking behavior (Eisenegger et al., 2011). It influences neuronal functioning by binding to the intracellular androgen receptors and regulates gene expression. It can further act as neuroactive steroid by modulating ligand-gated ion channels or G-protein coupled receptors. While the genomic effect requires a time period that lasts from minutes to hours, neuroactive steroids exhibit their modulatory effects during a millisecond to second time window (Rupprecht and Holsboer, 1999).

In this context sex differences in the prevalence of psychiatric disorders have to be taken into consideration: the prevalence of affective disorders in women has been

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http://dx.doi.org/10.1016/j.euroneuro.2012.04.013

reported to be twice as high as in men (Holsen et al., 2011), whereas alcohol abuse and dependence is predominantly found in men (Alonso et al., 2004). Men suffer more often from an antisocial personality disorder, tend to behave more violently and have a higher risk of committing suicide compared to women (Compton et al., 2005). Also the characteristics of distinct psychiatric disorders differ between men and women. The male depressive syndrome is characterized by low stress tolerance, low impulse control, antisocial behavior and suicide (Walinder and Rutz, 2001).

Patients who suffer from hypogonadism and hypoandrogenism develop depressive symptoms related significantly to the testosterone level (Wainwright et al., 2011; Wu et al., 2010). Similarly, disorders associated with hyperandrogenism in females (e.g., polycystic ovary syndrome) have also been associated with higher rates of depression (Weiner et al., 2004). Higher free testosterone levels were detected in women who tend to show more aggressive and antisocial behavior (Pajer et al., 2006). Abusing anabolic-androgenic steroids may potentiate psychiatric conditions ranging from mood changes (mania or depression) to personality changes and psychosis (Talih et al., 2007). Pharmacological treatment of psychiatric conditions related to hyper- or hypoandrogenism is accordingly inconsistent (e.g., selective serotonin reuptake inhibitors (SSRIs), antipsychotics or benzodiazepines) (Malone and Dimeff, 1992; Rashid, 2000).

Testosterone is converted to estrogen by the enzyme aromatase. It can thus modulate the serotonergic system by binding to estrogen receptors (Bethea et al., 2002). Aromatase belongs to the cytochrome P450 family and is a unique gene product of the CYP19 gene (Lephart, 1996). The distribution of aromatase has been examined in different species. Locations of high expression of aromatase in several species were observed in the hypothalamus as well as in limbic regions, whereas the highest activity was found in the amygdala and bed nucleus of the stria terminalis (Abdelgadir et al., 1997; Roselli et al., 1985, 1987, 1998). For the distribution of aromatase in the human brain, see Fig. 1. The highest concentrations were found in the thalamus and the amygdala, while having lower concentrations in the nucleus accumbens, pons, occipital and temporal cortices, putamen and cerebellum (Biegon et al., 2010; Sasano et al., 1998).

In an animal study focussing on male rhesus monkeys the preoptic area, the hypothalamus and the amygdala could be identified as targets of 3H-dihydrotestosterone (DHT) (Michael and Rees, 1982). A further study could similarly verify a high affinity for Methyltrienolone in the above mentioned regions in rhesus macaques (Handa et al., 1988). Additionally the dopamine inputs to the caudate putamen, the nucleus accumbens and the amygdala are influenced by androgens in rats (Creutz and Kritzer, 2004). A treatment study in rodents indicated regional sex differences in the expression of androgen receptors (AR) in the brain and dihydrotestosterone was found to downregulate the level of AR in female rats in a region specific manner (Feng et al., 2010). Apostolinas and colleagues could show that testosterone replacement for the duration of 1 week was sufficient to induce the numbers of neurons containing high concentrations of AR (e.g., amygdala or hypothalamus) within the range of normal male mice (Apostolinas et al., 1999).

Testosterone influences brain function of modulatory neurotransmitter systems, including key elements of serotonergic neurotransmission (Cahill, 2006). The pathophysiology of most neuropsychiatric disorders, e.g. mood disorders, is closely associated with a dysfunction of serotonergic neurotransmission (Kasper et al., 2002, 1988; Naughton et al., 2000). The estrogen receptor beta is expressed on serotonergic neurons that are therefore targets of testosterone converted to estrogen by aromatase (e.g., 5-HT_{2A} receptor) (Bethea et al., 2002; Fink et al., 1999). In Fig. 2 the distribution of estrogen receptors in the human brain is illustrated.

There are several neuroimaging papers describing the effects of estrogens and progesterone on the human brain (Adams et al., 2004; van Wingen et al., 2008b), however there is a lack of published data focused on androgens and neuroimaging. Therefore this overview aims to present the most relevant neuroimaging literature on structural, functional and molecular mechanisms associated with testosterone in the brain. The main results are summarized in the tables enclosed.

2. Structural findings by magnetic resonance imaging (MRI)

The majority of imaging studies examining the effects of testosterone on brain structure have been conducted using

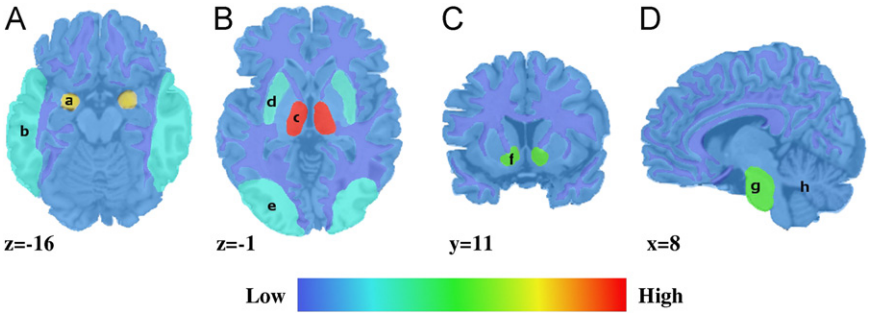

Figure 1 Aromatase distribution in the healthy human brain according to Biegon et al. (2010). Colors indicate the aromatase distribution superimposed on magnetic resonance images (triplanar sections with coronal (C), sagittal (D) and axial views (A and B)). Distribution volume values were measured using positron emission tomography with the radiolabeled aromatase inhibitor [N-methyl-^{11}C] vorozole. High aromatase distribution volumes can be found in the thalamus (c) and the amygdala (a), whereas lower concentrations were found in the nucleus accumbens (f), pons (g), occipital (e) and temporal cortices (b), putamen (d) and cerebellum (h). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)