Frontiers in Neuroendocrinology 35 (2014) 42–57

Contents lists available at ScienceDirect

Frontiers in Neuroendocrinology

journal homepage: www.elsevier.com/locate/yfrne

Review

Sex differences in anxiety and depression: Role of testosterone

Jenna McHenry [a,b,1], Nicole Carrier [c,1], Elaine Hull [a,b], Mohamed Kabbaj [b,c,*]

[a] Psychology Department, Florida State University, United States
[b] Neuroscience program, Florida state University, United States
[c] Biomedical Sciences Department, College of Medicine, Florida State University, United States

ARTICLE INFO

Article history:
Available online 24 September 2013

Keywords:
Testosterone
Sex differences
Depression
Anxiety
Estradiol
Dihydrotestosterone
Aromatization

ABSTRACT

Compelling evidence exists for pervasive sex differences in pathological conditions, including anxiety and depressive disorders, with females more than twice as likely to be afflicted. Gonadal hormones may be a major factor in this disparity, given that women are more likely to experience mood disturbances during times of hormonal flux, and testosterone may have protective benefits against anxiety and depression. In this review we focus on the effects of testosterone in males and females, revealed in both human and animal studies. We also present possible neurobiological mechanisms underlying testosterone's mostly protective benefits, including the brain regions, neural circuits, and cellular and molecular pathways involved. While the precise underlying mechanisms remain unclear, both activational and organizational effects of testosterone appear to contribute to these effects. Future clinical studies are necessary in order to better understand when and how testosterone therapy may be effective in both sexes.

1. Introduction

Anxiety and depressive disorders are the most common of all psychiatric disorders; however, current human and animal research has yet to provide a clear understanding of the neural mechanisms underlying their etiology. Demographic analyses illustrate not only their widespread prevalence, but also pervasive sex differences in these affective disorders. In fact, approximately 18% of the adult American population suffers from an anxiety-related disorder and another 7% from major depressive disorder each year (Kessler et al., 2005b). Further, females are more than twice as likely as males to be afflicted by mood disorders (Kessler et al., 2005a; Bekker and van Mens-Verhulst, 2007). These sex differences are observed, not only in the US, but are also documented worldwide (Seedat et al., 2009). This sex disparity indicates a potential role for gonadal hormones in the etiology of anxiety and depressive disorders. In fact, studies have revealed that women are more likely to experience mood disturbances, anxiety, and depression during times of hormonal flux, such as puberty, menopause, perimenstrual and post-partum periods (Ahokas et al., 2001; Parker and Brotchie, 2004; Douma et al., 2005; Solomon and Herman, 2009). While hormonal flux in females appears to increase the likelihood of experiencing mood disturbances, clinical and preclinical studies in males suggest that testosterone yields protective benefits against anxiety and depression. These beneficial effects may stem from both organizational and activational effects of testosterone. The possible underlying neurobiological mechanisms that mediate such protective effects, including the brain sites, biochemical factors, and molecular pathways involved are discussed herein. Understanding the influence of hormones on neurobiological systems that regulate anxiety and depressive behavior will increase our capacity to develop new drug targets to treat various mental illnesses in both men and women.

2. The influence of testosterone on anxiety and depressive behaviors in men and women

The relationship between testosterone levels, anxiety disorders, and major depressive disorder in humans is evident in males with hypogonadism, a condition in which reduced functional activity of the gonads results in decreased levels of testosterone. Hypogonadal men exhibit a significantly higher prevalence of anxiety disorders and major depressive disorder, compared to those with normal physiological levels of androgens (Shores et al., 2004; Zarrouf et al., 2009). Similarly, men treated with androgen-depleting drugs for prostate cancer have a greater likelihood of developing an anxiety disorder or major depressive disorder (DiBlasio et al., 2008). Moreover, hypogonadal men with human immunodeficiency virus are more likely to experience depressive moods, an effect reversed by testosterone administration (Rabkin et al., 2000). Collectively, several reports suggest that testosterone-replacement therapy in hypogonadal men greatly improves mood, alleviates anxiety, and mitigates symptoms of depression (Wang et al.,

* Corresponding author. Address: 1115 W. Call Street, College of Medicine, 2330G, Florida State University, FL 32306-4300, United States.
E-mail address: Mohamed.Kabbaj@med.fsu.edu (M. Kabbaj).
[1] Jenna McHenry and Nicole Carrier participated equally in this work.

0091-3022/$ - see front matter © 2013 Elsevier Inc. All rights reserved.
http://dx.doi.org/10.1016/j.yfrne.2013.09.001

1996; Pope et al., 2003; Kanayama et al., 2007; Zarrouf et al., 2009). However, this is not the case in all clinical studies. For example, one study reports that testosterone-replacement therapy in androgen-deficient men did not significantly alleviate symptoms of major depressive disorder, compared to placebo-treated controls (Seidman et al., 2001). Another study revealed that testosterone administration in elderly men with low levels of testosterone and mild cognitive impairments also did not improve symptoms of depression (Kenny et al., 2004). However, despite a few inconsistent reports, the majority of studies support the case that testosterone yields beneficial effects on mood in men, especially in those with lower than normal levels. Other important considerations in these discrepancies may include differences in age, degree of hypogonadism, and also the timing, dose, duration, and route of androgen replacement. In fact, studies indicate that route of administration may be an important factor, with transdermal application being more effective in improving mood than hormone injections (Zarrouf et al., 2009). Another major consideration is whether the individual tested had previously experienced a depressive episode or had never suffered from an affective disorder (Pope et al., 2003; Zarrouf et al., 2009). In general, testosterone appears to be most effective in alleviating symptoms of anxiety and/or depression in older hypogonadal men, but risk factors must also be assessed. For example, testosterone therapy also involves a potential increased risk of cardiovascular complications, sleep apnea, polycythemia, and prostate cancer (Surampudi et al., 2012). Therefore, additional studies are required in order to know more about when and how testosterone therapy may be effective in treating anxiety and mood disorders despite potential risks involved.

While the clinical studies of testosterone therapy in women are more limited, some evidence supports anxiolytic and antidepressant roles for testosterone. Administration of a low dose of testosterone in women with treatment-resistant major depressive disorder significantly improved ratings of depression, compared to placebo-treated subjects (Miller et al., 2009). In addition, surgical removal of the ovaries increased mood disturbances and depression, compared to placebo-treated controls, an effect reversed by testosterone (Shifren et al., 2000). Another study in women found that a single administration of testosterone reduced anxiety in the fear-potentiated startle response, compared to placebo-treated controls (Hermans et al., 2006). Furthermore, transdermal application of testosterone in women experiencing age-related declines in androgens resulted in substantially improved mood and psychological well-being, compared to placebo-treated individuals (Goldstat et al., 2003). However, some reports have noted that too much testosterone can also negatively impact mood in women and can even contribute to the onset of major depressive disorder (Rohr, 2002). Additional clinical studies in women are necessary in order to reveal whether, and under what conditions, testosterone alleviates symptoms of anxiety and major depressive disorder.

Additional information can be obtained from examining mood and behavior in both men and women during times of testosterone flux, often due to age-related declines or circadian function. In adolescent males, but not females, decline in salivary testosterone throughout the day due to circadian flux, is correlated with an increase in anxiety- and depressive-like measures (Granger et al., 2003). Lower salivary levels of testosterone are also observed in individuals with anxiety disorders and major depressive disorder. In fact, women with major depressive disorder or a type of anxiety disorder, including generalized anxiety, social phobia, or agoraphobia express lower levels of salivary testosterone, compared to emotionally healthy women (Giltay et al., 2012). Socially anxious men also display a significant drop in testosterone levels after being defeated in a competition, an effect not observed in non-anxious men (Maner et al., 2008). In addition, both women and men taking a serotonin reuptake inhibitor (SSRI) for major depressive disorder have higher levels of salivary testosterone, compared to depressed individuals not taking SSRI medication (Giltay et al., 2012). Also, in more senior men and women, lower levels of testosterone are associated with an increased prevalence of major depressive disorder (Barrett-Connor et al., 1999; Morsink et al., 2007).

Clinical evidence suggests that testosterone has anxiolytic and antidepressant benefits, with the potential to promote improved mood and mental health in both women and men. However, the neurobiological mechanisms underlying the protective effects of testosterone in males and females remain poorly understood. In addition, given testosterone's disparate routes of action, it is not clear whether actions of androgens at androgen receptors or conversion to estrogen are responsible for these effects. Human imaging studies that examine possible sites in the brain are necessary to better understand how testosterone and its metabolites and receptors may mediate central effects on mood in both men and women. Animal studies are also required to corroborate findings in human studies, establish causal relationships, and elucidate possible neural and molecular mechanisms underlying testosterone's benefits. Below, we first provide a background summarizing the biosynthesis of testosterone and its metabolites. Then we present the genomic and nongenomic molecular actions of testosterone. Lastly, we provide a comprehensive review of the animal models and experiments that begin to elucidate the brain sites and neurobiological mechanisms by which testosterone exerts its generally beneficial effects on anxiety and depression.

3. Molecular mechanisms of testosterone

3.1. Steroidogenesis, biosynthesis, and metabolism

Testosterone is often referred to as a male hormone, in part because males have about ten times higher concentrations of testosterone compared to women, although women are actually more sensitive to testosterone (reviewed in Durdiakova et al., 2011). The gonads and adrenal cortex are the primary sources of testosterone in most vertebrate species of both sexes. Peripheral testosterone can cross the blood brain barrier and have a number of effects on the brain. In addition, small amounts of steroids, including testosterone, are synthesized de novo from cholesterol or steroidal precursors in the brain, and are referred to as neurosteroids (Baulieu et al., 2001; Melcangi et al., 2008) and are discussed in more detail below.

Cholesterol is the precursor of all steroid hormones, including testosterone (reviewed in Ghayee and Auchus, 2007). The rate-limiting step of steroid synthesis is the transport of cholesterol from the cytoplasm to the inner mitochondrial membrane, where steroidogenic enzymes reside (reviewed in Sierralta et al., 2005; Abdulkarimi et al., 2012; Miller, 2013). A protein complex called the transduceosome forms at the outer mitochondrial membrane of gonadal and adrenal cells. The transduceosome includes steroidogenic acute regulatory protein (StAR), as well as protein kinase A (PKA), and several other mitochondrial and cytosolic proteins. The process is initiated by the binding of luteinizing hormone (LH) or chorionic gonadotropin (CG; hCG in humans) to their G-protein-coupled receptors, which results in cAMP activating PKA, which in turn phosphorylates and thereby activates StAR. StAR passes through the outer mitochondrial membrane, carrying cholesterol in its hollow, hydrophobic C-terminus, and attaches to the inner mitochondrial membrane, where the cholesterol side-chain cleavage enzyme desmolase is located.

Fig. 1 shows the series of reactions, beginning with the cleavage of a side-chain of carbons by the enzyme desmolase to form pregnenolone, an obligatory C21 steroid and prohormone to all other