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Testosterone administration in women increases amygdala responses to fearful and happy faces

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Summary Data from both rodents and humans show that testosterone reduces fear. This effect is hypothesized to result from testosterone's down regulating effects on the amygdala, a key region in the detection of threat and instigator of fight-or-flight behavior. However, neuroimaging studies employing testosterone administration in humans have consistently shown increased amygdala responsivity. Yet, no study to date has investigated specifically how testosterone affects the amygdala response to fearful emotional expressions. Such stimuli signal the presence of environmental threat and elicit robust amygdala responses that have consistently been associated with anxious traits. In the present study, we therefore used functional magnetic resonance imaging combined with a single administration of 0.5 mg testosterone in 12 healthy women to assess testosterone's effects on amygdala responses to dynamic fearful (and happy control) faces. Our results show that both stimuli activate the amygdala. Notably, testosterone increased the amygdala response to both stimuli, and to an equal degree. Thus, testosterone appears not to reduce fear by attenuating the amygdala response toward signals of threat. Data further show that testosterone selectively increases activation of the superficial amygdala (SFA) and, to a lesser extent, the basolateral amygdala (BLA). No effect was found in the central nucleus, which is involved in the generation of autonomic fear responses. Both the SFA and BLA are considered input regions, and enhanced activation by testosterone might reflect the role of this hormone in adaptive responding to socially relevant stimuli. Furthermore, literature on the distinct roles of the SFA and BLA in fear processing show that increased activation of these subregions of the amygdala is consistent with a fear reducing effect of testosterone.

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Introduction

Over the last decade, knowledge on the role of the steroid hormone testosterone in human social and emotional behavior has greatly increased. Working from models based on effects of testosterone in mostly rodents, efforts have been made to investigate the effects of testosterone in humans (Eisenegger et al., 2011; Bos et al., 2012b). One of the results of these efforts is the finding that testosterone, known to reduce fear in rodents (Aikey et al., 2002), has comparable effects in humans (van Honk et al., 2005; Hermans et al., 2006, 2007). In these studies, a single administration of testosterone resulted in reduced startle potentiation in response to threat of mild electric shock (Hermans et al., 2006), reduced sympathetic autonomic nervous system responses to threatening pictures (Hermans et al., 2007), and reduced automatic attention for fearful faces, which signal environmental threat (Whalen et al., 2004; van Honk et al., 2005). However, the neural mechanism by which testosterone exerts these fear-reducing effects is currently unknown.

A key structure implicated in anxiety and the detection of salient environmental features including threat is the amygdala (Davis and Whalen, 2001). Through its target regions such as the hypothalamus and the periaqueductal gray (PAG), the amygdala is tightly linked to networks involved in fear responses and the initiation of fight-or-flight behavior (Price, 2003). Considering this role, it is not surprising this region is very sensitive to emotional facial expressions (Phelps and LeDoux, 2005). Dynamic facial expressions in particular have been shown to elicit robust amygdala activation (Sato et al., 2004; van der Gaag et al., 2007). Also, amygdala responses to fearful faces presented outside of focal attention are enhanced in highly anxious, but healthy, individuals (Bishop et al., 2004), and especially in females (Dickie and Armony, 2008). Therefore, dysregulation of the amygdala has been proposed to underlie the etiology of mood and anxiety disorders. Indeed, patients suffering from mood and anxiety disorders show exaggerated amygdala responses to emotional faces compared to controls (Drevets, 2003; Monk, 2008), in particular toward fearful faces (Labuschagne et al., 2010). Moreover, the amygdala is an important target of testosterone, as it is rich in androgen receptors (Sarkey et al., 2008), as well as in aromatase, which converts testosterone into estradiol (Biegon et al., 2010). Estradiol receptors are also abundant in the human amygdala, although they do not seem to be located in the central nucleus of the amygdala (Österlund et al., 2000). Finally, males show faster attenuation of the amygdala in response to fearful faces accompanied by lower autonomic stress responses compared to females, who have lower baseline testosterone levels (Williams et al., 2005). Based on these findings, it can be hypothesized that testosterone exerts its fear-reducing properties by reducing amygdala responses to environmental threat cues.

However, studies investigating the effect of testosterone on the amygdala performed so far show positive correlations between endogenous testosterone levels and amygdala responses to facial stimuli (Derntl et al., 2009; Stanton et al., 2009; Manuck et al., 2010). Also, studies employing a single administration of testosterone, which in contrast to correlational methods can give causal insight, show increased amygdala responses to faces after testosterone administration (Hermans et al., 2008; van Wingen et al., 2009). These findings are not in favor of the hypothesis that testosterone reduces fear by inhibiting the amygdala response. However, such findings may also be explained by the fact that the studies by Hermans et al. (2008) and van Wingen et al. (2009) did not use fearful faces as stimuli to elicit amygdala activity. For instance, Hermans et al. used angry and happy faces, while van Wingen et al. presented fearful faces simultaneously with angry faces, making it impossible to distinguish amygdala responses to these two expressions. Facial expressions of fear are prototypical innate human danger cues that are thought to evoke amygdala activity because they convey the presence of threat without providing information about its source, thus prompting sensory vigilance (Whalen, 1998; Davis and Whalen, 2001). Indeed, fearful faces have been shown to elicit stronger amygdala responses than angry faces (Whalen et al., 2001), which are less ambiguous because they directly represent the source of threat (Adams et al., 2003), which is social in nature (van Honk et al., 2001; Hermans et al., 2008). For these reasons, amygdala responses to the expression of fear are thought to be more suitable to probe neural processes underlying anxiety (Whalen et al., 2001; Bishop et al., 2004; van Honk et al., 2005). The present study therefore aimed to assess the effect of testosterone on the amygdala response specifically to fearful faces.

In a counterbalanced placebo-controlled crossover design, 12 healthy women were sublingually administered 0.5 mg of sublingual testosterone. Functional magnetic resonance imaging (fMRI) was used to measure neural responses to dynamic happy and fearful emotional faces, of which the happy facial expressions served as a control condition (van Marle et al., 2009). Happy and fearful faces were presented in separate blocks to investigate the responses in our a priori region of interest, the amygdala, to both emotional expressions. This design allowed us to answer the question of whether testosterone would reduce amygdala responses toward signals of environmental threat, thereby potentially decreasing fear.

Methods

Subjects

Twelve healthy, adult women with normal or corrected-to-normal vision (age range 18—25; mean age 20.4) were tested in a double-blind, placebo-controlled, fully counterbalanced crossover design. Participants were mostly students recruited from the university campus by advertisements. Only women were included because the dosage and temporal parameters of neurophysiological effects induced by a single sublingual administration of testosterone are unknown in men. Exclusion criteria were, for fMRI safety procedures: history of closed-head injury, current pregnancy, and presence of metal objects in the body. To reduce interindividual variability and avoid unwanted interactions with drug administration the following exclusion criteria were applied: history of endocrine or psychiatric disorders, irregular sleep patterns, use of (recreational) psychotropic drugs within 2 weeks of testing, left hand dominance, and habitual smoking. Nine women used standard monophasic estrogen/progestagen oral contraceptives. For the remaining three