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The antidepressant effect of testosterone: An effect of neuroplasticity?

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ABSTRACT

Background: Rodent and human studies indicate that testosterone has an antidepressant effect. The mechanisms via which testosterone exerts its antidepressant effect, however, remain to be elucidated. Some studies assume downstream effects of testosterone on sexual function and vitality followed by improvement of mood. Emerging evidence suggests that testosterone may be acting in the brain within depression-relevant areas, whereby eliciting direct antidepressant effects, potentially via neuroplasticity.

Methods: Literature was searched focusing on testosterone treatment and depression and depression-like behavior. Due to the unilateral clinical use of testosterone in men and the different modes of action of sex hormones in the central nervous system in men and women, predominantly studies on male populations were identified.

Results: The two proposed mechanisms via which testosterone might act as antidepressant in the central nervous system are the support of neuroplasticity as well as the activation of the serotonin system. Additionally, testosterone downregulates glucocorticoid output and reduces levels of pro-inflammatory markers, thereby acting as important counter regulatory agent reducing levels of neurotoxic factors in the central nervous system.

Conclusion: Although it is possible that testosterone acts via the serotonin system or the downregulation of the immune or hyperactive stress physiological systems, recent evidence supports the hypothesis that testosterone also elicits anti-depressant effects via directly promoting neuroplasticity. Potential implementations of testosterone treatment in mood disorders are discussed.

1. Introduction

Testosterone treatment (TT) is currently emerging as a potential antidepressant treatment in men. While early studies did not consistently demonstrate beneficial effects of TT in depressed men (Seidman, Spatz, Rizzo, & Roose, 2001; Pope, Cohane, Kanayama, Siegel, & Hudson, 2003; Giltay et al., 2010; Pope et al., 2010; Seidman, Araujo, Roose, & McKinlay, 2001, 2009), a recent meta-analytic examination reported TT to be effective and efficacious in reducing depressive symptoms in males (Walther, Breidenstein, & Miller, 2019). In this analysis, the authors also identified a dose-response relationship, with higher TT dosage-regimens achieving larger effects (Walther et al., 2019). However, although TT-related antidepressant effects appear to be relatively robust, little is known about the underlying mechanisms causing the reduction of depressive symptoms in men. As a steroid hormone, TT crosses the blood-brain barrier and continues to act in the central nervous system by binding to the androgen receptor (AR). Previous studies found that testosterone administration leads to enhanced adult neurogenesis in the hippocampal dentate gyrus, promoting cognitive improvement and mood regulation in depressed individuals (Mahmoud, Wainwright, & Galea, 2016). Adult neurogenesis, the formation of new neurons in the adult brain, is a major contributor to neuroplasticity and impairments in this process have been linked to depressive symptoms (Boldrini et al., 2013; Egeland et al., 2017; Rimmerman, Schottlender, Reshef, Dan-Goor, & Yirmiya, 2017). Below we describe the literature examining the relation between low testosterone and depression from clinical observation studies and TT studies. Subsequently, after introducing the reader to the current knowledge on established antidepressants and neurogenesis, we will outline how TT potentially contributes to the improvement in mood via the modulation of adult hippocampal neurogenesis. Finally, we will delineate alternative mechanisms through which testosterone might exert its

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antidepressant effect related to stress physiological systems and inflammation.

2. Clinical aspects of low testosterone and its relation to depression

Although TT prescriptions have increased 3-fold between 2002 and 2016 (Baillargeon, Kuo, Westra, Urban, & Goodwin, 2018), TT is only recommended for men with symptomatic hypogonadism (Bhasin et al., 2018). Hypogonadism, which is defined by testosterone deficiency coupled with clinical symptoms, such as erectile dysfunction, is not uncommon in men. It has been reported to affect approximately 2.1% of the male population aged 40 to 79 years, and critically low total plasma testosterone levels (below 11 nmol/l) are present in 17% of men in this age group (Wu et al., 2010). Typical symptoms that are related to low testosterone levels are sexual dysfunction, redistribution of body composition with loss of muscle mass and an increase in visceral fat, metabolic syndrome, osteoporosis and worsening of cognitive abilities (Walther & Ehlert, 2015). Importantly, mood disorders, in particular an increased risk of depression, has been reported for young and older men suffering from hypogonadism (Giltay et al., 2017; Korenman, Grotts, Bell, & Elashoff, 2018; Shores et al., 2004). However, for the general relation of basal endogenous testosterone levels and depressive mood in men, a mixed picture emerges, with some studies demonstrating a negative association between testosterone levels and depressive burden (Almeida, Yeap, Hankey, Jamrozik, & Flicker, 2008; Barrett-Connor, Von Mühlen, & Kritz-Silverstein, 1999; Ford et al., 2016) and others showing no association (Kische et al., 2017; Wu et al., 2010). Moreover, several studies suggest a negative association between testosterone and depressive symptoms only to be present in subgroups of men, such as hypogonadal or elderly men (2001b, Seidman, Araujo et al., 2001, 2002), and subtypes of depression, including atypical depression (Rodgers et al., 2015). Furthermore, studies investigating basal testosterone levels in explicitly depressed compared with non-depressed men, suggest a link between reduced testosterone levels in men diagnosed with major depressive disorder (MDD) (McIntyre et al., 2006; Schweiger et al., 1999; Shores et al., 2004), however, no association has also been reported (Asselmann et al., 2019; Davies et al., 1992; Rubin, Poland, & Lesser, 1989; Sigurdsson, Palsson, Aevarsson, Olafsdottir, & Johannsson, 2014). Studies focusing on dysthymic disorder demonstrate a more consistent association with reduced testosterone levels and mood impairment (Markianos, Tripodianakis, Sarantidis, & Hatzimanolis, 2007; Seidman et al., 2002).

This is of particular interest since testosterone levels in men continuously decline with increasing age and it has been shown that an increased burden of depressive symptoms intensifies the age-related decline in testosterone and dehydroepiandrosterone levels (Walther, Phillip, Lozza, & Ehlert, 2016). Therefore, TT in men has been extensively studied and for male hypogonadism multifaceted beneficial effects are reported, including sexual function, body composition and mood (Bhasin et al., 2018). A previous meta-analysis showed a beneficial effect of TT on mood in hypogonadal men (Elliott et al., 2017) and a recent meta-analytic study reported that TT might act as an antidepressant also in eugonadal men with relatively low testosterone levels (Walther et al., 2019). However, while potential lower testosterone thresholds are of current debate, there is no threshold distinguishing men who won't profit from those who will profit from TT (Morgentaler et al., 2016). This is on one hand caused by different intraindividual thresholds for testosterone deficiency symptoms, while on the other hand related to interindividual differences in circulating sex hormone binding globulin (inactivating the biological active testosterone compound), androgen receptor distribution in the central nervous system and androgen receptor repeat length (modulating androgen receptor function) (Walther & Ehlert, 2015). The recent meta-analytic examination of TT and depressive symptoms in men suggests, that the mood-enhancing effect of TT in men is independent of the gonadal status, initial level of depression severity and age (Walther et al., 2019).

Importantly, due to the unilateral clinical use of testosterone in men and the different modes of action of sex hormones in the central nervous system in men and women, predominantly studies on male populations were identified. However, there are few studies investigating TT as adjunct therapy in women with diagnosed depression showing positive results (Dias et al., 2006; Miller et al., 2009). In addition, two randomized controlled trials using TT further report a mood improving effect of the treatment, though women with depression were explicitly excluded (Davis et al., 2006; Goldstat, Briganti, Tran, Wolfe, & Davis, 2003). Although these findings are promising, the low number and unwanted side effects of TT in women do not allow to further analyze the antidepressant effect of testosterone in women more precisely and the findings must be interpreted with respect to men.

Taken together, an antidepressant effect of TT emerges, while the underlying mechanisms responsible for this effect remain elusive. It has been discussed that the positive effect on sexuality and body composition due to TT may have a follow-on effect on mood, suggesting no direct mechanistic connection but a downstream effect due to the generally improved health and quality of life (Elliott et al., 2017). However, recent animal and human studies indicate potential direct mechanisms, through which TT may exhibit its mood-enhancing effect. Below we discuss a possibility how testosterone could also elicit direct antidepressant effects, potentially via the modulation of neuroplasticity.

3. Adult hippocampal neurogenesis and antidepressants

The hippocampus is the main brain area involved in the modulation of the psychophysiological stress response, providing negative feedback on the hypothalamic-pituitary-adrenal (HPA) axis activity (Jacobson & Sapolsky, 1991). In addition to its role in the regulation of glucocorticoid release, the hippocampal dentate gyrus is also the primary region, where neurogenesis, the generation of new neurons, continues during adulthood (Ming & Song, 2005). During this process, termed adult neurogenesis, neural stem cells that reside in a neurogenic niche, divide occasionally and give rise to progenitor cells, which then mature to functional granule neurons. With stress being a strong negative regulator of new neuron formation and a leading risk factor for developing mood-related disorders, adult hippocampal neurogenesis has been linked to emotional and cognitive processes underlying depression (Cameron & Gould, 1994; Dranovsky & Leonardo, 2012; Gould, Tanapat, McEwen, Flügge, & Fuchs, 1998; Lagace et al., 2010).

Initial studies have shown impaired adult neurogenesis in animal models of depression (Lee et al., 2006; Pham, Nacher, Hof, & McEwen, 2003), which could be reversed by antidepressant treatment (Duman, Nakagawa, & Malberg, 2001; Malberg, Eisch, Nestler, & Duman, 2000), although, the ablation of neurogenesis alone was not sufficient to induce a depressive phenotype (Eliwa, Belzung, & Surget, 2017; Petrik, Lagace, & Eisch, 2012). These results suggested an interesting link between the production of newly born neurons and stress-induced depressive disorders, positioning adult neurogenesis in the center of clinical depression paradigms.

Since these early observations, most effective treatments of mood disorders – fluoxetine (Malberg et al., 2000), lithium (Chen, Rajkowska, Du, Seraji-Bozorgzad, & Manji, 2000), electroconvulsive shocks (Madsen et al., 2000; Scott, Wojtowicz, & Burnham, 2000), antipsychotics (Benninghoff et al., 2013), thyroid hormones (Remaud, Gothié, Morvan-Dubois, & Demeneix, 2014) and newer antidepressants, such as ketamine (Keilhoff, Bernstein, Becker, Grecksch, & Wolf, 2004), all have been shown to boost adult neurogenesis and the increased production of new neurons seems fundamental for some behavioral effects of antidepressants in rodent models of depression (David et al., 2009; Hill, Sahay, & Hen, 2015; Santarelli et al., 2003; Surget et al., 2011). Adult neurogenesis is also implicated in efficient pattern separation and cognitive flexibility – hippocampal-dependent functions

that are commonly impaired in mood-related disorders (Kheirbek, Klemenhagen, Sahay, & Hen, 2012; Leal, Tighe, & Yassa, 2014). Evidence from animal studies suggests that the ablation of neurogenesis is sufficient to impair cognitive functions related to depression (Burghardt, Park, Hen, & Fenton, 2012; Nakashiba et al., 2012) and to potentiate depression-like behaviors following acute stress (Schloesser, Manji, & Martinowich, 2009). Together these observations underline the beneficial effects of pro-neurogenic therapies in mood-disorders.

Interestingly, recent evidence suggests that adult neurogenesis occurs throughout life also in the human hippocampus (Boldrini et al., 2018; Moreno-Jiménez et al., 2019; Spalding et al., 2013) and post mortem analysis revealed a decreased neural progenitor cell number in the dentate gyrus of depressed patients (Boldrini et al., 2009; Lucassen, Stumpel, Wang, & Aronica, 2010). Studies evaluating the effect of antidepressant treatment on neurogenesis levels in depressed individuals identified inconsistent results with no effect (Lucassen et al., 2010) or an increase (Boldrini et al., 2009) in neuronal progenitor cell number and proliferation following antidepressant therapy. Despite these discrepancies in the levels of neural progenitor cell proliferation, both post mortem and high-resolution magnetic resonance imaging volumetric studies consistently demonstrate smaller dentate gyrus volume and decreased total granule cells number in patients with depression (Wang et al., 2010; Boldrini et al., 2013; Huang et al., 2013), an effect that can be reversed by antidepressant treatment (2013, Arnone et al., 2013; Boldrini et al., 2014; Tendolkar et al., 2013). This may indicate that depression affects neurogenesis on the neuronal differentiation or survival stage rather than progenitor proliferation, and antidepressant induced hippocampal growth results reflects multiple forms of beneficial neuroplasticity.

Finally, although there is no definitive evidence that boosting neurogenesis alone is sufficient to reverse depressive behavioral phenotypes, studies originating from neurogenic theory lead to the identification of novel promising therapeutics such as P7C3 (Walker et al., 2015), baicalin (Gao et al., 2018; Zhang et al., 2016) or neurofibromin (Li, Li, McKay, Riethmacher, & Parada, 2012), that induce antidepressant-like effects via increasing hippocampal neurogenesis in rodent models of stress and depression. Alternatively, non-pharmacological manipulations that are associated with antidepressant effects in models of stress, could promote behavioral recovery via modulation of adult neurogenesis. Emerging examples are neurosteroids, such as androgens and estrogens. Both compounds can be produced locally in the in dentate gyrus granule cells, which carry complete steroidogenic systems to synthesize steroid hormones from cholesterol (Hojo et al., 2004; Mukai et al., 2006). Levels of locally produced dihydrotestosterone, which is derived from testosterone, were shown to increase after physical exercise (Okamoto et al., 2012), a strong positive modulator of adult hippocampal neurogenesis (van Praag, Christie, Sejnowski, & Gage, 1999; van Praag, Kempermann, & Gage, 1999). Interestingly, the increase in exercise-induced neurogenesis was absent after treatment with the AR antagonist flutamide (Okamoto et al., 2012), suggesting the involvement of androgens in this process. This endogenously activated neuroplasticity could counteract stress-induced cell loss and neuronal atrophy leading to maintenance of functioning neuronal networks involved in emotional and cognitive processing.

4. Does testosterone influence neuroplasticity?

Although evidence is still scarce, a few studies have indicated a direct link between testosterone administration and antidepressant effects via neuroplasticity (Carrier et al., 2015; Hamson et al., 2013; Wainwright et al., 2016). First, Hamson et al. examined adult hippocampal neurogenesis in two groups of male rats in which they eliminated endogenous androgen production through gonadectomy. In addition to castration, one group carried a mutation in the AR gene, which rendered the animals insensitive to androgen action while the control group had normal expression of the AR (Hamson et al., 2013). When testosterone was administered to both groups, only the control group, which was sensitive to androgen action, showed an increased survival of newborn cells in the dentate gyrus. Moreover, the authors reported that the survival of new neurons was significantly reduced after androgen antagonist administration compared to placebo treatment, indicating that androgen action promotes neuronal survival (Hamson et al., 2013). Although the presence of ARs throughout the hippocampal formation has been shown by others (Choate, Slayden, & Resko, 1998), Hamson et al. did not find AR expression within the immature neurons themselves, and suggested a non-cell autonomous mechanism through other hippocampal regions influencing the cell survival. However, AR-dependent enhancement of cell survival during the neurogenic process might occur at other stages of neuronal maturation, which have not been investigated in their study.

Second, Carrier et al. examined the antidepressant effects of testosterone using a rodent model of gonadectomized male rats, administering either testosterone, estradiol, or placebo (Carrier et al., 2015). Both testosterone and estradiol treatment led to a reduced depression-like behavior in the sucrose preference and open field tests compared with rats receiving a placebo. However, local infusion of an aromatase inhibitor into the dentate gyrus, which blocks the local conversion of testosterone into estradiol, in addition to testosterone administration, resulted in increased depression-like behavior (Carrier et al., 2015). This suggests that the anti-depressant-like effect of TT could be, at least in part, mediated through its metabolite estradiol that is produced locally via a site-specific conversion (Carrier et al., 2015). In the same study, gene expression analysis of dorsal hippocampus tissue from gonadectomized male rodents revealed that testosterone and estradiol treatment resulted in an overlap in changes in hippocampal gene expression, indicating shared genomic pathways for testosterone and estradiol in the reduction of depression-like behavior. Furthermore, by using gene expression profiling, the data suggested neurogenesis-related synaptic plasticity as the underlying mechanism of the antidepressant effects of testosterone and estradiol treatment (Carrier et al., 2015).

Third, Wainwright et al. suggested an anti-depressant effect of TT via neuroplasticity, using a rodent model of depression, the chronic unpredictable stress paradigm. The authors treated adult gonadectomized male rats with either testosterone, an antidepressant (imipramine) or both, where the administration of testosterone reduced depression-like behavior only following chronic unpredictable stress, but not in the absence of stress (Wainwright et al., 2016). Similarly, a number of studies reported that adult neurogenesis primarily reduces depression-like behavior following stress (David et al., 2009; Santarelli et al., 2003; Surget et al., 2011). Wainwright et al. also found that the combination of testosterone and imipramine led to enhanced imipramine-induced neurogenesis, indicating beneficial effects of additional testosterone administration. However, in contrast to the study by Hamson et al., the authors observed no increase in neurogenesis after the administration of testosterone alone (Wainwright et al., 2016). It is of note, however, that the duration of the TT was shorter (21 days in Wainwright et al., 2016 versus 30 days in Hamson et al., 2013), indicating that testosterone-related changes in neurogenesis may require more than 21 days of administration for the identification of potential effects. Moreover, the delayed effect suggests that structural changes may also be involved, such as neuroplasticity during neurogenic maturation. This discrepancy of the results fosters further investigation of the temporal dynamics of TT in regards to the investigated neurogenesis markers along the neurogenic process.

While the outlined studies indicate that testosterone has a direct effect on neuroplasticity, there is another line of research suggesting that testosterone exerts serotonin-dependent antidepressant effects. Current antidepressants, such as imipramine, act via the serotonin system, which also has implications in hippocampal neurogenesis (Alenina & Klempin, 2015; Gould, 1999). Studies have shown that testosterone has an activating effect on the serotonin system (Kranz

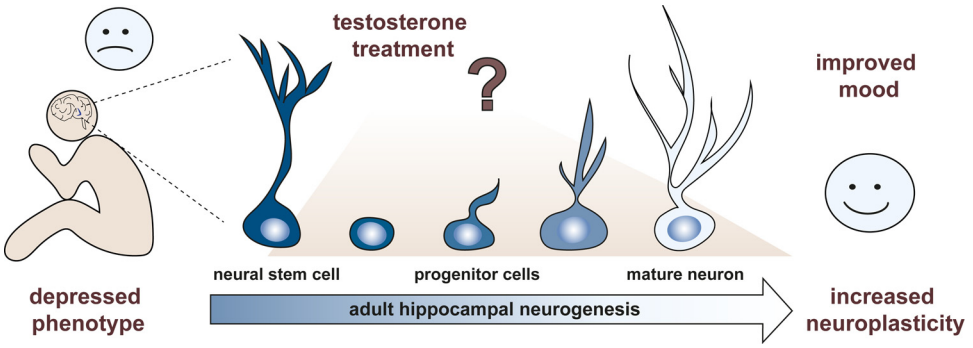

Fig. 1. Adult neurogenesis in the hippocampal dentate gyrus is an example of continued neuroplasticity throughout life. In this process, neural stem cells divide and give rise to proliferating progenitor cells, which pass through different developmental stages to mature into functional new neurons. Evidence suggest involvement of this process in depressive disorders and beneficial effects of clinical antidepressants. Testosterone treatment potentially contributes to the improvement in mood via the modulation of new neuron generation, likely via promoting the survival of the new born neurons.

et al., 2015), and a recent study identified a link between serotonin signaling in the hippocampus and plasma testosterone levels in healthy men (Perfalk et al., 2017). Therefore, in addition to the increasing evidence suggesting that testosterone directly affects neuroplasticity, an indirect route of testosterone influencing depression might be mediated through the activation of the serotonin system.

Taken together, these studies highlight the anti-depressant action of testosterone and suggest that the increase of neuroplasticity via adult hippocampal neurogenesis may be one potential mechanism that underlies this effect (Fig. 1).

5. Functional crosswalk between testosterone the HPA and the inflammatory system

Although the above studies suggest a direct effect of TT in the brain, testosterone, the main effector of the hypothalamic-pituitary-gonadal (HPG) axis, also contributes to changes along the HPA axis, which might indirectly influence neuroplasticity and mood. Studies in the field of the biological basis of MDD over the last 30 years have identified a hyperactivity of the HPA axis and a chronic low-grade inflammation as the most consistent biological markers in MDD (Pariante, 2017). Although, there is much contradictory literature, recent systematic reviews and meta-analyses conclude that depression is associated with increased cortisol levels (Juruena, Bocharova, Agustini, & Young, 2018; Stetler & Miller, 2011) and pro-inflammatory markers, such as interleukin-6 and C-reactive protein (Goldsmith, Rapaport, & Miller, 2016; Köhler et al., 2017). Basal cortisol levels were further suggested to predict the treatment response to psychological or antidepressant treatment (Fischer, Macare, & Cleare, 2017; Fischer, Strawbridge, Vives, & Cleare, 2017). In contrast, a meta-analytic examination showed a reduction in a pro-inflammatory cytokine profile after treatment (Köhler et al., 2018). All attempts to use these markers as predictors of depression or treatment response in clinical settings, however, fail due to the lack of specificity and considerable interindividual differences. However, the observed increased concentrations of glucocorticoids and pro-inflammatory markers in MDD and the well-established fact that high levels of glucocorticoids and pro-inflammatory factors are also associated with neurodegenerative diseases (Chen, Zhang, & Huang, 2016; Conrad et al., 2007; Kim, Na, Myint, & Leonard, 2016; Miller & Raison, 2016; Uno et al., 1994; Vyas et al., 2016), are of great relevance when examining potential alternative mechanisms through which testosterone may exert its mood-enhancing effects.

Testosterone was shown to down regulate the central stress response, including the HPA axis at the hypothalamic level by decreasing the secretion of corticotropin-releasing hormone and arginine vasopressin (Hermans et al., 2007; Johnson, Kamilaris, Chrousos, & Gold, 1992; Rubinow et al., 2005; Viau, 2002). Testosterone levels also negatively correlate with pro-inflammatory markers and white blood cell count in men (Haring et al., 2012; Maggio et al., 2006). Moreover, TT was shown to downregulate pro-inflammatory markers in conditions such as the metabolic syndrome (Kalinchenko et al., 2010). *in vitro* and *in vivo* studies suggest different pathways through which testosterone acts as anti-inflammatory factor, including the suppression of tumor necrosis factor alpha in glial cultures and decreasing toll-like receptor-4 expression and sensitivity in macrophages (Vasconcelos, Cabral-Costa, Mazucanti, Scavone, & Kawamoto, 2016). Thereby, testosterone and the entire HPG axis may act as important counter-regulatory system controlling the levels of glucocorticoids and pro-inflammatory markers, which otherwise may be present in excessive concentrations and thus exert neurodegenerative effects (Mondelli et al., 2011; Taki et al., 2013; Tene et al., 2018). Therefore, emerging sex specific models of depressive disorders paying respect to differing levels of sex hormones in men and women and integrating different biological systems, such as the endocrine system and the immune system, are highly promising to delineate the underlying pathophysiology (Schiller, Johnson, Abate, Schmidt, & Rubinow, 2016; Walther, Penz, Ijacic, & Rice, 2017; Walther, Rice, Kufert, & Ehlert, 2017).

6. Testosterone treatment – a potential new avenue to treat depression in men?

Accumulating evidence from longitudinal cohort studies on endogenous testosterone levels and TT studies suggests testosterone as a potential beneficial modulator of depressive symptoms in men. Furthermore, hypogonadal men are at increased risk for depressive disorders (Giltay et al., 2017; Korenman et al., 2018; Shores et al., 2004). However, due to uncertainty with regard to TT-related efficacy for the reduction of depressive symptoms or adverse events, TT is not recommended by clinical practice guidelines as an antidepressant treatment for depression (National Collaborating Centre for Mental Health UK, U., 2010) or by clinical practice guidelines for TT in hypogonadal men (Bhasin et al., 2018). Therefore, more pre-registered, high-quality randomized clinical trials investigating the effects of testosterone on depressive symptoms in men are needed. Moreover, when consistently showing beneficial effects, subsequent larger post-marketing surveillance studies will be required in order to determine whether TT may be associated with an increased risk of rare adverse drug reactions. This will be particularly important in order to render the potential of TT for the treatment of depressive disorders in men accessible to the general public.

Additional *in vitro* and *in vivo* studies are required to address the extent to which the outlined mechanisms are responsible for the antidepressant effect of testosterone. Moreover, it needs to be determined to which extent the activation of the serotonin system is integrated in these processes. Potentially, these changes in the neuroarchitecture are further accompanied by the additional beneficial actions of testosterone on the HPA axis reducing total glucocorticoid output as well as reducing pro-inflammatory markers in the periphery and the central nervous system.

7. Conclusion

This review highlights potential underlying pathways of the antidepressant effect of testosterone. Similar to other antidepressants, TT

may increase neuroplasticity and thereby promote the reduction of depressive symptoms. While testosterone might exert beneficial effects on mood and behavior through the activation of the serotonin system, the here discussed studies suggest that a serotonin-independent antidepressant mechanism is also involved. Additional beneficial effects of testosterone related to stress physiological systems as well as the immune system might further support the antidepressant effect of TT. However, it is of note that not only testosterone alone, but also its site-specific conversion to estradiol and other related metabolites may elicit antidepressant actions. In summary, the discussed studies prompt future research to determine the pathways that underlie the mood-enhancing effects of TT in order to potentially apply this approach for the treatment of depressive disorders in men.

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