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Serum testosterone levels are related to cognitive function in men with schizophrenia

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Summary
Background: Sex steroids such as oestrogen and testosterone are potent neurodevelopmental hormones that also play a role in neuromodulation and neuroprotection of the mature brain. Sex steroid hormones may also be involved in the pathophysiology of schizophrenia as reduced circulating sex steroid levels and changes in brain sex steroid receptors are found in people with schizophrenia compared to controls. In men with schizophrenia, recent studies have documented an inverse correlation between serum testosterone and negative symptoms. Our study sought to confirm whether men with schizophrenia had lower levels of testosterone relative to controls and to determine whether lower testosterone levels were related to higher symptom severity and impaired cognition.
Method: Circulating serum hormone levels (testosterone, oestrogen, and prolactin), cognitive function and symptoms were assessed in 29 chronically ill men with schizophrenia or schizoaffective disorder. Twenty healthy men were recruited as a comparison group. A series of regression analyses were performed to determine the extent to which circulating sex steroid hormone levels predict cognition and symptoms in men with schizophrenia.
Results: We did not find a significant difference in serum testosterone levels between groups. However, circulating testosterone levels significantly predicted performance on verbal memory, processing speed, and working memory in men with schizophrenia. With the exception of an effect of oestrogen on verbal memory, circulating sex steroid levels did not predict cognitive

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function in healthy men. Testosterone levels were not related to positive or negative symptom severity, but testosterone influenced excitement/hostility levels in our schizophrenia sample.
Conclusions: The results suggest that circulating sex steroids may modulate cognitive deficits associated with schizophrenia.

1. Introduction

Schizophrenia is a debilitating psychotic disorder with a prevalence of about one percent in the world population (McGrath et al., 2008). Gender differences in severity and course of the illness are suggestive of hormonal influences in schizophrenia pathophysiology. Schizophrenia has a slightly higher prevalence in men, with about 3/5 affected being male (Aleman et al., 2003; McGrath et al., 2004). In men with schizophrenia, symptoms tend to be more pronounced and less treatment responsive with men also experiencing earlier age of onset as compared to women (Abel et al., 2010). The onset of schizophrenia in males occurs most frequently in adolescence, which is also characterized by an increase in testosterone levels (Häfner et al., 1993). However, males expressing prodromal symptoms during this time show lower testosterone than healthy males (van Rijn et al., 2006). Some studies have also observed lower testosterone levels in adult males with schizophrenia or psychosis compared to healthy controls (Taherianfard and Shariaty, 2004; Akhondzadeh et al., 2006).

Changes in sex steroids have been associated with variation in symptoms in both men and women with schizophrenia. Women with schizophrenia tend to experience less severe psychotic symptoms during periods of high oestrogen such as pregnancy and experience symptom exacerbation at times low oestrogen such as post-partum and during menopause (Hallonquist et al., 1993; Huber et al., 2004; Ko et al., 2006). Men with schizophrenia display increases in negative symptom severity with lower testosterone levels (Shirayama et al., 2002; Akhondzadeh et al., 2006; Ko et al., 2007). Furthermore, studies have shown that exogenous testosterone supplementation may reduce negative symptoms in men with schizophrenia (Ko et al., 2008) and that exogenous oestrogen supplementation is associated with a reduction in psychotic symptoms in women with schizophrenia and possibly in men (Kulkarni et al., 2002, 2008, 2011). However, less is known about the relationship between low sex steroid levels and cognitive ability in people with schizophrenia and whether restoration of hormone levels may beneficially affect cognitive functioning.

There is evidence to suggest that sex steroids impact cognitive function in non-psychotic individuals. In healthy older men, lower testosterone levels are associated with impaired cognitive abilities of mental rotation (Young et al., 2010), and spatial and verbal memory improve with exogenous testosterone (Cherrier et al., 2001, 2007). Since testosterone can be converted to oestrogen in the male brain, some of these beneficial effects of testosterone may be mediated through oestrogen actions. Administration of a selective oestrogen receptor modulator (SERM) in older men delays age-associated cognitive decline and brain dysfunction related to episodic and working memory (Goekoop et al., 2005, 2006; DonCarlos et al., 2009).

In schizophrenia, cognitive deficits are commonly recognized as a core characteristic (Weickert et al., 2000) and predict functional outcome (Green, 1996). Previous work by our group has demonstrated molecular changes in oestrogen receptors in the frontal cortex of both men and women with schizophrenia, which could potentiate abnormal brain responses to sex steroids (Shannon Weickert et al., 2008). Other studies in men with schizophrenia have found associations between cognition (particularly memory) and dehydroepiandrosterone (sulphate) — DHEA(S) — a precursor steroid of both testosterone and oestrogen (Newcomer et al., 1998; Walder et al., 2000; Halari et al., 2004; Silver et al., 2005; Strous et al., 2007; Ritsner and Strous, 2010). Higher DHEA(S) concentrations appear to have a positive effect on verbal memory and executive functioning in men with schizophrenia (Silver et al., 2005; Strous et al., 2007; Ritsner and Strous, 2010). To our knowledge, only one study to date has examined the relationship between testosterone and cognition in men with schizophrenia (Halari et al., 2004) and failed to detect any associations. However, the results of the DHEA(S) studies suggest that changes in circulating sex steroid levels may impact cognitive performance in men with schizophrenia.

The present study therefore aimed to determine the relationships among circulating sex steroid levels (in particular testosterone), cognition, and psychotic symptoms in a sample of chronically ill men with schizophrenia. We expected that serum testosterone levels would be lower in men with schizophrenia than in healthy men. We also expected that higher serum testosterone levels would predict better cognitive performance and less severe psychotic symptoms in men with schizophrenia. Despite some preliminary evidence of beneficial oestrogen therapy effects in men with schizophrenia (Kulkarni et al., 2011), little is known about the relationship between circulating oestrogen levels and psychotic symptoms or cognition in men with schizophrenia. Thus, we also investigated the extent to which serum oestrogen levels would predict cognition and symptom severity in men with schizophrenia. Finally, prolactin levels were also examined to account for prolactin-raising properties of some antipsychotic medications (primarily first generation antipsychotics) which may alter hypothalamic-pituitary-gonadal axis functioning and confound the results by altering hormone production.

2. Methods

2.1. Participants

Twenty-nine men with a diagnosis of schizophrenia or schizoaffective disorder and twenty healthy men without a history of psychiatric disorder, all between 18 and 50 years of age, were included in the study. See Table 1 for the