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Testosterone and reward prediction-errors in healthy men and men with schizophrenia

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ABSTRACT

Sex hormones impact reward processing, which is dysfunctional in schizophrenia; however, the degree to which testosterone levels relate to reward-related brain activity in healthy men and the extent to which this relationship may be altered in men with schizophrenia has not been determined. We used functional magnetic resonance imaging (fMRI) to measure neural responses in the striatum during reward prediction-errors and hormone assays to measure testosterone and prolactin in serum. To determine if testosterone can have a direct effect on dopamine neurons, we also localized and measured androgen receptors in human midbrain with immunohistochemistry and quantitative PCR. We found correlations between testosterone and prediction-error related activity in the ventral striatum of healthy men, but not in men with schizophrenia, such that testosterone increased the size of positive and negative prediction-error related activity in a valence-specific manner. We also identified midbrain dopamine neurons that were androgen receptor immunoreactive, and found that androgen receptor (AR) mRNA was positively correlated with tyrosine hydroxylase (TH) mRNA in human male substantia nigra. The results suggest that sex steroid receptors can potentially influence midbrain dopamine biosynthesis, and higher levels of serum testosterone are linked to better discrimination of motivationally-relevant signals in the ventral striatum, putatively by modulation of the dopamine biosynthesis pathway via AR ligand binding. However, the normal relationship between serum testosterone and ventral striatum activity during reward learning appears to be disrupted in schizophrenia.

1. Introduction

Testosterone impacts male motivation, competitive drive and social behavior (Spear, 2000; Archer, 2006; Coates and Herbert, 2008; Richards et al., 2009; Morris et al., 2010). In schizophrenia, testosterone levels inversely correlate with negative symptoms, such as lack of motivation, flat affect and social withdrawal (Akhondzadeh et al., 2006; Ko et al., 2007). The negative symptoms of schizophrenia relate to abnormal activity in a fronto-striatal circuit during reward processing (Juckel et al., 2006; Schlagenhauf et al., 2008; Morris et al., 2012, 2014). However, the relationship between testosterone and neural activity during reward processing in schizophrenia is unknown.

Valence-specific changes in midbrain dopamine neuron firing are known to underpin successful reward learning from a neurobiological perspective (Schultz, 2013). Midbrain dopamine neurons projecting to the nucleus accumbens code for reward prediction-errors by increasing firing after unexpected rewards (URs) and by decreasing firing after unexpected reward omissions (UOs) (Schultz et al., 1997). Consistent with this, blood oxygenation level dependent (BOLD) responses in the healthy human ventral striatum reliably show increased activity to URs and decreased activity to UOs (D'Ardenne et al., 2008; Morris et al., 2012). This, and other evidence (Pessiglione et al., 2006; Knutson and Gibbs, 2007) suggests BOLD-related prediction-error signals in the ventral striatum reflect regionally-specific and temporally-specific input from midbrain dopamine neurons during reward-processing.

Testosterone may modulate the mesolimbic dopamine activity via direct action on midbrain dopamine neurons. Testosterone can bind to androgen receptors (AR) and after conversion by aromatase to estradiol, to estrogen receptors (ERα and ERβ). In rodents, most studies demonstrate that dopamine neurons express AR and both estrogen receptors (Shughrue et al., 1997; Perez et al., 2003; de Souza Silva et al., 2009; Purves-Tyson et al., 2012). Evidence from conditioned place preference studies in rodents (de Beun et al., 1992; Alexander et al., 1994) and

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anabolic steroid addiction in human males (Kanayama et al., 2009, 2010) suggest testosterone can act as a positive reinforcer. Furthermore, oral administration of testosterone to women increases BOLD activation in the ventral striatum during reward anticipation and has the greatest effect in women with low intrinsic appetitive motivation (Hermans et al., 2010). Thus, the effects of administering testosterone on the mesolimbic path are most marked in people with low motivation; however, the relationship between endogenous testosterone and ventral striatum BOLD activity in men, with or without low motivation, is unknown.

Our aim was to determine the extent to which endogenous circulating testosterone levels were associated with ventral striatal BOLD activity during prediction error among healthy men and men with schizophrenia, a group typically associated with anhedonia and motivation deficits. We also identified a potential mechanism by which testosterone could be working by determining whether human midbrain dopamine neurons have the capacity to directly respond to circulating testosterone via sex steroid receptors. Our hypotheses were: 1) that testosterone will be positively related to ventral striatal BOLD activity in healthy men during reward prediction-errors; 2) human nigral dopamine neurones will express AR and the level of expression will be related to dopamine synthesis capacity (as measured by tyrosine hydroxylase mRNA); and 3) low levels of testosterone will co-occur with abnormal BOLD ventral striatal activity in men with schizophrenia during reward prediction-errors, and low BOLD activity will be related to negative symptom severity.

2. Materials and methods

2.1. Participants

Fifteen healthy men and 21 chronically ill men with schizophrenia or schizoaffective disorder were recruited for this study. Three patients were excluded for excessive head motion (>2 mm), inadequate task performance (non-responding) or structural abnormalities leaving 18 men with schizophrenia, all of whom were receiving second generation antipsychotic medication. All participants were native English speakers, predominantly right-handed (as determined by the Edinburgh Handedness Inventory) and had no history of head injuries with loss of consciousness, seizures, central nervous system infection, uncontrolled diabetes or hypertension or alcohol or drug abuse in the last five years. Trained clinicians administered the Structured Clinical Interview for the Diagnostic and Statistical Manual IV (SCID) (First et al., 2007), and obtained premorbid and current IQ estimates using the Wechsler Test of Adult Reading (WTAR) and a short 4 subtest form of the Wechsler Adult Intelligence Scale-third edition (WAIS-III), respectively (Wechsler, 1997, 2001). Symptom severity ratings were obtained using the Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1987). All procedures involving humans or human tissue were approved by the University of New South Wales Human Research Ethics Committees (HREC 07121, 09187, 07261 and 12435) and the South Eastern Sydney and Illawarra Area Health Service HREC (07259, 09187), and written informed consent was obtained from all fMRI participants. See Table 1 for details on the fMRI participant demographics. Six of the men with schizophrenia and eight of the healthy men were included in a previous report on the neural substrate of prediction-errors (Morris et al., 2012). Thus, in the present study, an additional seven healthy men and 12 men with schizophrenia were assessed.

2.2. Hormone samples

Fasting intravenous blood samples were collected between 9:45 am and 11 am. Total testosterone was assayed using a solid-phase, competitive chemiluminescent immunometric assay (Siemens Healthcare Diagnostics Products Ltd, UK) and we also assayed prolactin since levels of prolactin can indicate dopamine antagonism by antipsychotic drugs. All hormonal assays were performed by the Prince of Wales Hospital South Eastern Area Laboratory Services. For testosterone, reference ranges were set at 7.2 to 25 nmol/L, sensitivity of assay was 0.7 nmol/L, and the interassay coefficient of variation (CV) was ≈10.8%. For prolactin, reference ranges were set at 0 to 372 ml U/L, sensitivity of assay was 11.0 ml U/L, the intra-assay CV was 6 and the interassay CV was ≈6.8%.

2.3. fMRI methods

2.3.1. fMRI acquisition

Imaging was acquired on a Phillips Achieva 3T scanner with an 8 channel bird cage head coil at Neuroscience Research Australia. We acquired 968 whole-brain T2* weighted echoplanar images (EPI) with a gradient echo sequence. The slice thickness was 3 mm with a 1 mm gap, consisting of 31 axial slices in ascending order, with a repetition time (TR): 2000 ms, echo time (TE): 30 ms, flip angle: 90°, matrix: 112 × 112, and field of view (FOV): 240 mm. A T1-weighted high resolution anatomical scan was obtained for each participant for registration and screening. The T1-weighted anatomical scan had a TR: 5.4 ms, TE: 2.4 ms, FOV: 256 mm, matrix: 256 × 256, sagittal plane, slice thickness of 1 mm with no gap, and 180 slices.

2.3.2. Reward prediction task

A series of cue-outcome trials were presented in which participants were instructed to predict a reward (an image of nine $50 dollar Australian notes) that was contingent upon presentation of one of

Table 1
Mean (SD) clinical, demographic and hormone results.

	SZ ($n = 18$)[a]	HM ($n = 15$)	t ($df = 31$)	p
Age	33.83 (8.92)	31.29 (8.34)	0.50	0.62
Years of education	13.83 (2.73)	15.00 (1.92)	1.36	0.19
WAIS-III IQ score	98.28 (12.75)	108.86 (13.61)	2.26	0.03
WTAR score	107.56 (10.67)	109.64 (7.47)	0.62	0.54
Handedness score	91.89 (14.13)	96.58 (9.15)	1.01	0.32
Testosterone (nmol/L)	15.93 (5.49)	17.24 (5.19)	0.68	0.50
Prolactin (mlU/L)	222.17 (194.23)	160.86 (134.73)	1.01	0.32
PANSS score				
(General)	32.72 (10.13)			
(Negative)	16.17 (3.90)			
(Positive)	15.06 (7.46)			

SZ: men with schizophrenia; HM: healthy males; WAIS-III: Weschler Adult Intelligence Scale, 3rd Edition; WTAR: Weschler Test of Adult Reading; PANSS: Positive and Negative Syndrome Scale for Schizophrenia.

[a] Antipsychotics (no. of patients): olanzapine: 6, clozapine: 3, risperidone: 2, amisulpride: 1, quetiapine: 1, clozapine & aripiprazole: 1, quetiapine & ziprasidone: 1, quetiapine & zuclopenthixol: 1, risperidone & amisulpride: 1, and risperidone & quetiapine: 1.

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