Psychoneuroendocrinology 89 (2018) 92–102

Contents lists available at ScienceDirect

Psychoneuroendocrinology

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

Testosterone, DHEA and DHEA-S in patients with schizophrenia: A systematic review and meta-analysis

Błażej Misiak[a,*], Dorota Frydecka[b], Olga Loska[c,d], Ahmed A. Moustafa[e], Jerzy Samochowiec[f], Justyna Kasznia[g], Bartłomiej Stańczykiewicz[h]

[a] Department of Genetics, Wroclaw Medical University, Marcinkowskiego 1 Street, 50-368 Wroclaw, Poland
[b] Department of Psychiatry, Wroclaw Medical University, Pasteura 10 Street, 50-367 Wroclaw, Poland
[c] Department of Forensic Medicine, Wroclaw Medical University, Mikulicza-Radeckiego 4 Street, 50-345 Wroclaw, Poland
[d] Department of Laboratory Diagnostics, 4th Military Hospital, Weigla 5 Street, 50-981 Wroclaw, Poland
[e] School of Social Sciences and Psychology, Marcs Institute of Brain and Behaviour, Western Sydney University, Penrith, NSW, Australia
[f] Department of Psychiatry, Pomeranian Medical University, Broniewskiego 26 Street, 71-460 Szczecin, Poland
[g] Inpatient Psychiatric Unit, Municipal General Hospital, Limanowskiego 20/22 Street, 63-400 Ostrów Wielkopolski, Poland
[h] Department of Nervous System Diseases, Wroclaw Medical University, Bartla 5 Street, 51-618 Wroclaw, Poland

ARTICLE INFO

Keywords:
Androgens
Psychosis
Hormone
Stress
Sex differences

ABSTRACT

Neuroactive steroids, including testosterone, dehydroepiandrosterone (DHEA) and its sulfate (DHEA-S) might play an important role in the pathophysiology of schizophrenia. Therefore, we performed a systematic review and meta-analysis of studies comparing the levels of testosterone, DHEA and DHEA-S in patients with schizophrenia and healthy controls. We searched electronic databases from their inception until Oct 29, 2017. Effect size (ES) estimates were calculated as Hedges' g. Data analysis was performed using random-effects models. Our analysis included 34 eligible studies, representing 1742 patients and 1604 controls. Main analysis revealed elevated DHEA-S levels in the whole group of patients (ES = 0.75, 95%CI: 0.23–1.28, p = 0.005). In subgroup analyses, patients with first-episode psychosis (FEP) had significantly higher levels of free testosterone (ES = 1.21, 95%CI: 0.30–2.12, p = 0.009) and DHEA-S (ES = 1.19, 95%CI: 0.66–1.71, p < 0.001). Acutely relapsed schizophrenia patients presented significantly higher levels of total testosterone (ES = 0.50, 95%CI: 0.21–0.70, p < 0.001). Total testosterone levels were also elevated in stable multi-episode schizophrenia (sMES) females (ES = 0.56, 95%CI: 0.33–0.80, p < 0.001) and reduced in sMES males (ES = −0.62, 95%CI: −1.07 to 0.18, p = 0.006). Increased levels of biologically active, free testosterone and DHEA-S in FEP suggest that these alterations might appear as a response to stress that becomes blunted during subsequent exacerbations of schizophrenia. Differential changes in total testosterone levels in male and female sMES patients might represent medication effects related to prolactin-releasing effects of antipsychotics.

1. Introduction

Schizophrenia is a neurodevelopmental disorder with complex etiology characterized by interactions between genetic and environmental factors that impact sensitive periods of brain development (Marin, 2016; Misiak et al., 2017). Several lines of evidence indicate that schizophrenia can be characterized by a number of sex differences. Indeed, there are studies showing earlier age of schizophrenia onset, worse premorbid functioning and less favourable long-term outcomes, higher rates of treatment-resistance and more frequent subtle neurodevelopmental brain abnormalities in male patients (Abel et al., 2010; Owens et al., 2017). It has been suggested that aberrant signalling by neuroactive steroids may contribute to the development of schizophrenia and impact sex differences observed in this disorder (Owens et al., 2017).

Neuroactive steroids, including i.e. testosterone, dehydroepiandrosterone (DHEA) and its sulphide ester (DHEA-S), play an important role in the brain development by influencing synaptic connectivity and neuronal differentiation (Melcangi et al., 2011; Reddy, 2010). Both DHEA and DHEA-S, produced by adrenal glands, are precursors for synthesis of testosterone in the Leydig cells. However, certain neurons are also prone to produce small amounts of DHEA and testosterone. Importantly, neuroactive steroids influence dopaminergic, glutamatergic and GABAergic neurotransmission systems that are believed to

* Corresponding author.
E-mail address: blazej_misiak@interia.pl (B. Misiak).

https://doi.org/10.1016/j.psyneuen.2018.01.007
Received 31 October 2017; Received in revised form 4 January 2018; Accepted 8 January 2018

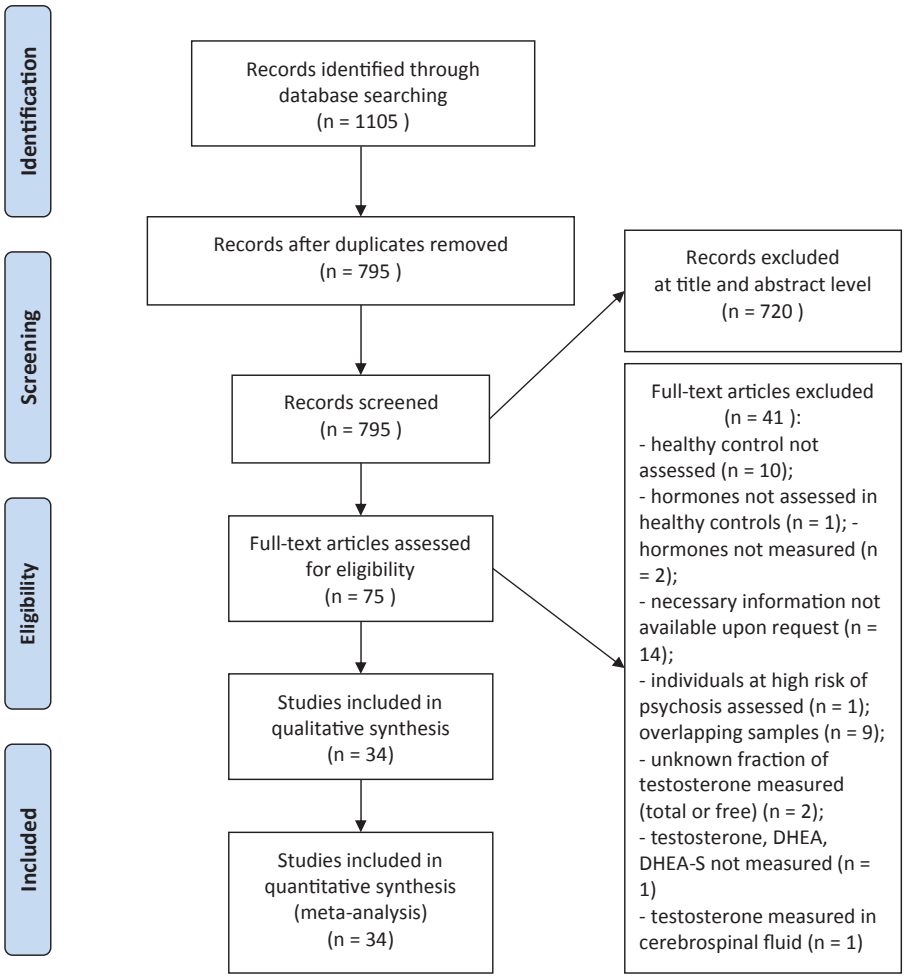

Fig. 1. Selection of studies.

act in the pathophysiology of schizophrenia (Melcangi et al., 2011). Additionally, DHEA acts as an important component of stress response by exerting potent antiglucocorticoid activities that protect hippocampal cells from neurotoxic effects of corticosterone (Handa and Weiser, 2014; Kimonides et al., 1999). Interestingly, a recent study by Hayes et al. (2014) revealed elevated levels of testosterone in the cerebrospinal fluid of first-episode schizophrenia patients and individuals at-risk of psychosis.

It has been reported, although inconsistently, that the levels of testosterone, DHEA and DHEA-S may impact psychopathological manifestation of schizophrenia. Specifically, several studies revealed a negative correlation between the levels of testosterone and a severity of negative symptoms or cognitive deficits (Akhondzadeh et al., 2006; Ji et al., 2015; Ko et al., 2007; Moore et al., 2013). These studies have provided grounds for clinical trials investigating the efficacy of neuroactive steroids in the treatment of schizophrenia. A recent quantitative review of double-blind, placebo-controlled, randomized trials addressing the efficacy of sex hormones in schizophrenia revealed no significant effects of DHEA augmentation on treatment outcomes (Heringa et al., 2015). Authors found only one study investigating the efficacy of testosterone that revealed beneficial effects of this augmentation strategy in terms of improving negative symptoms (Ko et al., 2008). At this point, it should be noted that studies measuring the levels of testosterone, DHEA and DHEA-S have provided mixed findings and thus it is difficult to generalize their results and personalize add-on treatments. Therefore, we decided to perform a systematic review and meta-analysis of studies investigating the levels of testosterone, DHEA and DHEA-S in patients with schizophrenia and first-episode psychosis (FEP) in comparison with healthy controls.

2. Methods

2.1. Search strategy

Independent online search was performed by two authors (BS and BM), using the combination of keywords from the following groups: 1) “androgen”; “neurosteroid”; “testosterone”; “dehydroepiandrosterone” and “DHEA” and 2) “schizophrenia” and “psychosis”. Publications were identified in the following databases: PubMed; CINAHL Complete; Academic Search Complete; ERIC and Health Source: Nursing/Academic Edition from database inception until Oct 29, 2017. In addition, we reviewed reference lists from eligible publications. We included studies that determined the levels of testosterone and/or DHEA and/or DHEA-S in patients with schizophrenia and/or FEP and healthy controls. Studies were included if required data was available in the article or upon request (via contacting corresponding authors). There were following exclusion criteria: 1) publications written in languages other than English; 2) non-original publications; 3) animal model studies; 4) studies without a group of matched healthy controls and 5) studies with a lack of data that were necessary to perform meta-analysis. Our search strategy followed the PRISMA guidelines (Moher et al., 2009).

2.2. Data analysis

We extracted the following data (mean ± SD or the number of cases) from eligible publications: 1) age; 2) the number of males and females; 3) chlorpromazine equivalent dosage (CPZeq); 4) body-mass index (BMI); 5) scores of the Positive and Negative Syndrome Scale