Asian Journal of Psychiatry 18 (2015) 2–14

Contents lists available at ScienceDirect

Asian Journal of Psychiatry

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

Review

Contribution of sex hormones to gender differences in schizophrenia: A review

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ARTICLE INFO

Article history:
Received 10 March 2015
Received in revised form 14 July 2015
Accepted 25 July 2015

Keywords:
Schizophrenia
Gender differences
Estrogen and progesterone
Testosterone
Dehydroepiandrosterone and its sulfate

ABSTRACT

Female patients with schizophrenia tend to have a more benign course and better outcomes than males. One proposed explanation is the differential influence of male and female sex hormones, including estrogen, progesterone, testosterone, and dehydroepiandrosterone (DHEA) and its sulfate (DHEAS). Such benefit may be mediated by their effects on neurotransmitters and neuroprotection. Besides altered estrogen and DHEA/DHEAS levels in female patients, data is equivocal on hormonal differences between patients and controls. However, several reports note a mostly negative correlation between estrogen levels and symptom severity in both genders, and a positive correlation between estrogen levels and neurocognition but mainly in females. Adjunctive estrogen appears to improve symptoms in both genders. Progesterone levels have inconsistent links to symptom severity in both genders, and correlate positively with neurocognition but only in males. Estrogen-progesterone combination shows preliminary benefits as augmentation for both symptoms and neurocognition in females. Testosterone levels correlate inversely with negative symptoms in males and have inconsistent associations with neurocognition in both genders. Testosterone augmentation reduced negative symptoms in male patients in a pilot investigation, but has not been evaluated for neurocognition in either gender. DHEA/DHEAS have mixed results for their association with, and clinical utility for, symptoms and neurocognition in both genders. Overall, data on the impact of sex hormones on clinical course or as treatment for schizophrenia is limited, but estrogen has most evidence for positive influence and clinical benefit. The possibly greater tolerability and broader impact of these hormones versus existing medications support further exploration of their use.

Contents

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http://dx.doi.org/10.1016/j.ajp.2015.07.016
1876-2018/

1. Introduction

Significant gender differences have been well documented in many forms of mental disorders. For example, depression, anxiety and somatoform disorders are more prevalent among females, while substance use disorders and impulse control disorders are more common among males (Baumeister and Härter, 2007; Kessler et al., 2005). More complex disorders, such as schizophrenia and bipolar disorder, tend to affect both genders equivalently, but course of illness often tends to differ, with mixed episodes and rapid cycling seen more in females with bipolar disorder and greater impairment reported in males with schizophrenia (Diflorio and Jones, 2010; McGrath et al., 2008). The markedly debilitating nature of schizophrenia, and the significantly better outcome of females, has led to evaluation of the role of sex hormones in the pathophysiology of the condition and their possible benefit as intervention.

Schizophrenia has a median lifetime morbid risk of 7.2 per 1000 persons (McGrath et al., 2008). Literature reviews indicate that though the prevalence of schizophrenia is similar in both genders, incidence is slightly higher among males (McGrath et al., 2008), who also have an earlier onset of illness that peaks in the mid-teens to mid-20s (Häfner, 2003). Females develop the illness about 3–5 years later than males (mid-20s to mid-30s), and also have a second, late onset peak in their late 40s to early 50s (Häfner, 2003). Of note, however, is that differences in onset are more evident in sporadic, and not familial, schizophrenia (Leung and Chue, 2000; Ochoa et al., 2012). Males also display worse pre- and post-onset psychosocial and neurocognitive functioning, and are more vulnerable to life stressors, including possible catalysts of illness onset (Leung and Chue, 2000). They also show poorer response to typical antipsychotics (but similar response to atypical antipsychotics), and also have greater likelihood of relapses, higher rates of institutionalization and hospitalization, and lower remission rates, than females (Ochoa et al., 2012).

Gender differences are also well documented in clinical presentation. Schizophrenia is characterized by three main symptom clusters – positive, negative and cognitive (Leung and Chue, 2000; Ochoa et al., 2012). Positive symptoms include hallucinations and delusions, while examples of negative symptoms are flat affect, amotivation, alogia and reduced socialization. Cognitive symptoms include impairments to executive function (e.g. working memory, reasoning and problem solving, multitasking), attention, processing speed, learning and social cognition. While both genders display positive symptoms to a similar degree, negative and cognitive symptoms are more prevalent in males. However, females with schizophrenia do tend to exhibit more of the affective symptoms that frequently co-occur with schizophrenia, such as depression, anxiety and irritability (Leung and Chue, 2000).

While positive and negative symptoms were once thought to have the most impact on patient outcomes in schizophrenia, it is now accepted that cognitive symptoms may contribute equally to illness burden and impaired function (Bowie et al., 2010; Green, 2006). They have also been noted to be a robust predictor of recovery. Neurocognitive function correlates positively with daily and community living, work and education outcomes, and social and interpersonal functioning (Green, 2006). In addition, social cognition skills, particularly emotion perception, appear to mediate between other cognitive skills and functional outcomes (Schmidt et al., 2011) and also to predict such outcomes (Irani et al., 2012). Attention, executive function, language and memory domains (Leung and Chue, 2000; Ochoa et al., 2012), and emotion perception and associated function outcomes (Carter et al., 2009; Irani et al., 2012), have been noted as better in female patients.

The brain regions primarily involved in neurocognition include the cerebrum (comprising the lobes), prefrontal cortex (PFC; which includes the dorsolateral prefrontal cortex and orbitofrontal cortex), anterior cingulate gyrus, hypothalamus, thalamus, and the limbic system (which includes the hippocampus and amygdala) (Cabeza and Nyberg, 2000; Goldstein, 2006). Compared to controls, male patients generally show more brain abnormalities than female patients, including smaller volumes of the amygdala, insula and PFC, while females exhibit decreased volumes of the orbitofrontal cortex and anterior cingulate, but increased volumes of the amygdala (Goldstein et al., 2002b; Gur et al., 2000, 2004; Walder et al., 2007). Hippocampal and temporal pole volumes are reduced in both patient groups (Gur et al., 2000; Walder et al., 2007). In imaging studies of neurocognitive function, female patients displayed better visuo-spatial ability (associated with more PFC activity) than males, whereas among controls, males showed better visuo-spatial ability than females (Jiménez et al., 2010; Mendrek et al., 2008b). Reduced hippocampal and anterior cingulate volumes were seen in both genders, but correlated with poorer executive and motor function only in male patients (Szeszko et al., 2000, 2002). Similarly, reduced hippocampal and PFC volumes, reported in both genders (with females also showing smaller anterior cingulate), correlated with worse verbal memory only in males (Abbs et al., 2011). Better emotional processing among female patients than males is another notable finding, consistent with more extensive activation of the occipital lobe, PFC, cerebellum and caudate among female patients, and opposite to the pattern seen in female and male controls (Mendrek et al., 2009). Similar reversed activation patterns were reported even in studies where both patient groups reported equivalent subjective response to emotional stimuli (Mendrek et al., 2005, 2007), suggesting more intensive emotion processing in female subjects.

Altered neurotransmission is implicated in the pathophysiology of schizophrenia. Key among the neurotransmitters is dopamine, whose receptor dysregulation is associated with positive symptoms in schizophrenia (Howes and Kapur, 2009). Serotonin receptor modulation has been suggested to alleviate negative and cognitive symptoms (Miyamoto et al., 2012). Similarly, glutamatergic activity has been linked to positive, negative and cognitive symptoms (Snyder and Gao, 2013). Gender differences in disruptions of these aminergic pathways have been noted in schizophrenia, particularly with dopamine pathways, and again favoring females, who show fewer disruptions (Leung and Chue, 2000). It has been proposed that such differences may account for some of the gender variance in symptom presentation.

Several biological, developmental and psychosocial explanations have been suggested for the above gender differences. One hypothesis suggests that since serotonin and dopamine receptors deteriorate faster with age in male brains than female brains, this may contribute to differential illness risk and presentation (Cidis Meltzer et al., 2001; Pohjalainen et al., 1998). A developmental perspective is that due to slower brain maturation, males may experience greater impact from possible neurodevelopmental risk factors for schizophrenia, such as prenatal/neonatal genotypic or environmental insults, or abnormal synaptic pruning in the brain during adolescence, resulting in earlier onset of illness, more brain abnormalities and chronicity, and poorer neurocognitive and psychosocial functioning (Castle and Murray, 1991; Keshavan et al., 1994; Saugstad, 1989). A social developmental view is that onset of illness in males (in late adolescence and early adulthood) occurs during a critical period for cognitive and psychosocial development, leading to greater impairment than for females, whose earlier maturation in these areas, and later illness onset, facilitate more consolidated interpersonal and occupational/academic skills (Krabbendam and van Os, 2002).

However, one theory that has generated some of the most research is that of the protective role of estrogen, the main sex