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Invited Review

Progesterone: The neglected hormone in schizophrenia? A focus on progesterone-dopamine interactions

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ABSTRACT

Sex differences appear to be an important factor in schizophrenia. Women with schizophrenia tend to exhibit less disease impairment than men, typically presenting with a later age-at-onset, lower overall incidence and less severe symptoms. These observations underpin the estrogen hypothesis of schizophrenia, which postulates a protective role of estrogen against the development and severity of the disorder. While there has been significant attention placed on the impact of estrogens in schizophrenia, less consideration has been afforded to the role of progesterone, the other main female gonadal hormone. This narrative review discusses the role of progesterone as a neuroactive steroid and how it may be dysregulated in schizophrenia. Preclinical and molecular studies relevant to schizophrenia are discussed with a particular focus on the interactions between progesterone and the dopaminergic system. Notably, existing data on progesterone in relation to schizophrenia is inconsistent, with some studies suggesting a neuroprotective role for the hormone (*e.g.* animal models of cognitive dysfunction and positive symptoms), while other studies posit a disruptive impact of the hormone (*e.g.* negative correlations with symptom modulation in patients). This review aims to thoroughly address these discrepancies, concluding that altogether the data suggest that progesterone is a key modulator of central systems implicated in schizophrenia. On this basis, we argue that a more inclusive, considered effort of future studies to understand the intricacies of the interactions between progesterone and estrogen. Such an effort may enhance our understanding of the roles of sex hormones in schizophrenia, thus leading to avenues for novel therapeutic approaches.

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1. Introduction

Schizophrenia is a neuropsychiatric disorder that affects nearly 1% of the world's population. The illness is characterized by a number of prevalent clinical dimensions including: positive symptoms such as auditory hallucinations and delusions, negative symptoms including apathy and asociality, disorganization, and cognitive deficits particularly affecting memory, attention and executive functioning (Buoli et al., 2012; van Os and Kapur, 2009). Whilst the complex pathophysiology of schizophrenia remains to be elucidated, it is well appreciated that dysfunctions in a multitude of neurotransmitter systems are likely to contribute, including dopamine (DA), glutamate, γ-aminobutyric acid (GABA), acetylcholine and serotonin (5-hydroxytryptamine,5-HT) (Benes and Berretta, 2001; Gibbons and Dean, 2016; Howes and Kapur, 2009). Since the introduction of the first antipsychotic 60 years ago, the current gold standard treatment of schizophrenia utilizes a pharmacotherapeutic approach whereby antipsychotics act at various neurotransmitter receptors, including DA D2 receptors, under the premise that DA dysregulation is the final common pathway to psychosis in schizophrenia (Howes and Kapur, 2009). Antipsychotics are generally considered to be effective for the treatment of positive symptoms, however their efficacy in mitigating negative and cognitive deficits associated with the illness remains largely undefined and controversial (Buoli et al., 2012; Desamericq et al., 2014; Harrow and Jobe, 2013; van Os and Kapur, 2009). One thing is clear, that there is substantial prevalence of treatment resistance (van Os and Kapur, 2009). As such, a better understanding of the pathophysiology of the disorder is needed as a foundation for developing better treatments with improved therapeutic reach.

Despite decades of extensive research, the aetiological underpinnings of schizophrenia remain elusive. Schizophrenia is being increasingly viewed as a neurodevelopmental disorder in that, it occurs in individuals with a genetic predisposition, where exposure to environmental "hits" throughout development consequently result in abnormal structural and biochemical trajectories in brain development [reviewed in (Rapoport et al., 2005)]. Significantly, a large genome-wide association study identified 108 schizophrenia-associated genetic loci, 83 of which had not previously been reported (Consortium, 2014) which shed some light on potential genetic predisposition. By contrast, promising findings relating to the use of the sex steroid hormone, estrogen, and its analogues to treat schizophrenia, are suggesting these may be factors that can modulate the severity of the disorder (Gogos et al., 2015).

This narrative review discusses the actions of progesterone as a neuroactive steroid and its interactions with estradiol in the central nervous system (CNS) with relevance to schizophrenia. First a brief overview of the biosynthesis of progesterone is provided, with considerations of the natural cyclic changes of estradiol and progesterone in humans and rodents. Evidence of progesterone dysregulation in schizophrenia is then addressed in detail, with discussion of how this may impact schizophrenia symptomology. This review will then describe preclinical and molecular studies examining the effects of progesterone alone and when combined with estradiol. The focus will primarily be on the dopaminergic system, as it is the core neurotransmitter system implicated in schizophrenia, and numerous studies have supported the notion that this system is an important target for gonadal hormones [for review see (Sánchez et al., 2010)].

2. Sex differences in schizophrenia

Sex differences in schizophrenia have been widely discussed in the literature [reviewed in (Gogos et al., 2015; Markham, 2012)]. For example, the incidence of schizophrenia is higher for men than women (1.4:1 ratio) (McGrath et al., 2004), particularly in younger men (up to 39 years) (Häfner, 2003; van der Werf et al., 2014). There is also a robust difference in the mean age-of-onset between the sexes; for men, this occurs between 18 and 24 years whereas for women it occurs 3–4 years later. Further, only women have a second peak age-of-onset at 45–49 years (Häfner, 2003). While the systematic review by van der Werf et al. (2014) did not show a second peak in incidence rate in women, they did however report that females have a higher risk of schizophrenia than men in the 50–70 year age group. Men have been reported to exhibit more withdrawal and isolation and a greater inability to function, whereas women express greater levels of impulsivity, paranoia, and affective symptomology such as depressive moods and obsessive thinking (Zhang et al., 2012). Female chronic schizophrenia patients also tend to exhibit more severe positive and general psychopathological symptoms whereas men expressed more severe negative symptoms (Zhang et al., 2012). It has been suggested that sex difference in illness symptoms, course and outcome are likely due to the age-of-onset sex difference: in women, a later age-of-onset and presentation of affective symptoms predicts a better prognosis, whereas an earlier onset and presentation of negative symptoms, mainly associated with men, predicts a worse course of illness and outcome (Gogos et al., 2015; Häfner, 2003). Further, pre-menopausal women tend to require lower doses of antipsychotic treatment than men (Seeman, 2004). In women, the second peak age-of-onset of schizophrenia may be attributed to the natural decline of gonadal hormones due to menopause (Häfner, 2003; Halari et al., 2004).

Increasing evidence has suggested that the observed sex differences in schizophrenia may be attributed to gonadal hormones. The "estrogen hypothesis" postulates that estrogen exerts a protective role in schizophrenia pathophysiology. This hypothesis has been well-supported by molecular, animal and clinical studies [reviewed in (Gogos et al., 2015; Kulkarni et al., 2012)]. However, the studies describing sex differences in schizophrenia suggest a role for sex steroids in general, not necessarily exclusively estrogen. There are two main female gonadal hormones: 17β-estradiol (considered the most potent endogenous estrogen, referred hereon as estradiol) and progesterone. Importantly, both these hormones naturally vary over endogenous hormonal cycles (see Fig. 1) and at times of changing hormone levels in women and thus both hor-