Review

The Role Estrogen In Schizophrenia: A Review Of Current Literature

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Abstract:

Background:

Schizophrenia, a chronic and complex neuropsychiatric disorder, has a profound impact on the quality of life, social environment and health care system of patients and their families, affecting more than 21 million people worldwide. Research over the past two decades has established a distinct neuromodulator role for estrogen in the pathogenesis and treatment of neuropsychiatric disorders, including schizophrenia. Schizophrenia is associated with an earlier age of onset, more severe disease course, poorer response to antipsychotic treatment, and disease adaptability in males with schizophrenia compared with females with schizophrenia. This neuropsychiatric disorder exhibits robust gender differences in many aspects of the disease. This review highlights the research invested in understanding the potential protective effects of estradiol in relation to these sex differences in schizophrenia. Molecular studies that have clearly demonstrated complex interactions with transmitter systems, particularly those involved in schizophrenia, have led to improvements in cognition and memory, or deficits that reflect positive, negative, and cognitive symptoms of schizophrenia.

Keywords: Estrogen, Schizophrenia, Review of current literature

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Introduction

Schizophrenia, a chronic and complex neuropsychiatric disorder, has a profound impact on the quality of life, social environment and health care system of patients and their families (1) affecting more than 21 million people worldwide (2). It is a severe and debilitating disorder that currently ranks among the top 10 causes of long-term disability worldwide (3). Symptoms usually develops in second or third decade of individual life (4, 5). The occurrence of schizophrenia can be related to different genetic, socio-demographic and environmental factors (6). The severe impact of this disease is reflected in the fact that approximately 70-92% of people with schizophrenia are unemployed (7). In addition, a schizophrenic patient is 13 times more likely to die by suicide than members of the general population (8) and their life expectancy is 10–25 years shorter than even after considering suicide (9). Schizophrenia is a disorder characterized by severe cognitive, emotional, and behavioral impairments (3), with symptoms divided into three main groups: positive symptoms, negative symptoms, and cognitive impairment (10). Positive symptoms in addition to normal function encompass hallucinations and delusions and negative symptoms (deficits) encompass blunted drive and affect (11).

Estrogen is a gonadal hormone that exerts powerful effects in many areas of the brain, resulting in effects on mood, cognition, and behavior (12). Research over the past two decades has established a distinct neuromodulatory role for estrogen in the pathogenesis and treatment of neuropsychiatric disorders, including schizophrenia. Estrogen is considered the primary “female” sex hormone, but it is present in both men and women (13). Evidence has led to the hypothesis that recurrent hormone surges in women act as protective factors in the early onset of schizophrenia (14).

This study aims to review the current literature about the relevance of estrogen in relation to the pathogenesis and therapeutics of schizophrenia in a clinical setting.

Gender and schizophrenia

Previous literature (15-17) stated that males consistently have earlier onset, decreased premorbid functioning, and different premorbid predictors of behavior. Men show more negative symptoms and cognitive deficits and have greater structural and neurophysiological abnormalities in the brain. They show more emotional symptoms, auditory hallucinations, paranoia, but increased side effects. Improved short- and medium-term disease progression in women has been observed in women. Male's families are more critical, and the emotions expressed have a greater negative impact on men.

There was an increased incidence in men (ratio 1.4 :1), which was confirmed by two independent meta-analyses, even after adjusting for various confounding factors such as age group, diagnostic criteria and hospital bias (18, 19). Premenopausal women with schizophrenia have better disease progression, fewer adverse symptoms, and respond better to antipsychotic treatment (i.e., need lower doses) than older women (20). An early study reported that of 276 women admitted to a mental hospital, 46% were admitted during or just before menstruation (21) and other study also showed improved symptoms during pregnancy (22) but exacerbated during post-partum (23). Women with schizophrenia are often low estrogen with circulating estrogen levels are much lower than normal reference range and they are more likely to experience menstrual irregularities (24, 25).

Estrogen and schizophrenia

As previous evidence showed gender differences in schizophrenia, it can be hypothesized that estrogen can play a

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protective role in developing schizophrenia (14, 26). The molecular mechanisms by which estrogen influences schizophrenia symptoms are still largely unknown. Perhaps the simplest explanation is that estrogen can modulate the dopaminergic system in the central nervous system (CNS) by influencing the expression and function of dopamine receptors and transporters (27, 28).

The role of estrogen in cognition is particularly important for schizophrenia, and the cognitive deficits associated with this disease are thought to be the most debilitating symptoms of social assimilation in patients (29), suggesting that these symptoms is poorly controlled with current antipsychotic drugs (30). Overall, studies have shown that different estrogen agonists, estrogen receptors, and brain regions have the ability to mediate different forms of learning and memory. Currently, it is difficult to isolate specific effects of ER on cognitive function.

Schizophrenia is associated with various structural changes in the brain, including: gradual decrease in global gray and white matter volume in several brain regions followed by continued ventricular enlargement (31). Neuroprotective effects are another important component of estrogenic action associated with schizophrenia (32). Early cell culture studies showed increased neuronal cell viability after treatment with estrogen under serum deprivation (33), and later studies showed that estrogen was protective against excitotoxic (34) and oxidative stress (35) and inflammation (36) and apoptosis (37). The evidence suggest that low estrogen levels make the brain more susceptible to insults and age-related changes, which may lead to the development of schizophrenia and increased symptom severity. Perlman et al. (38) also found a negative correlation between ERα mRNA expression in the dentate gyrus and age of onset, suggesting that ERα levels may confer susceptibility to disease. Moreover, people with major depressive disorder and bipolar disorder showed no difference in ERα expression compared with controls, so their findings appeared to be specific to diagnosis.

Conclusion

Schizophrenia is associated with an earlier age of onset, more severe disease course, poorer response to antipsychotic treatment, and disease adaptability in males with schizophrenia compared with females with schizophrenia. This neuropsychiatric disorder exhibits robust gender differences in many aspects of the disease. This review highlights the research invested in understanding the potential protective effects of estradiol in relation to these sex differences in schizophrenia. Molecular studies that have clearly demonstrated complex interactions with transmitter systems, particularly those involved in schizophrenia, have led to improvements in cognition and memory, or deficits that reflect positive, negative, and cognitive symptoms of schizophrenia.

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