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.

References

1. Baser O, Xie L, Pesa J, Durkin M. Healthcare utilization and costs of Veterans Health Administration patients with schizophrenia treated with paliperidone palmitate long-acting injection or oral atypical antipsychotics. Journal of medical economics. 2015;18(5):357-65.
2. Charlson FJ, Ferrari AJ, Santomauro DF, Diminic S, Stockings E, Scott JG, et al. Global epidemiology and burden of schizophrenia: findings from the global burden of disease study 2016. Schizophrenia bulletin. 2018;44(6):1195-203.
3. Mueser KT, Jeste DV. Clinical handbook of schizophrenia: Guilford Press; 2011.
4. Tsapakis EM, Dimopoulou T, Tarazi FI. Clinical management of negative symptoms

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of schizophrenia: An update. Pharmacol Ther. 2015;153:135-47.
5.Keskinen E, Marttila A, Marttila R, Jones P, Murray G, Moilanen K, et al. Interaction between parental psychosis and early motor development and the risk of schizophrenia in a general population birth cohort. European Psychiatry. 2015;30(6):719-27.
6.McGrath J, Saha S, Chant D, Welham J. Schizophrenia: a concise overview of incidence, prevalence, and mortality. Epidemiol Rev. 2008;30:67-76.
7.Ritsner MS. Handbook of schizophrenia spectrum disorders, volume III: Therapeutic approaches, comorbidity, and outcomes: Springer; 2011.
8.Saha S, Chant D, McGrath J. A systematic review of mortality in schizophrenia: is the differential mortality gap worsening over time? Archives of general psychiatry. 2007;64(10):1123-31.
9.Lambert TJ, Newcomer JW. Are the cardiometabolic complications of schizophrenia still neglected? Barriers to care. Medical Journal of Australia. 2009;190(S4):S39-S42.
10.Mueser KT, McGurk SR. Schizophrenia. The Lancet. 2004;363(9426):2063-72.
11.Tandon R, Gaebel W, Barch DM, Bustillo J, Gur RE, Heckers S, et al. Definition and description of schizophrenia in the DSM-5. Schizophrenia research. 2013;150(1):3-10.
12.Fink G, Sumner BE, Rosie R, Grace O, Quinn JP. Estrogen control of central neurotransmission: effect on mood, mental state, and memory. Cellular and molecular neurobiology. 1996;16(3):325-44.
13.Sayed Y, Taxel P. The use of estrogen therapy in men. Current opinion in pharmacology. 2003;3(6):650-4.
14.Seeman MV. The role of estrogen in schizophrenia. Journal of Psychiatry and Neuroscience. 1996;21(2):123.
15.Leung M.D. DA, Chue M. R. C. Psych. DP. Sex differences in schizophrenia, a review of the literature. Acta Psychiatrica Scandinavica. 2000;101(401):3-38.
16.Ochoa S, Usall J, Cobo J, Labad X, Kulkarni J. Gender Differences in Schizophrenia and First-Episode Psychosis: A Comprehensive Literature Review. Schizophrenia Research and Treatment. 2012;2012:916198.
17.Markham JA. Sex steroids and schizophrenia. Reviews in Endocrine and Metabolic Disorders. 2012;13(3):187-207.
18.Aleman A, Kahn RS, Selten J-P. Sex differences in the risk of schizophrenia: evidence from meta-analysis. Archives of general psychiatry. 2003;60(6):565-71.
19.McGrath J, Saha S, Welham J, El Saadi O, MacCauley C, Chant D. A systematic review of the incidence of schizophrenia: the distribution of rates and the influence of sex, urbanicity, migrant status and methodology. BMC medicine. 2004;2(1):1-22.
20.Seeman MV. Interaction of sex, age, and neuroleptic dose. Comprehensive Psychiatry. 1983;24(2):125-8.
21.Dalton K. Menstruation and acute psychiatric illnesses. British medical journal. 1959;1(5115):148.
22.Chang S, Renshaw D. Psychosis and pregnancy. Comprehensive Therapy. 1986;12(10):36-41.
23.Kendell R, Chalmers J, Platz C. Epidemiology of puerperal psychoses. The British Journal of Psychiatry. 1987;150(5):662-73.
24.Bergemann N, Mundt C, Parzer P, Jannakos I, Nagl I, Salbach B, et al. Plasma concentrations of estradiol in women suffering from schizophrenia treated with conventional versus atypical antipsychotics. Schizophrenia research. 2005;73(2-3):357-66.
25.Riecher-Rössler A, Häfner H, Stumbaum M, Maurer K, Schmidt R. Can estradiol

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modulate schizophrenic symptomatology? Schizophrenia bulletin. 1994;20(1):203-14.
26.Häfner H, an der Heiden W, Behrens S, Gattaz WF, Hambrecht M, Löffler W, et al. Causes and consequences of the gender difference in age at onset of schizophrenia. Schizophrenia Bulletin. 1998;24(1):99-113.
27.Chavez C, Hollaus M, Scarr E, Pavey G, Gogos A, van den Buuse M. The effect of estrogen on dopamine and serotonin receptor and transporter levels in the brain: an autoradiography study. Brain research. 2010;1321:51-9.
28.Sánchez MG, Bourque M, Morissette M, Di Paolo T. Steroids-dopamine interactions in the pathophysiology and treatment of CNS disorders. CNS neuroscience & therapeutics. 2010;16(3):e43-e71.
29.Green MF. What are the functional consequences of neurocognitive deficits in schizophrenia? The American journal of psychiatry. 1996.
30.Sass LA, Parnas J. Schizophrenia, consciousness, and the self. Schizophrenia bulletin. 2003;29(3):427-44.
31.DeLisi LE, Szulc KU, Bertisch HC, Majcher M, Brown K. Understanding structural brain changes in schizophrenia. Dialogues in clinical neuroscience. 2022.
32.McEwen BS, Alves SE. Estrogen actions in the central nervous system. Endocrine reviews. 1999;20(3):279-307.
33.Arimatsu Y, Hatanaka H. Estrogen treatment enhances survival of cultured fetal rat amygdala neurons in a defined medium. Developmental Brain Research. 1986;26(1):151-9.
34.Goodman Y, Bruce AJ, Cheng B, Mattson MP. Estrogens attenuate and corticosterone exacerbates excitotoxicity, oxidative injury, and amyloid β-peptide toxicity in hippocampal neurons. Journal of neurochemistry. 1996;66(5):1836-44.
35.Behl C, Skutella T, Frank LH, Post A, Widmann M, Newton CJ, et al. Neuroprotection against oxidative stress by estrogens: structure-activity relationship. Molecular pharmacology. 1997;51(4):535-41.
36.Sarvari M, Kallo I, Hrabovszky E, Solymosi N, Toth K, Liko I, et al. Estradiol replacement alters expression of genes related to neurotransmission and immune surveillance in the frontal cortex of middle-aged, ovariectomized rats. Endocrinology. 2010;151(8):3847-62.
37.Garcia-Segura LM, Cardona-Gomez P, Naftolin F, Chowen JA. Estradiol upregulates Bcl-2 expression in adult brain neurons. Neuroreport. 1998;9(4):593-7.
38.Perlman WR, Tomaskovic-Crook E, Montague DM, Webster MJ, Rubinow DR, Kleinman JE, et al. Alteration in estrogen receptor α mRNA levels in frontal cortex and hippocampus of patients with major mental illness. Biological psychiatry. 2005;58(10):812-24.

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