The author previously described a theoretical cause of schizophrenia based on the effects of estrogic endocrine disruption. In the current review, the author describes how increased estrogen during pregnancy increases susceptibility to certain viral infections associated with increased risk for schizophrenia. The review further discusses how prenatal estrogen exposure could explain associations of schizophrenia with autoimmune diseases, urban environments, and stress. Based on the association of increased estrogen with schizophrenia risk factors, the author proposes increased prenatal estrogen as a unifying factor, perhaps the primary event, in the etiology of schizophrenia.

Key words: endocrine disruption/psychosis/viruses/autoimmune/urban stress

Introduction

The author previously described an endocrine disruption theory of schizophrenia based on similarities of estrogic endocrine disruption to findings in schizophrenia. The author hypothesized that prenatal exposure to an excessive dose, timing, and/or duration of estrogen causes schizophrenia. The current review shows that estrogen increases susceptibility to certain viral infections associated with increased risk for schizophrenia. To find material for the review, the author retrieved information from Pubmed (http://www.ncbi.nlm.nih.gov/PubMed/). Literature searches first focused on studies that described the effects of estrogen on viral infections. Additional searches then located information on how estrogen relates to other risk factors for schizophrenia including autoimmune diseases, urban environments, and stress.

Estrogen and Schizophrenia

The possible role of estrogen in schizophrenia depends on whether the exposure is prenatal or in adulthood. Exposure to estrogen in the human fetal hormonal environment normally remains balanced by the so-called “maternal-fetal-placental unit,” which is described in online supplementary material. The author’s theory is that prenatal exposure to inappropriate estrogen causes schizophrenia even though estrogen supplementation reduces some symptoms of schizophrenia later in adult life. Neuroprotection by estrogen in adults may result in milder forms of schizophrenia observed in females compared with males but does not relate to the increased susceptibility of pregnant women to infection that lies at the core of viral theories of schizophrenia.

Estrogen Reduces Resistance to Certain Infections in Human Pregnancy

Estrogen reduces resistance to urogenital infections and RNA viruses in humans. These effects provide a mechanism for the commonly cited increased susceptibility to viral infections during pregnancy. In urogenital infections, estrogen reduces cell-mediated immunity in humans. In RNA virus infections, estrogen reduces human dendritic cell immune responses and stimulation of CD4 T-cell immune responses and inhibits type 1 interferon. Estrogen’s inhibition of dendritic cell maturation has important implications for schizophrenia. Through this mechanism, estrogen could increase vulnerability to more than one RNA virus associated with increased risk of schizophrenia including borna disease virus, mumps, influenza, and coronaviruses.

Estrogen, Viruses, and Autoimmune Disease in Schizophrenia

Estrogen’s blockage of the stimulation of T-cells by dendritic cells may explain the negative association between rheumatoid arthritis (RA) and schizophrenia. To explain this well-established negative association, Torrey and Yolken proposed an association of infectious etiologies of schizophrenia and RA, including Toxoplasma gondii, herpes viruses, and retroviruses, whereby “once a person gets one of the diseases then they are relatively immune to the other.” In contrast, the author’s estrogen theory is that increased estrogen of pregnancy enhances infection with T gondii and viruses. The low incidence of
RA in schizophrenia, the author holds, is not directly associated with infectious diseases but instead results from increased smoking by individuals with schizophrenia that suppresses inflammatory cytokines and the similar effects of atypical and conventional antipsychotics. RA also usually remits during pregnancy, which in the past has been attributed to rising levels of estrogen, but may also result from rising levels of cortisol, norepinephrine, and 1,25-dihydroxyvitamin D that suppress inflammatory cytokines.

The relationship of some autoimmune disorders like RA to schizophrenia in the context of increased estrogen is best illustrated by Sjogren’s syndrome in parents of schizophrenia patients. Sjogren’s syndrome is associated with increased aromatase activity, which is correlated with higher disease activity and elevated serum estrogen levels. Inflammatory cytokines stimulate aromatase that converts androgen precursors to 17-beta estradiol so that Sjogren’s is associated with elevated serum estrogen levels. In a study that examined the prevalence of autoimmune disorders in the parents of schizophrenia patients, the incidence of Sjogren’s in parents of schizophrenia patients was nearly 4 times normal and was most strongly associated with schizophrenia of 19 autoimmune diseases studied. Correlation of a medical condition known for high serum estrogen in the parents of persons with schizophrenia is consistent with the theme of this review that inappropriate prenatal estrogen exposure causes schizophrenia.

Estrogen Reduces Resistance to Specific Viruses Associated With Schizophrenia

The following sections discuss the effect of estrogen on specific infections correlated with increased risk of schizophrenia. Most of these studies examined the effects of estrogen in animal models although a few, where noted, studied human tissues.

*Toxoplasma gondii*

*T. gondii* is a strong candidate as an infectious cause of schizophrenia. More than one animal study found that estrogen enhances *T. gondii* infection. Overwhelming, *T. gondii* infection from reduced cell-mediated immunity occurs in mice and guinea pigs after treatment with hexestrol. Pharmacological doses of estrogenic compounds including 17 beta-estradiol, diethylstilbestrol, and alpha-dienestrol also increase susceptibility of mice to *T. gondii*, and female mice are more susceptible to small intestine infection with *T. gondii*. Some *T. gondii* infections have been associated with increased prenatal testosterone rather than estrogen (see online supplementary material where the author discusses these findings and how prenatal estrogen and/or testosterone might cause schizophrenia and/or autism).

**Herpes**

The association of herpes simplex virus (HSV), especially type 2, with schizophrenia is a frequent finding. In humans, but not in mice, estrogen increases HSV-2 infection, and in humans pregnancy can trigger the recurrence of HSV. In mice, the increased susceptibility to HSV-2 in pregnancy is likely secondary to rising levels of progesterone.

**Cytomegalovirus**

The association of cytomegalovirus with schizophrenia is also reported. Reactivation of cytomegalovirus in humans during pregnancy commonly occurs and likely results from increased estradiol. One study of human tissue found reactivation of cytomegalovirus occurred after cortisol exposure but was not further enhanced by 17 beta-estradiol.

**Other Viruses**

Other viruses associated with schizophrenia include coronaviruses and influenza. An animal study of avian infectious bronchitis virus (a coronavirus) found that estrogen, testosterone, and cortisol individually enhanced the replication of virus. Consistent with the previously mentioned impairment of resistance to influenza by estrogen, increased mortality of pregnant women from influenza occurred during both the 1918–1919 and 1957 influenza pandemics.

**Estrogen, Stress, and the Urban Environment**

If estrogen explains the association of prenatal infections with schizophrenia, how does the theory explain the association of schizophrenia with urban residence which is often used to support viral theories? The author proposes that the stress of urban life, perhaps modified by genetic factors, explains the urban characteristic of schizophrenia. Supporting this view are animal research models of schizophrenia that combine stress and genetic susceptibility. Furthermore, stress responses are modulated in the limbic portion of the brain by estrogen’s effect on the estrogen receptors (ERs) ER-alpha and ER-beta. Plasma estrogen levels in male rats are also under genetic control, as shown by Lewis rats in which stress increases plasma estrogen and in Fischer rats in which stress decreases plasma estrogen.

**Estrogen Receptors Guide Brain Growth Altered in Schizophrenia**

The distribution patterns of ER-alpha and ER-beta, the 2 receptors that not only modulate stress responses but also guide human cortex and hippocampus growth through the life span, have now been described. ER-alpha is expressed in Cajal-Retzius cells, which position cortical
neurons through interactions with reelin. Changes in Cajal-Retzius cells have been reported in schizophrenia, and altered Cajal-Retzius cells that produce less reelin are found in the cortex and hippocampus of influenza-infected mice. These findings support a role of estrogen in directing brain growth that could be involved in schizophrenia.

**Conclusion**

Prenatal viral infections have been proposed as independent risk factors for schizophrenia but are linked by association with increased estrogen during pregnancy. The discussion above described how increased estrogen could not only explain increased viral infection in schizophrenia but also the association of schizophrenia with autoimmune diseases, stress, and urban factors. Based on this and on previous work, the author proposes that inappropriate prenatal estrogen exposure is the unifying pathological characteristic of schizophrenia whether from excessive dose, timing and/or duration of estrogen exposure, and/or modification of estrogen receptor function. As described above, the distribution of ER-alpha and ER-beta was recently described in human cortex and hippocampus from gestation to adulthood. A test of the current theory could begin with a comparison of ER-alpha and ER-beta distribution in brains with schizophrenia compared with normal.

**Supplementary Material**

Supplementary material is available at http://schizophreniabulletin.oxfordjournals.org.

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