

Association of Increased Prenatal Estrogen With Risk Factors for Schizophrenia

James S. Brown, Jr^{1–3}

²Clinical Services, Crossroads Community Services Board, Farmville, VA; ³Department of Psychiatry, Virginia Commonwealth University School of Medicine, Richmond, PO Box 622, Midlothian, VA 23113

¹To whom correspondence should be addressed; tel: 804-897-6386, fax: 804-897-6386, e-mail: jbrown2185@aol.com.

The author previously described a theoretical cause of schizophrenia based on the effects of estrogenic 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 estrogenic endocrine disruption to findings in schizophrenia.¹ 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.¹ 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.² Neuroprotection by estrogen in adults may result in milder forms of schizophrenia observed in females compared with males³ 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 infections⁴ and RNA viruses⁵ in humans. These effects provide a mechanism for the commonly cited increased susceptibility to viral infections during pregnancy.⁵ In urogenital infections, estrogen reduces cell-mediated immunity in humans.⁴ In RNA virus infections, estrogen reduces human dendritic cell immune responses and stimulation of CD4 T-cell immune responses and inhibits type 1 interferon.⁵ 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,⁶ mumps,⁷ influenza,⁸ and coronaviruses.⁹

Estrogen, Viruses, and Autoimmune Disease in Schizophrenia

Estrogen’s blockage of the stimulation of T-cells by dendritic cells⁵ may explain the negative association between rheumatoid arthritis (RA) and schizophrenia.¹⁰ To explain this well-established negative association, Torrey and Yolken¹¹ 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.^{12–17} RA also usually remits during pregnancy, which in the past has been attributed to rising levels of estrogen,¹⁸ but may also result from rising levels of cortisol, norepinephrine, and 1,25-dihydroxyvitamin that suppress inflammatory cytokines.¹⁹

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.¹⁴ Inflammatory cytokines stimulate aromatase that converts androgen precursors to 17-beta estradiol so that Sjogren's is associated with elevated serum estrogen levels.¹⁴ 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.²⁰ 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.²¹ 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 hex-estrol.^{22,23} Pharmacological doses of estrogenic compounds including 17 beta-estradiol, diethylstilbestrol, and alpha-dienestrol also increase susceptibility of mice to *T gondii*,²⁴ and female mice are more susceptible to small intestine infection with *T gondii*.²⁵ 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.²⁶ In humans, but not in mice, estrogen increases HSV-2 infection,²⁷ and in humans pregnancy can trigger the recurrence of HSV.⁴ In mice, the increased susceptibility to HSV-2 in pregnancy is likely secondary to rising levels of progesterone.²⁸

Cytomegalovirus

The association of cytomegalovirus with schizophrenia is also reported.⁷ Reactivation of cytomegalovirus in humans during pregnancy commonly occurs and likely results from increased estradiol.²⁹ One study of human tissue found reactivation of cytomegalovirus occurred after cortisol exposure but was not further enhanced by 17 beta-estradiol.³⁰

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 cortisone individually enhanced the replication of virus.³¹ 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.⁵

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?³² 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.³³ 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.³⁴ 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.³⁵

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.³⁶ ER-alpha is expressed in Cajal-Retzius cells, which position cortical

neurons through interactions with reelin.³⁶ Changes in Cajal-Retzius cells have been reported in schizophrenia,³⁷ and altered Cajal-Retzius cells that produce less reelin are found in the cortex and hippocampus of influenza-infected mice.³⁸ 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,¹ 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.³⁶ 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>.

Acknowledgments

The author is self-supported and receives no financial or logistical support for this work.

References

1. Brown JS, Jr. Effects of bisphenol-A and other endocrine disruptors compared with abnormalities of schizophrenia: an endocrine-disruption theory of schizophrenia. *Schizophr Bull.* 2009;35:256–278.
2. Kulkarni J. Oestrogen—a new treatment approach for schizophrenia? *Med J Aust.* 2009;190(Suppl):S37–S38.
3. Canuso CM, Pandina G. Gender and schizophrenia. *Psychopharmacol Bull.* 2007;40:178–190.
4. Sonnex C. Influence of ovarian hormones on urogenital infection. *Sex Transm Infect.* 1998;74:11–19.
5. Escribese MM, Kraus T, Rhee E, Fernandez-Sesma A, Lopez CB, Moran TM. Estrogen inhibits dendritic cell maturation to RNA viruses. *Blood.* 2008;112:4574–4584.
6. Nunes SO, Itano EN, Amarante MK, et al. RNA from Borna disease virus in patients with schizophrenia, schizoaffective patients, and in their biological relatives. *J Clin Lab Anal.* 2008;22:314–320.
7. Dalman C, Allebeck P, Gunnell D, et al. Infections in the CNS during childhood and the risk of subsequent psychotic illness: a cohort study of more than one million Swedish subjects. *Am J Psychiatry.* 2008;165:59–65.
8. Brown AS, Vinogradov S, Kremen WS, et al. Prenatal exposure to maternal infection and executive dysfunction in adult schizophrenia. *Am J Psychiatry.* 2009;166:683–690.
9. Severance EG, Dickerson FB, Viscidi RP, et al. Coronavirus immunoreactivity in individuals with a recent onset of psychotic symptoms [published online ahead of print June 2, 2009]. *Schizophr Bull.* doi: 10.1093/schbul/sbp052.
10. Nakano K, Matsushita S, Saito K, Yamaoka K, Tanaka Y. [Dopamine as an immune-modulator between dendritic cells and T cells and the role of dopamine in the pathogenesis of rheumatoid arthritis]. *Nihon Rinsho Meneki Gakkai Kaishi.* 2009;32:1–6.
11. Torrey EF, Yolken RH. The schizophrenia-rheumatoid arthritis connection: infectious, immune, or both? *Brain Behav Immun.* 2001;15:401–410.
12. Lawrence D, Mitrou F, Zubrick SR. Smoking and mental illness: results from population surveys in Australia and the United States. *BMC Public Health.* 2009;9:285.
13. Zhang XY, Cao LY, Song C, et al. Lower serum cytokine levels in smokers than nonsmokers with chronic schizophrenia on long-term treatment with antipsychotics. *Psychopharmacology (Berl).* 2008;201:383–389.
14. Cutolo M, Capellino S, Sulli A, et al. Estrogens and autoimmune diseases. *Ann N Y Acad Sci.* 2006;1089:538–547.
15. Kim YK, Myint AM, Verkerk R, Scharpe S, Steinbusch H, Leonard B. Cytokine changes and tryptophan metabolites in medication-naïve and medication-free schizophrenic patients. *Neuropsychobiology.* 2009;59:123–129.
16. Mortimer AM. Relationship between estrogen and schizophrenia. *Expert Rev Neurother.* 2007;7:45–55.
17. Yde CW, Clausen MP, Bennetzen MV, Lykkesfeldt AE, Mouritsen OG, Guerra B. The antipsychotic drug chlorpromazine enhances the cytotoxic effect of tamoxifen in tamoxifen-sensitive and tamoxifen-resistant human breast cancer cells. *Anticancer Drugs.* 2009;20:723–735.
18. Ostensen M. Sex hormones and pregnancy in rheumatoid arthritis and systemic lupus erythematosus. *Ann N Y Acad Sci.* 1999;876:131–143.
19. Elenkov IJ, Wilder RL, Bakalov VK, et al. IL-12, TNF-alpha, and hormonal changes during late pregnancy and early postpartum: implications for autoimmune disease activity during these times. *J Clin Endocrinol Metab.* 2001;86:4933–4938.
20. Eaton WW, Byrne M, Ewald H, et al. Association of schizophrenia and autoimmune diseases: linkage of Danish national registers. *Am J Psychiatry.* 2006;163:521–528.
21. Yolken RH, Dickerson FB, Fuller TE. Toxoplasma and schizophrenia. *Parasite Immunol.* 2009;31:706–715.
22. Kittas C, Henry L. Effect of sex hormones on the immune system of guinea-pigs and on the development of toxoplasmic lesions in non-lymphoid organs. *Clin Exp Immunol.* 1979;36:16–23.
23. Kittas C, Henry L. Effect of sex hormones on the response of mice to infection with *Toxoplasma gondii*. *Br J Exp Pathol.* 1980;61:590–600.
24. Pung OJ, Luster MI. *Toxoplasma gondii*: decreased resistance to infection in mice due to estrogen. *Exp Parasitol.* 1986;61:48–56.
25. Liesenfeld O, Nguyen TA, Pharke C, Suzuki Y. Importance of gender and sex hormones in regulation of

- susceptibility of the small intestine to peroral infection with *Toxoplasma gondii* tissue cysts. *J Parasitol.* 2001;87:1491–1493.
26. Buka SL, Cannon TD, Torrey EF, Yolken RH. Maternal exposure to herpes simplex virus and risk of psychosis among adult offspring. *Biol Psychiatry.* 2008;63:809–815.
 27. MacDonald EM, Savoy A, Gillgrass A, et al. Susceptibility of human female primary genital epithelial cells to herpes simplex virus, type-2 and the effect of TLR3 ligand and sex hormones on infection. *Biol Reprod.* 2007;77:1049–1059.
 28. Gillgrass AE, Fernandez SA, Rosenthal KL, Kaushic C. Estradiol regulates susceptibility following primary exposure to genital herpes simplex virus type 2, while progesterone induces inflammation. *J Virol.* 2005;79:3107–3116.
 29. Kleinman D, Sarov I, Insler V. Reactivation of cytomegalovirus in endometrial cells by estradiol. *Gynecol Obstet Invest.* 1986;21:136–143.
 30. Koment RW. Lytic cytomegalovirus replication and the hormones of human pregnancy. *J Med Virol.* 1985;15:149–156.
 31. Ambali AG, Jones RC. The effects of three reproductive hormones and cortisone on the replication of avian infectious bronchitis virus in vitro. *Rev Roum Virol.* 1990;41:151–156.
 32. Torrey EF, Bowler A. Geographical distribution of insanity in America: evidence for an urban factor. *Schizophr Bull.* 1990;16:591–604.
 33. Oliver PL, Davies KE. Interaction between environmental and genetic factors modulates schizophrenic endophenotypes in the Snap-25 mouse mutant blind-drunk. *Hum Mol Genet.* 2009;18:4576–4589.
 34. Ter Horst GJ, Wichmann R, Gerrits M, Westenbroek C, Lin Y. Sex differences in stress responses: focus on ovarian hormones. *Physiol Behav.* 2009;97:239–249.
 35. Macho L, Rovinsky J, Kvetnansky R, Radikova Z, Fickova M, Zorad S. Hormone response to stress in rat strains of different susceptibility to immunologic challenge. *Endocr Regul.* 2008;42:23–28.
 36. Gonzalez M, Cabrera-Socorro A, Perez-Garcia CG, et al. Distribution patterns of estrogen receptor alpha and beta in the human cortex and hippocampus during development and adulthood. *J Comp Neurol.* 2007;503:790–802.
 37. Kalus P, Senitz D, Beckmann H. Cortical layer I changes in schizophrenia: a marker for impaired brain development? *J Neural Transm.* 1997;104:549–559.
 38. Fatemi SH, Emamian ES, Kist D, et al. Defective corticogenesis and reduction in Reelin immunoreactivity in cortex and hippocampus of prenatally infected neonatal mice. *Mol Psychiatry.* 1999;4:145–154.