Estrogen And Schizophrenia: Any Link?

S Chattopadhyay

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Abstract

Background: Schizophrenia is an important cognitive disorder having a prevalence rate 1.5% constant in the population. Treating schizophrenia is a challenge and optimally safer drugs are under exploration. Evaluating sex steroids as the 'biological resources' for the treatment of schizophrenia remains a continuous process since decades. A large number of epidemiological studies on schizophrenia have shown that females develop the illness later than males, usually have better course and response to the treatment. As females possess abundant natural
'estrogen', compared to males, it has been anticipated that estrogen may have some antipsychotic influence in the female brain, which is possibly one of the biological reasons behind such gender differences. Further, animal studies have confirmed that estrogen is a potent dopamine and serotonin receptor blocker alike atypical neuroleptics (e.g. Risperidone), and also a neuroprotective hormone.

Aim: The idea behind this article is to evaluate the 'physiological hormonal resources' in the treatment of schizophrenia.

Method and material: A Meta analytical approach following a thorough search of MEDLINE, Medscape, PsycINFO and PubMed for the relevant studies.

Result: Estrogen could be beneficial in schizophrenia, especially postmenopausal schizophrenics.

Conclusion: Tentative research proposals for further substantiation.

1. BACKGROUND:

1.1 COGNITION DEFICITS IN SCHIZOPHRENIA:

Literature survey observes primary cognition failure and poor cognitive outcome in the negative symptom, positive symptom and disorganized schizophrenia[1, 2, 3, 4]. Elaborating further, the association of visual motor processing dysfunction shows a closer association in case of ‘negative and disorganized schizophrenia' than the positive symptoms while the language disorders, verbal memory, and time controlled performance deficits are typically observed in ‘disorganized schizophrenia'[1]. On the other hand, poor attention (specially auditory type) due to the prefrontal cortex hypo function has been observed more with the ‘positive-symptom-schizophrenia'[2].

1.2 COGNITION DEFICITS IN GYNECOLOGY AND OBSTETRICS:

Apart from the psychiatric field, cognition deficits are also known features in the area of Gynecology and Obstetrics. Among many such noted disorders, Pre Menstrual Syndrome is associated predominantly with the decline in the working memory and mood fluctuations[5], Postmenopausal Syndrome is largely associated with decreased adaptability and vigilance[6], and Puerperal Psychosis shows several cognitive disorders (e.g. aggression, loss of memory, speech disorders.) and even may sometimes lead to the emergence of schizophrenia[7].

Studies have shown that estrogen supplementation in these estrogen-withdrawn-psychoses relieve the disease load at a considerable extent[8,9].

1.3 MALE-FEMALE HETEROGENEITY IN SCHIZOPHRENIA (THE ENTRY OF ESTROGEN HYPOTHESIS):

Onset and symptomatic variations, morbid differences, treatment responses and social outcomes between male and female schizophrenics are known issues. Most of the studies of the last two decades have shown that males have earlier

age at onset than females[10,11]. On the other hand, females develop the illness at particular periods of their lifetime when the serum estrogen level is low[12,13]. A large number of studies have also revealed that male babies are more vulnerable for developing schizophrenia in the later life than female babies despite being equally exposed to birth-related vulnerabilities[14], though few studies have shown contrasting pictures. Therefore researchers paid attention to evaluate if there was any chance that estrogen might have some roles behind such heterogeneity. They also hypothesized that biological sex bias in schizophrenia could have been originated from estrogen (The testable estrogen hypothesis).

1.4 THE LINK AMONG DOPAMINE, SEROTONIN AND ESTROGEN HYPOTHESIS OF SCHIZOPHRENIA:

Excessive discharges of mesolimbic and mesocortical dopaminergic neurons, alone, or in conjunction with serotonergic discharges influence the mood, memory etc, grossly distorted in schizophrenia[15]. Therefore it could be postulated that estrogen could have some influencing role in those neurotransmitters in the brain.

2.AIM:

The aims of this review study are as follows:

A. Critical evaluation of how estrogen plays its role in the brain, and

B. Proposing dual studies (clinical and neuroimaging) to evaluate the beneficial role of estrogen in the schizophrenic female population.

3. METHOD AND MATERIAL:

The present article is a Meta analysis of the relevant literature, available in the Medscape, MEDLINE, PubMed, PsycINFO in the World Wide Web. The present article thus includes animal studies as the principal source of how estrogen works in the brain at the backdrop of schizophrenia. This is because the mechanistic models of animal studies are useful to evaluate the underlying pathophysiological mechanisms of the human brain[16]. It has, otherwise included other studies, including reviews and empirical studies on human beings related to the estrogen hypothesis for further corroborations.

3.1 HOW ESTROGEN ACTS IN THE BRAIN:

A. ON THE DOPAMINE SYSTEM:

Sex steroids control the behavioral and movement patterns of animals and humans by manipulating dopaminergic systems in the hypothalamus and extra-hypothalamic regions of the brain[17]. Among sex steroids, estrogen has been studied extensively revealing that it modulates behavioral patterns usually through the basal ganglia, which are rich in dopaminergic neurotransmission[17]. This postulation has indirectly been supported by the fact that ovariectomy causes fall of striatal D_1 and D_2 densities and moreover estradiol replacement revives D_2 and not D_1 [18]. Striatum controls mood, memory and olfaction. To further support the postulation, studies have shown that estradiol reduces the dopamine receptor affinity to Sulpiride (a potent D_2 receptor blocker) 2.8 times and thus modifies dopamine agonist- and antagonist-induced behavior-pattern more clearly in neonatal than adult rats[19, 20, 21]. Studies also have revealed that high concentration of follicule stimulating hormone in the pituitary gland of the female foetus between 12 and 20 weeks of gestation matches the time of the maximum organizational effects of gonadal steroids in the foetal brain (i.e. 14-16 weeks of gestation) [22]. This organizational process facilitates the establishment of the primary neuronal connections, necessary myelinization and lateralization of brain function [22]. Possibly due to the higher susceptibility to estrogenic manipulation during the primary organizational process in the brain, neonatal rats might show a clearer dopamine-agonist-antagonist behavior pattern, although further studies are essential to corroborate the proposition that estrogen modulates the fetal brain better that the adult.

More over, estrogen has a restorative effect on the tyrosine hydroxylase enzyme system (a rate-limiting enzyme for dopamine synthesis) in the prefrontal cortex (related to mood, memory, cognition and socialization). Such revival is better when estrogen is combined with progesterone [23].

B. ON SEROTONIN SYSTEM:

Apart from modulating the dopaminergic system in the brain, estrogen has a significant influence on serotonin (5-HT) receptors (especially 5-HT_{1A} AND 5-HT_{2A}) too. A series of animal studies have observed that estrogen accentuates the 5-HT_{2A} receptor-binding sites and receptor densities in the cingulate area, anterior frontal cortex, primary olfactory cortex and nucleus accumbens, which are related to the expression of emotion, mood, cognition and olfaction[24, 25, 26]. Regarding possible estrogenic manipulation of other types of serotonin receptors, it is observed that estrogen plays an important role in controlling 5-HT_{1A} receptor mRNA levels in the brain. Using radioligand and radiographic studies using selective 5-HT_{1A} receptor antagonist [(3)H] WAY-100635, a study has showed that estradiol binds to 5-

HT_{1A} receptors in the limbic area and influences its function with regard to memory, cognition, learning, emotion projection and social behavior[27].

3.2 HOW TESTOSTERONE ACTS IN THE BRAIN (INDIRECT EFFECTS OF ESTROGEN):

Inquisitiveness regarding the role of male gonadal hormones in the brain, many studies nullified the possibility of any direct role of testosterone on the cerebral neurotransmitter system[19, 20, 21]. A few studies observed that testosterone could be another manipulator, provided it is converted to estrogen by the aromataze enzyme in the brain [26, 28]. It has been further corroborated by the observation that 5-alfa-dihydrotestosterone, a more potent male hormone than testosterone, could not play any neurotransmitter-modulating-role, as it could not be converted to estrogen by this enzyme in the brain[26, 28].

3.3 OTHER IMPORTANT FINDINGS:

The most important among the other observed findings are:

1) Estrogen prevents several neurodegeneratory processes in the brain by virtue of its nuclear-receptor-mediated-alteration of the estrogen-receptor-gene-expression that optimally programs the rate of neuronal apoptosis and thereby preventing the axonal degeneration. By this mechanism estrogen renders a generalized support to the neuronal system in the brain[29],

2) Level of serum estrogen has got a strong correlation with the cognitive function especially global cognition, verbal, spatial deceleration memory and perceptual motor speed[30],

3) Higher estrogen levels in female schizophrenics are associated with the better cognitive ability[30] and this view tantalizes us to evaluate estrogen as a novel antipsychotic agent against schizophrenia. Though further studies are needed to confirm this.

4) Estrogen can be supplemented in the menopausal (especially surgically induced) cognitive disorders and depression, postpartum depression, and in post-menopausal schizophrenic females[31].

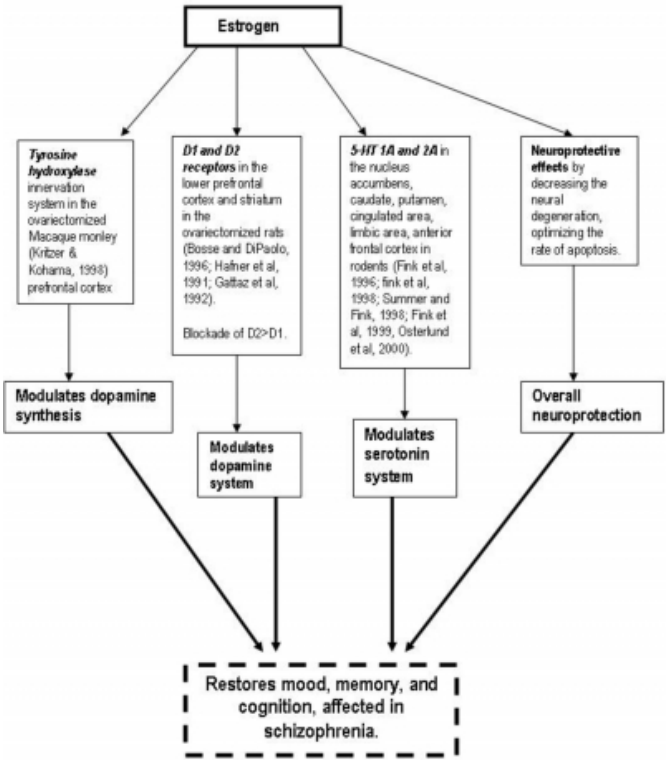
4. RESULT:

4.1 THE PROPOSED MODEL (ROLE OF ESTROGEN IN CEREBRAL NEUROTRANSMITTERS):

The article proposes a model for detail understanding of the estrogenic modulation of the dopamine and serotonin neurotransmitters in the brain as follows (Model 1).

Figure 1

Model 1: The proposed model (Role of estrogen in cerebral neurotransmitters)-contd.



5. CONCLUSION:

Despite of some light of hope regarding the possible use of estrogen as a novel antipsychotic in schizophrenic females, the present article has got its own limitations, as follows:

1. The article has excluded a few studies those are anomalous with the estrogen hypothesis,
2. No studies have been included showing the roles of estrogen on other metanephrines, related to schizophrenia, and
3. The study is unable to provide the ‘detail biomolecular mechanisms' how estrogen could reduce the different types of cognitive symptoms in schizophrenia paradigms (positive, negative and disorganized).
4. There are heterogeneous views regarding the benevolence of estrogen in the females. For example, it is also not clear why the dopamine-blocking effect of estrogen only lessens the symptom load in schizophrenics and not in manic patients22. Thus, dilemmas are prevalent and

estrogen hypothesis needs to be further clarified.

5. As the dosages are yet to be measured and matched against the impending life threatening risks (e.g. Endometrial and Breast cancers, especially), choosing estrogen itself is sometimes not very much encouraging. It emphasizes a multidisciplinary approach (Psychiatry, Gynecology and Obstetrics, and Sono oncologists).

Despite such hurdles, the present article has a dual research proposal to test estrogen as a novel antipsychotic drug in schizophrenia, which are as follows:

Clinical trials could be done with oral or transdermal estrogen (17-beta-estradiol preparations, because it is most potent among the natural estrogens, available) as an adjunctive on a sample of drug-naïve first-episode schizophrenic females with strict vigilance to the estrogen-related dangers, mentioned before. The changes of the target symptoms could be noted and matched with placebo-controlled first-episode drug naïve schizophrenic females and normal controls. We can also evaluate what subtype of schizophrenia (negative, positive or disorganized) could be more suited for adjunctive estrogen-therapy.

Utilization of modern Nuclear Imaging Techniques (Positron Emission Tomography or PET, Single Photon Emission Computed Tomography or SPECT.) to quantify the docking of estrogen with various metanephrine receptors in the specific brain areas affected in schizophrenia. Further, rationalization of the most effective dose of estrogen, derived from the central drug effect on the above neurotransmitter receptors could be measured in vivo. As PET results indicate that at least 65% of D_2 receptors occupancy is needed for clinical response to antipsychotics[32], it could be verified a) whether estrogen can occupy the same, b) if so, is that occupancy rate is sufficient to give antipsychotic effect, and c) if not what could be the optimum occupancy rate. This method could be very important to get optimum dosing for maximal therapeutic benefit but fewer side effects. This dual approach also facilitates the calculation of an equivalent dosage of the novel drug under the reference of a conventional drug (e.g. Chlorpromazine or Haloperidol) or atypical antipsychotic drug (Risperidone that blocks the D_2 and 5-HT_2 receptors in the relevant area of the brain affected in schizophrenia). Moreover, with the appropriate dosing the drug compliance can be enhanced. This approach could benefit particularly the drug-naïve-first-episode female schizophrenics (especially post menopausal with negative symptoms). Though their treatment mainly depends on antipsychotics, they are occasionally resistant to it, and often show an increased tendency to develop adverse effects with the antipsychotics like all first-onset cases.

PUBLICATION NOTE:

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CORRESPONDENCE TO

B-166, IIT KGP, KGP-721302, W.B. INDIA. Telephone: 91 03222 277054. E-Mail: subhagatachatterjee@yahoo.com

References

1. Cuesta MJ, Peralta V. Cognitive disorder in the positive, negative, and disorganization syndromes of schizophrenia. Psychiatry Research 1995; 58: 227-35.
2. Hoff AL, Harris D, Faustman WO, Beal M, DeVillers D, Mone RD, Moses JA, Csernansky JG. A neuropsychological study of early onset schizophrenia. Schizophrenia Research 1996; 20: 21-8.
3. Berman I, Viegner B, Merson A, Allan E, Pappas D, Green AI. Differential relationship between positive and negative symptoms and neuropsychological deficits in schizophrenia. Schizophrenia Research 1997; 25: 1-10.
4. Gold S, Arndt S, Nopoulos P, O'Leary DS, Andreasen NC. Longitudinal study of cognitive function in the first-episode and recent-onset schizophrenia. American Journal of Psychiatry 1999; 156: 1342-8.
5. Man MS, MacMillan I, Scott J, Young AH. Mood, neuropsychological function and cognitions in premenstrual dysphoric disorder. Psychological Medicine1999; 29: 727-33.
6. Saletu B, Anderer P, Gruber D, Metka M, Huber J, Saletu-Zyhlarz GM. Hormone replacement therapy and vigilance. Double-blind, placebo-controlled EEG-mapping studies with an estrogen-progestogen
7. Maturitas 2002; 43:165-81.
8. Ndosi NK, Mtawali ML. The nature of puerperal psychosis at Muhimbili National Hospital: its physical co-morbidity associated main obstetric and social factors. African Journal of Reproductive Health; 6:41-9.
9. Bech P, Munk-Jensen N, Obel EB, Ulrich LG, Eiken P, Nielsen SP.Combined versus sequential hormonal replacement therapy: a double-blind, placebo-controlled study on quality of life-related outcome measures. Psychotherapy and Psychosomatics 1998; 67:259-65.
10. Pfuhlmann B, Stoeber G, Beckmann H. Postpartum psychoses: prognosis, risk factors, and treatment. Current Psychiatry Reports 2002; 4:185-90.
11. Loranger AW. Sex difference at age at onset of schizophrenia. Archives of General Psychiatry 1984; 41: 157-161.
12. Chaves AC, Seman MV, Mari JJ, Maluf A. Schizophrenia: impact of positive symptoms on gender social role. Schizophrenia Research 1993; 11: 41-45.
13. Wieck A, Kumar R, Hirst AD, Marks MN, Campbell IC, Checkley SA. Increased sensitivity of dopamine receptors and recurrence of affective psychosis after childbirth. British

Medical Journal 1991; 303: 613.
14. Kirpinar I, Coskun I, Caykoylu A, Anac S, Ozer H. First case postpartum psychoses in Eastern Turkey: A clinical case and follow-up study. Acta Psychiatrica Scandinavica 1999; 100: 199-204.
15. Chattopadhyay S, Mandal, MK. Schizophrenia and Obstetrical Complications: Are they related? In MK. Mandal, S. Haque-Nizamie (eds.), Current developments in schizophrenia. New Delhi: Allied Publishers (accepted for publication); 2001.
16. Carpenter WT, Buchanan RW. Schizophrenia: introduction and overview. HI. Kaplan, BJ. Sadock (eds.) 6th ed. Comprehensive Textbook of Psychiatry. Baltimore: Williams and Wilkins; 1995.
17. McKinney WT. Animal research and its relevance to psychiatry in HI. Kaplan, BJ. Sadock (eds.). 6th ed. Comprehensive Textbook of Psychiatry. Baltimore: Williams & Wilkins; 1995.
18. DiPaolo T. Modulation of brain dopamine transmission by sex steroids. Reviews in Neuroscience 1994; 5: 27-41.
19. Bosse R, DiPaolo T. The modulation of brain dopamine and GABA A receptors by estradiol: a clue for CNS changes occurring at menopause. Cell, Molecule & Neurobiology 1996; 16: 199-212.
20. Gattaz WF, Behrens S, De Vry J, Hafner H. [Estradiol inhibits dopamine mediated behavior in rats-as an animal model of sex-specific differences in schizophrenia.] Fortschritte der Neurologie Psychiatrie 1992; 60: 8-16.
21. Hafner H, Behrens S, De Vry J, Gattaz WF. An animal model for the effects of estradiol on dopamine-mediated behavior: implication for sex differences in schizophrenia. Psychiatry Research 1991; 38: 125-134.
22. Hafner H, Behrens S, De Vry J, Gattaz WF. Estradiol enhances the vulnerability threshold for schizophrenia in women by an early effect on dopaminergic neurotransmission. Evidence from an epidemiological study and from animal experiments. European Archives of Psychiatry & Clinical Neuroscience 1991; 241: 65-68.
23. Rao K. Gender issues in schizophrenia. In MK. Mandal, S. Haque-Nizamie (eds.), Current developments in schizophrenia. New Delhi: Allied Publishers (Accepted for publication) 2001.
24. Kritzer MF, Kohama SG. Ovarian hormones influence the morphology, distribution, and density of tyrosine hydroxylase immunoreactive axons in the dorsolateral prefrontal cortex of adult monkeys. Journal of Computer & Neurology 1998; 395: 1-17.
25. Fink G, Summer BE, Rosie R, Grace O, Quinn JP. Estrogen control of central neurotransmission: effect on mood, mental state, and memory. Cell, Molecule & Neurobiology 1996; 16: 325-344.
26. Fink G, Summer BE, McQueen JK, Wilson H, Rosie R. Sex steroid control of mood, mental state and memory. Clinical & Experimental Pharmacology & Physiology 1998; 25: 764-775.
27. Summer BE, Fink G. Testosterone as well as estrogen increases serotonin 2A receptor mRNA and binding site densities in the male rat brain. Brain Research & Molecular Brain Research 1998; 59: 205-214.
28. Osterlund MK, Keller E, Hurd YL. The human forebrain has discrete estrogen receptor alpha messenger RNA expression: high levels in the amygdaloid complex. Neuroscience 2000; 95: 333-342.
29. Fink G, Summer BE, Rosie R, Wilson H, McQueen JK. Androgen action on central serotonin neurotransmission: relevance for mood, mental state and memory. Behavior & Brain Research 1999; 105: 53-68.
30. Garcia-Segura LM, Azcoitia I, DonCarlos LL. Neuroprotection by estradiol. Progressive Neurobiology 2001; 63: 29-60.
31. Hoff Al, Kremen WS, Wieneke MH, Lauriello J, Blankfeld HM, Faustman WO, Csernansky JG, Nordahl TE. Association of estrogen levels with neuropsychological performance in women with schizophrenia. American Journal of Psychiatry 2001; 158: 1134-9.
32. Usall J. Use of estrogens in the treatment of mental disorders. Actas Esp Psyquiatr 2003; 31 (4): 199-204.
33. Tauscher J, Kapur S. Choosing the right dose of antipsychotics in schizophrenia: Lessons from neuroimaging. CNS Drugs 2001; 15: 671-8.

Author Information

Subhagata Chattopadhyay, MBBS (cal) DGO (cal)
Medical Officer, , B. C Roy Technology Hospital, Indian Institute of Technology