REVIEW ARTICLE

Is oestrogen a ‘biological neuroleptic’?

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ABSTRACT

Objective: Oestrogen-hypothesis in schizophrenia is a largely debated issue. Being a multifactor disorder, schizophrenia has gained importance in the field of psychiatric research, especially to dig out the tentative aetiologies (genetic, biological, environmental etc.), still under tested or not tested. The present article is an attempt only to understand the possible role of oestrogen as a ‘core’ biological factor at the backdrop of male-female differences (in the onset, course, treatment response, prognosis) in schizophrenia barring other factors. This is to reduce the level of ‘conflict’ and ‘confusion’ in the article.

Method: Electronic data search is the mainstay of the literature bank, included in the article and only ‘supportive’ evidences (direct and indirect) are incorporated to understand the role of oestrogen in the brain at the backdrop of schizophrenia.

Result: The study comes out with a postulation that oestrogen has got a potential effect in moderating the process of schizophrenia in the females.

Conclusion: Oestrogen could be tested as the ‘novel’ therapeutic agent in the female schizophrenics with the necessary support from the modern Nuclear Imaging Techniques to get maximum therapeutic benefit in schizophrenia.

Key words: schizophrenia, oestrogen, dopamine, serotonin.

INTRODUCTION

‘Sex bias’ in schizophrenia is an ever interesting and well-nurtured topic, because it imparts a significant effect in the heterogeneity of schizophrenic population. Amidst so many controversies, the ‘bias’ stands on the basis of the observation that males usually develop the illness early (Chaves et al, 1993), sustain a more vulnerable course and often suffer from poorer prognosis than females (Meyer et al, 1993). On the other hand, females manifest the illness during their lifetime when the serum oestrogen level is low, for e.g. at the particular phase of menstrual cycle (Ruecher-Russler et al, 1994), after the childbirth (Davies et al, 1995) and after menopause (Hafner et al, 1993).

Among much possible aetiology in schizophrenia, it has been seen that birth-related complications lead to the development of schizophrenia in the susceptible babies (Chattopadhyay & Mandal, 2001). Now, the question comes, despite of equal vulnerability of development of schizophrenia in both the sexes at birth, why male babies show such preponderance? To answer the question, the present article is focused on the tentative roles of oestrogen, a potent pleiotropic hormone, responsible for the so-called “feminity”-a principal biological discriminator between two sexes. Other possible aetiological components (genetic, anatomical variations, environmental factors, stress etc.) are excluded from this article to concentrate only on the tentative role of oestrogen behind the sex-related-heterogeneity in schizophrenia.

METHOD

Electronic data search through PubMed (205) and current studies on oestrogen in schizophrenia. Among the studies, only the supportive evidences (empirical and review) have been included in the present paper to understand the function of oestrogen at the backdrop of schizophrenia for getting a maximally focused view on it.

RESULT

The literature search finds that oestrogen has gained tremendous significance in the field of biomolecular research because of its pleiotropic nature. It manipulates the pathophysiology of several diseases including psychiatric illnesses probably through its nuclear receptor gene expression (oestrogen has got a nuclear receptor).

Genetic modeling of oestrogen-metabolism shows that oestrogen is responsible for manipulation of diseases like breast, ovarian and colorectal cancers, PCOD (Polycystic ovarian Disease), Parkinson’s disease, alcoholism and schizophrenia (Huber et al, 2002). Further, psychobiological implications of oestrogen withdrawal in Postmenopausal syndrome are well-known facts. Impact of oestrogen on the psychobiology of females has directly been supported by the fact that oestrogen-therapy combats the adverse psychological symptoms in the postmenopausal females (Ozsoy et al 2002). Apart from that, oestrogen (transdermal) also has been found to be beneficial to liting the psychiatric symptoms of puerperal psychosis (Gregoire et al, 1996), an encouraging impact on the symptoms of schizophrenic females (Kulkari et al, 2001; Gregoriadis & Seeman, 2002), alleviating PCOD related psychological disorders (Kopala et al, 1997) and the premenstrual tension (Tiensrtr & Patel, 1998). Recent studies have showed that oestrogens replacement therapy improves the mood, memory and mental status in schizophrenic females at a large (linderer et al, 1997) mostly in conjunction with antipsychotics (Kulkari et al, 2001; Gregoriadis & Seeman, 2002), though effects may vary from individual to individual (Liao et al, 2002).

Gregoriadis & Seeman, (2002) also observed that oestrogen supplementation along with the antipsychotics prevent the occurrence of tardive dyskinesia, a very common side effect of antipsychotic medication.
Level of serum oestrogen has got a strong correlation with the cognitive function especially global cognition, verbal, spatial decleration memory and perceptual motor speed and higher oestrogen levels in female schizophrenics are associated with the better cognitive ability (Hoff et al, 2001). While evaluating the molecular process of such “oestrogenic effect” in the brain, Garcia-Segura et al, (2001) found that oestrogen prevents several neurodegenerative processes by virtue of its nuclear receptor mediated-alteration of oestrogen-responsive-gene-expression that modulates the rate of apoptosis, axonal degeneration and a generalized support to the neurons.

Now, if oestrogen has got modifying effect on the neuropsychiatric process in females then how it acts in the brain, especially in schizophrenia? The answer of it probably lies on the fact that oestrogen must have some modulating role on dopamine and serotonin receptors in the relevant part of the brain, affected in schizophrenia, as excessive dopamine and serotonin, discharges in the mesocortex and mesolimbic areas are one of the established pathophysiology behind the onset of schizophrenia (Carpenter & Buchanan, 1995). In support to the postulation, following animal studies have been reviewed to understand the biomolecular mechanisms of oestrogen action in the brain.

Using animal models, studies of Gattaz et al. (1992) and Bosse & Di Pascia, (1996) showed that oestrogen is a potent dopamine receptor blocker, especially D1 and D2. A series of studies of Fink et al., (1996), Fink et al., (1998), Summer and Fink, (1998), Fink et al., (1999), Osterland et al., (2000) documented that oestrogen can also block serotonin receptors too, especially 5HT1A and 5 lH2A.

**CONCLUSION**

Therefore, oestrogen, by blocking the dopamine and serotonin receptors in the brain probably serves like neuroleptics, which are either purely dopamine blockers (chlorpromazine, haloperidol, clozapine etc.) or dopamine plus serotonin blockers (Risperidone). Therefore, it could be postulated that oestrogen, by blocking the dopamine and serotonin receptors in the brain probably serves like neuroleptics in females (due to its natural abundance). Given such documentation, it seems that oestrogen could be a natural psycho protectant in females and it needs to be tested further.

Strategy for the future research to re-evaluate the effect of oestrogen on schizophrenia could be:

**A. Clinical trial**

First episode female schizophrenics may be tried with oral or transdermal oestrogen (available standard daily dose) alone for a particular period of time (may be for first three cycles or even beyond that according to dose-response graph) and symptom-variation could be noted using BPRS (Brief Psychiatric Rating Scale) and Hamilton's Rating Scale For Depression (HAM-D). Patients who do not respond may be added antipsychotic medication its the lowest possible dosage and the symptoms are rated using Nurses Observation Scale. ‘Observations’ and ‘ratings’ of the changes in the symptoms including the adverse effects of the drugs used should be matched with the serial estimation of serum oestradiol (the most potent among the biologically available oestrogen to titrate the most effective dosage of oestrogen or oestrogen plus antipsychotics.

**B. Utilization of Nuclear Imaging Techniques:**

Nuclear Imaging Techniques like PET (Positron Emission Tomography), SPECT (Single Photon Emission Computed Tomography) or fMRI (Functional Magnetic Resonance Imaging) could be the useful adjunct to usual clinical study by providing (i) the rate of receptor occupancy (dopamine and serotonin in the relevant areas in the brain) by oestrogen could be tallied with the sympromistic improvement, especially the maximum and the plasma oestrogen level at that time, ii) delineation of the change of metabolism of those parts, possibly affected by oestrogen, matched with the possible therapeutic benefit, and III) measurement of most effective dosage of oestrogen in the treatment of (A schizophrenia.

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