REVIEW

Estrogen and schizophrenia in women: animal models lend a hand in understanding cognition

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Abstract

Women experience a differential onset of schizophrenia symptoms and a bi-modal peak of onset in the early years of adulthood and in the post-menopausal period. Cognitive deficits that accompany schizophrenia are some of the more severe symptoms associated with the disease. The understanding of the mechanisms underlying cognitive dysfunction is still very limited and its understanding can bring important contributions to the adequate clinical management of the disease. Using rodent research to explore cognition, and how female hormones may affect cognitive decline with age in the context of schizophrenia can expand our understanding and perhaps offer more treatment options.

Keywords: Estrogen, Schizophrenia, Animal model, Cognition.

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ARC Publishing

Introduction

Schizophrenia is a severe psychiatric illness that affects individuals in multiple aspects of their lives. They experience psychotic symptoms, alterations to their grasp of reality and debilitating changes in cognition. The cognitive affects of schizophrenia effect patients on a diverse range of severity including changes in memory function and higher-level cognitive ability to process information and apply it. Treatment consists of both pharmacological interventions using typical and atypical antipsychotic drugs in conjunction with psycho-social treatment (therapy) and in some cases a combination of other supportive types of care. However, there is room for further improvement, including the treatment of cognitive deficits since sufferers with schizophrenia continue to struggle to manage the cognitive aspect of their illness [1].

We will focus on the effect of estrogen on cognition and the possible relationship to schizophrenia. Estrogen plays significant roles in female development throughout life, beginning in the fetal stages and into late age. Clearly estrogen has a critical role in reproductive functions, where fertility and pregnancy are highly specialized in women and dependent on a necessary suite of maternal hormones including but not limited to progesterone and estrogen [2]. Research done on animal models like rodents, alludes to neuro-protective benefits that hormones, such as estrogen, can have on brain function in females. In addition, estrogen may play an influential role in hormonal impact on symptom onset, illness course, and quite possibly cognitive deficits in women with schizophrenia. We will outline some of the advantages in using rodent models, to study the impact of estrogen on cognition, as well as creating a framework for further understanding schizophrenia in women that could improve treatment, and manageability of the illness.

Estrogen and the brain

Estrogen is produced by breast tissue, fat, gonads and the brain and is a key neurosteroid that plays important roles in fetal development, sexual differentiation, neuronal differentiation and synaptic connection formation. It is also known to increase synaptogenesis in brain areas that play a role in memory. It is also important in maintenance of synaptic density and plasticity in the CA1 region of the hippocampus (HIPP), an area important to memory [3,4], and can facilitate synaptic plasticity of dendritic spines in the CA1 region of the HIPP [5,6]. It can also alter firing rates in neuronal communication in key areas of the brain like the hypothalamus [7], alter membrane receptor expression [8] and modulate reactivity of supportive neuronal cells such as astroglia [9]. Estrogen has also been found to enhance verbal memory and maintain the ability to learn new material. The long reaching effects of estrogen are only briefly touched on in the above list. In addition, estrogen can also be neuro-protective in specific areas of the brain associated with cognitive function that may suffer detrimental changes in anatomy and function that can accompany natural aging, menopause and pathological diseases [3].

Estrogen has complex and varied effects on the brain. It has acute and long-term mechanisms of action. Its ability to effect change in the peripheral system (i.e. sexual characteristic differentiation) as well as in the central nervous system (i.e. neuro-protective effects) is indicative of its multi-functionality and importance. Furthermore, recurring hormonal fluxes in women, due to the menstrual cycle, may relate to estrogen serving as a protective factor during the development of schizophrenia and the diseases effects on cognition [10]. Studies have shown that there is an association between serum levels of estrogen and global cognitive score including 4 neuropsychological cognitive domains: verbal memory and spatial memory, perceptual speed and motor speed [11]. These findings support the idea that estrogen can affect not only the brain, but ultimately the course of neuropsychological diseases such as schizophrenia.

Estrogen and the schizophrenic brain

How estrogen actually affects schizophrenia (the mechanism through which it works) still requires much investigation. Mechanisms by which estrogen seems to affect cognition include promotion of cholinergic and serotonergic activity in key brain areas, maintenance of neural circuitry, favorable lipoprotein alterations and prevention of cerebral ischemia [12]. Existing data indicates that estrogen has a positive effect on preservation of cognitive function and dendritic spine density [13,14]. Some of the initial data support women experiencing a delayed onset of cognitive decline until at or around menopause. Further positive response to HRT resulting in preservation of cognitive function was first supported with rodent findings. Estrogen, in its various forms, is important in an obvious way to reproduction (pregnancy, fetal development, etc.); and rodent studies have shown that females that have undergone multiple motherhood experiences, or multiple pregnancies may indirectly reap benefits of neuronal preservative effects of estrogen and ultimately delay cognitive decline that occurs with age [15]. These type of rodent research findings are important in that they could possibly help inform more research being done on better understanding schizophrenia, diagnosing and potentially treating female patients with the disease taking into consideration the crucial influence of hormones.

Schizophrenia has been shown to exhibit a sexually dimorphic symptom onset. A later onset of schizophrenia in women may be primarily influenced by estrogenic activity [16] and appears related to the development of more positive symptoms. Men are diagnosed with the onset of symptoms on average 3-4 years earlier than women;

men at ages 16-25 [17] and women at 25-30 years of age [17,18]. Women that are premenopausal (during which time circulating estrogen has not yet significantly declined) have been shown to have a better course of illness [19, 20] and better response to pharmacological intervention [21] as compared to men [20].

In women there is a bimodal peak of onset; a primary peak during young adulthood (25-30 years of age) and a secondary peak at or around menopause (48-55 years of age) [18, 22-24]. The second uptick in incidence may be directly related to the drastic decrease in circulating estrogen, which may leave women vulnerable and without positive protective estrogenic effects. This pattern suggests estrogen's influence on schizophrenia onset and progression in women. It has been suggested that a woman's experience of motherhood, is accompanied by significant and necessary hormonal changes that may have an effect on certain aspects of symptoms associated with schizophrenia [25,26]. Since hormones can affect the onset and course of a disease, hormonal function should be a regular consideration in diagnosing and looking at prognosis of schizophrenia, especially in women.

Motherhood and schizophrenia

There is still a lot of work that needs to be done in understanding how the motherhood experience affects the symptoms and illness course of schizophrenia and also on the success in production of offspring in women suffering from schizophrenia. The number of babies born to mothers with psychosis aged 25 and older (accompanied by no affective symptoms) is lower than in the general population average for females [27]. However, there is no difference between women suffering from schizophrenia and healthy women in successfully reproducing over all ages. The lower rates may also be influenced by other variables not readily considered such as lower rates of sexual activity, difficulties maintaining stable romantic relationships [27], medication induced abnormalities in prolactin levels and menstruation (which can vary depending on which medication is taken) [28] and medication induced sexual dysfunction (30-80% in women) [29-31]. It has been shown that more than half of the women with psychosis in the sample for the McGarth group (1999) were mothers and had higher levels of fertility was associated with a later age at first diagnosis [32]. These findings may relate to the rodent findings where multiple pregnancies seem to have a positive neuro-protective effect on key areas in female rat brains associated with memory. Estrogen may be protective in delaying onset of schizophrenia in women [33]. Furthermore, women that are on estrogen replacement therapy (HRT) require a lower dose of antipsychotics to control their symptoms [34]. So, estrogens can influence the incidence, onset and severity of cognitive symptoms that are associated with schizophrenia, thus making the discussion of motherhood in patient diagnosis and prognosis important.

Much more investigation is needed; and doing that work in a rodent model would be advantageous and efficient compared to the difficulties of coordinating clinical longitudinal studies in humans.

Cognition and schizophrenia

Patients suffering from schizophrenia experience 3 distinctive types of symptoms: positive, negative and cognitive symptoms. The cognitive deficits associated with schizophrenia appear to occur in specific patterns and are not necessarily global. Meaning, not all patients suffering from schizophrenia will experience the same combination of cognitive deficits or have the same level of severity. Those affected fall along a continuum [35] making the suite of symptoms quite heterogeneous. These deficits can arguably be some of the more challenging symptoms of the illness that patients have to deal with, and are not successfully managed with medication.

Patients with schizophrenia perform on average 1.5 to 2 standard deviations lower than a healthy control subject on neuro-cognitive assessments, specifically in the areas of:
- memory
- attention
- working memory
- problem solving
- information processing speed
- social cognition [36].

Pharmaceutical interventions largely treat the positive symptoms of schizophrenia including:
- hallucinations
- delusions
- movement disorders (catatonia)
- thought disorder

The typical and atypical antipsychotics are not as effective at treating the negative symptoms (which detract from the normal/typical behaviors seen in healthy individuals) and can include:
- reduced or limited expression of emotion (both facial expression and vocal)
- inability to complete tasks begun
- loss of pleasure in normally pleasurable activities
- loss of interest or
- inability to maintain hygiene
- reduced communication and cognitive deficits

They are also relatively poor at treating the cognitive deficits in people with schizophrenia including:
- disorganized thought and speech
- poverty of speech and language
- working memory
- long-term memory
- reasoning
- executive function [37].

Changes in the brain that occur with schizophrenia

Changes in anatomy and physiology of the brain are also evident. PET scans of patients suffering with schizophrenia show an abnormal amount of blood flow (high) to the HIPP and abnormal activity when patients were tasked with a word retrieval assessment [38]. Abnormal changes in the brain are not singular or isolated to one particular area. The architecture changes of the neural matter are not the only abnormalities that occur in a schizophrenic brain. Alterations and abnormalities in the neural circuitry are also persistent along with changes in neurotransmitter systems and neural circuitry of the brain [39]. Changes in neural connectivity involving the glutamate, GABA and dopaminergic systems also occur [39]. Other abnormalities/deficits include decline of universal gray and white matter volume in the brain along with continuous ventricular enlargement [40], abnormal cyto-architecture, irregular synaptic organization, and neurons located in abnormal locations [41]. The schizophrenic brain is an amalgam of abnormal neural architecture, abnormal mass and divergent connectivity. Schizophrenia is not necessarily degenerative in the typical sense that we would categorize degeneration that occurs with age or with neurological diseases like Alzheimer's; it seems that excito-toxicity, related to the abnormal synaptic connectivity, plays a significant role in being mechanistically contributive to the cognitive deficits experienced with schizophrenia [42].

The need for more research on understanding cognitive deficits in schizophrenia is further supported by the fact that the drugs usually prescribed to treat schizophrenia do not always address cognitive symptoms. However, atypical drugs used to treat schizophrenia may more consistently address cognitive deficits [1]. For example, Risperidone appears to have consistent positive effects on working memory, executive functioning, and attention but inconsistent results with long-term memory and verbal learning [43] Olanzapine shows positive improvements in verbal learning and memory, working memory, visual learning and memory [44]. However with Clozapine the results are not reliable when it comes to working memory, verbal or spatial abilities.

Using Rodent Models to Investigate Cognitive Deficits in Schizophrenia

Given the complexities in understanding the way schizophrenia affects the brain and the role of hormones in disease onset and progression, using rodent models is an approach that presents key advantages that clinical study may not easily offer. Jones, Watson & Fone (2011) discusses a crucial point [45]. There is not enough research focused on understanding cognitive deficits in schizophrenic patients. Utilizing rodent models that contain analogous brain organization, differentiation and physiology (function), and

to the extent that model exhibits quantifiable behaviors that are comparative to symptoms seen in schizophrenic patients presents an excellent research opportunity. Rodent models offer manipulability, an advantageous shorter lifetime for developmental study and ease of building large data sets with potentially more powerful significance.

Jones, Watson & Fone (2011) also proposes, correctly, that an animal model for any disease, should meet the criteria for each aspect of a valid animal model triad. The animal model must meet all three in order to be considered valid enough to serve as a good model. First, is having face validity, where the animal is reflecting the correct phenotypes (the main symptoms that are associated with diagnosis) that are typical of the disease. In the case of schizophrenia, that would refer to the previously described positive, negative and cognitive symptoms. The second point in the triad is construct validity. The animal model must mimic physiological aspects of the disease, where for schizophrenia that would include enlarged ventricles, decreased synaptic activity and dopamine dysfunction. The third and last point is the model must have some predictive validity wherein the response by the model should be similar to or identical to the response that would be expected from a schizophrenic patient (i.e. drug therapy intervention/treatment) [45]. The major limitation of rodent research in schizophrenia is the extent that we can model these uniquely human behaviors and possibly symptoms in the rodent model. The experience of reality in humans suffering from schizophrenia may be impossible to model in a rodent. This means that we may not meet the face validity aspect of the triad. Despite this possible limitation, there may be aspects such as cognitive function where we can find clearer model measures in rodents.

Using rodent models of cognitive function in schizophrenia is that it allows for experimental manipulations, and replicability within a reasonable amount of time. The life span of rodents is much shorter than that of a human. Thus, better understanding neurocognition later in life is far more attainable than studying in a human who does not reach mid life until they have reached approximately 50 years of age as compared to a rodent which reaches mid life at approximately 1.5 years. In the context of looking at the advantages of the rodent life span and development, their gestation periods are also short (approximately 21 days), allowing for the long-term effects of multiple pregnancies to be investigated within a feasible time frame (1.5-2 years). Compared to human females, whose much longer life would require significantly more time, the financial investment to maintain such an extensive longitudinal study for the average national standard life expectancy of 78.8 years of age [46] is enormous. Added to the benefits of a shorter life span and a shorter gestation period in rodents, is the ease with which neuroanatomy can be examined, and treatment conditions can be applied within controlled environments both live and post-mortem. These reasons add to the appeal of using rodent or other animal models

to better understand human conditions such as schizophrenia. Along these lines, Morrison, Brinton Schmidt & Gore (2006) concur with rodent models being advantageous. They note that female rats are an ideal model in which to study reproductive aging offering the benefit of a shorter lifespan, and low cost purchase housing and maintenance, and perhaps most importantly their physiology allows for ease in hormonal experimental manipulation [47]. While humans are definitely complex, there are over 20 known rodent models of schizophrenia [45]. Not surprisingly, there is some overlap in the methods in which they are developed and the symptomologies that they demonstrate, though this may detract from their usefulness. They allow for 4 general models to look at mechanisms of schizophrenia. These 4 general models include: neuro-developmental, drug-induced, lesions and genetic manipulation models.

The neuro-developmental models utilize the existing evidence that the neonatal environment can play a role in the risk of developing schizophrenia. Negative environmental factors including but not limited to malnutrition, infection, maternal stress [45] have shown significant promise in that their face validity is good. Models created using this method do show relevant symptomology at around the typical age of onset in humans, in rats. They also appear to demonstrate some of the neuro-anatomical abnormalities in rats that are seen in human subjects with schizophrenia. Some example of this type of model includes the isolation-reared model where rodents are raised in a deprived environment from the time they are weaned at approximately 3 weeks of age (weaning) to adulthood. There are significant neuro-developmental and behavioral abnormalities that develop as a result that can parallel some of the symptomology found in patients suffering from schizophrenia. These rodents exhibit significant hyperactivity. Work has been done by quite a few groups to explore the response of this behavior to dopamine antagonists and they have had positive results wherein the hyperactive behaviors are reduced as compared to control animals. Neuro-architectural changes such as decreased volume and altered neuronal connectivity in the PFC and the hippocampus (HIPP) as well as changes in receptor expression (i.e. Dopamine receptor sensitivity and expression in the PFC, HIPP and Amygdala) in the rodent model can also be seen in schizophrenic patients (Jones, Watson & Fone, 2011). The physiological similarities are advantageous and support validity.

Drug induced models also prove effective and valid in their demonstration of schizophrenia associated symptomology (both anatomical and behavioral) and are far more feasible to do in rodents than humans. MAM (methylazoxymethanol), a naturally occurring chemical isolated from the seeds of the cycad plant is an anti-mitotic that facilitates the methylation of DNA. When given to female DAMS (rodent mothers) during pregnancy it selectively causes a decrease in morphological and physiological neural development in rodent offspring and thus mimics what is typical of what is seen in the offspring female patients with schizophrenia. This gentoxin (genetic toxin) induces not only morphological abnormalities, but also the accompanying behavioral changes seemingly linked to dysfunction of the frontal cortex and limbic dopaminergic inputs.

There are other models in rodent work that can be more directly described as drug-induced and demonstrate the development of schizophrenic symptoms as a result of drug use. One such model utilizes repeated overuse of amphetamines. This method is limited in that the associated effects are only seen in the PFC because amphetamines do not have any long-term detrimental effects on the HIPP and hippocampal-related cognitive function. Another drug-induced model uses PCP, which works through the glutamatergic system (a major excitatory neurotransmitter system) mimicking the positive symptoms of schizophrenia such as hallucinations and delusions. It is created through chronic PCP use, which seems to accurately produce cognitive symptoms that are comparable to positive schizophrenic symptoms and has been used to show that atypical antipsychotic drug treatment can reverse PCP induced schizophrenic-like symptoms.

The lesion-Induced model developed in the 1990's by the Lipska-Weinberger group involves lesioning of the ventral HIPP (vHIPP) in neonatal rats (which corresponds to the anterior hippocampus in humans) that results in them exhibiting abnormal behaviors at and after puberty and abnormal morphology of the HIPP [48]. Adult vHIPP lesioned rats show a marked decrease in the length of dendrites and reduced spine density [49,50]. They also show receptor expression alterations and overall connectivity abnormalities in the prefrontal cortex. Accompanying these changes in the brain, there are also changes in behavior (i.e. spatial working memory tasks like the radial arm maze and the T-maze) that are typically associated with hippocampal brain function [48, 51]. Schizophrenic patients during their first episode may have ventricular enlargement and abnormalities of the HIPP. This type of model is appealing because of its similarity in morphological brain abnormalities that could potentially further investigate neurophysiology and function, especially prefrontal cortical-hippocampal function [45]. The effects of the lesioning are evident as development progresses and the resulting behavioral abnormalities are thought to be similar to the negative symptoms of schizophrenia. The changes in neuro-chemistry and receptor expression in the PFC, significant impairments to memory-related tasks (hippocampal-associated behaviors) as well as significant reductions in dendritic length and spine density in the PFC and the Accumbens (Acc), are aspects of neural architecture that are affected and associated with cognition.

The genetic manipulation models are varied, and they investigate numerous molecular targets and their downstream effects as they relate to schizophrenic phenotypes, geared towards looking at the genes associated to specific sub-phenotypes of schizophrenia [45].

Conclusion

Using rodent models to continue investigating aspects of schizophrenia that are not as accessible in human research is crucial. Adding to the ever-growing body of literature on the cognitive effects of schizophrenia, how patients experience them, researchers and medical professionals are trying to identify more efficient and effective ways to treat and manage the negative cognitive symptoms is needed. Through research with rodents, the potential findings that would contribute to understanding symptomology and the effects of schizophrenia on the brain in women are very promising and quite honestly practical. Continuing to understand the long reaching effects of estrogen and potentially exploring the relationship between estrogenic effects on the onset and illness course of schizophrenia in women in rodents models is an ideal future direction of research on the illness. There is a large collection of review articles and primary papers that have acknowledged that there are inconsistencies and lack of clarity on the role(s) that estrogen plays in schizophrenia and the illnesses' effects on cognition and the brain. The purpose of this paper was to facilitate consideration and discussion of the influence of hormonally driven events in the life of a women with schizophrenia, the role of estrogen and recommend that research using rodent models is an important means of investigation.

Abbreviations

Acc: Accumbens; CA1: Cornu Ammonis Area 1 of the Hippocampus; DAM: Reproductively active female rodent with pups (female parent); DNA: Deoxyribonucleic Acid; GABA: Gamma-AminoButyric Acid; HIPP: Hippocampus; HRT: Hormone replacement Therapy; MAM: Methylazoxymethanol; PCP: Phencyclidine; PET scan: Positron Emission Tomography scan; PFC: Prefrontal Cortex; vHIPP: Ventral region of the Hippocampus.

Competing interests

The authors declare no conflict of interest.

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