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Female Hormones – Comprehensive Biomarkers for Psychiatry and Neuroscience – A Narrative Review

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Abstract

Recent medical research has provided a multitude of reliable biomarkers to the field of contemporary medicine. This practice of incorporating biomarkers in diagnosis and management of any given health condition has proven to increase the precision and the pace of medical practice. It is therefore essential to explore novel forms of biological indicators to improve the efficacy of therapeutic intervention. The objective of this paper is to review the potential of female sex hormones, particularly estrogens and progesterone, to acquire the status of comprehensive biomarkers for mental health using psychiatric, cognitive and neuroscientific evidences drawn from past research. The paper discusses the neuromodulatory and neuroprotective effects of female sex steroid on the brain circuitry and the positive impact on a wide range of cognitive abilities. The paper also reviews studies pertaining to menopausal women, critical window hypothesis and hormonal therapy. Finally, the buffer effect of female sex steroids on diathesis in acquiring a disorder is also discussed by compiling studies conducted on clinical samples of Neurodevelopmental disorders, Neurodegenerative disorders, Schizophrenia, Anxiety, Depressive Disorders Stress-related disorders.

Keywords:

Estrogen;
Progesterone;
Cognition;
Psychiatric disorders.

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1. Introduction

In the recent past, Preventive healthcare has gained momentum across the globe and Biomarkers have become statistically significant topics of research in medical as well as community health today. According to the National Institutes of Health, Biomarkers Definitions Working Group (1997, 2001), biomarker is defined as "a characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention or other health care intervention". According to Naylor (2003) "A biomarker is a characteristic that can be objectively measured and evaluated as an indicator of a physiological, as well as a pathological process or a pharmacological response to therapeutic intervention. They are useful in making informed treatment decisions right from diagnosis, to predicting outcomes, success, and intensity of intervention required as well as an individual's response to the same. According to FDA, the characteristics of an ideal biomarker are as follows: specific, safe and easy to measure, rapid, cheap, be able to give accurate results and consistent across gender and ethnic groups.

In the past few decades, the field of psychiatry has made efforts have been made to integrate biomarkers into practice with an aim to align its objectivity with fellow branches of medicine. Biological indicators enable the diagnostic and prognostic assessment of various mental disorders, which is extended to behavioral, cognitive and emotional aspects of functioning. A range of biomarkers have been found to be useful in psychiatry and are classified as follows for better understanding: a) *genetic*: carrier genes, Single-Nucleotide Polymorphisms (SNP), b) *neurobiological*: cortical thickness, neural circuit connectivity, c) *electrophysiological*: conductivity, EEG waves, fMRI, and PET activity, d) *biochemical*: neurotransmitters and hormones e) *cognitive*: executive functioning, and f) *behavioural*: endophenotypes. But, currently, only a handful of these biomarkers have proven to be robust indicators in Psychiatry.

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2. Female Sex Steroids

Estrogens and Progesterone are the two sex steroids that are synthesized in females contributing a lot to sexual dimorphism. Apart from inducing sexual motivation and reproduction, they are said to be involved in regulating other functions as well which would be discussed in detail during the course of this review. All vertebrates and a few insects have been identified to produce Estrogens in these forms Estrone (E1), Estradiol (E2) and Estriol (E3) and Estetrol (E4), out of which the former three are predominant and the latter one which is synthesized exclusively during pregnancy. 17-β estradiol is the most abundantly available and active form of endogenous estrogen. Estrogens have an infinite number of receptors distributed across the cells of the body. The binding of estrogens with their receptors modulate the phenotypic expression of many genes. There are two major receptors namely, ERα and ERβ (Koike, Sakai, & Muramatsu, 1987; Kuiper et al., 1996), which are spread across Pituitary, Renal, Adrenal, Uterine and Ovarian and Neural regions. Progesterone and its metabolites such as 5α-dihydroprogesterone and allopregnanolone, etc, have a wide range of functions such as respiration, bone strength, skin elasticity, and have receptors in Uterine, Ovarian, Hepatic, Dermal and Neural regions as well.

3. Neurosciene

Both Estrogen and Progesterone are identified to neurosteroidal properties. Neurosteroids are neuromodulators, and are neuroprotective, neurogenic, and regulate neurotransmission and myelination (Schumacher et al, 2005). **Progesterone** and its active metabolites help in regulating gamma-amino butyric acid (GABA) receptors (Stein, 2008), arresting neuronal apoptosis by inhibiting caspase-3 and cytochrome c which are responsible for cellular apoptosis (Espinoza & Wright, 2011; Deutsch et al., 2013) and promoting neuroregeneration by remyelinating axonal damage (Stein, 2008) and amplify the number of progenitor cells in circulation (Li et al, 2012).

Estrogen The ER receptors are found dispersed across a wide range of brain areas like the dentate gyrus of hippocampus (Weiland et al., 1997; Herrick et al., 2006), hypothalamus (ventromedial nucleus & arcuate nucleus), cerebellum, pre-optic area, nucleus of stria terminalis, and regions of the brain stem (Shughrue et al., 1997; Markou1, Duka, & Prelevic, 2005), that have genomic functions. ERβ receptors are majorly concentrated in the hypothalamus, amygdala, and the hippocampus (Shughrue & Merchenthaler, 2000). Neurosteroidal effects of estrogens are seen at the anatomical level: in the form of neurogenesis, synaptic transmission and neural network connectivity and also at the cellular level: mitochondrial energy transfer and aerobic glycolysis (Brinton, 2008).

Early research has shown us that estrogens also have neuroprotective effects in the following ways: boosting the survival of neurons even in condition of serum deprivation (Arimatsu and Hatanaka, 1986), oxidative stress (Behl et al., 1997), shielding against excitotoxic injuries (Goodman, Bruce, Cheng, & Mattson, 1996; Green, Gridley, & Simpkins, 1996; Singer, Rogers, Strickland, & Dorsa, 1996), neuronal apoptosis (Garcia-Segura, Cardona-Gomez, Naftolin, & Chowen, 1998), inflammation (Suzuki et al., 2007; Sávári et al., 2010) and maintaining mitochondrial function (Simpkins, Yi, Yang, & Dykens, 2010).

In rats, the administration of estrogens induced rapid cell proliferation relative to the dosage (Barha, Lieblich, & Galea, 2008). Research conducted by Galea (2008) has shown that steroidal hormones induce neuroplastic and morphological changes in the hippocampal region of primiparous rats, thereby causing robust changes in spatial memory.

Neuromodulatory effects of estrogens are widely studied in the hippocampal region for it is the core of learning and memory processes (Shibuya et al., 2003). Estradiol helps in the generation of novel dendritic spines and excitatory synapses (Li et al., 2004; Hao et al 2006), augment CREB phosphorylation (Zhou, Watters, & Dorsa, 1996), up-regulate NMDA receptor expression (Adams et al., 2004) and long-term potentiation (Smith, & McMahon, 2006), in the hippocampal region, an increase in the spines of pyramidal neurons at CA1 region of hippocampus in mice (Liu et al., 2008). Apart from these passive effects estrogens are also found to be involved in rapidly altering the electrophysiological parameters in slices of hippocampal tissues (Bi et al., 2000; Mukai et al., 2006).

Estrogens impact various neurotransmitter system namely, catecholaminergic, cholinergic, gamma-aminobutyric acidergic, serotonergic (McEwen, 2002), and dopaminergic systems (Sherwin, 2003).Morphological investigations have suggested that, during the pro-estrus stage, adult female rats have shown 50% increase in nascent proliferating cells in the dentate gyrus region when compared to their male counterparts, thus highlighting the mitogenic potential of estrogens (Tanapat, Hastings, Reeves & Gould, 1999).

Research has implicated that the period of pregnancy and motherhood is characterized by an augmentation in neuroplasticity (Pawluski & Galea, 2006). However, the 'Healthy Cell Bias' theory proposes that estrogens exert their neuroprotective effects on healthy neurons and aggravating death of cells that are already undergoing apoptosis (Hogervarst 2013).

4. Cognition

During the mid-luteal phase of the menstrual cycle, Estrogens and Progesterone positively impact speed and motor coordination (Hampson & Kimura, 1988), verbal memory, attention and visual memory (Phillips & Sherwin, 1992), fine motor dexterity and verbal fluency (Maki, Rich & Rosenbaum, 2002). Overall, it can be said that female sex steroids are crucial in promoting sexually dimorphic cognitive tasks (Sanders, Sjodin & de Chastelaine, 2002).

The pioneering study of Barbara Sherwin, conducted on women who underwent hysterectomy and ovariectomy, found that estrogen replacement treatment (ERT) improved their cognitive function. Newer research shows that ERT, among women of postmenopausal phase, has proven to increase verbal IQ, memory, abstract reasoning, and reaction times than placebo trials (Sherwin, 2003) and verbal fluency (Berent-Spillson et al., 2012). ERT also improves the performance of executive tasks (MacLennan et al., 2006) with a diminution in perseverative errors (Joffe et al., 2006). Estrogens have been known to have a positive impact on age and ischemic lesion-compromised cognitive functions (Gulinello et al., 2006; Sandstrom & Rowan, 2007).

A Multiracial study by Yaffe et al. (2006) demonstrated that low estradiol levels led to a decline in global cognitive function of women and verbal memory of men and women. However, the results of Women's Health Initiative (WHI) and its ancillary studies were not in consensus with that of the aforementioned and revealed that ERT may actually take a toll on the cognitive capacity of women of or older than 65 years of age (Shumaker et al., 2004). Nonetheless, endocrinologists critically reason out that 69% of the participants of the WHI study were heavier, 47.4% were less adherent to treatment and 74% were deprived of estrogen for a period longer than 10 years and that the study used synthetic drugs such as conjugated equine estrogens (CEE) and medroxyprogesterone acetate (MPA) instead of natural estradiol and progesterone (Turgeon et al., 2004).

Rodent studies indicated that Estradiol promoted working memory reference memory and spatial memory through neuronal plasticity in prefrontal cortex and hippocampus. Similarly, activation of ERβ receptors led to improvement in spatial memory of ovariectomized (OVX) rats while performing in the radial arm maze and Atlantis water maze (Luine et al, 2008). Earlier studies conducted on OVX rats, it was found that the rats in their pro-oestrous period displayed superior recognition memory than the ones in the other phases of oestrous cycle (Walf, Rhodes & Frye, 2006, Frye, Duffy & Walf; 2007), and superior spatial memory during the pro-oestrous phase as indicated by the water-maze performance (Frick & Berger-Sweeney, 2001). They are known to enhance memory: short-term memory (Ennaceur & Aggleton, 1994), working memory (Sandstrom & Williams, 2004; Luine, Jacome & Maclusky, 2003; Scharfman et al., 2007) and higher-order memory (Mumby et al., 2002) which can highlight the hippocampal involvement.

Estrogen treatment for a period of four hours improves inhibitory avoidance, object recognition and object placement (Luine, Jacome & Maclusky, 2003; Wal, Rhodes & Frye, 2006; Rhodes & Frye, 2006; Frye, Duffy & Walf, 2007). ERT in ovariectomized rats has proven to increase working memory capacity (Daniel, Hulst & Berbling, 2006), positively impact figural memory and negatively affect verbal memory (Resnik et al., 2006). Research conducted by Dumas et al. (2006) showed that estrogen prevents the anticholinergic drug-induced impairment in attention and speed.

5. Critical Window Hypothesis

Sherwin (2005) was the first one to note that commencing hormone therapy immediately after undergoing gonadectomy or natural menopause opens a window to conserve memory and that tardy treatment has little or no beneficial impact. Erickson et al. (2005) found that ERT for a span of a decade conserves grey matter in prefrontal cortex which is a better predictor of executive functioning, but ERT provided beyond a decade quickens the rate of deterioration in the prefrontal cortex, thereby accelerates the decline in executive functioning. Similarly, Maki et al. (2007) have found that initiation of hormone therapy in older women who have crossed years postmenopause has caused deterioration in verbal memory. A study by Lord et al. (2006) showed that ERT increased right hippocampal volumes when compared to non-users and past users and this increase was found to be inversely related indicating the existence of a critical window period. Whitmer (2010) has also proven that hormonal therapy started in mid-years, i.e. the time of menopause has protective effects on cognition when compared to later in life. A Review by Rocca, Grossardt & Shuster (2010) suggested that the critical window for oophorectomized as well as menopausal women would lie around 51 years of age.

6. Psychiatric Disorders

Decades of scientific research has indicated that ovarian steroids are involved in the etiology of many psychiatric disorders. The effects can be either direct in the form of genomic expression or indirect in the form of treatment. The involvement of estrogens in psychopathology is discussed below:

6.1 Neurodevelopmental disorders: Neuroblastoma cell studies indicated that ovarian steroids, particularly estrogens were involved in the up-regulation of retinoic acid-related orphan receptor-alpha (RORA) (Sarachana, Xu Wu, & Hu 2011), a novel candidate gene for autism, whose knock-out in RORA-deficient staggerer mice causes perseverative behaviour (Lalonde & Strazielle, 2008), limited maze patrolling (Goodall & Gheusi, 1987), anomalous object exploration (Lalonde, Botez, & Boivin, 1987). Estrogen has the properties to augment the calcitriol (Vitamin D) levels, both neural and cellular (Epstein and Schneider 2005; Currenti, 2011) and the deficiency of vitamin D causes cytochrome P450 gene polymorphism and defects in the CYP27B1 enzyme which is linked with autism. Milder autistic tendencies were also studied by Palomba et al., (2012) where it was demonstrated that daughters born for mothers suffering from PCOS had low emotional quotient and high systemizing quotient.

6.2 Neurodegenerative disorders: Early research has found that estrogen prevents the accumulation of β-amyloid plaques. Experimental studies conducted on rats showed that Progesterone and Estrogens have independently contributed to reducing the risk of Alzheimer's disease (Carroll et al., 2007). Rocca (2008) found that oophorectomies performed on premenopausal women increased the risk of Parkinson's disease in women. Estrogen improves aerobic glycolysis in aging brain which might arrest the usage of other forms of energy like ketone pathways which are proven to be a distinctive feature of Alzheimer's disease (Diaz & Brinton, 2008). Janicki and Schupf (2010) have reviewed that endogenous estrogen and SERMs are linked with improving cognition and reducing the genetic risk of dementia. Estrogens exert their neuroprotective effects on the dopaminergic system present at the nigrostriatal pathway whose deterioration is implicated in the etiology of Parkinson's disease (Quesada & Micevych, 2004).

6.3 Psychotic disorders: Mahé and Dumaine (2001) reviewed that estrogen withdrawal after delivery increased psychotic symptoms. Kulkarni et al. (2001) found that schizophrenic women receiving estrogen treatment showed fewer and milder extra-pyramidal side-effects which are common antecedents of anti-psychotic medication. Hoff et al., (2001) found strong positive correlations between estrogen level and Neuropsychological variables like global cognitive function, verbal and spatial declarative memory, and perceptual- motor speed Schizophrenic women. Seeman et al. (2004) showed that delayed menarche in females was associated with an earlier occurrence of schizophrenia. Researchers have identified hypo-estrogenism in female patients with schizophrenia (Rubin et al 2010) and estradiol had anti-psychotic properties on symptoms of schizophrenia (Faturous-Bregmann 2012). Moreover, Selective Estrogen Receptor Modulators (SERM) has also been advocated in managing schizophrenia (Kulkarni et al., 2006). Genetic studies by Weickert et al. (2008) indicated that endogen receptor-α (ESR1) gene variation is linked to the expression of schizophrenia. clinical and animal studies have shown that estrogens exhibit neuromodulator properties on the neurotransmitter systems targeted by the contemporary current antipsychotic drugs (Canuso & Pandina, 2007).

6.4 Anxiety, Depressive and Stress-related Disorders: Experiment by Pandaranandaka, Poonyachoti & Thongsong (2008) revealed that OVX rats under long-term estrogen treatment and Sham-Pro rats that have high bioavailable levels of estrogen display anxiolytic behavior. Estrogen receptors ERα and ERβ activation disrupt fear learning in female rats, which can be implicated in the etiology of phobia (Toufexis, Myers & Davis, 2006). Estrogen fluctuations have been associated with the etiology of bipolar disorders (Meinhard, Kessing & Vinberg, 2012), depression, anxiety and post-traumatic stress disorder (Peterlin, Katsnelson, & Calhoun, 2009). Lower levels of bioavailable estrogens are proven to increase the vulnerability for post-traumatic stress disorder in women mainly in terms of fear-potentiated startle responses, while high estrogen levels did not (Lebron-Milad, Graham & Milad, 2012).

A recent study reviewing the role of estrogen in stress-related disorders has advocated estrogen treatment to be "a putative pharmacologic adjunct in extinction-based therapies" (Glover, Jovanovic & Norrholm, 2015). *ESR1* gene that is responsible for higher expressions ERα receptors is found to be responsible for the reduction in the risk for obsessive-compulsive disorder and compulsive symptoms (Alonso, 2010). Rats treated with 17β-estradiol have shown an increase in the serotonin levels in the prefrontal cortex which can be implicated in neural mechanisms underlying depression (Inagaki, Gautreaux, & Luine, 2010).

7. Conclusion

Despite the limitations of diversity in the discipline and methodology of the reviewed studies, overall, research has implied the share of female sex steroids in genomic mechanisms, neural-regulation and health, thereby on cognition as well as the risk and etiology of many psychiatric disorders and in the treatment of few. Majority of literature supports the positive benefits of Estrogens on mental health. Assigning the status of an integrated biomarker requires further scientific exploration and would prove to be a value addition to the field of medicine as contemporary efforts in concerning preventive Psychiatry have been modest.

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