Gonadal Hormone Contribution to Substance Use Disorders and Neurodegenerative Diseases in Female

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Abstract: Sex differences have been long recognized to influence multiple systems in the human body, ranging from the cardiovascular system to the neurological system, and these differences have been attributed primarily to the influence of the gonadal hormone, estrogen. In most cases, estrogen functions as a protective agent against multiple diseases, e.g., neurodegenerative diseases, thereby making women generally less vulnerable than men. However, research studies have also shown that estrogen contributes to increased vulnerability in developing substance use disorders (SUD), where because women have higher concentration of circulating estrogen, setting them at a higher risk for development of SUD. While extensive research has revealed some of the underlying mechanisms through which estrogen influences both substance use disorders (SUD) and neurodegenerative diseases, current studies have yet to investigate situations in which these diseases coexist. Such investigations could potentially illuminate the nuanced relationship between the two conditions. In this comprehensive review paper, the mechanisms underlying gender-dependent vulnerability are discussed, along with more real-life dilemmas and questions that are posed. To address these questions, some potential preclinical and clinical experimental proposals are explored and discussed

Keywords: Estrogen, neurotransmitter, menopause, substance use disorders (SUDs)

1. Introduction

Substance use disorder (SUD) is defined by the uncontrolled chronic use of drugs and medications, such as cocaine and nicotine that leads to distress and harmful consequences in life [1]. Various research has shown vulnerability differences toward development of addiction across men and women, for instance men are more likely in abusing alcohol and illicit drugs than women. Whereas women have a higher tendency of developing comorbidity along with SUD, and seek help earlier than men do [1].

The gonadal hormone estradiol (E2) is believed not only play an essential role in the reproductive system and but also is believed to contribute to gender differences observed in SUD. The influence of the hormone extends beyond the scope of reproduction, affecting mood, motivation, memory and cognition [2]. E2 is generally found and synthesized in ovaries, fat tissue, and adrenal glands in female, whereas males produce them in the testicles, adrenal gland and pituitary glands [3]. Given the differences between males and females in production of estrogen, it suggests functional differences in response to hormone signaling within men and women. By directly regulating the dopaminergic,

serotonergic, and glutamatergic systems, E2 demonstrates crucial role in mood regulation and reward systems [3]. Many studies investigating psychiatric disorders using both animal models and patients have observed disturbances in estrogen level and its signaling, and these disturbances not only result in cognitive impairments but also amplifies the manifestation of symptoms, which could be treated by activating estrogen-signaling pathways with estrogen administration [4]. Disruptions of estrogen and estrogen-signaling pathways are related to a diverse spectrum of psychiatric disorders, such as major depression disorder (MDD), generalized anxiety disorder (GAD), schizophrenia, bipolar disorder, attention-deficit/hyperactivity Disorder (ADHD), autism spectrum disorder (ASD), post-traumatic stress disorder (PTSD), and eating disorders [4]. For women, because these sex differences contribute to the increased vulnerability toward these mood disorders and psychological problems [1,5], they are more likely to require initial drugs and medications for treatment, as a result, leading to a higher tendency of engaging in drug-seeking behavior.

2. Influences of Estradiol on Neurotransmitters Pathways

Estradiol is vital in regulating neurotransmitter systems as a neuroactive steroid, by mainly influencing neuronal circuits and brain functions such as learning, mood, reward and sexual behaviors [3]. Impact of estrogen on crucial neurotransmitter pathways - serotonin, dopamine, and glutamate are discussed.

2.1. Serotonin

Serotonin is a neurotransmitter and hormone that affects mood, digestion, sleep, wound healing and more. Research have shown a possible involvement of estrogen and estrogen receptors in the serotonergic pathway playing a role in regulating mood, therefore influencing mood disorders like anxiety and depression, which potentially lead to the initial drug seeking behavior [6,7]. Mood disorders is a common psychiatric comorbidity among SUD patients. Treating patients' mood disorders may consequently control SUD symptoms and reduce substance craving and abuse [8]. E2 binds to nuclear estrogen receptors α and β to exert its effect [9,10], where Erβ in particular influences the transcription of enzyme tryptophan hydroxylase (TPH), the regulatory enzyme of serotonin synthesis, which controls the amount of serotonin produced. Studies have also shown influences of E2 on serotonin reuptake transporter (SERT) which facilitates re-absoprtion of serotonin in the synaptic cleft [11]. Multiple research suggest that with ovariectomy caused decreasing in E2 level, SERT expression intensity, binding concentration, and 5-HT (+) cell concentration were significantly decreased [12,13]. Other studies discovered that in ovariectomized rats treated with estrogen showed increase in both expression and binding density in SERT mRNA [14]. In summary, by binding to receptor β, estrogen can up-regulate serotonin neuropathway, therefore participate in substance craving, learning, memory and emotional regulation.

2.2. Dopamine

Dopamine, as a neurotransmitter, serves as the "reward" of the brain and in many functions, including memory, movement, motivation, mood, attention and more. The ER subtypes ERα and Erβ are involved in regulating of tyrosine hydroxylase (TH) transcription, whereas TH is the rate-limiting enzyme of dopamine synthesis. Studies have suggested the two receptors work together in an alternating way to ensure tyrosine hydroxylase (TH) transcription rates remain at stable level, by responding differently to E2 concentrations. Maharjan and team reported increasing Erα activity when concentration of E2 is high, and decreased Erβ activity when E2 is presence, regardless its concentration. These results suggest Erα is up-regulated by E2 while Erβ is down-regulated. In addition to transcription within the dopaminergic system, E2 also exerts its effect on dopamine

receptor (D2), which is an auto-receptor in regulating the dopamine system. Parkinson's disease, schizophrenia, drug abuse and attention deficit hyperactivity disorder (ADHD) [15] are all related to disturbances in the auto-receptor activity. However, conflicting findings result in inconclusive outcomes in explaining the relationship between E2 and D2. Future experiments should be structured to ensure precise demonstration of relationship between E2 and dopamine. In addition, the need for incorporation of male subjects should also be taken into concern, and may offer insights to undiscovered new relationships between the two substances. By understanding better of the interplay among estrogen and its receptors linked to dopamine, development of potential treatments on neuropsychiatric disorders would be able to specifically target the influences of dopamine. Together, these studies suggest the significance of E2 in the dopaminergic system associated with reward and mood regulation [3].

2.3. Glutamate

With its excitatory function in the brain, glutamate plays a crucial part in neurotransmission, the onset of psychiatric disorders and synaptic plasticity, the latter one is considered to be the underlying mechanism of memory formation and learning. The N-methyl-D-aspartate (NMDA) receptor is a receptor of glutamate, where it binds to exert its excitatory effect to neurons. Many narcotics and drugs including ketamine and phencyclidine, two common drugs of abuse, inhibits the activity of neurons by blocking the NMDA receptor [16]. Interplay of glutamate with estrogen represents a crucial part in getting to know the underlying mechanism of mood regulation and mental health. Regulating synaptic function, estrogen is also considered crucial to emotional behavior, learning, and memory [3].

Treatments using E2 shown both enhancement in NMDA receptor-mediated excitatory postsynaptic potential, and increased number of NMDA receptor binding sites [17], suggesting a positive relationship between NMDA receptors and E2. The findings of enhancing hippocampal long-term potentiation [18], increase in dendritic spine density [19], and increased neural plasticity [3], pointing to the potential involvement of estrogen in neural plasticity. However, the contribution of estrogen to presynaptic function and the underlying signaling mechanisms of synaptic transmission governed by estrogenic regulation remains incompletely understood [3]. Experimental results indicate that estrogen excites the process of neural transmission by enhancing the increase of glutamate in the synaptic cleft. This is consistent with real life. Menopause is typically a significant period of low E2 for women during life time, and symptoms such as mood fluctuations are the result of decreased glutamate level in the medial prefrontal cortex. This relationship between estrogen concentration and glutamate levels may be an explanation for higher prevalence of depression in seniors [20].

Numerous studies have investigated the interaction between estrogen and glutamate, highlighting a complex relationship in neuro activities that includes excitatory neurotransmission, synaptic plasticity, and neuroprotection. While substantial efforts have been made in understanding the effects on postsynaptic mechanisms, the influence on presynaptic processes and the associated signaling pathway still require further investigation [3].

3. Estradiol Effect on the Dopamine Reward System

The system which mediates the transition from casual use to consistent substance use disorder are known as the reward system, as brain structures of the system are activated by rewarding stimuli signaled by intake of drugs. The pathways from the midbrain areas of the substantia nigra and ventral tegmental areas (VTA) releases dopamine, to nucleus accumbens, dorsal striatum, amygdala, and

prefrontal cortex, these are key structures in the brain contributing to development of addiction. All these projection pathways use dopamine as the neurotransmitter [21].

Adaptive rewarding stimuli will activate the dopaminergic reward systems within the ascending mesotelencephalic pathway. These stimuli, including food consumption, sexual behavior, and social interactions, are all necessary to produce motivation in retaining a healthy life and ensure reproductive success [22,23,24,25]. The incentive sensitization theory suggests the nature of drug addiction is the enhancement of the psychological feeling of "craving" resulted by repeated drug stimulation. This decreases dopamine receptors' sensitivity of and induces craving of drugs [25, 26]. Females are more sensitive to the above mentioned "incentive sensitization" than males, and this sensitivity was enhanced by the circulating estradiol. This fact could be the reason that explain why females have enhanced vulnerability of transitioning from intermittent drug use to chronic use [27, 28]. On the other hand, it was reported that women have stronger negative aspects of withdrawal effects, and this is the case for psychostimulants, and most other classes of drugs [1,29,30], and the severity of withdrawal effect is reported to be sync with gonadal hormones, this may be the evidence that estradiol is mediating drug use effects for women in both the positive and negative way [31].

Three main receptors of estradiol are E2 receptor alpha (α), beta (β), and GPER-1 [6]. Brain ER distribution studies have not found significant sex differences in ER expression, most likely because only limited studies that have include both males and females. But when experimental conditions are designed to optimize expression, certain sex-differences in ERs were noted in specific brain regions. Even though sex differences have not been studied in all brain regions, there are sex differences indicated in brain regions related to drug taking and addiction. Particularly, the ventral tegmental area and substantia nigra [32], the midbrain neurons projecting to prefrontal cortex [33], mesolimbic reward pathway [34], and striatal regions [35]. Therefore, these results indicate that estradiol could regulate habitual drug-seeking by affecting drug-related dopamine levels in these areas of the brain.

It is well known that either chronic or acute stress would very likely to cause drug seeking in both genders, because of the effect of estradiol on the hypothalamic-pituitary-adrenal (HPA) axis, this cause and effect is more obvious in female. Females have more obvious response to stress because of glucocorticoid production and their response to negative feedback is also enhance comparing to men [36,37]. Prenatal stress would result in drug-taking during adulthood in both males and females, but the mechanisms are different in them. During teenage years, along with growth spurt, with more sex differences appear, mood disorders usually have a higher incidence rate in females, which could be the reason for initial drug intake for self-medication. Once females become addicted, they also more likely to have stress-induced relapse than males. Males usually show a greater ability to get used to stress and therefore explain why stress is less of a risk factor for drug-seeking in this gender group [6] [38-41].

4. Discussion

Gender difference has been a special research field for many years, and the reasons for differences has been mostly attributed to gonadal hormones, namely estrogen and progestogen. In most cases, female hormones play a protective role, most well-known are cardiovascular diseases and endocrine diseases such as osteoporosis. In addition, estrogen also has been noted to work as protective factor on neurologic and psychiatric system. When we are looking into the gender differences among neurological and psychiatric disorders, the results seem to be quite interesting. While males seem to have higher prevalence of developmental onset disorders, for example, attention deficit and hyperactivity disorders (ADHD), autism spectrum disorders (ASDs), most neurodegenerative diseases, in another word, adult-onset disorders, such as Parkinson's disease (PD) and Alzheimer's disease (AD), have higher frequency in females [42,43,44], especially in menopause females, when circulating estrogen drops or depletes.

Investigations have been performed to understand the estrogens' function as neuroprotective agent. The result showed by binding to the receptor, E2 can regulate proliferation and differentiation in cells and act as anti-oxidants, increase DNA repair, improve cerebral blood flow and induce growth factor expression[45]. E2 has also been shown to have protective effect on dopamine neurons [46]. Interestingly, while estrogen works its neuroprotective role by stimulating dopamine and glutamate neurons, these effects also happen to be the mechanisms that potentiate females' vulnerability of addiction. In this case, there should be further study in investigating the estrogen effect during peri-menopause and menopause, as the circulating estrogen level drops; given its protective and risk factor role to neurodegenerative disorders and substance abuse, respectively. We would speculate that, when E2 decrease during menopause, it would reduce the vulnerability of addiction in women, whereas increase the vulnerability of degenerative diseases, such as AD and PD in this population at the same time. However, it was well known that, during menopause, E2 fluctuation causes more mood swing, requiring the need for medication in women. In addition, hormone replacement therapy has been widely used to treat different symptoms during this time, but could possibly potentiate the vulnerability of substance abuse and addiction. Future studies should examine how to balance hormone therapy to reduce menopause symptoms, protect the degenerative neurological disorder, and at the same time, reduce the risks for development or relapse of substance abuse.

Studies showed there are three different kind of estrogen receptors (Alpha, Beta, and novel G-protein-coupled receptor 1 (GPER1) located in different areas of the brain [47]. As well-known that, above mentioned three estrogen receptors all have protective role in cardiovascular system, they also have neuroprotective role in nervous system. Particularly, ERα can prevent the development of neurodegenerative diseases by stimulating Ca2+ influx and glutamate receptors [48], whereas activity of E2 and ERβ demonstrates a negative relationship [49]. All these evidences may potentially suggest that, by activating different estrogen receptors, different aspect of the estrogen function maybe stimulated, therefore can particularly avoid some of the unwanted side effects.

Literature search regarding the comorbidity of aging and addiction has been performed, which may impact on progression of disease and treatment outcomes in aging individuals who also happen to have history of substance use. A big gap has been noted in these fields of research, which has jeopardized the understanding and treatment choice for substance use disorders (SUDs) as well as aging related disorders, especially in women who are experiencing sudden reproductive cycle transitions during aging. It was also noted that when preclinical research was carried in the aging and addiction field, most experimental design usually failed to examine co-existing neurobehavioral mechanisms that may make these diseases worse. For instance, in the literature about preclinical study of addiction, people do not usually consider aging as a biological variable, in contrary, most researches only focus on young adult or adolescent animals [50]. Review also revealed that although some of the studies have the focus on aging and addiction interactions, most of them were just limited in tobacco and alcohol use, there are much more substance abuse related to aging need to be studied, ideally in both clinical and preclinical levels.

SUDs can be induced in progressive Parkinson animal models that created by chronic administration of neurotoxins [51]. Because of normal aging animals related to long time housing and limited feasibility, ovariectomy (OVX) could be performed to mimic menopause in already established SUD animals. Continue substance use or withdrawal behavior, as well as symptoms related to Parkinson should be monitored before and after the OVX, to monitor the reduced estrogen effects. Then, hormone replacement therapy can be provided by giving estrogen injection, or placebo as control, again substance addiction behavior and Parkinsons should be continuously monitored. Ideally, dynamic change on neurotranmitter, namely serotonin, glutamate and dopamine levels regulated by different concentration of estrogen could be monitored, a dose responsive curve be

generated. Neuroprotective vs addition potentiating effect hopefully can be monitored along the curve, to figure out a dosage regiment for hormone replacement therapy.

There are three different types of E2 receptors, they are known to be located in the different areas of the brains, and the location differs between two genders. This would potentially provide pharmacological targets and locations for hormone-based treatments in both males and females. In order to evaluate potential targets in the brain for the pharmaceutical development of addiction treatment drugs, it will be crucial to identify the receptors' characters including identity, location, function, and mechanism of action. In a study carried up by Shughrue group., a comprehensive review of whole brain, ER distribution and densities were compared among many different brain regions [40]. When comparing data for male and female, there are quite some data missing for male animals. By thoroughly studying and understanding their differences, there is potential possibility to use particular estrogen receptor agonist or antagonist to regulate more specific neurofunctions.

5. Conclusion

Estrogen alone has direct impacts on both neurodegenerative diseases and substance abuse, acting as a protective agent for the former and risk factor for the latter. This dual role is due to estrogen's regulation of three main neurotransmitters: dopamine, glutamate and serotonin. All three neurotransmitters have specific roles in the development of neurodegenerative diseases and substance abuse, up-regulation by estrogen through particular regulatory mechanisms, e.g. the neurotransmitters' rate-limiting enzymes activity and binding density of the estrogen receptors, give rise to diverse influences. Increase in estrogen level corresponds to increase in risk of substance abuse, but at the same time lowers the potential development of neurodegenerative diseases. The negative correlation between these disorders directs future studies in examining cases where the two disorders coexist. This includes exploring how treatments, such as hormone replacement therapy can be optimized to alleviate symptoms of neurodegenerative disorders without simultaneously increasing risk of substance abuse.

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