REVIEW

Sex Steroid Hormones in Depressive Disorders as a Basis for New Potential Treatment Strategies

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Summary

The sex steroid hormones (SSHs) such as testosterone, estradiol, progesterone, and their metabolites have important organizational and activational impacts on the brain during critical periods of brain development and in adulthood. A variety of slow and rapid mechanisms mediate both organizational and activational processes *via* intracellular or membrane receptors for SSHs. Physiological concentrations and distribution of SSHs in the brain result in normal brain development. Nevertheless, dysregulation of hormonal equilibrium may result in several mood disorders, including depressive disorders, later in adolescence or adulthood. Gender differences in cognitive abilities, emotions as well as the 2-3 times higher prevalence of depressive disorders in females, were already described. This implies that SSHs may play a role in the development of depressive disorders. In this review, we discuss preclinical and clinical studies linked to SSHs and development of depressive disorders. Our secondary aim includes a review of up-to-date knowledge about molecular mechanisms in the pathogenesis of depressive disorders. Understanding these molecular mechanisms might lead to significant treatment adjustments for patients with depressive disorders and to an amelioration of clinical outcomes for these patients. Nevertheless, the impact of SSHs on the brain in the context of the development of depressive disorders, progression, and treatment responsiveness is complex in nature, and depends upon several factors in concert such as gender, age, comorbidities, and general health conditions.

Key words

Affective disorders • Sex steroid receptors • Androgens • Brain structures • Molecular mechanism • Potential treatment strategy

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Introduction

Depression is not a unitary concept. Depressive disorders are classified as affective disorders according to the Diagnostic and Statistical Manual of Mental Disorders 5 [1]. There are many forms of depression including major depressive disorder, persistent depressive disorder (dysthymia), peripartum (postpartum) depression, disruptive mood dysregulation disorder, psychotic and seasonal depression, and premenstrual dysphoric disorder [2-4]. According to the World Health Organization, depressive disorders are among the most common psychiatric disorders that affect humans of all ages, with an estimated 3.8 % of the population suffering from at least one form of depression (including 5.0 % among adults and 5.7 % among adults older than 60 years) [5]. Along with other affective disorders, depressive disorders represent a worldwide problem with both socio-economic and general health burdens [6-8]. Interestingly, a recent meta-analysis showed that

depressive disorders are 2-3 times more common in women than men, while no differences are reported among the age groups [9]. Such sex differences in the prevalence of depressive disorders implies the sex steroid hormones (SSHs) play at least some role in the development of depressive disorders.

SSHs, including androgens, estrogens, and progesterone (P4) are crucial during the development of various brain structures throughout the critical prenatal and perinatal periods. These critical periods are known as organizational windows and are characterized by the interaction of hormones with immature neurons. This results in permanent changes in the structure and thus function of the brain with subsequent gender differences in behavior [10,11]. The organizational effects can be seen mainly within perinatal growth when the brain is more prone to the structural alterations. There are several other periods well known for structural organization within the brain, i.e. during puberty and adolescence. These organizational changes in the structure are believed to be long-term and last through adulthood [12,13]. One of the most well-known changes due to early androgen presence of the so-called sexually dimorphic nucleus includes the medial preoptic area of the hypothalamus. Early exposure to testosterone (T) characteristically organizes (increased density of neurons, increased dendritic spine density) this area towards more masculine behavior in adulthood [11]. Another example includes androgen induced neurogenesis and enhanced new neuron survival in the hippocampus (HIP) [14]. The mechanism behind these changes includes decreased basal activity in the hypothalamo-pituitary-adrenal axis (HPA) [15]. The list of brain structures involved in brain organization due to androgens is broad and is reviewed elsewhere [16].

On the other hand, the same SSHs have additional activational effects on neurons, thus affecting physiology and behavior. More about activational effects is described in chapter 5. These changes depend on the actual SSHs concentration in blood, especially when considering hormonal cycles (i.e. diurnal, circatrigintan or annual). Therefore, activational effects are usually fast, reversible, and short-term [10,11]. Generally, activational effects can play a role mainly in adulthood once organizational processes in brain structures are over, acting independently as well as in combination with organizational effects [12]. Overall, the effect of imbalanced SSHs on brain can result in the development of depressive disorders. Therefore, both organizational and activational effects of SSHs on the brain could affect behavioral outcomes later in life, particularly the development of depressive disorders [17,18].

Puberty and early adulthood are time periods with a high incidence of depressive disorders [7,19]. Aging is associated with SSHs concentration decline while on the other hand, the incidence of affective disorders and psychiatric syndromes increase. Though this is true for both, men and women [20], there is gender variability, indicating that females are approximately twice as prone to the development of depressive disorders when compared to males. Indeed, the females undergo more variation in the SSHs concentration, i.e. hormonal fluctuations during menstrual cycles, pregnancy, and after delivery, menopause, etc. [21]. Apart from such hormonal variation, it is believed that females are more prone to distress consequences, which may exacerbate affective disorder development [22]. Taken together, SSHs are significant regulators of cognitive functions and mood during prenatal/postnatal development but also in adulthood, and SSHs dysregulation may lead to the development of depressive disorders [23,24]. SSHs raised interest worldwide in terms of brain and behavior research for both animals [25-27] and humans [28-30]. In this review, we will focus on the role of SSHs in the context of depressive disorders *per se*, it will not include all disorders in which depressive syndrome may occur including for instance bipolar disorder, borderline personality disorder, etc.

Brain regions implicated in depressive disorders

Many brain regions are involved in depressive disorders including regions with higher functions related to stress response, memory formation, or emotion handling. The brain regions discussed in this review include the prefrontal cortex (PFC), amygdala (AMY), HIP, and hypothalamus (HYP). Implication of these brain regions can be gender specific [11,13]. Impairment of the structure or function of the PFC, AMY, HIP or HYP may result in affective disorders including depressive disorders [31].

The PFC manages cognitive functions related to executive decisions, social feeling [32,33] as well as self-control, self-esteem [34], and attention or planning [35,36]. Certainly, there are connections between the PFC and other brain regions, specifically to the AMY. This reciprocal link helps to regulate anxiety or fear in both

genders [37]. Apart from the interconnections with the PFC, the AMY plays a significant role in development of depressive disorders on its own. Fearful and threating stimuli are processed and tagged for their emotional value in the AMY along with further emotional processing and adequate response [38-40]. Functional magnetic resonance imaging studies consider the AMY as one of the main structures involved in the development of depressive disorders and its treatment [41]. Spatial navigation, emotions, and HPA axis regulation are part of HIP functioning [42]. Moreover, the linkage of the ventral HIP to the AMY predisposes the HIP to take its part in contextual fear conditioning [43,44] and thus potentially in the development of depressive disorders. Lastly, the HYP is part of a major neuroendocrine system and HPA axis, together with the hypothalamus-pituitary-gonadal (HPG) axis, are implicated in stress response, hence they may contribute to the regulation of depressive disorders [45].

Several neuroimaging studies revealed that impairment to neural structures or pathways of any of the PFC, AMY, HIP or HYP, especially in the critical organizational periods, can lead to the development of depressive disorders later in adolescence or adulthood [46-48]. Additionally, depressive disorders may be a result of a disarrangement of emotional or cognitive centers in the PFC [47] or HYP [48]. These brain areas express SSHs receptors, both intracellular and membrane-associated androgen (AR), estrogen (ERα, ERβ) or P4 receptors [49-52]. Recently, the transmembrane G-protein coupled estrogen receptor 1 (GPER1) has been found within the brain [53,54]. Also, the transmembrane receptor for androgen – Zinc transporter protein 9 (ZIP9), primarily found in the prostate, has also been detected in the brain [50,52].

As such, this review will discuss the perinatal influence of androgens, estrogens, and P4 on the PFC, AMY, HIP and HYP in the context of depressive disorders. Subsequently, the molecular mechanism of the pathogenesis of depressive disorders as well as the potential contribution of SSHs for new treatment strategies, will be reviewed.

Animal research

Depression-like behavior is assessed in laboratory rodents using various behavioral tests such as the forced swim test, tail suspension test, sucrose preference test [55], or novelty-induced hypophagia test [56]. In males, the effect of physiological concentrations of prenatal T may also be associated with neurogenesis and increased dendritic spine density in the HIP. This was shown in male rats treated neonatally with an antagonist of AR, flutamide, and tested prior to puberty with the forced swim test and sucrose preference test, in which authors observed a significant increase in a depression-like behavior. Moreover, neonatal treatment with flutamide inhibited neurogenesis (microtubular associated protein-2 neurons in cornu ammonis 1 region, and dentate gyrus), as well as the formation and decrease in neuronal dendritic spine density in the cornu ammonis 1 region of pre-pubertal male rats. These results indicated the antidepressant and neuroprotective properties and organizational effects of T *via* AR in pre-adolescent male rats [57]. During studies on non-human primates, the determination of prenatal T is even more challenging. The second digit to fourth digit ratio (2D:4D) represents a potential proxy marker for prenatal androgen concentration. Digit ratio 2D:4D correlates negatively with fetal T and positively with fetal estrogens, therefore, males have usually lower ratio in comparison to females [58,59]. For example, the measurement of prenatal T exposure was determined by the 2D:4D digit ratio *via* X-ray imaging in female cynomolgus monkeys (*Macaca fascicularis)*. The protective effect of physiological levels of prenatal T in female monkeys was observed. The longer 4th finger as well as lower 2D:4D ratio was observed in the control group in comparison to female monkeys with naturally occurring depression-like behavior [18]. These results indicate that higher 2D:4D ratio in females is positively correlated with depression-like behavior and so it may provide a predictive diagnostic tool for such behavior in non-human primates. The neuroprotective action of T in the HIP may include its ability to ameliorate the negative effects of stress or depression-like behavior and activate the signaling pathways leading to cellular growth, proliferation, and survival [60].

Human research

In children, prenatal and early postnatal dysregulation of T (lower salivary concentration) and cortisol (higher salivary concentration) represent a risk factor for affective disorder pathophysiology, especially in girls, who are more vulnerable to hormone dysregulation [61].

In boys, not only does the concentration of

prenatal T possibly influence depressive disorders but it also influences other components of the T signaling pathway, such as the genetic polymorphism of AR [62,63]. The importance of AR and its polymorphisms in the modulation of depressive disorders has been investigated in a clinical study that reported an association between CAG trinucleotide repeats in the AR gene and major depressive disorder in male children and adolescents. The length of CAG trinucleotide repeats, which codes the glutamine amino acid, is between 8-35 repetitions in healthy individuals. There is a negative correlation between the CAG repetitions and AR expression which negatively affect sensitivity and affinity to androgens [64-66]. A significant negative correlation between scores of the Center for Epidemiologic Studies Depression Scale and the Patient Health Questionnaire-9, that measure the severity of depressive symptoms, and the length of AR CAG repetitions, together with low salivary T, was found in male adolescents with major depressive disorder [62,63].

Genetic polymorphisms of the ERα gene play a significant role in the predisposition to depressive disorders in women. The genetic variant G allele (rs9340799) or C allele (rs2234693) of ERα have been specifically associated with an increased risk of recurrent depressive episodes in aged homozygous women (65 years old). In another study of ERα, the *PvuII* polymorphism of ERα appeared to be involved in the regulation of its expression. A significant positive association between *PvuII* ERα and major depressive disorder was found only in women subjects as compared to healthy women controls but not in depressed men compared to healthy men. This sex-different association may be another explanation to the twice-as-high level of susceptibility to depressive disorders in women [67]. In addition, genotype frequencies of single nucleotide polymorphisms in genes related to 17β-estradiol (E2) synthesis or metabolism in women suffering from depressive disorders were studied, where different polymorphisms in different genes were associated with greater odds of depressive disorders in pre-/peri-menopausal women from these ethnic groups: 1. Caucasian women with CC and AC genotype of rs2606345 polymorphism in cytochrome P450 (CYP) 1A1 gene compared to AA genotype (2-fold); 2. African American woman with CC genotype of rs2606345 polymorphism in CYP1A1 gene compared to AA genotype (10-fold); 3. Japanese women with TT genotype of rs936306 polymorphism in CYP 19 gene compared to CC (5-fold), and CT (9.6-fold) genotypes; 4. Chinese women with TT genotype of rs615942 polymorphism in 17HSD gene compared to GT (11-fold) and GG (>7-fold) genotypes [68].

To conclude, there is a very important genetic factor that affects the impact of SSHs on early brain development. Genetic variants of SSHs receptors or the polymorphisms of genes involved in SSHs signaling influence the effect of prenatal SSHs in both women and men. Certain polymorphisms in AR (CAG repetitions) or ERα (allele variant) may contribute to the development or the pathophysiology of depressive disorders in humans.

Regulation of depression-like behavior by SSHs and molecular interactions

In multiple animal and human studies, the antidepressant effects of SSHs were observed through classical signaling pathways of SSHs receptors such as the AR [69], ERβ [70], and P4 receptors [26,71]. However, non-classical signaling *via* transmembrane receptors such as GPER1 also appears to play a significant role in the pathophysiology of depressive disorders in both animals [17,72] and humans [73]. The relationship between the transmembrane AR ZIP9 and depressive disorders has not yet been described. Nevertheless, its expression has been detected not only in the gonads but also in the brain [51] suggesting a potential role of AR ZIP9 receptors in the development of affective disorders but this is the subject of future research.

SSHs receptors-related pathways in animal studies

The major signaling pathway of T in the development and progression of depressive disorders may be through AR. Intracellular AR deficiency exaggerates depression-like behavior in both male and female mice in sucrose preference and forced swim tests through brain-derived neurotrophic factor (BDNF) modulation in the chronic mild stress model of depression [74]. There is evidence that AR deficiency in male mice accelerates the development of depression-like behavior in a mouse model *via* altering miR-204-p3/BDNF/proteinkinase B/mitogen-activated protein kinase signaling pathways in the HIP [74]. Regarding the activational effects of T on depression-like behavior, treatments with physiological levels of T reversed depression-like behavior in socially isolated and gonadectomized adult male rats in sucrose

preference and novelty-induced hypophagia tests [56].

On the other hand, primiparous female rats also exhibit higher depression-like behavior 3 weeks postpartum, with recovery at 5 or 10 weeks postpartum compared with nulliparous females in the diestrus phase of the menstrual cycle. These behavioral changes were associated with lower ERα but not ERβ expression in the medial AMY. These results indicate that E2 *via* ERα signaling in the medial AMY may be responsible for the onset of depression-like behavior, at least in postpartum rats [75].

In nulliparous ovariectomized mice, lower depression-like behavior is the result of activation of ERβ but not ERα. This suggests an antidepressant effect of E2 *via* classical ERβ signaling pathways [76,77]. Similarly, lower depression-like behavior in the forced swim test was observed in ovariectomized rats following administration of ERβ selective modulators into the HIP [78]. These mechanisms are mediated predominantly by ERβ, but not by ERα signaling pathways in the HIP of ovariectomized mice [70,79]. In addition, ERβ signaling is involved in NACHT, LRR and PYD domains-containing protein 3 regulation, which may decrease depression-like behavior in ovariectomized mice [80].

Apart from "classic" signaling using ERα and ERβ, antidepressant-like effects of E2 might also be stimulated through the non-classical GPER1 pathway. This is supported by an experiment, wherein aged female rats were injected with GPER1 agonists such as G-1 (1-[4-(6-bromobenzo[1,3] dioxol-5yl)-3a,4,5,9b-tetra-hydro-3H-cyclopenta [c] quinolin-8-yl]-ethanone), E2, diarylpropionitrile, and subsequently tested in forced swim test, in which the rats spent significantly less time immobile compared to control rats. Moreover, G-1 enhanced hippocampal antioxidant capacity and stimulated the expression of ERα and ERβ [81]. GPER1 is also responsible for the inhibition of mitochondrial permeability transition pore opening and improvement of cardiac function through activation of mitogen-activated protein kinase signaling, which suggests its potential protective role in the brain [82]. Additionally, reduction of GPER1 or its impaired signaling during prenatal periods lead to depression-like behavior later in life [17]. Similarly, intracerebroventricular administration of the GPER1 antagonist G15 ((3aS*,4R*, 9bR*)-4-(6-Bromo-1,3-benzodioxol-5-yl)-3a,4,5,9b-3H-cyclopenta [c] quinoline), as well as genetic deletion of the GPER1 gene, in ovariectomized rats resulted in depression-like behavior in forced swim tests [72]. The antidepressant effects of GPER1 signaling might be mediated through protein kinase A signaling which further elevates translocation, protein phosphorylation, and normalizes the redox status in menopausal rats [72]. Moreover, prenatal reduction of GPER1 or its impaired signaling results in depression-like behavior in both female and male mice [17]. Results from these experiments indicate the neuroprotective and antidepressant-like effects of the GPER1 agonist G-1 and should be considered in the pathophysiology of depressive disorders.

Non-SSHs receptors-related pathways in animal studies

Lastly, ciliary neurotrophic factor (CNTF) has a key sex-specific role in the regulation of depression-like behavior in mice. Wild-type (WT) $CNTF^{+/+}$ female mice exhibit higher depression-like behavior compared to WT $CNTF^{+/+}$ male mice. Alternatively, $CNTF^{-/-}$ females exhibit lower depression-like behavior (reduced immobility time) compared to $CNTF^{-/-}$ males (higher immobility time) in the forced swim test. The sex-specific role of CNTF in the regulation of depression-like behavior was also confirmed by higher CNTF expression in WT $CNTF^{+/+}$ females than WT $CNTF^{+/+}$ male mice. Furthermore, P4 treatment reduced the expression of CNTF in the AMY of $CNTF^{+/+}$ females but not in $CNTF^{-/-}$ females. This study indicates relatively new sex-specific treatments for depression-like behavior, such as P4 in females and CNTF-stimulating drugs in males [83]. On top of that, several studies have examined the potential contribution of allopregnanolone (ALLO), which is a neuroactive metabolite of P4, in depression [84,85]. ALLO can be employed not only as a transcription factor, but also as a modulator of neuronal excitability by binding to the steroid binding site on the GABA A receptor [86]. In the HIP of female proestrus rats, high ALLO concentrations appear to have anti-depressant-like effects [87]. The role of the neuroactive steroid ALLO in depression-like behavior is associated with an elevation of BDNF/tropomyosin receptor kinase (Trk) B signaling in the HIP or PFC [85,88], activation of dopamine receptor-2, stimulation of glutamate neurotransmission, and increased Ca^{2+} release in both male and female rodents [85,89]. These molecular changes appear to be necessary for ALLO to provide anti-depressant-like effects, however, this association provides only circumstantial evidence for a causal relationship. The molecular mechanisms are summarized in Figure 1.

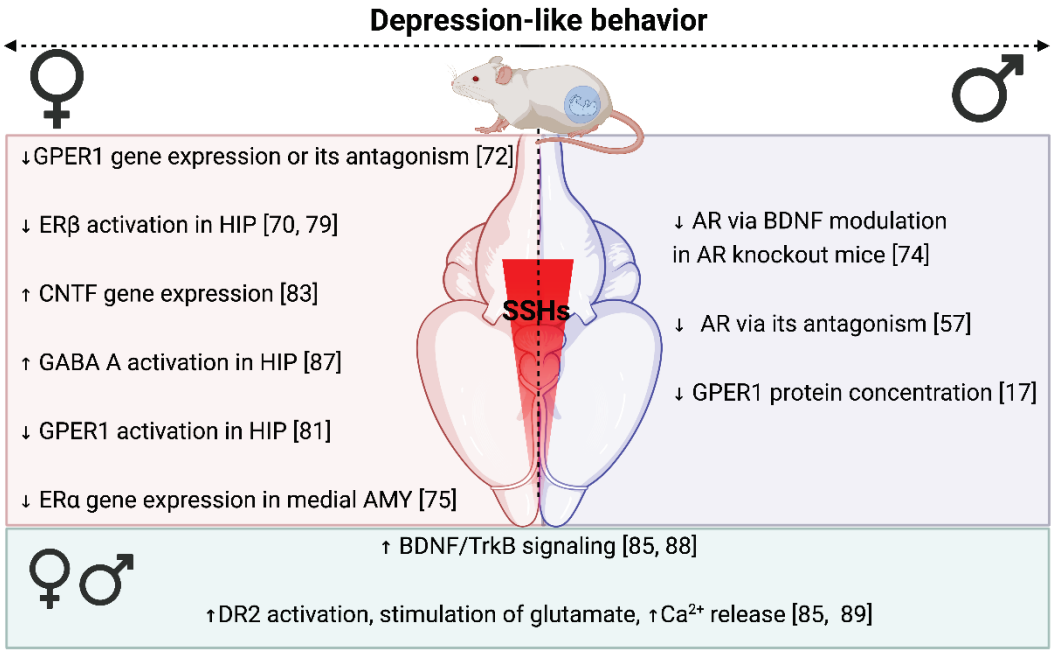

Fig. 1. Molecular mechanisms behind depression-like behavior in female and male rodents. AR – androgen receptor, ERα – estrogen receptor alpha, AMY – amygdala, HIP – hippocampus, GPER1 – G-protein-coupled estrogen receptor 1, CNTF – ciliary neurotrophic factor, GABA A – gamma-aminobutyric acid A, BDNF/TrkB – brain-derived neurotrophic factor/tropomyosin related kinase B, DR2 – dopamine receptor 2. Created with BioRender.com.

SSHs receptors-related pathways in human postmortem studies

The HYP and HIP are involved in depressive disorders through the HPA axis, which is a primary neuroendocrine system activated in stress situations. The pathway starts with increased corticotropin-releasing hormone release from the paraventricular nucleus of the HYP ending with cortisol release from the adrenal glands [90]. Estrogen-responsive elements are responsible for the beginning of the corticotropin-releasing hormone gene transcription [91], while androgen-responsive elements repress it. T is also believed to stop HPA activity [92]. In contrast, E2 likely activates the HPA axis *via* ERα [91]. Impaired equilibrium in receptor expression could interfere with the activation of the HPA axis in patients with depressive disorders.

GPER1 concentration in serum is higher in patients with major depressive disorder (18-50 years old) when compared to age-matched controls. Moreover, the authors found a positive correlation between the concentration of GPER1 in serum and depression scores. Elevated GPER1 concentration in serum was accurate in predicting the presence of depressive disorders and could be a candidate for a peripheral biomarker in generalized depressive disorders in both women and men [73]. These results are contradictory to the results from animal research, where reduction in GPER1 leads to higher depression-like behavior. The main reason for those discrepancies may be that the human study was limited to a small number of patients (34 women, 22 men) which also included only fertile individuals. Moreover, the cross-sectional design of human study limited obtained data. The GPER1 concentration in serum before and after treatment were missing. In rodent studies, animals are in controlled conditions, where the researchers may control the estrous/T diurnal cycles by ovariectomy/gonadectomy. Moreover, the role of GPER1 may be tested using various experimental designs involving GPER1 antagonists/agonists, knockout mice, and multiple molecular analyses of rodent tissue, which is not possible in human studies. Further studies need to be done to clarify the role of GPER1 in major depressive disorder in humans.

Non-SSHs receptors-related pathways in human postmortem studies

Regarding organizational changes of the brain during critical periods, BDNF is an important factor. It is responsible for the development, differentiation, and survival of neurons, growth of neurites, synaptic plasticity, synthesis of differentiating factors, and homeostasis, as well as modulation of affective-related behaviors [93-95]. Interestingly, a recent study showed, that a single nucleotide polymorphism of the BDNF gene

(Val66Met) appears to be implicated in the development of major depressive disorder more in men than women [96]. Another factor, the nerve growth factor (NGF), is a growth factor similar to BDNF. NGF is necessary for sympathetic and sensory neuron survival and maintenance, and is involved in the regulation of stress responses *via* the HPA axis [97,98]. Post-mortem studies of suicidal patients [99] or patients with major depressive disorder [100-102] showed morphological (e.g. cellular death, lower neurogenesis, and smaller neuron soma size) as well as molecular changes (e.g. reduced BDNF/TrkB and NGF/TrkA) in the HIP [103] suggesting that not only BDNF/TrkB signaling but also NGF/TrkA appears to be involved in pathophysiology as well as treatment for depressive disorders. SSHs such as T, E2, and P4 are implicated in the regulation of BDNF or NGF through which they may provide neuroprotection, neuron survival, and also antidepressant effects (Fig. 2) in human [96,101,102,104,105] and animal studies [79,88, 106-108].

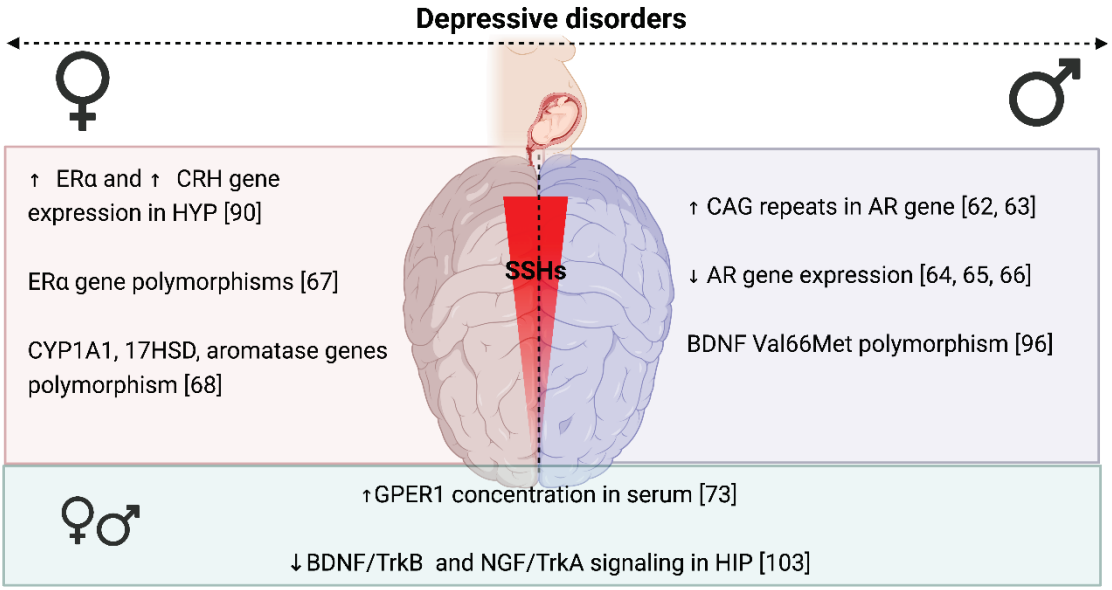

Fig. 2. Molecular mechanisms behind depressive disorders in women and men. AR – androgen receptor, ERα – estrogen receptor alfa, HIP – hippocampus, HYP – hypothalamus, CRH – corticotropin-releasing hormone, BDNF/TrkB – brain-derived neurotrophic factor/tropomyosin related kinase B, NGF/TrkA – nerve growth factor/tropomyosin receptor kinase A. Created with BioRender.com.

Where are we in clinical research?

Probably the best example is the postpartum depression. Recently, the Food and Drug Administration office approved intravenous ALLO treatment (brexanolone injections) for the treatment of postpartum depression in women [109]. The Food and Drug Administration office approved this medication based on the positive results from the 3 phases of clinical trials focused on safety and efficacy of brexanolone use for the treatment of moderate to severe post-partum depression [110]. The role of ALLO – the positive allosteric modulators of GABA A receptors in humans, is in motivation for the promotion of social contact. ALLO is increased during stress responses in humans [111]. In a pilot study, the expression of the enzyme converting P4 into ALLO – 5α-reductase 1, was examined in the PFC (Brodmann's area 9) of patients with depressive disorders. In depressed patients, the expression of 5α-reductase mRNA was approximately 3-times lower in comparison to healthy subjects. However, ALLO concentrations increased in depressed subjects after treatment with selective serotonin reuptake inhibitors or tricyclic antidepressants compared to non-treated depressed subjects [112]. Moreover, the concentration of ALLO was lower in the cerebrospinal fluid of patients with depressive disorders [113]. ALLO is considered one of the most potent SSHs with anti-depressant effects [114,115]. Several clinical studies are testing drugs that have potential anti-depressant effects *via* ALLO, such as fluoxetine [116,117], fluvoxamine [117], mirtazapine [118], olanzapine [119], carbamazepine [120,121], and brexanolone [122-124]. Another potential target for depressive disorder treatment related to the synthesis of ALLO appears to be the translocation protein, which is located on the outer mitochondrial membrane and

transports the cholesterol onto the inner mitochondrial membrane [85,125]. These studies of antidepressant drugs demonstrate the pharmacological effects and therapeutic potential of ALLO for the treatment of depressive disorders in humans [89].

In men, age-associated T deficiency (its concentrations in plasma declines for approximately 0.11 nmol/l each year after the age of 30) is strictly not comparable to women during menopause, although there is some overlap in its effect on mental health, i.e. it may lead to affective disorders including depressive disorders [126]. Clinically significant depressive symptomatology was also observed in 92.4 % of hypogonadal men (20-80 years-old). These symptoms were improved after 3 months of T replacement therapy and this improvement was maintained after 12-months in subcohort of less than 60-years-old patients [127]. Systematic reviews and meta-analysis of the antidepressant effects of T revealed significantly positive effects of T therapy in patients with depressive symptoms (men, 18-70 years old). Furthermore, the most efficient route of administration appeared to be the application of T gel [128]. However, a positive correlation between higher concentrations of T and anti-depressant effects is not broadly supported because of conflicting results from some controlled and randomized trials, discussed in the review [109,116-124]. The authors concluded that T therapy may have anti-depressant effects in specific populations such as men with early onset depressive disorders, hypogonadal men, or in men who are resistant to antidepressant drugs [129]. In another study, the group of patients that were more responsive to T treatment included hypogonadal men and middle-aged men with less severe depression or treatment for refractory depression [130]. Furthermore, T replacement therapy improves depressive symptoms in adult men who suffer from the type of depression with late-onset T deficiency; however, it is not an effective treatment in patients with major depressive disorder [131]. These results indicate that T should not be considered as a universal treatment for depressive disorders in men, but rather as a treatment with antidepressant effects in groups with certain health condition such as men with hypogonadism or with HIV/AIDS.

Conclusions

The high prevalence of depressive disorders warrants the search for additional pathophysiology processes to understand the basis of the disease along with potential novel therapies apart from standard therapy. Given the differences in the incidence of depressive disorders between females and males, the SSHs with their organizational and activational effects on brain structures [16] play a role in mood modulation. However, the metabolism of SSHs and neurosteroids is complex with a variety of activated membrane and/or intracellular receptors. Apart from AR and ERβ activation, GPER1, BDNF/TrκB signaling, and GABA A receptors within the serotonergic system can be implicated in both females and males and have a huge therapeutic potential. Those pathways should be considered in possible future treatment targets for research in the context of depressive disorders.

In conclusion, the studies discussed in this review indicate that SSHs and their metabolites (mainly ALLO) play a major role in the development of depressive disorders but their effect depends on the gender, age, comorbidities, general health condition, and the type of depressive disorder. The current state of the research does not allow us to conclude with a specific answer on which SSHs/pathway should be used as a treatment for depressive disorders but rather shows us the directions for future research. Future experiments should investigate the possible treatment strategies involving ALLO signaling *via* GABA A receptor, E2 signaling *via* GPER1, or BDNF/TrκB signaling alone or in combination with currently available treatment (selective serotonin reuptake inhibitors/tricyclic antidepressants). Specific types of depressive disorders as well as gender, age and health conditions should also be considered in experimental designs. Various combination strategies thus ought to be developed so as to bolster the positive mental health of both males and females.

Conflict of Interest

There is no conflict of interest.

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Abbreviations

2D:4D – second digit to fourth digit ratio, ALLO – allopregnanolone, AMY – amygdala, AR – androgen receptor, BDNF – brain-derived neurotrophic factor, CNTF – ciliary neurotrophic factor, CYP – cytochrome P450, E2 – estradiol, ER – estrogen receptor, GABA – gamma-aminobutyric acid, GPER1 – G-protein coupled estrogen receptor 1, HIP – hippocampus, HPA – hypothalamus-pituitary-adrenal axis, HPG – hypothalamus-pituitary-gonadal, HYP – hypothalamus, NGF – nerve growth factor, P4 – progesterone, PFC – prefrontal cortex, SSHs – sex steroid hormones, T – testosterone, TrkA – tropomyosin receptor kinase A, TrkB – tropomyosin receptor kinase B, WT – wild-type, ZIP9 – zinc transporter protein 9.

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