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Advances in Neurobiochemical Studies of Schizophrenia and Polycystic Ovary Syndrome

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Abstract: *Schizophrenia is a common and severely disabling mental disease, which has the characteristics of recurrent attacks, diverse clinical manifestations, complex pathogenesis, and can be accompanied by a variety of endocrine diseases. Polycystic ovary syndrome (PCOS) is an endocrine disorder disease characterized by androgen excess, ovulation dysfunction and polycystic ovary morphology. This article summarizes and briefly describes the related literature on neurobiochemistry, mainly including 5-hydroxytryptamine(5-HT), norepinephrine (NE), dopamine (DA), β-Endorphin(β-EP), acetylcholine(Ach)γ-Research progress on the changes of aminobutyric acid(GABA), glutamic acid and other neurotransmitters and receptors between schizophrenia and polycystic ovary syndrome. It can be concluded that schizophrenia and polycystic ovary syndrome are closely related in neurobiochemistry, and multiple neurotransmitters are involved in the occurrence and development of both. The changes of neurotransmitters directly or indirectly affect the development and remission of diseases, which provides a new treatment idea for the treatment of two diseases, comorbidity or prevention.*

Keywords: *Schizophrenia, Polycystic ovary syndrome, Neurobiochemistry, Review*

1. Introduction

Schizophrenia is a common and severely disabling chronic mental disorder of the brain.Late adolescence or early adulthood is the high incidence stage of the disease. Due to the high complexity of the neural circuit behind the cognitive abnormalities of schizophrenia, little is known about the cause of schizophrenia. In addition to the symbolic symptoms of psychosis (delusions, hallucinations, thinking disorders), individuals may experience negative symptoms (apathy, loss of emotional expression) and cognitive deficits[1]. Although the incidence of this disorder is relatively low (median 15.2 cases per 100 000 people per year), its lifetime prevalence is about 1%, and it is one of the major factors contributing to the global burden of disease, with one of the highest mortality rates among all mental disorders[2–4]. New meta-analysis believe that the risk of a premature death in patients with schizophrenia are twice as likely to, the average life expectancy shortened 15 years or so [5,6]. Among patients with schizophrenia, up to 40% of female patients have menstrual dysfunction, cycle disorder and metabolic abnormalities[7] ,compared with schizophrenic women with menstrual cycle disorder, female patients with regular menstrual cycle have better overall cognitive function[8].

Polycystic ovary syndrome (PCOS) is one of the most common metabolic disorder among women of childbearing age, affecting 6% - 10% of women of childbearing age and often developing in adolescence[9]. PCOS presents with typical clinical features of hyperandrogenism (including acne, hirsutism, and male pattern alopecia) and reproductive dysfunction (including oligomenorrhea and associated subfertility), of which excessive androgen production by the ovaries is a key feature of PCOS[10]. Moreover, PCOS is associated with a variety of metabolic diseases, including insulin resistance, impaired glucose tolerance, type 2 diabetes, dyslipidemia, compensatory hyperinsulinemia, obesity, etc[11]. Previous studies have confirmed that PCOS patients have a high prevalence of mental complications,56.9% of PCOS women have at least one mental disorder, of which emotional disorder is the dominant, and the prevalence of clustering is as high as 80% [12]. Previous studies have found that the incidence of PCOS in female patients with schizophrenia treated with atypical antipsychotics is significantly higher than that in normal controls, and the hormone levels of these patients may be related to low testosterone and different luteinizing hormone (LH) levels, and atypical antipsychotic

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treatment is associated with metabolic syndrome, which can lead to type 2 diabetes and/or high lipid deposition[13,14].

Previous studies showed that patients with PCOS to increase the predisposition to schizophrenia, it may be associated with common potential mechanism between them. At the same time, there are clinical similarities between the adverse reactions of atypical antipsychotics and the symptoms of PCOS. Chen et al.[15] found that patients with PCOS increased risk for schizophrenia, treatment with metformin PCOS has positive effect to the schizophrenia. In addition, for women with PCOS and schizophrenia, antipsychotic treatment can worsen the symptoms of PCOS, and have a negative impact on women's reproductive potential and quality of life[16]. The above research shows that the pathogenesis of the two diseases is similar in neurobiochemical aspects. This article discusses the changes between schizophrenia and PCOS from the perspective of neurotransmitters, and briefly elucidates the correlation between them.

2. Neurotransmitters

2.1 Dopamine (DA)

DA is an important monoamine neurotransmitter in the brain, produced in the ventral tegmental area (VTA) of the substantia nigra, especially in the hypothalamus and midbrain, and is a modulator of reproductive function at many levels along the hypothalamic-pituitary-gonadal axis[17]. Ganesh et al.[18]found that DA in pain regulation, social behavior and reproductive plays a different role. Javaid et al.[19] found that the plasma DA level of women with PCOS was significantly higher than that of normal women. However, in patients with schizophrenia, the increased synthesis and release of subcortical DA are closely related to positive symptoms as well as hallucinations and delusions, indicating that the symptoms of psychotic patients tend to worsen[20]. A large amount of evidence has proved that the mesolimbic and nigrostriatal DA system responsiveness is higher and DA synthesis is enhanced in schizophrenia[21]. Frankle et al.[22] found that subjects with schizophrenia had an excess of presynaptic DA and a release defect in the cortical regions of the brain. The dysfunction of DA function in cerebral cortex is considered to be a central part of the pathophysiology of schizophrenia. The increase of DA in the striatum is considered to be the basis of the positive symptoms, a high level of DA associated with psychotic symptoms. In the ventral striatum, low levels of DA are associated with negative symptoms[23]. From these studies, we can find that changes in DA function, especially high DA levels, are associated with psychotic symptoms and PCOS. Although different researchers have different opinions, it is clear that emotional transmitters affect the hypothalamic-pituitary-gonadal axis, thereby affecting the release of GnRH, and then the diversification of clinical symptoms caused by the endocrine disorders of PCOS.

2.2 Noradrenaline (NE)

NE is synthesized and secreted by sympathetic postganglionic neurons and noradrenergic neurons in the brain, mainly present in the locus coeruleus nucleus of the brainstem, and extensively projected to the whole brain and spinal cord, regulating behavior and consciousness related to various neurological diseases. Studies have found that sympathetic overactivation is related to the pathogenesis of PCOS in humans and rodents, and NE as an important activator has a positive correlation with PCOS. NE in the ovary regulates steroid hormone secretion and follicular development through its action on β-adrenergic receptors in ovarian follicles[24]and has a bidirectional regulation effect on the release of 5-HT, and can also interact with 5-HT. Its mode of action mainly depends on the type and location of the receptor. Among them, 3-methoxy-4-hydroxyphenyl diol (MHPG), a central metabolite of NE, has been found to be significantly increased in plasma and urine of PCOS patients, and MHPG is positively correlated with LH, and MHPG is positively correlated with dehydroepiandrosterone sulfate (DHEA-S). Women with PCOS have an increased density of ovarian adrenergic fibers, which may affect ovarian steroidogenesis [25]. Similarly, NE is related to negative and cognitive symptoms of schizophrenia, and regulates brain function through interaction with the DA system[26]. Carnac et al.[27] found that the expression of norepinephrine transporter (NET) increased in schizophrenia model mice, and the increased NET expression led to increased neuronal uptake of NE and DA from extracellular, which resulted in increased presynaptic conversion of DA to NE, and then affected the reduction of DA level and increase of NE level in presynaptic neuronal vesicles. Savransky et al.[28] examined the relationship between cumulative overnight urinary NE levels and memory ability in patients with schizophrenia and healthy controls and showed that high peripheral overnight urinary NE levels were

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associated with reduced memory ability in patients with schizophrenia, suggesting that high levels of central NE may contribute to memory impairment. The above studies suggest that NE is involved in the pathogenesis of PCOS and schizophrenia, but the causal relationship between the level of NE and the two still needs further research and demonstration.

2.3 5-hydroxytryptamine (also known as serotonin, 5-HT)

Most 5-HT in the human body is synthesized, stored and released by intestinal chromaffin cells, and a small part of 5-HT is produced in the brain as a neurotransmitter through tryptophan hydroxylase 2 (TpH2) in serotonergic neurons, playing an important role in neural regulation[29]. Previous studies have shown that 5-HT axons terminate on GnRH neurons in the hypothalamus and that 5-HT regulates the gene expression and secretion of GnRH by activating specific 5-HT receptors, which then act on pituitary gonadotropins to stimulate the synthesis and release of FSH and LH[30]. Previous studies have shown that when the synthesis of 5-HT in brain tissue is reduced, the synthesis of GnRH in hypothalamus is limited, which further affects the level of LH in peripheral blood, mainly by inhibiting its secretion[31]. Some studies have found that there is a positive correlation between DA and sensorimotor activity of the cerebral cortex, while there is an opposite relationship between 5-HT and sensorimotor activity of the cerebral cortex[32], which can be understood as increasing the effectiveness of 5-HT, the sensorimotor activity of the cerebral cortex decreases. Cardinale et al.[33] found that the levels of 5-HT and its metabolite 5-hydroxyindoleacetic acid (5-HIAA) were significantly reduced in infertile patients with PCOS, and low levels of serum 5-HT and DA metabolites were associated with changes in LH secretion. In addition to the regulation of 5-hydroxytryptamine at hypothalamic level on ovarian function, 5-HT is also directly involved in the regulation within the ovary[30]. It is reported that the negative symptoms of schizophrenia are related to the dysfunction of DA and 5-HT neurons[34]. In schizophrenia, stress-induced 5-HT overload in the dorsal raphe nucleus (DRN) can interfere with the activity of cortical neurons, and chronic extensive stress-induced 5-HT overload in the cerebral cortex, especially in the anterior cingulate cortex (ACC) and dorsolateral frontal cortex (DLFL), is the basis for the development of the disease[35]. Some scholars found that in patients with chronic schizophrenia, the concentration of 5-HT and 5-HIAA in their blood, urine and cerebrospinal fluid are significantly increased[36]but another scholars found that the lower the serum 5-HT level of schizophrenia patients, the greater the nerve damage, the more serious the condition[37]. A molecular positron emission tomography (PET) study has shown that serotonergic neurotransmission is involved in insight deficiency in schizophrenia and that there is a significant negative correlation between insight level and the availability of 5-HT transporter in the prefrontal lobe[38] .

Therefore, the abnormal level of 5-HT in both schizophrenia and PCOS patients may indicate a certain relationship between the pathogenesis of schizophrenia and PCOS. 5-HT plays the role of synthase in nerve cells, and also affects the regulation of other neurotransmitters. However, the research hypothesis of 5-HT on schizophrenia is still different, and further research is needed.

2.4 γ- Aminobutyric acid (GABA)

GABA neurons play a very important role in the reproductive system and cognitive function. Increased GABA activity in the brain and hyperactivity of the hypothalamic-pituitary-gonadal axis (HPG) are both related to the pathogenesis of PCOS. The long-term selective activation of gabaergic neuron terminals in the arcinate nucleus of PCOS patients leads to abnormal increase of GABA level in cerebrospinal fluid, which in turn promotes the hyperactivity of GnRH neurons and a significant and continuous increase in LH secretion[39]. GABA is also related to the development of schizophrenia,and the lack of GABA will lead to cognitive dysfunction, usually affecting the working memory of patients with schizophrenia. So far, several studies have shown that alterations in GABA neurotransmission, particularly in the dorolateral prefrontal cortex, contribute to impaired working memory in schizophrenia[40]. Sawahata et al.[41]found that in the prefrontal cortex and hippocampus of schizophrenic patients, the amount of reelin secreted by GABA neurons was significantly reduced.

2.5 Acetylcholine (Ach)

Previous studies have shown that GnRH inhibitory neurotransmitters decreased in PCOS patients, such as Ach, 5-HT and GABA, and increased major excitatory neurotransmitters such as glutamate. In a clinical study, after excluding patients who had recently ovulated, serum LH concentration and LH/FSH ratio in PCOS women increased by 75% and 94% respectively, persistently elevated LH

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concentration and increased LH/FSH ratio suggest an overactive GnRH secretion and ultimately aggravate the progression of PCOS[39]. Linares et al. found that in PCOS rats, the cholinergic system regulates the secretion of steroid hormones in a stimulating manner, for example Ach, which is involved in the regulation of progesterone secretion[42]. In addition, there is substantial evidence that cholinergic dysfunction is associated with schizophrenia, nicotinic Ach receptor down-regulation is associated with negative symptoms, muscarinic Ach receptor down-regulation is associated with positive symptoms, and down-regulation of both Ach receptors is associated with cognitive impairment[43].

2.6 Other neurotransmitters

In addition, β-endorphin (β-EP), glutamate and other changes are associated with schizophrenia and the pathogenesis of PCOS. Urban et al.[44,45] successively reported two studies, which found that the level of β-EP in patients with schizophrenia was significantly higher than that in healthy controls, especially in patients with chronic schizophrenia. β- EP directly inhibits the activity of GnRH neurons by binding to its receptors, thereby inhibiting GnRH secretion. Some scholars' studies on PCOS animals and patients have pointed out that acupuncture can regulate the production and secretion of β-EP in the central and peripheral areas, thereby affecting the release of GnRH[46]. Kialka et al.[47] found that compared with healthy controls, such as β-EP higher levels of PCOS group, β-EP associated with other sex hormone levels at the same time, it shows that endogenous opioids play a role in the pathogenesis of PCOS, and the increase of plasma concentration of β-EP can increase pressure pain threshold value, can adjust the pain perception of PCOS women. Glutamate , the precursor of GABA, has an opposite effect on psychiatric symptoms. Glutamate has an important impact on anxiety, cognitive function, and motor muscle function. When its concentration is low, it can show positive symptoms such as restlessness, excitement, hallucination, and delusion.

3. Summary and Outlook

Reviewing previous research results, there are multiple evidences proving the common connection between schizophrenia and PCOS. Their pathogenesis and clinical manifestations are complex and diverse, and even at the same time have a variety of neurotransmitters participate in the pathogenesis of both, each kind of dynamic change of the neurotransmitter directly or indirectly affect the development of both diseases. For a long time, although our research on both diseases has been deepening and the understanding of disease pathophysiology has been greatly improved, but the potential neurobiological determinants of schizophrenia remain largely undefined, and there are no reliable biomarkers to help objective diagnosis and clinical treatment, so further in-depth research is needed.

As a kind of endogenous chemical substance, neurotransmitter plays a vital role in maintaining normal life activities of human body. If the level of abnormal neurotransmitters in the body can be adjusted through artificial intervention treatment, and then the overall neuroendocrine function can be regulated, it provides a new treatment idea for the treatment of two diseases, comorbidity or prevention. Therefore, exploring how the neurotransmitters in the human body jointly participate in the pathogenesis and treatment of schizophrenia and PCOS to find reliable biomarkers is still the focus of future research. In addition, previous studies have proved the coexistence of neurotransmitters by using a variety of chemical methods, that is, a neuron in the central and peripheral nervous systems contains a variety of neurotransmitters, and various neurotransmitters are inextricably linked. Changes in the concentration of a neurotransmitter, or even its concentration in a certain organ or tissue, may induce a series of psychiatric and endocrine symptoms, Therefore, the study of the interaction between the neurotransmitters has gradually shown significant research potential. In addition, we can also clarify the pathogenesis of both diseases from the perspective of histone modification on the regulation of neurotransmitters. Through further experimental research and analysis, we can further promote the development of pathogenesis and find effective therapeutic targets as soon as possible.

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