Relevant Factors of Depressive Disorders: From the View of Lung Diseases and Serotonin

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Abstract: Long term clinical studies suggest that some lung diseases patients are always experiencing depression after diagnosis. Especially for lung cancer and inflammatory reaction, patients feel depression and even worsen into depressive disorder in a high rate. Recent year, studies about neurotransmitters and hormones are showing that serotonin related pathways could play an important role in triggering depression and finding possible treatments. This review mainly focuses on relative topics and discuss possible direction of future research. Depression disorder is a very common type of mental disorder. Long term clinical studies suggest that patients with some kind of lung diseases sometimes have relative higher risk of experiencing depression after diagnosis. Especially, patients' feeling of depression might even gradually worsen into depressive disorder. With more and more research and clinical reports about lung disease patients presenting, lung cancer and inflammation on lung are identified as main types of lung diseases that commonly accompany with depression. Recent studies about neurotransmitters and hormones are showing that serotonin related pathways in lung could play an important role in triggering depression and finding possible treatments. Genetic study about mutation in patients' lung indicate the concentration of serotonin is affected by several different pathways including serotonin re-uptaking and transportation. This review mainly focuses on topics related to serotonin and lung, discussing possible direction of future research.

1. Introduction

Facilitated by the increasing instrumental versatility and accuracy, modern science has built a deep understanding about the cellular and molecular mechanism of emotion regulation. Traditional thinking about psychiatric disorders (or emotion disorder) mainly focuses on the neural circuits inside the brain, which, of course, dominate most neural activities of human. Many

research about neurotransmitters for example, Glutamate and γ-aminobutyric acid (GABA) have been attributed to the function of modulating neural signaling and in further step, affecting the activities of major components of brain like hippocampus and amygdala in order to change emotion [1]. Specifically, many neurological diseases such as major depressive disorder (MDD) have been shown that they have very direct connection with the neuro-status of amygdala. Analysis of functional magnetic resonance imaging (fMRI) data getting from patients with MDD have directly proven that this type of depression is associated with amygdala [2].

However, rather than solely studying these pathological pathways in central nerve system (CNS), genetic deficiencies or dysfunction in other body systems are also capable to excite action potential (AP) through peripheral nervous system (PNS) to disrupt the normal functionality of some important parts including amygdala in central nerve system. One typical example would be the lung and brain. New pollution research has shown that neuroimmune effects in CNS and concentration of many signaling ligands in immune system including several different types of chemokine could be changed through "brain-lung axis" using animal-based models [3]. Besides, recent study also shows that central

nerve system could be affected by the environment through lung, which indicate the relation between lung and CNS from another angle [4]. To further understand depression, this review will primarily discuss neuro-pathology in nerve system from the view of lung and serotonin.

2. Clinical manifestation of relation between lung and mental disorder

2.1 Cancer-depression demographic relation

Modern pathological analysis has helped scientists find more clues of possible mechanisms under mental disorders. For many different types of neural diseases for instance, depression and anxiety, it has been found that lung is affected by some other factors including lung cancer and then in-directly related with depression and anxiety. Regional research with 1022 young lung cancer patient database in Taiwan applies mathematic algorithm to analyzing the risky factors among those patients, showing that lung cancer patients with other distinct kind of diseases including asthma, cardiac diseases, liver cirrhosis and so on are all living with the feeling of depression and anxiety in various levels [5]. In fact, patients with lung cancer in many different places around the world have shown such relation. Another long-term research with even larger patient group (27234 patients) also suggest that the relation of depressive disorder and lung cancer is somewhat general, which has no significant difference with different gender, age, race and color [6].

Besides, the possibility of patients with lung cancer getting depressive disorder is also not same with those who have other kind of cancer, which have particular medical interest in helping decrease the level of depression for those patients. In the last twenty years many related studies are carried, trying to explicate the reason behind this. Today, scientists have basically conformed that patient with lung cancer might have higher chance to be diagnosed as depressive disorder, especially those who are in elder age [7]. Study conducted to investigate the cellular and molecular reason why there is such a positive relation have found that hypothalamic–pituitary–adrenal (HPA) axis and pro-inflammatory cytokines might be one key factor associate with lung cancer patients' depressive symptomatology [8]. However, until today, scientists still not fully understand why lung cancer is related with depression.

2.2 Lung immune activities related depression

Apart from lung cancer, lung's immune activities commonly like inflammation is also a well-known factor associated with depressive disorder and now many studies imply they might have a positive relation. Especially with the development of psychoneuroimmunology, by studying and identifying different immunological biomarkers' role in different system containing brain and lung, more and more molecular mechanisms about biological signaling pathways are combined into interdisciplinary study like neuroscience to help explain why patients get psychiatric disorders and develop related clinical treatment [9]. Recent chemical analysis of immunological pathways has suggested a positive relation between depression patients and activation of inflammatory pathways, which include concentration increasing of proinflammatory cytokines, acute-phase proteins and the genetic expression level of chemokines [10]. For lung cancer patients, this inflammation-relation is becoming particular obvious. After measuring and analyzing the amount of several different interpretable chemical markers like C-reactive protein and albumin, the result from lung cancer patients manifests some interesting relation: lower albumin and higher CRP are coupled with depressive symptom in a relative high level, which could be used to help identify inflammation related depression [11].

3. Serotonin related pathways of depressive disorder and relation with lung

For lung, it has been figured out that the amount of serotonin could control the development

3.1 Serotonin related genes' effects on depression

Serotonin is a common neurotransmitter in nerve system throughout the body. It also has the ability to act as hormones. Many types of genes mutation could affect the concentration serotonin and the amount of serotonin receptors. Those genes regulate the activity of nerve system and then link to

patients' depression. Until now, many different mutations have been identified to be relevant with depressive disorder. Early study about a short variant of the serotonin transporter (5-HTT) gene reveals that 5-HTT increase the depression in patients for both male and female by affecting 5-HTT linked functional polymorphic region (5-HTTLPR), which may alleviate stress level of patients [12]. Nowadays, scientists' understanding about how serotonin related genetic mutations regulate have been improved due to the development of new bio-chemical approaches. Selective 5-HT reuptake inhibitors (SSRIs) could change the rejuvenate serotonin and combining with neurotrophic BDNF's effect, make it capable of rearranging developmental plasticity [13]. When neuroplasticity is changed, synaptic plasticity is changed as well. This change is attributed to induce some kind of depressive disorder because they might mediate the signal transduction between long term synapsis, which is the reason why it might cause long-term depression (LTD) [14]. Serotonin up-taking related proteins are also found have direct association with depression. Several studies of major depressive disorder (MDD) indicate that chemicals like SSRIs, serotonin–norepinephrine reuptake inhibitors (SNRIs) and agomelatine could affect serotonergic receptor 5-hydroxytryptamine receptor 2C (5-HT-2C) antagonism to treat MDD, where agomelatine seems to be the most promising candidate due to its unique chronobiotic effects [15].

3.2 Serotonin's effects on lung

Gene expression of serotonin in lung is very crucial for human developmental process and large amount of serotonin is produced by or affect lung cells. Environmental factors could alter serotonin related activities on lung to further impact neural system. When ozone pollutants are existing in the environment, there is an obvious disturbance to the expressional level of serotonin related genes including both 5-HT2AR and 5-HT4R, which not only changes the concentration of serotonin but also trigger irregular immune reactions based on animal model [16]. In fact, immune system is relatively sensitive to the serotonin changing, meaning that many genetic pathways of serotonin are affected through immunological activities like inflammation. For instance, another animal-model based experiment also shows that serotonin transporter (SERT) in lung tissues could seriously increase the lung inflammation under and even increase mortality [17]. Therefore, by regulating the immune reactions, serotonin-controlled genes on lung are capable of other systems normal functionality and normal developmental process.

4. Future direction: lung and depression

For future researchers, there are three main questions that need to be answered to get a comprehensive result of the relation between lung and depression. First question: how and which part in CNS are connected with lung and lung related depression. The most important function of lung is to control breathing. Specific parts of human brain like amygdala are closely associate with breathing activities. Actually, there has been large-scale demographic study found that limitation of lung function is always combined with higher possibility of mental health disorder [18]. Functional magnetic resonance imaging measurement of MDD patients with specific methylation changing in serotonin transporter gene (SLC6A4) expression have found that patients show decreasing in amygdala reactivity, which might be theoretically attributed to stress-adaptive epigenetic process [19]. Thus, apart from impacting immune system through lung, serotonin and brain could have rather direct "communication". However, relative studies about how it is associated with lung is rather restricted.

Second question: which kind of lung diseases are typically relevant to depression? Researchers did show some relation from the angle of respiration and depression: clinical symptoms that could limit breath ability like Chronic Obstructive Lung Disease (GOLD) are always psycho-pathologically combining with comorbidities including depression and anxiety, which is a direct inflammatory response of the lungs [20]. Recent chronic obstructive pulmonary disease (COPD) analysis exhibits the mental state of COPD patient is strongly affect by depression with some patients even thinking about suicide [21]. If inflammation of lung is an important reason of depression, in the future, researchers might combine the serotonin related inflammation pathways to understand the reason of

depressive disorder in the further step. Other types respiration difficulties also relate lung and depression tightly. Especially for patients with asthma or chronic bronchitis, the restriction of airflow in lung generally links with mental health issue including anxiety and depression [22]. Research about smoking suggest that SLC6A4 gene variation influence depressive symptoms perhaps through COPD etiology as well [23].

Third question: Could lung affect depression through other systems? Another interesting depression pathways might be the possible effects of serotonin on cardiac system combining with serotonin and respiration system, which have shown linkage between serotonin related gene's variants and mental stress clinically, but molecular mechanisms still need further clarifying [24].

5. Conclusion

Until now, many clinical relations between lung diseases and depression have been found by patient studies. What is the exactly bio-chemical pathway of depression through lung still remain mysterious. However, genetic reasons are showing that mutation affect neural system through changing serotonin concentration, which shed the light on how lung diseases related depressive disorder possibly forms. More studies need to be done in the future to figure out the relation of lung diseases and depression.

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