Depression and the immune system

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According to the National Institute of Mental Health, depression is one of the most common mental disorders experienced by Americans (NIMH, 2018). There is leading evidence to conclude that this mental disorder involves malfunctioning parts of the immune system. This research paper aims to discuss a brief overview of the disease, the various treatment options that are available for patients, how macrophages play a key role in depression, and the various areas of research that are still poorly misunderstood such as the food-gut allergy behavior axis, several brain stimulation therapies, and how depression is linked to various parts of the neuroendocrine system.

Depression is a mental disorder that is characterized by persistent feelings of sadness, anxiety, hopelessness and worthlessness, fatigue and low energy, difficulty concentrating and sleeping, appetite or weight fluctuations, and suicidal thoughts (McCarron, 2016). It has the capacity to affect individuals differently and can occur for weeks, months or several years (McCarron, 2016). Depression is diagnosed when an individual displays 5 or more of the symptoms included in the DSM-5 (diagnostic and statistical manual for mental disorders fifth edition revised) criteria (McCarron, 2016). Studies from 2016 show that 16. 2 million adults in the United states experienced a major depressive episode, which is a 2-week period that involves depressed mood along with displaying at least 4 symptoms of depression in the DSM-5 criteria (NIMH, 2018). The prevalence of these major depressive episodes in adults were also higher in women than men (NIMH, 2018). This mental disease is oftentimes diagnosed in adulthood and is caused by a variety of genetic, psychological, and environmental factors (NIMH, 2018). Risk factors associated with depression include alcohol dependence, female sex, family

history of depression, postpartum, chronic medical illnesses, and recent stressful events (McCarron, 2016).

Treatment of depression usually involves antidepressant medications, psychotherapy, or a combination of both (NIMH, 2018). Factors that decide which treatment option is the most beneficial for the patient include patient preference, past treatment history, and the severity of depression (McCarron, 2016). When these traditional therapies do not work for patients with severe depression, brain stimulation therapies may be considered. However, many of these stimulation therapies are still being researched and studied for efficacy. Antidepressants alter the way the brain secretes neurotransmitters that control a person's mood (NIMH, 2018). Drug selection depends on the patient's tolerability, safety, severity of depression, cost, potential for drug-drug interactions, and the presence of severe medical conditions (McCarron, 2016). Clinicians have a variety of antidepressants to choose from including SSRIs (selective serotonin reuptake inhibitors), TCA (tricyclic antidepressants), and MAOIs (monoamine oxidase inhibitors) (McCarron, 2016). Psychotherapy, on the other hand, involves face-to-face therapy and counseling including cognitive-behavioral therapy, interpersonal therapy, and problem-solving therapy (NIMH, 2018). Psychotherapy is usually considered for treatment options when the patient exhibits interpersonal problems, psychosocial stressors, or personality disorders (McCarron, 2016).

Based on studies and research done on depression, there is evidence to conclude that macrophage activation plays a key role in the development of this mental disease (Smith, 1991). Specifically, there is strong evidence that suggests that the secretion of various monokines from macrophages leads to

neuroendocrine abnormalities that are characteristic of depressed patients (Holtzheimer, 2006). Macrophages secrete various monokines such as IL-1, TNF (tumor necrosis factor), and INF-alpha that directly influence the endocrine system (Smith 1991). Specifically, IL-1 is linked to HPA (hypothalamic-pituitary adrenal axis) activity and stimulates the secretion of several hormones including ACTH (adrenocorticotropic hormone), PRL (prolactin), and GH (growth hormone) (Smith 1991). Patients that suffer with depression oftentimes have decreased functionality of the HPA axis that can lead to hypersecretion/hyposecretion of certain hormones. According to the Macrophage Theory of Depression, patients with depression often have hypersecretion of cortisol, which is directly linked to the hormone ACTH stimulated by macrophages (Smith, 1991). Patients with depression also tend to have abnormal levels of GH and PRL during their sleep and wake cycles (Smith, 1991). People with depression typically have higher levels of GH and PRL secreted when they are awake and reduced amounts secreted when they are asleep. In contrast, people without depression typically have lower levels of GH and PRL secreted when they are awake and higher amounts secreted when they are asleep (Smith, 1991). The monokine IL-1 secreted by macrophages seems to be directly linked to the stimulation of secretion for GH and PRL. Therefore, these hormone imbalances may provide strong evidence explaining how altered circadian hormone cycles in depressed patients may be linked to macrophage secretion of monokine IL-1 (Smith, 1991). There have been various studies conducted on volunteers given macrophage monokines that indicate that the secretion of these molecules is directly linked to depression (Smith, 1991). In a study conducted on 9 lung cancer patients given the macrophage monokine INF-

alpha, the volunteers began to show depression symptoms just after 6 days (Smith, 1991). The lung cancer patients displayed more than 5 of the symptoms needed for depression diagnosis in the DSM-5 criteria. Their symptoms included fatigue, slower motor skills, hypersomnia, anorexia, confusion, inability to concentrate, and insomnia (Smith, 1991). Another study conducted on 50 cancer patients given TNF intravenously, results showed that over half of the patients displayed depression symptoms including fatigue and anorexia (Smith, 1991). These studies clearly show strong evidence that the monokine INF-alpha secreted by macrophages has a direct influence on producing depression symptoms.

Macrophage activation has lead researchers to conclude that certain cohorts, such as women and Asians, and certain diseases, such as atherosclerosis and rheumatoid arthritis, are more prone to developing depression than others (Smith, 1991). For example, there is evidence to believe that estrogen in women is directly linked to macrophage activation because this hormone has been shown to have the ability to increase phagocytosis in macrophages (Smith, 1991). This immunological finding could be the answer to why rates of depression are 2 to 3 times higher in women than in men (Smith, 1991). Premenopausal women are the most commonly affected by depression and range from the ages of 18-44 (Smith, 1991). Past the age of 45, The National Institute of Health Epidemiologic Catchment Area Study (ECA) reported a sharp decline in depression in menopausal women (Smith, 1991). In a study conducted on rat macrophages of the peritoneum given high amounts of estradiol (predominant estrogen produced in premenopausal women), macrophage production of the monkine IL-1 increased dramatically (Smith,

1991). This study supports the idea that estrogen has a direct influence on the activation and stimulation of macrophages and also explains why there is such a sharp decline in depression in menopausal women (Smith 1991). Another interesting cohort that is being studied regarding macrophage activation and depression are people who live in Japan. Research has concluded that fish oil consumption decreases macrophage activity (Smith, 1991). It is postulated that people in Japan have lower rates of depression due to their high consumption of fish oil. In a 6-week trial involving volunteers taking fish oil, it was concluded that macrophages secreted 61% less IL-1 and 40% less TNF (Smith, 1991). Therefore, fish oil is thought to be a prophylactic against depression (Smith, 1991)

Atherosclerosis is a disease that directly involves the activation of macrophages in the arterial walls. This disease causes the arterial walls to constrict and narrow due to the buildup of fats and cholesterol and has the potential to lead to other problems such as coronary heart disease and stroke (Smith, 1991). Studies show that there is a direct link between depression and atherosclerosis, particularly patients who have suffered from having a stroke (30% of post-myocardial infarct patients show signs of major depression) (Smith, 1991). Due to the tissue damage in the brain after a stroke, blood monocytes and microglia (the macrophages that are found in the brain) secrete monokines that provide evidence for explaining the high rates of depression in post myocardial infarct patients (Smith, 1991). After an experimental penetration of the brain (similar to surgical trauma), the immune system responded in a similar manner like after a stroke. There were elevated levels of monocytes and microglia (brain macrophages) and

IL-1 (Smith, 1991). Therefore, post-myocardial infarct depression is directly linked to macrophage (blood monocyte and microglia) activation within the brain. According to the National Institute of Mental Health, other physical illnesses and diseases involve macrophage activation such as heart disease, diabetes, cancer, and rheumatoid arthritis (NIMH, 2018). In patients with rheumatoid arthritis, an important immunological characteristic often displayed is increased levels of the TNF secreted by macrophages (Smith, 1991). Therefore, depression may be a direct consequence of the activation of macrophages in RA patients.

There are various areas of depression research that are still poorly misunderstood and that should be further researched such as the food-gut allergy behavior axis, the efficacy of several brain stimulation therapies, and how depression is linked to various parts of the neuroendocrine system. Research done on the food-gut-allergy behavior axis shows that food can alter and affect a person’s mood and behavior. This topic is an important place to look for evidence that supports the macrophage theory of depression (Smith, 1991). Proinflammatory cytokines released during the inflammatory response induced by food seem to play a key role in the development of depression (Clapp, 2017). Elevated levels of proinflammatory cytokines such as TNF have the capacity to increase blood-brain barrier permeability; therefore, the release of these cytokines from macrophages has a major effect on brain function and can ultimately lead to depression (Clapp, 2017). As mentioned before, proinflammatory cytokines, such as TNF, released by macrophages specifically affect the functionality of the HPA-axis of the brain. There is evidence showing that probiotics have the

capacity to suppress the release of proinflammatory cytokines and therefore reduce depression symptoms (Clapp, 2017). Probiotics are beginning to be used as a form of therapy to treat depression induced by food. A particular 30-day study done on volunteers given either probiotics or antidepressants indicated that those who received probiotics had reduced depression symptoms and improved HPA-axis functionality (Clapp, 2017). Other studies conducted on patients suffering from certain inflammatory diseases, such as inflammatory bowel disease, have been shown to have decreased levels of TNF when they used probiotics as a form of antidepressant therapy (Clapp, 2017). When antidepressants and probiotic therapy were used in mice studies, similar results were also shown. From these studies, there is an obvious link between the brain, gut, and microbiome (Clapp, 2017). There is growing evidence that support this link, which makes it an area of research that is extremely valuable for future discoveries pertaining to the macrophage theory of depression. When antidepressant therapies and psychotherapy fail to work for patients with major depression, brain stimulation therapy may be considered. There are many different types of brain stimulation therapies including vagus nerve stimulation (VNS), transcranial magnetic stimulation (TMS), magnetic seizure therapy (MST), and deep brain stimulation (NIMH, 2018). ECA (electroconvulsive therapy) is the most commonly used form of brain stimulation therapy and involves a series of electrical impulses that stimulate small seizures in the brain of depressed patients (NIMH, 2018). However, ECA does require the patient to be under anesthesia and comes with some side effects that can include headache, upset stomach, memory loss, disorientation, and muscle aches, and confusion (NIMH, 2018). In contrast to ECT, TMS can be used to target a

specific part of the brain using magnetic field of the brain (Holtzheimer, 2006). TMS also reduces the chances for side effects commonly associated with ECT (NIMH, 2018). However, future studies are needed to help clarify if TMS is a clinically significant form of antidepressant therapy (Holtzheimer, 2006). MST uses components of both ECT and TMS with a goal of minimizing cognitive side effects associated with ECT; however, conformational data is still lacking with this form of therapy. (Holtzheimer, 2006). VNS, on the other hand, works through an electrical stimulator surgically placed underneath the skin that send electrical impulses to the brain through the left vagus nerve (Holtzheimer, 2006). VNS was originally developed to treat patients with epilepsy, but also proved to show favorable results in mood regulation for depressed patients (Holtzheimer, 2006). Further research concluded that the electrical impulses affected areas of the brain that were indeed associated with mood regulation (Holtzheimer, 2006). The impulses also affected certain neurotransmitters such as serotonin, norepinephrine, and GABA. According to Holtzheimer, there is evidence that shows that decreased levels of GABA have a direct influence on the development of depression (Holtzheimer, 2006). VNS is usually not a first line treatment for depressed patients due to mixed results of early studies being done (NIMH, 2018). The potential mechanisms for how VNS directly helps depressed patients is also highly misunderstood (Holtzheimer, 2006). Lastly, DBT is the most invasive therapy and was originally designed to treat patients with Parkinson’s disease to reduce symptoms of stiffness and tremors. However, research is underway of how it can also treat depression (NIMH, 2018). DBT is a surgical procedure where two holes are drilled into the patient’s skull. The surgeon then feeds small tubes down into the brain and places

electrodes on each side of specific areas of the brain (NIMH, 2018). According to the National Institute of Mental Health, “ Area 25”, or the subgenual cingulate cortex, is a particular area that is said to be overactive in depressed patients. Once the electrodes are attached to the brain, they are attached to wires that run down the body into the chest and are attached to a pair of battery operated generators (NIMH, 2018). This setup ensures that electrical impulses can be continuously delivered to stimulate brain activity in the areas that are associated with depression (NIMH, 2018). Studies indicate that DBT may be an effective treatment option for depressed patients; however, like VNS, the mechanism behind how this treatment works is largely misunderstood and obscure (NIMH, 2018). Given the amount of brain stimulation treatment options that are available, there needs to be further investigation into which ones are the best for treating depression.

It is still poorly understood how depression is linked to various parts of the neuroendocrine system, including the HPA axis and the HPT (hypothalamic-pituitary-thyroid axis) axis. As already mentioned, the HPA axis is abnormally active in patients that suffer from depression. In order to better understand this area of research, there needs to be a clearer understanding of the interactions between the HPA-axis and the monoamine neurotransmitter systems, which include norepinephrine, serotonin, and dopamine. (Holtzheimer, 2006). Research needs to be done on developing antidepressants that specifically target the HPA axis directly. Some of the possible antidepressant therapies being studied that target the HPA axis include CRF (corticotropin releasing factor), receptor antagonists and

glucocorticoid synthesis inhibitors (Holtzheimer, 2006). Another area of particular interest revolves around the HPT axis because hypothyroidism has been routinely observed in depressed patients (Holtzheimer, 2006). Specifically, depressed patients have shown elevated levels of thyroid-releasing hormone (Holtzheimer, 2006). Thyroid hormone augmentation has been shown to have antidepressant effects, however, like the HPA-axis, future research is needed to better understand the connection between the HPT-axis and depression (Holtzheimer, 2006). Another area of possible research revolves around GABA, which are major inhibitory neurotransmitters of the central nervous system (Holtzheimer, 2006). There is evidence that shows that decreased levels of GABA have a direct influence on the development of depression. Animal and human models of depression indicate decreased levels of GABA concentration (Holtzheimer, 2006). The most promising research with GABA inhibitors revolves around the use of GABA antagonists, which have shown the ability to have antidepressant properties in animal models (Holtzheimer, 2006).

The obvious link between depression and the neuroendocrine system provides a large area of research that could lead to some very promising discoveries regarding the treatment of depression.

Resources

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