



Review of the Effects of Depression on the Human Immune System

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In this scholarly review essay, Zachary Waldroup synthesizes diverse scientific findings on the connections between depression and physiological wellbeing of the immune system. This essay was written for Scientific Writing with Dr. Rachel Jones.

ABSTRACT

Depression has an effect on a person's overall health, specifically on the immune system. A person's level of depression can cause an increase in pro-inflammatory cytokines and significantly lower levels of anti-inflammatory cytokines. The low levels of anti-inflammatory cytokines allow for those who are depressed to become ill quicker due to low immune system response. Depression also leads to high levels of cortisol in adults, teens, and, in some cases, children. Cortisol is a stress/depression hormone that suppresses the immune system, allowing inflammation and illness. Vitamin D also plays a major role in the immune system, as well as with those who battle depression. It has been shown that those who have depression or are suicidal have low levels of Vitamin D. The purpose of this paper is to tie together all

these factors and discuss how they affect the immune system together.

Keywords: immune system, depression, cytokines, vitamin D, cortisol, inflammation, stress, interleukin

INTRODUCTION

DEPRESSION HAS MANY DIFFERENT effects on the human body, but not all these effects are only mental or emotional, as many may think. Depression is a mental health disorder, causing extreme disinterest in daily activities, which leads to impairment of daily living. Recent studies have shown that depression is not just a mental health problem, but that it can stem from changes in brain activity, to altered neural circuit activity in the brain. Depression has a number of effects on the human body and has been known to have effects on the immune system. Depression has been found to change elements of the immune system, such as increasing pro-inflammatory cytokines and decreasing anti-inflammatory cytokines. It is also important to identify which age groups are most affected.

CYTOKINES

CYTOKINES ARE PROTEINS, PRODUCED by many cells in the human body, and are primarily signaling proteins. They play a major role primarily in the immune system, signaling the body when infection, inflammation, or any pain is detected (Smith, 1997). Cytokine proteins cause these effects when they are released by cells; thus, the nearby cells' behavior will change. In other words, cytokines are what notify the body of invading bacteria or injury. While cytokines are signaling proteins, they are also receptors for the immune system. Cytokines promote and suppress the inflammatory response in

the human body and are also responsible for the numerous variations of T helper cells that fight inflammation (“Cytokines and Inflammation,” n.d.).

Pro-inflammatory cytokines are responsible for disease such as chronic inflammation, Crohn’s disease, and varying other inflammation-related illnesses, such as tumor necrosis factor-alpha (TNF- α). although pro-inflammatory cytokines can cause excessive inflammation response, they are extremely necessary in the human body because without pro-inflammatory cytokines, the human race would have succumbed to illness a long time ago (Smith, 1997). Pro-inflammatory cytokines are held in check by anti-inflammatory cytokines, which signal the body when it’s time to stop producing pro-inflammatory cytokines to fight infection after illness has ceased (Smith, 1997; “Cytokines and Inflammation,” n.d.). Anti-inflammatory cytokines can also be produced at an excessive rate and lead to immunosuppression, which instead of causing excessive inflammation and leading to pain, leads to infection due to the pro-inflammatory cytokines not responding or being produced due to suppression. The suppression of the pro-inflammatory cytokines leads to lower counts of neutrophils and lymphocytes being produced by immune system receptor proteins (Marcuzzi, Piscianz, Valencic, Monasta, Brumatti, & Tommasini., 2015). Cytokines have also been found to be a part of the central nervous system and generally influence all areas of the body, along with contributing to the blood-brain barrier. Cytokines can enter the brain via volume diffusion and produce pro-inflammatory versions of themselves that attach to the IL-1 receptors of the brain (Hashmi, Aftab, Mazhar, Umair, & Butt, 2013; Guo & Jiang, 2017).

DEPRESSION AND INFLAMMATION

INFLAMMATION IS CAUSED BY WHITE blood cells’ response to infection and increases blood flow into the afflicted area. This process is altered by behavioral sickness, which is similar to depression in many

ways, such as loss of interest in activities, troubles sleeping, and loss of appetite (Hashmi et al., 2013). While behavioral sickness and depression overlap, behavioral sickness will not lead to higher levels of infection, since it is theorized that the human body divides energy to fight infection, and that the remaining energy is directed towards keeping the psychological aspect of the person intact, in a sense (Hashmi et al., 2013; Guo & Jiang, 2017).

Depression and inflammation have been linked together through the tumor necrosis factor-alpha (TNF2) allele, along with the single nucleotide polymorphism (SNP) allele, which are two critical genes for T cell functions that were associated with depression (Hashmi et al., 2013). Depression affects cytokines, making them either overproductive or underproductive. If pro-inflammatory cytokines are produced at an excessively high rate, then TNF2 and SNP proteins will also be produced at an overly high rate by the T cells, which has led researchers to believe that those with high pro-inflammatory cytokines will have depression (Crews, 2012). The increase in these alleles/proteins has been shown to increase the likelihood of depression in someone; however, it has been observed that those who display the -511T allele from the IL-1beta gene had less severe depressive symptoms (Hashmi et al., 2013).

Anti-depressants have anti-inflammatory properties. Anti-depressant drugs that contain Clomipramine and Imipramine have been shown to reduce the production of nitric oxide (NO), and TNF- α in microglia and astrocytes (Hashmi et al., 2013). This also significantly weakened the expression of pro-inflammatory cytokines by decreasing their production at mRNA levels, which in turn helps decrease depression in individuals (Hashmi et al., 2013; Duda et al., 2017). The drugs fluoxetine, paroxetine and sertraline were used in human trials where the patients suffered from major depression, with high cytokine levels before treatment. After treatment, interleukin 1 beta (IL-1 β), a gene/protein that produces fever, was lowered, leading to the conclusion that anti-depressants do lower anti-

inflammatory cytokines (Hashmi et al., 2013). Reduction of inflammation through the usage of antagonists of the TNF- α protein such as etanercept or inflixmab without the usage of anti-depressants has shown patients to have decreased signs of depression (Hashmi et al., 2013).

CORTISOL

CORTISOL, A COMMON PROTEIN IN the human body, is produced in the adrenal gland. Cortisol is released into the bloodstream in response to low blood sugar and stress. Cortisol is also capable of suppressing the immune system by preventing the release of substances into the body that cause response to inflammation (Suarez & Sundy, 2017). Cortisol is also a stress-response hormone, which also corresponds with depression. When the mind becomes depressed, which is a form of stressor to the mind, the body produces cortisol which suppress the immune system when in high enough levels (Suarez & Sundy, 2017).

When the cortisol protein begins suppressing the immune system, it inhibits the production of interleukin 12 (IL-12), interferon gamma (IFN- γ), and interferon type I (IFNs) (Suarez & Sundy, 2017; Slavich & Irwin, 2014). At the same time, it upregulates the production of interleukin 4 (IL-4), interleukin 10 (IL-10) and interleukin 13 (IL-13). Interleukins 10 and 13 are both anti-inflammatory cytokines/proteins, and when the body has increased amounts of stress or depression, the cortisol levels will increase the production of these two proteins; with too many of these proteins in circulation, the body will be incapable of fighting infections (Slavich & Irwin, 2014). Cortisol also inhibits the production of T-helper cells, which, if a person is suffering from high levels of stress/depression, will lead to inflammations and ultimately illness due to the lack of the cells present, along with increased IL 10, and IL 13 levels (Suarez & Sundy, 2017; Slavich & Irwin, 2014).

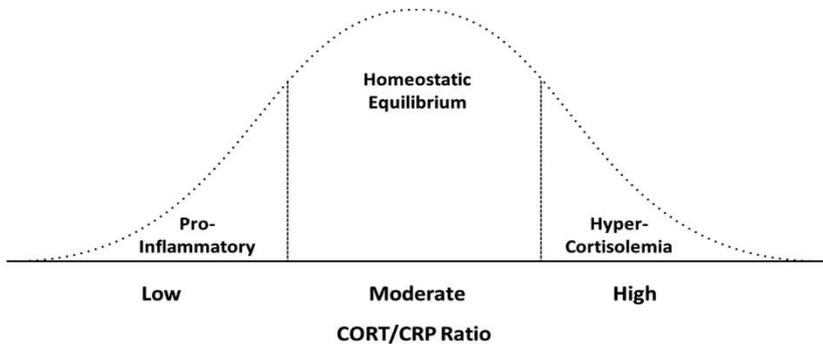


Figure 1. Levels of cortisol that will lead to either pro-inflammatory or hypercortisolemia. The human body must have a moderate level of cortisol present to function properly, for it regulates blood sugar, and helps in the metabolism of fats, protein, and carbohydrates. From Suarez & Sundry, 2014, p. 853.

VITAMIN D

VITAMIN D IS AN IMPORTANT compound that is necessary in the human diet. Sources of Vitamin D consist of sun light, fish, fruit and pork. Vitamin D is important to many aspects of the body, from the immune system and autoimmune system to bone health and even cancer prevention. When the immune system is lacking in vitamin D, the body is susceptible to risk of viral infection. Vitamin D is also shown to have an effect on depression levels through cytokine interleukin 6 (IL-6) and interleukin 1B (IL-1 β) (Grudeta, Malmb, Westrina, & Brundind, 2014).

The lack of vitamin D with those who show signs of depression, or any major stressor disorder, is linked to inflammatory markers IL-6 and IL-1 β (Grudeta et al., 2014). The presence of these cytokines leads to higher levels of inflammation in those with depression and who are vitamin D deficient. Those who have a higher amounts of vitamin D in their plasma are less susceptible to depression or inflammation from depression-related causes, and from excessive cytokine production, especially if it is serum 25OH-D (Jääskeläinen et al., 2015). The presence of serum 25OH-D, which is a vitamin D

supplement variant, shows increasingly low risks of depression, and inflammation (Jääskeläinen et al., 2015). The higher the level of vitamin D, the less likely depression-like symptoms are to spawn from pro-inflammatory cytokines IL-6, IL-1 β , and TNF- α (Jääskeläinen et al., 2015; Grudeta et al., 2014; Hashmi et al., 2013; Guo & Jiang, 2017).

GENETICS

GENES PLAY A MAJOR ROLE IN the how people can combat depression. Cytokines occur on a genetic level and are produced in a majority of cells in the human body (Crews, 2012; Hashmi et al., 2013). Cytokines are proteins and necessary for the human body to function effectively, yet they can be set off by any sort of imbalance, such as introduction of alcohol to the body (Crews, 2012). Monocytes are responsible for the production of cytokines, and monocytes are sensitive to alcohol, for it causes TNF- α to enter a hyperglutamagic state, causing a cortical focusing problem (Crews, 2012; Hashmi et al. 2013). It causes the receptors of glutamate to slack and inhibits glutamate transportation into and out of the cells (Crews, 2012). This also causes an increased production of inflammatory cytokines, including TNF- α , IL-4, IL-10 and IL-13 (Crews, 2012).

Because all humans produce cytokines, all humans are vulnerable to harm through the introduction of substances that increase inflammatory cytokine production (Crews, 2012; Hashmi et al., 2013; Guo & Jiang, 2017). An increase in inflammatory cytokines is harmful to the immune system, which causes it not to properly function (Hashmi et al., 2013). Substance abuse causes the genes of a person to struggle with proper function, and, if done on a daily basis, will cause overall damage to how the person's body functions at a cellular level (Crews, 2012).

ADOLESCENT DEPRESSION

DEVELOPMENT OF THE HUMAN BODY at the early stages of life is important. If the body is not properly developed at the right time at the right stages, complications can occur later in life. Depression in children can greatly affect their immune system later in life, causing them to be more susceptible to potential infections and inflammation (Mills, Scott, Wray, Cohen-Woods, & Baune, 2013). Cytokines present in children or adolescents are present during the critical times of development, such as puberty, during which the body undergoes hormonal changes that cause major production of cells, including cytokines, as a result of the chemical imbalances of puberty (Mills et al., 2013)

Signs of inflammation from inflammatory cytokines can be found in those going through hormonal changes such as puberty (Mills et al., 2013). However, the production of cytokines can also come from trauma suffered as a child; whether it is physical or mental is unclear (Mills et al., 2013). Genetic background also plays a part in whether a child will have problems with cytokine production, causing immune system problems. If the parents of the child have the genetic traits of depression, this does not preclude the child from inheriting an allele that will cause over-productive cytokines (Mills et al., 2013).

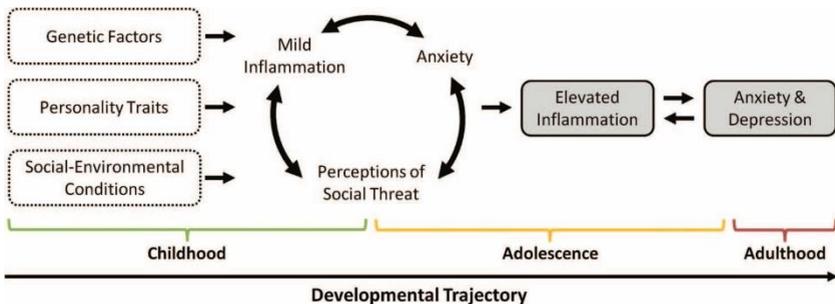


Figure 2. Depiction of how depression can stem from childhood to adolescence to adulthood through three main factors. From Slavich & Irwin, 2014, p. 797.

SOCIAL STRESSORS

SOCIAL INTERACTIONS AND SOCIAL settings have an impact on the immune system. Social settings can trigger anxiety, depression, and even PTSD responses in a person (Hicks-Nelson et al., 2017). The body responds to social anxieties and depression the same way it would through any other situation, through cytokines and inflammation. In social settings, IL-6, TNF, and IFN are the responding cytokines, which appear most responsive for social anxiety and depression in juveniles (Hicks-Nelson et al., 2017).

It is through cytokines in social settings that someone can feel sick in a social setting, or ill for no apparent reason. The pro-inflammatory cytokines will promote unnecessary inflammation (Hicks-Nelson et al. 2017; Hashmi et al. 2013). This explains why people will begin to feel hot or sick to the stomach in social confrontations or settings that cause anxiety. At the same time, this also weakens the immune system, for it attempts to fight an infection that is not actually there, so actual infection can occur if promoted by the surrounding bacteria (Hicks-Nelson et al., 2017; “Cytokines and Inflammation,” n.d.; Pfau & Russo, 2015).

CONCLUSION

THE OVERALL EFFECT THAT stressing factors such as depression have on the human body are anywhere from mild to severe. It is understood that the prime factor behind all of these variables that cause immune system errors are cytokines. As depression in a person increases, so do the cytokines, but the effects can vary from pro-inflammatory, causing unknown fevers, to anti-inflammatory, allowing for infection to occur unchecked.

Although cytokines are at the source of what greatly affects the immune system, what necessarily causes them to act in this way is unknown. There are far too many variables, from depression to vitamin D deficiency to genetics and the properties alleles. The cause

behind depression affecting the immune system through cytokines requires further study.

The relationship between depression and cytokines needs to be further advanced before any real assumption can be made that cytokines and depression are directly correlated. Yet, at the moment, studies do continue to advance, showing that depression and inflammatory cytokines suppressing the immune system are correlated in some way, which are potentially linked through one of many cytokine proteins. It has been shown that those who are depressed show signs of inflammation, which indicates a connection between depression and inflammatory cytokines.

The overall purpose of this paper has been to discuss some of the varying factors that correlate depression to the immune system, such as social stress factors, proper intake of vitamins, and how general depression can cause inflammation. Suggested further research on this topic would be to study the production of cytokines in those who do not have depression and place them in varying scenarios/situations that can spur anxiety or depression. Comparison with someone who has been diagnosed with depression could show how the two vary in cytokine production and how such production affects the two subjects individually. Studying an individual's genetic history to see if they possess any potential family history that could lead to depression or high cytokine production could ensure early detection. ►►

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