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The Role of Diet in the Onset of Depression: A Biochemical Connection

Between Nutrition and Mental Health

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Abstract

Depression is a major clinical concern, having a complex onset and the presence of multiple, often unidentifiable causes. Depression affects millions of individuals worldwide, with a high prevalence in regions of the world with a Western-style diet as compared to regions with a Mediterranean diet. A Western-style diet consists of foods high in sugar, fat, and processed meats and grains, whereas the Mediterranean diet contains significantly more vegetables, fruits, lean meats, and whole grains.

The link between diet and mental health disorders has implications for individuals of all ages who are hesitant to turn to medication. In addition to presenting a closer examination of the biochemical foundation of depression, this review focuses on the effects of factors such as food-related inflammation, nutrition, and probiotics in symptom development.

The Role of Diet in the Onset of Depression and Anxiety: A Biochemical Connection
Between Nutrition and Mental Health

Humans often experience moments or days where they feel uneasy, unhappy, disconnected, or lacking in their normal motivation and drive. Instead of feeling content or joyful, they are filled with worried thoughts about something that they cannot quite identify. For some people, this feeling is not fleeting, but rather lasts for days, weeks, and sometimes years. The underlying worry eventually develops into a desperation for relief and a change in their state of mind. They are depressed and are therefore exhibiting the characteristics associated with depression — dampened mood, appetite changes, loss of energy, feelings of hopelessness and worthlessness, loss of interest, and thoughts of suicide. These signs of depression often manifest after an individual has wrestled with its common precursor — anxiety. Depression is not simply an unpleasant state of mind; rather, it is a clinically significant condition and the leading cause of disability worldwide, affecting over 300 million people globally (1,2).

Depression is a complex condition; there are numerous causes and numerous treatments available. Some of the most common medications are selective serotonin reuptake inhibitors (SSRIs), which increase the presence of the neurotransmitter serotonin in the brain by blocking its reabsorption into presynaptic neurons (Figure 1). Drugs in this class of antidepressants include citalopram, paroxetine, fluoxetine, and sertraline. Other drugs fall into the category of serotonin and norepinephrine reuptake inhibitors (SNRIs) and work similarly to SSRIs with the added action of altering the norepinephrine balance in tissues (3). Although these drugs are useful for treating depression, they are attempting to correct an assumed imbalance and therefore are therapeutic, not prophylactic. This leads to the questions, what caused the neurotransmitter imbalance in the first place, and is there a non-medicinal way to remedy this? If more progress is

made toward identifying the causes of depression, there will consequently be more progress towards identifying nutritional habits that can prevent it before its onset.



Figure 1. Selective serotonin reuptake inhibitors (SSRIs) increase synaptic levels of serotonin by preventing the reabsorption of serotonin into the presynaptic nerve. From “Selective Serotonin Reuptake Inhibitor (SSRI) Use during Pregnancy and Effects on the Fetus and Newborn: A Meta-Analysis,” by K. A. Lattimore, S. M. Donn, N. Kaciroti, A. R. Kemper, C. R. Neal Jr., and D. M. Vazquez, 2005, *Journal of Perinatology*, 25, p. 596.

The research in this thesis focuses on one factor of depression that is currently under much investigation, and that is the role dietary choices have in affecting mood. Studies have demonstrated that there is a higher likelihood of depression in the Western regions of the world that consume foods high in sugar, fat, and processed meats and grains. This is in comparison to diets consisting of more vegetables, fruits, lean meats, and whole grains, which are more

common in Mediterranean regions of the world (4). Although correlation does not always lead to causation, it does raise interest as to the possible reason behind the correlation. There is reason to suspect that molecules present in certain foods and the body's reaction to these molecules can contribute to a depressed mood and a decrease in overall mental well-being. Further research into the physiological and biochemical mechanisms related to development of depression could provide people around the world with a manageable, medication-free approach to improving depression-related symptoms. Acknowledging the fact that diet is not the exclusive cause of depression, the correlation is significant enough to warrant further research. Its results may become immediately applicable to all people without the necessity for added expense or prescriptions.

Refining the exact etiology by which depression operates is a daunting task; however, significant progress has been made by researchers. In addition to the fact that multiple pathways exist for how depression brings about its characteristic symptoms, including the neurotransmitter imbalance alluded to earlier, these pathways are each very complex and can involve or affect most every organ system in the body.

Depression and Anxiety

Comparison of Symptoms

Before proper analysis can be performed on the role of diet in the onset of depression and anxiety, the terms must be further defined. A shallow analysis would lead to the conclusion that depression is simply a deeper, more developed form of anxiety. This is only partly true, as there is more to the comparison than a measure of intensity. Depression most often refers to major depressive disorder, which is the diagnosis given to someone who has experienced five or more of the following symptoms for a minimum of 2 weeks: depressed mood, lack of interest in

enjoyable activities, a significant alteration in appetite or weight, insomnia or hyposomnia, slowing of movement, lack of energy, feelings of guilt or worthlessness, trouble concentrating or indecisiveness, or suicidal thoughts or behaviors. In comparison, anxiety can refer to generalized anxiety disorder, which is the diagnosis given to someone who has experienced the following symptoms for the majority of 6 or more months: excessive worry, restlessness, being easily fatigued, trouble concentrating, irritability, sleep disturbance, or muscle tension (5,6).

Although these symptoms seem very similar, there are some key differences in the appearance of people with depression as opposed to those with anxiety. Depressed individuals tend to physically move and react slower, and mentally have a “defeated” mindset and outlook on life. Anxious individuals tend to be more active mentally and physically, as they are constantly worried or panicked about the future but have not resigned into a complete state of hopelessness. Occasionally individuals will fluctuate between both states, as one can lead to the other, and approximately half of the people diagnosed with depression will also be diagnosed with some form of an anxiety disorder (6).

Despite these technical differences, the conditions are similar in the context of their onset, symptoms, treatment, and causes. Therefore, an analysis of both conditions will be given as they have a very close, yet admittedly complicated association. It is reasonable and perhaps even beneficial to hold the viewpoint that dietary remedies for depression can also translate to improvement for people who suffer from anxiety, and vice versa.

Importance and Prevalence

Depression and anxiety are important conditions to address because they affect everything a person does not only physically, but mentally. People’s perceptions about the world and their outlook on their future can drastically change, and this drastic change can occur so

gradually that they do not realize their situation until they are deep in an anxious mindset. Loss of a sense of hope for the future can affect the current decisions an individual makes — decisions regarding work, family, relationships, education, and the will to keep on living. Depression affects as much as 20% of the general population worldwide, and women tend to be approximately 2.5 times more prone to the condition than men. Furthermore, about 16% of the population is expected to experience major depressive disorder at least once in their lifetime, and of the total that are diagnosed only about 33% receive treatment (5,7). Many choose not to pursue treatment because they do not recognize their symptoms and feel as though their thoughts are normal. Other reasons for avoiding treatment may include the aversion to taking medication for something that is not seen as an immediate threat to well-being, along with not feeling the need to alert a doctor if the individual believes it is only a passing “phase of life” that will soon improve.

Etiology

The causes of depression vary widely and include genetics, environmental factors such as stressful life events, and the more recently considered factor of diet and nutrition. Causes of depression can be categorized in two ways: those related to psychiatric illness and those associated with non-psychiatric (physical) illness. Environmental factors and stressful life events fall under the category of psychiatric illness. These do not directly affect the physical well-being of an individual, but they can lead to indirect physical effects. Non-psychiatric illness includes more physical stressors such as infectious diseases, abnormalities in normal physiological processes, various genetic factors, endocrine disorders, and deficiencies in proper nutrition (8).

Physiological and Biochemical Process

Key to understanding the specifics of the diet's effect on mental health is a knowledge of how the body develops depression and attempts to handle its effects. Generally, depression can result from any number of disruptions in the normal function of neuronal chemical transmission. Three molecules in particular — norepinephrine (NE), serotonin (5-HT), and dopamine (DA) — are essential in the regulation of motivation, mood, and awareness (5; Figure 2). Disruptions to the normal homeostatic levels of these molecules, including changes in their respective receptors, production, storage, and release, have been correlated with depressed mood, although the resulting decreased levels of these neurohormones alone cannot account for the onset of depression. Successful results in the treatment of depression by prescribing medications that increase the body's concentrations of serotonin and norepinephrine also attest to the importance of these molecules in the physiology of depression.



Figure 2. The monoamines dopamine, norepinephrine, and serotonin are necessary for the normal function of neuronal chemical transmission. Sketch made using ACD/ChemSketch software.

Much scientific discovery concerning neuroscience occurred in the 20th century. Late in this time period, disruption of monoaminergic function was hypothesized as one of the biochemical mechanisms of depression. Norepinephrine, serotonin, and dopamine are all monoamines and function as neurotransmitters in the brain. Under normal circumstances, these neurotransmitters are released from secretory vesicles in the presynaptic neuron through a Ca^{2+} -dependent process and subsequently bind to their respective receptors on postsynaptic neurons. This receptor binding causes downstream cell-signaling processes to become initiated, such as the activation of guanine nucleotide-binding proteins (G-proteins) attached to the intracellular side of the receptor. G-proteins can regulate further effector systems, called second messengers, which enhance the signaling cascade and elicit a cellular response that ultimately results in a biological alteration of brain function (5).

The monoaminergic hypothesis suggests that depressive symptoms are caused by a deficiency in any of these three monoaminergic neurotransmitters in neuronal synapses. Conversely, it suggests that manias are caused by an excess of these neurotransmitters in the brain. The foundation of the hypothesis lies in experiments where NE, 5-HT, or DA were depleted, and the experimental animals demonstrated symptoms resembling depression. A specific example of this was found in patients treated with the drugs reserpine and α -methyl dopa, which deplete monoamines. These patients experienced a consistent incidence of depression in about 15% of the treated individuals. Furthermore, increasing the concentrations of serotonin and/or norepinephrine by inhibiting their re-uptake into presynaptic cells was already determined as the mechanism of action for many antidepressant medications (5,9).

Disruption of the normal neurotransmission process can include anything from an alteration in the synthesis of the neurotransmitters from their precursors, an issue with their

storage, an issue with their release from the presynaptic neuron, or an issue with the sensitivity of their receptors/second messengers in the postsynaptic cell. Although the monoaminergic hypothesis has significant foundation in the molecular process of depression, this system of thought is too simplistic on its own to explain every symptom. It is understood to be a crucial, but not a sole, reason for the observed symptoms. Because much of the study of depression relates to neurotransmitter balance, any subsequent dietary analysis should also be focused on what food types do to the normal neurotransmitter balance.

Nutrition and Diet

The term nutrition most simply refers to the nourishment required for an individual to grow and be healthy throughout his or her life. The study of nutrition is far too vast to encompass every aspect of its relation to depression, but there are a few key aspects that can be further elucidated to greatly help in this discussion. One of these aspects is the role of food-related inflammation, which provides some of the most important clues into the relationship between diet and depression.

The Dietary Inflammatory Index

Food-related inflammation refers to the presence of inflammatory cytokines after consumption of a pro-inflammatory diet. Although inflammation is common in the body when attacking infection, a low-level inflammatory response is sometimes chronically portrayed in certain individuals, especially those who are obese. Recent studies have suggested a method of measuring this low-grade, food-related chronic inflammation called the Dietary Inflammatory Index (DII). This method assigns values to diets according to their pro-inflammatory (positive value) or anti-inflammatory (negative value) characteristics. Pro-inflammatory responses are determined by measuring immune cytokine levels — an increase in the cytokines IL-1B, IL-6,

TNF- α , or C-reactive protein (CRP) indicate a pro-inflammatory response because they are only released during an inflammatory reaction of the body's immune system. Conversely, IL-4 and IL-10 are anti-inflammatory cytokines, and so decreased levels of these molecules indicates a pro-inflammatory response as well, while increased levels indicate an anti-inflammatory response. In this way, various diets have been evaluated, as well as the ingredients that compose the diets (10). This system goes beyond simply defining the level of healthiness in a food; it gives a point of comparison between different food types based on the reaction the food induces in the body.

A 2014 study on food-related inflammation used the DII to compare inflammatory levels of three different diets — fast food, macrobiotic, and Mediterranean. Subjects were instructed to eat certain foods for a single day, each adding up to 2,000 kcal for the full day so as to encourage a more standardized study. Then, the DII was used to calculate an inflammatory value for each diet. The fast food diet, which was meant to encompass the Western-style diet routine, was composed of high levels of sugar, fried foods, refined grains, and high-fat dairy products and resulted in a pro-inflammatory DII score of +4.07. The macrobiotic diet, which was meant to closely represent the traditional Japanese diet, consisted of many whole grains, vegetables, and beans, with a comparatively low intake of fruits, sweeteners, and fish, and resulted in an anti-inflammatory DII score of -5.54. Finally, the Mediterranean diet, which consisted of high amounts of whole grains, fish, olive oil, and green leafy vegetables with a considerably lower intake of red meat, butter, and alcohol, resulted in an anti-inflammatory DII score of -3.96. More specifically, the exact food components that were associated with anti-inflammatory responses were identified as fruits, vegetables, omega-3 polyunsaturated fatty acids, vitamin E, fiber, β -carotene, vitamin C, and magnesium. The specific food components associated with pro-

inflammatory responses were identified as saturated fatty acids, trans-fatty acids, and cholesterol (10). These results indicate that physical health and well-being can be significantly influenced by the food an individual consumes, which in turn can be greatly influenced by the location and culture in which the individual resides.

The Connection Between Diet and Depression

Unhealthy Diets Worsen Depression

The DII has been established as a good method of measuring the physical health of individuals regarding their inflammatory responses to their daily diet (10). However, there is also significant and very recent data being published correlating this inflammation with depression, a disorder that is more emotional and mental in its presentation. Beyond the simplistic assumption that individuals with life-altering disease such as cancer or obesity may tend to have depressed thoughts regarding their symptoms and life-outlook, there is increasingly more concrete evidence that the association may be more direct and molecular than previously understood.

Beginning in 2014, there have been two cross-sectional and five longitudinal studies in various countries seeking out the correlation between DII results and depression. The most recent, a longitudinal cohort study focusing on the American population, studied 3,648 individuals and found intriguing results. Of the population sample, the group that received the highest pro-inflammatory diet (high DII score) was 24% more likely to develop depressive symptoms when compared with the group that received the lowest pro-inflammatory diet (low DII score), even after accounting for other depression-related factors such as socioeconomic status and health issues (2). Furthermore, population groups with already confirmed depression were examined and found to have high levels of inflammatory cytokines such as CRP, IL-6, and TNF- α . The pro-inflammatory cytokine interferon- α (IFN- α) is considered one of the most

influential inflammatory cytokines, as administration of therapeutic IFN- α has been shown to lead to clinical depression (11). The reasoning behind this correlation may lie in the effect of pro-inflammatory cytokines on the function of neurotransmitter release and metabolism, as well as regional brain activity and the function of neuroendocrine molecules. For example, neuroinflammation caused by pro-inflammatory cytokines disrupts the survival of serotonergic neurons and hinders the development and growth of new neurons (2,4,11).

Sugar. A hallmark of Western-style diet is a high level of sugar intake. The topic of sugar intake encompasses much of the leading dietary links to depression that are currently being researched. A study on the prevalence of major depression and per capita consumption of sugar was performed in the countries of Korea, United States, France, Germany, Canada, and New Zealand, and results revealed positive correlation of the data (12; Figure 3). Part of the correlation may be due to the effect sucrose has once removed or reduced from the diet after habitually consuming significant amounts.

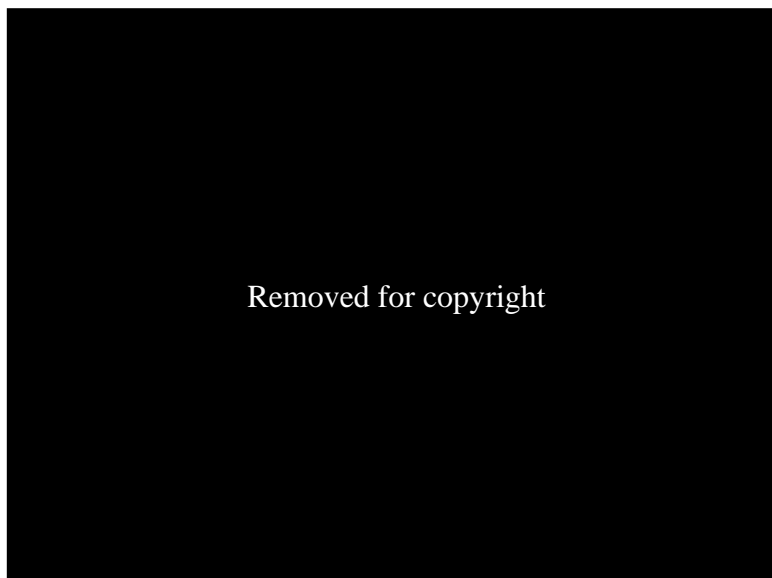


Figure 3. Graph representing refined sugar consumption in six countries compared to annual rate of major depression in these locations. From “A cross-national relationship between sugar consumption and major depression?,” by A. N. Westover and L. B. Marangell, 2002, *Depression and Anxiety*, 16, p. 119.

Animal studies have demonstrated that when there is a continual intake of sucrose, its removal significantly reduces dopamine levels, and therefore dopamine signaling, in the test subjects. It also simultaneously causes overexpression of a certain K^+ channel common in neural tissue, known as Kir2.1. When dopamine levels are reduced, there is less activation of their D1 receptors in the medium spiny neurons of the brain. This means less cellular signal transduction: less cytosolic cAMP levels, leading to less protein kinase A activation, and therefore less phosphorylation of molecules such as cAMP response element binding protein (CREB). Because CREB is believed to act as a repressor of Kir2.1, when the action of CREB is inhibited or reduced in such a way, it has a direct effect on Kir2.1 channels and elevates their expression. Elevated amounts of Kir2.1 means more positive charge is transferred out of cells, and the cells hyperpolarize. This results in the neuron being less likely to fire an action potential, and the neuronal excitability decreases. The main area of the brain affected by this loss of neuronal activity is the nucleus accumbens, a location in the forebrain important in dopamine release in response to reward-based stimuli and mainly composed of medium spiny neurons. The nucleus accumbens has also been associated with mood disorders, obesity, and addiction patterns. Furthermore, overexpression of Kir2.1 leads to negative behavior and mood symptoms even without overconsumption of sucrose, indicating that Kir2.1 upregulation appears to be the defining mechanism, or “turning point” in this process. In addition to testing with sucrose consumption alone, the same study provided high-fat/sugar diets to obesity-prone rats in the same manner and measured responses to withdrawal. Here, the study found that there was a significant decrease in D1 receptor expression, along with behavioral and physiological signs of anxiety and depression (13). Population groups that would experience such a response to sugar withdrawal are those who are prone to an overconsumption of sugar in their daily diets.

Caffeine. Caffeine consumption, similar to sugar consumption, may have detrimental effects on mental health. Caffeine has been demonstrated to affect hippocampal neurogenesis in a dose-dependent manner. Neurogenesis is the process of developing new neurons in neural circuits that already exist. The hippocampus is of special interest in regard to depression because neurons in this location continue to generate well into the adulthood of mammals, and it also has far-reaching effects in learning, memory, and depression throughout adulthood. Significant changes in neurogenesis in the hippocampus mean significant consequences to these areas of function. Caffeine affects neurogenesis in many ways, some of the more indirect being its association with lack of sleep and vasoconstrictive action, both of which are associated with depressed and disrupted neurogenesis in adults. One study conducted in 2009 followed the response of experimental mice given various doses of caffeine in order to document any observations or changes in neural proliferation of the hippocampus. Doses of caffeine in the 20-30 mg/kg/day range, equivalent to approximately 5-7 cups of coffee for humans (625 mg), were found to depress neurogenesis in the hippocampus (14). Further research is needed to determine the biochemical pathways involved in this neurogenesis disruption, and to differentiate how much of the observed response is due to behavioral responses to caffeine versus more direct molecular changes.

Healthy Diets Improve Depression

Although eating healthier has obvious advantages for the body, certain food ingredients have been specifically linked to a decrease in depressive symptoms and are therefore at the forefront of research seeking to improve and/or eliminate dietary depression and anxiety. Among the most prominent examples are omega-3 fatty acids, probiotics, vitamin D, and magnesium.

Studies often find that individuals with lower circulating IL-6 concentrations are more responsive to antidepressant medication, and therefore high pro-inflammatory cytokines may be contributing to the treatment resistance that some non-medication-responsive individuals experience. Working to improve diet and lower DII score may reveal a better response to antidepressants and is a worthwhile endeavor (4). Turning anti-inflammatory meal consumption into a dietary habit is the first step in approaching this better emotional well-being.

Omega-3 polyunsaturated fatty acids. Lowering pro-inflammatory cytokines has been attempted by utilizing anti-inflammatory medications, but often with adverse side effects. An alternative nutritional method, involving elevated intake of omega-3 polyunsaturated fatty acids, has shown promise as a viable and safer alternative. Omega-3 fatty acids are a form of unsaturated fat, meaning that there is more than one double bond in the fatty acid chain. This particular form of polyunsaturated fatty acid is termed omega-3 because the first double bond is located at the third carbon atom when approached from the methyl end of the molecule (15; Figure 4). A lower prevalence of both general mood disorders and major depressive disorder has been found in people groups that consume a high amount of fish, and therefore, a high amount of omega-3 fatty acids. Conversely, people with major depressive disorder have consistently low levels of omega-3 fatty acids in their blood and brain tissues (11). Fish oils contain two omega-3 fatty acids that have particular associations with relieving mood disorders; the greatest effect is observed from eicosapentaenoic acid (EPA), and a lesser but still significant effect is observed from docosahexaenoic acid (DHA).

Low levels of DHA have been associated with postpartum depression and bipolar disorders, and low levels of both DHA and EPA have been associated with social anxiety disorder. Part of their benefit may be due to their anti-inflammatory action as established in

studies using the DII. Their benefit in treating people who suffer from various forms of depression is a reason for their common use as supplements to anti-depressant medications already in use. Doses as low as 1g/day have been shown to provide improvement, which is about the same dose as eating salmon three times a week (11,16). It is not common to eat fish meals this frequently in Western-style diets, and omega-3 fatty acids are scarce in these countries; however, many more Eastern-style diets have fish multiple times a week, often daily. Furthermore, omega-3 fatty acids are a natural molecule and have no known side-effects to consumers, meaning they are safe for use by children and pregnant women experiencing depression and to whom antidepressant medications may not be a safe option. The most potent food sources of omega-3 fatty acids include flax and chia seeds; fish such as salmon, halibut, mackerel, herring, and sardines; soybeans; broccoli; cauliflower; spinach; and olive oil — ingredients recommended for a healthy diet (17).

Molecularly speaking, mammals are not able to synthesize omega-3 fatty acids by their own metabolic processes. They must obtain the appropriate short-chain precursors, such as α -linolenic acid, through their diet. Then, the body uses these precursors to produce the long-chain omega-3 fatty acid EPA, discussed earlier. EPA consists of 20 carbons and five double bonds as compared to its precursor α -linolenic acid, which consists of 18 carbons and only three double bonds. EPA can further be utilized to synthesize DHA, which consists of 22 carbons and six double bonds. These long-chain fatty acids are then ready to aid in cell signaling and cell structure functions. For example, they are attached to the glycerol moiety in construction of many membrane phospholipids such as plasmalogens and phosphatidylserine (15,18; Figure 4).

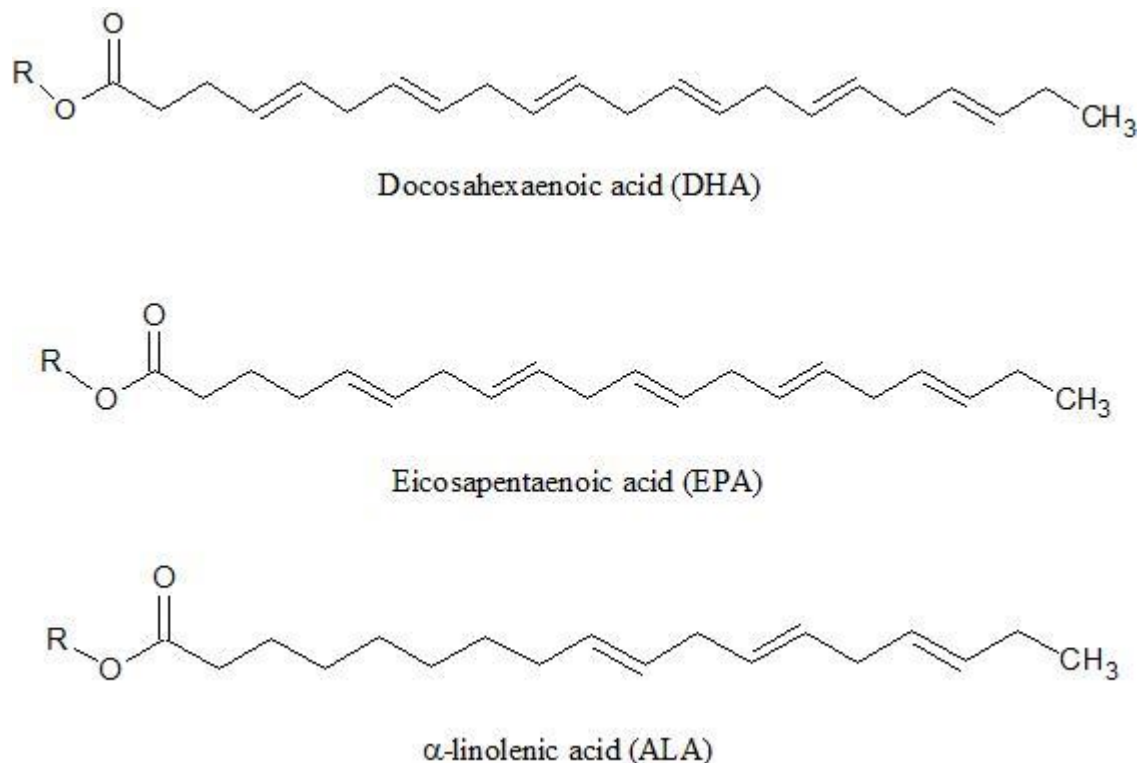


Figure 4. The short chain fatty acid precursor α -linolenic acid is utilized to synthesize the omega-3 fatty acid eicosapentaenoic acid, which is further utilized to synthesize the omega-3 fatty acid docosahexaenoic acid. Sketch made using ACD/ChemSketch software.

Furthermore, DHA levels can be measured in mother's breast milk and correlated with the mother's consumption of seafood; the higher the consumption of seafood by a lactating mother, the more DHA found in her breastmilk. High levels of DHA in breastmilk have been correlated with a significantly reduced occurrence of postpartum depression experienced by the mother. When the topic of inflammation is considered, DHA and EPA both do their part by hindering the release of IFN- γ , TNF- α , IL-1 β , IL-2, and IL-6, all of which are major proinflammatory cytokines. In adolescent populations with major depression disorder that was resistant to SSRIs, the measured DHA levels were markedly below normal. Supplementation

with omega-3 fatty acids via fish oil was effective in increasing long chain omega-3 fatty acid concentrations and boosting the antidepressant effects of the SSRIs (15).

The location that contains the highest concentration of DHA is the synaptic membranes of the nervous system, although it is also found in mitochondria and microsomes. DHA is a component of approximately 30-40% of the phospholipids in the gray matter of the cerebral cortex, which may explain why a higher intake of DHA is related to increased gray matter in regions of the brain that are associated with mood disorders (15,18). Studies have shown a direct relationship between increasing DHA in the diet of experimental mice and the amount of phospholipid content in their synaptic plasma membranes. Without these nutrients present, there is insufficient synaptic membrane material available to form membrane vesicles during the synaptic transmission process.

DHA works directly on synaptic vesicle function by enhancing the fusion mechanism of synaptic vesicles with the plasma membrane of the presynaptic cell. It does this by aiding in the expression of the SNARE complex protein syntaxin-3 and encouraging its interaction with SNAP-25. This is an essential step in the v-SNARE/t-SNARE complex that allows vesicles to be “pulled” into the plasma membrane with enough biological strength to fuse the phospholipid bilayers and release the neurotransmitters into the synapse, where they can elicit a subsequent action potential in the postsynaptic cell. DHA also affects the vesicle storage of all three of the monoamines described earlier that are potent in regulating depressive symptoms — norepinephrine, serotonin, and dopamine. Specifically, norepinephrine release is enhanced in experimental cells that contained a high membrane DHA content. The neuroprotective effects of DHA have already been established in studies focused on age-related deficiencies in omega-3 fatty acids and subsequent deficiency in learning and memory performance (18). The unique

biological effects of DHA on neuronal transmission are many and all appear to contribute to an enhanced overall neural function.

Magnesium. Unfortunately, magnesium has been largely reduced from Western-style diets by processing and refining. Studies have reported that approximately 70% of all Western-style diets contain less than the daily recommended 400-600 mg of magnesium. Furthermore, approximately 20% have less than 200 mg of magnesium, representing a severe deficiency. Magnesium is almost completely removed from drinking water, and 84% of magnesium is removed from whole wheat when it is converted to refined flour (19).

The refining process of grains and other foods began in the year 1905 as a means to prevent spoilage, and it is revealing to note that of Americans born before 1905 only 1% ever experienced depression before they were at the age of 75, whereas post-refinement era Americans had a much higher rate of depression: of the Americans born in 1955 alone, 6% developed depression by the much younger age of 24 (19). Because of the refinement process, only unprocessed whole wheat and other food sources such as nuts, buckwheat, fish, soybeans, and broccoli are considered high in magnesium. Green vegetables of any type will contain magnesium because the chlorophyll molecule contains magnesium at its center (17). The usefulness of magnesium as an anti-stress molecule has been well established for many decades, as it has been used in homeopathic circles in the form of magnesium chloride to treat anxiety, despair, depression, irritability, restlessness, insecurity, and discontent, among other symptoms. Current research is finding that there is a well-established relationship between magnesium deficiency and depression, and chronic stress has been shown to decrease free total plasma ionized magnesium, meaning there is a significant need for increased magnesium intake when individuals are in a period of life with chronic stress. The resulting magnesium deficiency means

there will be a downward spiral of depressive symptoms, which can worsen when paired with the pre-existing chronic stress, ultimately leading to a vicious cycle. Magnesium is necessary in more than 325 enzymes in the body, the majority of which are related to brain function; because of this, it can be hard to pinpoint etiology for the molecule's association with depression, but its role is all the more significant because of the molecule's broad scope of impact and far-reaching effects (19).

Several case studies have attested to the necessity of magnesium in any antidepressant endeavors. A 2006 case study focused on four individuals with various depression-related histories, where each individual was given doses ranging from 125-300 mg of magnesium with their meals and before bedtime and subsequently monitored in order to record any observations. The first case study was of a 59-year-old man with a previous, long-standing history of mild depression who quickly became suicidal after a period of extreme pressure and poor dieting, as he was eating mainly fast food. Even though he was unresponsive to many prescribed antidepressants, he showed immediate improvement with magnesium treatment. The first day of treatment resulted in a night with normal sleep, and within the next four days his depression improved significantly, especially within the 4-6 hours immediately following each dose of magnesium. The second case study involved a 23-year-old woman who had a good portion of her short-term memory and also some of her IQ lost due to a traumatic brain injury five years before starting the magnesium study. She became depressed at this period of her life due to poor diet and the declining academic performance she was experiencing as a result of her brain injury. Only one week after treatment with magnesium, she became completely depression-free and even recovered her IQ, short-term memory, and mental acuity — a rapid recovery considering the traumatic event occurred five years prior. The third case study involved a 35-year-old woman

who suffered from severe postpartum depression with each of her three past deliveries and took magnesium in preparation for her fourth delivery. The result was a healthy baby, and no occurrence of postpartum depression. A main theory for the development of postpartum depression lies in the fact that the fetus and placenta absorb extremely large amounts of nutrients from the mother, including magnesium. Lactation also results in the loss of magnesium, and when the mother does not restore this magnesium and overall nutrient loss, it may lead to the depression often experienced by new mothers post-delivery. The final case study was a 40-year-old man who was moderately depressed and had a history of poor diet, a ravenous appetite, alcoholism, smoking, and drug use. Treatment with magnesium doses resulted in him being symptom-free of depression within the first week, as well as decreased craving for food, smoking, cocaine, and alcohol (19).

One method of influence that magnesium has on the neurons of the brain is its regulation of calcium ion flow. Magnesium is essential in the regulation of Ca^{2+} movement through neuronal calcium channels, and its deficiency causes neuronal damage that can portray itself outwardly as depression. This neuronal damage is coupled with depression and a host of other symptoms because of the insufficiency of the neuronal network to function at par. In postsynaptic neurons, there is an *N*-methyl-D-aspartate (NMDA) receptor channel through which calcium ions and sodium ions pass into the cell, and potassium ions leave the cell. Magnesium ions will block the NMDA channel and hinder its function. Therefore, a deficiency in magnesium would effectively lead to less NMDA-receptors being blocked and an inflow of calcium ions that lead to excitotoxic calcium cascades. Too much calcium inflow into the postsynaptic neuron can be pathological and high calcium ion concentration has been documented in nearly all cases of depression. Calcium is used in the postsynaptic neuron for the

production of nitric oxide, which serves as a retrograde messenger that can cause synaptic dysfunction if produced in pathologic quantities (Figure 5). During the time period when magnesium was prevalent in food sources, there was emphasis on increasing calcium intake relative to magnesium intake. However, current refining methods have made this thought process obsolete, as it is becoming increasingly understood that Western-style diets are perhaps too calcium-rich and lack enough magnesium. Now, the ratio of magnesium must increase with relation to calcium if proper neuronal signaling in areas of the brain crucial to mood disorders is to be maintained (19,20).

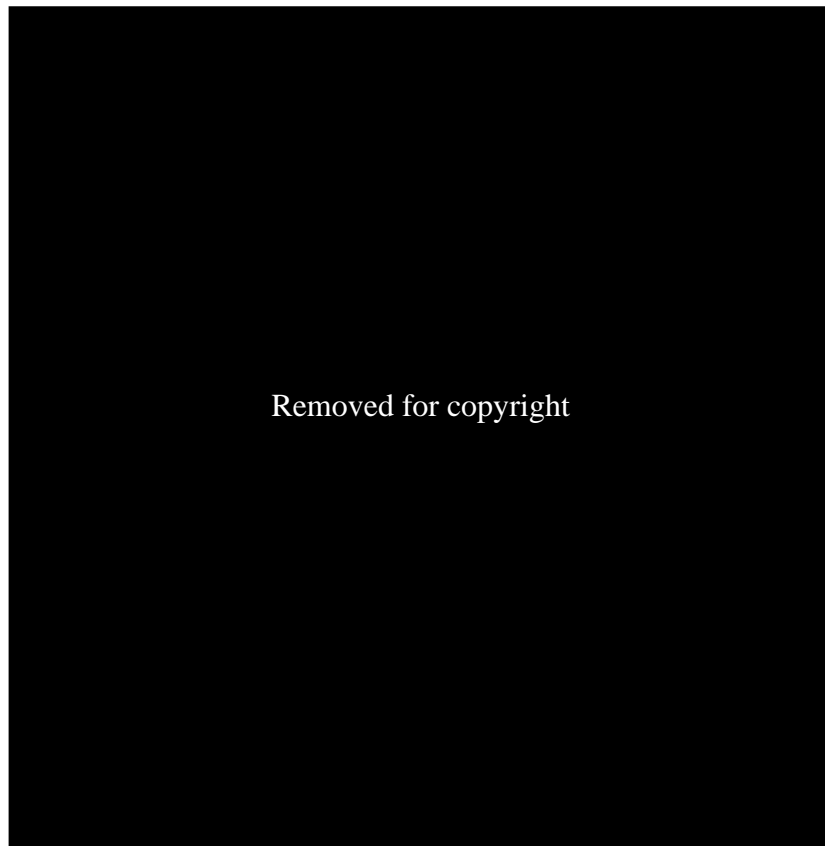


Figure 5. Magnesium regulates calcium ion flow in neurons by blocking the action of NMDA channels located in the postsynaptic neuron. From “Rapid recovery from major depression using magnesium treatment,” by G. A. Eby and K. L. Eby, 2006, *Medical Hypotheses*, 67(2), p. 366.

Vitamins. Deficiencies in B and D vitamins present another source of dietary concern. B vitamins are maintained in the diet by consuming foods such as asparagus, broccoli, spinach, bananas, potatoes, apricots, fish, nuts and legumes, whole grains, and various dairy products. Conversely, deficiencies in this vitamin occur when there is an over-consumption of caffeinated drinks, alcohol, and foods that are full of refined sugars. The B vitamins have long been associated with optimal neuronal performance, as vitamin B₁ is known to modulate cognitive performance, vitamin B₉ (folate) is essential in brain development and helps preserve memory throughout the aging process, and vitamin B₆ is necessary for the formation of some neurotransmitters and for the absorption of magnesium (17,19).

Vitamin D is strongly associated with seasonal affective disorder (SAD), common when an individual is deficient in this vitamin. Its increased incorporation into the diet of individuals has been shown to lead to improvement of SAD and overall general mood. One study in particular reported a 3.5x higher chance of developing depression for vitamin D-deficient individuals versus individuals who were maintaining sufficient vitamin D levels. Hypotheses for its function include its role in upregulating serotonin in the brain by regulating the gene coding for tryptophan hydroxylase, the rate limiting enzyme in the production of serotonin from its tryptophan precursor. Other hypotheses focus on the ability of vitamin D to maintain a low level of calcium ion in neurons by down-regulating channels in the hippocampus, such as the L-type calcium channel, and promoting the function of calbindin and parvalbumin, proteins necessary in stabilizing calcium concentrations in cells. Foods such as milk, tuna, and especially salmon are high in Vitamin D, which emphasizes the importance of keeping fish a part of any healthy meal plan (1,17).

Amino acids. In addition to vitamins and minerals, amino acids must be maintained in the diet in order to give the body the necessary precursors it requires to synthesize neurotransmitters. Tryptophan is the precursor for serotonin production, and tyrosine is necessary for the production of dopamine and norepinephrine. An average individual will convert approximately 1% of metabolized tryptophan into serotonin, which is accomplished in two steps by the enzymes tryptophan hydroxylase, which adds a hydroxyl group to tryptophan to form 5-hydroxytryptophan, and tryptophan decarboxylase, which removes a carboxyl group from this intermediate to form 5-hydroxytryptamine, or serotonin (9; Figure 6). Studies have found that depletion of dietary tryptophan can cause as much as a 30-60% decrease in brain serotonin levels and an increase in depressive symptoms, which shows great support for the monoaminergic hypothesis that places a high emphasis on the depression-altering effects of these crucial neurotransmitters (21). Food sources that help with maintaining proper levels of tryptophan include chicken, fish, peanuts, pumpkin seeds, turkey, soy, and eggs, although there are many sources for the essential amino acids.



Figure 6. Serotonin is produced from the precursor amino acid tryptophan. First, the enzyme tryptophan hydroxylase catalyzes the reaction from tryptophan to 5-HTP. Second, the enzyme tryptophan decarboxylase catalyzes the reaction from 5-HTP to serotonin. From “Serotonin, serotonin receptors and their actions in insects,” by R. Vleugels, H. Verlinden, and J. V. Broeck, 2015, *Neurotransmitter*, 2(1), p. 2.

Probiotics. Certain probiotic formulations have also been associated with anti-depressive metabolite production. The reasoning behind this lies in the fact that repeated stress alters the microbiome of the intestines, resulting in a reduction of beneficial microorganisms and providing for the growth of harmful microorganisms. Subsequent worsening of stress and anxiety due to this imbalance often leads to depression, and probiotics are a vehicle for reversal of this downhill

process. Probiotics are essentially any microorganisms that can be consumed and subsequently maintain or restore populations of beneficial bacteria in the digestive tract.

The microbiome contains more than 70 unique phyla of bacteria, accounting for 1-3% of total body mass for an individual. A healthy microbiome has been associated with the production of anti-inflammatory compounds such as short chain fatty acids and antioxidants, and also beneficial molecules such as serotonin and gamma-aminobutyric acid (GABA), another signaling molecule that helps quell anxiety. Although the gut microbiome is always present, its composition can change from person to person and depends greatly on the food and nutrients the individual consumes. Common species that have been associated with reductions in anxiety and depressive behavior include *Lactobacillus helveticus*, *Lactobacillus rhamnosus*, and *Bifidobacteria longum* (8,22,23,24).

A gut microbiome that is not healthily established is prone to pathogenic influence. Infections by pathogens lead to immune responses characterized by the release of the pro-inflammatory cytokines IL-1, IL-2, IL-6, and TNF- α , which have an influence on depression that is well documented in the inflammatory theory of depression. Essentially, these cytokines can alter the function of enzymes needed to synthesize molecules such as dopamine from their precursors. Probiotics act against pathogens, and thus the inflammatory responses they can cause, by physically displacing them and their adhesion to the gut on their way through the digestive tract. Healthy bacteria compete for the receptors of epithelial cells and exclude pathogenic binding, along with decreasing the pH of the lumen and causing epithelial cells to produce the protein defensin, which both contribute to an environment unfit for pathogens. Furthermore, probiotics produce molecules that are antagonistic of the inflammatory cytokines and thus promote anti-inflammatory effects. *Bifidobacterium infantis* has been associated with

normalizing concentrations of inflammatory cytokines, and the subsequent decrease in pro-inflammatory cytokines has been associated with an increased amount of regulatory T cells that play a role in down-regulating chronic inflammation via the immune system (8,22,24).

In regard to neurotransmitter function, probiotics are known to encourage the production of tryptophan and tyrosine, the key precursors to the neurotransmitters that influence mood. More specifically, *Bifidobacterium infantis* can elevate levels of tryptophan and therefore serotonin, and *Lactobacillus*, *Lactococcus*, *Streptococcus*, and *Bifidobacterium* strains of bacteria can all increase GABA concentrations. Bacteria produce these amino acids because they metabolize various proteins and lipids from ingested food and therefore enhance the availability of these amino acids as well as fatty acids such as omega-3 fatty acids. Effective probiotic foods include yogurt, cheese, fermented fruits and vegetables, olives, and kimchi (8,22,24).

Conclusion

The previous discussion has highlighted various leading hypotheses for the etiology of depression, including the inflammation theory and the monoamine theory. Furthermore, the incorporation of diet into these methods of depressive onset has been analyzed by delving into specific food influences. Those that are indicative of an unhealthy diet and have been associated with an increase in depressive symptoms include pro-inflammatory diets, high sugar intake, and high caffeine intake. Those that are indicative of a healthier diet and have been associated with a decrease in depressive symptoms include anti-inflammatory factors such as omega-3 fatty acids; ample nutrition via proper vitamins, minerals, and amino acids; and natural probiotics.

The observed correlation between improper fulfillment of dietary needs and the onset of depression seems to be biologically supported, and many plausible mechanisms of action for these correlations have been discovered. Although medications are helpful and sometimes

necessary, they can often pose serious risks and should be considered after a thorough analysis of an individual's diet has been attempted and adjustments made where needed. If an individual's likelihood of depression can be reduced by non-medicinal means, it is preferable to pursue that method, as it allows the body to develop natural homeostatic responses that serve to strengthen its future responses to similar homeostatic disruptions. Dietary analysis is applicable to all individuals and, with further research, can lead to critical contributions for the medical field and future mental health diagnoses.

The food we consume is directly converted into the resources our bodies can utilize, and we should understand that the food provided to us is not necessarily tested for long-term, unforeseen impacts such as depression. We can end up starving our body not of calories or energy but of essential molecules needed for its proper function. Therefore, we must be discerning in our dietary choices and remember how to keep our brains healthy and our neurons functioning the way they were designed to function.

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