The Underlying Mechanisms of Brain Allergies

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Introduction

The term "brain allergy" came into popular use several years ago to describe the phenomena of psychiatric symptoms related to substances in one's diet and environment. This paper will focus on the role of nutrition in brain allergies. Brain allergies will be explored as either immune mediated or nutrition mediated malfunctions. Within these two categories, several hypothetical mechanisms are discusssed. Mechanisms underlying the disorders are proposed to provoke further hypotheses.

Most mental disorders are attributed to an imbalance of brain chemicals. Psychopharmacological treatment is the preferred mode of therapy for almost all psychiatric problems at present. Unfortunately, efficacy is minimal, debatable, and wrought with side effects and organ damage. While antidepressants and antipsychotics do alter brain chemistry, they do not correct the primary dysfunction. It is a naturopathic mandate to attempt to treat the root of the problem. Therefore, it is imperative that the naturopathic physician understand the underlying mechanisms of the problem. Though it may be difficult to treat the "root" when it is not fully known, there is merit in supporting the body's natural defenses and providing for its needs, as is done in naturopathic medicine.

Mind-Body Connection

Psychiatry so often overlooks the impact of oral chemical input as a contributing factor to brain chemistry. This seems ironic since pharmaceuticals are intended to correct brain chemistry. The North American diet commonly contains neuroactive foods such as coffee, tea, cola, chocolate, and certain spices and these effects vary depending on the individual. Many of us are familiar with the augmented alertness, sweaty palms, and increased heart rate associated with the consumption of a cup of coffee. Clearly, effects on the physical and mental planes can be directly linked to dietary input. Nevertheless, it is the fact that some reactions become debilitating that makes the process pathological.

Good mental health depends on good nutrition. The brain is the organ of the mind and very much part of the body. Brain chemistry functions on neurotransmitters, neuropeptides, and hormones made from building blocks such as amino acids and cholesterol. These building blocks are obtained from the gastrointestinal tract. Proper functioning of the gastrointestinal tract requires healthy brain chemistry. The interdependence is inevitable.

Many psychiatric disorders are not confined to the mind but are accompanied by a host of physical complaints such as indigestion, fatigue and headache. Even the psychoactive medications used to treat mental disorders have physical side effects such as dry mouth, weight gain, and tremor. As mental symptoms do not occur in isolation, so should treatment not be limited. It is the holistic health practitioner who will offer treatment in accordance with the mind-body unity and ultimately promote real recovery.

Psychoneuroimmunology

A connection between mood and the immune system has been suggested, with brain chemistry as the link. Ader suggests that the limbic system is where chemical messengers from the immune system have action.[1] Felten noticed that the autonomic nervous system can be affected by emotions; in particular, insulin and blood pressure regulation. He also discovered synapse-like contacts linking the autonomic nervous system with lymphocytes

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and macrophages.[2] Apparently, neurotransmitters regulate immune cells.

The most vulnerable place in the brain for immune signal effects is the hypothalamus because it lacks a blood brain barrier (BBB). During a cold, the hypothalamus receives cytokine stimulation that alters homeostatic set points leading to fever, loss of appetite, insomnia and diaphoresis. Even the common cold can make a person feel irritable, restless, achy, and down. One might assume that humoral cytokines and histamines would not enter other brain structures because of protection by the BBB but that assumes that the integrity of the BBB is intact. Some people may have compromised barriers leaving them with more widespread effects of unwelcome substances.[3]

Psychoimmunoendocrinology

The elucidation of synaptic transmission as the means of neuronal communication in the brain was revolutionary. It is convenient to think of the synaptic event as a packaged phenomenon, but neurotransmitters are not selective, their receptors are. The distribution of receptors and synaptic vesicles for specific neurotransmitter substances do not correlate well within regions of the brain. Less than two percent of neuronal communication actually happens at the synapse.[4] A neurotransmitter substance can bind a postsynaptic receptor, bind a presynaptic autoreceptor, be degraded by enzymes, be taken up presynaptically, or diffuse into the environment of the brain until it can influence receptors distal to the site of release. In other words, the brain's communication system resembles the endocrine system. This concept opens up a wide range of possibilities for chemical influences at various sites in the brain.

Endocrine and immune influence on the mind occurs via receptors present on brain tissue. The brain has receptors for sex hormones. *In utero*, the developing brain is gender specific under the influence of estrogen and testosterone.[5] The release of certain neuropeptides may be modulated by feedback mechanisms. For example, thyrotropin releasing hormone is upregulated by dopamine and down-regulated by serotonin.[6] Histamine, a common secretion of immune activity, has at least three types of receptors to choose from in the brain.[7] Histamine is now being recognized as a neuoractive amine on top of its role in the rest of the body. Furthermore, hormones and cytokines have effects on the enzymes controlling brain communicating substances. For example, conjugated estrogen inhibits monoamine oxidase activity thereby elevating mood.[8]

Allergic Reactions

Symptoms: Adverse reactions from food are usually termed "food allergy" if it is histamine related or "food hypersensitivity" if it is otherwise. Allergic reactions to food exposure can range from the very mild, as in hives, to severe, the most serious being anaphylaxis. That type of response, however, is not the focus of this discussion, which intends rather to explore the "masked allergy" that may or may not involve the immune system directly but does have an impact on brain's function: i.e., food intolerance that slowly inhibits wellness.

What Pfeiffer called the "allergy-tension-fatigue syndrome" involves a variety of symptoms ranging from hyperactivity to somnolance. The most commonly incriminated foods are cow's milk, wheat, beef, bananas, chocolate and sugar. The neurological symptoms he noticed in his patients when they ate some of these foods included:[9]

1. Specific learning disability
2. Perceptual-motor deficits
3. General coördination deficits
4. Hyperkinesis
5. Impulsivity
6. Emotional lability

7. Short attention span
8. Abnormal EEG
9. "Equivocal" neurological signs (eg. speech impairment, transient eye paralysis, altered finger coördination)

Bates believes that a person should consider food hypersensitivity when experiencing such symptoms as:[10]

1. Headache
2. Insomnia
3. Depression
4. Irritability
5. Food cravings
6. Anxiety
7. Fatigue attacks
8. Mental cloudiness
9. Nightmares

Some believe that childhood allergies may be outgrown, but what might actually be happening is the development of tolerance and addiction. Randolf describes a continuum between allergy and addiction. In food addiction, exposure to the allergenic food provides partial relief and the emergence of a delayed reaction that subsides upon eating the offending food repeatedly. This addiction can be converted back into allergic reaction by reintroducing the offending food after a 4-6 day fast. After the fast, the body resensitizes itself to the allergen and reacts against it.[11]

Immune Mediated Factors

Leaky Barriers: Presumptions are made that selectively permeable barriers are perfect. In medicine, it behooves the practitioner to consider that extraneous factors may alter the functioning of such membranes. Therapeutically, the permeability of the BBB can be increased by inducing fever or through electroconvulsive therapy. This would decrease the lag time of drug effectiveness. Conceivably, abnormal electrical activity in the brain or the presence of pyrogenic cytokines could have similar effects. Since abnormal EEG readings and cytokine-like symptoms (see below) can occcur after eating allergenic foods, the brain could be susceptible to chemical influences beyond the norm.

Histamine: Histamine is made from the amino acid histidine. It is interesting that the same L-aromatic amino acid decarboxylase that converts histidine into histamine also converts L-dopa into dopamine. Histamine is then stored in magnocellular neurons of the posterior hypothalamus or in mast cells throughout the body. Histamine undergoes calcium dependent release upon depolarization from neurons in the hypothalamus. Turnover is rapid along its divergent, mostly unmyelinated fibers that project to telencephalic, mesencephalic and cerebellar structures with few synaptic contacts.[12] Histamine originating from mast cell degranulation, on the other hand, is initiated by immunoglobulins (IgE), weak membranes, or cytokine activity. This histamine ends up in the tissue of the immediate vicinity until it gets carried in the blood and spreads to the rest of the body. This type of histamine is more likely to be vagrant and have effects perhaps unintended.

In serum, histamine is usually bound to protein.[13] This would make protein intake and metabolism assessment appropriate when investigating histamine levels. Histamine in the blood has the ability to chelate Cu and Zn.[14] This may or may not be useful in modulating mineral levels, depending on the person's ability to further process and excrete histamine metabolites.

There are three classes of histamine receptor: H1, H2, and H3. The first type, H1, is partnered with inositol phospholipid hydrolysis using a G protein second messenger. Stimulation leads to contraction of smooth muscle, increased capillary permeability, hormone release and brain glycogenolysis. The fact that the brain's glucose supply is controlled somewhat by histaminergic activity means that thought and mood can be influenced. The H2 receptor uses adenylate cyclase and a G protein to change levels of cAMP. H2 stimulation pro-

motes smooth muscle relaxation, gastric acid secretion, positive chronotropic and inotropic actions and inhibition of the immune system. The third type of histamine receptor is considered an autoreceptor that controls synthesis and release. It can also inhibit the presynaptic release of other monoamines and peptides in the brain and peripheral tissues.[15] Any problem with production or function of the H3 receptor would result in overproduction or excessive release of histamine such as in a hypersensitive individual. Since the brain histamine distribution is richest at the hypothalamus, histamine is thought to control some of the homeostatic functions including appetite, thirst, thermoregulation arousal, autonomic activity and hormone release. Common side effects of antipsychotic medication are sedation, dry mouth, and weight gain. Antipsychotics are very much like antihistamines.

Histamine is implicated in the manifestation of schizophrenia. Two extremes have been observed in schizophrenic patients. One is histapenia where serum levels of histamine are low. This situation produces the overstimulated type of schizophrenia. The other extreme is called histadelia when histamine levels are high in the serum. Histadelic schizophrenics tend to be suicidally depressed.[16] The profound effects associated with histamine may not be causal, but there might be a deeper malfunction affecting several neuroactive substances. Many schizophrenics have high blood copper which could also tie into the erratic histamine levels. It has been noticed that schizophrenics seldom exhibit a typical allergic response (hives, hayfever) and it has been suggested that histadelic schizophrenia is actually a kind of allergic response–perhaps even a food allergic response.[17] It is important to note that histamine and other amines can be produced in the large bowel.[18] Food can stimulate not only histamine release but also its synthesis.

Antibody: The antibody's role in food allergy is one of a mistaken invader. Food as sustenance is mandatory for survival and the digestive system is designed to process it. Sometimes, the process is fallable and results in an immune response. The variable region of an antibody is suposed to bind to foreign proteins in the blood. In the "leaky gut" syndrome, protein particles get absorbed while they are too large to evade the immmune system. When immuno-globulins agglutinate on a food protein they may then bind via the crystaline fragment to signal immune cells, the most common of which is the mast cell, hence histamine release. Sometimes the agglutination contaminates the blood and taxes the liver and kidneys. Coppo found that high amounts of IgA immune complexes in the blood led to primary IgA nephropathy which would clear when the same patients were on a gluten-free diet.[19] Kovacs studied the relationship between intestinal permeability and IgA nephropathy. He detected high IgA antibody titres especially to gliadin, soy, oat, and ovalbumin.[20] Among psychiatric sufferers, 20 percent of schizophrenics have an antibody to wheat gliadin and 50 percent showed lymphocyte reactivity to glutenin. These figures are more frequent than in controls.[21]

Cytokines: Some activated antibodies will attach to T and B cells. Such activation will result in cytokine signals, antibody replication, and clone formation. A cow's milk protein called alpha S1 casein can stimulate CD8 and T cell clones to express receptors for Interleukin-4. Once conjugated, gamma-interferon is secreted.[22] Cytokines in the blood stream have a variety of physiological consequences that are interpreted as symptoms, (see Table 1, p.9). Cytokines tend to be high in hypersensitive people.[23]

PGE1 Deficiency: Prostaglandin E1 (PGE1) deficiency has been proposed as being implicated in the etiology of food allergy and the development of some mental disorders such as schizophrenia. PGE1 regulates calcium uptake in neurons and therefore in-

fluences neurotransmitter activity. A deficiency is associated with disturbed gut absorption and malregulation of T suppressor cells. Chronic alcohol use or a genetic enzymatic defect (D6D enzyme) will create a PGE1 deficiency that leaves the gastrointestinal tract high in histamine and gastric acids while being low in protective mucus.[24] This would set the stage for the "leaky gut" scenario previously discusssed and the subsequent hypersensitive individual. The imbalance of eicosanoids and prosta-glandins can then harm the brain via inflammatory reactions and result in depression or other mental illnesses. Horrobin hypothesized a PGE1 deficiency model of schizophrenia which was supported by Kaiya who watched schizophrenic symptoms improve with intravenous infusions of PGE1.[25]

Nutrition Mediated Factors

Vitamins and Mineral Deficiencies: Many nutrients when deficient can cause improper functioning of human physiology, but here the focus is on those that produce mental or emotional symptoms.

The most well known of the vitamins that modulate mood is vitamin B_3, with B_6 running a close second. Niacin is required for formation of nicotinamide-adenine dinucleotide (NAD). Much of the brain's chemistry needs adequate NAD. Vitamin B_3 deficiency symptoms include anxiety, depression, chronic fatigue, hyperactivity, insomnia and aprehension, not to mention vague somatic complaints. The syndrome resembles pellagra. While 20 mg/d niacin is adequate to prevent pellagra, once a deficiency has ensued, needed doses rise dramatically to 1-2 g/d in acute and 2-4 g/d in chronic cases.[26] Niacin deficiency has been largely implicated in schizophrenia and Hoffer and Osmond demonstrated that administration of B_3 significantly reduced hospitalizations.[27]

B_6 is important as it is required for metabolism of all the amino acids and maintaining a stable immune system. It is also part of trytophan-niacin metabolism. A deficiency of these vitamins could lead to a tryptophan overload which causes undesirable perceptual and mood changes.[28] Such a situation would be greatly aggravated by tryptophan rich foods (eg. milk).

Table 1. Cytokines and their physiological effects.*

Symptoms	Cytokines Involved
Fever	IL1, IL2, INFa,b,g, TNF
Somnolence	IL1, INFa
Agitation	IL2
Combative	IL2
Impending Doom	INFa
Hallucinations	INFa
Inertia	INFa,TNF
Memory Loss	TNF
Dysphasia	TNF, INFa
Headache	INF's, TNF
Loss Of Appetitie	TNF, IL2
Fatigue	INF's

*Taken from Gislason S, 1998 IL = Interleukin INF = Interferon TNF = Tumor Necrotizing Factor

A deficiency of vitamin B_1 can produce: loss of appetite, irritability, depression, confusion, memory loss, lack of concentration, sense of impending doom, and acute sensitivity to noise. A fairly large dose of vitamin B_1 should alleviate the symptoms.[29]

Folic acid deficiency is often paired with high copper. This duo has been found in patients with an allergy to wheat gluten. Wheat gluten sensitive patients usually are simultaneously low in histamine. Pfeiffer treats this condition with vitamins B_3, B_{12}, and folic acid (2 mg/d)to make histamine rise and psychiatric symptoms improve.[30] This should be done carefully because too great a rise in histamine could result in high histamine depression.[31]

Vitamin B_{12} deficiency is common in mental patients. Aside from pernicious anemia, symptoms range from poor concentration to stuporous depression and may include agitation and hallucinations. Deficiency brings with it danger of demyelination of the spinal cord and brain. Treatment involves 1000 mcg/ml hydroxycobalamin injections weekly or monthly.[32]

When pantothenic acid is deficient, symptoms are the following: emotional upset, irritability, depresion, and dizziness. Specific requirements vary widely but pantothenic acid suports the adrenal gland. Supplementation allows the person to withstand more physical and emotional stress.[33]

Vitamin C also supports the adrenal gland. This antioxidant quenches stress aswell as free radicals. Schizophrenics tend to have low blood concentration of ascorbic acid and some can take up to 40 g/d before it spills into the urine.[34] Low levels of vitamins A and D leave one with overreactive mucus membranes. These vitamins are useful in asthma and might prove to be helpful in treating cerebral allergies and schizophrenia because of their benefit to gastric mucosa. Vitamin A at 10000 IU TID and vitamin D at 400-1250 IU TID should be sufficient but severely allergic patients may require slightly more for a while.[35]

Magnesium levels fluctuate according to dietary calcium, antioxidant utilization, alcohol intake and enzyme activity. A deficiency can produce depression, irritability, and when severe, paranoia.[36] Magnesium is being investigated as a therapy in depression and schizophrenia.

Mineral Excess: The most significant excess associated with mental symptoms is that of copper. As previously mentioned, high copper levels are correlated with low folic acid, low histamine and histapenic schizophrenia. One can lower copper by administration of manganese and by giving zinc. Zinc will compete with copper for absorption.[37] Rutin (60 mg/d) will also decrease copper through a mechanism that elevates histamine at the same time. The mechanism could involve a lessening of the activity of histaminase, a copper-containing enzyme that usually destroys histamine.[38]

Chain Reaction

There seems to be a direct relationship between nutritionally deficient states and maladaptive allergy, food addiction, or chemical reactivity. Lack of variety and quality of food uses up enzymes while not providing sufficient nutrients for health. A nutritionally deficient state can be in the cells, tissues or organs. Nutrient deficiency allows an acute histaminic reaction. Immediate inflammation and edema decrease oxygen to the tissue which favors invasion by microörganisms. Once infected, toxins are produced that lead to a secondary nutrient deficiency as the body attempts to resolve the infection. Eventually, immune defenses get depleted and hence invite more infections. This chain reaction culminates in more severe allergic sensitivity.[39] Addressing nutrient deficiency is a good place to start in treatment of hypersensitivity.

Dysbiosis

Dysbiosis is a concern because it affects the proper functioning of the digestive tract. One type of gut flora contami-

nant is aspergillus, a fungus found in peanuts. Aspergillus produces aflatoxin which alters the hepatic feedback mechanism for biosynthesis of cholesterol. Too much of this aflatoxin increases cholesterol levels only to have it incorporated into cell membranes making them rigid. Unstable cell membranes are more likely to break. When mast cells are fragile, they will more readily release histamine, presenting as a hypersensitive allergic state.[40]

People with many food sensitivities could really be suffering from a toxic dysbiotic gut. Cott found that these patients responded adversely to all food challenge testing and that they got well during a fast. When the incriminated microorganisms were starving, they could not produce the toxic byproducts that aggravate the host system.[41]

Pancreatic Dysfunction

Malfunction of the pancreas leads to problems of pH, amino acid deficiency, protenemia, and low lipase activity all of which disturb the central nervous system. Stress may act as an etiological factor in the development of food allergy in the following. The pancreas is sensitive to emotional and physiological stress, to which it responds by producing less pancreatic bicarbonate. Insufficient bicarbonate can lead to metabolic acidosis after a meal. Because pancreatic enzymes need an alkaline medium to function, they do not breakdown proteins properly and end up getting denatured themselves. Hence, an amino acid deficiency develops. Undigested proteins are then absorbed into the blood through intestinal mucosa and evoke a kinin-inflammatory reaction throughout the body.[42] This sounds remarkably like the "leaky gut" syndrome. Kinin reactions in the brain alone can lead to diagnosis of schizophrenia, bipolar disorder, psychotic depression, hyperkinesis, hallucinatory and delusional disorders, autism or learning disabilities.[43]

Amino Acid Disproportion

Protein malnutrition frequently predates amino acid deficiency. Logically, low caloric intake could produce an amino acid deficiency. Because amino acids are building blocks for enzymes and neuro-transmitters, a deficiency would have far reaching consequences. Availability and balance of amino acids contribute to brain function. Sulphur-rich amino acids (methionine, cysteine and cystine) are known to quench free radicals and chelate heavy metals, like lead, mercury, and aluminum.[44]

Therapeutically, certain amino acids may be used to reestablish balance. Methionine is considered a brain detoxifier because it clears the body of histamine. This would be beneficial in treatment of histadelic schizophrenia or depression (200-1000 mg/d with Mg and B_6.[45] Histidine, on the contrary, should be used with caution in histadelic conditions because it is a precursor of histamine. Therefore, histidine would benefit histapenic schizophrenia.

Aminoaciduria is a condition that occurs from the inheritance of an autosomal recessive trait, kown as Hartnup disease. The problem arises from malabsorption in the small intestine of tryptophan, phenylalanine, methionine, and other monoaminomonocarboxylic amino acids. The accumulation feeds gut flora and certain byproducts like indoles, kynurenine and serotonin are absorbed via the bowel and later appear in the urine. This disease also carries with it defective conversion of tryptophan to niacinamide and it manifests much like pellagra with the rash and mental symptoms which aggravate with stress and poor nutrition.[46] A similar problem with amino acid transport across the wall of the small intestine and compromised formation of niacinamide has been suggested as part of the etiology of schizophrenia.

Another way that tryptophan can be involved in neurochemical imbalance is by culpable microrganisms. Tryptophan can

be synthesized from erythrose-4-phosphate and phosphoenolpyruvate by Escherichia coli and other microorganisms.[47] Excess tryptophan in the system can lead to excess amounts of serotonin and possibly serotonin induced depression.

The ability of the brain to create serotonin is contingent on the availability of tryptophan and other amino acids in the blood. Tryptophan levels in the brain are increased by high serum tryptophan or low serum concentration of other amino acids competeing for absorption. Since blood tryptophan is not regulated, levels reflect food intake. Interestingly, insulin has the effect of favoring tryptophan entering the brain, promoting serotonin production.[48] Perhaps this helps explain why eating sweets makes one feel good at first, but too much can make one feel bad.

Metabolite Opioids

Opioids derived from enzymatic hydrolysis of milk and wheat have been incriminated in mental symptomotology.[49] Milk protein fragments are capable of binding opioid receptors. Some milk derived opioid agonists include alpha-casein, beta-casein, alpha-lactalbumin, and beta-lactoglobulin.[50] The concept that neuropeptides can be food-born, especially from milk, is supported by Chabance.[51] Gastric absorption of these exorphins could be responsible for certain neurological reactions and the addiction phenomenon of food allergy.

Treatment

Supplements: While allopathic medicine tends to use antihistamines and various tranquillizers to treat allergies and psychological symptoms, it might be more prudent to attempt to rebalance the body's systems through supporting natural processes. The truly healthy body does not overreact to everyday environment. Various hypersensitivity reactions should be viewed as warning signs of inefficient health.

Supporting the body with vitamins and minerals could give the allergic person the boost needed to begin repair. Vitamins B_3, B_6, B_1, B_{12}, folate, pantothenate, C, A, and D are worth investigating in any case of food allergy. Magnesium might also be appropriate. The relationship between copper and histamine seems to be a significant factor in a psychological continuum. This metal probably has more action than previously thought.

In cases of leaky intestinal mucosa or fragile cellular membranes, essential fatty acids would be highly indicated. Additionally, digestive enzymes may prove effective at preventing macromolecular absorption of allergenic proteins. Enzyme supplementation could help the pancreas recover and begin to function normally again.

Probiotics are suggested if a dysbiotic gut is suspected. Reducing toxin load could lessen irritation of the gastrointestinal linings and return proper functioning.

Elimination Diet: Elimination diets have proven to be relatively sucessful once intensive testing has confirmed the allergen(s). Sometimes a modified elimination diet or brown rice diet is embarked upon in order to better heal the gastrointestinal tract and prevent immune initiation. Later, a four day rotation diet may be adequate to avoid hypersensitivity.

If the problem lies in an amino acid tranport malfunction as in Hartnup disease, serious limitations on protein sources must be embraced. Niacin supplementation is adjunctively indicated. In the case of an E. coli colonization, antimicrobials might be effective at controlling the byproduct contamination.

Moderation: "Moderation" has become a popular motto. With all the stress of modern lifestyle it is a challenge to maintain good health. The overuse of stimulants and the lack of nutrient-dense food contribute to a precarious state of health. Even eating too much of the same kind of food can be harmful, as it can overload the

digestive processes, especially certain enzymes. Therefore, variety is very important.

Psychotherapy: Psychotherapy must be mentioned because it does have an effect on the mind. When allergies affect the brain, it can be very confusing for the patient. Perceptions and cognitions are altered and therapy can help with interpretations and coping mechanisms. One purpose of this paper is to emphasize the legitimacy of food sensitivities in the etiology of psychiatric disorders. There is some speculation that many hypersensitive people have a history of emotional trauma. When this is true, psychotherapy certainly has a role to play. If it is not the case, therapy must be secondary to nutritional therapy.

Conclusion

Empowerment To Patient: Every individual has his or her own optimums and they should be respected if optimal health is the goal. For those who have suffered without significant relief, they are encouraged to reassess the situation. The problem of brain allergies is complex but it deserves attention. A well devised individualized protocol and some willpower may be the solution that makes the difference.

Prevention: A wonderful message here is not only one of alternative treatment, but also of the power of prevention. Much of what has been discussed is preventable through good nutrition, stress management, and lifestyle. It is not wise to wait until there is a problem that needs fixing. The body and mind depend on one another, use the mind to help the body to protect itself.

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