Balancing Brain Chemistry to Treat Depression

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Introduction

It is taking a long time for the scientific community to fully accept that what a person eats can influence their mental state but in the last few decades progress in this area has been rapid. Taking a very basic view of the subject there can be no doubt that nutrition is intimately involved with mental health as the brain and its chemical messengers are ultimately derived from food. Convincing doctors used to the traditional approach of treating mental disturbance and depression (drugs or psychotherapy) to consider the nutritional treatment approach is more difficult than simply pointing out this fact. Fortunately there is now a large amount of research supporting the view that nutrition has a role to play in promoting mental health, this article will review some of this research.

It is well established that neurotransmitter imbalances can lead to mental dysfunction and depression and in fact most drugs currently being used in this area of disease aim to restore chemical balance within the nervous system (1). As some of the research mentioned in this review shows, certain nutritional factors may be able to promote chemical normality in the same way as current pharmaceutical treatments but without the side effects associated with drug therapy.

Within a discussion about depression there must be some mention of genetic factors as there is no denying that the risk of developing depression, particularly a severe form, is influenced by genetics (2). It is likely that certain people are born with a predisposition to biochemical imbalances within the brain and then an inadequate nutrient intake compounds the problem. Eventually the situation deteriorates until there is expression of disease. What this means however, is that even disease with a genetic component may possibly be reversed given the correct nutrients to balance brain chemistry.

Brain chemistry

The brain is composed of about 100 billion neurones, the cells of the nervous system that communicate messages to each other, making up what is termed grey matter. The processes that extend from the cells to meet up with other cells constitute the white matter of the brain. Amongst the neurones are cells called neuroglia. Their role is to support, protect, and repair the neurones.

Neurotransmitters are chemical substances that pass between neurones relaying messages. Examples include acetylcholine, histamine, adrenaline, noradrenaline, dopamine, and serotonin. All of these are well-studied neurotransmitters, and the effects of too much, or too little on the mental state are well observed. In addition neuromodulators and neurohormones are further classes of chemicals that affect nervous function. Neuromodulators modulate signal transmission either pre- or post-synaptically and neurohormones behave like neurotransmitters but act at a site distant

from their release. In practice it is not possible to categorise these units of chemical communication so rigidly as many substances have actions that apply to each group.

In truth scientists have only realised relatively recently just how complex the body's system of chemical messengers is. It is very unlikely that current knowledge describes the full story.

Nutrients and neurotransmitter balance

The neurotransmitters most closely associated with depression are noradrenaline and serotonin and low levels of these compounds are implicated in some forms of the condition [3,4].

These and other neurotransmitters such as histamine and dopamine are derived from amino acids. The precursor amino acid of serotonin, for example, is tryptophan. Other neurotransmitters such as aspartate, glutamate and gamma-aminobutyric acid (GABA) exist simply as amino acids without modification.

As the links between neurotransmitters and amino acids are so close it is easy to imagine how deficiencies of these nutrients could lead to changes in the pattern of neurotransmitter production. It is relatively rare to find general protein deficiencies in people living in developed countries, however deficiencies of specific amino acids are more common and could be a feature of an inadequate diet such as an ill thought-out vegan diet.

For general good health and the prevention of depression a balanced diet providing the full complement of essential amino acids would be recommended. For the treatment of such conditions however, some scientists have considered the possibility of manipulating the levels of amino acids in the brain in order to influence neurotransmitter production [5].

Tyrosine is a very important amino acid in terms of nervous function as it is required for the formation of catecholamine-type neurotransmitters, dopamine, noradrenaline and adrenaline. Very few studies have investigated the effects of tyrosine on depression. Of the research that has been done, some studies suggest that tyrosine is an effective anti-depression treatment in some individuals [6,7] others, however, suggest that it is not [8].

Phenylalanine is a precursor of tyrosine and has proved to be more successful in the treatment of depression than tyrosine [9,10]. This is probably due to the fact that, aside from its role in catecholamine synthesis, this amino acid can be decarboxylated to phenylethlamine (PEA) [11]. This compound has amphetamine-like stimulant properties and is suggested to be an endogenous stimulatory or antidepressive substance in humans. Low urinary levels have been found in depressed patients [11,12,].

Tryptophan is another amino acid that has been used to manipulate neurotransmitter levels as it is the precursor to serotonin [13,14]. Tryptophan is not available to buy as a supplement because of a contamination incident that occurred in the 1980s however 5-hydroxytryptophan (5-HTP), which is a compound occurring further along the serotonin pathway, is available. 5-HTP has shown more consistent positive results in the treatment of depression compared with tryptophan [15-18]. 5-HTP's increased effectiveness is

probably due to the fact that it does not require a transport molecule to cross the blood-brain barrier, unlike tryptophan. Also not all tryptophan is converted to serotonin, some follows an alternative biochemical pathway and is converted to a compound called kynurenine. 5-HTP is not converted to kynurenine and therefore more is available for serotonin production. Double-blind studies have shown 5-HTP to have 'equipotency' with serotonin reuptake inhibitors (SRIs) and tricyclic antidepressants in terms of effectiveness and to offer several advantages in that it is less expensive, better tolerated and associated with fewer and much milder side effects. (16,18).

Based on findings that a high carbohydrate meal induces feelings of calm and reduced tension compared to a high protein meal, R. J. Wurtman proposed that the levels of serotonin in the brain could be influenced by the proportions of carbohydrate and protein in the diet.

Wurtman suggested that a high carbohydrate diet increases the ratio of the plasma concentration of tryptophan relative to the other large neutral amino acids e.g. tyrosine, phenylalanine, leucine, isoleucine and valine (19). This occurs because insulin released in response to the carbohydrate load facilitates uptake of most amino acids into peripheral tissues, but not tryptophan. Since tryptophan and the other large neutral amino acids compete for entry into the brain, and the rate limiting enzyme for serotonin production (tryptophan hydroxylase) is not fully saturated with substrate under normal conditions, an increase in the plasma ratio of tryptophan to the other large neutral amino acids leads to an increase in brain serotonin synthesis. In contrast, consumption of a meal high in protein can be expected to have the opposite effect, primarily because most dietary proteins contain relatively little tryptophan.

This theory is the most prominent and extensively tested idea concerning the effects of food on mood. The results however have not been consistent. One study found that individuals highly prone to stress who were subjected to uncontrollable stress situations were less likely to show signs of stress such as depression, decline in vigour and cortisol elevation if they were following a carbohydrate rich, protein poor diet compared with a carbohydrate poor, protein rich diet (20). Similar results have been obtained in several other trials (21,22,23). On the other hand another study comparing the effects of a high protein breakfast, a high carbohydrate breakfast and no breakfast found that the group of people consuming the high protein breakfast felt more contented, interested, sociable and out-going than those in the other two groups (24).

At present it is still not clear whether a high carbohydrate diet can lead to a reduction in depression and although it is established that carbohydrate can have an effect on brain tryptophan and serotonin levels, some scientists believe that this effect is not sufficient to alter mood (25). Also adding to the argument is the issue of hypoglycaemia, which is implicated in depression (26,27). Hypoglycaemia may be aggrevated by a high carbohydrate diet.

Hypoglycaemia

In normal subjects, consumption of a solution containing 50g of glucose is associated with a rapid rise in blood glucose and a large insulin response. The latter stimulates

peripheral glucose uptake to such an extent that the rate of glucose use exceeds the rate of absorption and the blood glucose concentration falls below the fasting level 2-4 hours after the glucose load [28]. High blood glucose levels are associated with increased energy and decreased tension [26], however as glucose levels fall mood alters as low blood glucose levels are associated with tension, depression and other negative mood states [27].

A diet that promotes steady blood sugar levels is one that consists of foods with a low glycaemic index, the glycaemic index (G.I) being a way of ranking foods based on their overall effects on blood sugar levels. Although it is not always as straightforward as classing all refined carbohydrate foods as those with a high glycaemic index, this does work as a general guideline. A blood sugar-friendly diet would also be free of stimulants such as caffeine, which lead to an adrenaline rush and therefore cause a rapid rise in blood glucose. It is thought that a diet with moderate levels of protein will lead to steadier blood sugar levels as protein does not stimulate insulin release in the same way as carbohydrate [29]. For this reason a diet combining moderate levels of protein with low G.I. foods may be the best option for someone trying to combat depression.

The link between the brain and the immune system

Carl Germano, one of the authors of 'The Brain Wellness Plan' [30], believes that brain diseases require treatment of the immune system as well as the brain itself. He states that 'there exists a complex communication pathway that connects your brain with your endocrine, cardiovascular, and immune system via neurotransmitters and immunotransmitters (chemical messengers produced from the immune system)'. It is true that neurotransmitters have receptors on various components of the immune system and are therefore able to influence the immune response. It seems that the reverse is also true, that in certain areas of the brain, neurones have receptors for immunotransmitters (cytokines) [31].

Cytokines are to the immune system what neurotransmitters are to the brain. They are crafted to deliver warnings to speed up or slow down the immune system's response. Three of the most important cytokines are interleukins, tumor necrosis factor, and interferon. Research suggests that these chemicals can profoundly alter the way neurotransmitters are released or inhibited [31]. Strong evidence now exists indicating that certain cytokines are 'offensive' to the immune system and brain, causing fatigue, slowed thinking, and depression [32,33].

The links between the brain and the gut

The gut is very intimately involved with the nervous system and in fact, unlike any other organ, it contains an intrinsic nervous system. In other words the gut is home to a part of the nervous system that is able to mediate reflexes in the complete absence of input from the brain or spinal cord [34]. This part of the nervous system is known as the enteric nervous system. This is not a small proportion of the nervous system, in fact there are more nerve cells in the gut than in the entire remainder of the peripheral nervous system. In addition each one of the classes of neurotransmitter found in the brain is also present within the gut [34].

One of the neurotransmitters present in large amounts in the enteric nervous sysytem is serotonin. In fact a far greater amount of this neurotransmitter is present in the enteric nervous system than in the brain [34]. It is currently not known the extent to which and exactly how neurotransmitters released in the gut affect the brain but it is known that a steady stream of messages flows back and forth between the gut and the brain via the vagus nerve [34].

Allergic reactions

There is another way that the gastrointestinal tract can influence mental function. This phenomenon involves the immune system as well. More and more scientists and doctors are recognising the condition known as 'Leaky Gut Syndrome', which basically describes a hyperpermeable intestinal lining.

A healthy intestinal tract provides an effective barrier against excessive absorption of food antigens. However, increased gut permeability allows greater quantities of antigens to penetrate the intestinal lining resulting in an overly sensitised, reactive immune system [35]. As already mentioned cytokines released during an immune reaction can disrupt brain function. Research data confirms that those suffering from allergies often experience depression [36].

There is also evidence that partially digested proteins passing from the gut into the blood stream can have a direct effect (without the involvement of the immune system) on the nervous system leading to depression and other mental dysfunction [37,38]. These peptides have the ability to act on brain opiate receptors and have been named exorphins (exo = exogenous, orphin = morphin, an opium), the opposite of endorphins [39]. Much of the work carried out in this area has been conducted by Fukudome and Yoshikawa, in the last decade [40,41], who have identified and characterised five distinct exorphins in the pepsin digests of gluten. Eight distinct exorphins have also been identified in the pepsin digests of milk [42].

Depression is one of the most common symptoms in those with coeliac disease [43,44], these people having an intolerance to gluten. However, this phenomenon is not limited to those with such food intolerances. Clear evidence exists showing that exorphins can be absorbed through the intestinal mucosa and into the circulation of a significant minority of apparently healthy members of the general population [45].

Vitamins and minerals as biochemical cofactors

It has been known for a long time that vitamins and minerals have a part to play in promoting and preserving mental health. The most profound demonstration of this has been the observation of people with deficiencies in certain nutrients.

It is the famous psychiatrist Dr Carl Pfeiffer as well as others such as Dr Abraham Hoffer that are responsible for some of the most important work in the area of nutrition and mental health. Carl Pfeiffer identified many diseases that are related to specific nutrient deficiencies and he developed treatment approaches for balancing nutrient levels and correcting brain chemistry leading to great improvements in disease symptoms [46].

Neurotransmitter production is regulated by enzyme catalysts, which are dependent on specific nutrients acting as essential cofactors. Often methylation occurs in the neurotransmitter pathways and certain nutrients act either as methyl group acceptors, or donators. Without these essential cofactors biochemical pathways, often involving more than one neurotransmitter, are inhibited (47). Folic acid, vitamin B12, and a form of the amino acid methionine known as SAM (S-adenoyl-methionine), function as 'methyl donors'. Supplementation of these nutrients and the promotion of methylation reactions have been shown to increase serotonin levels (48,49) and be effective against depression (49,50).

Vitamin B6 is another of the B vitamins closely associated with depression. It is required for the synthesis of two neurotransmitters that are involved in the regulation of anxiety: serotonin and GABA. Vitamin B6 is also important for its role in general amino acid metabolism and also the metabolism of essential fatty acids. Symptoms of vitamin B6 deficiency include irritability and depression (51).

Apart from the B vitamins, deficiencies of other nutrients lead to symptoms of depression. These include vitamin C (52) and certain minerals such as calcium and magnesium (53,54). Magnesium has also been found in levels higher than for controls in some with depression (55). This could be due to the fact that calcium and magnesium have an antagonistic relationship and therefore high magnesium levels are associated with low calcium levels. Copper is another mineral for which high levels are associated with depression (56, 57).

It is unlikely that many doctors treating patients with depression would consider checking a person's vitamin and mineral levels. Considering the widespread deficiencies of many nutrients in the average UK diet (58), such a policy could prove valuable.

The importance of essential fatty acids

Essential fatty acids are the main components of cell membranes. They help hold proteins in the membrane by the electrostatic attractive forces of their double bonds, and thus they are involved in the traffic of substances in and out of the cells. They also help create the electrical potentials across membranes of neurones so that electric transmissions may occur.

The essential fatty acids are required for prostaglandin synthesis. Prostaglandins being hormone-like substances with many functions in the body including, according to fairly recent research, influencing the activity of neurotransmitters and their receptors (59).

Research has found that deficiencies in essential fatty acids, particularly the omega-3 type, lead to an increase in depression (60,61,62). During the famous Framingham Study, the largest ever to examine the relationship between lowered cholesterol and decreased heart disease, researchers made a disconcerting discovery. People participating in the study who lowered their cholesterol did suffer less from heart disease. However, more of the study's participants committed suicide compared to the rest of the population. Scientists suggest that low cholesterol may be a risk factor for depression but it appears

that the lipid balance as a whole, and in particular low levels of omega-3 fatty acids are the most important factors [62].

Conclusion

The aim of this article has not been to give advice on possible treatment protocols for depression but to outline some of the ways in which nutrition can promote biochemical balance within the brain and nervous system as a whole. The exciting thing is that more and more research is showing that using these nutritional strategies can lead to positive benefits for those with depression. With increasing research in this area expected health professionals can look forward more extensive information to support their work in the treatment of depression.

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