

How to increase serotonin in the human brain without drugs

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For the last 4 decades, the question of how to manipulate the serotonergic system with drugs has been an important area of research in biological psychiatry, and this research has led to advances in the treatment of depression. Research on the association between various polymorphisms and depression supports the idea that serotonin plays a role, not only in the treatment of depression but also in susceptibility to depression and suicide. The research focus here has been on polymorphisms of the serotonin transporter, but other serotonin-related genes may also be involved.¹⁻⁵ In the future, genetic research will make it possible to predict with increasing accuracy who is susceptible to depression. Much less attention has been given to how this information will be used for the benefit of individuals with a serotonin-related susceptibility to depression, and little evidence exists concerning strategies to prevent depression in those with such a susceptibility. Various studies have looked at early intervention in those with prodromal symptoms as well as at population strategies for preventing depression.⁶⁻¹¹ Obviously, prevention is preferable to early intervention; moreover, although population strategies are important, they are ideally supplemented with preventive interventions that can be used over long periods of time in targeted individuals who do not yet exhibit even nonclinical symptoms. Clearly, pharmacologic approaches are not appropriate, and given the evidence for serotonin's role in the etiology and treatment of depression, nonpharmacologic methods of increasing serotonin are potential candidates to test for their ability to prevent depression.

Another reason for pursuing nonpharmacologic methods of increasing serotonin arises from the increasing recognition that happiness and well-being are important, both as factors protecting against mental and physical disorders and in their own right.¹²⁻¹⁴ Conversely, negative moods are associated with negative outcomes. For example, the negative mood hostility is a risk factor for many disorders. For the sake of brevity, hostility is discussed here mainly in relation to one of

the biggest sources of mortality, coronary heart disease (CHD). A meta-analysis of 45 studies demonstrated that hostility is a risk factor for CHD and for all-cause mortality.¹⁵ More recent research confirms this. Hostility is associated not only with the development of CHD but also with poorer survival in coronary artery disease (CAD) patients.¹⁶ Hostility may lead to decreased social support and social isolation,¹⁷ and low perceived social support is associated with greater mortality in those with CAD.¹⁸ Effects are not just limited to CHD. For example, the opposite of hostility, agreeableness, was a significant protective factor against mortality in a sample of older, frail participants.¹⁹

The constitution of the WHO states "Health is a state of complete physical, mental and social well-being and not merely the absence of disease or infirmity."²⁰ This may sound exaggerated but positive mood within the normal range is an important predictor of health and longevity. In a classic study, those in the lowest quartile for positive emotions, rated from autobiographies written at a mean age of 22 years, died on average 10 years earlier than those in the highest quartile.²¹ Even taking into account possible confounders, other studies "found the same solid link between feeling good and living longer."¹² In a series of recent studies, negative emotions were associated with increased disability due to mental and physical disorders,²² increased incidence of depression,²³ increased suicide²⁴ and increased mortality²⁵ up to 2 decades later. Positive emotions protected against these outcomes. A recent review including meta-analyses assessed cross-sectional, longitudinal and experimental studies and concluded that happiness is associated with and precedes numerous successful outcomes.²⁶ Mood may influence social behaviour, and social support is one of the most studied psychosocial factors in relation to health and disease.²⁷ Low social support is associated with higher levels of stress, depression, dysthymia and posttraumatic stress disorder and with increased morbidity and mortality from a host of medical illnesses.²⁷

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Research confirms what might be intuitively expected, that positive emotions and agreeableness foster congenial relationships with others.^{28,29} This in turn will create the conditions for an increase in social support.

Several studies found an association between measures related to serotonin and mood in the normal range. Lower platelet serotonin₂ receptor function was associated with lower mood in one study,³⁰ whereas better mood was associated with higher blood serotonin levels in another.³¹ Two studies found that greater prolactin release in response to fenfluramine was associated with more positive mood.^{32,33} The idea that these associations indicate a causal association between serotonin function and mood within the normal range is consistent with a study demonstrating that, in healthy people with high trait irritability, tryptophan, relative to placebo, decreased quarrelsome behaviours, increased agreeable behaviours and improved mood.³⁴ Serotonin may be associated with physical health as well as mood. In otherwise healthy individuals, a low prolactin response to the serotonin-releasing drug fenfluramine was associated with the metabolic syndrome, a risk factor for heart disease,³⁵ suggesting that low serotonin may predispose healthy individuals to suboptimal physical as well as mental functioning.

Nonpharmacologic methods of raising brain serotonin may not only improve mood and social functioning of healthy people — a worthwhile objective even without additional considerations — but would also make it possible to test the idea that increases in brain serotonin may help protect against the onset of various mental and physical disorders. Four strategies that are worth further investigation are discussed below.

The article by Perreau-Linck and colleagues³⁶ (page 430 of this issue) provides an initial lead about one possible strategy for raising brain serotonin. Using positron emission tomography, they obtained a measure of serotonin synthesis in the brains of healthy participants who underwent positive, negative and neutral mood inductions. Reported levels of happiness were positively correlated and reported levels of sadness were negatively correlated with serotonin synthesis in the right anterior cingulate cortex. The idea that alterations in thought, either self-induced or due to psychotherapy, can alter brain metabolism is not new. Numerous studies have demonstrated changes in blood flow in such circumstances. However, reports related to specific transmitters are much less common. In one recent study, meditation was reported to increase release of dopamine.³⁷ The study by Perreau-Linck and colleagues³⁶ is the first to report that self-induced changes in mood can influence serotonin synthesis. This raises the possibility that the interaction between serotonin synthesis and mood may be 2-way, with serotonin influencing mood and mood influencing serotonin. Obviously, more work is needed to answer questions in this area. For example, is the improvement in mood associated with psychotherapy accompanied by increases in serotonin synthesis? If more precise information is obtained about the mental states that increase serotonin synthesis, will this help to enhance therapy techniques?

Exposure to bright light is a second possible approach to

increasing serotonin without drugs. Bright light is, of course, a standard treatment for seasonal depression, but a few studies also suggest that it is an effective treatment for nonseasonal depression³⁸ and also reduces depressed mood in women with premenstrual dysphoric disorder³⁹ and in pregnant women suffering from depression.⁴⁰ The evidence relating these effects to serotonin is indirect. In human post-mortem brain, serotonin levels are higher in those who died in summer than in those who died in winter.⁴¹ A similar conclusion came from a study on healthy volunteers, in which serotonin synthesis was assessed by measurements of the serotonin metabolite 5-hydroxyindoleacetic acid (5-HIAA) in the venous outflow from the brain.⁴² There was also a positive correlation between serotonin synthesis and the hours of sunlight on the day the measurements were made, independent of season. In rats, serotonin is highest during the light part of the light–dark cycle, and this state is driven by the photic cycle rather than the circadian rhythm.^{43,44} The existence of a retinorecipient tract may help explain why, in experimental animals, neuronal firing rates, *c-fos* expression and the serotonin content in the raphe nuclei are responsive to retinal light exposure.^{44–48} In humans, there is certainly an interaction between bright light and the serotonin system. The mood-lowering effect of acute tryptophan depletion in healthy women is completely blocked by carrying out the study in bright light (3000 lux) instead of dim light.⁴⁹

Relatively few generations ago, most of the world population was involved in agriculture and was outdoors for much of the day. This would have resulted in high levels of bright light exposure even in winter. Even on a cloudy day, the light outside can be greater than 1000 lux, a level never normally achieved indoors. In a recent study carried out at around latitude 45° N, daily exposure to light greater than 1000 lux averaged about 30 minutes in winter and only about 90 minutes in summer⁵⁰ among people working at least 30 hours weekly; weekends were included. In this group, summer bright light exposure was probably considerably less than the winter exposure of our agricultural ancestors. We may be living in a bright light–deprived society. A large literature that is beyond the scope of this editorial exists on the beneficial effect of bright light exposure in healthy individuals. Lamps designed for the treatment of seasonal affective disorder, which provide more lux than is ever achieved by normal indoor lighting, are readily available, although incorporating their use into a daily routine may be a challenge for some. However, other strategies, both personal and institutional, exist. “Light cafes” pioneered in Scandinavia have come to the United Kingdom,⁵¹ and an Austrian village that receives no sunshine in the winter because of its surrounding mountains is building a series of giant mirrors to reflect sunlight into the valley.⁵² Better use of daylight in buildings is an issue that architects are increasingly aware of. Working indoors does not have to be associated with suboptimal exposure to bright light.

A third strategy that may raise brain serotonin is exercise. A comprehensive review of the relation between exercise and mood concluded that antidepressant and anxiolytic effects have been clearly demonstrated.⁵³ In the United Kingdom the National Institute for Health and Clinical Excellence, which

works on behalf of the National Health Service and makes recommendations on treatments according to the best available evidence, has published a guide on the treatment of depression.⁵⁴ The guide recommends treating mild clinical depression with various strategies, including exercise rather than antidepressants, because the risk–benefit ratio is poor for antidepressant use in patients with mild depression. Exercise improves mood in subclinical populations as well as in patients. The most consistent effect is seen when regular exercisers undertake aerobic exercise at a level with which they are familiar.⁵⁵ However, some skepticism remains about the antidepressant effect of exercise, and the National Institute of Mental Health in the United States is currently funding a clinical trial of the antidepressant effect of exercise that is designed to overcome sources of potential bias and threats to internal and external validity that have limited previous research.⁵⁵

Several lines of research suggest that exercise increases brain serotonin function in the human brain. Post and colleagues⁵⁶ measured biogenic amine metabolites in cerebrospinal fluid (CSF) of patients with depression before and after they increased their physical activity to simulate mania. Physical activity increased 5-HIAA, but it is not clear that this was due to increased serotonin turnover or to mixing of CSF from higher regions, which contain higher levels of 5-HIAA, with lumbar CSF (or to a combination of both mechanisms). Nonetheless, this finding stimulated many animal studies on the effects of exercise. For example, Chaouloff and colleagues⁵⁷ showed that exercise increased tryptophan and 5-HIAA in rat ventricles. More recent studies using intracerebral dialysis have shown that exercise increases extracellular serotonin and 5-HIAA in various brain areas, including the hippocampus and cortex (for example, see^{58–60}). Two different mechanisms may be involved in this effect. As reviewed by Jacobs and Fornal,⁶¹ motor activity increases the firing rates of serotonin neurons, and this results in increased release and synthesis of serotonin.⁶² In addition, there is an increase in the brain of the serotonin precursor tryptophan that persists after exercise.⁶³

The largest body of work in humans looking at the effect of exercise on tryptophan availability to the brain is concerned with the hypothesis that fatigue during exercise is associated with elevated brain tryptophan and serotonin synthesis. A large body of evidence supports the idea that exercise, including exercise to fatigue, is associated with an increase in plasma tryptophan and a decrease in the plasma level of the branched chain amino acids (BCAAs) leucine, isoleucine and valine (see^{64,65} for reviews). The BCAAs inhibit tryptophan transport into the brain.⁶⁶ Because of the increase in plasma tryptophan and decrease in BCAA, there is a substantial increase in tryptophan availability to the brain. Tryptophan is an effective mild hypnotic,⁶⁷ a fact that stimulated the hypothesis that it may be involved in fatigue. A full discussion of this topic is not within the scope of this editorial; however, it is notable that several clinical trials of BCAA investigated whether it was possible to counter fatigue by lowering brain tryptophan, with results that provided little support for the hypothesis. Further, exercise results in an increase in the plasma ratio of tryptophan to the BCAAs before the onset of fatigue.^{64,65} The conclusion of these studies is that, in humans,

a rise in precursor availability should increase serotonin synthesis during and after exercise and that this is not related to fatigue, although it may be related to improved mood. Whether motor activity increases the firing rate of serotonin neurons in humans, as in animals, is not known. However, it is clear that aerobic exercise can improve mood.

As with exposure to bright light, there has been a large change in the level of vigorous physical exercise experienced since humans were hunter-gatherers or engaged primarily in agriculture.⁶⁸ Lambert⁶⁸ argued that the decline in vigorous physical exercise and, in particular, in effort-based rewards may contribute to the high level of depression in today's society. The effect of exercise on serotonin suggests that the exercise itself, not the rewards that stem from exercise, may be important. If trials of exercise to prevent depression are successful, then prevention of depression can be added to the numerous other benefits of exercise.

The fourth factor that could play a role in raising brain serotonin is diet. According to some evidence, tryptophan, which increases brain serotonin in humans as in experimental animals,⁶⁹ is an effective antidepressant in mild-to-moderate depression.^{67,70} Further, in healthy people with high trait irritability, it increases agreeableness, decreases quarrelsomeness and improves mood.³⁴ However, whether tryptophan should be considered primarily as a drug or a dietary component is a matter of some dispute. In the United States, it is classified as a dietary component, but Canada and some European countries classify it as a drug. Treating tryptophan as a drug is reasonable because, first, there is normally no situation in which purified tryptophan is needed for dietary reasons, and second, purified tryptophan and foods containing tryptophan have different effects on brain serotonin. Although purified tryptophan increases brain serotonin, foods containing tryptophan do not.⁷¹ This is because tryptophan is transported into the brain by a transport system that is active toward all the large neutral amino acids and tryptophan is the least abundant amino acid in protein. There is competition between the various amino acids for the transport system, so after the ingestion of a meal containing protein, the rise in the plasma level of the other large neutral amino acids will prevent the rise in plasma tryptophan from increasing brain tryptophan. The idea, common in popular culture, that a high-protein food such as turkey will raise brain tryptophan and serotonin is, unfortunately, false. Another popular myth that is widespread on the Internet is that bananas improve mood because of their serotonin content. Although it is true that bananas contain serotonin, it does not cross the blood–brain barrier.

α -Lactalbumin, a minor constituent of milk, is one protein that contains relatively more tryptophan than most proteins. Acute ingestion of α -lactalbumin by humans can improve mood and cognition in some circumstances, presumably owing to increased serotonin.^{72,73} Enhancing the tryptophan content of the diet chronically with α -lactalbumin is probably not practical. However, increasing the tryptophan content of the diet relative to that of the other amino acids is something that possibly occurred in the past and could occur again in the future. Kerem and colleagues⁷⁴ studied the tryptophan content of both wild chickpeas and the domesticated chickpeas that were

bred from them in the Near East in neolithic times. The mean protein content (per mg dry seed) was similar for 73 cultivars and 15 wild varieties. In the cultivated group, however, the tryptophan content was almost twice that of the wild seeds. Interestingly, the greater part of the increase was due to an increase in the free tryptophan content (i.e., not part of the protein). In cultivated chickpeas, almost two-thirds of the tryptophan was in the free form. Kerem and colleagues⁷⁴ argue that there was probably selection for seeds with a higher tryptophan content. This is plausible, given another example of an early strategy to increase the available tryptophan content of an important food source. Pellagra is a disorder caused by niacin deficiency, usually owing to poverty and a diet relying heavily on corn (maize), which has a low level of niacin and its precursor tryptophan. Cultures in the Americas that relied greatly on corn used alkali during its processing (e.g., boiling the corn in lime when making tortillas). This enhanced the nutritional quality of the corn by increasing the bioavailability of both niacin and tryptophan, a practice that prevented pellagra.⁷⁵ The Europeans transported corn around the world but did not transport the traditional alkali-processing methods, thereby causing epidemics of pellagra in past centuries. Breeding corn with a higher tryptophan content was shown in the 1980s to prevent pellagra⁷⁶; presumably, it also raised brain serotonin. In a recent issue of *Nature Biotechnology*, Morris and Sands⁷⁷ argue that plant breeders should be focusing more on nutrition than on yield. They ask, "Could consumption of tryptophan-rich foods play a role in reducing the prevalence of depression and aggression in society?" Cross-national studies have reported a positive association between corn consumption and homicide rates⁷⁸ and a negative association between dietary tryptophan and suicide rates.⁷⁹ Although the idea behind such studies is interesting, any causal attribution must remain speculative, given the possible confounds. Nonetheless, the possibility that the mental health of a population could be improved by increasing the dietary intake of tryptophan relative to the dietary intake of other amino acids remains an interesting idea that should be explored.

The primary purpose of this editorial is to point out that pharmacologic strategies are not the only ones worthy of study when devising strategies to increase brain serotonin function. The effect of nonpharmacologic interventions on brain serotonin and the implications of increased serotonin for mood and behaviour need to be studied more. The amount of money and effort put into research on drugs that alter serotonin is very much greater than that put into nonpharmacologic methods. The magnitude of the discrepancy is probably neither in tune with the wishes of the public nor optimal for progress in the prevention and treatment of mental disorders.

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