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The Quest of Happiness-Increase Happy Neurotransmitter Serotonin in the Brain

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1. Abstract

When discussing happiness, it's worth noting that serotonin, a magical substance found in the body, is essential to achieving a state of well-being. Serotonin is a naturally occurring monoamine neurotransmitter that transmits signals between nerve cells throughout the body, contributing significantly to mood stabilization and supporting other bodily functions such as digestion, blood clotting, and sleep. When serotonin levels in the brain are low, it can cause changes in mood and disrupt sleep patterns, which can lead to depression. However, it's important to note that although 95% of the serotonin in the body is produced in the gut, it cannot cross the "blood-brain barrier" and thus has no impact on emotional status. Increasing serotonin levels in the brain appears to enhance communication between brain cells, resulting in an uplifted mood and reduced depression symptoms. Prescription antidepressants like Selective Serotonin Reuptake Inhibitors (SSRIs) are frequently employed to treat clinical depression and other mood disorders by increasing serotonin levels in the brain via blocking the Serotonin reuptake process. The 5-HT system is also thought to be a connection between the circadian system, stress, and mood. 5-HT not only plays a part in generating non-photic phase shifts, but it also counteracts the effects of light in the SCN (Suprachiasmatic nucleus) . It has been found that food and exercise can increase serotonin levels in the brain. Thus SSRIs use can be minimized (Figure 1).

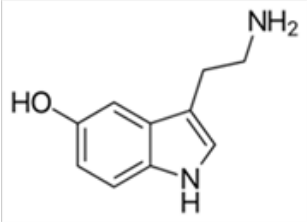

Figure 1: Structure of Serotonin

2. Introduction

While serotonin is often referred to as the "happy" neurotransmitter, it is important to note that it is not only responsible for happiness. Serotonin is just one of many neurotransmitters and chemicals in the brain that are involved in regulating mood and emotions. Research suggests that while low levels of serotonin can contribute to feelings of sadness and anxiety, simply increasing serotonin levels is not enough for happiness. Other factors, such as social support and a sense of purpose, also play important roles in determining our overall sense of well-being. Serotonin is involved in regulating the circadian rhythm, which is the body's internal clock that helps regulate sleep and wake cycles. Serotonin is produced in the brain's pineal gland, which is responsible for releasing the hormone melatonin that helps regulate sleep. During the day, serotonin levels are typically high, which helps promote wakefulness and alertness. As the day turns into night, serotonin levels decrease and melatonin levels increase, which helps promote sleep. This is why serotonin is often referred to as a "daytime neurotransmitter" and melatonin is referred to as a "nighttime hor-mone". Research has also shown that disruptions in serotonin levels can contribute to disruptions in the circadian rhythm, leading to sleep disorders such as insomnia or sleep apnea. For example, medications that increase serotonin levels, such as selective serotonin reuptake inhibitors (SSRIs), have been used to treat sleep disorders such as insomnia [1].

3. Aim of the Present Mini Review

The importance of Serotonin in maintaining our body's well-being is evident, and it's incredibly challenging to establish a balance of this substance, particularly in individuals who have low levels of Serotonin, which can lead to mood disorders and clinical depression. To achieve our goal of optimizing and controlling the balance of Serotonin in the body, we intend to conduct a series of research projects in this field. This research may have a significant impact, not only by changing how we prescribe drugs like SSRIs to patients but also by introducing new methods of controlling Serotonin levels that are free of side effects. The following are some of the research tasks that we propose to include in our mini-review (Table 1).

Table 1:

What	How	Potential Impact
1. Establish how genetic alterations in the human SERT* gene (SLC6A4) can impact the Serotonin reuptake rate by the neuroreceptors *The serotonin transporter (SERT) is a presynaptic 68 kD transmembrane protein that regulates the concentration of serotonin in the extraneuronal space by taking serotonin back up into presynaptic neurons after it has been released	Experiment on genetically modified mice (with an altered SERT gene) to understand the Serotonin reuptake rates and establish how reuptakes can be inhibited or slowed down, leading to high Serotonin levels in the brain.	This may lead to developing high-impact therapies for acute clinical depression patients who especially don't respond well to SSRIs
2. Use Artificial Intelligence and chronopharmacology techniques to predict the most efficient way to administer SSRIs to patients	AI models with sufficient data on Serotonin reuptake rates by neuro receptors at various times (day/ night) and conditions (light, heat) can accurately predict the most efficient way of administering SSRTs to patients by optimizing for dosage quantity, frequency etc. Also, by combining chronopharmacology techniques we can add more accuracy to the data which in turn will produce much better results	This will greatly reduce the cost, efficiency and side effects of antidepressants
3. Explore how we can move and use Serotonin produced in the gut (periphery) into the brain.	As the gut produces Serotonin in abundance, it is an untapped resource that may provide the right levels that the brain requires. We may explore sneaking in Trojan horses to help serotonin cross the blood- brain barrier in a seamless cost -effective manner.	We may end up finding a way to maintain and regulate serotonin levels in a controlled way without artificial SSRIs and it's associated side effects.

3.1. The Serotonin System

Based on research findings, it was determined that on average, a single 5-HT neuron connects with at least half a million other neurons in the brain, indicating its role as a modulatory neurotransmitter. The midbrain raphe nuclei, which innervate multiple points in the limbic circuit, are believed to be responsive to various types of stressors including physical, psychological, and metabolic, making them capable of regulating fear and anxiety. The malfunction of the 5-HT system has been linked to Major Depressive Disorder [3].

3.2. Function of Serotonin in the Brain

Serotonin, produced naturally by both the intestines and brain, aids in transmitting messages between nerve cells and has an impact on emotions, mood, and digestion. The connection between serotonin and depression has been studied through "tryptophan depletion," an acute dietary manipulation that reduces the availability of the amino acid precursor tryptophan in the brain, leading to a temporary decrease in serotonin activity. One of the 14 different 5-HT receptor subtypes, the G-Protein coupled receptor 5-HT2AR, is expressed in the mammalian brain, much like almost all the other subtypes[3] (Figure 2).

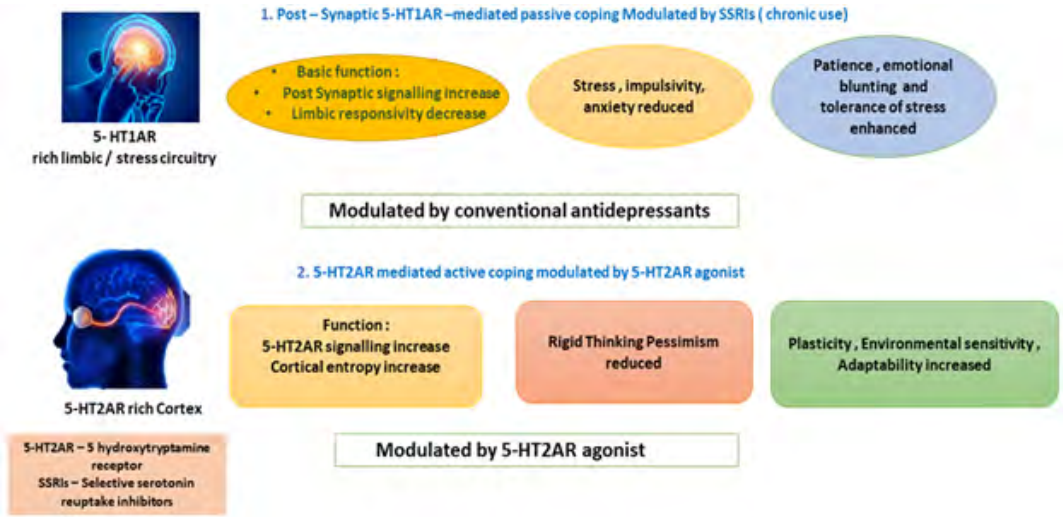

Figure 2: Model of Brain Serotonin function

3.3. The Connection between Serotonin and the Circadian Clock

According to [4], the 5-HT system serves as a link between the circadian system, stress, and mood. In addition to this, 5-HT is involved in producing non-photic phase shifts and counteracting the effects of light in the SCN [5]. The circadian rhythm controls the 5-HT system, with regular rhythmic secretion of glucocorticoids driving the synthesis of serotonin due to rhythmic 5-HT release in the SCN and other limbic projection areas [6].

3.4. Regulating the Circadian Clock with Serotonin

Research shows that during the day, 5-HT produces non-photic phase shifts and that selective 5-HT receptor agonists shift SCN activity by around three hours during the middle of the light phase [7]. Furthermore, manipulating 5-HT levels in the brain can significantly alter endocrine and behavioral circadian rhythms [8].

3.5. Circadian Clock and Serotonin Levels

Studies have found that 5-HT levels are higher during the active phase in both nocturnal and diurnal rodents [9]. Moreover, midbrain raphe nuclei exhibit significant time-dependent changes in 5-HT transporter mRNA expression and in vivo 5-HT reuptake activity, with generally higher levels during the dark phase and lower levels in the light phase [10].

3.6. Serotonin Related to Sleep-Wake Cycle

Serotonin as a `sleep' neurotransmitter: Data have suggested that serotonin may play a role in deactivating waking rather than directly inducing sleep, as administering 5-HTP alone has been found to increase drowsiness and hypersynchrony in waking rather than promoting sleep [11]. Serotonin synthesis in healthy volun-teers was measured through assessments of the serotonin metabo-lite 5-HIAA in the venous outflow from the brain, which revealed a positive correlation between serotonin synthesis and hours of sunlight independent of the season [12]. In rats, serotonin levels are highest during the light part of the light-dark cycle, which is driven by the photic cycle rather than the circadian rhythm [13,14] . The existence of a retinopathy tract may help explain why neu-ronal firing rates, c-fos expression, and serotonin content in the raphe nuclei are responsive to retinal light exposure in experimental animals [14, 15]. In humans, there is certainly an interaction between bright light and the serotonin system, as the mood-low-ering effect of acute tryptophan depletion in healthy women is blocked in bright light. However, people today may be living in a society that is deprived of bright light, despite evidence of the beneficial effects of bright light exposure in healthy individuals. Strategies such as the use of lamps designed for seasonal affec-tive disorder treatment, "light cafes," and better use of daylight

in buildings can be employed [17] . Exercise has also been found to raise brain serotonin, and the National Institute for Health and Clinical Excellence recommends treating mild clinical depression with strategies like exercise rather than antidepressants [18,19]. Some scepticism remains about the antidepressant effect of exercise, and ongoing clinical trials are attempting to overcome potential biases and threats to validity [20]. Research has suggested that exercise increases brain serotonin function in humans, as seen in the increased levels of 5-HIAA in patients with depression who increased their physical activity to simulate mania [21].

3.7. Exercise and Food in Relation to Serotonin

Scientists [22] 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 28–30). Two different mechanisms may be involved in this effect. As reviewed by Jacobs and Fornal [22], motor activity increases the firing rates of serotonin neurons, and this results in increased release and synthesis of serotonin [23]. In addition, there is an increase in the brain of the serotonin precursor tryptophan that persists after exercise [23]. 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 [24, 25]. The BCAAs inhibit tryptophan transport into the brain [26]. 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 [26], 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 [24, 25]. 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 [26]. scientists 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 [27]. 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, is an effective antidepressant in mild-to-moderate depression [26, 27]. Further, in healthy people with high trait irritability, it increases agreeableness, decreases quarrelsomeness and improves mood [24]. However, whether tryptophan should be considered primarily as a drug or a dietary component is a matter of some dispute [28]. 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 rea-sons, 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 [28]. 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 a protein. There is competition between the various amino acids for the transport system, so after the ingestion of a meal contain-ing protein, the rise in the plasma level of the other large neutral amino acids will prevent the rise in plasma tryptophan from in-creasing 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 bananas indeed 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-lactal-bumin by humans can improve mood and cognition in some circumstances, presumably owing to increased serotonin [22, 23]. 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 colleagues [24] 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 cultivars and 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. Scientists [24] argue that there was probably a 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. [25] The Europeans transported corn around the world but did not transport the traditional alkali-processing methods, thereby caus-ing epidemics of pellagra in past centuries. Breeding corn with a higher tryptophan content was shown in the 1980s to prevent pellagra 6 presumably, it also raised brain serotonin. In a recent issue of Nature Biotechnology, scientists [26, 27] 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 rates [28]. and a negative association between dietary tryptophan and suicide rates [25]. 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 [29, 30].

3.8. Serotonin as a 'Wake' Neurotransmitter

Regarding serotonin's role as a "wake" neurotransmitter, subsequent data emerged that challenged the notion that serotonergic raphe neurons directly facilitate sleep [31]. The simple hypothesis could not be maintained. Extracellular levels of serotonin in all investigated brain regions appear to mirror the pattern of the raphe neurons, with the highest levels during W, lower levels during SWS, and the lowest levels during REM sleep [31].

3.9. Synthesis of Serotonin in Brain

The synthesis of serotonin occurs in the brain from tryptophan. Serotonin travels across the blood-brain barrier alongside tyrosine and other amino acids [3] (Figure 3).

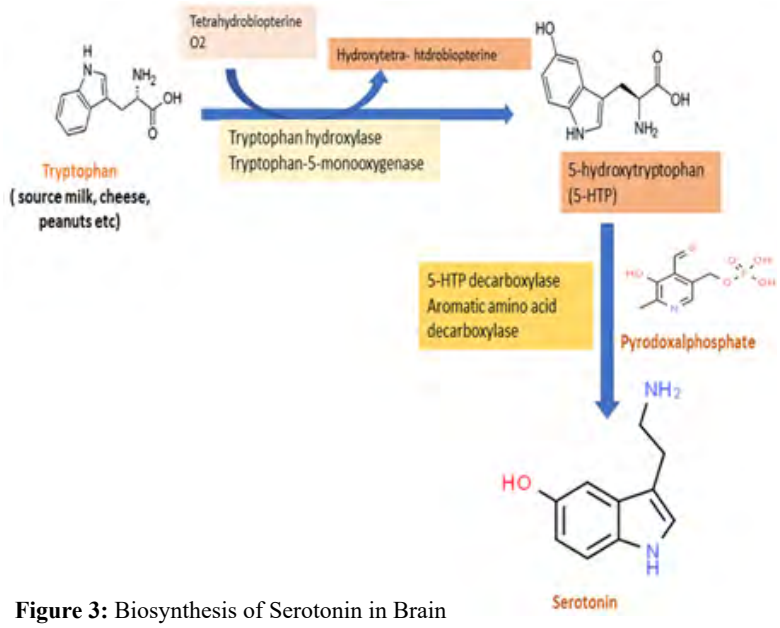

Figure 3: Biosynthesis of Serotonin in Brain

3.10. Mechanism of Action of Serotonin in the Brain in Other Ways

For the last 40 years, the manipulation of the serotonergic system has been a vital research area in biological psychiatry that led to advancements in treating depression. The connection between various polymorphisms and depression supports the idea that serotonin plays a role in treating depression and susceptibility to depression and suicide [32]. The serotonin transporter has been the main focus of polymorphism research, but other genes related to serotonin may also be involved. Genetic research in the future will increase the accuracy of predicting who is susceptible to depression [33, 34]. Strategies to prevent depression in those with serotonin-related susceptibility have received little attention [35, 37]. Studies have investigated early intervention in individuals with prodromal symptoms and population strategies for preventing depression, but prevention is preferable to early intervention[33, 34]. Preventive interventions can be used for an extended period in targeted individuals who do not even show nonclinical symptoms. Since pharmacological approaches are not appropriate, nonpharmacologic methods of increasing serotonin are potential candidates to test their ability to prevent depression (Figure 4).

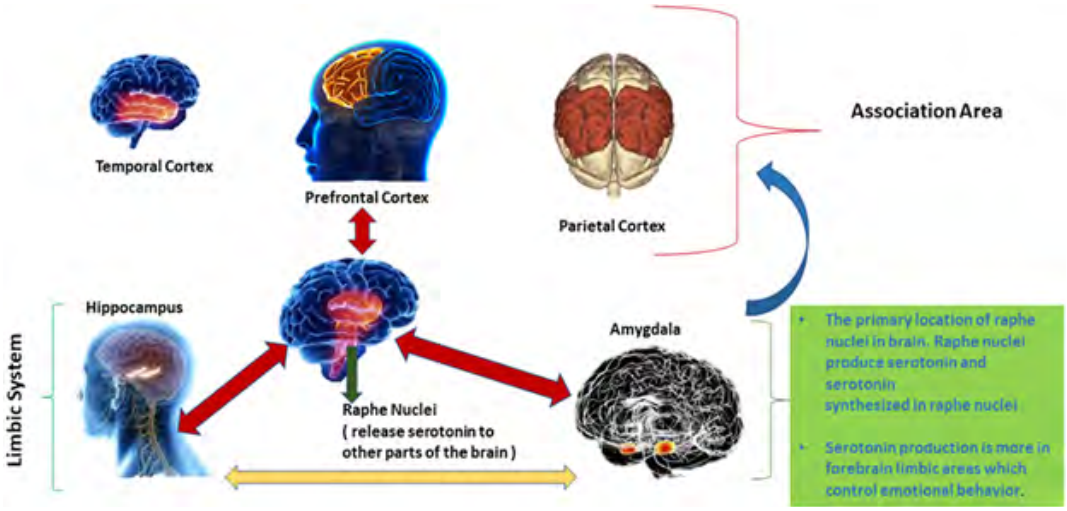

Figure 4: Mechanism of action of serotonin in brain

Nonpharmacologic methods of increasing serotonin can help prevent various mental and physical disorders [21, 22, 27]. Happiness and well-being are essential factors in protecting against mental and physical disorders. Negative moods, such as hostility, are associated with negative outcomes, such as an increased risk of coronary heart disease (CHD) [35, 36]. Hostility is also associated with poorer survival in coronary artery disease (CAD) patients. Social support is an essential psychosocial factor in health and disease, and low social support is associated with higher levels of stress, depression, dysthymia, and posttraumatic stress disorder [35, 37]. Positive emotions and agreeableness foster congenial relationships with others, which, in turn, creates the conditions for an increase in social support [39, 20].

For example, the opposite of hostility, agreeableness, was a significant protective factor against mortality in a sample of older, frail participants [39]. 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 a 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 suicide 24 and increased mortality 25 up to 2 decades later. Positive emotions are 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 about 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]. Research confirms what might be intuitively expected, that positive emotions and agreeableness foster congenial relationships with others [38, 29]. Several studies have found an association between measures related to serotonin and mood in the normal range [21, 22]. In healthy people with high trait irritability, tryptophan decreased quarrelsome behaviors, increased agreeable behaviors, and improved mood [23]. Lower platelet serotonin receptor function was associated with the lower mood study, whereas better mood was associated with higher blood serotonin levels [25-27]. Serotonin may be associated with physical health as well as mood, as low serotonin may predispose healthy individuals to suboptimal physical as well as mental functioning. Nonpharmacologic methods of raising brain serotonin can improve the mood and social functioning of healthy people and test the idea that increases in brain serotonin may help protect against the onset of various mental and physical disorders [38, 29].

Presented below are four strategies that merit further investigation. In this issue, Perreau-Linck and colleagues discuss one potential strategy for increasing brain serotonin levels. They used positron emission tomography to measure serotonin synthesis in healthy individuals who underwent positive, negative, and neutral mood inductions. The study found that serotonin synthesis in the right anterior cingulate cortex was positively correlated with reported levels of happiness and negatively correlated with reported levels of sadness. It is not a new idea that changes in thought can alter brain metabolism, and studies have shown changes in blood flow in such circumstances. However, there are fewer reports regarding specific transmitters. In a recent study, meditation was found to increase the release of dopamine [22]. The study by Perreau-Linck and colleagues is the first to suggest that self-induced mood changes can affect serotonin synthesis, raising the possibility that the interaction between serotonin and mood may be reciprocal [36]. Clearly,

more research is necessary to explore this area, such as whether an increase in serotonin synthesis accompanies an improvement in mood during psychotherapy. If we obtain more accurate information about the mental states that boost serotonin synthesis, can it help enhance therapy techniques? Exposure to bright light is another way to increase serotonin levels without drugs. Bright light is commonly used to treat seasonal depression, but studies suggest it can also effectively treat nonseasonal depression and reduce depressed mood in women with premenstrual dysphoric disorder and pregnant women suffering from depression [23]. The evidence linking these effects to serotonin is not direct. However, serotonin levels are higher in the postmortem brain of individuals who died in summer than in those who died in winter [26, 28, 29].

3.11. Melatonin's Relationship with Serotonin

Serotonin is a potent neurotransmitter, which is a biosynthetic precursor of melatonin [40]. Serotonin levels are correlated to different processes and diseases including neurological disorders like drug addiction, depression, and migraines [41]. At the initial steps in the melatonin biosynthetic pathway, it varies between organisms and serotonin is found in as diverse of clades as melatonin [42]. The majority of melatonin is found in the supplements one is sourced from the porcine pineal gland and the other is more frequently produced synthetically [44]. Generally, serotonin will be found in these supplements [43]. The presence of unrecognized but significant quantities of serotonin in melatonin supplements is a particular concern and the supplements are poorly controlled [45, 46].

4. Conclusion

The aim of this review is to emphasize that exploring non-pharmacologic approaches to enhance brain serotonin function is equally significant as pharmacologic strategies. Further investigation is required to examine the impact of non-pharmacologic interventions on brain serotonin and the potential outcomes of increased serotonin levels on mood and behaviour. Research indicates that diet and physical activity play a crucial role in regulating serotonin levels in the brain. Additionally, regardless of the season, there is a positive association between serotonin synthesis and the number of daylight hours at the time of measurement. In rats, the light phase of the light-dark cycle is linked with elevated serotonin levels, which are influenced by the photic cycle rather than the circadian rhythm. While the research on drugs that alter serotonin receives more financial and resource support, non-pharmacologic interventions can be incorporated into treatment to lower drug intake and minimize toxicity. The substantial difference in research allocation may not align with public preferences or be ideal for making advancements in preventing and treating mental health disorders.

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