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# Role of serotonin in seasonal affective disorder

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**Abstract. – This review was prepared with an aim to show role of serotonin in seasonal affective disorder. Seasonal affective disorder, which is also called as winter depression or winter blues, is mood disorder in which persons with normal mental health throughout most of the year will show depressive symptoms in the winter or, less commonly, in the summer.**

**Serotonin is an important endogenous neurotransmitter which also acts as neuromodulator. The least invasive, natural, and researched treatment of seasonal affective disorder is natural or otherwise is light therapy. Negative air ionization, which acts by liberating charged particles on the sleep environment, has also become effective in treatment of seasonal affective disorder.**

*Key Words:*
Serotonin, Seasonal affective disorder, L-tryptophan, Light therapy.

## Introduction

Serotonin is a monoamine neurotransmitter derived biochemically from L-tryptophan. It is mainly found in the gastrointestinal tract (about 90% in enterochromaffin cells), platelets and in the central nervous system of humans and animals. It is an important biogenic amine that play combined role of neurotransmitter as well as neuromodulator[1]. It is thoroughly known contributor to feelings of well-being. The serotoninergic system is known to alter mood, emotion, sleep and appetite and, thus, is involved in the control of various behaviors related to physiological functions. Decreased serotoninergic neurotransmission due to disturbances in central serotonergic systems has been proposed to be involved in the seasonal affective disorder (SAD)[2-3]. SAD is the term applied to a clinical subtype of mood disorder consisting cyclic complaint characterized by periodic episode of winter depression changes with period of spring or summer euthymia (normal non-depressed, reasonably positive mood) or hypermania[4-5]. SAD can occur in patients with either major depressive disorder, or with bipolar disorder. Patients with bipolar disorder exhibit symptoms of both depression and mania or hypomania, as opposed to recurrent depression. SAD is distinguished from non-seasonal depression in the presence of a regular progressive relationship between the onset of depression and the time of year; full diminution of depressive symptoms at certain time of year[6].

### Serotonin

Serotonin, a neurotransmitter synthesized in the brain, acts importantly in the functioning of the cardiovascular, renal, immune, and gastrointestinal systems. Any disruption in the synthesis, metabolism or uptake of this neurotransmitter has been found to be partly responsible for certain manifestations of schizophrenia, depression, compulsive disorders (type of anxiety disorder delineated by continued, persistent, unwanted, and unpleasant thoughts) and learning problems. Serotonin can be released in response to several stimuli such as mechanical distortion, mucosal stroking, or electrical stimulation of enteric neurons on release. Serotonin activates enteric neurons (directly controls the gastrointestinal system) to affect motor responses in the gut[7]. Serotonin is widely present in the plant and animal kingdoms. It may appear in vertebrates, tunicates, mollusks, arthropods, coelenterates and also in edible fruits and nuts. It may occur in diverse venoms, along with the common stinging nettle and in wasps and scorpions[8]. Serotonin activity in the brain, complementary that of the other monoamine neurotransmitters is directed by a sodium chloride-dependent transporter present in the plasma membrane of the cell[9]. After release of serotonin, the pre-synaptically presented 5-hydroxy-tryptamine (5-HTT) returns serotonin in the cell for recycling or metabolic degradation[10]. The serotonin transporters (SERTs) are present in

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the membrane of serotonergic neuron terminals and play a major role in the control of serotonin in the synaptic cleft[11].

### Synthesis of Serotonin

Serotonin is mainly found stored in three main cell types:

1. Serotonergic neurons in the CNS and in the intestinal myenteric plexus (network of nerve fibers located within the layer of muscular tissue that lines the esophagus, stomach, and intestines);
2. Enterochromaffin cells (present in the epithelia lining the lumen of the digestive tract and the respiratory tract) in the mucosa of the gastrointestinal tract; and
3. In blood platelets.

Serotonergic neurons and enterochromaffin cells use amino acid L-tryptophan in the synthesis of serotonin. Serotonin in the brain is synthesized from the essential amino acid tryptophan. The hydroxylation of tryptophan to 5-hydroxytryptophan by the enzyme tryptophan 5-mono oxygenase is the rate limiting step in the synthesis of serotonin**.** The rate of this reaction is influenced by a diversity of factors including tryptophan concentration, firing frequency of the neuron, $Ca^{2+}$ dependent phosphorylation of the enzyme and cofactor availability[12]. The synthesis of serotonin from the essential amino acid tryptophan is done by two main enzymatic steps. The early step is hydroxylation of tryptophan (the rate limiting step) yield 5-hydroxytryptophan. The step catalyzed by enzyme aromatic L-amino acid decarboxylase is decarboxylation of 5-hydroxytryptophan to produce serotonin[8] (Figure 1).

### Metabolism of Serotonin

Serotonin in tissue can be metabolized very rapidly, chiefly due to the activity of monoamine oxidase and aldehyde dehydrogenase. In the kidney and liver, the conversion of serotonin to 5-hydroxyindole acetic acid is catalyzed by the enzyme monoamine oxidase and aldehyde dehydrogenase, which is excreted in urine.

Conversion of serotonin into inactive molecules is done by the process of biotransformation:

- Oxidative deamination of the lateral amino chain by monoamine oxidase, leading to 5-hydroxy-indol-acetaldehyde which is then oxidized into 5-hydroxy-indol-acetic acid (5-HIAA).
- Conjugation of hydroxyl group OH in 5-position by glucuronic acid or sulfate[13].

### Serotonin Receptors

The serotonin receptors family is larger group of G-protein coupled (GPCR) neurotransmitter receptors: 13 distinct genes encoding for receptors of the G-protein coupled seven-tran membrane class. In addition, there is one ligand-gated ion channel[14]. These receptors are branch into seven distinct classes' 5-$HT_1$, 5-$HT_2$, 5-$HT_3$, 5-$HT_4$, 5-$HT_5$, 5-$HT_6$; and 5-$HT_7$ widely on the basis of their structural and operational features[15]. The 5-HT1, 5-$HT_2$ are then subdivided into 5-$HT_{1A}$, 5-HT1B, 5-$HT_{1D}$, 5-$HT_{1E}$, 5-$HT_{1F}$ and 5-$HT_{2A}$, 5-$HT_{2B}$, 5-$HT_{2C}$ receptor respectively[16]. 5-$HT_3$ receptors belong to the ligand-gated ion channel receptor superfamily. The receptors are present on central and peripheral neurons, where

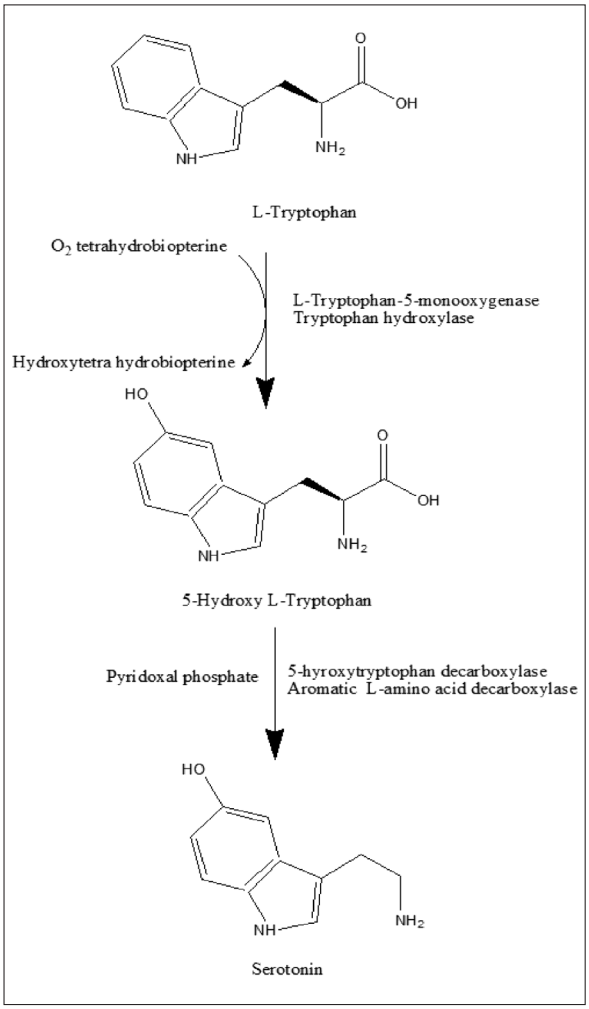


**Figure 1.** Synthesis of serotonin.

opening of non-selective cation channels ($Na^+$, $Ca^{++}$ influx, $K^+$ efflux) trigger their rapid depolarization[17].

### Seasonal Affective Disorder

Seasonal affective disorder is a subtype of chronic depression that involves an ordinary sequential pattern of major depressive illness onset in winter months with full remission in the spring[18-20]. The diagnosis of SAD is depend on the validated Research Diagnostic Criteria for major depression[21], SAD diagnostic criteria are:

- A history of depression fulfilling Research Diagnostic Criteria for major affective disorder, depression;
- A history of minimum two chronological years of fall/winter depressive episodes remission in the spring or summer;
- The destitution of other major psychiatric disorder or psychosocial abstraction for the seasonal mood changes.

While SAD patients accomplish standard diagnostic criteria for major depression, they also recurrently manifest the so-called "atypical" depressive[22] features of hypersomnia (disorder characterized by excessive amounts of sleepiness), increased appetite, weight gain, and fatigue (general decrease of attention), which are relatively uncommon in major depression[23]. The symptoms of SAD start in the second or third epoch of life. It is four times more commonly appears in women than men, a female preponderance greater than for most other psychiatric disorders[24]. The prevalence of SAD increases in people who are living beyond the equator[25-26]. The study basis for the genetics of SAD is of three types:

**Familiality**: Familial contribution on development of SAD is suggested by studies on the prevalence of psychiatric disorders among relatives of patients.

**Heritability**: A survey of a cohort of twins showed that genetic effects exert a worldwide action across a variety of behavioral traits and measured for at least 29% of the variance in seasonality in men and women;

**Molecular genetic research**: the two genetic variants associated to serotonergic transmission, the 5-HTTLPR is related to seasonality and the 5-$HT_{2A}$-1438G/A gene promoter polymorphisms, are correlated with SAD[27].

### Symptoms of Seasonal Affective Disorder (SAD)

Common type of SAD includes: a change in hunger, increase weight, a awkward feeling in the arms and legs, a decrease in energy level, fatigue, a tendency to increasing sleep, difficulty, concentrating, irritability, increased sensitivity to social rejection and keeping away of social situations (hibernation). More severe cases develop the more prototypal symptoms of depression such as: feelings of blameworthiness, loss of interest or pleasure in activities, growing feelings of hopelessness or helplessness, as well as physical problems as headaches and stomach aches. The most severe cases also show suicidal ideation[28].

### Neurotransmitter Function in SAD

The major monoamine transmitters implicated in mood disorders (i.e., serotonin, dopamine and norepinephrine) are functionally linked at many levels, making it unconvincing that an isolated abnormality in a single transmitter system is responsible for a given disorder[29]. There has been special concernment in serotonin, given the ample evidence that seasonal variation of brain and peripheral serotonin occurs in healthy people. For example, recent studies showed that both serotonin turnover[30-31] and accessibility of hypothalamic serotonin transporter sites, as assess by single photon emission computed tomography, are minimum in winter than in summer[32].

### Role of Serotonin in Seasonal Affective Disorder

In past decade there has been a lot of researches on serotonergic activity in all mood disorders, there is a unique commandment to ascertain as a hypothesis that serotonergic dysfunction plays an important role in SAD in particular. In animals and normal humans, various amplification of serotonin activity alters reasonably across the seasons[25]. The serotonin content in the hypothalamus in human post mortem samples has a considerable seasonal variation, with the minimum levels found during the winter months of December and January[33]. Given the role of hypothalamic serotonin in indulgence and feeding regulation, this could explain the complexion of patients with SAD to desiderate carbohydrates and increase weight during winter depressive episodes. 5- hydroxyindoleacetic acid (5-HIAA) is the major metabolite of serotonin, and cerebrospinal fluid (CSF) 5-HIAA levels are derived from various factors, including serotonin synthesis and

turnover, the firing rate of serotonin neurons, and the acid transport system responsible for 5-HIAA excretion. The finding of low CSF 5-HIAA levels in spring time is approximately prospering[34], and may (or may not) revert the cumulative effect of low brain serotonergic activity over the winter. Seasonal variation in other monoamine metabolites have been described as well, but the magnitude of these changes is highest for the serotonin system. L-tryptophan is necessary for synthesis of serotonin, and various measures of tryptophan metabolism and approachability, have been compared across seasons. In a longitudinal study, the highest levels were found in April and May, whereas levels lordotic considerably in the late summer or early fall[35]. Another study also showed that a plasma level of free tryptophan is higher in the spring, with significant lower levels in both the early summer and winter periods[36]. These findings were not simply attributable to dietary fluctuations; however, their overall significance remains unclear in that several other factors, such as protein intake, influence the degree to which plasma tryptophan crosses the blood-brain barrier. Moreover, the fact that tryptophan levels are highest when 5-HIAA levels are lowest is more difficult to justify using a singular model of serotonin activity. Patients with SAD summary show increased activation following high-carbohydrate diet, while the normal controls feel more sedated condition[37].

This may be dependable with change tryptophan and serotonin metabolism in patients with SAD, since the dietary carbohydrates are believed to intensify serotonin synthesis and transmission via increased tryptophan uptake into the brain[38-39]. Two discrete studies have shown that patients with SAD in remission after light therapy experience the tryptophan depletion with clear relapse of depressive symptoms[40-41]. In another study, atypical symptoms such as carbohydrate craving were especially sensitive to the depletion protocol, shown an important role for serotonergic mediation of this symptom assemblage in particular. These results also spot to a serotonergic mechanism for light therapy in SAD. During summer remission, the effects of tryptophan depletion, however, are less invariable: one study showed relapse[32], while another study did not[42].

Taken as a conclusion, tryptophan- depletion study data offer significant evidence that serotonin plays a major role in SAD. However, the study reports that patient with nonseasonal depression are also sensitive to tryptophan depletion calls into query the specificity of these results to SAD[43]. Another type of research has summarized tryptophan as a potential treatment for SAD. The studies compared light therapy with tryptophan in a repeated-measures crossover design, finding similar efficacy for the above mentioned two treatments[44]. There was affirmation, that recurrence after withdrawal from treatment was slower as compared to tryptophan discontinuation[45]. Adding tryptophan produced a robust response in many patients with SAD that was either to some extent or completely nonresponsive to light therapy[46]. It is evident that these assumptions support the hypothesis that serotonin plays a major role in the pathophysiological features of SAD. Other treatments that enhance serotonin function by other mechanisms also have additive effects in SAD. D-fenfluramine, a serotonin-releasing medication, was found to be effective in controlled studies[47]. A larger study shows that the serotonin reuptake inhibitors fluoxetine[48] and sertraline[49] are also effective in SAD. Double-blind, placebo controlled studies showed that, when compared the normal controls with patients suffering from SAD had blunted hormonal responses, and accomplished an increased subjective activation euphoria responses, after administration of the postsynaptic 5-$HT_2C$ agonist m- chlorophenylpiperazine (m-CPP)[50-51]. There was a decrease symptoms of the subjective responses after successful light therapy, showed that activation euphoria in response to a post-synaptic serotonergic agent may be a cause for winter depression, treated by an alteration in the sensitivity of postsynaptic serotonin receptors[50].

### Treatment of Seasonal Affective Disorder

There are various treatments for seasonal affective disorder, including light therapy, medication, ionized-air administration and cognitive-behavioral therapy.

### Light Therapy

The least offensive, most natural, and most studied treatment of SAD is light therapy. The original theory behind light therapy was that it would cause a normalization of the phase-shift delay in SAD. It was then thought to increase the photoperiod in winter in those with SAD. It has also been used to abolish the production of melatonin by the pineal gland. Whatsoever the mechanism of action of light therapy on the body, it has been evident in various patient populations to be

an effective method of treatment of SAD. It has a generally positive treatment response of up to 70 percent, with hardly any side effects. The study of SAD treatment uses bright light (3300 lux), medium light intensity, and dim light, all with positive clinical response. The day timing of light therapy has also been studied abundantly, and it arises that morning, afternoon, and evening application is effective. The full spectrums with ultraviolet, full spectrum without ultraviolet, cool white light, red spectrum of light, and blue/green/yellow spectrum of light have been used with positive result[52]. In a four-week study by SIGH-SAD (Structured Interview Guide for the Hamilton Depression Rating Scale, Seasonal Affective Disorders) early morning bright light therapy (2500 lux cool white light box) for two hours (6-8 am) make body temperature normal[53]. When analyzing single-time-period (morning, afternoon, or evening) with a regimen using morning and evening light application, a notably increased response was observed in the morning and evening light group. Therefore, it is not critical when light therapy is used if it is done once in a day, although, a better effect will be shown by a morning-evening combination[54].

### Negative Air Ionization Therapy

The negative air ionization therapy uses the air ionizers as an experimental important non-pharmaceutical treatment for SAD. The negative air ion generator generates ion with flow rates of $4.5 \times 10^{14}$ ions/second (high-density exposure) or $1.7 \times 10^{11}$ ions/second (low-density exposure). The ionizer was placed at the subject's bedside, with the ion emitter directed to the pillow at a distance of 61 cm. Ion flow toward the body was increased by use of a grounded conductive bed sheet and activated by a timer for 93 minutes before wake-up time, accord to the dawn simulation interval above 0.001 lux[55-56].

### Medication

Some people with seasonal affective disorder may benefit from treatment with antidepressants, especially if symptoms are severe and light therapy has no more beneficial effect over the symptoms[57].

## Conclusions

It has been concluded from the whole study that serotonin, an endogenous chemical plays an important role in mood depressive case seasonal affective disorder. Different study easily depicts the fact that decrease in the level of serotonin directly intensifies this disorder. Serotonin is also used in the treatment of various disorders, including anxiety, depression, obsessive-compulsive disorder, schizophrenia, stroke, obesity, pain, hypertension, vascular disorders, migraine, and nausea.

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