



Secondary to excessive melatonin synthesis, the consumption of tryptophan from outside the blood-brain barrier and melatonin over-signaling in the pars tuberalis may be central to the pathophysiology of winter depression



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ABSTRACT

Seasonal affective disorder is defined as recurrent episodes of major depression, mania, or hypomania with seasonal onset and remission. In this class of mood disturbances, a unipolar major depressive disorder known as winter depression is common in populations living in northern latitudes far from the equator. Winter depression repeatedly occurs in the autumn or winter and remits in the spring or summer, and its etiopathogenesis is currently unknown. However, one can surmise that excessive melatonin production during the reduced duration of daily sunlight in the autumn and winter plays a role in its pathophysiology. Melatonin is synthesized from tryptophan within the pineal gland, which is located outside the blood-brain barrier, and overproduction of melatonin may lead to augmented consumption of tryptophan, from which serotonin is synthesized. As tryptophan is captured from the blood and excessively utilized by the pineal gland, tryptophan blood levels may decline; as such, it is more difficult for tryptophan to pass through the blood-brain barrier and reach the serotonergic neurons as the ratio of tryptophan to the other amino acids that compete for the same transporter to enter the brain is diminished. As such, less tryptophan is available for serotonin synthesis. Moreover, melatonin is known to modulate thyrotropin expression in the thyrotrophic cells of the pars tuberalis of the pituitary gland, and overproduction of melatonin in the autumn or winter months may cause excessive signaling in the pars tuberalis, diminishing its release of thyrotropin and resulting in central hypothyroidism. Both conditions reduced serotonin production and central hypothyroidism may cause depression. Furthermore, the excessive synthesis of melatonin during the autumn and winter may negatively affect the expression of neuromedin U in the pars tuberalis, causing an increased appetite, which is common in winter depression patients. The hypersomnia common in winter depressive patients can be ascribed to excessive circulating melatonin, a hormone that increases the propensity for sleep. Furthermore, central hypothyroidism may also increase sleepiness, as it is known that hypothyroid patients usually experience excessive somnolence. In this theoretical article, we also propose studies to evaluate winter depression patients with regard to the necessity, or not, of offering them an increased amount of tryptophan in their diets during the autumn and winter. We also suggest that the administration of triiodothyronine to winter depressive patients may mitigate their central hypothyroidism.

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Introduction

Seasonal affective disorder (SAD) refers to mood disorders, major depression, mania, or hypomania that regularly occurs and

resolve in specific seasons of the year [1]. Major depression that regularly occurs in the fall or winter and remits in the spring or summer, also known as winter depression (WD), is the most common presentation of SADs. WD is not considered a separate mood disorder but rather a subtype of major depression; it is common and associated with significant psychosocial impairment; and when it is in a milder presentation it is known as sub-syndromal WD [2,3]. One striking characteristic of WD is that its symptoms

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occur when the periods of the day with sunlight (photoperiod) are short — also known as short photoperiods (SP) — and remit when the photoperiods are long (LP); as such, WD is more common in subjects living in northern latitudes than in countries where the difference of time duration between SP and LP is not as significant, such as near the equator [2,3]. In this article, we discuss the possible causes of WD and as premises for our hypotheses, we present circumstances and biological facts relating to the topic of our argument.

Both melatonin and serotonin derive from the same parent amino acid, tryptophan

Melatonin, a hormone produced by the pineal gland, is synthesized in much greater quantities during the dark periods of the day; and as a consequence, its production is increased during SP days and decreased during LP days [4]. The timing, duration, and quantity of melatonin synthesized during the dark periods vary greatly between subjects, and there can be a greater than 10-fold disparity in the levels of nocturnal melatonin in some individuals [4,5]. The parent chemical of melatonin is the essential amino acid tryptophan (TRP), which is drawn from circulation by the pineal gland and converted into serotonin (5HT). The enzyme serotonin-N-acetyltransferase then converts 5HT to N-acetylserotonin; thereafter, N-acetylserotonin is converted into melatonin through the enzyme hydroxyindole-O-methyltransferase [6]. Importantly, part of the N-acetylserotonin is lost during the reaction and is released without having been converted into melatonin [7,8]. The extent to which this biochemical process may ultimately induce a waste of the TRP captured from circulation by the pineal is unknown. TRP is required for the synthesis of melatonin and is also indispensable for the production of 5HT [9] (which is itself a substrate for melatonin synthesis). 5HT is synthesized from TRP in a two-step pathway, in which TRP-hydroxylase is the first enzyme utilized and acts as the rate-limiting enzyme in the pathway. TRP-hydroxylase is not regulated by end-product inhibition, and it is not saturated with substrate in the brain; as such, the amount of TRP influences the brain's production of 5HT [10]. The neurons that synthesize 5HT in the brain, mainly in the raphe, are located inside the blood-brain-barrier (BBB), and TRP is actively transported into the BBB with a carrier that also transports other large neutral amino acids, such as isoleucine, leucine, phenylalanine, tyrosine, and valine [10]. There is competition between these various amino acids for entry into the brain; thus, brain TRP levels depend on plasma TRP and the levels of all amino acids that compete (CAAs) with TRP to enter the brain [10,11]. Therefore, when the ratio of TRP to CAAs increases, it also increases the rate of entry of TRP into the BBB; when this ratio is diminished, this entrance also diminishes, and the availability of TRP for 5HT synthesis is reduced [11]. The pineal gland is located outside the BBB, [12] and the availability of TRP for this gland is easy, almost inexhaustible. The availability of TRP for the raphe nuclei inside the BBB is subject to the level of TRP and the levels of the previously mentioned other amino acids in the circulation, which may vary under nutritional or physiological circumstances, thus altering the availability of TRP for serotonergic neurons [13].

Thyroid hormone is vital to the normal physiology of the central nervous system

Thyroid hormone (TH) acts on virtually every organ system in humans. TH increases the basal metabolic rate, heat production, and oxygen consumption, in addition to many other physiological activities [14]. Many of the functions of TH are performed through genomic actions; nonetheless, its non-genomic actions are also noteworthy. Non-genomic TH actions on mitochondria enable TH

to play an important role in the physiology of the nervous system [14–17]. TH increases the amount and activity of mitochondria, which are responsible for adenosine triphosphate (ATP) production [14]. Neurons depend on ATP production for neurotransmitter synthesis and signaling [14,18,19]. TH increases the velocity of synaptic neurotransmission and thinking processes and enhances memory and learning abilities. TH exerts excitatory effects on the nervous system and increases the responses to various stimuli and the amplitude of reflexes of the peripheral nervous system [14,19]. TH increases the level of alertness and assists the central nervous system in curtailing drowsiness [17,20]; hyperthyroidism may impair sleep, and hypothyroidism causes excessive somnolence [14,17]. It is reasonable to say that TH confers stamina to the central nervous system.

The thyroid stimulating hormone of the pars tuberalis is essential for normal actions of the thyroid hormone in the central nervous system

The pars tuberalis (PT {tubular part}) is the most rostral part of the anterior lobe of the pituitary gland. It wraps around the pituitary stalk in a highly vascularized sheath along the ventral aspect of the median eminence. PT is in direct contact with cerebral spinal fluid, which contains melatonin levels 20-fold higher than those in the circulating blood, suggesting a functional link between melatonin and PT [7,21,22]. Three main groups of cells form PT: (1) folliculostellate cells (non-secretory); (2) gonadotrophs that are similar to those of the pars distalis; (3) and PT-specific cells which are melatonin-responsive and produce TSH, thyrotrophs that are remarkably different from the thyrotrophs of the pars distalis of the pituitary [21]. The PT-specific cells display a high density of the melatonin receptors MT1 (primarily) and MT2 [7,22]. The capillary bed of the median eminence through the long portal vessels is connected to the parenchyma of the PT [23]. Coming from the hypothalamus, tanycyte processes project to the PT, and folliculostellate cells form cistern-like structures that make close contact with the PT thyrotrophic cells, portal capillaries and tanycytes [23,24]. The thyroid-stimulating hormone (TSH) produced by the thyrotrophs from the PT is identical to that produced in the PD, but its production is not under the control of the thyrotropin-releasing hormone or thyroxine (T4) because these cells lack the receptors for these hormones [25]. Instead, these PT thyrotrophs are melatonin-responsive; that is, melatonin regulates their activity. TSH production activity in these thyrotrophs displays dramatic melatonin-dependent photoperiodic changes, with high and low levels under LP and SP, respectively [21,22,26]. Melatonin has a longer duration of production in SP days than in LP days; therefore, it appears that melatonin modulates TSH synthesis in the PT, and increased synthesis of TSH (consequent to the diminished production of melatonin) transmits information about the presence of long daylight lengths [21]. TSH from the PT enters the 3rd ventricle [21,27–31] and binds to the receptors of PT-specific cells and the tanycytes that line the ventricular surface, leading to the transcription of deiodinase enzyme type 2 (DIO2), which converts the poorly active T4 into its much more active derivative, triiodothyronine (T3). Enhancing this conversion results in high concentrations of T3 in the 3rd ventricle and the adjacent hypothalamic region [21,27–31]. A unique glycosylation of TSH in the PT prevents the resulting small amounts of it from a direct stimulation of the thyroid gland [27,32]. These intricate structures and complex functions provide animals living in temperate climates with the conditions to cope with dramatic environmental seasonal changes to ensure better survival, also known as seasonality [23,33]. Whether humans are truly seasonal is debatable; nonetheless, there is evidence suggesting that humans maintain at least a residual tendency toward seasonality [33].

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