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Review Article

SEASONAL CHANGES EFFECTS ON THE SEROTONIN AND MELATONIN TRANSMISSION

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ABSTRACT

Neurotransmission of serotonin and its derivative is said to be effected by changing of season in temperate countries. The effect of photoperiod and temperature can alter the production of serotonin and melatonin in body. The depression in serotonin availability in brain leads to a depressive or bipolar disorder. The activity of tryptophan hydroxylase to synthesis serotonin and monoamine oxidase (MAO) to inactivate serotonin is affected by season change. Calcitriol can stimulate tryptophan hydroxylase to produce serotonin. CREM gene works by memorizing work base on previous memory on how much serotonin will be produce. Melatonin it's a serotonin derivative act as endocrine because it produce from pineal gland and retina. Melatonin has diurnal circadian pattern. Melatonin production is not decline by increasing in age. Arylalkylamine N-acetyltransferase (AA-NAT) gene is one of the cAMP inducible genes is an enzyme important in production of melatonin.

Key words: Serotonin, melotonin transmission, depression, calcitriol

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Serotonin is also known as 5-hydroxytrytamine (5-HT) is widely distributed in plant and animal tissues, venoms and stings. It is a monoamine neurotransmitter synthesize in serotonergic neurons in the central nervous system and enterochromaffin in the gastrointestinal tract in humans and animals. This neurotransmitter like the other is found both periphery and brain. The neurochemical mechanisms that regulate 5-HT transmission such as synthesis and activation are generally the same either in the brain or periphery.

Precursor of serotonin is from tryptophan, one of the essential amino acid in the body. Tryptophan containing food such as poultry meats, milk, and other high-protein foods, tryptophan is released from these proteins and enters the circulation. Tryptophan is taken up b mast cell in intestinal tract and metabolized into serotonin. A lesser, but equally important

amount is taken up by the brain through an active, energy-requiring transporter pump, large neutral amino acids (LNAA). This transporter also take up other LNAA's thus when a person taking large amounts of protein, less tryptophan will carried out to the brain. While when a person eating high carbohydrate-low protein meal, the amount of tryptophan entering the brain will be significantly increased compared with the normal situation (John W. C., 2001).

Tryptophan is converted into 5-hydroxytryptohan by tryptophan hydroxylase then converted into serotonin of 5-hydroxytryptamine by aromatic L-amino acid decarboxylase. After synthesis of serotonin, this free amine is stored or is rapidly inactivated by usually by oxidation catalyzed by the enzyme monoamine oxidase (MAO). Serotonin is the precursor of melatonin synthesis. The synthesis of melatonin occurs in pineal gland and retina. Serotonin regulates functions in the body like mood, sleep, appetite, temperature regulation, perception of pain regulation of blood pressure and vomiting. Serotonin is said to have relation in depression, anxiety and migraine.

Serotonin has no clinical applications as drug. But the receptor subtype selective agonist proves to be values. There are several types of serotonin receptor subtype that already identified. Each of this receptor subtypes are distributed in different area in brain and gastrointestinal tract. Example of serotonin agonists are buspirone, nonbenzodiazepine anxiolytic and dexfenfluramine as appetite suppressant. Not even that, sumatripan and its congeners are agonists effective in treatment of acute migraine and cluster headache. While to inhibit the bad effect of inducing serotonin receptors like vomiting, a serotonin antagonist like ondansetron is used. Melatonin is been studied for several functions in the body including contraception, protection against endogenous oxidants, prevention of aging and treatment for depression, HIV infection and variety of cancer. Melatonin is most often administered to induce sleep and to prevent jet lag. Both in vitro studies and in vivo studies have shown that melatonin is a potent scavenger of the highly toxic hydroxyl radical and other oxygen-centered radicals, suggesting that it has actions not mediated by receptors. In one study, melatonin seemed to be more effective than other known antioxidants (e.g., mannitol, glutathione, and vitamin E) in protecting against oxidative damage. But the antioxidant effect is concentration dependant. It needs higher concentration of melatonin than peak nighttime serum concentration. Melatonin secretion does not change during the menstrual cycle in normal women. Similarly, substantial increases in serum estradiol concentrations do not alter melatonin secretion in infertile women with normal cycles (Amnon B., 1997).

Seasonal affective disorder during season change in temperate countries

Season is different in tropical countries and temperate countries. In temperate countries, the changes in season are influence by the changing of amount of sunlight. People in temperate and polar region experience four distinguish season that are spring, summer, autumn (fall), and winter. Northern part of the world experiences opposite season as in south part. This changing of season usually accompanied by seasonal affective disorder (SAD), one of the common conditions in temperate countries. It occurs especially starting from September or October and ending in April or May (Sabra L. K. W. *et al*., 2006). This SAD is affecting 1-3% of adults in temperate climates and more prevalent in women (Magnusson A. *et al*., 2003).

According to Jacobs G.D. (2004), mood and energy in winter are poorest during winter. This led to theory that lack of exposure to sunlight affects the population as a whole and may be contributing to an overall increase in mood disorders in the general population. The supplementary light in winter might have widespread benefit for those individuals who are

"normal" but are more vulnerable to seasonal depressive symptom. Symptoms of SAD include irritability, sadness, anxiety, increased appetite and a craving for carbohydrate, weight gain, decreased activity and a need for more sleep, drowsiness during the daytime, and problems with work and relationships (Miller AL, 2005).

The severity of depressive or bipolar disorder is vary to each people according to Partonen T (1998). He also stated that at first, SAD was related to abnormal melatonin metabolism but later findings did not support this. Hypothesis of brain serotonin function support the hypothesis of disturbed activity in SAD patient. While according to Yang H.D. (1997), mania attack is significantly higher in spring and summer (71.4%) than in fall and winter (28.6%) while depressive attack is higher in fall and winter (63.4%) than in spring and summer (36.6%), which shows there are clear relations between affective disorder attack and seasonal change, and support the circadian rhythm-melatonin hypothesis. Yang H.D. also suggests that there are not gender differences between mania attack and depressive attack and seasonal change.

Magnusson A *et al*. (2003) stated that the role of circadian rhythms in SAD needs to be clarified. The phase-delay hypothesis holds that SAD patients' circadian rhythms are delayed relative to the sleep/wake or rest/activity cycle. This hypothesis predicts that the symptoms of SAD will improve if the circadian rhythms can be phase-advanced. The retinal hyposensitivity hypothesis for SAD support by the retina sensitivity was significantly lower) in SAD patients compared with normal control subjects conducted by Marc H. *et al*. (2004), but the explanation for lower rod photoreceptor sensitivity in SAD is not known. They also proposed that brain neurotransmitter dysregulation may be at the origin of both the mood disorder and retinal sensitivity change.

Despite of ugly effect of SAD, the symptoms also promoted healthier pregnancies and gave rise to enhanced female–male pair-bonding which improved the survival chances of both mothers and babies. Hypomania in spring and summer also served to increase the likelihood of procreation at the optimal time of year. But recurrent winter depression can become a reproductive disadvantage (Eagles J.M., 2004).

Selective serotonin reuptake inhibitor or SSRI like citalopram, fluoxetine and sertraline (BNF 51, 2006) are used in treatment of depression. Number of SSRI been prescribe to adult Swedish reduce as increase of 1˚C from and more SSRIs were dispensed to men and women in Sweden during relatively cool Julys during the period 1991–1998 (Hartig, T., *et al*. 2007). This shows that depression will increase as temperature decrease. People are more depress in winter rather than in summer. The involvement of serotonin cause the depression.

Relationship of serotonin with seasonal changes

Mood can be seasonal according to temperature and season we experience. The amount of sunlight that enters into our retina will enhance the “happy” neurotransmitter release, serotonin. Serotonin is involved in mood, behaviour and affective disorder. Light can induce synthesis of serotonin. It proved in Chanut E. *et al*. (2002) origin of serotonin, precursor of melatonin, in the retina of adult rat, where no immunoreactivity for serotonin or tryptophan hydroxylase had ever been detected. Tryptophan hydroxylase is the initial and rate limiting enzymes in the biosynthesis of serotonin neurotransmitter. This enzyme not only determines the amount of serotonin produced at any given time but also involve in influence of functional status of the serotonin neuronal system. For these reason, physiological conditions or pharmacological

treatments which modify tryptophan hydroxylase can have short or long term effects on serotonin system

Melatonin is produced in pineal gland and retina. Retinal circadian rhythms are driven by an intrinsic oscillator, using chemical signals such as melatonin, secreted by photoreceptor cells. It is proven in this experiment by Chanut E. *et al*. (2002) that tryptophan hydroxylase substrate concentration was higher in the dark period than in the light period, and formation of hydroxylated compounds was increased. They confirmed the presence of tryptophan hydroxylase mRNA in the rat retina by RT-PCR.

Tyrosine hydroxylase gene expression can also be stimulated by calcitriol that accumulates in the nuclei of adrenal medullary cells. Adrenergic input to the pineal gland at night induces the transcription of CREM gene. Partonen T. (1998) stated that CREM gene is either subsensitive or supersensitive to induction, depending on the photoperiod of the prior night. This memory of past photoperiod, either experience long dark period as in winter or long day period as in summer, induced changes in melatonin either inhibitory or stimulatory effects on bodily functions. Body works by storing information that will be needed to control the body function. The author also stated that the involvement of calcitriol in increase serotonin levels because of inhibition of melatonin binding to nuclear retinoid Z receptors. Serotonin production is also thought to depend on duration of light exposure the previous summer.

Serotonin is inactivated usually by oxidation catalyzed by the enzyme monoamine oxidase (MAO). Involvement of MAO in inactivation of serotonin is important in serotonin level in body. One experiment open field of Yakut ground squirrels (Citellus undulatus) was done. The objective of this study is to study the changes of MAO in brain with changes of season. The experiment was done by Semenova TP (2004) showed that in summer, all parameters of exploratory activity in the open field and holeboard test reached the values characteristic of summer animals very rapidly, within a few days or (in some cases) even within the first 24 hours after the arousal from hibernation in the middle of April. In autumn these parameters decreased to their minimum values 1.5-2 months prior to hibernation. He also found that activity of MAO A measured with serotonin as a substrate in the hippocampus was 1.8 times higher than the activity of MAO A with respect to noradrenaline. In contrast, in autumn the MAO A activity determined with noradrenaline as a substrate was 2.5 times higher than the activity a MAO A with respect to serotonin. This shows that seasonal features of the higher nervous activity of hibernating animals depend on the balance between serotonergic and noradrenergic systems in different periods of the annual cycle.

Changes of mood are apparent in winter in temperate countries rather than in tropical countries. This is probably because of changes of amount sunlight with changing of season. In winter, people in temperate countries will experience short days and long nights with extreme temperature. The different of climate may lead to depression. In winter, turnover of serotonin is the lowest according to Lambert GW *et al*. (2002). It also proven by them that the production of serotonin was directly related to duration of sunlight and increase in synthesis with increase in luminosity.

In other research conducted by Ohshima K. *et al*. (1999), the seasonal variations in serotonin immunoreactivity and ultrastructure of the secretory rudimentary photoreceptor cells (SRPC) were studied in the pineal organ of the Japanese grass lizard, *Takydromus tachydromoides* in relation to the environmental temperature. The different in temperature from spring to summer

shows increase intensity of immunoreactivity and weaker as the temperature drop in winter. They also stated that, the SRPC of the lizard showed distinct seasonal variations in number and size of the dense-cored vesicles correlated to the serotonin immunoreactivity. But, the changes in size of the lysosomes and nucleoli of the SRPC were inversely proportional to that of the dense-cored vesicles. Furthermore, the lysosomes ingested some dense-cored vesicles after the autumn, and they coalesced to form huge autophagosomes or residual bodies during the winter.

Relationship of melatonin with seasonal changes

Melatonin is produce from serotonin. Melatonin is abundance in dark period as compared to day period. Melatonin is normally made at night and may be considered to act as a signal of darkness to the body. In all life forms so far studied it seems to act as a time signal for the organisation of daily (circadian; sleep-wake) or seasonal rhythms, or both. Melatonin seems to play an important part in setting the correct timing of sleep-wake cycles in mammals in the perinatal period and of subsequent pubertal development. When given to humans it has rapid, transient, mild, sleep inducing effects, and it lowers alertness, body temperature and performance during the three or four hours after low doses have been given. Correctly timed, it is able to shift the internal "body clock" both to later and earlier times and so melatonin has a potential value as a treatment for problems with sleep and other body functions that have been disordered by time effects.

Melatonin in human pineal gland is augment only during long photoperiod. There is a partial effect of photoperiod on melatonin secretion. This may result from living in an artificial light environment or due to other nonphotic signals involved in generating melatonin rhythm. Research by Rafael L. *et al*. (1998) proved that melatonin production with changes of season indicated that day–night difference in pineal melatonin levels was evident only in the long photoperiod (April–September) with significantly higher melatonin concentrations occurring at night (2200–1000 h). Nighttime values in the long photoperiod were significantly higher than the nighttime values during the short photoperiod (October–March). During winter or short photoperiod, they suggest that a possible in phase delay in melatonin secretion.

Rafael L. *et al*. (1998) also found that day night difference is an age related. They found that day–night difference was evident in young subjects (30–60 years), but not in elderly subjects (61–84 years). Elderly subjects had lower total melatonin levels (day and night values) although statistically not significant. Thus they concluded that the production of melatonin is not decline with increase age and no significant day–night difference in melatonin levels.

Amnon B. (1997) suggested that there are two photoreceptive systems that are one involve in melatonin secretion and other mediating conscious of perception light. This is because he found that blind person with no papillary light reflexes and no conscious visual perception has light-induced suppression of melatonin secretion. This suggests that blind person cannot be affected by changing of sunlight and mood with different season.

The nocturnal biosynthesis of melatonin in the rat pineal depends on strongly enhanced expression of the enzyme arylalkylamine *N*-acetyltransferase (AA-NAT). During constant darkness like in winter time, the amplitudes of AANAT and melatonin rhythms were significantly lower (by 50-80%) than those found under the daily light-dark cycle (Zawilska JB *et al*., 2006). This indicates that melatonin production in pineal gland and retina is regulated by both light and the endogenous circadian clock. The rapid slowing of the rhythms under constant darkness suggests that of these two regulatory factors, environmental light may be the primary

stimulus in the maintenance of the high amplitude melatonin production in the turkey. Without much light also can lead to decrease synthesis in melatonin.

Arylalkylamine N-acetyltransferase (AA-NAT) gene is one of the cAMP inducible genes. Study by Spessert R. *et al*. (2006) showed that all cAMP inducible genes tend to display higher maximum expression under short photoperiod than in long photoperiod. They suggested that all cAMP-inducible genes are influenced by photoperiod and depend on the cycle of darkness. Thus AANAT will cause more melatonin production in dark period as compared in day period.

N-acetyltransferase (AANAT) is important in production of melatonin. Adrenergic inputs to pineal gland from suprachiasmatic nucleus (SCN) stimule transcription of AANAT during darkness. This lead to activation of pinealocyte adrenoceptors involves in cAMP-dependent stimulation of protein kinase A (PKA). In Lydia E. *et al*. (2004) study, they found that the nocturnal rise in AA-NAT depends on the lighting conditions. As compared with light/dark (LD) 12:12, the delay between dark onset and the nocturnal rise in AA-NAT is shortened under long photoperiods and prolonged under short photoperiods. They suggested that rapidity of nocturnal AA-NAT induction depends on cAMP inducibility of the gene. Accordingly, cAMP produces a strong AA-NAT response in pineals obtained from rats housed under long photoperiods and a weak AA-NAT response under short photoperiods. Changes in AA-NAT inducibility are fully developed not earlier than after seven cycles. This observation suggests that long-term changes in the photoperiod are necessary to achieve full adjustment of cAMP inducibility of the gene. A direct relationship was found between cAMP-dependent AA-NAT inducibility and the pineal protein kinase A (PKA) activity. As compared to LD 12:12, PKA activity was increased under long photoperiod and decrease under short photoperiod.

Melatonin is synthesized in diurnal or circadian rhythm and produce large at night. The amount of light can affect the production of melatonin. The melatonin synthesis is related with 14-3-3 proteins. It is a large family of proteins that exist primarily as homo- and heterodimers within all eukaryotic cells. It has been demonstrated that cAMP levels and PKA activity in melatonin-synthesizing cells (pinealocytes and retinal photoreceptors) increase at night. Phosphorylated of serotonin N-acetyltransferase (AANAT) by PKA will bind to 14-3-3 proteins. Thus this formation will form complex and protects from proteolytic destruction. Not even that, this complex will induce changes of the AANAT molecule resulting in an increase of the enzyme activity; this in turn enhances melatonin production by several folds. Light can cause intracellular cAMP decrease and dephosphorylation of phosphorylated AANAT. It can also enhance dissociation of pAANAT from 14-3-3 complex and turning off melatonin production (Rosiak J *et al*., 2006).

During winter, there is restriction of movement. Because of heavy snow, people cannot go out and do normal activities. The effect of latitude and melatonin production is seen in experiment by Kriya L. D. *et al*. (2007). They use sled dog because of its nature that is elite athletes. They study both effect of exercise and non exercise dogs from 2 distinct latitudes. Melatonin production was prolonged in high latitude dogs (65° N) as compared with lower latitude dogs (45° N). This suggests that as latitude goes higher, the season changes are more apparent. Melatonin secretion is increase as the amount of sunlight is reduced. They also stated that melatonin production increase in winter as compared to in summer. As for exercise, there is reduction in winter melatonin levels at both latitudes. Adaptation to season can also affect the melatonin production. They also found out that sled dogs in Alaska had lower melatonin levels than sled dogs in New York. This probably because sled dog in Alaska experience colder

temperature as compared to sled dog in New York. The low melatonin mechanism is not well understood.

Immune and antioxidant defenses, hemostasis and glucose regulation are depend on melatonin signal for circadian organization. Melatonin also proved to stabilizes and strengthen coupling of circadian rhythms, especially of core temperature and sleep-wake rhythms (Bruno C. *et al*., 2005). Melatonin is also important in gonadal activity. The circadian disturbances related to production are probably subsequent to the seasonal change. Both spermatogenesis and folliculogenesis are also proved to be influence by melatonin. According to Partonen T. (1999), the exposure to bright light may be useful in treatment of infertility in couples with abnormal melatonin metabolism.

Different region of animal has their own mechanism to coordinate changing of season. As for example animal at nontropical region will hibernate to restore its own body temperature. They adapt to photoperiod to coordinate changes in behaviour and physiology. Rodents shows increased in aggression in short, “winter like” as compare to “summer-like” day length. They result from Aaron M. J. *et al*. (2002) showed that short-day hamsters underwent gonadal regression and displayed increased aggression compared with long-day animals. Melatonin treatment also increased aggression compared with control hamsters without affecting circulating testosterone. Collectively, the results of the present study demonstrate that exposure to short days or short day-like patterns of melatonin increase aggression in male Syrian hamsters. In addition, these results suggest that photoperiodic changes in aggression provide an important, ecologically relevant model with which to study the neuroendocrine mechanisms underlying aggression in rodents

Photoperiod influences lots of body function. It can regulates the timing of seasonal cycles in reproduction, energy metabolism and other seasonal characteristics, and the effects are transduced through changes in the duration of nocturnal melatonin secretion from the pineal gland. Summer like physiology (short daily melatonin signal) and winter like physiology (long melatonin signal) cause signal in specific target in the brain and pituitary gland, each governing a different component of the seasonal adaptation. The pars tuberalis (PT) of the pituitary regulates prolactin release and provides a tractable model system to investigate the molecular decoding mechanism. In the PT, melatonin onset at dusk activates cryptochrone (*Cry*1) gene expression and melatonin offset at dawn activates period (*Per*1) gene expression (Amanda J. F. C. *et al*., 2003), thus the *Cry*/*Per* interval varies directly with nightlength, and inverse to daylength (Gerald A. Lincoln, 2006). The author proposed that photoperiod-induced changes level of CRY/PER protein heterodimer formation thus under long days, prolactin secretion is stimulated.

CONCLUSION

Serotonin is a neurotransmitter that release from brain and gastrointestinal tract is related with light exposure. Serotonin regulates functions in the body like mood, sleep, appetite, temperature regulation, perception of pain regulation of blood pressure and vomiting. Melatonin is a serotonin derivative is not a neurotransmitter and it is secreted from pineal gland and retina. Melatonin has diurnal and circadian rhythm. Melatonin is been studied for several functions in the body including contraception, protection against endogenous oxidants, prevention of aging and treatment for depression, HIV infection and variety of cancer. Melatonin is most often administered to induce sleep and to prevent jet lag. Melatonin secretion is increase in dark period while serotonin is increase in day period. Serotonin and melatonin is related in seasonal changes.

Depression of serotonin release in winter will lead to a condition name seasonal affective disorder (SAD). Amount of photoperiod through out the season affect the production of serotonin and melatonin. Serotonin is said to have relation in depression, anxiety and migraine.

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