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Potency of Melatonin in Living Beings

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ABSTRACT : Living beings are surrounded by various changes exhibiting periodical rhythms in environment. The environmental changes are imprinted in organisms in various pattern. The phenomena are believed to match the external signal with organisms in order to increase their survival rate. The signals are categorized into circadian, seasonal, and annual cycles. Among the cycles, the circadian rhythm is regarded as the most important factor because its periodicity is in harmony with the levels of melatonin secreted from pineal gland. Melatonin is produced by the absence of light and its presence displays darkness. Melatonin plays various roles in creatures. Therefore, this review is to introduce the diverse potential ability of melatonin in manifold aspects in living organism.

Key words : Melatonin, Reproduction, Circadian rhythm, Antioxidant, Immunity

INTRODUCTION

Every living being inhabiting on Earth undergoes periodical rhythms, such as circadian rhythm that happens daily, seasonal rhythm that happens periodically, and annual rhythm that develops yearly. The creatures have survived by adapting those rhythmical fluctuations present in ambient environment. Thus, periodic changes in environment seem to be imprinted as a biological rhythm in both one-cell creature and even multicellular one, including human. It is not likely to befall that the physiological phenomena developing rhythmically within the creatures coincide in phase with the external rhythms. It is believed that the incidents are worked by external and practical signals repeating periodically, corrected depending on the needs, and nowaday reflected in living being.

Day and night cycle exists as a result of rotation of the Earth, leading to similar cyclic pattern of atmospheric temperature. This cycle of 24 hours is imprinted into living body and fixed as an endogenous clock in the process of revolution for eternal period of time. The term ‘circadian’, originated from Latin language, is coined by combining ‘circa’ (meaning about) and ‘dian’ (meaning day). Thus, the word circadian implies changes recurring with 24 hours within the living body, called endogenous clock. A cycle that is less than 24 hours or longer than 24 hours is referred to as ultradian and infradian cycle, respectively. Living beings require a particular sensation apparatus to cognize cyclic environmental signals. The rhythm of day and night cycle on daily basis is detected by eyes and the light information is transmitted to suprachiasmatic nucleus (SCN) of brain through retino-hypothalamic tract (RHT). The SCN sends the message ultimately to pineal gland that produces melatonin. The external environmental signal, as a German term Zeitgeber (time signal or time donor), is transformed to an internal circadian rhythm within living

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organism. The Zeitgeber is important in correcting biological clock that is a circadian system.

Since the biological clock, in general, is slightly deviated from the exact 24 hour cycle, precise correction is needed. Therefore, the biological clock is required daily to adjust in advance or back. The circadian rhythm takes place in an everyday affair, including locomotor activity, feeding behavior, body temperature, and memory process (Hurd et al., 1998; Stokkan et al., 2001; Chaudhury & Colwell, 2002; Castillo et al., 2005).

This review is to introduce potential ability of melatonin, in various aspects, that transduces light signal of environment into chemical signal in living organism.

ACTIVITIES OF MELATONIN

1. Melatonin synthesis

Melatonin was first discovered in 1950s (Lerner, 1958). Following this discovery, much about reproductive function of seasonal breeding animals has been found (Reiter et al., 2009). Melatonin exhibits in a rhythmical pattern in almost all animals, and it is generated mainly from the pineal gland. Since it is elevated only at night without respect to diurnal or nocturnal animal, it is called a hormone of night or a messenger of night. While various functions of melatonin in living beings have been found in succession, the general discussion of the functions is being expanded.

Melatonin is produced mainly in pineal gland at night, but it is also made in retina, bone marrow, and ciliary body as well (Martin et al., 1992). A small amount of melatonin is generated from other tissues such as gastrointestinal tract and skin, which act locally (Reiter & Tan, 2003a). The synthesis and secretion of melatonin are controlled by photoperiod. The concentration of melatonin in blood is low during daytime and high at night, due to light availability to inhibit the activity of an enzyme involved in the production of melatonin.

The signal of light impinges on photoreceptor in the retina of the eye and is transmitted to SCN through RHT. The information is then moved to paraventricular nucleus of hypothalamus, and to superior cervical ganglion via spinal cord. The message then reaches the pineal gland by way of neurons called nervi conarii along with blood vessel. The neuron secretes norepinephrine at the pineal gland and it binds to β1 adrenergic receptors on the cell membrane of pinealocyte. Then G-protein coupled adenylate cyclase receives the information and cyclic adenosine monophosphate is produced in the cytoplasm and moved toward nucleus of the cell. At this time arylalkylamine N-acetyltransferase (AANAT) is inactivated and melatonin is not generated. The AANAT in the absence of light signal is activated and serotonin is transformed to melatonin.

Melatonin begins to synthesize by the action of tryptophan-5-hydroxylase on tryptophan. Once tryptophan is converted into 5-hydroxytryptophan (5HTP), it is transformed to 5-hydroxytryptamine (serotonin) by an enzyme 5HTP-decarboxylase. Serotonin is converted into N-acetylserotonin by an enzyme serotonin-N-acetyltransferase (NAT), also known as AANAT. Melatonin is synthesized from serotonin by the action of the acetyl serotonin-O-methyltransferase (hydroxyindole-O-methyl transferase) (Reiter et al., 2010). Melatonin is a hydrophobic substance, is not stored, is secreted directly to the circulatory system without particular portal blood vessel, has no particular target organs, and acts on the cells with melatonin receptors.

Melatonin is transformed into 6-hydroxymelatonin in liver. Ninety percent of it binds to sulfate to convert into 6-hydroxymelatonin sulfate while 10% binds to glucuronide to convert into 6-hydroxymelatonin glucuronide which is then metabolized. Also, very tiny amount of melatonin is secreted into saliva. Melatonin is also metabolized into other substances, such as cyclic 2-hydroxymelatonin, N-γ-acetyl-N-2-formyl-5-methoxykynurenamine, and N-γ-acetyl-5-methoxykynurenamine (Pandi-Perumal et al., 2006).

Since synthesis of melatonin is regulated by light, circadian rhythm, and activity of enzyme along with time, melatonin is suggested to be useful as a detecting reader to record the noradrenergic function after antidepressant administration (Cowen et al., 1985; Palazidou et al., 1992). The function

of melatonin is being found in many directions: circadian rhythm including regulation of reproductive function in seasonal breeding animals, promotion of neural development, a reducing action of inflammation with enhancing defensive power by acting immune system, metabolism control, especially lipid metabolism control, and powerful antioxidant and oncostatic effects of breast cancer (Waldhauser et al., 1984; Aldhous et al., 1985; Hojo et al., 1997; Ray, 2003; van der Zwan et al., 2010; Kostovski et al., 2011; Syrseloudis et al., 2011). Melatonin exerts its effects through membraneous melatonin receptor (MT1 and MT2).

2. Reproductive endocrine system

Mammals inhibiting in temperate regions have long lived with adaptation to the distinctly recognizable four seasons. They have maintained their species by reproducing during the limited period of time chosen for satisfactory survival of themselves and their offsprings against hot summer weather and severe climate in winter. A wide range of studies are underway for various purpose in the hamster, sheep, squirrel, mink, fox, bear, wallaby, deer, and ape.

Photoperiod is expressed as a lighting period of time in a day at which long photoperiod is referred to the period longer than 12 hours. Animals recognize present time in a year by utilizing the photoperiod, in other word, by identifying the time when melatonin is produced (Stetson et al., 1975). Since the photoperiod is associated with temperature and food availability, it is speculated that photoperiod is used as a critical tool to regulate reproduction. But not all animals use the same photoperiod; There are some differences among even hamsters.

The hours of sunlight in natural environment alter gradually, and it is not easy to perceive initiating and terminating time of reproductive function. Thus, the photoperiod can be determined by experimenting adult animals under constant temperature and fixed photoperiod in the laboratory. In the case of golden hamsters, the reproductive activities are maintained or promoted with treatment of photoperiod from more than 12.5 hours to 24 hours in a day (Hoffman & Reiter, 1965a, 1965b; Gaston & Menaker, 1968). If the daylight time is set to less than 12.5 hours, the sexual activities are entirely regressed in 8 week of exposure (Choi, 1996; Choi & Lee, 2012). Thus, 12.5 hours of time in a day is referred to threshold of photoperiod to define reproductive function in them. In Djungarian hamster (*Phodopus sungorus*) the photoperiod to maintain sexual function is 13−14 hours and in Turkish hamster (*Mesocricetus brandti*) it is between 15 and 17 hours. The lighting period of time that is shorter than 15 hours or longer than 17 hours in a day similarly leads to gonadal regression in suitable days of time.

As for sheep, the estrous cycle is at 17-day intervals in autumn and winter, when they mate. Following is the gestation period of 152 days and 1 or 2 offsprings are born in spring. A lamb just born sucks dam's milk and eats feed grains in a month. The lamb is weaned in 3−4 month old. The survival rate is optimal with the benefit of favorite temperature and abundant food. The environmental signal to regulate this seasonal reproduction is photoperiod. Sheep reproduce with understanding of present time in the course of photoperiod (Lehman et al., 2010). The sexual activity is activated under short photoperiod (SP) and inhibited under long photoperiod (LP). The relatively shorter melatonin signal presented under long photoperiod induces non-breeding season with pause of estrous cycle by suppressing the release of gonadotropin releasing hormone.

These effects of photoperiod start to work from birth and vary among different animals. Golden hamsters exhibit reproductive activity after passing through puberty without respect to photoperiod. But Djungarian hamsters do not have reproductive function even after puberty if they are exposed to SP. In Turkish hamsters, sexual activity is not furnished under shorter photoperiod (<15 hours) than threshold and longer photoperiod (>17 hours) than threshold photoperiod. Like these, photoperiod used by animals represents species specific properties in both adulthood and developing stage.

The information of photoperiod is not reflected in golden hamsters if the pineal gland is removed by surgical operation. In other words, reproductive activity is eternally kept.

This result implies that the pineal gland is definitely involved in the seasonal breeding animals. Because of the association of pineal gland, melatonin secreted from the pineal has been focused (Lehman et al., 2010). The long day breeders have active sexuality in summer and have completely regressed period for several months in winter when the period of melatonin elevated in a day is the longest in a year. The sexually regressed outcome is recovered by removal of pineal gland. The consequence of reproductive regression is displayed because the elevated period of melatonin secretion is lengthened, hence melatonin is called antigonadal or antigonadotrophic agent. At present, this definition is appeared as a mistake. This is because animals are observed in a sexually active state in SP. The short day breeder (sheep, white-tailed deer, etc.) virtually is equipped with reproductively active capacity in winter when daylength is the shortest in a year and the elevated level of melatonin is the longest at night (Coelho et al., 2006; Chemineau et al., 2008; Wagner et al., 2008). Therefore, melatonin is referred to progonadotrophic in these species.

Rather, melatonin can be defined as a passive chemical signal that provides hypothalamus-pituitary-gonad axis with time of one year, because nocturnal melatonin information alters yearly. That is, the length of melatonin means an information of one full year.

Animals regulate physiological events of gonads (testes and ovaries) by using melatonin rhythm altering distinctly upon seasons in the reproductive endocrine system. With this strategy, animals decide the time of lactation at a particular time of a year for successful mating and give birth to offsprings when the temperature is suitable and food is available abundant (spring and summer). Birth time is substantially far more important than mating time. Thus, the seasonal breeders have parturition time at spring by exerting the signals of annual clock (Reiter, 1980). When the seasonal breeders determine the reproductive ability, the daylength is absolutely critical. In other words, it also implies that the period of elevated melatonin is fundamental (Elliott, 1976; Carter & Goldman, 1983). Although the daylength after winter solstice gets gradually longer (elevated period of melatonin becomes shorter due to shorting period of night), the reproductive endocrine system of golden hamsters is still remained to be in quiescent state (Reiter, 1980). If golden hamsters are housed for longer term in SP (corresponding to winter season), they no longer respond to the SP, meaning spontaneous recovery of sexual activity. this is called refractory event. The mechanism involved in this result has not been exactly known yet.

Regardless of the type of photoperiodic breeding, seasonal changes of gonadal ability in animals whose reproduction is determined by photoperiod rely on the annual changes of day and night, and this in turn is dependent on the elevated period of nocturnal melatonin (Barrett et al., 2003; Lincoln, 2006; Dupre et al., 2008; Choi, 2013). The photoreceptors whose reproductive ability are regulated by coincident time of the year are present in extremely specialized retinal cell of the eyes and they contain melanopsins that are unique photopigments (Qiu et al., 2005). The cells transmit the information of lengths of day and night to SCN, where the clock is, through RHT (Moore et al., 1995; Hatter et al., 2002). As mentioned above, SCN sends the information to pineal gland by way of central nervous system and sympathetic neurons of peripheral nervous system (Moore, 1978). Then the pinealocytes influenced by norepinephrine released from the neuronal terminals produce melatonin at night and the level of melatonin peaks in plateau.

If the pathway of sympathetic neurons guiding the light information to pineal gland is entirely severed (by superior cervical ganglionectomy in both sides), melatonin is not generated and pineal no longer regulates the reproductive endocrine system (Reiter & Hester, 1966). As a result, these animals reproduce at any time, and the consequence could be absolutely cruel to them for survival under the surrounding situation with natural changes.

When golden hamsters are administered with melatonin in the afternoon, although the animals are housed in long photoperiod condition (light of 14 hours in a day), the

reproductive function is regressed and reproductive hormones alter similarly to levels of animals exposed to the situation of SP (Reiter, 1980). But if animals are kept for long time in SP or received melatonin for long term, they no longer respond to the treatments (SP or afternoon melatonin injections) and their gonads naturally recover the sexual ability. This situation happens at early spring in nature (refractory phase), and it can be speculated because sensitivity to melatonin is lost.

The physiological mechanism by which melatonin acts on reproductive endocrine system is control of the release of pituitary gonadotropins and involves prolactin (Dardente et al., 2008; Guillaume et al., 2008; Choi & Lee, 2012). Melatonin exerts its effect via melatonin receptors (Reppert, 1997; Choi et al., 2002). Studies find that melatonin acts multi-stepwise, involving hypothalamus, pituitary, and gonads. It is considered that the precise mechanism will be analogously revealed in many mammals, although much investigation is not performed in different animals.

It has been found that photoperiod and melatonin influence seasonal breeding by a great deal of examinations using LP and SP breeding animals. In a consequence, the seasonal reproduction of sheep can be antedated by employing melatonin pharmacologically, estrous cycle would be induced, and offsprings could be born during seasonal anestrous cycle (Haresign, 1992; Abecia et al., 2008). These actions of melatonin are represented by improvement of ovulation rate, development of corpus luteum, and increased survival rate of embryos (Abecia et al., 2002; Zuniga et al., 2002; Forcada et al., 2006). Although information about pineal gland and melatonin has been widely known up to date in relation to seasonal reproduction, various roles of melatonin are continuously being revealed.

It has been reported that melatonin plays a role in choosing spouse. When male zebra finch (*Taeniopygia guttata*) feeds carotenoid (100 /) and melatonin (50 /) in drinking water, the color of bill becomes brightened. The males with bill pigmented brightly are better chosen as a spouse by female zebra finch, thus it is regarded that melatonin plays a part in choosing a spouse. Like melatonin, carotenoid is a scavenger of removing free radical and an antioxidant (Sies, 1993; Tan et al., 2007; Peyrot & Ducrocq, 2008). But how much the animal feeds melatonin can not be accounted, nonetheless the physiological level of melatonin would not be greatly deviated because of vast range of its fluctuation (Tan et al., 1999).

Melatonin can influence the color of bill by other means that does not directly involve the preservation of carotinoid. But if the pigment was attractive to spouse, the effect of melatonin ultimately is thought to be the same (Hartley & Kennedy, 2004). The melatonin receptors were identified in neuronal cells of brain that are associated with song control circuit essential to pattern of song in male zebra finch (Jansen et al., 2005). Melatonin receptors were found in peripheral nervous system that is a part of song circuit. When melatonin was treated in brain slices containing song control circuit present in neuronal cells, the firing rate of the cells was inhibited. Therefore, melatonin is suggested to modify the ability of singing.

When a melatonin antagonist (S20928) was administered to male zebra finch at early night prior to elevation of melatonin concentration, the lengths of song and motif were reduced and the length of syllable of a song was affected on next day. But the pattern of temporary singing was not altered. In light of spoiled song induced by melatonin receptor antagonist, it is known that the circadian rhythm of this animal was not changed. Because female zebra finch are allured by lengthened song and motif length, this result implies that melatonin plays a role in courtship of male. The consequence is worthy of notice because sexual activity of spouse is provoked by singing ability of male (Harding et al., 1983). In general, colorful plumage presents genetic signal of superior quality, thus it is common strategy for most of avian to use as a sexual attraction. A bright pigment at a particular part of body is used for courtship in some animals (reptile, amphibian, and mammal). Therefore, the impact of melatonin on skin should be extensively investigated. It was speculated that melatonin regulates growth of hair, pigment modifi-

cation, and molting in different animals due to melatonin receptor identified in skin and hair follicle of mammals (Fischer et al., 2008a, 2008b). But the mechanism of action remains to be examined.

3. Circadain rhythm and jet lag

Living beings live in an environment altering in a cycle of 24 hour or so per day on Earth. Also the periodical changes express seasonal alteration occurring over several months and annual alteration emerging once a year. Like natural phenomena recurring periodically, very simple creatures as well as human demonstrate endogenous rhythm. The physiological processes exhibiting periodically in living body are not consistent by accident with the phase of external rhythm; it is managed and reset by reflecting within living body through physical cues with periodicity (Takahashi & Zatz, 1982). The research about the endogenous rhythm seen in the living organisms nowadays is known as circadian biology.

The environmental rhythm such as periodicity of daylight that originated from the Earth's rotation and the related atmospheric temperature have an impact on biological clock intrinsic to living beings. The impact requires specialized sensing structure that detects fluctuation of environment occurring on a daily basis. As mentioned above, the eyes are organs that daily senses day and night cycle, and transmits light information to the pineal gland to produce melatonin.

The clock regulating rhythmically the synthesis of melatonin is placed in SCN. The SCN is connected to the pineal gland by multi-synaptic pathway. In contrast to the rhythm of melatonin production that SCN intervenes, the pineal-oscillator-dependent rhythm that generated locally was identified in various vertebrates (Zimmerman & Menaker, 1975; Cahill, 1996).

Melatonin is associated with sleep in human. This is because elevated nocturnal level of melatonin is in phase with sleep induction and sleep time (Hughes et al., 1998; Baskett et al., 2001). Besides this circadian rhythm, melatonin is in the limelight as an agent healing physiological and psychological effect against jet lag and disturbance of circadian rhythm (Arendt & Broadway, 1987; Petrie et al., 1989).

People who travel long distance to east or west or who ought to serve shift work at night are unstable with fatigue and show slightly confused orientation sensation. These matters are because the internal clock is inconsistent with environmental cues by the Sun. In other words, the internal clock is in the state of dyssynchrony to the external day/night cycle of 24 hours in circadian rhythm sleep disorder. The patients typically present insomnia or serious dreamy state. These disorders seem to happen as intrinsic disorder such as delayed or advanced sleep phase disorder and in air traveller passing through lines of longitude or in shift workers. The solution is to improve the resetting of the internal clock (Kolla & Auger, 2011).

A site that regulates behavior of living beings, physiological process, and sleep-wake rhythm is SCN neurons of hypothalamus. Most people's circadian length is typically slightly longer than 24 hours, but it is set to 24 hours by different external signal zeitgeber (Czeisler et al., 1999).

When the internal clock is not accord with the cycle of the Sun, the inconsistency induces helplessness at day time and leads to symptoms of insomnia, hypersomnia, complaint with shift, feeling disturbance, and gastrointestinal pain. Especially because long distance air flight or night work goes beyond the ability of internal clock that could be reset, jet sleep disorder or shift work sleep disorder is caused. Most people complain poor sleep at night and feel languor during day time, and show unstableness and gastrointestinal pain. But the differences vary from individual to individual.

Travelling to west is easier than travelling to east, because going to west undergoes less suffering from jet lag than going to east does. Thus the internal clock resets backward rather than forward, the length of circadian rhythm is due to longer than 24 hours (Eastman et al., 2005).

More standard time zones to pass through, more time

is needed for circadian pacemaker to re-entrain. Thus, jet lag symptoms will be exhibited for longer and more intensely. Travelling across standard time zone only one or two will experience simple transient problems.

Whether age has influence on jet lag is not known. From the study of simulation experiment, middle-aged people (37−52 year old) underwent more fragmented sleep under polysomnography than younger people in 6 hours advance test. This means that middle-aged people have greater disorder in daytime alertness and that the phase tolerance, which is a capacity taking sleep in other time, not in the regular sleeping time, is diminished with age (Moline et al., 1992). But the results mentioned above are contradictory to the outcomes that middle-aged people overcame jet lag well (Waterhouse et al., 2002).

Exposure to light is most important in setting circadian clock and the setting orientation is dependent on the exposing time of a day (Burgess et al., 2002). The core body temperature drops to nadir point 2−3 hours before waking up from sleep. Exposure to bright light at the time at which body temperature is dropping resets internal clock slowly (phase delay). That is just like moving from the east to the west. On the contrary, exposure to bright light after nadir of body temperature resets internal clock fast (phase advance).

Assume that a traveler moves to the east passing by standard time zone 7 times. When the traveler arrives at 08:00 at local time of destination, the internal clock of traveler is yet remained at 01:00. Moreover, core body temperature of the traveler would stay 04:00 at nadir at the local time of departure. Thus, the core temperature when approaching in arrival place is underway of going down. If the traveler is exposed to bright light, the phase delay is arisen, not the phase advance. Thus, circadian re-entrainment is relatively delayed (Daan & Lewy, 1984).

Other factors causing fatigue in moving long distance include insufficient sleep (prior to or during flight), temporary unstability at takeoff, and excessive alcohol and caffeine intake. These effects are merely reduced when arriving at destination, but the jet lag will persist until re-entrainment of circadian cycle in living beings (Muhm et al., 2007). Remedy of jet lag sleep disorder is to reset the circadian rhythm fast and efficiently and minimize the symptoms.

Travelers want to stay comfortably for long time at the destination, so a strategy is to control the light (avoidance and exposure). Moving to east deprives the traveler of time and moving to west adds time. But in case of time deprivation of more than 8 hours, phase delay is rather easily achieved. People moving to east have to adjust clock to be phase advance, so they should be kept at darkness for 3 hours until the core temperature arrives at nadir. And right after that, they should be exposed to light for 3 hours. For those traveling to east need to stay at hotel after arrival, or put on sunglasses when going out and to avoid exposure to light. In order to delay circadian rhythm, the pattern of day and night is to be reversed.

It was reported that taking melatonin dosage (2−8 ㎎) at night improves the quality of sleep and can alleviate symptoms caused by jet lag (Claustrat et al., 1992; Petrie et al., 1993; Suhner et al., 1998). The effect better appeared when melatonin was taken at once, regardless of the direction of travel. If 10 mg of melatonin is taken for a short term, it was reported to be safe.

Shift work is referred to the nonstandard schedule involving continual work at night. Although the shift workers may have abundant time to sleep during the day, they appeal difficulties with sleep disorder, such as chronic insomnia and sleepiness not matched with sleep/wake timetable. Their stable and healthy quality of life is influenced. Aged people are regarded as having greater danger of shift work. Following work at night for several days, the recuperative power of the aged people is more abated than that of young people.

Nocturnal work environment is enhanced by using bright lighting. Workers who are exposed to periodical bright light of 6 hours at shift work showed prominent phase delay than the people who were not exposed to the bright light (Boivin & James, 2002). People who are exposed to

bright light are also encouraged to use sunglasses during commute.

Taking melatonin (5−6 ㎎) to sleep at day time heightens quality of sleep (Yoon & Song, 2002). But dose of 6−10 ㎎ was reported not to have the effect mentioned above (James et al., 1998). Thereupon, the differences may be due to different experimental conditions (shift work schedule, concentration of melatonin taken, and time to take melatonin).

4. Antioxidant

It has been 20 years since melatonin directly exhibited the activity of free radical scavenger. There is also a report that melatonin reduces highly responsive hydroxyl (OH) radical *in vitro* (Tan et al., 1993). It has found that melatonin eliminates nitrogen and oxygen responsive substances and stimulates antioxidant enzymes (Reiter et al., 2000; Hardeland, 2005; Tan et al., 2007; Peyrot & Ducrocq, 2008). Melatonin working as a universal antioxidant acts optimally on cells and organs, including reproductive system (Tamura et al., 2008a, 2008b; Tamura et al., 2009).

Although the direct action of melatonin scavenging free radicals is fulfilled without specific receptor, the effect of melatonin on antioxidant enzyme seems to work by binding membranous receptors or receptors present in nucleus and cytoplasm (Tomas-Zapio & Coto-Montes, 2005). Melatonin receptors are identified in the hypothalamic neuronal cells governing release of pituitary gonadotropic hormones, in the gonads of both male and female, and in the accessory reproductive organs (Roy et al., 2001; Johnston et al., 2003). The concentration of melatonin collected from the antrum of Graafian follicle within ovary of human is considerably higher than the concentration of melatonin gained from the plasma at the same stage (Brzezinski et al., 1987; Nakamura et al., 2003). As in other bodily fluid, melatonin can be concentrated in follicular antrum, and can be synthesized in granulosa cell of ovary and secreted into follicular fluid (Itoh et al., 1999).

It has been proposed that melatonin, as its function in follicular fluid, reduces natural death of important cells and directs to provide ovulatory egg with complete maturation prior to ovulation (Tamura et al., 2008b). The quantity of 8-hydroxy-2-deoxyguanosine (8-OHdG) arising from the damage of free radical on DNA in ovary was compared by measuring the concentration of melatonin in follicular fluid in the process of egg collection for *in vitro* fertilization-embryo transfer. 8-OHdG is used as a criterion to evaluate the degenerating degree of egg. The follicular concentration of melatonin resulted in reverse proportion to the amount of 8-OHdG in the egg, and it was proposed that melatonin spreaded over the cumulus oophorus and egg in follicular fluid and prevented from the damage by free radical.

It seems to happen that melatonin increases approximately 2 times the possibility in the course of fertilization and implantation in performing *in vitro* fertilization and embryo transfer (Arendt, 2005). Thus, as the ovaries in women with low release of melatonin is easily damaged by free radical, a baby would be delivered in higher danger with specific cause of a disease (Down syndrome, spinal bifide etc.). If a woman who approaches to menopause wants to have a baby, she could become pregnant with the melatonin administration because the level of melatonin diminishes with the age (Zeitzer et al., 1999).

There is a report that the mouse egg that was treated with melatonin was protected from oxidative stress. When mouse egg is cultivated with an oxidant H_2O_2, the proportion of gradually immature egg (development of first polar body) was augmented with the more concentration of H_2O_2 (Tamura et al., 2008b). On the other hand, when melatonin was treated with H_2O_2, the egg was matured in a dose-dependent manner. These results were also reported in other animals (Voznesenskaya et al., 2007; Kang et al., 2009; Manjunatha et al., 2009). Melatonin protects spermatozoa from damage of oxidant. Diazinon is widely used as an organophosphorus pesticide that causes spermatozoa toxicity with free radical mechanism. The spermatogenesis is damaged in exposing to the reagent and the action is prevented by melatonin (Sarabia et al., 2009). Therefore, it was speculated that melatonin alleviates the effects caused by toxic substances (Korkmaz et al., 2008).

In order for spermatozoa to fertilize, they are endowed

with fertilization capacity, acrosome reaction should be worked, and tails have to move energetically. A reason that the tails of spermatozoa should move actively is to penetrate zona pellucida of the egg and contact egg membrane. As melatonin is contained in human semen and melatonin receptors are reported on the cell membrane of spermatozoa, it was proposed that melatonin influences the activation of spermatozoa tail (Bomman et al., 1989; Fujinoki, 2008). There is also a report that the administration of melatonin augments the activity of spermatozoa and these increases of activity is suppressed by the administration of luzindole, a melatonin receptor antagonist. But it is not clear whether the effects of melatonin are arisen from physiological concentration (Bomman et al., 1989).

As women largely give birth to baby at night (time of maximum concentration of melatonin), it was speculated that uterine muscular layer cells might have melatonin receptor, and the receptors were found (Schlabritz-Loutsevitch et al., 2003). The result was identified in rat (Steffens et al., 2003). It has been found that the expression level of melatonin receptor is elevated in uterine muscular cell layer of a pregnant woman under parturition. Moreover, melatonin enhances synergistic action in cooperation with oxytocin and encourages muscle contraction and gap junction important for uterine contraction (Sharkey et al., 2009). These observations also were appeared in *in vitro* culture of uterine cells. Uterine muscle layer will be powerfully contracted by dual actions of melatonin and oxytocin for successful parturition.

At late term of pregnancy, a preeclampsia, a toxemia of pregnancy would be observed. Major symptoms are hypertension, urine protein, and edema. These features are appeared in both pregnant woman and fetus. The woman suffers from kidney and liver disorders, paroxysmal cerebral edema, HELLP syndrome (hemolysis, elevated liver enzyme, and low platelet counts syndrome), and death. The frequent disorders in the fetus are low body weight, prematuration, and death. The preeclampsia condition is great oxidative stress, with highly synthesized free radical and low antioxidant. The placenta is presumed to be a place that produces free radical and lipid peroxidation. In the light of antioxidant effect of melatonin, this is considered to decrease oxidative stress related to the preeclampsia (Simko & Paulis, 2007). Melatonin would alleviate preeclampsia by acting as antihypertensive and anticonvulsant as well. It was reported that melatonin mitigates tissue damage by anoxia and hypoxia in the process of flowing of oxygen-rich blood into tissues (Bertuglia & Reiter, 2007; Kurcer et al., 2007; Kim & Lee, 2008). Melatonin reduces symptoms of ischemia/reperfusion (I/R) injury. Melatonin protects placenta injured by free radical, is transmitted to fetus through the placenta, and preserves the fetus (Schenker et al., 1998; Wakatsuki et al., 2001). At parturition, if blood supply is temporary prevented, fetal asphyxiation could be happened. The most serious case is brain damage arisen from harm of cells by excessive oxidant and nitrosative (Fulia et al., 2001). But the evidence lacks for confirming the efficacy. Melatonin is uncommonly safe hormone without nearly toxicity although a pregnant woman takes melatonin in high dose. If the research consequences mentioned above rightly exert their functional effect, it could be considered that melatonin generally influence reproductive endocrine system, including gamete formation, embryo development, and even parturition (Choi et al., 2008; Vasquez et al., 2009).

5. Cardiovascular system and blood pressure

Melatonin receptors are immunologically discovered in avian heart, subsequently identified at left ventricular cells of human. But its function is not yet known. Melatonin lessens the muscular contraction power in rat. MT1 and MT2 receptors are found in coronary arteries of human. From the animal research, vascular contraction is occurred after MT1 receptor is activated, but vascular relaxation is generated after MT2 receptor is activated, thus the dual effect of blood vessel is suggested depending on the type of receptors activated.

The atherosclerosis is a chronic vascular disease and the major cause is usually inflammation and oxidative stress. Initial stage of plaque formation is associated with

activation of endothelial cells caused by inflammatory cytokine, low density lipoprotein (LDL) oxidized, and endothelial shear stress. Melatonin shows antioxidant effect against LDL. It was reported that melatonin lessened blood cholesterol, very low density lipoprotein cholesterol, LDL cholesterol in hypercholesterolemic rat (Tengattini et al., 2008). Melatonin performs the works by enhancing endogenous cholesterol clearance. Melatonin easily enters lipid phase of LDL particle because of its hydrophobic characteristics and prevents lipid peroxidation response. Reports remark that high level of blood LDL oxidized during nighttime in patient with acute myocardial infarction is related to low level of melatonin (Dominguez-Rodriguez et al., 2005). The findings support that melatonin diminishes total amount of cholesterol, reduces oxidation of LDL, and protects against cardiovascular diseases.

When melatonin is administered in pharmacological dose, it acts on hypothalamus, decreases the level of catecholamine, relaxes smooth muscles, and lessens blood pressure. Report referred to that melatonin has an effect of hypotension lowering blood pressure (Tengattini et al., 2008). The rate of melatonin production is slow in patient with coronary artery diseases and the concentration of blood melatonin is consistent with the severity of the diseases. That is, melatonin generation is greatly reduced in patient with serious danger of myocardial infarction and sudden death. However, it is not clear whether the lowered level of melatonin results from the consumption of melatonin that prevents free radicals from producing or the reduction of protection ability against oxidative stress caused by decrease of melatonin production.

Melatonin reduces farc size/risk and reperfusion arrhythmia against I/R injury. Ischemia is associated with reactive oxygen species/nitric oxide synthase formation from residual molecular oxygen, thus ability of melatonin may be involved in heart protection efficacy by removal of free radical and of induction of the expression of antioxidant enzyme (Reiter & Tan, 2003b; Dominguez-Rodriguez et al., 2010a).

The metabolites of melatonin as well as melatonin itself can neutralize free radicals and their derivatives. Melatonin stimulates antioxidant enzymes within cells, including superoxide dismutase and glutathione peroxidase. Also melatonin drives activation of γ-glutamylcysteine synthetase and inspires glutathione that is a antioxidant within other cells.

Melatonin alters calcium signal transduction in platelet by increasing oxygen and nitrogen responsive substances and incites clotting in I/R injury. Melatonin is produced not only in pineal gland, but in megakaryocyte and platelet. The amount of melatonin within the platelet is associated with 'no-reflow' exhibiting in the ST-segment elevation myocardial infarction (STEMI) patient bearing primary percutaneous coronary intervention. It was reported that patient with angiographic no-reflow had low level of melatonin within platelet and high level of systemic oxidative stress (Dominguez-Rodriguez et al., 2010a, 2010b). The concentration of melatonin is related to ischemia-modified albumin that is a marker of myocardial ischemia. There is a report that the venous administration of melatonin to STEMI patient suppresses I/R damage (Dominguez-Rodriguez et al., 2007). Melatonin enters cardiac cells by going through barriers because it easily and rapidly spread all over the body due to its hydrophobic property. These results strongly suggest that melatonin reduces myocardial damage of I/R by acting as a powerful antioxidant.

High level of cellular melatonin is detected in mitochondria. The distribution of melatonin are important because mitochondria is a place where free radicals are produced and oxidative stress is imposed (Dominguez-Rodriguez et al., 2012).

Blood pressure daily fluctuates in a cycle of day. The pattern of daily alteration of blood pressure is a critical factor determining complication of cardiovascular system in hypertensive patient (Verdecchia et al., 1993; Cuspidi et al., 2004). If bloop pressure is not diminished at night, target organs vulnerable to blood pressure could get damages and be associated with diseases of cardiovascular system due to complication. A mechanism that provokes the reduction of blood pressure during sleep and pathophysiological cause of undescended blood pressure has not yet been

found.

Melatonin, as a night signal, plays a role in regulating diverse circadian rhythms, including sleep (Brzezinski, 1997). The exogenous administration of melatonin induces hemodynamic effects in both healthy males and females (Cagnacci et al., 1998; Arangino et al., 1999). The effects of melatonin on nocturnal blood pressure are inconsistent with the different outcomes of decrease, constancy, and increase (Lusardi et al., 1997; Lusardi et al., 2000; Scheer et al., 2004; Rechcinski et al., 2010). The discrepancy is probably due to different methods that melatonin is administered. From the recent work, if melatonin in supplement of antihypertensive drug is treated in controlled-release at night, nocturnal hypertension is dropped, but not any effect from the administration by fast release (Grossman et al., 2011). This consequence results in anticipation of decrease of cardiovascular danger caused by high hypertension at night. However, melatonin could be clinically applied only after the effect of melatonin is certainly established through more experiments for longer term.

Taken together, melatonin surely has various effects on cardiovascular pathology, such as hypertension, diabetes, dyslipidemia, and I/R injury. It is worth fully to use melatonin clinically with the consideration of the severity of those diseases and the low toxicity of melatonin. It could be anticipated that melatonin exerts its protection effect to support the heart of human if any harmful defects are not found from the work performed in animal.

6. Depression

Low concentration of blood melatonin was reported in depressed people (Beck-Friis et al., 1985; Paparrigopoulos, 2002; Parry et al., 2008). And there is a suggestion that the level of melatonin is low in both unipolar and bipolar depression patient at night. The degree of depression is in inverse proportion to the sensitivity of pineal β adrenoreceptor and to levels of nocturnal blood melatonin as well (Beck-Friis et al., 1985). In comparing the concentration of nighttime melatonin before and after the treatment of atenolol, a β adrenoreceptor antagonist, more the concentration of melatonin decreases, more the extent of depression becomes serious (Paparrigopoulos, 2002). Moreover, period of time at which melatonin emerges in blood is mutual proportion to symptomatology (Parry et al., 2008). In studies that focused on the degree of depression in depression patients, melatonin was increased a little and was lowered in blood in comparison to the control (Brown et al., 1985).

It has been reported that postpartum depression is associated with high level of blood melatonin and family history of depression (Parry et al., 2008). The mechanism by which abnormal release of melatonin is occurred in depression patient is not known, but melatonin seems to exert its effect as a anti-depression agent from a study using animal such as mouse. Namely, melatonin is like to prevent change of behavior, coat state, and increase of concentration of hormone cortisol in animals when they are exposed to unexpectable stressor (Detanico et al., 2009). It was reported that MT1 receptor knockout mouse showed lengthened immobility time in forced swim test (Weil et al., 2006). MT1 receptor is spread over the hypothalamus, a part of pituitary, and pineal gland and is discovered in a place of corticotropin release hormone neuronal cell (Wu et al., 2006). The regions are sites that control circadian rhythm system as neuroendocrine regulatory sites. Thus, melatonin could be regarded as pathogenesis of neuroendocrine damage happening in depression patient (Rosenwasser, 2009). From the population study in which people with recurrent depression were compared to control people, it was found that there is a polymorphism of an enzyme acetylseronin methytransferase (Galecki et al., 2010). Also it was reported that the expression of the enzyme was significantly reduced in depression patient. These investigations strongly suggest relationship between melatonin and causes of depression.

Depression patient shows unusual circadian rhythms, including not only sleep/wake cycle getting up early, an alteration of sleep architecture with shortened REM latent period, and a preceded REM sleep phase 1 in the phase 3 of sleep cycle, but also diurnal mood changes, seasonal

change, variation of time of lowest body temperature, a different time of peak of cortisol release, and change of initiation time of melatonin secretion (Germain & Kupfer, 2008). It is assumed that seasonal affective disorder (SAD) is developed if circadian rhythm is disturbed (Lam & Levitan, 2000). Phase shift theory is then proposed and it was demonstrated that light therapy has efficacy to treat SAD and nonseasonal affective disorder (Golden et al., 2005). SCN that is a center regulating circadian rhythm possesses clock cells where clock genes operate actively. The cells generate electric signals, transmit to various organs through sympathetic and parasympathetic neurons, and lead to production of many hormones. These hormones regulate circadian rhythm by acting as negative feedback for resetting time of clock cells. The clock genes were also discovered in adrenal gland where mutants of the genes modify daily releasing time of corticosteroid (Pilorz et al., 2009). It was then reported that adrenocorticotropic hormone (ACTH) and cortisol are secreted earlier in depression patient and that the release concentration of the cortisol is elevated (Linkowski et al., 1985). Also, reports remark that depression patients showed high level of cortisol and low level of melatonin during nighttime (Souetre et al., 1989).

Depression symptom is more serious if difference in circadian rhythm is abated and is cured if the difference is recovered. ACTH promotes synthesis and release of cortisol in adrenal gland and melatonin lessens these effects of ACTH, thus the alteration found in depression patient can be explained. Melatonin is low in the patient, thus the level of cortisol would be high. Therefore, it was emphasized that aberrant neuroendocrine system such as circadian disorder arises from depression patient by anomalous release of melatonin.

7. Inflammation and immunity

Inflammation system is activated in depression patient. It was reported that the patient showed cytokine, IL-6, and IL-1-β in high levels (Owen et al., 2001; Tiemeier et al., 2003; Bouhuys et al., 2004; Alesci et al., 2005). Depression patient also showed high level of acute phase protein like C-reactive protein (Danner et al., 2003). Inflammation markers are increased proportionally to the depression danger and reflect the responsiveness against antidepressant (Yu et al., 2003; Thomas et al., 2005). The administration of cytokine induces depression symptoms in depression patient without mental health issue and inflammatory-induced depression can be cured by antidepressant (Pariante et al., 1999; Musselman et al., 2001). The activation of immune system could be a mechanism resulting in aberrant neuroendocrine system referred to depression.

Pineal gland influences development and function of immune system because melatonin receptors were detected in lymphoid and immune cells (Skwarlo-Sonta et al., 2003). Melatonin synthesis can be mediated by inflammatory-induced substances. A tumor necrosis factor leads to accumulate N-acetylserotonin by inhibiting transcription of AANAT. Thus, cyclic disorder of melatonin reported in depression patient would be happened at the initiation of inflammation response. In mice either maintained at constant condition or injected with β-adrenergic receptor blocker (propranolol, inhibitor of melatonin synthesis), response of antibody production was weakened, thymus and spleen cells were diminished, and autologous mixed lymphocyte reaction was suppressed. But those effects were inversed if melatonin was administered in the afternoon (Maestroni et al., 1986). The β-adrenoceptor receptor blocker displays immune suppressive effect when melatonin was injected in the evening, time of highest effect of immune promotion (Paparrigopoulos, 2002). Therefore, exogenous administration of melatonin reverses immune suppression induced by β-blocker and enhances immune parameters. The factors influencing melatonin effect are sex, age, maturation and activation effect on immune system, and stress condition.

8. Aging

Everybody has a desire to live longer. But it is not evident that there is a means preventing or slowing down

aging, either the elixir of life or permanent fountain of youth. As life expectancy of animals, including human, was not greatly altered in either historic record or pictures, it seems to be genetically determined.

Aged people are increasing with the benefit of development of medicine and dietary cure. Bodily anatomical and physiological changes occurring throughout life time are associated with reproduction. In looking at the changes in the process of menopause in both males and females, not only the releases of sex steroid hormones are reduced but also syntheses and releases of metabolic hormones (growth hormone, ACTH, thyroxine, melatonin etc.) are decreased (Touitou & Haus 2000; Bubenik & Konturek, 2011). As the release reduction of those hormones is due to the sex steroid hormones estrogen and androgen, estrogen replacement therapy in females and androgen replacement therapy in males are widely prevailed.

All the living beings possess internal biological clock, measuring circadian rhythm and even annual cycle as well. The alteration of time is obvious either a day or a year, and melatonin is secreted depending on the changing time daily and annually (Reiter, 1995).

The pineal gland of neonate does not function fully, but the baby can receive melatonin signal through mother's milk (Illnerova et al., 1993; Touitou, 2001). Thus, a baby who is fed by mother's milk has better sleep rhythm than a baby who is nourished by dairy formula. Melatonin level at night quickly increases with age in infanthood, peaking at 2−4 year old. The concentration of melatonin in blood start to decrease from the top at puberty when sexual maturation develops (Waldhauser et al., 1998). Melatonin concentration steadily diminishes from the puberty until the aged (Pandi-Perumal et al., 2005). The reduction of melatonin is regarded as predisposing factor of neural degenerative disease such as Alzheimer.

Day and night changes of blood melatonin indicate circadian time. The difference of concentration of melatonin between day and night is quite evident, but that in the 60 year old is dropped by 80% in comparison to the difference of concentration of melatonin at puberty, thus virtually disappeared. It is yet premature to make conclude because there is big difference among individuals. Although it has not been known whether the modification of the melatonin rhythm is cause or result of aging process, melatonin has apparent antioxidant function, slows down aging, and expands the life expectancy, thus it might be safe and effective remedy that excludes aging-related diseases (Touitou & Haus, 2000; Poeggeler, 2005).

Melatonin is a natural substance that causes great hypnotic effect, and induces geriatric insomnia in the absence of circadian rhythm. The sleep disturbance is the most common complaint that aged people suffer. They recognize the alteration of sleeping time and more and more experience fragmented sleep. The initiation of sleep is related to low body temperature. Generally young people begin to sleep right after body temperature reaches to lowest. Interestingly, melatonin lessens body temperature. Therefore, these features may be a mechanism by which melatonin plays a role as soporific agent. But it has not yet been known what causes the reduction of melatonin in old people. Nonetheless, the event of reduction of difference of melatonin concentration between day and night is presumed as a signal of getting old. Under the assumption, melatonin replacement treatment is proposed and being practiced by many people over the world.

There is great efforts to lengthen span of life for past decades. But a remedy established is only restricted food (Masoro, 1992). It should be start at young age and the reduction of 40% in aspect of calory extended life expectancy to the extent of 30−50% in mouse, rat, dog, and ape. They mature very gradually and arrive at puberty late. The satiating animals suffer from the tumors and cataract in aged, but the moderately eating animals are healthy in the elderly. These effects of preventing aging is related to melatonin. When the food is persistently limited, release of melatonin at night sustains at peak, but when aged animals reach freely food, that is faded out (Reiter, 1995). If mouse takes continuously melatonin, the span of life is extended, immunocompetence is en-

hanced, the weights of thymus, adrenal gland, and testes are heavier, and blood concentrations of testosterone and thyroid hormones are increased (Pierpaoli & Regelson, 1994; Pierpaoli & Bulian, 2001). The injection of melatonin strengthened the immune function in other researches. Melatonin also curtailed immunosuppressive effect caused by stress (Pierpaoli & Maestroni, 1987).

It was reported that the extract of pineal gland expanded the life expectancy 30−40% in mouse and rat and lessened the spontaneous generation of tumor. In other reports, the administration of melatonin lengthened the span of life and reduced cancer development in colon, mammary gland, and uterine cervix (Anisimov et al., 2001). When the middle aged rat, showing certain difference of melatonin between day and night, drank waters including melatonin, abdominal fat of the animal was lessened (Rasmussen et al., 1999). Therefore, food in a small amount or melatonin would be taken in order to live healthier and longer. And the effect of dietary control (restriction) on life expectancy can be mediated by melatonin produced in gastrointestinal track (GIT), not melatonin generated from the pineal gland (Roky et al., 1999).

The GIT is the source of bodily melatonin and melatonin is secreted from the enterochromaffin cell in mucosa layer of GIT (Raikhlin & Kvetnoy, 1976). It was reported that GIT contained melatonin more than 400 times than pineal gland because it is very long (Huether, 1994). Melatonin is found in large amounts in large intestine, specially colon. Detoxification of pollutant substances in GIT is occurred by antioxidant. Melatonin is a strong antioxidant. But it has not been shown that melatonin generated in the intestine is diminished with the age.

The effect of melatonin on aging can be interpreted differently. If melatonin rhythm is deteriorated, other circadian rhythm is also weakened, and vital rhythms would not be synchronized. Thus, the length and magnitude of melatonin secreted in large amount at night may determine the rate of aging (Masoro, 1992; Reiter, 1995). There is a hypothesis that aging rate is associated with the accumulation of free radicals. As melatonin protects DNA and other macromolecules damaged by free radicals, it can work as an important factor to determine the aging rate (Guerrero, 1999).

Melatonin is a very effective antioxidant to scavenge hydroxyl radical with severe toxicity and far more effective several times than vitamin E neutralizing the peroxyl free radical (Pieri et al., 1994; Reiter, 1995). melatonin is a hormone to better adapt to the changes of environment.

Melatonin has an efficacy in preventing neural degenerative diseases. It reduces the toxic effect of beta amyloid for prevention against diseases in animals and totally blocked cell death in experimental model suffering from the Alzheimer disease (Pappola et al., 1997).

Melatonin also decreased oxidant damage in the Parkinson model. When melatonin was administered to one of identical twin for 3 years, the symptoms of Alzheimer was exhibited weakly than the other partner (Brusco et al., 1998). It was also reported that the effect of cognitive impairment, a symptom preceding dementia, is lessened with the supplement of melatonin (Cardinali et al., 2010). The loss of melatonin rhythm in aged people causes senile neuro-degenerative diseases to be serious degree (Reiter, 1998). There are reports that melatonin increases span of life and tumor development in females as well (Savaskan, 2002; Srinivasan et al., 2006). Those results are inconsistent with the findings mentioned above. Therefore, it rings an alarm bell to be cautious in using melatonin as an anti-aging agent.

9. Memory

Melatonin has been reported to be associated with the complicated process such as learning and memory (Bob & Fedor-Freybergh, 2008). It is reason that melatonin has an effect on hippocampus of brain that plays an important role in memory processing. It is also reported that melatonin disturbs neuronal transmission and long-term potentiation (LTP) in the dentate gyrus of hippocampus. But the mechanism by which melatonin exerts its effect is not clear. It has been proposed that the action of melatonin on the LTP and neuronal transmission is achieved

through N-methyl-D-aspartate (NMDA) receptor (Collins & Davis, 1997). And a report represents that the inhibiting action of melatonin on LTP is mediated by synaptic efficacy and hippocampus neuronal excitement (Hogan et al., 2001). Thus, the rhythmicity of melatonin demonstrating day-night cycle about 24 hours can potentially modify the function of hippocampus, and influence memory processing. The effects of melatonin on excitatory postsynaptic potential can be weakened when the function of melatonin receptor is suppressed by treatment of melatonin receptor antagonist such as luzindole (Wang et al., 2005). The special function of melatonin on hippocampal LTP could be demonstrated by using animals who lack the expression of melatonin receptors. Melatonin has an effect via melatonin receptors and adenylate cyclase-protein kinase (AC-PK) pathway (Roberson & Sweatt, 1996). It has been reported that the inhibiting action of melatonin on LTP is associated with AC-PKA in hippocampus (Wang et al., 2005). And the inhibiting effect of melatonin on LTP was not observed in mice whose melatonin receptors (MT1 and MT2) had been removed but demonstrated in MT1 receptor knockout mice, which implies the involvement of MT2 receptor. The inhibiting effects can be prevented by using 4-phenyl-propionamidotetraline (4P-PDOT) that acts as the MT2 receptor antagonist. A similar outcome was reported from the SCN, and a negative response in signal transduction resulted from the activation of MT2 receptor (Reppert et al., 1995). The LTP in mice without MT2 receptor was significantly reduced in comparison to the control (Larson et al., 2006). Therefore, melatonin has influence in memory and it is speculated that melatonin with rhythmical release has function to mediate the memory process.

Another evidence that the circadian rhythm influences learning and memory processing came from collapse of the system composing of circadian rhythm (Tapp & Holloway, 1981; Antoniadis et al., 2000; Devan et al., 2001; Gerstner et al., 2009). The collapse of the system in rat was applied and trained passively or actively to the escape learning impacts on memory capacity of animals by altering the memory retrieval. But in navigating learning, the collapse of structural system of circadian rhythm has a damaging effect on memory consolidation (Devan et al., 2001). In many learning examples, memory processing such as acquisition, consolidation, and retrieval is likely to be regulated by circadian rhythmic system in animals.

Aplysia californica, a kind of slug, has been subjected to research of brain because of a few neurons. It has been known that the consolidation process was effective when trained during subjective day and inhibitory at subjective night (Lyons et al., 2005). In fear-conditioning paradigm of mouse, the two steps of memory process (acquisition and retrieval) seemed to be mediated by circadian rhythm. The learning ability of mouse is augmented in inactive time by retrieving the conditioned situation (Chaudhury & Colwell, 2002). As the experiment was performed in constant condition without any clue about outer time, the rhythm of memory processing (acquisition, consolidation, and retrieval) must be regulated by circadian rhythm system in living being.

A diurnal animal zebra fish (*Danio rerio*) was placed in each partition that divided water bath into two compartments in same size, and moved freely. they were trained that lighting compartment is safety environment and dark compartment is dangerous environment with weak electric shock. When the animals were trained at day time (active behavior) in day-night cycle, it was demonstrated that the time required to meet learning criteria was reduced in comparison to the animals trained during nighttime. When the animals were again trained after 24 hours in order to measure whether memory was shaped, performance capacity was improved in animals trained at lighting time. The diurnal pattern of the acquisition rate persisted in even constant condition (darkness), but there are clear differences in the magnitude of the rhythm. The relearning rate at subjective day time after 24 hours was considerably diminished compared to the animals trained under the day-night cycle. Thus, it was speculated that the lower concentration of melatonin at day time lessens the inhibiting effect of memory consolidation. Melatonin in fact was demonstrated to have inhibiting

effect on memory consolidation.

Melatonin effectively disturbs long-term memory and has no effect on memory retrieval. It was surmised that nighttime damage of memory consolidation is disappeared by blocking the melatonin signal using melatonin antagonist. The improving effect was not remarkable in aspect of acquisition and performance capacity at day time when animals whose pineal gland is removed were compared to control animals. In case of training of the pinealectomized animals, it was reported that nighttime memory capacity was similar to performance capacity of animals trained during daytime in normal environment. Thus, the elevation of melatonin illustrates inhibiting ability of performance capacity. Nonetheless, it has not been known whether those effects of melatonin are species-specific or dependent on active moving time of animals (diurnal or nocturnal). But in the event of zebra fish, it was concluded that circadian rhythm system changing periodically at physiological level could be memory processing mechanism.

The finding that melatonin at night suppresses memory consolidation can reflect similar role of melatonin in human. Research about direct effect of melatonin on the action of cognition of human is unsatisfactory in the physiological situation. But a connection between melatonin rhythm and cognition process was analyzed in population in association with abnormal incident of melatonin rhythm (Beverdorf et al., 2000; Savaskan et al., 2005; Brunner et al., 2006). Although nighttime melatonin is not anticipated to be deleterious on the memory consolidation acquired at day time, it is assumed that nocturnal melatonin plays a part in memory learned during nighttime. The memory improvement occurred by blocking the nocturnal melatonin signal in zebra fish resembles the symptoms in person with autism spectrum disorder representing both 24 hour melatonin level that is either abnormally low or arrhythmic and high memory capacity (Beversdorf et al., 2000; Melke et al., 2008). It was demonstrated that melatonin treatment takes a turn for the better some symptoms related to autism. But because the memory improvement is secondary to those individuals, the effects of melatonin on mind needs to deeply investigated. The finding that night acquisition becomes long-term memory by obstructing melatonin signal is so courageous that more researches are required for people with abnormal sleep-wake rhythm cycle to use as remedy or short-term cognition compensation agent in order to improve temporary defect in psychometric performance.

10. Epilepsy

Apart from the multi-action of melatonin mentioned above, melatonin is reported to control the electric activity of central nervous system. Melatonin blocks inflow of calcium ion to the neuronal cells in its concentration of nighttime, inhibits the activity of nitric oxide synthase, reduces the production of NO, and diminishes the exciting effects of NMDA as a result (Muñoz-Hoyos et al., 1998). Melatonin elevates the concentrations of γ-aminobutyric acid (GABA) in the brain to increase the inhibiting function through the GABA synapse (Wan et al., 1999; Stewart & Leung, 2005). It regulates Ca^{++} by acting as an antagonist to L type of calcium ion channel (Acuña-Castroviejo et al., 1997). It reduces striatal dopaminergic activity by way of dopamine D1 and D2 receptor and inhibits release of glutamate (Stewart, 2001). Its small amounts are metabolized into N-acetyl-N-formyl-5-methoxykynuramine and N-acetyl-5-methoxykynuramin, which act as very strong Antioxidants and cyclooxygenase inhibitors. Thus, it is thought that there would be various effective anti-inflammatory agent (Kabuto et al., 1998; Mayo et al., 2005). These actions are related to the sedative, sleeping pill, antianxiety drug, anticonvulsant, and analgesic effects. In a result examined the convulsion phenomenon in a daily cycle, the maximum efficacy appeared at nighttime (Reiter, 1995).

Despite the precise mechanism about the periodicity of convulsion has not been known, a sensitive circadian rhythm of convulsion could be related to the time-dependent biological signals developing as an intrinsic neuronal oscillators present within biological body. Incidentally, the circadian pattern of normal release of melatonin

is associated with the time of active convulsion as epilepsy patients demonstrate more than two times higher than normal control in nocturnal release of melatonin. The rise and fall of melatonin at different stages in the reproductive cycle of woman reduces the convulsant symptoms during menopause of epilepsy woman, thus it could explain the fact that the convulsion activity is increased during menstruation and pregnancy. But the mechanism has not yet been established.

A possibility is arisen from a few researches that melatonin can lessen the convulsion. There are reports that the convulsion behavior is improved if melatonin is treated in combination with an existing anticonvulsant juvantia and is returned to previous condition if the treatment is paused (Peled et al., 2001). It is also reported that melatonin has effects vanishing the drug tolerance convulsion (Molina-Carballo et al., 1997). As a neonate girl with initiation of the convulsive spasm was diagnosed severe myoclonic epilepsy at 1.5 month old, various anticonvulsants (valproic acid, phenobarbital, clonazepam, vigabatrin, lamotrigine, and clobazam) are administered in different combinations, but she was not cured. After melatonin was treated with phenobarbital for one month, the convulsions were regulated for one year. The patient showed unstable condition if the concentration of melatonin administration is reduced and recovered to stable state if melatonin is administered to previous high amount (Gupta et al., 2004). It was reported that the concentration of melatonin in saliva is low in epilepsy patient who does not show effects of drugs (Bazil et al., 2000). The repetitive symptoms of convulsion can be avoided in case of elevation of melatonin after convulsion. It has been observed that the metabolites of melatonin is increased in 24 hours after convulsion spasm in patient with severe convulsion. It is interesting that the concentration of metabolites of melatonin is diminished in urine of the patient treated with carbamazepine (Schapel et al., 1995). It is general tendency that melatonin acts as an anticonvulsant in research of animals about convulsion but there is inconsistent with statement of the convulsion-inducing agent.

11. Hair follicle

In the culture of skin cells of mammals, melatonin inhibits the melanogenesis and suppresses growth of the melanocyte to protect from ultraviolet (Slominski & Pruski, 1993; Bangha et al., 1997; Iyengar, 2000; Nickel & Wohlrab, 2000). Melatonin promotes the growth of hair follicles in *in vitro* culture (Ibraheem et al., 1994), alternates seasonal growth of hair follicles in various animals (Rose et al., 1987; Nixon et al., 1993; Nixon et al., 1995; Johnston & Rose, 1999), and increases growth rate of hair at the developing stage in women with hair loss (Fischer et al., 2004). These results suggest that hair follicles are responsive tissues to melatonin, thus melatonin receptors are reported to be expressed, but the regulation mechanism has not been known.

The melatonin receptors (MT1 and MT2) are expressed in central nervous system (Poirel et al., 2003; Witt-Enderby et al., 2003). MT1 is detected in different organs, such as heart, kidney, liver, and lung of Murine and MT2 is found in lungs of mouse (Naji et al., 2004). The binding sites of melatonin was observed on the epidermal cells of mouse and hair follicle (Slominski et al., 1994), and it has been reported that membranous melatonin receptors MT1 and MT2 are weakly expressed in the skin cells of human with high affinity in *in vitro* culture (Slominski et al., 2003).

Human skin expresses primarily MT1 and mouse skin expresses MT2. Thus, there are some differences among species. It is reasonable to speculate that each animal expresses one melatonin receptor or more. As the skin of mammals has enzymes to be required to synthesize melatonin, it arouses curiosity whether hair follicle is like to produce melatonin. Melatonin is produced mainly in the pineal gland, and in some degree from retina, intestine, liver, kidney, spleen, ovaries, bone marrows, leukocyte, and lymphocyte (Finocchiaro et al., 1991; Menendez-Pelaez et al., 1993; Itoh et al., 1997; Tosini & Menaker, 1998; Kvetnoy, 1999; Conti et al., 2000; Bubenik, 2002; Carrillo-Vico et al., 2004). The major enzymes involved in the melatonin synthesis are expressed in the skin

of mammals and in the culture of keratinocyte, melanocyte, dermal fibroblast, and dermal papilla fibroblast containing the hair follicle keratinocyte (Gaudet et al., 1993; Slominski et al., 2003). The concentrations of melatonin in the mouse skin, mouse vibrissae, and human scalp hair follicles cultured are greatly increased than each control, and are considerably augmented in treating with epinephrine (Kobayashi et al., 2005).

The transcripts of MT2 receptor are observed in skin of mammals and the level fluctuates with the hair-cycle dependent manner. The melatonin receptor inhibits keratinocyte apoptosis. Therefore, it is demonstrated that the hair follicle is an organ where melatonin is produced and where melatonin acts. But further investigations are required.

CONCLUSION

The pineal gland has been know as a vestigial organ until middle of the 20th century. But with a proposal that a major hormone melatonin secreting from the pineal played a role in seasonal breeding animals, the function of melatonin has started to slowly be uncovered. From the research work up to date, melatonin demonstrates so various activities in diverse tissues as mentioned above. Melatonin, as a derivative of amino acid and the characteristics of hydrophobicity, works just like a companion of life in all cells within living body. There is no doubt whether multifacet function of melatonin is unveiled in many living bodies in the future. One expects that melatonin is to be great benefit to the welfare of mankind by laying out a device to make the best use of melatonin in real life.

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