Review

Melatonin: an ancient note in a contemporary wrap

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Running Title: Functional evolution of melatonin

Received: March 9, 2021; Accepted: September 18, 2021

ABSTRACT

At the beginning of life, natural selection is and still the principal driving force for the evolution of all organisms to adapt in the particular environments of the earth. As a result, ultimately neither the strongest, nor the supreme intelligent but the most adaptable species win the race. Not only the organisms, but also the elements which are necessary for survival of them also undergo extreme evolution. These include DNA, proteins and other biochemical molecules. However, melatonin, an indoleamine, presents in the early life form remains unchanged in its structure from unicellular organisms to mammals. When it was discovered, it was considered to be a neuronal hormone produced exclusively in the pineal gland of vertebrates. The latter discovery of its presence in primitive bacteria drives the melatonin research in different directions. Its primary function is serving as an antioxidant in all organisms. Its chemical structure is perfect to scavenge free radicals and thus, this molecule is preserved from bacteria to mammals. However, this molecule acquired many additional functions during evolution. These include circadian regulation, immuno-enhancement, oncostatic, anti-inflammatory and anti-aging activities. In the review, we are trying to present hypothetical and most plausible chronological events in the functional evolvements of melatonin during the process of evolution.

Key words: origin of life**,** melatonin, evolution, pineal gland, receptor, antioxidant, oxidative stress.

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1. INTRODUCTION

The environments, in which we inhabit, have undergone drastic changes in both of its physical and chemical context with time and these lead to adaptation of its habitats. Since nature is the primary cue to all such amendments, natural selection has been the driving force for evolution.

At the early stages of life, completely anaerobic environment facilitates the existence of obligatory anaerobes only, who can survive merely without oxygen (O_2) (1). With

advancement of time, primitive bacteria, which rely upon anoxygenic photosynthesis for carbon assimilation, evolved to facultative anaerobe like proteobacteria, where O_2 no longer remains toxic for existing organisms. This change was triggered by the environment itself since the oxygenated atmosphere was gradually formed in the earth (2). The poorly reduced primordial anoxic atmosphere was predominated by carbon dioxide (CO_2) (3, 4) and gradually O_2 became one of the most widespread elements of earth (5). A photochemistry model speculated the formation of O_2 rich atmosphere as a result of abiotic photolysis of water (H_2O) and CO_2 (6). In contrast, abiotically produced hydrogen peroxide (H_2O_2) from pyrite/aqueous suspension has also been considered as the source of O_2 (7). In addition, the activities of the microbes, particularly cyanobacteria also contribute to the formation of oxygenated atmosphere (8). The extreme alterations of the environment took place about 2.5 billion years ago, in early Proterozoic era with happening of Great Oxygen Event that drove extinction of many obligatory anaerobic species and ensured the survival of aerobic organisms (9, 10). This landmark event was triggered by cyanobacteria, an organism from one of the most ancient evolutionary lineages. Cyanobacteria was the first to be evolved with photosystem II, advancing towards oxygenic photosynthesis which leads to the appearance of oxygen in atmosphere and subsequent changes in earth system (8, 11, 12). Along with this atmospheric modulation, due to the continuous exposure of organisms to oxygen and owing to oxygen dependent energy metabolism, deleterious free radicals also generated and inevitably cause oxidative stress to these organisms (13). To reduce the deleterious impact of the oxidative stress, some oxygen consuming species have to give rise to antioxidants to help them coping with reactive oxygen species (ROS) for their survival. Eventually, some molecules with reduced capacity have been selected to be antioxidants. Around 1.5 to 2 billion years ago, the pro-eukaryotes have been emerged. Based on the theory of endosymbiosis, a pro-eukaryote engulfs an alpha-proteobacterium. This alpha-proteobacterium avoids digestion by the host cell and symbiotically lives inside the host cell. This bacterium has the capacity of oxidative phosphorylation and generates ATP with high efficiency and provides extra energy to the host cell. The pro-eukaryote and alpha-proteobacterium are beneficial to each other. This endosymbiotic relationship between the host and intruder finally results in the mitochondrial formation from the alpha-proteobacterium (14). It is hypothesized that the secondary endosymbiosis of the eukaryotes with cyanobacteria leads to the generation of plants and the cyanobacteria are the precursors of the chloroplasts (15, 16). Currently, evidence has been shown that archaea may involve in the origin of eukaryote and mitochondria (17, 18). Interestingly, in animals and plants, both mitochondria and chloroplasts are the major sites for synthesis of melatonin (19), a molecule having both free radical scavenging and endogenous antioxidant enzyme stimulating properties (20-22) while mitochondria and chloroplasts are the main sources of ROS production (19).

Since its discovery (23), scientists have continuously extended their investigations to establish the functional relevance of its existence. It is broadly present from primitive bacteria to high ranks of eukaryotes and this indicates the pleiotropic roles of this indole among species (24). Though the presence of this molecule in archaea is still under investigation, the horizontal gene transfer from bacteria to archaea (25, 26) as well as collateral emergence of both archaea and bacteria bring speculation on its presence in the domain of archaea (26). Moreover, the emergence of eukaryotes from archaea carries a confirmatory note of melatonin synthesis in archaea (27, 28) since eukaryotes possess well developed machineries for melatonin synthesis (29). While its unchanged chemical structure throughout evolution leads to the concept of its primary function to be an antioxidant, its circadian rhythm observed in most of the species also suggests it as an entrainer of 'biological clock' (30). For example, dinoflagellates as well as several microalgae, chlorophyceans, the photoautotrophs all possess melatonin biorhythm with prominence (26, 31-33). This rhythm has been identified also in many plants, irrespective of

their classifications (34, 35). The protection of plants from various biotic and abiotic stressors during daylight has been assumed to be the factor behind such a diurnal rhythm (26). In contrast, evolution has brought a dedicated pineal gland in vertebrates to secrete melatonin with circadian rhythm (23). This molecule seems to regulate the sleep/wake cycle (36, 37), peripheral organ oscillation (38) and reproductive physiology of vertebrates (39, 40) via master clock, the suprachiasmatic nucleus (SCN) in hypothalamus (41). The actions are mediated by melatonin receptor. For example, anti-inflammatory and anti-cancerous effects of melatonin are receptor-dependent (42-44). Hence, functional evolution of melatonin in organisms for adaptive responses make them surviving under different (or changeable) environments.

2. MELATONIN: THE OMNIPRESENT MOLECULE IN CHRONICLE OF LIFE

Despite the co-existence of aerobic and anaerobic species, oxygen-centric surroundings drive the environment in favour of oxygen dependent aerobic organisms. During early emergence of lives, the discharged oxygen was utilized in making up the organic materials and earth crust (1). Progressively, the increased oxygen level in atmosphere trigged a mass extinction of anaerobes (2, 45, 46) while selected aerobic organisms. However, when the one electron reduction of oxygen (known as the ROS) reaches some levels it can induce deleterious effects even on the aerobic organisms. This can happen because these ROS, particularly the hydroxyl radical can injure macromolecular structures rapidly (13, 47, 48). Thus, the organisms have to develop mechanisms to tolerate ROS and reduce oxidative damage. Cyanobacteria were reported as the most ancient oxygen tolerant species (1) to counter superoxide anion radical, hydroxyl radical and many other reactive species. Thus, the endogenous antioxidants become necessary for those organisms who survive in the oxygenated ambience. Here, melatonin becomes most relevant to be discussed due to its diverse antioxidative properties and its ubiquitous presence throughout lineages of organisms (21, 49) (Figures 1, 2).

Melatonin has been first isolated from the pineal gland of cow in Twentieth century (23) to concrete the idea of its existence in high-ranking organisms. However, with advancement of research, a unicellular flagellate has also been reported as a residence of the indole (31, 50, 51). When a dinoflagellate *Lingulodinium polyedrum* exposed to a temperature, below its optimal one, its antioxidant enzyme level was reduced along with a sudden elevation in its melatonin production (52, 53). Moreover, physiological dose of melatonin in culture medium protects these algae against hydrogen peroxide induced oxidative damage (52). Subsequently, presence of melatonin has been identified in photosynthetic bacteria and fungi including euglenoids, trypanosomids, chlorophyceans (54-56) as well as in plants (57- 60). Although there is scarcity of evidence regarding the synthesis of melatonin in the domain of archaea, the tolerance of archaea on harsh environments including extremely high temperature (61) similar to some extremophil bacteria might be relevant for the presence of melatonin in this domain (62). In vascular plants, melatonin was first detected mainly in mono- and dicotyledon edible plant families in their roots, shoots, leaves and seeds (35, 58, 63-66). All of these discoveries have raised a question whether melatonin is conserved in evolution either due to necessity of all organisms or it is only beneficial for those species who acquire it from food chain.

Endosymbiotic theory of mitochondria and chloroplast origin explains the crucial presence of melatonin in organisms. The earliest alpha-proteobacterium, a precursor of mitochondrion and cyanobacterium, a precursor of chloroplast have already had the capacity to synthesize melatonin. As a result, organelles evolved from these bacteria also retain this capacity and became specific sites for melatonin synthesis in all organisms. Mitochondria and chloroplasts both are the heart of energy metabolism in animal and plant, respectively which have made these structures highly vulnerable to oxidative stress (19, 67). Hence, *de novo* melatonin synthesis in these organelles add advantages for them to detoxify on-site generated ROS. This

mystery was unveiled by the breakthrough discovery of antioxidant property of the indoleamine (20) and led to the extensive investigations of its diverse antioxidant mechanisms in microorganisms, plants and animals (68-70). The natural selection has preserved this bio-weapon as an obvious requisite to combat with noxious free radicals in all organisms.

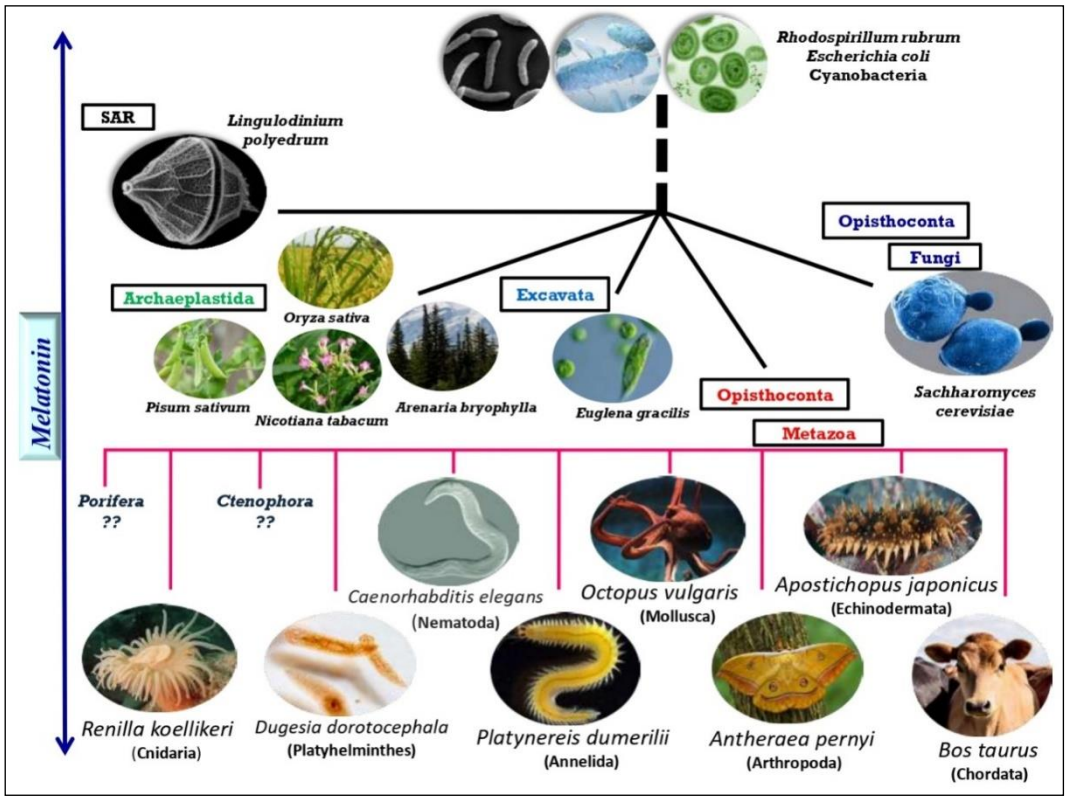

Fig.1. Ubiquitous presence of melatonin from Prokaryotes to Eukaryotes.

From Prokaryotes to Eukaryotes including Plants, Fungi and Animalia, melatonin has emerged in all life forms. At the top of the figure, presence of melatonin has been shown in unicellular prokaryotes such as in R. rubrum (24), E. coli (56), Cyanobacteria (102,26). With evolution, multicellular Eukaryotes have preserved their melatonin synthetic ability. In the superclade SAR (Stramenopila, Alveolata, Rhizaria), the dinoflagellate Lingulodinium polyedrum have developed melatonin circadian rhythm. In modern taxonomy, another superclade of eukaryotes mentioned as Archaeaplastida, comprises of green plants. When plants emerged in evolution, melatonin acquires more diverse actions including controlling photoperiodic reproduction, flowering along with its primary antioxidative actions evidenced in P. sativum (147), O. sativa (91), N. tabacum (57), A. bryophylla (35,64). The melatonin production in another eukaryote Euglena gracilis of superclade excavate exhibits circadian rhythm (54,56,62,148). Fungi, which belongs to superclade Opisthoconta, possess melatonin in members including S. cerevisiae (149) and N. crassa (56) as well as diurnal rhythm was evidenced with melatonin synthetic function in the latter. Presence of melatonin became more pertinent in Metazoans, from the same supergroup Opisthoconta. With appearance of invertebrates, melatonin showed its excellence in preserving their behavioural pattern and locomotor activities. The need of melatonin become more relevant when vertebrates appear with evolutionary alterations. Prominent sleep/wake cycle maintenance, rhythmic behavioural pattern preservation, anti-inflammatory as well as anti-cancerous activities have been affixed for this molecule in many dorotocephala species e.g., in R. koellikeri (150, 151), D. Dorotocephala (152), C. elegans (153), P. dumerilii (154), O. vulgaris (155), A. pernyi (156), A. japonicas (157), B. taurus (23). The horizontal lines are not indicative of distance.

3. DIVERSE PATHWAYS CONVERGE AT MELATONIN SYNTHESIS

Bacteria, fungi and plants are capable of synthesizing melatonin at their own through shikimic acid pathway utilizing either carbon dioxide or erythrose-4-phosphate or phosphoenolpyruvate as the source (42, 71, 72). However, the amino acid tryptophan has been identified as the initial precursor of melatonin synthesis in animals. For some animals, due to lack of tryptophan synthesizing enzymes they can only obtain it from the dietary source (42).

Even though melatonin remains structurally unchanged throughout evolutionary adaptations, its synthetic pathways have been diversified depending on the species. For example, in the initial step of melatonin synthesis, tryptophan undergoes decarboxylation by tryptophan decarboxylase to produce tryptamine in plants, while animals utilize tryptophan hydroxylase to hydrolyse tryptophan to form 5-hydroxytryptophan. Involvement of different chemical reactions toward formation of a single amine molecule indicates the diversity of enzyme-substrate specificity as well as of enzyme coding genes among different taxa. The tryptamine and 5-hydroxytryptophan, two different molecules converge to serotonin through catalytic actions of tryptamine-5-hydroxylase and aromatic amino acid decarboxylase in plants and animals respectively (29, 73-75). Serotonin undergoes two steps catalytic process to produce melatonin where, two enzymes serotonin N-acetyltransferase (SNAT) and N-acetylserotonin O-methyltransferase (ASMT) work consecutively but order of their catalysis depends on the substrate specificity of enzyme in particular species. In plants and bacteria, serotonin seems to show more specificity towards ASMT while the terminal step has been found to be catalyzed by SNAT. Nevertheless, in a contrasting manner, in animals, acetylation has been energetically favoured over methylation of serotonin and thus the final step of melatonin synthesis has been catalysed by ASMT (76-79). Hence, it seems that evolution has selected the enzymes to act upon their substrates.

Here, the question arises that even if all organisms possess the similar capacity to synthesize melatonin, why the selectivity of enzymes to substrates has evolved with time? A variety of homologs of *SNAT* and *ASMT* discovered in plants and animals have answered this important evolutionary question. These diversities may come from the horizontal gene transferring from different bacteria and archaea. However, in vertebrates, vertical inheritance of *SNAT* has been identified and the homology with catalytic regions of the gene is from the phylogenic ancestors. The differences in structure and DNA sequences of N-terminal as well as C-terminal regulatory regions of *SNAT* in vertebrates were considered as the results of natural selection during evolution (26). Only one isoform of SNAT has been identified in mammals while non-mammalian vertebrates possess various isoforms as evidenced in fish. Exclusive expression of *SNAT2* has been found in pineal gland of fish (80) whereas *SNAT1a* and *SNAT1b* were reported to be expressed in retina and other sites, respectively (81). In a similar manner, two isoforms of *SNAT* have been identified in rice. These *OsSNAT1* and *OsSNAT2*, have dissimilar DNA sequences and kinetic patterns, experimented to respond in different environmental cues (82). Additionally, diversification in stimulants for various *SNAT* homologs has also been observed. For example, some are upregulated by photoperiodic changes and others by oxidative stress (83). Apart from melatonin synthesis, SNAT in vertebrates also involves in sclerotization of insects, indicating the functional diversity of this enzyme (84, 85). The homologs of *SNAT* found in unicellular green algae, fungi and bacteria possess distinct sequence pattern from its vertebrate homolog. Though catalytic domain of vertebrate SNAT shares the similarity with bacterial and/or fungal SNAT, the regulatory region, being dissimilar, confirms the natural selective power during evolution (86). Striking dissimilarities have been demonstrated between *SNAT* sequences of different domains of life. Vertebrate SNAT has been reported to have two histidine residues (at position 120 and 122) whereas fungi have only one and bacteria don't possess any (86, 87). Presences of various isoforms such as SNAT1a, SANAT1b and SNAT2

have been detailed in *Drosophila melanogaster* (85) when another two forms SNAT5b and SNAT7 have been evidenced in *Aedes aegypti* (88, 89). Both SNAT and ASMT in plants showed a wide temperature tolerance range of 4 °C to 95 °C while their animal isoform exhibited a narrow range of tolerance between 25 °C to 45 °C (86, 90- 93). This variation also authenticated the evolutionary selection of enzymes with different optimum temperature since immobile plants have to face tremendous atmospheric alterations (1, 94). Other than SNAT, contribution of another form of N-acetyltransferase on melatonin synthesis has been explained in mammals (95, 96). For example, NAT-1 was reported to be involved in melatonin synthesis in mammalian skin (97), especially in the situation of SNAT deficiency (98). In addition, NAT-2 mediated N-acetylation of serotonin has been found in hamster skin (99).

The NATs of cyanobacteria and archaea share few amino acid residue homologies while sequence homologies of NATs have been confirmed between archaea and eukaryotes (62, 100, 101). Cloning and characterization of a thermophilic archaeal hypothetical acetyltransferase (NAT) that belongs to GCN5-related N-acetyltransferase (GNAT) superfamily has the function similar to SNAT of cyanobacteria (100, 102). Therefore, despite of having sequence dissimilarities, the functional resemblance as well as appearance of GNAT in both bacteria and archaea surmises the potential melatonin synthetic function in archaea.

The diversities of NATs among plants, animals and microorganisms suggest horizontal gene transfer among those taxa (85, 103, 104). However, scientists assume presence of divergent evolution also due to the limited residual similarities (105). It suggests independent emergence of NAT in different taxa with post endosymbiotic acquired modifications. Experimental evidence of considerable similarities in NAT DNA sequence and protein residues of cyanobacteria *Synechocystis* and plant species *Oryza sativa* (rice) supported symbiotic association between them (62, 91, 102). The rate limiting enzyme of melatonin synthesis has been found to be resided in plant's chloroplast and in DNA of its precursor, cyanobacteria which further supports the theory of endosymbiosis (73, 91, 106, 107). On the other hand, sharing striking homology in DNA sequences of NAT gene between *Rhodospirillum rubrum* and different eukaryotes again bring confirmation to endosymbiotic theory since *Rhodospirillum* is assumed to be the precursor of mitochondria (85, 105).

Consequently, the trail of origin of melatonin has been embedded some billion years ago which is running forward owing to its high functional relevance and regard in present day.

4. THE SITES OF MELATONIN SYNTHESIS

Endosymbiotic theory explains the presence and synthesis of melatonin in chloroplast and mitochondria. Both organelles are the major sources of ROS formation. This substantiates the presence of melatonin in both of them. The natural selection thus, preserves melatonin synthetic capacity in these most metabolically active organelles in plants and animals.

The existence of melatonin in chloroplasts is suggested from its presence in cyanobacteria, but also confirmed by the presence of rate limiting enzyme SNAT in them (73, 91, 106). Chloroplast is the site of plant photosynthesis, the major energy harvesting house of plant. During photosynthesis, as an obvious consequence, the oxygen is excited to form singlet oxygen which triggers peroxidation of poly unsaturated fatty acids in thylakoid membrane resulting into declination in photosynthetic efficiency of plants (1, 71, 108, 109). In addition to the singlet oxygen, hydrogen peroxide is another ROS to cause oxidative stress in plants. Hydrogen peroxide is formed in thylakoid membrane and chloroplast stroma by superoxide anion dismutation either enzymatically or automatically (108). In some conditions, the deficiency of catalase, glutathione peroxidase and ascorbate peroxidase (110) result in an accumulation of hydrogen peroxide within chloroplast causing injury to photosynthetic system (111). The efficacy of melatonin in scavenging hydrogen peroxide and subsequent hydroxyl

radical from chloroplast has made this molecule critical for plant survival (70, 112-114) and this is also the advantage of natural selection. Apart from chloroplast, plant mitochondria also participate in the melatonin synthesis. SNAT has been identified in plant mitochondria and isolated apple mitochondria have been verified to generate melatonin (92). Since plants have to combat with countless biotic and abiotic stressors, perhaps natural selection has chosen both organelles to synthesize melatonin to ensure much high magnitude of melatonin level in plants comparing to animals. Melatonin protects plants against a variety of environmental insults including heat, cold, draught, water stress, soil pollutants etc. which goes parallel with protection by exogenously administered melatonin against chlorophyll degradation (26, 62, 115-122). Very high melatonin level of 230 μg/gm has been evidenced in pistachio nut (123). Various vegetables, herbs and fruits have been identified as source of melatonin (109, 124, 125). Moreover, evolution has loaded plants with all the enzymes required to synthesize tryptophan, the precursor of melatonin so that scarcity of tryptophan can't limit the synthesis of the indoleamine in plants (72) such as in animals. Hence, exposure of plants to severe oxidative stress is the driving force in selecting melatonin as an on-site antioxidant to protect them from environmental insults (126, 127).

In animals, mitochondria are energy generating house and also melatonin synthetic site. Melatonin can effectively protect mitochondria from ROS damage (67, 128, 129). For example, respiratory electron transport chain (ETC) inhibition can be alleviated by melatonin (130-133). Melatonin can also reduce ruthenium red induced mitochondrial calcium channel blockage and subsequent mitochondrial damage (134). Most importantly, melatonin can maintain normal mitochondrial milieu to retard aging and several disorders (135, 136). In addition to mitochondria and chloroplasts, melatonin synthetic enzymes have been found in cytoplasm including ASMT (91), tryptophan hydroxylase (73, 75). Since melatonin synthesis requires the substrate acetyl-coenzyme A which is mainly generated in the mitochondria and chloroplasts, from the point of view of substrate availability, the cytoplasm melatonin synthesis is less efficient than that occurs in mitochondria and chloroplasts (137). Cytoplasm melatonin synthesis may play a complementary role to the two organelles in organisms.

The varied subcellular localizations of melatonin synthesis make the cell be much stronger to combat stress. Assay of level of melatonin in rodent cerebrocortical cells indicates highest concentration of melatonin within mitochondria followed by membrane, nuclei and cytosol (129). Its presence has been recognized beyond mitochondria and chloroplasts. Most of the cells and tissues have the capacity to synthesize melatonin due to the fact that they contain mitochondria. For example, gastrointestinal tract is a huge source of melatonin where enterochromaffin cells of gastric mucosa secrete melatonin. The amount of melatonin generated by gastric tissue is estimated to be several hundred-fold than pineal melatonin (138). An exocrine gland, Harderian gland in some mammals secretes melatonin with circadian rhythm (139, 140). Skin produces melatonin at a very high concentration (141). This extra pineal melatonin synthesis indicates the evolutionary choice to alleviate oxidative attack on site where free radicals produced rather than to expense time to obtain melatonin from other places.

5. FUNCTIONAL EVOLUTION OF MELATONIN

Melatonin was first isolated from pineal gland of cows with circadian rhythm (142). With further progress in research, retina was identified as another source of this indoleamine (143-145). Both pineal gland and retina share many common features comprising their neural origin (146). Subsequently, many tissues and organs have been identified also to produce melatonin. A turning point come from the discovery of presence of melatonin in unicellular organisms of

algae and bacteria (31, 52, 54, 55). It appears that melatonin may function with different purposes in early life forms rather than maintaining light-dark biorhythm in the vertebrates.

Even though the primitive photosynthetic bacteria *Rhodospirillum rubrum* exhibit light/dark melatonin circadian rhythm similar to the vertebrates (24), this rhythm has not been observed in other microorganisms including *Escherichia coli*, fungi (*Saccharomyces cerevisiae*) (56, 158). In *Saccharomyces cerevisiae*, melatonin's production is governed by availability of its precursors, but not by the photoperiod (123). In contrast, night time surge in melatonin level has been evidenced in *Neurospora crassa*, whereas no indoleamine has been traced in photophase (56). It is now understandable that the absence of melatonin in photophase and high level in dark phase in some microorganisms has a different reason from vertebrates. It is hypothesized that the bacteria including *Rhodospirillum rubrum*, synthesize melatonin in a constant rate during the photo phase or scotophase. The reduced level of melatonin in photo phase is due to melatonin consumption as an antioxidant to scavenge free radicals induced by UV irradiation and photosynthesis (159). Thus, the primary function of melatonin in early life form is not circadian regulator but serves as the first line defence as potent antioxidant. Other functions are acquired during evolution (Figure 2).

As discussed earlier, plants have already equipped with dual melatonin synthesizing organelles to ensure high level of melatonin production. This high level of melatonin in plants significantly strengthens antioxidative capacity of plants for their survival under biotic and abiotic stressful environments (104). Melatonin protects *Pisum sativum* from excess copper toxicity (66). Under the UV irradiation, *Nicotiana tabacum* and *Glycyrrhiza uralensis* shield themselves by elevating their endogenous melatonin concentrations to combat the UV induced oxidative injury (57, 160). It appears as a common feature that plants under harsh environments always do enhance their melatonin production to protect themselves (35, 64). This phenomenon has also been observed in plants exposed to the chemical and metal pollutants including NaCl, $ZnSo_4$ and H_2O_2 (122). Melatonin can preserve photosystem by hindering chlorophyll degradation (161) and collaborate with other phytohormones including auxin, salicylic acid, jasmonic acid, ethylene, etc. (162-64).

Melatonin is distributed in all parts of plants including seeds, leaves, fruits and roots (35, 165, 166). It not only plays a defensive role but also promotes plant growth. It acts parallelly to the major plant growth hormone auxin stimulating growth of plants (167- 170). These stimulatory actions include promoting plant growth rate, number and length of lateral and adventitious roots (170- 172), flower development (173). In some species, such as *Chenopodium rubrum* and *Arabidopsis thaliana* melatonin may delay their flowering depending on the length of the photoperiods (33, 174). This may relate to the responses of different isoforms of melatonin synthetic enzymes on different light exposure conditions (175). The different functions of melatonin in plants are evolved to make the plants to adapt to the environmental changes (159).

For animals, the functional varieties are even more colourful than those in the plants. Melatonin and its diurnal oscillation modulate ciliary swimming, locomotor activity and behaviour pattern in diverse species of invertebrates (176-181). An anti-inflammatory activity of melatonin is another example which helps the organisms to adapt the perceived stimuli. Inflammation is a normal physiological response of organisms against viral or bacterial invasions. Overaction will damage tissues and sometimes has the lethal outcome. Melatonin can suppress the excessive inflammatory reaction by up-regulating anti-inflammatory cytokines along with promoting down-regulation of TNF-α, pro-inflammatory cytokines, pro-inflammatory enzymes like COX2 (26,182- 184). This anti-inflammatory property of melatonin contributes in alleviating many diseased conditions like cardiomyopathy, diabetes, ischaemia, gastrointestinal injury and even neurodegenerative disorders (184-187). Inhibition

of eosinophil peroxidase by melatonin has been reported in human, which suggests its role in blocking phagocytosis (188).

As mentioned above, mitochondria are the major site of melatonin synthesis. The question is why melatonin is also present in the red blood cells (RBC) which are mitochondria free (189). In addition, RBCs are always exposed to high concentration of oxygen and enormous ROS and need melatonin's protection. The fact is that RBC not only can extract melatonin from blood stream but they also have the capacity to synthesize melatonin *per se* (190). Melatonin can protect RBC from haemolysis and prolong their storage time (190).

During evolution, the pineal gland of vertebrates evolves into a specific organ to exclusively produce melatonin (23). Unlikely other organs, pineal gland releases its melatonin into circulation as an environmental photoperiodic clue to other tissues and organs which cannot directly detect the light. The other pathway is that pineal gland directly releases melatonin into the third ventricle and acts on the melatonin receptors located in the SCN to entrain dark/light information (191). Hence, functional diversification of melatonin comes with evolution based on its spatial differentiation (Figure. 2).

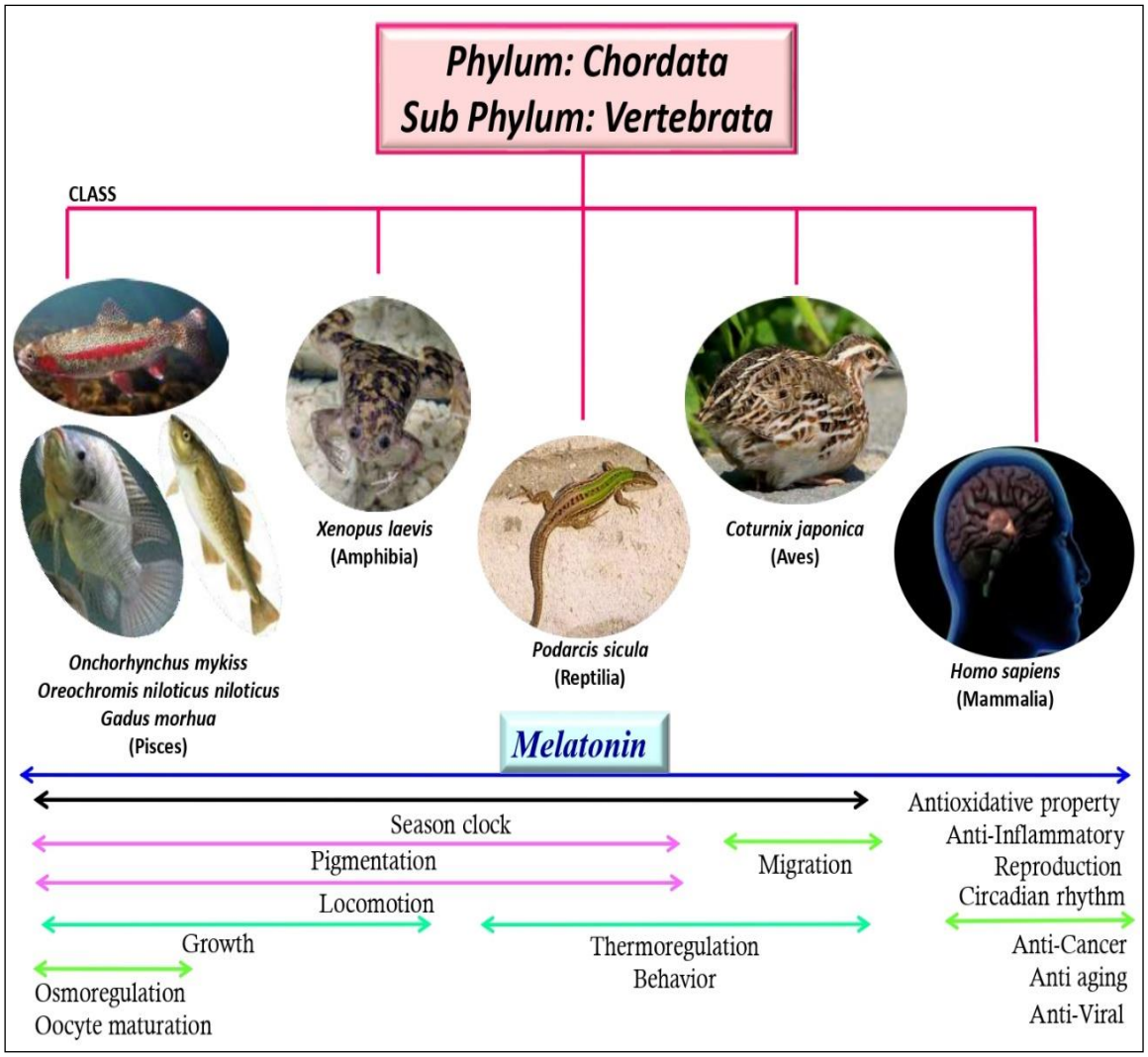

Fig. 2. The functional acquirements of melatonin during evolution.

Melatonin undergoes tremendous functional acquirements during evolution. Melatonin originally acts as an antioxidant, then it acquired other functions that have been shown here starting from Pisces to Mammalia.

6. RELEVANCE OF PINEAL GLAND IN EVOLUTION

Since, animals have evolved their unique metabolic systems, they do not depend on photon energy assimilation for energy generation any more (26). At that time, retina became the sensor of light to synchronize the physiological activities of the internal tissues and organs of organisms to adapt the light and dark cycle with the help of melanopsin pigment (26, 192). In this respect, melatonin is selected as the chemical expression of day/night cycle to regulate physiological function of organisms. It is obvious that vertebrates inherit this signalling pathway from their ancestors. In this pathway, the ganglion cells of retina act as the sole light sensors or photoreceptors to convert it as a neural signal to reach SCN of hypothalamus (26, 158, 193). Although retina can synthesize melatonin, this melatonin will not release into circulation (194, 195), except some exceptions (196) such as in amphibian, pinealectomy doesn't cause complete elimination of melatonin from circulation due to retinal contribution (194, 197, 198). Fish circadian clock is also regulated by melatonin from both pineal gland and retina (199, 200). For amphibians and fish, their retina and pineal gland seem to have the similar functions, that is to serve as the photoreceptor as well as to release melatonin into circulation as the circadian regulator. In the mammals, retina has dedicated to photo-perception and pineal gland evolves to an organ for exclusive melatonin synthesis (201, 202). Both organs are differentiated from diencephalon, and exhibit the intricacy rhythm, even in absence of external cues such as in humans residing in underground bunker (203). Evidence shows that pineal gland may evolve from retina since remnants of rods and cones have been identified within pineal gland (204). In contrast, in some lower vertebrates, and even in higher vertebrates like birds, pineal gland still has the ability to sense light (205, 206). In invertebrates, those are devoid of pineal gland, the locally synthesized melatonin may serve as autocrine and paracrine signal which perhaps did not respond to diurnal rhythm (42). In some unicellular organisms, they also have melatonin circadian rhythm. Whether the circadian pattern of melatonin production in vertebrates inherits from ancient microorganisms is debatable. Melatonin secreted from pineal gland exclusively performs as an endocrine signal to provide light/dark information to all organs in order to synchronize their physiological functions (42, 50, 207, 208). Melatonin circadian rhythm as the photoperiodic signal can help the organisms protect against various disease conditions including diabetes (209). It also has the important physiological relevance. For example, in seasonal breeders, their reproductive activity depended on environmental photoperiodic information and melatonin usually provides this information (210). The seasonal breeders identify the season with high nocturnal melatonin level and duration as winter and short dark period with low nocturnal melatonin as summer. The deer, goat, hamster respond to this melatonin circadian rhythm to adjust their breeding time (211-213). The significance of pineal gland became more evident. For example, when the signal of reproductive season is interrupted in seasonal breeding animals by pinealectomy, this makes them breeding at the wrong season which will increase the mortality of their offspring (214). In some seasonal breeders including Syrian hamsters and palm squirrels, high melatonin level and duration inhibit their reproductive activity by acting on the hypothalamo hypophyseal gonadal axis (215-217). This has great impact on long photoperiodic reproductive animals. The winter associated high melatonin information inhibits them to give birth in the cold winter and increases the survival rate of their offspring (159, 218). Thus, the emergence of pineal melatonin as the biological rhythm regulator brings pulse to the life of organisms, necessary for their survival.

Rhythmical melatonin secretion from pineal gland also influences sleep-wake cycle by binding to master clock SCN as a ligand. The night-time decrease in temperature is associated with nocturnal melatonin surge and subsequent sleep (219). In diurnal organisms, the daily clock during dark period, promote sleep while in nocturnal animals, the high melatonin level

reminds them about foraging activities (220) and thus this molecule brings temporal synchronization in activities of different organisms.

7. MELATONIN RECEPTOR: PERSPECTIVE OF ITS EMERGANCE

In unicellular organism, the secretion of melatonin and its action were limited within a small boundary where the indole acted as the on-site protector against free radicals. This action is receptor-independent since melatonin receptors have not been reported in unicellular organisms (26, 159). But, melatonin binding site may be present in these organisms (221).

In multicellular organisms, for the long-distance signal relay, melatonin receptors have been emerged. Non-mammalian vertebrates have initiated MT3 receptor with relatively low affinity for melatonin ligand, thereafter, all mammals have developed high affinity MT1 and MT2 which are predominant in brain and retina (222-224). Other peripheral tissues including Harderian gland, spleen, gut, testis, ovary and smooth muscle, cells of immune system all have melatonin receptors (225, 226). The presence of melatonin receptors in SCN is selected for regulation of bio-clock and homoeostasis by nature (227, 228).

The MT1 and MT2 subtypes have distinct molecular structures, chromosomal sites and pharmacological specifications (229, 230-232). They can function in monomeric, in homodimeric or even in heterodimeric forms (233). These complexes of receptor configurations make the functional variable of these receptors. For example, considering the involvement of melatonin in learning process, MT2 knock-down in mice results in cognitive dysfunction (234); however, MT1/MT2 double knockout displays better performance in learning and memory in mice (235). Presence of both MT1 and MT2 receptors in pancreas reduces excessive insulin secretion and insulin resistance (209). The cardio-protective effects of melatonin require both MT1 and MT2 participation. MT1 activation suppresses adenylate cyclase and reduction of intracellular cAMP level (236) while effects of MT2 are mitochondria dependent. Hence, distinction in involvement of receptor sub-types in diverse pathological situations has been evidenced based on their locations.

8. CONCLUSION REMARKS

In summary, the pleiotropic nature of melatonin makes this molecule more acceptable and appropriate for organisms. Due to its multiple functions acquired during evolution, melatonin gradually gains the advantages over other naturally occurring molecules. For example, the synthetic ability of vitamin C and vitamin E has been lost in many mammals during evolution while the melatonin synthetic capacity has been preserved and even strengthened in all animals. This can be reflected by the diversities of melatonin synthetic pathways and enzymes which converge to generate the final product, melatonin and secure the sufficient melatonin level for life surviving and thriving. This review projects the chronological events of genesis of melatonin as an essential and indispensable molecule of life.

ACKNOWLEDGEMENTS

A Junior Research Fellowship (JRF) under WBDST [304(Sanc.)/STP/S&T/1G-67/2017DATED 29.03.2018] is greatly acknowledged by AB. Dr. AC is supported by funds available to her from Department of Science and Technology, Govt. of West Bengal. Dr. DB gratefully acknowledges the support he received from Departmental BI Grant and DST-PURSE Program awarded to the University of Calcutta. Dr. DB also extends grateful thanks to UGC, Govt. of India, for being awarded as a principal investigator under Centre with Potential for Excellence in a Particular Area (CPEPA) at University of Calcutta. Dr. DB also gratefully

acknowledges the contribution of Dr. DunXian Tan, Editor-In-Chief, Melatonin Research, for critically reading the manuscript, making thought provoking editorial corrections which has surely increased the scientific and readership quality of the article.

AUTHOR'S CONTRIBUTION

DB initiated the concept, revised the manuscript and approved it. AC contributed in critical review and approval. AB prepared, drafted and edited the manuscript and figure.

CONFLICT OF INTEREST

Authors declare no conflict of interests.

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Please cite this paper as:
Banerjee, A., Chattopadhyay, A. and Bandyopadhyay, D. 2021. Melatonin: an ancient note in a contemporary wrap. Melatonin Research. 4, 3 (Sept. 2021), 453-478. DOI:https://doi.org/https://doi.org/10.32794/mr112500105.