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Multi-author Reviews

Melatonin and the light-dark zeitgeber in vertebrates, invertebrates and unicellular organisms

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Introduction. Melatonin and the light-dark zeitgeber in vertebrates, invertebrates and unicellular organisms

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Melatonin, 5-methoxy-N-acetyltryptamine, is an evolutionary highly conserved molecule which occurs in organisms as different as algae and humans and structurally related tryptophan metabolites may be present in all organisms[12]. The formation of melatonin and other methoxylated indoleamines such as 5-methoxytryptamine has been demonstrated in unicellular organisms, invertebrates and vertebrates (authors of this review).

Many cells and tissues are able to synthesize this indoleamine in vertebrates, but only recently highly efficient extraction methods have become available to evaluate the importance of extrapineal sites of melatonin formation (Huether, this review). In all organisms which have been studied melatonin is almost exclusively synthesized during the night and it mediates information concerning the temporal position and duration of darkness[1,3,10,14,17] (authors of this review). However, at least in extrapineal tissues such as the gastrointestinal tract melatonin formation may be also highly dependent on nutritional factors which regulate the synthesis of this indoleamine. It has been proposed that these tissues may contribute significantly to the levels of circulating melatonin and the total amount of this indoleamine present in the gut is approximately 1000 times higher than the total melatonin content of the pineal gland[7].

The important role of this chronobiotic in mediating clock and calendar information has been demonstrated in vertebrates, invertebrates and even unicellular organisms (authors of this review) and it is widely accepted now that melatonin is the most important endogenous mediator of photoperiodic information[1,3,10,14,17]. However, our understanding of the biological functions and the physiological significance of melatonin is still substantially expanding. Melatonin is a highly diffusible compound which crosses all biological barriers and enters every cell compartment with ease. In general, it appears that this substance ubiquitously acts as a fine tuner of organismal physiology[5]. However, it seems to accumulate selectively in the nucleus of cells (Armando Menendez-Pelaez, personal communication). Recently its potent radical scavenging activity has been detected (Hardeland and Reiter, this review). Due to its unique physicochemical properties, the highly electroreactive melatonin molecule can detoxify reactive oxygen species[6,13,16]. Since melatonin can act as a highly efficient electron donor, it is feasible that this indoleamine may also repair biomolecules damaged by radicals and catalyse one-electron-reactions thereby increasing energy metabolism efficiency.

From an evolutionary standpoint, melatonin and other tryptophan-derived indole pigments may have evolved at the time when photosynthetic organisms started to produce large amounts of oxygen and other cells began to rely on this highly reactive natural oxidant for respiration and metabolism[6,13,16] (Hardeland and Reiter, this review). It has been proposed that indolic compounds such as melatonin are involved in the regulation of electron transfer and the control of peroxidative processes[6,13,16] (Hardeland and Reiter, this review). It may also act as a morphogen which influences cell shape, division and development by binding to calmodulin intracellulary[2,4,10] (Benitez-King, Csaba, Morita and Best, this review). These regulatory effects may represent another ancient function of melatonin effecting every cell in all organisms. Since calmodulin is an ubiquitous Ca^{++}-binding protein, the calcium-calmodulin interaction probably constitutes an important primary mechanism for regulation and synchronization of cell physiology by melatonin[2] (Benitez-King, this

review). Considering these very basic functions of melatonin, it is evident that the most important actions of this molecule can be mediated without the activation of specific membrane receptors in certain brain areas. Although melatonin is the endogenous messenger of the photoperiodic information 'darkness' and the physiologic effects of this mediator are best defined in terms of the marked regulatory effects on reproductive cycles, particularly the timing of seasonal reproductive cycles, there is suggestive evidence now that melatonin's influence by far transcends one system (authors of this review). Indeed, it now appears that there may be no cell in the body which escapes the influence of this ubiquitously acting substance.

The potent anti-stress and anti-aging effects of melatonin and its powerful immunostimmulatory activities indicate that we have only uncovered very few actions of melatonin, perhaps not even the most important ones[11]. Studies on the evolutionary biology of aging have provided us with some understanding of aging and developmental processes[13]. The important clinical impacts of melatonin and melatonin-driven biorhythms have been studied only recently (Waldhauser, Ehrhart and Foerster, this review). In general, the aging process is associated with desynchronization, degeneration and dysdifferentiation in all multi-cellular organisms[11,13,15,16,18]. The contributions to this review emphasize on the interdisciplinarity of melatonin research and demonstrate nicely that progress in experimental and clinical medicine is highly dependent on basic investigations in comparative biochemistry and physiology.

The light-dark cycle and the aging process are the major factors which determine melatonin synthesis and secretion in vertebrates[11,13–16,18]. It has been demonstrated conclusively that aging and development are associated with a substantial drop in the nocturnal melatonin formation[15,18]. The melatonin deficiency in aged animals and humans is accompanied by an enhanced sensitivity to oxidative stress in senescent organisms[13,16]. It has been suggested that the age-associated deterioration of the melatonin rhythm could contribute to the aging process per se as well as to age-related diseases which may have as their basis free radical toxicity[11,13,16]. Hydroxyl radical generation and detoxification are strongly correlated with the rate of aging in a broad range of organisms and hydroxyl radical mediated oxidative damage has been shown to accumulate exponentially with senescence[13,16]. Since melatonin is the most potent hydroxyl radical scavenger detected to date this indoleamine could be indeed a very important endogenous longevity assuring factor[11,13,16].

In this regard it is instructive to speculate on the evolution of specific functions of melatonin and to investigate and compare the actions of this indoleamine in many organisms with different physiology and adaptation strategies (authors of this review). As Hardeland and Reiter suggest, melatonin's initial function might have been to detoxify reactive oxygen species. Since melatonin is degraded by oxygen radicals, a passive rhythm was instantaneously established after the evolution of this indoleamine which later has been coupled to the endogenous circadian oscillator[6]. Tryptophan metabolites such as melatonin might have been evolved to improve electron transfer and energy metabolism and there are striking similarities between melatonin and other indolic and non-indolic pigments. In this regard it is important to recall that melatonin was discovered in 1958 by the dermatologist Lerner as the skin-lightening substance which influences the aggregation of the indole pigment melanin[8,9]. Since melatonin binds to microtubules and effects their assembly in several systems, it is reasonable that this indoleamine modulates cellular and intracellular movements[2] (Benitez-King and Csaba, this review). In general, melatonin would cause movements to a dark-adapted state; its absence in the light would allow these movements to be reversed[2,4,10] (Benitez-King, Csaba and Morita and Best, this review). By acting on microtubuli, melatonin could in principle not only regulate pigment granule aggregation, but also cell shape, development and division, axoplasmatic flow and secretion[2,4,10] (Benitez-King, this review).

This Multi-author Review focuses on the evolution of the physiological functions of melatonin and structurally related indoleamines at all levels of phylogeny and provides the reader with new challenging aspects and fascinating ideas about the important role of this tryptophan metabolite in unicellular organisms such as dinoflagellates, the most primitive eumetazoans: planarians, invertebrates such as insects, mollusces and crustaceans and lower and higher vertebrates such as lizards, birds and mammals[1,3,4,6,7,10,12,17]. I collected a set of articles which cover the broad spectrum of the comparative biology of melatonin[1,2,4–6,10,11,13,16–18]. The contributions feature those structures, processes and compounds which are involved in the generation and regulation of biological rhythms in the living world. I hope that this Multi-author Review will contribute to our understanding of how organisms perceive, differentiate and integrate environmental information. It is explained in detail how melatonin entrains circadian and seasonal rhythms, enables organisms to anticipate environmental changes and acts as an internal zeitgeber and an endogenous biochemical correlate of darkness[1,3,6,10,11,14,17] (Binkley, Hardeland, Morita and Best, Reiter, Vivien-Roels and Pevet, this review). The important role of this indoleamine is now generally recognized in chronobiology and medicine (Binkley, Hardeland, Morita and Best, Reiter, Vivien-Roels and Pevet, Waldhauser, Ehrhard and Foerster, this review). Since melatonin can trigger and synchronize many

physiological processes depending on the specific adaptation of the organism and its needs, this endogenous compound may, in general, act as a biological response modifier and adaptogen[5,17] (contributions to this Multi-author Review). The authors provided us with a comprehensive and lively picture of the current research on melatonin and structurally related bioactive indoleamines and I am sure that this review will strongly stimulate our efforts to explore the evolution of the functions of melatonin. The diversity of topics makes it very difficult to integrate all the exciting new aspects on melatonin's presence and effects in unicellulars, invertebrates and vertebrates into one single comprehensive concept. The pleiotropy of actions exerted by this unique molecule is obviously not limited to the transduction of photoperiodic information[6,17] (contributions to this Multi-author Review). To draw an ultimative conclusion on the functions of melatonin and structurally related tryptophan metabolites in organisms at different levels of phylogeny would be premature and presumptuous. However, all presentations raise many interesting questions, which when properly addressed, will soon lead to new, significant discoveries in this exciting field of comparative physiology.

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