Melatonin and Quality of Life

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Summary  There is substantial evidence that fragmented sleep, delayed sleep phase syndrome (DSPS), insomnia, and impaired daytime alertness are the result of disorders in brain functioning that are closely linked to disruptions in the regulation of circadian rhythms. In children suffering from neurodevelopmental disabilities, such as attention deficit hyperactivity disorder (ADHD) and epilepsy, sleep disturbance and behavioral problems are significant correlated symptoms. There is also evidence that by addressing these problems directly, significant improvements can be made in the quality of life (QOL) experienced by the affected individuals. Children with ADHD exhibit impairments in the circadian pacemaker as shown by studies confirming an associated delay in the peak melatonin output under dim light conditions. Therapy involving melatonin administration to these children not only improves their sleep onset and efficiency but also improves their health status and QOL. The QOL of young adults who suffer from DSPS is significantly impaired by the resulting symptoms of insomnia and tiredness. Treatment of DSPS patients with melatonin has been reported to improve QOL dimensions such as physical functioning, mental health, and emotional well-being, as well as social functioning and general health. In patients suffering from chronic fatigue syndrome, melatonin improved QOL by enhancing vitality and energy and by reducing pain perception and fatigue. Melatonin has also been demonstrated to improve the quality of sleep of elderly insomniacs. Strategically timed administration of melatonin is useful for reducing the symptoms of jet-lag in intercontinental travelers. Additionally, melatonin has been found to enhance the nighttime alertness of shift workers and to improve their sleep during the daytime. Melatonin has a promising role in cancer patients not only as an oncostatic drug but also in promoting their general physical health and well-being. Meditation, besides improving QOL, coincidentally enhances the secretion of melatonin from the pineal gland, thus suggesting that melatonin may be an important physical mediator of the meditation experience.

Keywords  Melatonin · attention deficit hyperactivity disorder · chronic fatigue syndrome · epilepsy · jet-lag · shift work · quality of life · cancer · meditation

Learning objectives:
- To understand how melatonin is linked to quality of life in normal physiology.
- To examine the association of melatonin dysregulation to various medical and mental disorders.
- To assess the potential application of melatonin to improve quality of life in various clinical conditions.

Introduction

Technological advancements such as rapid forms of transportation and the use of a 24-h lighting system have not only increased day to day comfort but have also created a number of health problems for modern man. For example, physical activity no longer needs to coincide with daylight hours and extends to the whole 24-h period (i.e. the “24-hour/7 days Society”). From an evolutionary perspective, this is an abrupt “environmental mutation.” In such conditions, the brain loses its capability to sense internal and external rhythms, as reflected by the increased incidence of sleep/wake cycle disorders. As a result, people around the world often suffer from sleep problems, tension, and anxiety and mood disorders.

The technological impact of modern life has increased mean life expectancy, which in turn has increased the size of the elderly population (over the age of 60). The increased number of elderly persons has also resulted in increased incidence of persons suffering from chronic insomnia, age-related
neurodegenerative disorders, such as Alzheimer’s disease (AD) or Parkinsonism, cancer, and cardiovascular disease (1–4). There is thus an urgent need to develop therapeutic agents that improve the quality of life (QOL) not only in young individuals who are forced to work both night and day or who undertake rapid travel across different time zones, but also in elderly persons who suffer from sleep disturbances, neurodegenerative disorders, or cancer. Inasmuch as melatonin is a neurohormone that is critically involved in the regulation of sleep and circadian rhythms generally, it has been suggested that this biological agent can make a significant contribution to public health (5–11).

In recent years, it has been increasingly recognized that children with neurodevelopmental disorders such as attention deficit hyperactivity disorder (ADHD) and epilepsy also suffer from behavioral problems and sleep disorders and that these difficulties may be due to disruptions in circadian rhythms. Several clinical studies have now shown that melatonin significantly improves the QOL in those children (12–18).

**Melatonin Biosynthesis and its Regulation**

Melatonin is primarily secreted by the pineal gland of all mammals, including humans. In addition, melatonin synthesis occurs in other organs and tissues such as the eye (19), the gastrointestinal tract (20), lymphocytes (21), and skin (22). Melatonin biosynthesis starts by the conversion of tryptophan to 5-hydroxytryptophan and then to 5-hydroxytryptamine (5-HT, serotonin). 5-HT is acetylated to form N-acetylserotonin by the rate-limiting enzyme arylalkylamine N-acetyltransferase. N-acetylserotonin is then converted into melatonin by the enzyme hydroxyindole-O-methyltransferase (HIOMT) (23).

Pineal melatonin synthesis has a circadian rhythm with a peak synthesis occurring during the night and followed by lower output levels during the day. This circadian rhythm in the secretion of pineal melatonin is generated by the central circadian pacemaker located in the suprachiasmatic nuclei (SCN) of the hypothalamus and is synchronized to a 24-h day–night cycle by environmental light acting through the retinohypothalamic tract (24). Special retinal ganglion cells containing melanopsin are involved as the photoreceptive elements in this pathway (25).

The melatonin rhythm normally develops in humans during the third to fourth month of life and reaches its highest amplitude at around 4–7 years of age (26, 27). Inasmuch as elderly individuals have lower melatonin levels than young individuals, the decline in melatonin production during old age may be a primary reason for the associated decline in sleep quality and changes of sleep/wake rhythm. Additionally, as evidence cited below suggests, reduced melatonin output may possibly be a contributing factor to the increased incidence of neurodegenerative diseases seen in the elderly (9, 28).

Circulating melatonin is metabolized mainly in the liver where it is first hydroxylated in the C6 position by cytochrome P450 monoxygenases (isoenzymes CYP1A2, and CYP1A1) and thereafter conjugated with sulfate to be excreted as 6-sulfatoxymelatonin (aMT6s) (29). Its clearance from the peripheral circulation is biphasic with half lives of about 3 and 45 min (30). Melatonin is also metabolized non-enzymatically in many cells and also extracellularly by free radicals and by few oxidants. For example, through this pathway, it is converted into cyclic 3-hydroxymelatonin by a direct scavenging of two hydroxyl radicals (24). In addition, melatonin is metabolized in the brain to form N1-acetyl-N2-formyl-5-methoxykynuramine (AFMK) and N1-acetyl-5-methoxykynuramine (AMK) (25), two compounds with important antioxidant properties (29).

**Melatonin Receptors**

Inasmuch as melatonin easily diffuses through biological membranes, it can influence processes in almost every cell in the body. Some of its effects are receptor-mediated while others are receptor-independent. Melatonin is involved in various physiological functions such as sleep propensity (31, 32), control of sleep/wake rhythm (33), blood pressure regulation (34, 35), immune function (36–38), circadian rhythm regulation (6, 39), retinal functions (19, 40), detoxification of free radicals (29, 41), control of tumor growth (42, 43), bone protection (44), and the regulation of bicarbonate secretion in the gastrointestinal tract (20).

Melatonin action involves interaction with specific receptors in the cell membrane (45), with nuclear receptors (46) and with intracellular proteins such as calmodulin (47), dihydronicotinamide riboside : quinone reductase 2 (48), or tubulin-associated proteins (49). In addition, melatonin is a potent antioxidant acting as a free radical scavenger as well as through induction of antioxidant enzymes, down-regulation of pro-oxidant enzymes, or stabilization of mitochondrial membranes (29, 41, 50).

Several major actions of melatonin are mediated by the membrane receptors MT1 and MT2 (45). They belong to the superfamily of G-protein-coupled receptors containing the typical seven transmembrane domains. These receptors are responsible for chronobiological effects at the SCN, the circadian pacemaker. MT2 mainly acts by inducing phase shifts and MT1 by suppressing neuronal firing activity in the SCN. MT1 and MT2 are also expressed in peripheral organs and cells and contribute, for example to several immunological actions or to vasomotor control (45).

A third binding site, initially described as MT3, has now been characterized as the enzyme quinone reductase 2 (51). Quinone reductases participate in the protection against oxidative stress by preventing electron transfer reactions of quinones (52). Melatonin also binds to nuclear receptors of the retinoic acid receptor family, RORα1, RORα2, and RZRβ.