Journal of Psychosomatic Research 86 (2016) 20–27

Contents lists available at ScienceDirect

Journal of Psychosomatic Research

Review article

Physiological melatonin levels in healthy older people: A systematic review

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ARTICLE INFO

Article history:
Received 29 October 2015
Received in revised form 21 April 2016
Accepted 9 May 2016

Key words:
Melatonin
Aged
Ageing
Elderly
Circadian rhythm
Pineal gland

ABSTRACT

Objective: Melatonin plays a major role in maintaining circadian rhythm. Previous studies showed that its secretion pattern and levels could be disturbed in persons with dementia, psychiatric disorders, sleep disorders or with cancer. Also ageing is a factor that could alter melatonin levels, although previous research provides contradicting results. As melatonin supplementation is increasingly applied in older persons as sleep medication, it is important to know if melatonin levels decrease in healthy ageing and/or secretion patterns change. The objective of this study is to determine physiological levels and secretion patterns of melatonin in healthy older people.
Methods: We performed a systematic review and searched PubMed and Embase for studies published between January 1st 1980 and October 5th 2015 that measured melatonin in healthy persons aged ≥65 years.
Results: Nineteen studies were retrieved. The number of participants ranged from 5 to 60 per study. Melatonin was mostly measured by radioimmunoassay (RIA) and the number of measurements per 24 hours varied from 1 to 96. Sixteen studies showed a secretion pattern with a clear peak concentration, mostly at 0200 h or 0300 h. Maximum concentrations varied greatly from 11.2 to 91.3 pg ml^{-1}. Maximum melatonin level in studies with participants mean aged 65–70 years was 49.3 pg ml^{-1} and in studies with participants mean aged ≥75 years 27.8 pg ml^{-1}, p-value <0.001.
Conclusion: Total melatonin production in 24 hours seems not to change in healthy ageing, but the maximal nocturnal peak concentration of melatonin might decline. It is important to take this into account when prescribing melatonin supplementation to older people.

1. Introduction

Melatonin or *N*-acetyl-5-methoxytryptamine is a hormone mainly produced in the pineal gland. It is synthesized from the essential amino acid tryptophan via serotonin into melatonin. Melatonin production is regulated by the suprachiasmatic nucleus (SCN) under the influence of darkness and has a distinct daily pattern. Melatonin plays a major role in maintaining circadian rhythm and sleep. It also has other functions like regulating parts of the immune system, gene expression, body temperature and it has also anti-oxidative properties. Melatonin binds to receptors of the M1 and M2 type that can be found in the retinae and in the brain but also in the heart, gut, lymphocytes and liver [1–4].

During the evening plasma melatonin levels increase until the maximum concentration is reached, usually between 0100 h and 0400 h. Afterwards, melatonin levels decrease again and are nearly undetectable during the day. In diverse conditions alterations in melatonin concentrations have been described. Bartsch, Lissoni and Mazzoccoli [5–10] investigated melatonin concentrations in breast, lung and prostate cancer patients and compared the levels in different stages of disease. They found a relationship between the stage of disease and the peak melatonin concentration, which decreased in advanced cancer, and appeared to be lower than in healthy persons. In psychiatric disorders like schizophrenia and depression night time melatonin levels were shown to be lower than in healthy subjects [11,12]. In persons with sleep disturbances, differences in timing of melatonin onset were found [13–16]. Post-operative melatonin levels also tend to decrease [17].

During lifetime melatonin levels change as well. In young children nocturnal melatonin levels are the highest, approximately 325 pg ml^{-1}, and these decline gradually [1]. In older persons melatonin peak concentrations and total melatonin production could reduce, [18,19] although a great interindividual variability exists [20]. It is hypothesized that a lower

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http://dx.doi.org/10.1016/j.jpsychores.2016.05.005
0022-3999/

melatonin concentration makes older people more vulnerable for circadian rhythm disturbances like sleep disorders and delirium [21,22]. Higher melatonin levels are suggested to play a major positive role in healthy ageing and longevity [23,24].

So far, melatonin is particularly measured in unhealthy subjects and not much is known about the concentrations in the general population, especially not in healthy older people. In order to gain a better insight in physiological levels, we performed a systematic review to search for studies that measured serum or plasma melatonin levels in healthy older people. More specifically, our objectives were:

1. To determine the maximum level of plasma or serum melatonin in older persons.
2. To determine the time of reaching the maximum plasma or serum melatonin concentration in older persons.
3. To assess the influence of increasing age on (maximum) melatonin levels, the time of reaching the maximum level, and total melatonin production in twenty four hours.

2. Methods

2.1. Search strategy

We performed a systematic literature search in PubMed(Medline) and Embase and searched for studies describing persons mean aged 65 years and older in whom melatonin levels were determined and were published between January 1st 1980 and October 5th 2015. We used a search strategy combining search terms on melatonin and older age (see appendix A). We manually checked all reference lists of the selected articles for eligible articles and retrieved these as well.

2.2. Selection procedure

Based on title and abstract we included all articles that mentioned melatonin levels in healthy older persons. In case of an interventional study, we only included the control group. We excluded case reports, reviews, comments and guidelines. Furthermore publications on melatonin concentrations measured in other material than blood were excluded (e.g. urine, saliva, cerebrospinal fluid). We excluded research done in the Arctic's and light experiments. All retrieved articles were assessed independently by two authors (RS and MK).

2.3. Data extraction

Every outcome of serum or plasma melatonin concentration or rhythm measured in healthy older people was noted. In case of publications in which results were shown in a graphic, we first attempted to retrieve the numerical data directly from the author(s). If we were unable to receive numerical data we increased the picture of the graphic by computer to measure the melatonin concentrations as precise as possible. We converted all units into pg ml^{-1}, in order to make melatonin levels comparable.

2.4. Analyses

We used the mean levels reported in the articles or obtained from the authors as individual measurements were usually not reported or provided. With these mean levels we calculated a weighted mean value for each time point according to the sample size of the included study. The time of reaching the maximum melatonin levels was determined. We considered the secretion pattern as unchanged or physiological as the maximum concentration was reached between 0100 h and 0400 h, if there was a clear peak concentration and if there was only one peak concentration per 24 hours.

Subsequently, we divided the retrieved studies equally into three age groups by mean age of the participants of the study, i.e. studies concerning participants mean aged 65–70, 70–75 and 75 years and older. We calculated weighted mean melatonin levels per group based on the sample size of each study for all time points and compared these with a Kruskal-Wallis test. Minimal, maximal and delta (Δ = maximal concentration – minimal concentration) melatonin levels were obtained. Furthermore, we calculated the area under the curve (AUC) for each group to assess total melatonin production per twenty four hours. We used a Kruskal Wallis test to assess if the maximum melatonin levels, time of reaching maximum levels, Δ melatonin levels and AUC per group differed. To assess the difference in maximal melatonin levels, Δ melatonin levels and AUC between groups we performed a Mann Whitney *U* test.

The level of significance for all analyses was set at a p-value <0.05. All analyses were performed with Statistical Package for the Social Sciences (SPSS) version 22.0. If a mean melatonin level is mentioned in this paper, this always is the weighted mean melatonin level.

2.5. Quality assessment

In order to evaluate the risk of bias, the quality of included studies was assessed with the Newcastle-Ottawa Scale (NOS) for observational studies. A score of 0–3 was considered low quality, 4–6 intermediate, and 7 or more high quality [25].

3. Results

3.1. Search results

The search terms yielded 1004 articles. One hundred and fifty-four duplicates were found and removed. Screening titles and abstracts resulted in 65 candidate articles for inclusion. Main reasons for exclusion were that the research was not performed in humans or in older persons, it were interventional studies without control group or in which exogenous melatonin was administered, it concerned light experiments, measurements were done in non-healthy subjects or melatonin concentrations were not measured in blood. After full text review 18 studies were included. The reference lists of the candidate articles were screened and 1 additional article was found. In total 19 studies were included [7,26–28,9,29–35,10,36–41]. Fig. 1 shows the flow diagram of the selection procedure.

3.2. Characteristics of the included studies

The total number of participants in the included studies was 361, ranging from 5 to 60 per study. (See Table 1) The description of the studied population of the included studies differed. Most studies used descriptions like 'healthy elderly', 'physically and psychiatrically normal' or 'no abnormalities in physical and biochemical evaluation'. Two studies included older men with benign prostate hyperplasia and two studies included older persons admitted for minor somatic diseases. Because these four studies excluded participants with conditions or use of drugs that could possibly influence melatonin levels, we considered these healthy as well. We included 18 observational studies (mostly case-controlled studies) and one cross over study. The studies were performed for various reasons like sleep disturbances, the influence of ageing on hormone production, research at Alzheimer's disease or in cancer. The number of measurements per twenty-four hours varied from 1 to 96. Thirteen studies collected serum and six studies plasma. Melatonin was mostly measured by radioimmunoassay (RIA). (See Table 2).

Two studies were conducted in summer, two in winter, two in autumn, two collected blood samples in autumn and in winter, four throughout the year, and seven did not mention the season. In studies that did mention the season, no clear relation was found with the level of melatonin. Ten studies were performed in Europe, of which four were conducted in Italy, six were performed in Japan, one in