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Changes in Melatonin Concentration Depending on the Severity of Chronic Cerebral Ischemia and Seasonality

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ABSTRACT

Chronic cerebral ischemia (CCI) accounts for almost 2/3 of cerebrovascular diseases and causes cognitive impairment. Melatonin deficiency also causes the development of cerebral disorders due to the deterioration of cerebral circulation due to atherosclerotic damage to cerebral vessels and degenerative processes of nervous tissue. In our article, we studied the changes in melatonin concentration depending on the severity of chronic cerebral ischemia and seasonality. 80 patients with CCI were examined. The mean age of the patients was 57.8±11.4 years. Patients were divided into 3 groups depending on the stage of CCI disease and the date of collecting blood serum. It is determined that as the stage of the disease increases, the concentration of melatonin in patients decreases. The lowest concentration was in summer, and the highest concentration was determined in winter.

Keywords: seasonality, chronic cerebral ischemia, melatonin.

INTRODUCTION

«Chronobiotics» are defined as drugs that exhibit the ability to synchronize or increase the amplitude of circadian rhythms, of which melatonin is a prototype [1,6].

The light-dark changes in melatonin synthesis define the essential role of melatonin as a chronobiological substance [7].

Melatonin «opens the door to sleep» by suppressing the arousal tendency originating from the suprachiasmatic nucleus (SCN) in the late evening [12,13].

Melatonin, on the other hand, is the chemical code for darkness and is important information for the neuroendocrine system [15].

Although melatonin in mammals is primarily produced by the pineal gland [8], it is also synthesized within various cells, tissues, and organs [3,16].

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Extensive research has indicated that melatonin is generated in all animal cells containing mitochondria [18,21].

Its multifaceted role includes the removal of harmful free radicals and the facilitation of immune response regulation, ultimately promoting cellular protection [9].

Melatonin is not only generated and metabolized in the mitochondria, but it was recently claimed that the neuroprotective effects of melatonin on the brain injury induced by ischemia/reperfusion were mediated by MT1 receptors located in the mitochondria but not in the membrane [20].

This is remarkable because a GPCR (G-protein coupled receptor) like the MT1 is known as a cell-surface receptor that transmits extracellular signals into the cell.

Melatonin, an amphiphilic substance, can penetrate cell membranes. In the cytoplasm, melatonin interacts with calmodulin and tubulin [11].

Melatonin also enters the cell nucleus where the receptor sites were supposed to belong to the orphan receptor superfamily RZR/ROR [9].

However, RZR/ROR demonstrably does not bind melatonin. Rather, melatonin may act indirectly via this transcription factor, e.g., by affecting the circadian accessory oscillator component RORα through sirtuin-1 (SIRT-1) activation [10].

The cytoprotective activity of melatonin exceeds that mediated via receptors. The amounts of melatonin found in almost every cell are much higher than those in circulation [2].

Although the capacity of mitochondria to synthesise melatonin is confirmed, intracellular melatonin does not get the extracellular space. Indeed, the doses of melatonin needed to change intracellular melatonin concentration are much higher than those employed as a chronobiotic [22, 19].

It is known that with age the pineal gland, like the thymus, undergoes involution. The number of active secretory elements of the gland (pinealocytes) decreases with limited production of melatonin. In older people, compared to adolescents, melatonin production is reduced by half. At the same time, the amplitude and dynamics of daily melatonin secretion change in older people [24].

According to the literature, pineal melatonin is actively involved in maintaining normal functioning of the brain and cardiovascular system, due to its immunomodulatory properties it optimizes the immune status, limits tumours, etc. Ageing and weakening of epiphyseal activity appear to be closely related to cause and effect. Changes in the functioning of the pineal gland are not only the result of the progression of complex systemic disorders in the body, but also themselves serve as a probable source of a number of disorders characteristic of old age with damage to the brain, internal organs, immune system, development of cancer, etc. [5,14,17].

Today it becomes obvious that, among other things, melatonin deficiency also causes the development of cerebral disorders due to deterioration of cerebral circulation due to atherosclerotic damage to cerebral vessels and degenerative processes of nervous tissue. At the same time, the physiological weakening of the secretory processes of the pineal gland is obviously responsible both for the formation of the pathology itself and for the symptoms that arise on its basis. Epiphyseal insufficiency as a pathogenetic factor in the age-related deterioration of cerebrovascular hemodynamics can be determined by a weakening of the antioxidant, neuroregenerative, antitoxic, immunotropic and several melatonin properties described below, on which its protection from other types of cerebral vascular pathology is based. As for the consequences of circulatory disorders, they also manifest themselves in monotonous symptoms, primarily in the form of deterioration in the cognitive activity of the brain (disorders of memory, perception, attention), chronobiological defects in the form of insomnia, and somatic disorders [23,4].

Considering the above, it seems relevant to study the level of melatonin depending on the severity of chronic cerebral ischemia.

The purpose of the study is to identify the level of melatonin depending on the severity of chronic cerebral ischemia.

MATERIALS AND METHODS

80 patients with CCI were examined. The average age was 58.3±12.1 years, for women – 57.8±11.1 years, for men – 59.7±13.6 years.

The diagnosis of CCI in patients was confirmed based on clinical data and neuroimaging methods. In all patients, blood was drawn to study the concentration of melatonin at 22:00, followed by a blood test in the laboratory of Shox International Hospital, using the enzyme-linked immunosorbent (ELISA) assay to determine the serum melatonin concentration using a Mindray MR 96A machine.

The reference values for melatonin concentration in the blood were 180 pg/ml.

Statistical analysis of the results was carried out using parametric methods.

The obtained data are presented as relative values (%), as well as M±m.

To assess the difference in arithmetic means, a Student's t-test was used.

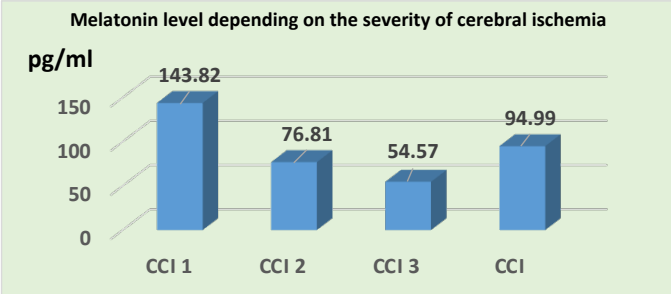
RESULTS

As a result of the studies, as can be seen from Table 1, we obtained the following data: the average values of melatonin levels in the blood in patients with CCI were 2-2.5 times lower than the reference values in healthy young people. This confirms the fact that melatonin levels decrease with age. In addition, when analyzing melatonin level indicators depending on the severity of CCI, a decrease in its level was revealed.

Table 1.
Melatonin level depending on the severity of cerebral ischemia

Group	n	Serum melatonin, pg/ml
CCI **1**	32	143.82±74.9
CCI **2**	17	76.81±60.9
CCI **3**	31	54.57±28.9
All patients	80	94.99±65.4

Figure 1. Serum melatonin in patients with CCI depending on the severity of cerebral ischemia



Next, we analyzed seasonal fluctuations in melatonin levels in patients with cerebral ischemia. Studies have shown that the lowest levels of melatonin in patients are observed in the summer months, i.e., during the season with predominant daylight.

As the duration of the daylight hours decreased - from summer to winter - the concentration of melatonin in patients increased, reaching a maximum in winter. And from the transition from winter to summer – i.e. with an increase in the duration of the daylight period, a decrease in the concentration of melatonin in the blood of patients was detected (Fig. 2).

From our studies, we can conclude that melatonin concentrations in the blood are subject to seasonal changes in the duration of daylight.

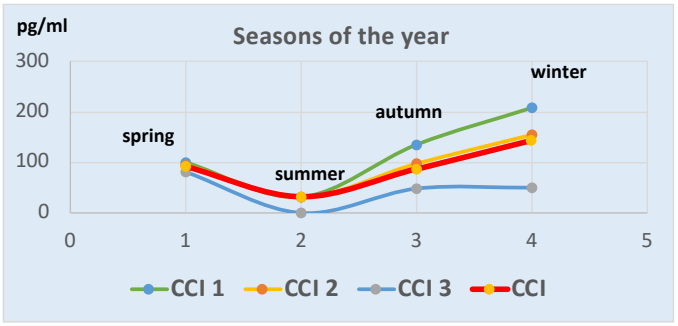


Figure 2. Seasons of the year and melatonin in patients with CCI

Thus, from our research we can draw the following conclusions:

1. The concentration of melatonin in the blood is subject to seasonal changes in the duration of daylight with maximum values in winter and minimum values in summer.

2. With increasing age, there is a decrease in the concentration of melatonin in the blood.

3. With an increase in the severity of cerebral ischemia, a decrease in the concentration of melatonin in the blood is observed.

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