Current View of the Problem: A New Approach to Covid-19 Treatment

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Abstract

Coronavirus infection COVID-19 (acronym for *Corona Virus Disease 2019*), formerly Coronavirus infection 2019-nCoV is a potentially severe acute respiratory infection caused by SARS-CoV-2. It is a dangerous disease that can take the form of an acute respiratory viral infection of the lung or a severe form, the specific complications of which may include viral pneumonia leading to acute respiratory distress syndrome or respiratory failure with a risk of death.

Keywords: *Melatonin, cell, production, infection, treatment*

Introduction

The disease is caused by a new virus, people have no acquired immunity to it, people of all age categories are susceptible to infection[1]. The virus is spread by airborne droplets through inhalation of sprayed droplets with the virus by coughing or sneezing, as well as through the virus getting on the surface and then getting into the eyes, nose or mouth. Effective preventive measures include frequent hand washing and observance of respiratory hygiene rules[2].

In about 15% of cases, the disease is severe with the need for oxygen therapy, and in 5% more patients are critical. Globally, as of 01 April, the mortality rate is estimated at around 5%. According to the analysis of data for 1099 patients as of February 28, 2020, 91.1% of patients with COVID-19 were diagnosed with pneumonia[3]. Figures may change over time.

On 11 March, the spread of the virus was declared a pandemic[4]. The epidemic is the first ever verifiable pandemic in human history[5]. It makes sense for Governments to prepare lists of trained personnel who can take control of the situation, as well as lists of medicines[6], personal protective equipment, supplies and equipment needed for treatment[7]. World Health Organization (WHO) encourages countries to train hospitals, protect health workers and decide whether some form of social distancing is necessary[8].

In response to the epidemic, the World Health Organization (WHO) has declared a public health emergency of international concern, and risks at the global level are assessed as very high[9]. The situation is developing rapidly, with a daily increase in the number of cases and deaths. Various scientific and clinical studies are being conducted[10].

The 2019-nCoV strain was first detected in December 2019 as a result of nucleic acid analysis in a patient with pneumonia[11].

Since the nucleic acid content is highest in the cell nucleus, it was named after the Latin word “nucleus” (“cell nucleus”, Latin).[12] However, nucleic acids are not only found in the nucleus, where they are definitely the most, but also in chloroplastics and mitochondria[13]. DNA and RNA nucleic acids are present in cells of all living organisms and perform the most important functions for storage, transfer and realization of hereditary information[14].

The coronavirus infection COVID-19 enters deeply into the cells to the level of the nucleus[15]. Once the virus (or its nucleic acid) penetrates the cell, the cell resources are switched to the synthesis of viral nucleic acid and proteins[16]. The genes are expressed. Gene expression is the process by which genetic information from a gene (DNA nucleotide sequence) is transformed into a functional product - RNA or protein.[17]

Some stages of gene expression can be regulated: transcription, translation, RNA splicing and the stage of posttranslational modification of proteins.[18] The process of activating gene expression in short double-stranded RNA is called RNA activation.[19]

When the cellular resources are exhausted, its shell is torn and ready viral particles are poured out of it.[20] This way, other cells are affected. Fibrous tissue is formed in the place of the bloated cell.[21]

Expression of genes is a substrate for evolutionary changes, as control over time; place and quantitative characteristics of the expression of one gene may have an impact on the functions of other genes in the body as a whole.[22] This is called a gene mutation. [22,23]

There are no specific antiviral treatments or prophylaxis against the disease yet. Since, to the level of the nucleus is not yet reached any antiviral drug.[24]

In most cases (about 80%), no specific treatment is required and recovery takes place on its own.[25] Severe forms of disease are more likely to develop in older people and in people with certain diseases, including asthma, diabetes and heart disease. In severe cases, means are used to maintain the functions of vital organs[26].

Today we want to tell you about melatonin, the "sleep hormone".

Melatonin is a hormone that is naturally secreted by our body and whose functions are crucial for our physical and mental well-being.[27] It is closely linked to the control of circadian rhythms, our biological clock, and thus helps us sleep better.[28]

Among other things, this substance is involved in neuroendocrine, neurophysiological and immune processes, which are necessary for many vital tasks of the body.[29] However, its production takes place only at night and, if something prevents it, a person has trouble sleeping and a good rest.[30]

Melatonin hormone was discovered in 1958 by A.B.Lerner. It is the main hormone of epiphysis - the organ that transmits information about the light regime of the environment into the internal environment of the body.[31] Changes in melatonin concentration have a noticeable daily rhythm - usually a high level of the hormone during the night and low levels during the day.[32] Maximum concentrations of melatonin in human blood are observed between midnight and 5 am local sunshine time. Melatonin is produced by the main secretory cells of epiphysis - pinealocytes.[33]

The biological half-life time of melatonin is 45 minutes. This means that for research purposes, blood samples must be collected at short intervals in order to determine the period of melatonin production.[34] In addition, a patient's sleep disturbance during the night in order to collect samples may affect the blood melatonin levels. These problems can be avoided by determining melatonin metabolite levels: melatonin sulfate (6-sulfatoxymelatonin) and 6-hydroxyglucuronide in urine. 80-90% of melatonin is secreted to the urine as melatonin sulfate. The concentration of melatonin sulfate in the urine correlates well with the total level of melatonin in the blood during the collection period. [35]

Melatonin synthesized in epiphysis enters the blood and cerebrospinal fluid, the liquor, through which it accumulates in the hypothalamus. In addition to blood and cerebrospinal fluid, melatonin is found in urine, saliva and amniotic fluid[36].

Melatonin is a rare example of a hormone that has both membrane and nuclear receptors[4].

In the human body melatonin is synthesized from the amino acid tryptophan, which is involved in the synthesis of neurotransmitter (neurotransmitter) serotonin, and it in turn turns into melatonin under the influence of the enzyme N-acetyltransferase.[38] Melatonin has been shown to be an indole derivative of serotonin and to be synthesized at night by the enzymes N-acetyltransferase and hydroxyindol-O-methyltransferase. About 30 μg of melatonin is synthesized in an adult during the day, its concentration in serum at night is 30 times higher than during the day, and the maximum concentration is about 2 hours of the night local sun time, on average for many observations.[39] Melatonin is transported by serum albumin, after liberation from albumin it binds to specific receptors on the membrane of target cells penetrates into the nucleus and there performs its action. Melatonin is quickly hydrolyzed in the liver and excreted with urine; the main metabolite is 6-hydroxymelatonin sulfate, the content of which allows to indirectly judging the production of melatonin epiphysis.[40]

The body also contains melatonin, which is formed outside the epiphysis. This discovery was made in 1974 by Russian scientists N.T. Reichlin and I.M. Kvetnoy, who discovered that melatonin is synthesized in cells of the worm-like intestinal process.[6] Then it turned

out that melatonin is also formed in other parts of the gastrointestinal tract, as well as in many other organs.

The secretion of melatonin is subject to the daily rhythm, which in turn determines the rhythmicity of gonadotropic effects and sexual function. Synthesis and secretion of melatonin depend on the illumination - excess light reduces its formation, and a decrease in illumination increases the synthesis and secretion of the hormone. In a person with a normal daily routine (sleep at night), melatonin accounts for approximately 70% of the daily production of melatonin. In clinical conditions, it has been established that sleep deprivation during night hours leads to a disturbance in the daily rhythm of melatonin production - production at night is reduced and approaches the daily level.[2,13]

Melatonin secretion rhythm shift also occurs when flying to other time zones.

Melatonin is also known as N-acetyl-5-methoxytryptamine and N-[2-(5-Methoxy-1H-indol-3-yl) ethyl] acetamide.

Melatonin production depends entirely on the biological clock of the human body and the change of the natural day-night cycle. Since melatonin production depends on the length of the daylight, many animals use it as a «seasonal clock». People, like animals, have *less melatonin in summer than in winter*.

So, melatonin can regulate the functions that depend on the photoperiod - reproduction, migration behavior, seasonal molting. In bird and mammal species that breed at long bottoms, melatonin suppresses gonadotropin secretion and reduces sexual activity. In animals that breed at a short light day, melatonin stimulates sexual activity. The effect of melatonin on reproductive function in humans has not been sufficiently studied. During puberty the peak (night) concentration of melatonin decreases sharply. In winter the number of menstrual cycles not ending in ovulation is on average higher than in summer. In women with pituitary amenorrhea the concentration of melatonin is reliably higher than in healthy women. These data suggest that melatonin suppresses reproductive functions in women.

Melatonin is a solid, absorbing or dissolving fat, a water-soluble substance that is a powerful *natural antioxidant*. By synthesizing it, the body is protected from the excessive formation of free radicals - metabolic products that cause rapid aging and cancer.

Melatonin has a unique ability, unlike other antioxidants, to penetrate into any cell in any part of the body and have a specific protective effect on the nucleus - the central structure of the cell containing DNA, i.e. the structure that *allows the damaged cell to recover*. Melatonin is known to have a stimulating effect on the enzyme glutathionoperoxidase, which has antioxidant properties. Melatonin may also exist in a synthetic form, which is used as an additive with sleeping pills and antioxidant properties. This becomes relevant with age when the activity of the body's internal secretion glands dies out.

Antioxidant Effect: Melatonin neutralizes the damaging effects of oxidation processes, which are the main cause of skin aging and ageing. The most important function of melatonin is its antioxidant activity, which manifests itself everywhere in the body, as melatonin penetrates all organs and tissues. The mechanism of antioxidant action is manifested in the fact that melatonin has a pronounced ability to bind free radicals, including those formed by the lipid peroxidation of hydroxyl radicals, and exogenous carcinogens, and it activates glutathione peroxidase - a factor in protecting the body from free-radical damage. The main functions of melatonin's antioxidant action are aimed at *protecting DNA*. To a lesser extent, it protects proteins and lipids.

Melatonin is the strongest known endogenous free radical absorbers. In recent years, there has been evidence that melatonin can be found not only in plasma, but also in the nuclei of cells and protect the nucleus macromolecules from oxidative damage in all subcellular structures.

Immune stimulating effect: An important consequence of long-term stress is stress immunodeficiency. Melatonin helps to normalize immunological indicators.

Melatonin and other epiphyseal hormones may be classified as geroprotective. A connection has been established between the degree of age-related epiphysis involution and tissue shriveling. It is known that in aging the degree of immunological protection decreases, and melatonin, as has been repeatedly stated, has immunomodulatory activity. With age, the concentration of melatonin in human blood decreases. When its level decreases below 20% of the norm, the leukocytes stop recognizing parasites in the blood and viruses, the infection of the organism starts.

Melatonin stimulates the immune system (immunostimulant) as it participates in the regulation of thymus and thyroid function, increasing the activity of T-cells and phagocytes, which is a warning for a number of diseases and, as laboratory studies show, slows down the growth of seven types of cancer cells, including breast and prostate cancer cells.

Lack of melatonin in the body: Experiments on laboratory animals showed that with melatonin deficiency caused by the removal of receptors, animals began to age faster: earlier menopause began, free radical cell damage accumulated, insulin sensitivity decreased, obesity and cancer developed.

Melatonin extrapine synthesis: The amount of hormone that is produced in the pineal gland is not enough to provide so many biological effects of melatonin. Studies have shown that significant amounts of melatonin are found in the blood of experimental animals after pineal gland removal. It is now firmly established that the pineal gland is not a monopolistic organ of melatonin production. Extrapineal sources of melatonin synthesis are enterochromaffin cells of gastrointestinal tract (EC-cells), main serotonin depot cells (contain up to 95% of all endogenous serotonin) - melatonin precursor. This hormone has been synthesized in a large number of neuroendocrine cells of airways, lungs, in the cortical layer of kidneys and along the border between the cortical and cerebral adrenal layer, under the hepatic capsule, in paraganglia, ovaries, endometrium, prostate, placenta, gallbladder and inner ear. Melatonin synthesis has also been found in non-endocrine cells such as fat cells, lymphocytes, platelets, eosinophilic leukocytes, in the thymus, pancreas, cerebellum, eye retina and in some endothelial cells.

Functionally, many cells producing melatonin belong to the so-called diffuse neuroendocrine system - a universal system of adaptation and maintenance of homeostasis in the body.

Within this system there are two melatonin links in the producing cells:

- Central (includes the pineal gland and visual system cells), where the rhythm of melatonin secretion coincides with the rhythm of "light-dark";
- Peripheral - all other cells where the secretion of the hormone does not depend on light.

With age, the activity of epiphysis decreases, so the amount of melatonin decreases, sleep becomes superficial and restless, sleeplessness is possible.

Symptoms of melatonin deficiency

- Insomnia and other sleep disorders
- Violation of sleep and waking cycles
- Weakening the immune system
- Fluctuations in blood pressure
- Disorders of mental adjustment
- Anxiety and depression conditions

The main causes of disturbance of natural melatonin production:

- Disturbances in sleep and waking,
- Regular consumption of alcohol and nicotine
- Unbalanced nutrition
- Natural decrease in melatonin production with age
- Shift schedule, night shifts
- Sleeping in an illuminated room

Aspirin, beta-blockers can reduce melatonin levels in the body. Sedative antidepressants, tranquilizers and other sedatives may reduce the expected effect.

Returning to the beginning, almost all bats (as well as winged bats in general) lead nightlife and sleep during the day. In addition, bats often take shelter in cracks in trees, rocks or cracks in buildings. Sanctuaries can be caverns in trees, caves, grottoes and various artificial structures, both aboveground and underground. Bats are able to fall into a daze, accompanied by reduced metabolic rate, breathing intensity and heart rate; many can fall into prolonged seasonal hibernation (up to 8 months). Retinol and tocopherol levels in bats have been found to be high enough to withstand the absence of bonded antioxidants for a long time while maintaining the reserves required for reproduction.

Bats are a natural reservoir of rabies and, according to the WHO, Marburg, Ebola and coronavirus viruses are among the most dangerous infections, a list of the most dangerous known pathogens for humans that cause fatal diseases. There is evidence of the involvement of bats in transmission.

Conclusions

1. Melatonin production decreases with age, which may adversely affect the clinical course of coronavirus infection COVID-19.
2. Unhealthy lifestyle reduces melatonin production.
3. Medicines reduce melatonin levels.
4. Melatonin makes bats not die, but become carriers of infection.
5. The number of coronavirus infected during the summer months may increase by lengthening the daylight hours. Excess light reduces melatonin formation.

Recommendations: The usage of Melatonin in the treatment of patients with coronavirus COVID19 may have a beneficial effect on the outcome and outcome of treatment. Thus, Exogenous Melatonin activates killer cells and monocytes in both bone marrow and spleen with a latency period of 7-14 days. These are components of nonspecific immune protection; some authors believe that melatonin can block tumor growth and destroy infected cells. Melatonin has been found to stimulate the synthesis and release of opioid peptides and thus participate in the regulation of cell hemopoiesis and humoral immunity. The introduction of melatonin in vaccination potentiates the production of specific antibodies. It is known that under stressful and significant physical activity there is an activation of pro-inflammatory factors (cytokines and eicosanoids), the level of alpha tumor necrosis factor (TNF-α) increases, and the level of lymphocytes in blood increases. Lipopolysaccharides (LPS) potentiate these effects - a situation that can occur under inadequate, draining the body's defenses physical activity. At the same time, there are increasing manifestations of oxidative stress, which leads to the violation of the integrity of the hemato-intestinal barrier and LPS in the blood. The fact that melatonin suppresses the inflammatory reaction in response to physical activity should be taken into account in the preparation of athletes and recovery activities in people engaged in hard physical work. Due to its antioxidant and anti-inflammatory properties, melatonin can reduce stomach mucosa damage caused by many damaging factors: stress, alcohol, bile and non-steroidal anti-inflammatory drugs.

Activation of macrophages in pathological conditions leads to an increase in nitric oxide (NO) production. This process is not indifferent to the body and can lead to the development of degenerative diseases. Melatonin inhibits these changes by inhibiting the expression of inducible macrophage NO-synthesis. The introduction of pharmacological doses of melatonin prevented the development of damage in vivo, and inhibited peroxidation and induction of NO in cell culture of the large intestine.

Thanks to intensive research in recent years, there have been reports of the successful use of melatonin in bacterial meningitis as a protection for brain neurons from damage, to normalize sleep and general condition in attention and hyperactivity disorder, in sleep phase disorders syndrome, migraine and headache attacks, in complex therapy of multiple sclerosis, chronic fatigue syndrome, bronchial asthma night attacks, fibromyalgia, irritable colon syndrome, respiratory distress of newborn syndrome.

Nevertheless, the research of the chemical and biological properties of melatonin allows its wide application in medical practice, as experimental data confirm its positive effect on the course of both physiological processes and leveling of many pathological conditions.

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