Commentary

Melatonin: Its expanding universe

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ABSTRACT

Dr. Russel J. Reiter was awarded his fifth honorary title by the National University of Cuyo, Argentina, for his exemplary contributions towards unraveling the mysteries of the pineal gland and, importantly, its major secretory product, melatonin. This commentary provides a glimpse of his accomplishments and a summary of his speech during the ceremony.

Key words: Russel J. Reiter, National University of Cuyo, Doctor Honoris Causa, melatonin, antioxidant, mitochondria

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The prestigious National University of Cuyo of the Argentine Republic awarded Prof. Russel J. Reiter his fifth honorary title, “Doctor Honoris Causa”. At the ceremony, Prof. Reiter, a pioneer in the dissemination of science worldwide, was distinguished and received the diploma and the corresponding resolution from the rector, Esther Sánchez (Figure 1). The Dean of the Faculty of Medical Sciences, Roberto Miatello, presented him with the medal, and the Secretary for Research, International and Graduate Studies, Teresa Damiani, presented him with the book "Guanacache" by Roig Matóns, painter of the desert.

Prof. Reiter received a Bachelor of Biology from St. John's University in 1959, a Master’s degree in Anatomy in 1961, and a PhD in Anatomy in 1964 (specialty in Endocrinology) from the Bowman Gray School of Medicine. Prof. Reiter's scientific career, spanning almost 60 years since his first publication on melatonin in 1965, was initially focused on the pineal gland, that led him to discover the multiple actions of melatonin. In this sense, he made numerous contributions to pineal gland research, including the discovery of the gland's role in regulating the circadian rhythm and the broad spectrum of the effects of melatonin on humans and other organisms, such as its role in regulating reproductive physiology and seasonal breeding in rodents including Syrian hamsters (1, 2), as well as its effects on the function of the immune system.

The collaborations between Prof. Reiter and the National University of Cuyo began in 2018 through the Translational Pharmacology Laboratory of the Faculty of Medical

Sciences and IMBECU-CONICET and the Department of Cell Systems and Anatomy, UT Health San Antonio Long School of Medicine, where studies focused on the cardiovascular protective effects of melatonin and vitamin D. As a collaborative result between both institutions, scientific papers were published in high-impact international journals. He also participated as a keynote speaker in a scientific meeting chaired by Walter Manucha, professor and researcher at the University and CONICET, with the aim of training on topics of common interest to both institutions and also on new therapeutics for SARS-CoV-2. He has had a clear and fruitful association with the National University of Cuyo, having collaborated especially with scientific groups from the Faculty of Medical Sciences of the educational institution.

Fig. 1. Dr. Russel Reiter (right) receiving the "Doctor Honoris Causa" diploma from Esther Sánchez (left), the rector of the National University of Cuyo, Argentina.

At the close of the brilliant ceremony, Prof. Reiter highlighted the current state of knowledge on melatonin with his keynote address, summarized below:

"Melatonin is an ancient molecule that has existed for an estimated 2.5 billion years and was developed in prokaryotic organisms. Another exciting aspect about melatonin is that its structure has been conserved throughout its evolution (3). There are relatively few such molecules. Moreover, melatonin is not a toxic molecule over a vast range of doses, being safe and beneficial for cardiovascular, nervous, and many other systems. There is not a single organ in the body that has not benefited from its availability.

Melatonin was discovered by Dr Aaron B. Lerner at Yale University, who was investigating the lack of pigmentation of skin, a condition called vitiligo. He spent 10 years finally isolating a small amount of white powder, which he identified as melatonin, never realizing the phenomenal actions of this molecule (4). He was unaware of what is now commonly known: the blood levels of melatonin are significantly higher at night as compared to their levels during the day (5).

Everything we now know about melatonin suggests that the more we have of this molecule, the better. To preserve our nighttime levels of melatonin, we should avoid light. Light at night suppresses the melatonin rhythm and deprives the organism of this essential molecule. Light pollution, existent in all the cities in the world, is affecting people's health. When Thomas Edison invented artificial light (the light bulb) in 1879, he said: "The good thing about light is that there are no pathologies associated with it". However, we now know that many pathologies are associated with light, not only for humans but

for plants and animals (5). In many primitive amphibians, the pineal gland is directly sensitive, but in mammals, the eyes perceive light and regulate the pineal gland. The connection between our eyes and the pineal gland is well known. The exciting thing is that pineal melatonin is unrelated to the rods and cones, which have a vital role in vision. Light perception by the pineal gland is by a small number of ganglion cells that contain one photo pigment called melanopsin. This photo pigment responds to a specific wavelength of light, namely blue light. Only the blue wavelength on the visual spectrum can inhibit pineal melatonin secretion. The problem is that white light contains blue wavelengths. Therefore, if you turn on the light at night, the pineal gland immediately ceases melatonin release. Hence, light should never be turned on at night, and people should have much more darkness than what we see today (6).

Melatonin is, by far, the best antioxidant available. Other antioxidants (vitamins E, C, etc.) are not comparable with melatonin. When the first primitive eukaryotic organisms appeared, they engulfed bacteria as food. Eventually, this became a symbiotic relationship: bacteria were beneficial for the cells, and vice versa. These bacteria became integrated into our cells as mitochondria, which were already producing melatonin. Because of that, mitochondria present in all human cells produce melatonin. Thus, we have two sources of melatonin: the pineal gland and the mitochondria. The total amount of melatonin synthesized by the pineal gland is miniscule as compared to the total weight of an adult human. However, pineal melatonin exhibits a rhythm that determines the circadian cycle because it is released into the blood and cerebrospinal fluid. Therefore, it provides the body with an understanding of the time of day and seasonal information as a chemical message (7). Together, melatonin rhythm in the pineal gland is both a clock and a calendar but represents a tiny portion of the melatonin produced in the body.

Melatonin produced by mitochondria is not released into the blood but is used by each individual cell for its survival. This is extremely important because oxygen, while necessary to live, also produces free radicals, thereby damaging and ultimately destroying the cell. Aging is believed to be partly due to the accumulation of all the damage accumulated by cells in every organ when using oxygen for producing energy. Multiple diseases are associated with free radical-indued damage, such as atherosclerosis, macular degeneration, Alzheimer's disease, and Parkinson's disease (8). Thus, while mitochondria are critical for a cell as its energy powerhouse, this organelle is also the site of production of many free radicals (9). In this context, melatonin is a potent and superior scavenger of these free radicals, while also participating in multiple protective systemic and cellular mechanisms such as autophagy, apoptosis, epigenetics, mitochondrial physiology, extracellular matrix maintenance, metabolism, circadian rhythms, as well as many aspects related to the gastrointestinal tract, immune system, cancer, cardiovascular system, among others (10).

Melatonin is not unique to animals. It is also found in plants (chloroplasts are plant cell analogues of mitochondria) (11, 12). For example, melatonin participates in several plant processes, such as root development and growth, seed germination, flowering, leaf senescence and movement, and prevention of several bacterial and fungal infections. Thus, melatonin is a truly ubiquitous and multifunctional molecule (13).

Unfortunately, synthesis of melatonin is considerably reduced with aging, placing older individuals in a vulnerable state as they lose their best protection against aging. Therefore, it is essential to consume melatonin during aging, as an effective way to protect human health (14)."

Dr. Reiter's work has had a profound impact on the understanding of human health and well-being, and his legacy will continue to shape the field of pineal gland and melatonin research for years to come.

AUTHORSHIP

All authors contributed towards writing of this editorial. All authors have read and approved the final version of the manuscript.

CONFLICT OF INTEREST

The authors report no conflicts of interest.

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