Review

Transient responses of melatonin to stress

Scott Zimmerman*[1] and Russel J. Reiter[2]

[1]Silas Inc., Basking Ridge, New Jersey, 07920, USA
[2]Department of Cell Systems and Anatomy, UT Health Science Center at San Antonio, Texas, 78229 USA
* Correspondence: scott.zimmerman@silas.tech; Tel: +01-9732707414

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ABSTRACT

Melatonin and its metabolites are ubiquitous antioxidants that are produced in response to reactive oxygen species (ROS) in virtually all cells of the body. The highest reported melatonin values in plasma and sweat occur during heavy exercise both indoors and outdoors during the day. The advent of sweat biosensors with sufficient melatonin sensitivity provides pseudo real-time evidence that melatonin is produced throughout the body not just in the pineal gland. The role of the pineal gland appears to be to provide cyclic production of melatonin for the regulation of circadian rhythms as well as supplemental melatonin during periods of low cellular activity. Melatonin from the pineal gland represents only a small fraction of the body's production capacity. Greater than 5 pg/ml min ramp rates for plasma and sweat melatonin have been reported during strenuous exercise in sunlight as compared to 0.15 pg/ml min ramp rates for plasma melatonin under dim light melatonin onset (DLMO) conditions. Sunlight and exercise, like fever, generates transient elevated levels of ROS in tissues with time constants measured in minutes or even seconds making this systemic antioxidant response potentially protective. Based on a simple accounting of ROS generated by sunlight, ROS we breathe, ROS we drink, and exercise, it appears that the body maintains a heightened basal level of ROS as part of its pathogen defense mechanisms. Current human lifestyles and modern enclosed spaces have substantially eliminated over 90% of the ROS which undermines one of the body's primary defenses. With advanced age, the inability to maintain this protective barrier appears to make us more susceptible to disease.

Key words: extrapineal, melatonin, exercise, reactive oxygen species, biosensors, transient response

1. INTRODUCTION

The body has adapted to survive over 30,000 day/night cycles ranging from up to 30 megajoules (MJ) during the day to a few kilojoules (KJ) at night. Sunlight and the reactive oxygen species (ROS) create both exogenous and endogenous sources of ROS in the body that can fluctuate in a matter of seconds as humans move about. The advent of sweat biosensors allows for pseudo real-

time measurements of biomarkers like melatonin. The observed rate of change in melatonin levels during heavy exercise calls into question the role of the pineal melatonin beyond its circadian effects.

As we discussed in a previous publication (1), sunlight elevates ROS levels in the body which we believe in turn activates a host of the antioxidant defenses such as melatonin, T-cells, blood flow, and natural killer cells. Melatonin provides an excellent biomarker for elevated ROS levels with the highest concentration levels occurring during intense exercise both indoors and outdoors as shown in Figure 1 using data published by Zhu (2). The loss of antioxidant protection in advanced age relates to the marked drop in endogenous melatonin level that persistently occurs throughout life (3, 4) (Figure 2).

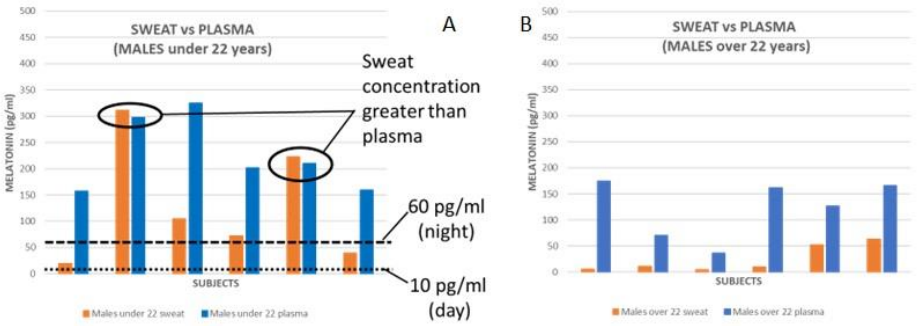

Fig. 1. Effects of intense exercise and aging on male athletes' melatonin production.
A. A comparison of sweat and plasma melatonin levels in six young male test athletes during heavy exercise in artificial lighting indoors and sunlight outdoors. (orange- sweat, blue-plasma) Sweat and plasma measurements were taken for each of the six male subjects under 22 in this study. Both sweat and plasma levels were up to five times higher than typical pineal generated plasma melatonin levels at night. Sweat melatonin levels in some individuals exceeded plasma melatonin levels. B. A comparison of sweat and plasma melatonin levels for the six older male athletes in the study during heavy exercise. Both sweat and plasma melatonin levels are significantly reduced in older athletes despite similar sweat volume.

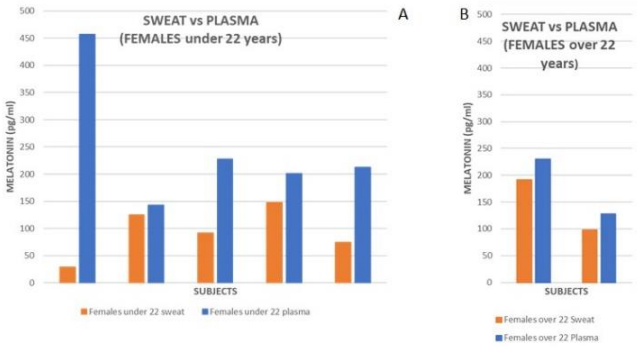

Fig. 2. Effects of intense exercise and aging on female athletes' melatonin production.
A. A comparison of sweat and plasma melatonin levels in the five under 22 young female athletes in the study during heavy exercise. Both sweat and plasma melatonin levels in young females were equal to or greater than young males despite sweat volume being approximately half that of the six young male participants. B. A comparison of sweat and plasma melatonin levels in the two older female athletes in the study during heavy exercise. Both sweat and plasma melatonin levels in older female athletes appear to be less impacted by age than older males.

It is proposed that during aging the body's ability to maintain the ROS/antioxidant balance degrades as shown in the older athletes by Zhu (2).

Despite the limited number of older female participants in Zhu's study, it appears that older females maintain an advantage regarding extrapineal melatonin production despite lower levels of sweat. Average sweat volumes were 600 µL for young males, 596 µL for older males, 310 µL in young females, and 140 µL in older females. While observational, this does correlate with the suggestion of Tan and Hardeland (5) that females are better able to maintain melatonin levels as they age than males.

As shown in Figure 3, a replot of Theron's data (6), shows that plasma melatonin levels plateau after 20 minutes of exercise. It is speculated that an equilibrium is reached between melatonin production within the muscles and possibly other non-pineal cells and melatonin secreted via sweat. After 4 hours, exercise was stopped and in less than an hour the participants plasma levels returned to normal daytime values. In this work the participants were young extremely fit black males. Zhu (2) did not provide ethnicity data for the study's participants and there is insufficient data to provide further statistics.

Figure 3 also combines Theron's exercise data with typical night-time circadian-induced plasma melatonin levels. Clearly, two very different mechanisms are at play. While there is no doubt that the suprachiasmatic nucleus (SCN) pathway under low light and stress conditions induces pineal gland to provide supplemental melatonin at night (7, 8), it seems equally apparent that the pineal gland is not responsible for the huge melatonin spike that occurs during intense exercise during the day. Exercise induced an increase rate of greater than 5 pg/ml min compared to circadian response being less than 0.15 pg/ml min. Mitochondria of the skeletal muscle cells is a likely source of this extrapineal melatonin (9, 10); accumulating evidence indicates that melatonin originating from these cells is consistent with the ability of perhaps the mitochondria in all cells to synthesize this important molecule (11, 12).

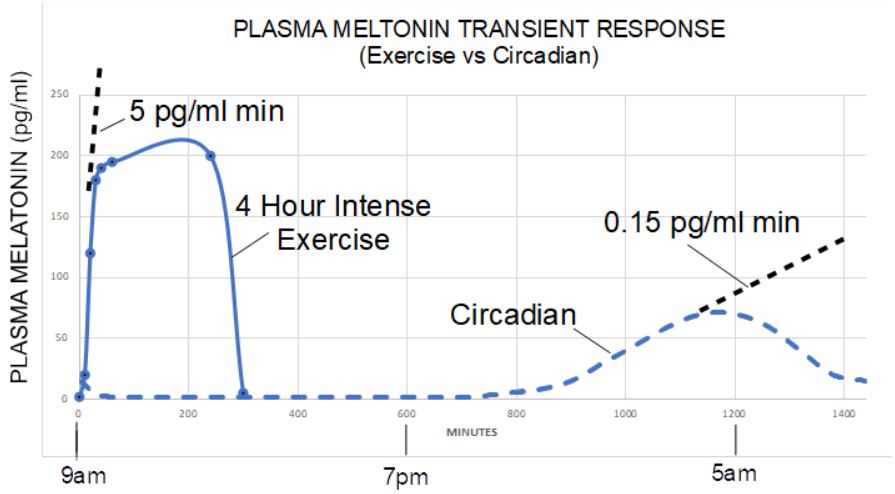

Fig. 3. The plasma melatonin levels as a function of time during heavy exercise and circadian time.

During 4-hour intense exercise session plasma melatonin levels increased to 200 pg/ml in 20 minutes followed by plateau for the duration of the exercise (five test subjects with indwelling catheter measured plasma melatonin at 10, 20, 30, 40, 50, 60, 240, and 300 minutes, respectively).

Combining the Theron plasma data with Zhu's plasma and sweat data is shown in Figure 4.

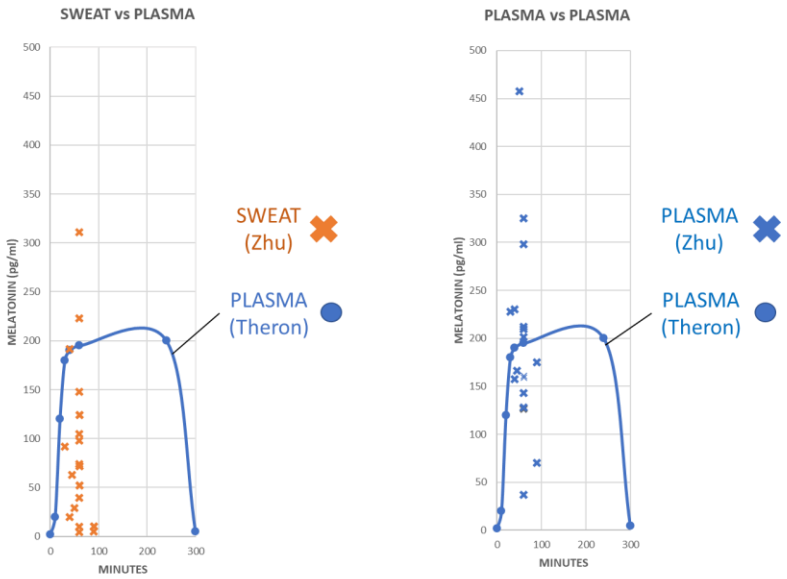

Fig. 4. An illustration of Zhu's plasma and sweat melatonin levels as a function of time compared to Theron's plasma data during heavy exercise.

Zhu's sweat and plasma data supports earlier Theron measurements indicating very rapid increases in melatonin that are unlikely to be pineal based.

Zhu's participants exercised from as little as 30 minutes to as much as 90 minutes. While only single-point measurements were obtained they do provide peak concentration over a given time frame, it is obvious that in most cases both plasma melatonin and sweat melatonin ramp rates were equivalent to Theron even when measured outdoors. This may also explain the large range of results from other melatonin studies which relied on slower methods of sample collection and did not consider the transient nature of melatonin concentrations.

2. FUNCTION ROLE OF EXTRAPINEAL MELATONIN: MAINTAINING REDOX HOMEOSTASIS

Herein we propose that at least regarding extrapineal-produced melatonin, its primary role is to modulate ROS levels and to maintain redox homeostasis in all cells (13). Cells maintain a basal level of ROS, which is essential for life (11). ROS have been shown to be an integral part of our body's innate immune response (14, 15). At the cellular level, too few ROS is just as problematic as too many ROS as illustrated in Figure 5. Fever, exercise, sunlight (to the skin) and other stressful stimuli elevate intracellular ROS production (16, 17, 18). In a compensatory response, cells rapidly synthesize melatonin, and stimulate B-cells, T-cells, blood flow, NK-cells, etc., to protect against the damaging actions of extra ROS. The published data suggest that intracellular melatonin production is upregulated as a defensive maneuver during periods of high ROS production. There is ample published precedence for such responses. In both plant and animal cells, melatonin has been shown to be upregulated when subjected to many different stressors (19, 20).

The elimination of UVB/UVA and NIR/IR from our homes, offices, and schools, coupled with a sedentary indoor lifestyle has dropped average ROS levels by an estimated 90% in the body

(gray area in Figure 5). As discussed, this is especially true for children, black populations, and the elderly due to the optics of each group (1). The Black community's elevated melanin levels provide protection against melanoma but the reduced melatonin production with less environmental sunlight exposure increase their susceptibility to hypertension, obesity, dementia, rickets, myopia, and COVID deaths (21, 22). Up to six times higher solar exposure is required to stimulate equivalent cellular processes in a black individual than that in other ethnic groups. In contrast, Sub-Saharan Africa (agrarian societies, lowest vaccination rates, inadequate health care) COVID death rates are over forty times lower than African Americans living with significantly lower solar exposure and average ROS levels.

What is concerning is that by most measures COVID is a weak virus. During the Spanish flu, Africa was devastated with large percentage of villagers dying in days. The COVID pandemic may in part be a product of developed countries and current lifestyles. By understanding how the body protects itself we can hopefully reduce the severity or prevent future pandemics. Consistent with this is that many scientific publications have suggested the use of supplemental melatonin to combat COVID-19 infections (23-25) and, when it has been used for this purpose, it was shown to be highly effective in reducing the symptoms and lowering the death rate of SARS-CoV-2 infected individuals (26-28). It is reasonable to argue that the combination of exogenous melatonin with lifestyle changes that maximize extrapineal melatonin (solar exposure, exercise, and fresh air) is worth further research.

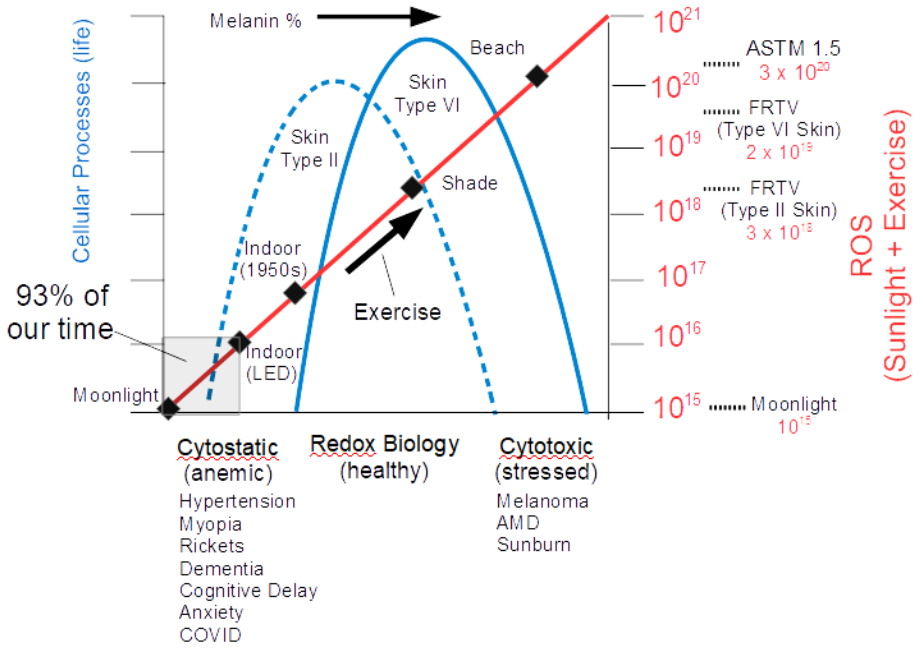

Fig. 5. In light of Mittler and Zastrow, our body uses ROS to facilitate numerous cellular processes. Too little and too much ROS both lead to disease.

For illustrative purposes relative ROS levels due to Sunlight are shown (eight-hour exposure clear spring day 1 square meter of exposed skin). Modern lifestyle and homes tend to create an anemic (low ROS) environment that encourages disease. The optimum ROS level depends on age, health, gender, and ethnicity.

Mechanistic Bio-optical Models developed by the authors (1) based on Zastrow (29) and more recently Meinke (30) provides Electron Spin Resonance (ESR) data of human skin (1) allowing for quantification of ROS levels under different lighting conditions and skin types (Fitzpatrick Scale).

Based on the published data it seems that the body has the capacity to produce massive amounts of melatonin within mitochondria of all cells during the day and night in response to rapidly changing exogenous and endogenous ROS production. This response is localized and transient making it difficult to measure. The advent of biosensors that are pseudo real time are now able to detect melatonin and other hormones. The published data indicates that melatonin is produced in sufficient quantities during heavy exercise for an excess to be secreted in sweat. It is not clear how or whether pineal-derived melatonin is part of this response especially during the day. Related to this, forcing rats to a highly stressful swim at night when circulating levels of melatonin are elevated, causes a very rapid drop of blood melatonin levels even though the pineal synthetic machinery remains elevated (31); the rapid depletion of circulating levels of melatonin under these stressful conditions indicates it may be rapidly taken up by cells to fight against the highly elevated ROS concentrations. This indicates that melatonin released from the pineal gland at night may also have some role in combatting oxidative stress when animals are under stress. Based on these data, we proposed that the SCN/pineal pathway provides supplemental melatonin via pineal secretion during periods of low ROS and low extrapineal melatonin generation. Like a trickle charger, the pineal gland appears to supply a protective level of melatonin through the night to active cells such as the brain. Additionally, however, the day/night fluctuation of pineal-secreted melatonin provides an important signal for circadian rhythm regulation (32). Based on the interpretation of the collective findings, under real world conditions it is likely that sleep disorders are primarily caused by lack of sunlight and exercise during the day rather than just blue light exposure at night (33, 34). Moreover, we feel that DLMO protocols create an artificial situation that overestimates circadian effects and importance.

3. CONCLUSION

As real-time biosensors are developed for a wide range of hormones and antioxidants a more accurate picture of the transient responses of cells is being revealed. Huge rapid fluctuations in melatonin in plasma and sweat support the premise that most of the melatonin is produced where and when ROS are being created and defense against them is needed. The ROS generation rates from exercise and sunlight exposure fluctuate on the time scales of minutes and seconds. The body appears to maintain a basal level of ROS to thwart disease and support other cellular functions. Given that modern developed countries have overseen the largest reduction in solar exposure and exercise in human history, ROS generation rates in the body have dropped by over 90% so has the melatonin production. Children, black populations, and elderly are most susceptible to this cytostatic/anemic artificial environment.

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AUTHORSHIP

SMZ conceived and wrote initial draft with RJR providing critical review and supporting references.

CONFLICT OF INTERESTS

Both authors have no conflicts of interest.

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