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Short Communication

Melatonin as an Anti-cancer Agent: Time of Administration May Be Critical

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Commentary

The scientific literature is replete with publications documenting the cancer inhibitory activity of the endogenously-produced molecule, melatonin. While this has been documented for many cancer types [1], much of the research has been directed to the role of melatonin in suppressing the initiation, progression and metastasis of breast cancer [2].

Melatonin is best known as an endocrine product of the pineal gland with its synthesis and secretion exhibiting a circadian rhythm such that highest blood levels occur at night when individuals are in darkness [3]. During the daylight hours, blood levels of melatonin are often barely measurable. Exposure of individuals to light at night, provided it is of adequate intensity and the proper wavelength, causes a precipitous drop in pineal melatonin production and in its concentrations in the blood. The circadian nature of melatonin is common to all vertebrates, including the human, and as a result it has often been identified as a circadian rhythm modulator; it is perhaps best known as a sleep-inducing agent in humans and when used as a supplement, it is invariably taken in the evening before bedtime.

To ensure adequate energy and the necessary extra molecules for accelerated growth, many tumors change their metabolism to what is referred to a Warburg-type [4]. In this case, tumor cells avidly take up glucose which undergoes glycolysis to pyruvate during which ATP is rapidly produced as are the additional molecular building blocks for accelerated metabolism via the hexose monophosphate shunt. In normal cells, pyruvate is taken into the mitochondria where it is metabolized to acetyl co-enzyme A by Pyruvate Dehydrogenase (PDH). Conversely, in tumor cells, PDH is downregulated by Pyruvate Dehydrogenase Kinase (PDK) restricting the entrance of pyruvate into mitochondria. As an alternative, pyruvate is converted to lactate-by-lactate dehydrogenase; lactate is then released from the tumor cell via the monocarboxylate transporter thereby acidifying the cellular microenvironment which improves the invasive and metastatic potential of the cancer. Thus, Warburg-type metabolism assists tumor cells to continue their rapid growth.

It has been assumed that Warburg-type metabolism of tumor cells persists throughout the 24-hour period; this may not always be the case, however. When MCF-7 breast cell tumors growing in immune compromised rats were evaluated over a 24-hour period at 4 hour intervals, their metabolism was dramatically different between the day and the night [5]. During the day, the tumors were obviously exhibiting. Warburg-type metabolism with very high glucose uptake, lactate release, and high DNA content indicative of cell proliferation with similar changes in other parameters, i.e., they were displaying typical cancer cell metabolism. In tumors collected at night, their metabolism was typical of that of non-cancerous (normal) cells; thus, they took up glucose sparingly, lactate production was low and DNA levels were diminished. Clearly, the tumors were of the cancer phenotype during the day but were functioning as more normal tissue at night. This marked rhythm in tumor metabolism was driven by the circadian blood melatonin cycle, since preventing the nocturnal rise in melatonin (by exposing the animals to light at night), caused the tumors to exhibit Warburg-type metabolism over the entire 24-hour period; this change was associated with a more rapid growth of the tumors as well. Thus, the breast tumors were described as only parttime cancers [6]. The ability of physiological melatonin levels to convert tumor cell metabolism from the Warburg-type a normal phenotype is a critical observation (5) because Warburg metabolism is typically a requirement for accelerated tumor growth. The mechanism by

which melatonin reverses Warburg-type metabolism presumably involves its ability to inhibit hypoxia inducible factor 1a (HIF-1a); this prevents the upregulation of mitochondrial PDK leading to a disinhibition of PDH allowing pyruvate to enter the mitochondria as in normal cells [6].

These findings have important implications for cancer cell biology since rarely (if ever) are in vivo tumors collected at night in darkness (to preserve high melatonin levels); thus, these day/night differences in tumor metabolism would not be detected. Likewise, this rhythm would not be seen in cultured tumor cells since they are not exposed to a melatonin cycle.

When melatonin is used by humans as a supplement, it is usually taken at night to coincide with its normal nocturnal endogenous increase. When it is used as a cancer treatment, it may be best to administer it during the day to reverse Warburg type metabolism and more effectively suppress tumor growth; to give it at night would seemingly be of little value for cancer inhibition since the tumor cells are already functioning as more normal cells. Likewise, in animal studies on cancer drug resistance, which also is associated with Warburg-type metabolism, melatonin is known to prevent both chemo and radioresistance and this likewise involves reversing the metabolism of the cancer cells [7]. Thus, tumor drug resistance in humans should consider the use of melatonin to prevent its development. Interestingly, the abnormal metabolism exhibited by cancer cells also is common to many other pathological cells where melatonin has been shown to be protective [8]. So, melatonin should also be considered in the treatment of these conditions.

Finally, cancer is often an age-related disease; its frequency increases coincident with the age-associated loss of the melatonin rhythm. As a result, it is anticipated that cancers in older individuals exhibit Warburg type metabolism 24/7. Thus, if melatonin, which is normally endogenously synthesized and which essentially lacks toxicity over a very large dose range, is used as an anti-cancer agent in the elderly, it would likely be optimal to give it both in the day and at night, a process that would be aided by currently available nanocarriers for this important molecule [9].

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