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Melatonin-Deficient Balb/c Mice and Their Use in Cancer Research

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A recent paper published in this journal[1] reported the effects of chronic 30 minutes per night exposure to light of various spectral properties. The authors concluded that there was a negative correlation between wavelength and melatonin suppression. The reported melatonin suppression was further correlated with tumor burden. The experiments used Balb/c mice, which, as outlined below, are an inappropriate animal for investigating the effects of suppression of endogenous melatonin production. It has been known for over 30 years and widely published that Balb/c mice are melatonin deficient due to mutations in the genes for the 2 critical enzymes (AANAT and HIOMT) in the pineal gland melatonin synthetic pathway.[2-5] Of the laboratory mouse strains commonly used in biomedical research, only C3H and CBA mouse strains are capable of producing melatonin.[6,7] The genetic evidence presented by Kasahara and colleagues in particular is overwhelming for Balb/c and other strains. Indeed, acceptance of melatonin-deficient mouse strains is evident in the recent development of a congenic melatonin proficient C57Bl/6J strain[8] and melatonin proficient melatonin receptor knockout mice, for example.[9]

The use of Balb/c mice in their experiments has been justified previously by this group[10,11] by a paper that reported plasma melatonin levels in the strain[12] (which actually used data from an still earlier paper.[13] It used radioimmunoassay (RIA) that had not been validated in mice or any other species and not only reported daytime levels of melatonin in the range of 60 pg/mL but also no statistically significant increase in melatonin at night. This is to my knowledge the only publication reporting plasma melatonin in this strain and the results are unreliable due to the high daytime levels.

The authors of the current study, however, used the measurement of 6-sulphatoxymelatonin to monitor the effects of light of various wavelengths on pineal melatonin production. 6-Sulphatoxymelatonin is a known metabolite of melatonin in several species, for example, humans and rats, but not mice. We and others have shown that in both melatonin proficient and deficient mouse strains, 6-sulphatoxymelatonin is not the major urinary melatonin metabolite Kennaway.[6,14,15] 6-Glucuronyl melatonin is the overwhelming major excreted melatonin metabolite. There has been a report of a contrary finding indicating that mice can indeed produce 6-sulphatoxymelatonin,[16] but the published rhythm of excretion in C3H mice is difficult to interpret, since excretion of the immunoreactive 6-sulphatoxymelatonin occurred almost immediately after lights out, contrary to the established onset of melatonin production in such mice late into the dark phase. The current paper used a human 6-sulphatoxymelatonin enzyme-linked immunosorbent assay kit (not validated for mice) and reported a rhythm that would appear to follow the rhythm of urine excretion which is highest at night.

As mentioned in a commentary[17] about a previous publication by this group,[11] the current study has provided us with interesting and challenging observations on the effect of chronic light pulses of various wavelengths of light on tumor growth. The effects observed are, however, clearly not due to alterations in endogenous melatonin production or levels. The mouse strain used cannot produce melatonin and the assay used to monitor production was not appropriate for measuring melatonin metabolites in this strain anyway. In view of the wavelength effects, the authors may wish to focus on the role of the melanopsin photoreceptors and their target cells in the suprachiasmatic nucleus and elsewhere in the hypothalamus.[18]

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