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Physiologically based modelling of circadian dynamics of melatonin and its metabolite aMT6s

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Background and Objectives: The central circadian clock in the hypothalamus controls 24 hour rhythms in the human body, from sleep and alertness, to mood, metabolism, and immune response among many others. Knowledge of the phase of the clock is central to design of treatments for circadian rhythm disorders, including shiftwork disorder, jetlag, delayed sleep-wake phase disorder, and non-24-hour sleep-wake rhythm disorder. Melatonin concentrations in plasma and saliva, and the excretion rate of the major urinary melatonin metabolite, 6-sulfatoxymelatonin (aMT6s), are often used as markers of circadian phase. The relationship between these markers is complex, and measuring melatonin or aMT6s can be impractical, however, so quantitative models would prove useful to aid experimental procedures or to design treatments. Here a unified model of arousal and melatonin dynamics is presented that predicts the rhythms of melatonin and aMT6s in multiple body fluids under varying light, sleep, and circadian misalignment conditions.

Methods: We used an established model of arousal dynamics in which ordinary differential equations simulate the flip-flop switch between the sleep- and wake-active neuronal populations, and a dynamic circadian oscillator accounts for the effect of light exposure on circadian phase. This model is extended to incorporate the circadian-controlled production of melatonin in the pineal gland, its dynamics in the blood and saliva as well as its conversion to aMT6s, and ultimate excretion. Importantly, the model also includes suppression of melatonin synthesis by light exposure, which is a key confounding factor in experiments.

Results: The model predicts melatonin levels over the sleep-wake/dark-light cycle and enables prediction of widely used melatonin-based circadian phase markers, such as dim light melatonin onset (DLMO) and aMT6s acrophase under conditions of both normal sleep and circadian misalignment. The model is tested against data from ten published experimental studies, including real-world shiftwork studies, and is found to quantitatively reproduce the key features of melatonin and aMT6s dynamics, including the timing of release, peak concentrations, and response to controlled lighting.

Conclusions: Our model is the first to quantitatively predict the relationship between light exposure, circadian phase, melatonin, and aMT6s dynamics, and successfully reproduces experimental data from a variety of experiments.

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