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A NEW 0.5 MG MELATONIN PHASE RESPONSE CURVE IN HUMANS

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Introduction: We published a phase response curve (PRC) to 3.0mg melatonin, a dose often used for its soporific effects (J Physiol 2008). Here we present a new PRC to 0.5mg melatonin, a lower dose often used for phase shifting the circadian clock.
Methods: So far 18 young healthy subjects participated in two 5 day laboratory sessions. Each session began with a phase assessment, to measure the dim light melatonin onset (DLMO), followed by 3 days in an ultradian light-dark cycle (LD 2.5:1.5), and then a final phase assessment. Each subject received one pill per day at the same clock time each day, during the 3 ultradian days (melatonin or placebo, double blind, counterbalanced). Each individual's phase shift to melatonin was corrected by subtracting their phase shift to placebo (a free-run).
Results: The resulting PRC illustrates how 0.5mg melatonin can phase shift the circadian clock in the absence of conflicting light exposure. The results suggest that if 0.5mg melatonin is taken about 3 hours before the DLMO (about 5.5 hours before habitual bedtime) for 3 days, the circadian clock will advance by about 1.3 hours. Similarly, 0.5mg melatonin taken about 12 hours after the DLMO (shortly after habitual waking) for 3 days, can phase delay the clock by about 1.5 hours. These numbers may change slightly as more subjects complete the study. When 0.5mg melatonin is taken at usual bedtime, minimal phase shifts result.
Conclusion: This PRC demonstrates (1) the best times to administer a low dose of melatonin to achieve desired phase shifts, (2) that even a low dose of melatonin can phase delay as well as phase advance, (3) that using a low dose of melatonin as a sleep aid at night has minimal phase shifting effects, (4) that PRCs to different doses of melatonin have different shapes.
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A COMPROMISE CIRCADIAN PHASE POSITION FOR PERMANENT NIGHT WORK IMPROVES NIGHT SHIFT ALERTNESS AND IS COMPATIBLE WITH LATE NIGHTTIME SLEEP ON DAYS OFF

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Introduction: This is the final study in a series designed to produce and maintain a compromise phase position for permanent night work, in which the sleepiest circadian time is delayed out of the night work period and into the first half of daytime sleep, improving night shift alertness and subsequent daytime sleep, but not precluding late nighttime sleep on days off.
Methods: Subjects underwent 3 night shifts (23:00-7:00), two days off, 5 more night shifts, and two more days off. During night shifts, an experimental group (n=9) received four 15-minute pulses from light boxes (~ 4,100 lux, ~1,200 μW), interspersed by 45 minutes of room light. The first pulse began at 00:45 and the last ended at 4:00. Subjects wore dark sunglasses (~15% transmission) when outside. Home sleep episodes in darkened bedrooms occurred from 8:30-15:30 after night shifts, 8:30-13:30 after the last night shift in a block, and 3:00-12:00 on days off. Subjects went outside for ≥15 minutes after awakening to receive a "light brake" to keep them from delaying past the compromise phase position, defined as a dim light melatonin onset (DLMO) of 3:00. A control group (n=10) remained in room light during night shifts, wore lighter sunglasses (~36% transmission), and had unrestricted sleep and outside light exposure.
Results: The final DLMO for the experimental group was close to the target compromise phase position, and significantly later than the control group (3:22 ± 2.0 vs. 23:24 ± 3.8 h, $p < 0.001$). Subjects who phase delayed close to the target phase performed better during night shifts.
Conclusion: A compromise circadian phase position for permanent night shift work improved performance during night shifts, allowed sufficient sleep during the daytime after night shifts and during the late nighttime on days off, and can be produced by feasible interventions.
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0130

DIURNAL VARIABILITY OF C-REACTIVE PROTEIN (CRP) IN OBSTRUCTIVE SLEEP APNEA (OSA)

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Introduction: Inflammation is a hallmark of the pathophysiology of OSA and represents a pathway linking OSA to increased cardiovascular morbidity. CRP is an acute phase response protein implicated in broad range of cardiovascular diseases. This study examined the diurnal variability of CRP in OSA.
Methods: Forty-four individuals with untreated OSA (mean apnea/hypopnea index = 37.5, SD ± 28) and 23 healthy adults with no OSA were studied at the UCSD Gillin Laboratory of Sleep and Chronobiology. Over a 24-hour period, blood was collected every two hours and CRP levels were determined. Participants had their sleep monitored with polysomnography to verify OSA diagnosis. The time-course of CRP levels over the 24-hour period was analyzed using a linear mixed-effects model fitted with restricted maximum likelihood methods.
Results: There were significant main effects for body mass index (BMI) (with higher BMI being associated with higher CRP levels; regression coefficient = 0.094, $p < 0.001$) and gender (with CRP levels being higher in women; regression coefficient = 0.667, $p = 0.04$) for the 24-hour period. Adjusting for age and gender, a group by time interaction (regression coefficient = 0.081, $p = 0.01$) showed that patients with apnea had higher CRP levels during the daytime (8:00am - 8:00pm) versus the nighttime (10:00pm until 6:00am) ($p < 0.001$). Non-apneics showed no change in CRP levels during the 24 hours.
Conclusion: Studies in OSA show increased risk for cardiovascular events in the daytime and this risk is attributed to several mechanisms, including local and systemic inflammation. Our findings indicate that OSA patients have disproportionately elevated CRP levels in the day versus the nighttime, possibly as a result of carryover effects of nighttime arousal into the daytime. Our findings suggest that fine-grained chronobiological analysis with frequent blood sampling is invaluable to better understand inflammatory variables in OSA.
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0131

EARLY MORNING NADIR IN ENDOTHELIAL FUNCTION

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Introduction: There is a growing awareness of the importance of the endothelium in regulating vascular tone via the production of the potent vasodilator nitric oxide. Endothelial dysfunction is a reliable biomarker of future cardiovascular events and poor clinical outcomes. Previous studies demonstrated circadian rhythm in vascular tone with a nadir at the early morning hours. The purpose of the present study was to investigate the 24-h pattern of endothelial function under different sleep-wake conditions.

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