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Presentation Abstract

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Title: The cardiovascular and sleep phenotype of VPAC2 receptor knockout mice lacking a functional suprachiasmatic nucleus clock

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Abstract: VPAC₂ receptor null (*Vipr2*^{-/-}) mice, lack a functional circadian “master clock” in the suprachiasmatic nuclei (SCN) of the hypothalamus, and do not exhibit robust circadian rhythms of wheel running behavior and corticosterone secretion when given *ad libitum* access to food (Sheward *et al.*, J Neurosci 27, 4351-4358, 2007). We have investigated (1) rhythms of heart rate, blood pressure and locomotor activity in these mice using implanted radio-telemetry devices (PA-C10, DSI, St Paul, MN) and (2) sleep and wakefulness in similar mice implanted with electroencephalograph (EEG) electrodes. Mice were housed individually, initially with a 12:12 light:dark cycle (LD). In LD, *Vipr2*^{-/-} mice demonstrated significantly less wakefulness and more NREM sleep time than wild-type (WT) controls. In contrast to WT, which displayed strong circadian variation in sleep times between light and dark, *Vipr2*^{-/-} mice showed bouts of sleep and wakefulness throughout the day and night. Consistent with EEG data, *Vipr2*^{-/-} mice had absent or attenuated diurnal

rhythms of heart rate, activity and blood pressure compared to WT, and the predominant rhythms were ultradian with a period of about 2-3h. The ultradian component was also present in WT mice, but was less prominent and had the stronger circadian rhythm superimposed. After transfer into constant dark (DD) conditions *Vipr2*^{-/-} mice showed significantly more NREM and REM sleep bouts during the rest phase however they failed to demonstrate any significant difference from WT in overall sleep time. The ultradian nature of rhythms of activity and the cardiovascular parameters in the *Vipr2*^{-/-} mice were increased in DD conditions. Mice were returned to LD and given access to running wheels. The presence of the running wheel imposed a strong diurnal rhythm of activity, blood pressure and heart rate in *Vipr2*^{-/-} mice, which were replaced with a strong ultradian rhythm after transfer to DD conditions.

We have shown that (i) the VPAC₂ receptor appears to play an important role in not only the diurnal distribution of the sleep/wake cycle but also in the regulation of the total amount of NREM sleep and wake under entrained conditions; (ii) heart rate, blood pressure, activity, sleep and wakefulness showed a clear 24h rhythm in WT mice, whereas in *Vipr2*^{-/-} mice the rhythms were largely ultradian in nature; (iii) unlike wheel running, general locomotor activity was not greatly suppressed by light in mice. The main function of the SCN clock is to impose a partitioning of the day into subjective night (largely active) and day (largely at rest); in the absence of SCN control an ultradian rhythm of sleep and wakefulness is the main determinant of heart rate and blood pressure.

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