Abstract

Breathing around the clock: novel circadian and light-driven mechanisms that govern daily breathing behavior in mice

Aaron A. Jones, B.A.

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Breathing, like many physiological functions, exhibits a daily rhythm in mammals that coincides with periods of wakefulness and increased metabolic activity. Dysregulation of daily breathing rhythms has been implicated in a variety of respiratory diseases with time-specific symptomatology including sleep apnea, asthma, chronic pulmonary disease, sudden unexpected death in epilepsy, and COVID-19. While the daily rhythm in breathing is controlled by the endogenous circadian clock in the brain, the underlying physiological and cellular mechanisms regulating daily breathing behavior remain largely unknown. Light is the most potent synchronizer of the circadian system in mammals and is likely the principal driver of respiratory behavior across the day. In Chapter I of this dissertation, I discuss the neural basis of breathing and provide evidence for the potential role of light in driving breathing. Then, I present a series of experiments demonstrating that manipulation of the light environment and/or circadian timing/mechanisms reorganizes daily ventilatory rhythms. First, I demonstrate that changing the number of available light hours in the day (*i.e*., photoperiod), reorganizes the daily rhythm in minute ventilation and alters the relationship between breathing rhythms and metabolic rate (Chapter II). Then, using transgenic mouse models of circadian disruption, I demonstrate that the molecular circadian clock plays a pivotal role in regulating daily rhythms in ventilation and chemoreflex in a time- and tissue-specific manner (Chapter III). Next, using a desynchronized feeding protocol, I provide additional evidence that the daily rhythm in minute ventilation is not solely dictated by circadian patterns of metabolic rate, but is simultaneously optimized by other clock-derived mechanisms such as clock gene expression in the neural respiratory network (Chapter IV). Lastly, using a forced desynchrony protocol and additional transgenic mouse lines, I reveal that light can organize daily ventilation rhythms independent of the central circadian clock by acting through the Opn4-Brn3b(+) retinal circuit (Chapter V). I conclude with an overall discussion and suggest future directions for this revitalized and exciting field (Chapter VI).