Combinatorial Measurement of Sleep and Wheel Running Activity to Examine the Interaction Between Light and Drug Administration in Mice

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ABSTRACT

A billion dollar industry exists to manipulate sleep and alertness. These drugs are psychoactive compounds that work by interacting with neurotransmitter transporters or receptors in the brain to alter brain activity. Possibly, the most common and widely used example of one of these psychoactive compounds is caffeine. Caffeine has been shown to diminish drowsiness while increasing alertness. In high doses, it can cause increased activity and even tremors [1-4]. Another potent influencer of sleep and wakefulness, though commonly overlooked, is light. In humans, light input is known to increase alertness, while in nocturnal animals, such as mice, light input has the opposite effect [5-6]. Interestingly, an acute light pulse is sufficient to induce a dramatic increase in sleep in mice [6]. What is not known, however, is whether light and drugs interact to influence sleep.

METHODS AND RESULTS

Previous work has shown that administration of a 3-hour light pulse two hours after the lights offset is sufficient to induce a decrease wheel running activity, an effect termed masking[7]. Recent work from the lab has shown that a similar light pulse results in a decrease in the amount of time spent awake, which has been used to explain the decrease in wheel running activity [6]. To examine the potential interaction between light and drug administration, I utilized this masking light pulse. Specifically, I administered either caffeine or modafinil [8], both of which are psychostimulants, to mice in absence of as well as prior to the 3-hour masking light pulse and measured wheel running activity as well as sleep.

To measure wheel-running activity, adult male mice are individually housed in cages with a running wheel and access to food and water ad libitum. Mice are allowed to acclimate to the cage for one week prior to testing and are kept in a light cycle of 12-hour light: 12-hour dark. Treatments are always separated by one week to allow mice to readjust to baseline situation. Wheel running activity is recorded using Vitalview (MinitMitter; Respironics).

To measure sleep in mice, a two channel EEG and one channel EMG (Pinnacle Technology) head mount is affixed to the skull of mice while under ketamine/xylazine-induced anesthesia. Mice were allowed two weeks to recover in a 12:12LD cycle. Mice were then transferred to sleep recording cages, tethered with a preamplifier and allowed to acclimate to the cage for one day. The following night, treatments were administered and sleep measured. The sleep/wake stage of the mouse is determined by the experimenter based on the frequency and amplitude of EEG and EMG using Neuroscore (DSI). Sleep can essentially be separated into two stages, slow wave sleep (SWS) and rapid eye movement (REM). SWS is defined by low frequency (1-4 Hz), high amplitude EEG with little to no activity detected by EMG, whereas REM is defined by high frequency (8Hz) low amplitude EEG and no EMG. Wake is defined as high frequency (8-10Hz) low amplitude EEG and high frequency EMG.

Mice received an injection (i.p.) of caffeine 15-minutes prior to the 3-hour light pulse. Caffeine administration in the absence of a light pulse as well as vehicle administration were used as controls. The same procedure was used to examine modafinil.

In summary, I found that the administration of high levels of caffeine increased wakefulness in the absence of a light pulse and was sufficient to keep mice awake in the presence of a light pulse. However, this amount of caffeine decreased

wheel running activity in the absence of a light pulse and activity was decreased further during a light pulse. Administration of a decreased concentration of caffeine does not change wheel running activity or wakefulness in absence of a light pulse. Interestingly, while it is sufficient to keep mice awake during a light pulse, there is no change in their wheel running activity. These results were also found upon administration of the stimulant modafinil.

As the administration of a 3-hour light pulse has been shown to decrease both wheel running activity and sleep, these findings allow us to actually separate these two behaviors. This is in addition to the new insight that these two measures provide in the examination of the interaction between light and psychoactive compounds.

All animal experiments were done according to the institutional regulations of Johns Hopkins University (Baltimore, MD).

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