September 22, 2020

Neurobiology

Stop all the clocks: the hidden long-term consequences of sleep loss

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This Break was edited by Max Caine, *Editor-in-chief* - TheScienceBreaker

ABSTRACT

Sleep loss perturbs the molecular circadian clock inside our cells. This effect persists long after the organism has recovered from sleep loss at the behavioral level.

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The function of sleep is still elusive despite the well-known effects of sleep loss or poor-quality sleep on cognitive function and long-term health. When and how long animals (including humans) sleep is determined by, on the one hand, their internal circadian clock, which aligns physiology and behaviour to the time-of-day. On the other hand, by a homeostatic process which keeps track of how long the organism has been awake. One way to gain insight into sleep's elusive function is to identify the genes and gene products (gene transcripts and encoded proteins) involved in the regulation of sleep, as well as the relative contribution of the circadian and the homeostatic processes to the regulation dynamics of those genes under undisturbed conditions as well as conditions of perturbed sleep.

Epidemiological studies have linked chronic sleep perturbations (e.g. poor-quality sleep or shift work) with non-transmittable diseases such as type 2 diabetes. This hints at the idea that "something" accumulates with the repeated sleep perturbations imposed by work schedules or lifestyle. One possible scenario is that changes in the regulation of our genes at the very core of our cells, are, if not durably established, at least maintained by the repeated sleep perturbations, and it would be this altered state that would cause disease on the long term. Such an alteration of state is thought to be mediated by how the DNA and its associated proteins (the "chromatin") increases or decreases the activity of genes (their "expression"), by enabling or preventing the access of the relevant proteins to specific genes ("chromatin accessibility").

To begin to investigate this hypothesis, we decided to examine the effects over time of a single sleep deprivation (SD) episode on gene expression and its epigenetic regulation. To this end, we kept mice awake during the first 6 hours of the light phase of the 24-hour period, which is otherwise the natural resting period for these nocturnal animals. We monitored gene expression and chromatin accessibility in the cortex of their brains before, during and for 48 hours after the SD, and developed mathematical models to classify the genes according to their expression dynamics over the whole duration of measurements, and decide whether they are regulated according to a circadian process, a sleep-wake driven homeostatic process, or a combination thereof.

Our most striking discovery was that the genes of the circadian clock (clock genes) were almost all affected by sleep deprivation. In that, their regular 24-hour oscillation in expression was strongly diminished in amplitude. This was all the more intriguing since the changes persisted even after the mice had caught up on the lost sleep and resumed their usual sleep-wake patterns. The modelling approach confirmed the ambivalence of the clock gene expression in the cortex. Indeed, the core clock genes, *Npas2* and *Clock*, had to be categorised as distinctly sleep-wake driven and not as circadian, while all others (with one exception) were regulated by a combination of both processes.

Another bonus of looking at effects over time is that we found genes which were not immediately changed by SD, but were durably perturbed later on in the time course. These genes were not found in previous studies, which have overwhelmingly focused on the single time point at the end of the 6-hour SD.

How do these changes in expression relate to changes in the chromatin state? By correlating expression dynamics with chromatin dynamics, we found that the response to sleep deprivation was mediated by regulatory elements far away from the genes, while gene promoters remained stably accessible. The response and recovery at the chromatin level were fast and overwhelmingly followed homeostatic dynamics.

Thus, sleep deprivation leaves a trace at the regulatory level in the cells of the cortex, even after the organism seems to have recovered at the level of sleep-wake behaviour and brain activity. Most remarkably, our results challenge the prevailing notion that circadian rhythms driven by clock genes control behaviours and physiology without being influenced by them. On the contrary, we found that a change in behaviour which impacts physiology was able to perturb the regulation of the clock genes. Though we found that all changes had normalised 7 days after SD, we can hypothesise that, if a second SD (or any other perturbation for that matter) occurs before gene expression and epigenomic changes return to their initial state, the response would be different than without SD. Repeated SD could also further perturb, or even stabilise the altered state, which could potentially prepare the ground for the diseases associated with poor sleep, and since clock genes are very much intertwined with metabolic processes, it stands to reason that their long-term perturbation after sleep loss relates to the aetiology of metabolic disorders such as type 2 diabetes.