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Common biomarkers of sleep debt found in humans, rats, study finds

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Stating that sleep is an essential biological process seems as obvious as saying that the sun rises every morning. Yet, researchers' understanding of the molecular mechanisms underlying the effects of sleep loss is still in its earliest stages. The risk for a host of metabolic disorders, including weight gain, diabetes, obesity, and cardiovascular disease, associated with reduced sleep is driving basic investigations on the topic.

In a study published this week in the *Proceedings of the National Academy of Sciences*, Amita Sehgal, PhD, a professor of Neuroscience at the Perelman School of Medicine at the University of Pennsylvania and a Howard Hughes Medical Institute investigator, along with co-first authors Aalim M. Weljie, PhD, a research assistant professor of Systems

Pharmacology and Translational Therapeutics, and Peter Meerlo, PhD, from the University of Groningen, The Netherlands, found common molecules signifying perturbed metabolism in response to sleep restriction in a comprehensive metabolic profiling of blood from both rats and humans. Their findings point to an overall shift in how lipids are metabolized and evidence of systemic oxidative stress due to decreased sleep in both species.

Oxidative stress and lipid metabolism are important factors in metabolic diseases, although further work needs to be done to establish a mechanistic link between the markers found and specific diseases, stress the researchers.

"One possibility is that sleep drives metabolite clearance and so acts as a reparative process at the metabolic level," says Sehgal. "The impact of sleep restriction on circadian biology is particularly relevant given what we now know about how metabolites also oscillate in humans on a daily basis." Metabolites are chemical intermediates or end products of metabolism, so while they are generated through the breakdown of fats, carbohydrates, and proteins, their function is not restricted to these processes.

They also have roles in signaling, regulating enzymatic activity, growth, and development.

Of Rats and Humans

The team subjected rats and humans to chronic sleep restriction over five days. Sleep restriction, versus sleep deprivation, curtails sleep time, but does not eliminate sleep. "Sleep restriction more closely represents real-world situations in humans and is a condition experienced by millions of people every day," notes Sehgal.

In both studies, metabolite levels were compared in blood that was collected following adequate sleep opportunity in rats and humans to establish a baseline and then following restricted sleep. The team then produced a comprehensive metabolite profile from the blood of sleep-restricted rats and humans. Of the 38 metabolites they found to be unique in the sleep-restricted rats, half were known lipids. A majority of the metabolites from the sleep-restricted human participants were also lipid or fatty acid-related compounds.

Seven types of a phospholipid called plasmalogens, related to oxidative stress, were elevated in the sleep-restricted rats. Overall, they found a significant shift in lipid metabolism, with sleep restriction, with higher levels of phospholipids in both rats and humans. The team found that some neurotransmitters and gut metabolites (possibly from intestinal microbes) are also altered due to sleep restriction.

"While we don't yet know why the lipids are changed in both species, these shifts are very intriguing, given the epidemiological links between restricted sleep and metabolic disorders, such as diabetes, obesity, and metabolomics syndrome," says Weljie. "I'm sure there's a connection."

When they compared the list of significantly altered metabolites in rats and humans compared to the baseline before sleep restriction, they found that two metabolites—oxalic acid and diacylglycerol 36:3 – were depleted under sleep-restricted conditions and restored after recovery sleep in both species. Oxalic acid is a waste product derived from processing foods in the diet such as plants, primarily from the breakdown of vitamin C and some amino acids. Diacylglycerol is a precursor molecule in the production of triglycerides, a molecule in which most fat is stored in the body, and also has a function in signaling in cells. The researchers suggest that these two molecules could serve as potential biomarkers since they are present in both species.

"These cross-species markers are exciting for a couple reasons," adds Weljie. "First, there is a need for quantitative markers of sleep debt and sleep quality, and this approach suggests that metabolites may be useful in this regard. Second, because we found the same metabolites in the humans and rats, it opens the door for us investigate mechanistic questions regarding the metabolic effects of sleep in rats that may have clinical and therapeutic application."

Overall, this work provides a potential link between the known pathologies of reduced sleep duration and metabolic dysfunction. "This is consistent with other studies that suggest that one of the functions of sleep is restorative, involving clearance of metabolites in the brain and reinstating an antioxidant balance in peripheral tissues. Sleep loss, on the other hand, induces an oxidative metabolic state," says Sehgal.

Namni Goel, Arjun Senguptaa, Matthew S. Kayser, Ted Abel, Morris J. Birnbaum (now with Pfizer, Inc.), and David F. Dinges, all from Penn, are co-authors.

More information: "Oxalic acid and diacylglycerol 36:3 are cross-species markers of sleep debt." *PNAS* 2015 ; published ahead of print February 9, 2015, DOI: 10.1073/pnas.1417432112

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