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Sleepy metabolites: sleep-related changes in the human metabolome

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Objectives: Recently, we described the human circadian metabolome in saliva and plasma using liquid and gas chromatography coupled with mass spectroscopy (LC/GC-MS) (Dallmann et al. PNAS, 2012). In a constant routine (CR) study, strictly controlled for sleep and wake, body posture and food intake, about 15% of all identified metabolite levels varied in a circadian fashion. Interestingly, some of the identified metabolites showed a monotonic increase or decrease throughout the 40 h of sleep deprivation (SD) during the CR study. In order to investigate the effect of sleep pressure on metabolism, we conducted a second experiment in which we compare the effects of SD with a frequent Nap protocol that keeps sleep pressure at a low level throughout the 40-h CR study. Methods: Four healthy male volunteers participated in this study. Two weeks prior to the CR, habitual sleep time was determined and healthy sleep habits were established for all participants. In a balanced cross-over design, volunteers underwent both a 40-h CR and a 40-h CR with naps (NAP, alternating cycle of 160 min of wakefulness and 80 min of sleep). Saliva samples were taken before and after each nap or at corresponding times during the SD protocol (a total of 20 timepoints). Samples of individuals were pooled according to timepoints and conditions. Then 20 pools each for SD and nap were analyzed by LC/GC-MS to quantify all identifiable metabolites in the saliva. We used a permutation algorithm to identify rhythmic compounds. Results: In total, we identified 260 metabolites in the saliva samples in the SD and Nap pools. As in the previous study, we identified about 15–20% oscillating metabolites in the circadian range and, in addition, found some in the ultradian (8 h) range. Interestingly, there were about twice as many circadian metabolites in the SD compared to the Nap group. Conversely, there was roughly twice the number of ultradian metabolites in the Nap group. Conclusion: We confirmed the previously published circadian variation of metabolite levels in human saliva. Moreover, we found multiple metabolites that were influenced by frequent naps and showed ultradian patterns. This novel and puzzling finding suggest that sleep is interacting with the circadian control of metabolism to an under-appreciated degree.