Morning Enzymatic Activity of DPP-4 Is Differentially Altered by Sleep Loss in Women and Men

https://doi.org/10.2337/dc17-1762

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No study to date has investigated whether the activity of circulating dipeptidyl peptidase 4 (DPP-4) is affected by sleep loss. DPP-4 is an enzyme that catalyzes a variety of important physiological processes in humans by cleavage of, e.g., the incretin hormones glucagon-like peptide 1 (GLP-1) and gastric inhibitory polypeptide (1). Both chronic sleep loss and an increased activity of DPP-4 have been implicated in the development of several diseases, including type 2 diabetes (1–4).

Twenty-five normal-weight healthy adults (aged 18–28 years; 13 women, using oral monophasic contraceptives) participated in two in-laboratory experimental conditions separated by about 1 week: one night of regular sleep (scheduled 2230–0630) and one night of total sleep loss, in a counterbalanced order. In the morning (~0730), fasting blood samples were taken to measure the enzymatic activity of DPP-4, as previously described (3). The effects of sleep loss on DPP-4

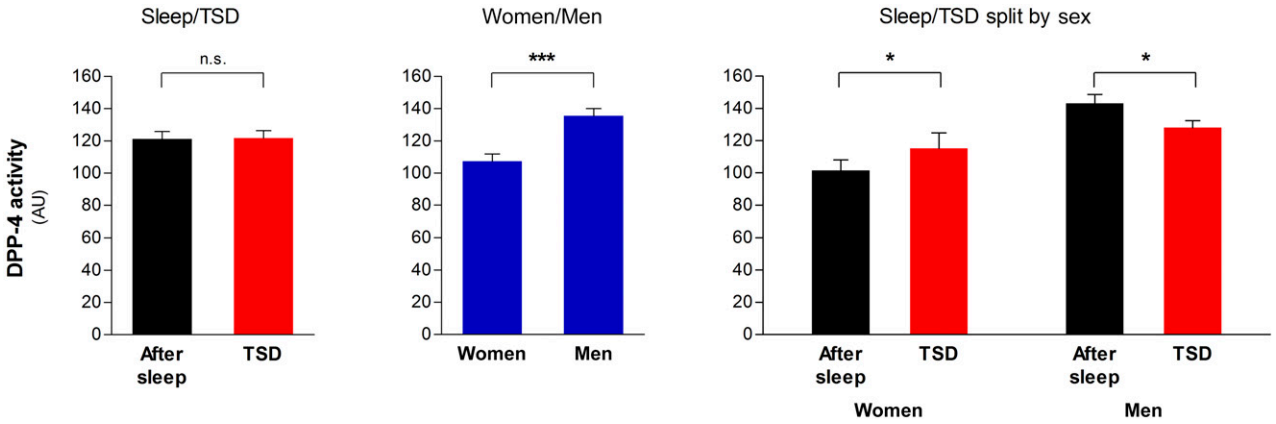

Figure 1—Measured enzymatic activity of circulating DPP-4 after a full night of sleep and after a night of total sleep loss in women and men. Left: DPP-4 activity following sleep (black bars) and total sleep deprivation (TSD) (red bars). Numbers are derived from the estimated means for the main effect of experimental condition (sleep/TSD) in the linear mixed model ($N = 25$). Middle: DPP-4 activity in women ($N = 13$) and men ($N = 12$). Numbers are derived from the estimated means for the main effect of sex in the linear mixed model. Right: Mean DPP-4 activity following sleep as well as TSD, split by sex. Wilcoxon signed rank test was used to test for differences in DPP-4 activity between the experimental conditions (sleep/TSD) in women ($N = 11$) and men ($N = 12$), respectively. The linear mixed model showed an interaction between experimental condition and sex ($P = 0.029$). The direction of the interaction is demonstrated by this graph. One of the data points for two of the participating women are missing due to technical and blood drawing failure. Therefore, these two participants were not part of the Wilcoxon signed rank tests (but included in the linear mixed model), nor were they included in the means used to generate the right panel. Error bars represent SEM. AU, arbitrary unit; n.s., not significant. *$P < 0.05$; ***$P < 0.001$. (A high-quality color representation of this figure is available in the online issue.)

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Received 23 August 2017 and accepted 18 October 2017.

activity were examined by using a linear mixed model (restricted maximum likelihood method; scaled identity as covariance matrix) with the fixed factors experimental condition (sleep/total sleep deprivation) and sex (women/men), as well as their interaction. All participants gave written informed consent and the study was approved by the regional ethics review board in Uppsala (dnr 2015/347).

During the experimental sleep condition, participants slept 7.36 ± 0.05 h (mean ± SEM), as measured by polysomnography. The enzymatic activity of circulating DPP-4 was similar irrespective of whether the participants had been asleep or awake during the preceding night (Fig. 1, left panel; $F_{1,44} = 0.007$; $P = 0.932$). Men generally had higher DPP-4 activity than the women (Fig. 1, middle panel; $F_{1,44} = 19.2$; $P = 0.00007$). Importantly, sleep loss altered DPP-4 activity differently in male and female participants (Fig. 1, right panel; $F_{1,44} = 5.1$; $P = 0.029$ for experimental condition × sex).

Activity of circulating DPP-4 increased by about 14% in women, whereas it decreased by about 11% in men following sleep loss. Although the changes in women are smaller than previously observed increases in DPP-4 activity in patients with type 2 diabetes compared with control subjects (~29%) (4), the change in DPP-4 activity seen in women following sleep loss may nonetheless be of clinical concern. Although our findings could be seen as a favorable metabolic response of men to sleep loss, it must be noted that chronic poor sleep patterns increase the risk of developing metabolic diseases in both sexes (2). Moreover, we only collected one morning fasting blood sample following total sleep loss. Thus, one has to be cautious when extrapolating our findings to different types of sleep loss, other times of the day, and nonfasting conditions. The wider metabolic implications of our findings, e.g., GLP-1, remain to be elucidated. A previous study found decreased GLP-1 concentrations during afternoon hours in women but not men following short sleep (5). In contrast, blood concentrations of the hunger-promoting hormone ghrelin were increased in men but not women following short sleep (5). In line with these results, our findings add to the emerging evidence suggesting that sleep loss may cause metabolic disruptions via separate pathways in men and women.

Acknowledgments. The authors thank Misty Attwood and Nipuni Welihinda, Department of Neuroscience, Uppsala University, Uppsala, Sweden, and Pablo Vallejos, Fusion Plasma Physics, Royal Institute of Technology, Stockholm, Sweden, for their insightful comments on the manuscript.

Funding. This work was supported by the Swedish Folksam Research Foundation (to C.B.), Novo Nordisk Foundation (NNF14OC0009349 to C.B.), the Swedish Brain Research Foundation (FO2016-0092 to C.B.), the Swedish Research Council (2015-03100 to C.B.), and the German Federal Ministry of Education and Research and the Brandenburg State (DZD grant 82DZD00302 to H.V.).

The funders did not have any role in study design or interpretation of the results, nor in the writing process.

Duality of Interest. No potential conflicts of interest relevant to this article were reported.

Author Contributions. F.H.R. and C.B. designed the study. F.H.R., F.S., and C.B. analyzed the data. F.H.R., F.S., H.V., and C.B. interpreted the data. F.H.R., S.K., and P.A. collected the data. J.W. and H.V. analyzed the blood samples. All authors contributed to writing and have approved the final manuscript. F.H.R. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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