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Effect of circadian rhythm on brain NAD: an MRS study at 7T

Zhiwei Huang[1], Bernard Cuenoud[2], Mickael Hartweg[3], Daniel Wenz[1], Ying Xiao[1], Song-I Lim[1], Mark Stephan Widmaier[1], Lijing Xin[1]

1. Center for Biomedical Imaging, Ecole Polytechnique Fédérale de Lausanne, Lausanne, Switzerland.
2. Nestlé Health Science, Epalinges, Switzerland
3. Clinical Research Unit, Nestlé Research and Development, Lausanne, Switzerland

BACKGROUND

- The circadian rhythm (CIR): regulating cellular, physiological and behavioral processes.
- Mammalian CIR coordinated with metabolic activity through controlled expression of Nicotinamid Phosphoribosyl transferase (NAMPT)[1]. Regulation of NAMPT could result in oscillating NAD^+, an important metabolite involved in bioenergetics and cellular signaling processes[2]. The rhythmic oscillation of NAD^+ could serve as a feedback timer in turn.
- Preclinical findings: CIR is linked with the NAD levels and the NAD redox ratio[3].
- No relevant clinical study has been reported in human.

Aims

To explore the molecular basis of circadian rhythm, especially how could circadian rhythm influence the brain NAD level.

METHODS

To detect a similar effect size as observed in the red blood cells and mice livers [4, 5], 25 male subjects aging between 18-40 years old were recruited. One-week sleeping diaries were recorded prior to experiments to ensure regular sleeping habits. The experiment was implemented in fasted morning condition (8 am) and later afternoon condition (3 pm) during a day, each consisting of:

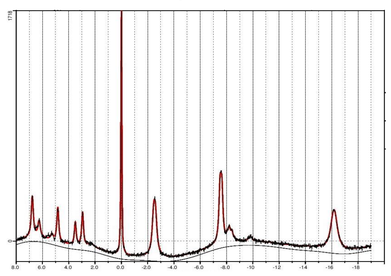
- the saliva sample collected and analyzed to determine the cortisol level.
- MR experiments performed on a 7T/68cm MR scanner (Siemens Medical Solutions, Erlangen, Germany) with a ^{1}H surface coil and a single-loop ^{31}P coil (7cm-diameter) for the occipital lobe.
    - ^{31}P-MRS: a pulse-acquire sequence (TR=3s, NA = 320), NADH and NAD^+.
    - ^{1}H-MRS: a short-TE STEAM sequence (TE/TM/TR=4.5/25/5500ms, NA = 64, voxel size = 35x20x25mm^3) , lactate.
- BART[6] (Inquisit Lab) was implemented as a measure of individual risk taking propensity.

RESULTS

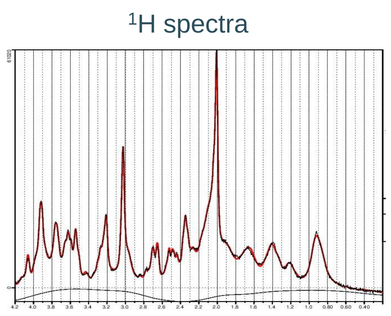
- The cortisol level and BART performance were significantly higher in the morning and afternoon respectively.; the BART performance was significantly higher in the afternoon.
- The redox ratio variance was significantly larger in the AM. By stratifying the subjects into a High(H) group and a Low (L) group relative to the AM ratio median value, significant increase of NAD ratio in the afternoon was found in L group, driven by the decrease of NADH, and the opposite was found in H group.

Schematic illustration of circadian clock regulation in the NAD + salvage pathway[7]

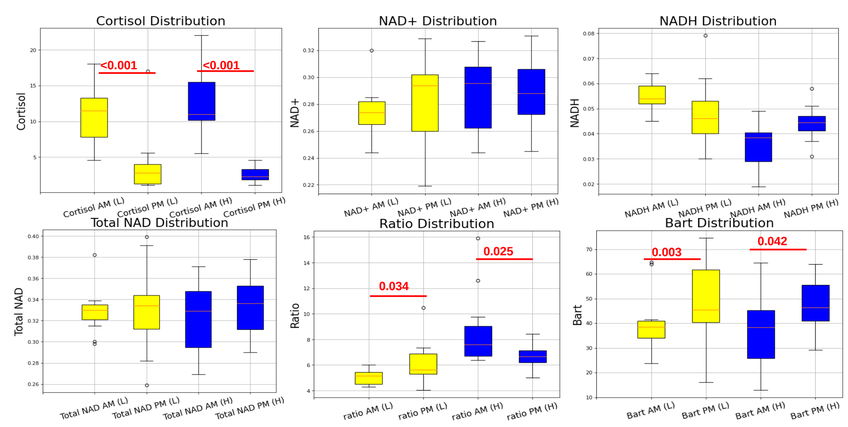
^{31}P spectra



^{1}H spectra



	average	SD	% diff PM v.s AM	P value PM v.s AM	variance	P value variance
NAD ratio AM	6.78	2.73	-5.96	0.455	7.45	**<0.001**
NAD ratio PM	6.38	1.35			1.82	
BART AM	38.40	14.21	24.95	**<0.001**	201.92	0.2
BART PM	47.96	13.50			182.23	
Total *NAD* AM	0.32	0.03	1.46	0.548	0.0009	0.07
Total *NAD* PM	0.33	0.03			0.0009	
Cortisol AM	11.88	4.48	-72.56	**<0.001**	20.07	**<0.001**
Cortisol PM	3.26	3.26			10.63	



CONCLUSIONS

This is the first study to explore the relationship between CIR and brain metabolites in human. The success of the project could contribute to a greater molecular understanding of the CIR in human and open therapeutic perspectives for diseases. That H and L group exhibited different changes of the redox ratio during the day indicated that there might be two different metabolic processes.

Reference:

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