Disruption of the body's internal clock causes disruption of metabolic processes

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Chronobiologists from Charité – Universitätsmedizin Berlin have shown that the body's carbon monoxide metabolism is closely linked to the body's circadian (internal) clock. Carbon monoxide, a toxic gas found in exhaust fumes and cigarette smoke, is also an endogenous by-product of the degradation of heme, the hemoglobin cofactor responsible for giving red blood cells their color. The production of carbon monoxide is regulated by the body's internal clock, and this clock, in turn, is regulated by carbon monoxide. An article discussing the close reciprocal relationship between these two regulatory mechanisms has been published in the current issue of the journal *Nature Structural & Molecular Biology*.

A close link between metabolic processes and the body's internal clock ensures that our bodies are optimally adapted to environmental conditions, such as the availability and timing of meals. Cell-based circadian clocks, which detect signals from metabolic processes, also cause the relevant cellular metabolic processes to adapt in response to these signals. The disruption of one of these regulatory mechanisms results in the disruption of the other - a phenomenon manifested by the occurrence of conditions such as diabetes or metabolic syndrome in people whose internal clocks are disrupted e.g. as a result of shift work. Under the leadership of Prof. Dr. Achim Kramer, Head of the Chronobiology Research Unit at Charité's Institute for Medical Immunology, a team of researchers has been studying the role of heme (the iron-containing red pigment in red blood cells) for the body's circadian rhythms. Heme is a complex molecule that is part of numerous

other proteins and acts as a metabolic sensor.

"Our research has shown that carbon monoxide, a toxic gas that is also a by-product of the degradation of heme, has a crucial role in keeping the body's internal clock ticking as it should," explains Prof. Kramer. He adds: "The production of this molecule inside the cells of the liver can be disrupted through pharmacological inhibition, or by genetically switching off the expression of heme oxygenase - the enzyme required for its synthesis. As a result, normal internal rhythmicity is disrupted, the clock is slowed down." Perturbations of this kind result in the dysregulation of hundreds of different genes, which also happen to be responsible for essential metabolic processes, such as the synthesis of glucose. Results from this study help us to further understand how metabolic disorders and the body's internal clock are interlinked. By identifying the molecular mechanisms responsible for the body's circadian rhythms, we may be able to develop targeted therapies.

More information: Roman Klemz et al, Reciprocal regulation of carbon monoxide metabolism and the circadian clock, *Nature Structural & Molecular Biology* (2016). DOI: 10.1038/nsmb.3331

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