

Novel hormone replacement therapy trial demonstrates improved memory function in adrenal patients

April 9 2018

Better timing for cortisol replacement therapies, to more closely replicate the secretion patterns of people with normal levels of the hormone, has shown a significant improvement in patients' cognitive function. This is the striking finding from a new trial led by University of Bristol scientists including Professor Stafford Lightman and published in the *Proceedings of the National Academy of Science (PNAS)*. The findings are potentially important and underline the case for novel therapeutic approaches, as patients on cortisol replacement therapy often have side effects that make it difficult for them to lead normal lives.

Cortisol is a key hormone that is critical for the maintenance of life. It regulates a wide range of physiological functions from metabolism and immune responses through to [blood pressure](#) and blood sugar levels. It plays an important role in memory formation and other cognitive processes, and helps the body respond to stress. Low levels of cortisol are associated with debilitating fatigue, muscle weakness, dangerously low blood pressure and depression.

Cortisol-deficient patients who are diagnosed with adrenal insufficiency and placed on treatment recover from their worse symptoms with daily hydrocortisone replacement therapy. However, the condition is life-long and even with current optimal regimes of cortisol replacement this oral therapy is associated with impaired quality of life affecting cognitive function, mood, sleep and immune response.

In people with normal levels of the hormone, cortisol is secreted in an oscillating pattern with pulses of hormone released at multiple times throughout a 24-hour day. In this study, the authors recruited 15 male volunteers between 20 and 33-years. Participants were provided with cortisol replacement therapy either via a continuous infusion replicating normal human secretion frequencies, or received the same level of cortisol without these oscillating patterns via either oral tablets or a continuous infusion. The study then assessed the effect on participants' memory, emotional responsiveness and brain activity across the three treatment methods.

The team found significant variation in the response patterns of certain glucocorticoid-sensitive brain regions to emotional images of facial expression, when they compared outcomes across the three treatment methods that study participants undertook.

Compared with the other treatments, oscillating pulsed hydrocortisone dosing most closely replicates normal human patterns of cortisol secretion. Study participants performed significantly better across the range of cognitive tasks they were assigned, during this treatment and were observed to have improved working memory capacity under high-cognitive demands.

Participants reported poorer sleep quality during a constant non-pulsatile hydrocortisone infusion over 24 hours, compared with the two other treatments they undertook during this trial. This finding is consistent with outcomes in a previous international study of continuous hydrocortisone infusion outcomes, but remains unexplained.

Stafford Lightman, Professor of Medicine and a neuroendocrinology expert at Bristol Medical School, said: "The pharmaceutical industry has invested heavily in providing new and more potent drugs. However, our findings suggest that rather than needing any new drugs, it is the timing

of cortisol delivery- in line with the body's own rhythmic pattern of [cortisol secretion](#) - that is important for normal cognition and behaviour. This has major implications for the use of chronobiology (timing biology) to improve therapies by taking account of the importance of the pattern of drug presentation to the tissues of the body. This could be important not only for improving [cortisol](#) replacement therapy but also has major implications understanding the role of glucocorticoid dynamics in stress and psychiatric disease."

Katherine White, Chair of Addison's Disease Self-Help Group (the charity for adrenal patients in UK and Ireland) said: "This is an ambitious study and its findings offer a welcome insight into the quality of life impairments experienced by many adrenal patients. The study's reported conclusions suggest an exciting potential for chronobiological approaches in endocrine replacement [therapy](#) to improve cognitive function and sleep quality for adrenal patients."

More information: K. Kalafatakis et al., "Ultradian rhythmicity of plasma cortisol is necessary for normal emotional and cognitive responses in man," *PNAS* (2018).

www.pnas.org/cgi/doi/10.1073/pnas.1714239115

Provided by University of Bristol

Citation: Novel hormone replacement therapy trial demonstrates improved memory function in adrenal patients (2018, April 9) retrieved 23 June 2024 from

<https://medicalxpress.com/news/2018-04-hormone-therapy-trial-memory-function.html>

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