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NEURODEGENERATIVE DISEASE

A good night's sleep

We all know that disrupted sleep patterns can negatively affect our mental health. Disturbed sleep is also a symptom of many neurodegenerative diseases, including Huntington's disease (HD). Morton and colleagues have now shown that modulating abnormal sleep patterns by pharmacological means can improve cognitive function in a mouse model of HD.

Previously, Morton's laboratory revealed that the R6/2 mouse, which has motor and cognitive deficits that are typical of the human disease, suffers from disrupted sleep–wake patterns, including an increase in daytime activity (wild type mice usually sleep during the day) and a decrease in nocturnal activity. Eventually the sleep–wake cycle disintegrates. Reasoning that disrupted sleep might underlie some of the cognitive deficits, they investigated whether normalizing sleep patterns would improve cognition.

R6/2 mice were previously shown to exhibit altered expression of genes that are associated with circadian pacemaking, including period 2 and prokineticin 2, in their suprachiasmatic nuclei (SCN). However, the authors found that the R6/2 SCN, when it was isolated from the rest of the brain, showed normal firing behaviour and rhythmic fluctuations in gene expression. This implied that regions up or downstream of the SCN are the source of the disrupted sleep patterns.

To increase their daytime sleeping, the mice were treated once a day with the benzodiazepine tranquilizer Alprazolam, for up to 12 weeks. This imposed 2–3 hours of sleep each day. Consistent with an improvement in circadian timekeeping, Alprazolam partially normalized the expression of period 2 and prokineticin 2 in the SCN. When tested in a two-choice swim tank test (which measures the ability to learn to associate a visual cue with the position of a submerged escape platform), the performance of Alprazolam-treated R6/2 mice was improved, both when treatment started before disease symptoms became apparent and when treatment began postsymptomatically.

The mechanisms by which imposed daytime sleep is linked to improvements in cognitive function are unclear at present. Potential safety risks or tolerance issues that might be associated with drugs such as Alprazolam also remain to be addressed. However, the possibility that similar manipulations could have comparable effects in patients with HD or other neurodegenerative diseases will be an interesting subject for further research.

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ORIGINAL RESEARCH PAPER Pallier, P. N. *et al.* Pharmacological imposition of sleep slows cognitive decline and reverses dysregulation of circadian gene expression in a transgenic mouse model of Huntington's disease. *J. Neurosci.* **27**, 7869–7878 (2007)