Nature Reviews Neuroscience | AOP, published online 13 July 2011; doi:10.1038/nrn3072

PSYCHIATRIC DISORDERS

The dark side of depression

Depression is associated with disruptions in circadian rhythms, including altered sleep–wake patterns, and with immune system activation, as indicated by increased levels of pro-inflammatory cytokines. Monje *et al.* now show that nuclear factor-κB (NF-κB) might be the molecular link between the two in a mouse model of depression based on circadian disruption.

The authors housed mice in constant darkness (DD) or a regular light–dark pattern (LD) for 4 weeks. After this period, DD mice showed depression-like behaviour in forced-swim and tail-suspension tests and a reduced preference for sucrose over water, which is suggestive of an anhedonia-like state. These animals also showed evidence of immune activation, with higher levels of interleukin-6 (IL-6) in plasma than LD mice, and higher levels of IL-6 and IL-1 receptor type 1 in hippocampal tissue. Thus, exposure to constant darkness induces changes that parallel changes found in humans with depression. In addition, neurogenesis in the hippocampal dentate gyrus was reduced in DD mice compared with LD mice.

The authors next examined what mediated the observed effects of constant darkness. They focused on NF-κB, as this transcription factor is known to be activated by stress and disruptions in sleep–wake patterns and has a role in coordinating immune responses. The DNA-binding activity of NF-κB in nuclear extracts of hippocampal tissue was greater in DD mice than in LD mice. The possible involvement of NF-κB was further tested by injecting mice with inhibitors of NF-κB activity. This treatment had no effects in LD mice, whereas it reduced depression-like behaviour in the forced-swim test and normalized hippocampal IL-6 levels and hippocampal neurogenesis in DD mice. Together, these findings indicate that NF-κB mediates depression-associated alterations induced by circadian disruption.

NF-κB controls the expression of several pro-inflammatory cytokines, including IL-6. The authors showed that the effect of constant-dark exposure on behaviour in the forced-swim test was reduced in mice lacking IL-6. This suggests a model in which circadian disruption increases NF-κB activation, thereby inducing IL-6 expression, which is required for the expression of depression-like behaviour.

The authors also showed that hippocampal expression of PER2 and NPAS2 — protein products of clock genes that have been associated with depression — was altered in DD mice, with PER2 levels being lower and NPAS levels being higher in DD mice than in LD mice. Treatment with an NF-κB inhibitor normalized PER2 and NPAS2 expression in DD mice, suggesting that NF-κB may regulate the transcription of these clock genes. Interestingly, PER2 has been shown to regulate adult hippocampal neurogenesis, which suggests that altered PER2 levels in DD mice may play a part in the reduced hippocampal neurogenesis found in these mice.

Immune activation and disruptions of circadian regulation have been independently associated with depression in humans, and this study provides evidence that these two processes are linked. Whether immune activation plays a part in the effects of other circadian rhythm disturbances, such as in jet lag, could be an interesting topic for future research.

Leonie Welberg

> “the effect of constant-dark exposure on behaviour in the forced-swim test was reduced in mice lacking IL-6”

ORIGINAL RESEARCH PAPER Monje, F. J. *et al.* Constant darkness induces IL-6-dependent depression-like behavior through the NF-κB signaling pathway. *J. Neurosci.* **31**, 9075–9083 (2011)
FURTHER READING Dantzer, R. *et al.* From inflammation to sickness and depression: when the immune system subjugates the brain. *Nature Rev. Neurosci.* **9**, 46–56 (2008) | Wulff, K. *et al.* Sleep and circadian rhythm disruption in psychiatric and neurodegenerative disease. *Nature Rev. Neurosci.* **11**, 589–599 (2010)