TNF-alpha suppresses the expression of clock genes by interfering with E-box mediated transcription

Summary / Zusammenfassung
Production of TNF-alpha and IL-1 in infectious and autoimmune diseases is associated with fever, fatigue and sleep disturbances which are collectively referred to as sickness behavior syndrome. In mice TNF-alpha and IL-1 increase non-rapid eye movement sleep. Since clock genes regulate the circadian rhythm and thereby locomotor activity and may alter sleep architecture we assessed the influence of TNF-alpha on the circadian timing system. TNF-alpha is shown here to suppress the expression of the PAR bZip clock-controlled genes Dbp, Tef and Hlf and of the period genes Per1, Per2 and Per3 in fibroblasts in-vitro and in-vivo in the liver of mice infused with the cytokine. The effect of TNF-alpha on clock genes is shared by IL-1beta, but not by IFN-alpha, IFN-gamma, and IL-6. Furthermore, TNF-alpha interferes with the expression of Dbp in the suprachiasmatic nucleus and causes prolonged rest periods in the dark when mice show spontaneous locomotor activity. Using clock reporter genes TNF-alpha is found to inhibit CLOCK-BMAL1 induced activation of E-box regulatory elements dependent clock gene promoters. We suggest that altered behavior with fatigue, as seen in infectious and autoimmune diseases, may occur due to TNF-alpha evoked impairment of clock function.

Publications / Publikationen

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