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A role for the CREB-binding protein in behavioural regulation

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The circadian clock regulates behaviour and a large array of physiological functions such as metabolism, cell proliferation and neuronal activity in synchrony with the 24 hour cycle of day and night. The heterodimeric complex of the transcription factors CLOCK (CLK) and CYCLE (CYC) constitutes the positive element of the circadian clock that controls genome wide transcription in *Drosophila* and mammals. We screened duplication mutants for circadian behavioural phenotypes in *Drosophila* and identified a role for the transcription co-activator CREB-binding protein (CBP) in the circadian clock, as a co-activator of CLK/CYC-dependent transcription. Over-expression of CBP causes behavioural and molecular arrhythmicity and partial loss of function results in a sever long-period phenotype. We show a physical interaction between CBP and the CLK/CYC complex. Increased or reduced levels of CBP enhance or decrease CLK/CYC-dependent transcription respectively, demonstrating that circadian transcription depends on limiting amounts of the transcription co-activator. We also found that cell signalling pathways, which control CBP function, such as cyclic nucleotide/PKA, calcium/CaMK II and Ras/MAPK pathways regulate CLK/CYC-dependent transcription. Although regulation of CBP by these pathways is well established, we show that CaMK II and p42-MAPK also phosphorylate CLK directly. Our results identify CBP as new clock gene in *Drosophila* that acts as a regulatory component for clock controlled behaviour and physiology. In addition we identified two CLK kinases, CaMK II and p42-MAPK, which may contribute to a synchronisation of circadian transcription with vital cellular activities.