

Mathematical Modeling for Pacemaker-neuron-dependent Molecular Rhythm Alteration by *Drosophila* Clock Mutant

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ABSTRACT

In *Drosophila*, circadian (~24h) behavior is regulated by about 150 pacemaker neurons. To generate and maintain 24h rhythm, circadian gene expression in each pacemaker neurons is driven by transcriptional-translational feedback loop (TTFL). In TTFL of *Drosophila*, dCLOCK-CYCLE (dCLK-CYC) binds to the E-box (CACGTG) and activates the expression of period (*per*) and timeless (*tim*). Translated PER and TIM proteins repress their own transcription by removing dCLK-CYC dimer from the E-box. Interestingly, dCLK- Δ , which is a mutant of dCLK deleted amino acids (AA) 657-707 region and has impaired binding with PER, induces different effect on molecular rhythms depending on pacemaker neurons. For oscillation of PER, amplitude is largely reduced in ventral lateral neurons (LN_vs), but not in dorsal neurons (DNs). However, how dCLK- Δ /CYC controlled TTFL operates differently in pacemaker neurons is unclear. To investigate this unexpected phenomenon, we established the mathematical model for the TTFL in *Drosophila* and predicted that pacemaker-neuron-dependent alteration of the molecular clockwork is caused by the difference of molecular composites between LN_vs and DNs. This is confirmed by the follow up experiment. This work shows that clockworks at the molecular level have a critical role for specific functions of each pacemaker neurons.