Mammalian circadian clock in peripheral organs, molecular mechanism and entrainment

The circadian system controls timing of behavioral and physiological processes in most organisms. In mammals, central oscillator is located in the suprachiasmatic nuclei (SCN) of the anterior hypothalamus. Apart from the SCN, peripheral oscillators are located in numerous organs like liver, heart, lung, muscle, intestine etc. The central and peripheral oscillators need to be synchronized by external cues (Zeitgeber). The SCN coordinates and entrains the phase of the clocks in numerous peripheral tissues via neuronal and humoral signals. For the SCN, dominant synchronizer is external light-dark cycle. Peripheral oscillators are cell-autonomous, they could work also independently of the SCN as a consequence of a feeding cycle. The basic molecular core clock mechanism responsible for generating circadian rhythms in the central and peripheral clocks is composed of transcriptional/translational feedback loops between the clock genes and their protein products.

The aim of the present thesis was to ascertain whether the clock gene and protein expressions exhibit circadian rhythms in the rat intestine and whether the core clock mechanism drives expression of a cell cycle regulator *rWee1*. Next aim was to reveal how the circadian rhythms in expression of clock genes develop in the rat colon during prenatal and early postnatal ontogenesis.

Daily expression profiles of clock genes *rPer1*, *rPer2*, *rBmal1*, *rRev-erb-α*, *rClock*, *rCry1* and clock-controlled gene *rWee1* were examined by quantitative PCR within different parts of epithelium of the rat intestine, namely of the duodenum, jejunum, ileum, colon. *rPer1*, *rPer2*, *rBmal1*, *rRev-erb-α* and *rWee1* genes were expressed rhythmically in all studied parts of the gut. The rhythms in gene expression exhibited differences in their phases, such that the rhythm in duodenum was phase-advanced to the colon. rPER1 and rBMAL1 proteins were localized in the colonic epithelium by immunocytochemistry. Colonic clock developed gradually during ontogenesis. The phase of the developing rhythms shifted during postnatal period likely due to changes in the feeding habits.

Understanding the molecular mechanism of the circadian clock within the intestine may facilitate treatment of diseases caused by malfunctions of the circadian system, like colorectal cancer.