

# ABSTRACT

The circadian system controls the timing of behavioral and physiological processes in most organisms with a period of about 24 h. In mammals, the circadian system consists of the central oscillator in the suprachiasmatic nuclei (SCN) and peripheral oscillators located in numerous organs such as the liver, heart, lung, muscles, intestines etc. Peripheral oscillators are cell-autonomous, they could also work independently of the SCN entrained by a feeding cycle. The misalignment of the endogenous timekeeping system, due to e.g. irregular daily schedule or shiftwork, may lead to the development of severe diseases including sleep disorders, gastrointestinal (GI) problems and various types of cancer. Therefore, understanding the molecular mechanism of the circadian clock may facilitate the treatment of diseases caused by malfunction of the circadian system.

In my PhD thesis, I focused on the determination and synchronization of circadian clocks within the rat digestive system and on their development during ontogenesis. Moreover, the circadian system of a rat strain with pathology, i.e., spontaneously hypertensive rat (SHR) was also studied.

We identified the circadian clocks in the individual parts of the intestine and ascertained that these clocks are mutually synchronized with the phase-delay along the cranio-caudal axis of the alimentary tract.

Our data further showed that the GI clocks differ in their resistance to disruption by prolonged exposure to constant light. Distorted rhythmicity may be restored by a restricted feeding regime (RF) with various efficiency in individual GI tissues. The colonic clock seems to be more sensitive to changes in external conditions than the hepatic and duodenal clock.

The rhythmic expression of clock genes in the colon developed gradually during the postnatal ontogenesis, with changes in their mutual phasing and amplitudes until an adult-like state at postnatal day 30. Prenatally, the maternal circadian phase may modulate further development of the colonic clock. Postnatally, the presence/absence of rhythmic maternal care affected the phasing of the clock gene expression profiles in the colon.

Finally, we proved that the organization of the circadian system in SHR differs to that of control normotensive Wistar rats. These changes may result in poor temporal control of gene expression in peripheral organs. Moreover, SHR were more sensitive to feeding challenge at behavioral level which correlated with the responsiveness of their hepatic clock. The potential role of *Bmal2* gene in the adaptation of the hepatic clock to the RF was suggested.