Summary:

The circadian system plays an important role in human physiology and pathophysiology. It controls all processes that repeat in our body within a 24-hour period. It is a complex system that works from the behavioral level to the molecular level. This system is controlled from the central brain structure located in the hypothalamus, but its rhythmic manifestations can also be observed in almost any individual body cells.

Disruption of this system in humans is often associated with the development of affective disorders or neurodegenerative diseases. The affective disorder has often been associated with a phase shift in some of the circadian driven outputs, as for example, rhythm in their physical activity. The patients with neurodegenerative disorders are seen to have circadian amplitude damping in a series of circadian rhythms. Therapeutic approaches which aim to stabilize and strengthen the circadian rhythms have also a positive long term effect on the course of these diseases. Interestingly, in the genetic studies of these diseases, a couple of specific polymorphisms have been identified in areas related to the molecular mechanism of the internal clock.

In this thesis, I tried to look at the human circadian rhythms from several different angles. In the first part of this thesis I tried to identify changes in the human circadian system during the early stages of neurodegenerative diseases. The first study was focused at patients with Alzheimer's disease, in whom we found a decrease in nocturnal melatonin production. In the second study, we studied patients with a REM behavioral disorder, which is associated with development of Parkinson's disease. In these patients, we described a phase delay in the melatonin onset and the disappearance of rhythmic oscillations of some clock genes.

In the second part of the thesis, I studied the ability of the human circadian system to cope with the conditions of the polar day. Our subjects were exposed to a day cycle lacking the natural alternation between a light and dark period, which serves as the main synchronization signal for our internal clock. The study showed that circadian rhythms can maintain their rhythmic oscillations and the clocks are likely to use the non-photic synchronization cues as could be regular food intake or a fixed daily schedule. Although the polar day affected melatonin onset, its production was rhythmic but significantly delayed in the same fashion as with physical activity. The clock genes expression in peripheral clocks remained unaffected.

The last part of the thesis was focused on the circadian rhythms in patients with bipolar disorder studied *in vitro* and post-mortem circadian oscillations in the anterior cingulate in patients with unipolar depression. As with the *in vitro* model, we chose transformed lymphocytes cell lines collected from bipolar patients. Unfortunately, we found that transformed lymphocytes are not suitable for studying the circadian oscillations.

The results from the whole-transcriptom circadian analysis in anterior cingulate from unipolar patients revealed a loss of rhythmic oscillations of the core clock genes compared to healthy controls. These results are consistent with the previous studies that imply impaired internal clock function in patients with unipolar depression.

Key words: circadian rhythms, bipolar disorder, unipolar disorder, Alzheimer disorder, REM behavior disorder, clock genes