

## Circadian Rhythmic Expression of Choroid Plexus Membrane Transport Proteins

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**Abstract :** The choroid plexus (CP) epithelial cells form the blood-cerebrospinal fluid barrier. This barrier is highly important for brain protection by physically separating the blood from the cerebrospinal fluid, controlling the trafficking of molecules, including therapeutic drugs, from blood to the brain. The control is achieved by tight junctions between epithelial cells, membrane receptors and transport proteins from the solute carrier and ATP-binding cassette superfamily on the choroid plexus epithelial cells membrane. Previous research of our group showed a functional molecular clock in the CP. The key findings included a rhythmic expression of Bmal1, Per2, and Cry2 in female rat CP. and a rhythmic expression of Cry2 and Per2 in male rat CP. Furthermore, in cultured rat CP epithelial cells we already showed that 17 $\beta$ -estradiol upregulates the expression of Bmal1 and Per1, where the Per1 and Per2 upregulation was abrogated in the presence of the estrogen receptors antagonist ICI. These findings, together with the fact that the CP produces robust rhythms, prompt us to understand the impact of sex hormones and circadian rhythms in CP drug transporters expression, which is a step towards the development and optimization of therapeutic strategies for efficiently delivering drugs to the brain. For that, we analyzed the circadian rhythmicity of the Abcb1, Abcc2, Abcc4 Abcg2, and Oat3 drug transporters at the CP of male and female rats. This analysis was performed by accessing the gene expression of the mentioned transporters at 4 time points by RT-qPCR and the presence of rhythms was evaluated by the CircWave software. Our findings showed a rhythmic expression of Abcc1 in the CP of male rats, of Abcg2 in female rats, and of Abcc4 and Oat3 in both male and female rats with an almost antiphasic pattern between male and female rats for Abcc4. In conclusion, these findings translated to a functional point of view may account for daily variations in brain permeability for several therapeutic drugs, making our findings important data for the future establishment and development of therapeutic strategies according to daytime.

**Keywords :** choroid plexus, circadian rhythm, membrane transporters, sex hormones

**Conference Title :** ICC 2024 : International Conference on Chronobiology

**Conference Location :** Paris, France

**Conference Dates :** December 30-31, 2024