

## Circadian-Clock Controlled Drug Transport Across Blood-Cerebrospinal Fluid Barrier

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**Abstract :** The development of therapies for central nervous system (CNS) disorders is one of the biggest challenges of current pharmacology, given the unique features of brain barriers, which limit drug delivery. Efflux transporters (ABC transporters) expressed at the blood-cerebrospinal fluid barrier (BCSFB), are the main obstacles for the delivery of therapeutic compounds into the CNS, compromising the effective treatment of brain cancer, brain metastasis from peripheral cancers, or even neurodegenerative disorders. It is thus extremely important to understand the regulation of these transporters for reducing their expression while treating a brain disorder or choosing the most appropriate conditions for drug administration. Based on the fact that the BCSFB have fine-tuned biological rhythms, studying the circadian variation of drug transport processes is critical for choosing the most appropriate time of the day for drug administration. In our study, using an in vitro model of the BCSFB, we characterized the circadian transport profile of methotrexate (MTX) and donepezil (DNPZ), two drugs involved in the treatment of cancer and Alzheimer's Disease symptoms, respectively. We found that MTX is transported across the basal and apical membranes of the BCSFB in a circadian way. The circadian pattern of an ABC transporter, Abcc4, might be partially responsible for MTX circadian transport. Furthermore, regarding the DNPZ transport study, we observed that the regulation of Abcg2 expression by the circadian rhythm will impact the circadian-dependent transport of DNPZ across the BCSFB. Overall, our results will contribute to the current knowledge on brain pharmacoresistance at the BCSFB by disclosing how circadian rhythms control drug delivery to the brain, setting the grounds for a potential application of chronotherapy to brain diseases to enhance the efficacy of medications and minimize their side effects.

**Keywords :** blood-cerebrospinal fluid barrier, ABC transporters, drug transport, chronotherapy

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