PROSTAGLANDIN E₂ EFFLUX TRANSPORT VIA THE BLOOD-BRAIN BARRIER IN LIPOPOLYSACCHARIDE-INDUCED INFLAMMATORY MODEL MICE
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[Purpose] Bacterial infection increases the cerebral concentration of the prostaglandin E₂ (PGE₂), which induces inflammatory-responses such as a fever. Under normal condition, PGE₂ is eliminated from brain across the blood-brain barrier (BBB) with a half-life of 16 min. We hypothesized that inflammation affect the PGE₂ efflux transport at the BBB, thus causing the accumulation of PGE₂ in the brain. The purpose of this study was to investigate the BBB efflux transport of PGE₂ in the inflammatory model mice.

[Methods] Inflammatory model mice were generated by 3.0 mg/kg lipopolysaccharide (LPS) intraperitoneal administration. [³H]PGE₂ elimination across the BBB was analyzed by mouse brain efflux index method.

[Results and Discussion] [³H]PGE₂ elimination across the BBB was prolonged with a half-life of 125 min and inhibited by unlabeled PGE₂ co-administration in LPS-treated mice. Although intracerebral and i.v. administration of cefazolin inhibited the [³H]PGE₂ elimination in normal mice, the administration of cefazolin had little effect in LPS-treated mice. The administration of cefmetazole inhibited the [³H]PGE₂ elimination both in normal mice and in LPS-treated mice. These results suggest that the BBB efflux transport function of PGE₂ is attenuated in LPS-treated mice and by cefmetazole administration.

[Conclusion] Attenuation of PGE₂ efflux transport at the BBB might enhance the accumulation of PGE₂ in inflammatory model mice.

PREDICTION OF DIFFERENCES BETWEEN DRUG CONCENTRATIONS IN THE EXTRACELLULAR FLUID IN THE BRAIN AND CEREBROSPINAL FLUID
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[Purpose] The unbound drug concentration in the brain (C_u,brain) is a critical factor for the pharmacological effects/adverse reactions in the central nervous system. The concentration in the cerebrospinal fluid (CSF) (C_CSF) has been generally used as a surrogate for C_u,brain because of the difficulty in measuring it directly, although C_u,brain is different from C_CSF in some drugs. We elucidated that active efflux by P-gp and/or Bcrp accounts for a large gap between C_u,brain and C_CSF. In the present study, we performed the quantitative prediction of the gap using the in vitro permeability clearance and transport activities by P-gp and Bcrp. [Method] A three-compartment model which consists of blood, brain and CSF compartments was used. A non-linear least squares method was performed using WinNonlin for simultaneously fitting the equations obtained under steady-state to unbound brain-and CSF-to-unbound plasma ratio (K_p,brain or K_p,CSF) of 22 compounds in rats to obtain the kinetic parameters and scaling factors. Permeability clearance was measured using artificial membrane, PAMPA. Transport activities by P-gp and Bcrp were determined by measuring the transcellular transport across the stable transfectants. [Results] There was a reasonable agreement between the predicted and actual K_p,brain and K_p,CSF with the predicted values of 20 compounds being within three-fold of the observed values, whereas genistein and dantrolene were outliers. The predicted K_p,CSF values of 21 compounds were within 3-fold of the observed values except for dantrolene, which was underestimated. [Conclusion] The present study suggests that the passive permeability and the in vitro transport activity of Bcrp and P-gp are useful parameters to quantitatively predict the difference between C_CSF and C_u,brain and to judge if C_CSF can be used as a surrogate for C_u,brain.