Abstract

The migration of substances between the blood circulation and the central nervous system (CNS) is regulated by the blood-brain barrier (BBB). Small, lipophilic molecules such as carbon dioxide, oxygen or ethanol can pass the BBB by passive, transcellular diffusion, while the paracellular transport of hydrophilic substances is restricted by intercellular tight junctions. Due to accessory transport systems, the BBB is able to regulate specifically the permeation of substances (e.g. nutrients) (Ballabh et al., 2004).

Non-steroidal anti-inflammatory drugs (NSAIDs) are among the most commonly used substances world-wide, yet little is known about their ability to cross the BBB. Since NSAIDs may exhibit CNS side effects including dizziness, headaches and drowsiness we sought to study the transport of several NSAIDs (celecoxib, diclofenac, ibuprofen, lornoxicam, meloxicam, piroxicam and tenoxicam).

Both single studies and group studies were carried out applying either a single substance or several substances simultaneously across the BBB *in vitro* model based on the human cell line ECV304. The permeability data were normalized to the internal standards diazepam and carboxyfluorescein to account for cell layer's variabilities.

According to our studies, it was confirmed that crossing of ibuprofen and diclofenac through the BBB is strongly dependent on their free fraction in plasma. Comparisons with other studies carried out with cell line Caco-2 pointed to a relation between an unknown efflux system and the decreased influx of ibuprofen into the brain. Carboxyfluorescein used as a paracellular marker showed some interactions with other substances (ibuprofen, diclofenac) and thereby may not be the perfect internal standard. Addition of transporter blocker probenecid did not show any effects on ibuprofen transport, but significantly inhibited the transport of tenoxicam. Finally, the second used blocker verapamil revealed a possible relation to celecoxib. Overall, our findings suggested that the transport of ibuprofen, diclofenac, carboxyfluorescein, tenoxicam and celecoxib is supported by still unknown transport systems.

Furthermore, these results link the individual permeability coefficients with the incidence and severity of CNS side effects of the individual substances and may guide future NSAIDs drug design.