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Transport of NSAIDs across the Blood-Brain Barrier *in vitro*

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The migration of substances between blood circulation and 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) [1].

Non-steroidal antiinflammatory 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 (Diclofenac, Ibuprofen, Piroxicam, Meloxicam, Lornoxicam and Tenoxicam) across the BBB.

We carried out both single studies and group studies, applying either a single substance or several substances simultaneously to a 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. The permeability coefficients of the fastest substance Diazepam were in the range of 26-40 µl/min in the single studies. Diclofenac was the slowest NSAID with a factor of 7,10 ± 1,22 related to Diazepam, followed by the oxicams and Ibuprofen (f = 3,51 ± 0,27). Together with previous data from our group these findings suggest that the transport of Ibuprofen is supported by a still unknown transport system. 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 NSAID drug design.

[1] Ballabh P, Braun A, Nedergaard M. The blood-brain barrier: an overview. Stucture, regulation, and clinical implications. Elsevier. Neurobiol Dis. 2004; 16: 1–13. doi:10.1016/j.nbd.2003.12.016