The role of Pgp genotype in Blood-Brain-barrier permeability for antidepressant drugs

The blood-brain barrier (BBB) serves as a crucial interface between the bloodstream and the brain, regulating the transport of nutrients and other substances. Its highly selective nature poses a significant challenge for delivering medications targeting brain disorders. The function of the BBB relies on multiple processes, including drug transport by the efflux pump P-glycoprotein (P-gp) located at the luminal (blood-facing) membrane of brain capillary endothelial cells. This positioning allows it to actively efflux substrates back into the bloodstream, limiting their brain penetration. Studies on mdr1a (-/-) mouse models, lacking the the Pgp showed a higher concentrations of different antidepressants like venlafaxine, paroxetine and doxepine in brain.

However, the activity of P-gp can be affected by genetic polymorphisms (mostly single nucleotide polymorphisms, SNPs) as well as by the presence of inducers or inhibitors. The most prominent SNPs include three exon SNPs rs1045642 (3435T>C; Ile1145Ile), rs2032582 (2677 T>G/A; Ser893Ala/Thr) that may result in the TTT or CGC haplotype. Interestingly, there are also two intron SNPs rs2235015 (G>T) and rs2032583 (T>C) that were shown in the human association study, to have an impact on the remission rates in patients with major depression.

Many antidepressants are substrates of P-gp, yet their effectiveness varies: approximately 30% of patients do not respond to treatment, while another 30% experience only partial recovery. The project will focus on the correlation of the mentioned SNPs within Pgp with the antidepressant drug efficacy.

This project offers the master student to gain a practical hands-on experience with cell culture, molecular biology and genotyping tools to understand the role of Pgp genotype on blood-brain-barrier permeability.

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