Blood Brain Barrier group

Multi drug resistance and P-glycoprotein efflux transporter: physiological roles and circumvention for drug delivery

P-glycoprotein (Pgp) or MDR1 is a member of the ABC (ATP-binding cassette) transporter family expressed in many tissue barriers (e.g. gut, lung, blood-brain barrier) and secretory epithelia (e.g. kidney, bile ducts, blood-CSF barrier). Pgp can transport a wide variety of substances, including antibiotics, chemotherapeutics, antidepressants, steroid hormones, in an energy dependent manner and most often acts as an efflux transporter limiting cellular and tissue entry of endogenous toxins and xenobiotics, or facilitating their removal from target organs [1]. Pgp limits access of many drugs to the brain and has been the subject of intensive research in the last 10 years in an effort to understand more about its substrates, transporter location and how to circumvent efflux to allow drug access to the central nervous system. In a series of recent papers, the King’s College London Blood-Brain Barrier group has examined Pgp function and substrate specificity in three CNS barriers – blood-retinal, blood-brain and blood-CSF barriers – and evaluated circumvention strategies.

The outer blood-retinal barrier (retinal pigment epithelial cells, RPE) acts as a significant permeability barrier for delivering drugs to retinal neurones but only recently has Pgp been identified as a contributor to this barrier. Professor Joan Abbott and colleagues [2] evaluated whether three human RPE cell lines express Pgp so as to determine their suitability as in vitro models predicting drug transport. Using RT-PCR and immunocytochemistry, MDR1 mRNA and protein was detected in only 2 of the 3 cell lines. Of these two, they assessed functional Pgp expression using rhodamine 123 uptake, demonstrating function for the first time in cell line D407 but not in the commonly used h1RPE, concluding that only D407 has the potential to be used as a screen for candidate drugs across the RPE.

At the blood-brain barrier, results from Dr Sarah Thomas and colleagues [3] have suggested a revised role for Pgp in the regulation of glucocorticoid brain distribution. Previous evidence suggested that Pgp actively removes glucocorticoids from CNS, thus participating in hypothalamus-pituitary adrenal axis regulation. Using in situ brain perfusion in Pgp knockouts (KO) compared with wild-type mice, a role for Pgp in regulating CNS levels of dexamethasone (consistent with current dogma) and hypothalamic cortisol was shown. However, brain distribution of the mouse endogenous glucocorticoid, corticosterone, was unaffected in the KO mice. Subcutaneous injection of ³H-corticosterone and ³H-cortisol showed some increased brain accumulation in KO mice after 2 hrs, but HPLC analysis revealed that the majority of the ³H was not attached to corticosterone or cortisol, thus explaining the high brain accumulation of radio-label in previous in vivo studies. Although a role for Pgp in glucocorticoid regulation is not ruled out, this study highlights the need for revision of previous interpretations.

At the blood-CSF barrier, Dr Jane Preston and colleagues [4] also suggest a revised role for Pgp – this time in relation to thyroid hormone homeostasis in CNS. Compared to the blood-brain barrier, Pgp at the blood-CSF barrier appears to be pointing the ‘wrong way’, transporting substrates from barrier tissue (the choroid plexuses) into the CSF rather than effluxing into blood. As a result, the physiological significance of Pgp at the blood-CSF barrier has been questioned. By infusing ¹²⁵I-thyoxine into the cerebral ventricles in vivo, or using in vitro choroid plexus incubations and inhibiting Pgp with verapamil or antibody C219, the choroid plexuses accumulated 2-3x as much thyroxine as controls. This accumulation, when functional Pgp is blocked suggests that the transporter normally extrudes thyroxine into CSF, so ‘recycling’ the hormone and helping to maintain CSF levels and normal CNS metabolism.
In order to circumvent Pgp and deliver drugs to the CNS, Dr David Begley and colleagues [5] evaluated a nanoparticle delivery system for the chemotherapeutic drug doxorubicin DOX, in CNS-tumour bearing mice (glioblastoma). Ordinarily, DOX is efficiently excluded from the CNS by Pgp. They showed that pre-coating ‘empty’ 14C-labelled nanoparticles with surfactant (polysorbate-80), improved delivery to both intact and tumour bearing brain after i.v. injection. Nanoparticles pre-loaded with DOX before coating showed reduced delivery at the tumour site compared ‘empty’ nanoparticles due to altered charge, however, the actual concentration of DOX delivered exceeded that in normal brain due to the additional effects of enhanced permeability and retention (ERP) at the tumour site. The authors conclude that DOX loaded, surfactant coated nanoparticles have potential in the treatment of CNS glioblastomas.

Key references


