Intrinsic human multidrug transporters as helpers against Alzheimer's Disease

The cause(s) of Alzheimer's Disease (AD) is still unknown, so is a proper method for diagnosis. AD is a widely occurring form of neurodegeneration that is considered to affect 47 million people worldwide, according to the World Alzheimer's Report. Besides the social challenges for patients and their caregivers, AD is a huge financial and economic burden for society, with estimated costs of a trillion US$ worldwide for 2018.

AD is characterized by the loss of neurons, which leads to the characteristic symptoms like memory loss, speech disorder, apathy, and disability of self-service. Mechanistically, many target structures and metabolic processes have been identified to take part in this syndrome. One group of target proteins are the β-amyloids, which accumulate in affected neurons, leading to aggregates and plaques. One possible mechanism to overcome or at least diminish the progress of AD is to decrease the intracellular concentration of these harmful proteins. One way to achieve this is to increase the export of these proteins out of the affected neurons to reduce the intracellular fibrils.

ABC transporters are possible target structures to achieve this goal. Mostly known to confer multidrug resistance (MDR) in cancer, these energy-driven efflux pumps have been shown to transport β-amyloid proteins. Besides P-glycoprotein (P-gp, ABCB1) and Breast Cancer Resistance Protein (BCRP, ABCG2), Multidrug Resistance-associated Protein 1 (MRP1, ABCC1) is a very famous representative with high recognition in medicinal chemistry, not only in terms of cancer treatment, but also AD.

Activators of MRP1 have rarely been described. Besides the cardiovascular drug verapamil and derivatives, glutathione analogs, specific flavonoids and phenothiazines, no activators of MRP1 have been reported. Besides the lack of potency, most of these compounds have severe side effects and are not usable as therapeutics. Purines and pyrrolopyrimidines, compound classes more associated with reversal of MDR in cancer, contain representatives that activate MRP1-mediated transport of xenobiotics in low nanomolar concentration range, with no noteworthy cytotoxicity.

Two MRP1 overexpressing cell lines have been used, the human small-cell lung cancer cell line H69AR and the transfected Madin Darby Canine Kidney (MDCKII) MRP1 cells. Additionally, two different substrates of MRP1, calcein AM and daunorubicin, were used. A transport activation could be observed in both cell lines and for both substrates in sense of decreased intracellular concentrations of these substrates. The pyrrolopyrimidines and purine analogs were nontoxic and with regard to the other mentioned transporters, P-gp and BCRP, selective activating. It was shown that the compounds led to an increased affinity toward the substrates. It can be concluded that the activator binds to a binding site that is not associated with substrate binding (allosteric), and increases the affinity of the substrate toward the transporter by a conformational change.

To be metaphoric: let's imagine, the substrates are travelers at the airport (brain), who want to get from terminal A (intracellular) to terminal B (extracellular). Under normal conditions, some travelers

find and use the moving walkway (transporter), some don't. Let's say the activator is a signaler, who stands beside (allosteric) the walkway, and says: 'please use moving walkway'. The tendency (affinity) of the travelers (substrates) to use the walkway is strongly increased, as they pay much attention to the signaler. While the transport process itself has the same speed, the full capacity of the automatic floor is used.

This perspective is promising, since the compounds are much more activating than inhibiting or toxic, and the activation might also be used with respect to the β-amyloid proteins in Alzheimer's Disease.

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Publications

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