Journal of Spine & Neurosurgery

Review Article A SCITECHNOL JOURNAL

Modulation of P-Glycoprotein in the Blood Brain Barrier for the Enhancement of Drug Delivery

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Received date: July 02, 2021; **Accepted date:** July 16, 2021; **Published date:** July 23, 2021

Abstract

Many types of research are going on for the development of novel drugs to treat neurodegenerative diseases like epilepsy, Parkinson's disease, Alzheimer's disease, but the major problem during the drug development is that the pharmacotherapy of such drugs is restricted by the actions of drug transporters in the blood-brain barrier. P glycoprotein is also one of the drug transporters in the blood-brain barrier which is there to restrict the entry of many substances like xenobiotics, toxicants into the brain cells. It also effluxes drug content from the cells which is the main reason for the reduced pharmacotherapy. To obtain the maximum therapeutic effect drug have to enter into the cell which is difficult when P glycoprotein is in action that's why we have to modulate or inhibit the P glycoprotein action in the blood-brain barrier.

Keywords: Neurodegenerative diseases; P glycoprotein; The blood-brain barrier

Introduction

The drugs that are using to treat neurodegenerative diseases encounter an issue at the blood-brain barrier which is their inability to enter the brain cells because the blood-brain barrier contains many drug transporters. Those transporters act as gatekeepers and prevent the entry of many drugs. P glycoprotein is one of the drug transporters which have a wide range of substrates that play a key role in drug transportation. P glycoprotein is an ATP binding cassette transporter. It acts as an efflux transporter in the brain which transports substances like xenobiotics, toxicants out of the cells [1,2]. It exhibits a defensive mechanism by inhibiting the entry of inappropriate particles into the cell. It pumps out drug content from the cell which shows the effect on drug plasma concentration then automatically reduces the pharmacological effect of the drug. At that time we have to increase the dose to achieve therapeutic plasma concentration. On frequent usage of higher doses of a specific drug, there may be chances of the development of drug resistance. Like this P glycoprotein is responsible for the development of multidrug resistance. So we have to modulate the action of P glycoprotein. We can modulate P-gp by influencing the hMDR1 gene which is encoded for the expression of P glycoprotein by DNA methylation and histone acetylation. We can also modulate the P-gp without influencing the gene modulation which includes the post-translational mechanisms like degradation of protein, protein Phosphorylation.

P Glycoprotein Involvement in Alzheimer's disease

Alzheimer's disease is the most common form of mental illness. The major pathological symptom of Alzheimer's Disease (AD) is the deposition of Amyloid-β plaques in the brain. Deposition of Amyloid-β (Aβ) in the brain occurs in normal aging but in case of AD the deposition of Aβ gets increased. Aβ secretion is the triggering point in the AD pathogenesis. The 'is released from the neurons into the intestinal fluids, there it undergoes proteolytic degradation, then it transport across the BBB [3,4]. The Aβ peptide is formed by cleavage of Amyloid Precursor Protein (APP). The first cleavage of APP is the rate limiting step in the Aβ peptide formation. The cleavage is carried out by the β-site APP Cleaving Enzyme (BACE). This cleavage leads to formation of isoforms which are resistant to degradation.

P-gp involves in the clearance of Aβ from the brain. We can modulate the P-gp pharmacologically by using some drugs which enhance its activity can improve Aβ clearance from brain. This effect was observed in a clinical trial conducted in patients with mild to moderate AD using rifampicin [5,6], which is potent inducer of P-gp. Result of this study states that a reduced cognitive decline after 12 months of treatment with rifampicin because this antibiotic was able to improve the clearance of Aβ from the brain *via* the enhancement of P-gp mediated transport. similarly, a reduction has been found in the Aβ level in cerebrospinal fluid of guinea-pigs induced by some inhibitors of 3- hydroxy-3-methylglutarylcoenzyme A reductase (3-HMG CoA), known as statins; this could be explained, at least in part, by modulation of P-gp expression at the blood-brain barrier, since statins, such as simvastatin, modulate the expression of P-gp and consequently its activity [7,8].

However the possibility of using P-gp inducers may be a valid approach to reduce the level of Aβ in the brain in the early stages, during the advanced stages of the pathology, the overexpression of P-gp represents itself the main limit for the efficacy of the current pharmacological therapies this efflux pump may be a limit for the effectiveness of the current pharmacological therapies. Recent papers have shown that many BACE1 inhibitors that may be used to lower the Aβ formation are effective only at high doses because they are also P-gp substrates. The co-administration of BACE1 inhibitor together with a P-gp inhibitor induced a strong reduction of Aβ in the brain [9,10].

P Glycoprotein Involvement in Parkinson's disease

Similarly to AD, PD is also one of the incurable neurodegenerative disorders in current circumstances. The common symptom of Parkinson's disease is loss of dopaminergic neurons in the substantianigra. Catecholaminergic neurons in the mid brain also get damaged. The protein aggrigates known as Lewy Bodies (LBs) are found in PD like in the AD. The pathogenesis of PD is still unknown; however, the formation of LBs seems to be played a key role in the PD pathogenesis. The LBs composed of α-synuclien, a soluble neuronal protein which in pathological conditions converted into insoluble oligomers. It is still unknown whether the α-synuclein involved in the

neuro-degeneration in PD may be transported by P-gp, but conversely, it has been widely demonstrated that P-gp involves in the efflux of some pesticides and other environmental toxins which are responsible for the PD onset [11]. Indeed exposure to the neurotoxins such as the P-gp substrate MPP+ could contribute to brain tissue malfunction, and may cause a parkinsonian syndrome strongly resembling PD. P-gp is an important component in the BBB and has a special impact on the bioavailability of many drugs, it has been recently investigated for its clinical relevance and efficacy in some existing therapies useful for the treatment of PD. In particular, bupidine an N-Methyl-D Aspartate (NMDA) antagonist which has indirect dopaminergic effects has proved to be also a P-gp substrate, and therefore it is actively extruded out of the brain.

Even if this drug is not usually administered for the treatment of PD, the extrusion of bupidine out of the brain through P-glycoprotein could explain, at least in part, the fact that no correlation exists between the bioavailability of CNS drugs and their beneficial and/or their unsought effects. Furthermore, it has been observed that also other anti-parkinson drugs such as L-DOPA and bromocriptine are P-gp substrates. In particular, a recent investigation into the possible interaction between bromocriptine and P-gp at the BBB *in vivo* showed that this drug is transported by P-gp, even if the chemical inhibition of this efflux pump with P-gp inhibitors such as valspodar or elacridar is only partial, thus indicating that P-gp is not the only mechanism by which bromocriptine crosses the BBB. On the whole, these results highlight that the cerebral concentration and the subsequent toxicity of many anti-parkinson drugs could be affected by P-gp. Therefore, the co-administration of a modulator or an inhibitor of this kind of transporter may be a useful tool, either to improve the efficacy of the anti-parkinson therapy or to reduce the toxicity quite often associated with the use of these drugs [12,13].

P Glycoprotein Involvement in Epilepsy

Epilepsy is a neurological disorder which is characterized by recurrent generalized seizures. The epilepsy affects mostly 1%-2% of the world's population. In current situations much progress has been made in the innovative strategies for the treatment of epilepsy because the usual therapies became pharmacoresistant [14]. The Anti-Epileptic Drugs (AEDs) are acting through different mechanisms. But the main aim of AEDs is to control the epilepsy by showing effect on epileptogenic region. The entry of these AEDs is restricted by the expression of drug transporters especially p-gp in the BBB. This p-gpacts as a gatekeeper restricts the entry of many AEDs into the brain. The first evidence of a high expression of P-gp in the brain of refractory epileptic patients was provided by Tishler et al. and subsequently confirmed by others. To evaluate the involvement of P-gp in the onset of drug-resistance epilepsy, many studies have been carried out, to evaluate the effects of co-administration of AEDs and P-gp inhibitors [14]. Recently, it was investigated whether P-gp is involved in the efflux transport of Phenol Barbital (PB), the first choice drug for generalized epilepsy. A study carried out in PB-resistant rats showed that the co-administration of tariquidar, a selective P-gp inhibitor, and PB was able to overcome the established pharmacological resistance suggesting involvement of P-gp in the efflux transport of PB from the BBB. Many other studies support the existence of a direct correlation between the over-expression of P-gp and the AED resistance. In particular, it has been demonstrated that the ineffectiveness of phenytoin in refractory epilepsy is linked to its modest input to the CNS because of P-gp activity [15]. Furthermore, many other drugs such as lamotrigine, carbamazepine, felbamate, and topiramate support that several AEDs can interact with P-gp [16]. Up to date, the results of many published studies seem to be quite controversial. The discrepancy evidenced among the disparate data obtained using different cell lines that over express P-gp do not make itpossible to extend any conclusion to the human P-gp expressed at the BBB level.

All these findings show that the co-administration of P-gp inhibitors together with PB or phenytoin may improve the anti-epileptic properties of anticonvulsant drugs, by increasing local concentrations of AEDs through interference with P-gp, with consequent amelioration of seizure control in patients with refractory epilepsy [17]. In addition to the over expression of P-gp in epileptogenic brain regions of patients with AED-resistant epilepsy recent evidence also suggests that several first-line antiepileptic drugs seem to be P-glycoprotein substrates [17].

P Glycoprotein Involvement in Amyotrophic Lateral Sclerosis (ALS)

Regulation of P-gp and BCRP articulation at the slim endothelium of the BBB includes numerous flagging pathways, which can be enacted by different improvements. Mind slim endothelium communicates a few ligand-initiated atomic receptors, of significance, Pregnane-X Receptor (PXR), Constitutive Androstane Receptor (CAR), Peroxisome Proliferator-Actuated Receptor α (PPARα), and Glucocorticoid Receptor (GR). These ligand-actuated atomic receptors manage P-gp/BCRP articulation through various pathways. They can be invigorated by numerous synthetic substances and food fixings that initiate efflux carriers' demeanor alongside stage I and II Cytochrome-P450 (CYP-450) proteins' appearance. The mechanism involves binding of stimuli to the specific receptor, translocation of the complex to the nucleus, and binding to the promoter region of the targeted gene. Other mechanisms involve indirect activation of transcription factors through stimulation of plasma membrane receptors, with activation of multiple signaling pathways that converge into nuclear translocation of the ABC transporter master regulator, Nuclear Factor Kappa-light-chain-enhancer of activated B cells (NFKB), and stimulation of ABC target genes. Upregulation of P-gp and BCRP through receptor-mediated activation can result from several cell stressors, inflammatory mediators, and extracellular glutamate. Most CNS disorders are characterized by inflammation and are associated with alterations in several pro-inflammatory mediators. One common inflammatory mediator is the Tumor Necrosis Factor-α (TNF-α), which has been found to modulate P-gp expression in endothelial cell culture and rodent-isolated brain capillaries. TNF-α upregulates P-gp articulation, through incitement of NFKB atomic movement, by initiating a course of upstream particles including TNF Receptor 1 (TNFR1), iNOS, and Protein Kinase C isoform β2 (PKCβ2) [18-22]. An elective pathway of actuated TNFR1 causes a prompt decrease in P-gp action without adjusting its protein articulation by initiating PKCβ1 rather than PKCβ2. Astrocytes communicating the ALS-causative transformations SOD1-G93A or SOD1-A4V when co-refined with endothelial cells improves articulation and action of P-gp through the arrival of Receptive Oxygen Species (ROS) and incitement of record factor Nrf2. Likewise, ongoing investigations indicated that going with ROS changes, there was an expansion in the fundamental degree of the proportion of glutathione disulfide (GSSG)/diminished glutathione (GSH) in ALS patients [23,24]. Interestingly, glutathione, a significant

cancer prevention agent, was appeared to manage P-gp articulation at the BBB by directing ROS cerebrum level and shielding the BBB endothelial cells from oxidative pressure [25,26]. In any case, the immediate relationship of decreased glutathione and P-gpupregulation at the BBB in ALS has not been examined. Proposed studies may incorporate tending to whether changes in the GSSG/GSH proportion saw in ALS patients could be associated to changes in P-gp articulation, which could be a valuable biomarker for drug-safe patients. Also, astrocytes holding another ALS causative freak protein, FUS-H517Q, drive P-gp upregulation through incendiary pressure, specifically by discharging TNF-α which is known to eventually actuate NFkB. Since both familial and irregular ALS types are portrayed by up regulation of P-gp at the BBB, it very well may be presumed that factors that up regulate P-gp articulation don't rely upon explicit sickness driven transformations. It merits referencing that the expansion in P-gp articulation at the BBB in ALS happens at the protein level as well as at the mRNA level. Likewise, there is an increased transcriptional action of NFKB, an expert regulator of P-gp. Besides, Western blot contemplates indicated that the increase in P-gp articulation happened in the plasma film portion as well as in the complete protein test from cell or tissue lysate, recommending that P-gp up regulation is credited to an expansion in its once more blend instead of dealing from cytoplasm to plasma layer compartment [27,28]. However, more experiments should be done on this line of investigation to make more firm assessments.

P Glycoprotein Involvement in Other Neurodegenerative Disorders

Huntington's Disease (HD) as well as Creutzfeldt-Jakob Disease (CJD) share some features with the neurodegenerative disorders previously discussed. HD is a neurodegenerative condition characterized by movement disorders, cognitive decline, and psychiatric disturbance, whereas CJD is the most common form of the human transmittable spongiform encephalopathies, also known as prion disease, which ultimately results in death. The main characteristic of both neuropathies is the accumulation of mis-folded proteins within the brain. Indeed, the primary cause of HD is a molecular and cellular dysfunction induced by anomalous Hun Ting Tin protein (HTT) which induces protein mis- folding and aggregation. The involvement of P-gp in this pathology has not been investigated so far. CJD is characterized by the accumulation of an abnormal isoform (PrPSc) of the Prion Protein (PrP), which forms aggregates. The increase in PrPSc concentration in the brain was associated with a decrease in cerebrovascular p-gp expression [29-32]. Thus a protective role for P-gp was also suggested in CJD, where decreased P-gp expression was suggested to facilitate the accumulation of PrPSc prions, leading to neuro-degeneration. ALS pathogenesis involves mis-folding and aggregation in the cell of Superoxide Dismutase 1 (SOD1), a protein produced by mitochondria which converts the superoxide anion to H2O2. A role of P-gp in ALS treatment has been suggested [28]. Riluzole is the only agent with a small delaying effect on disease progression in clinical trials in ALS patients. It was suggested that minocycline may improve the benefit of riluzole by increasing its brain concentration through inhibition of p-gp function, although higher doses of minocycline in combination with high riluzole concentrations lead to neurotoxicity [27]. Finally, toxin exposure is also associated with atypical Parkinsonism syndromes. Plants from the Annonaceae family are involved in the development of a syndrome with Parkinsonism strongly resembling Progressive Supranuclear Palsy (PSP) [12,13,33-35].

Conclusion

Plants from this family contain lipophilic substances called acetogenins, from which annonacin is the most well-known. Annonacin provokes apoptosis of dopaminergic and GABAergic neurons by inhibition of mitochondrial complex I and has a stronger neurotoxic effect than MPTP or rotenone. Acetogenins were studied for their capacity to reverse multidrug resistance by efflux transporters on human tumoral cells. For example Roemerine, leaf extract of *Annona senegalensis*, enhanced vinblastine toxicity in tumal cells by inhibition of P-gp. Thus, it is hypothesized that the protective role of P-gp at the BBB could be inhibited by acetogenin, leading to accumulation of neurotoxins and enhancing neuro-degeneration.

Acknowledgment

We thank Dr. Santhivardhan Chinni for assistance during this review and for providing guidance. The study was supported by a grant from the Raghavendra institute of pharmaceutical education and research-autonomous, Ananthapuramu.

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