Pharmacokinetic Implications of Intestinal P-glycoprotein in Diabetic Complications

Abstract

This study was designed with an objective to understand the effect of intestinal P-glycoprotein on pharmacokinetic profile of its substrates (verapamil and atorvastatin) in diabetes with hyperlipidemia. Mechanistically, the change in intestinal P-glycoprotein expression and activity with progression of diabetes and its effect on intestinal uptake as well as pharmacokinetics of its substrates was evaluated. In this study, the mechanism of action of epigallocatechin-3-gallate (EGCG) which is reported as a potential P-glycoprotein inhibitor was also elucidated. Initially, the animal model for diabetes with hyperlipidemia was developed. This was followed by intestinal mucosal protein content analysis which inferred that total protein increased from duodenum towards the ileum and with the progression of diabetes. Thereafter, single pass intestinal perfusion study was performed in normal and diabetic rats. It was observed that effective permeability of P-glycoprotein substrates *viz*. verapamil and atorvastatin decreased from duodenum to ileum and also with progression of disease. Co-perfusion of EGCG with verapamil or atorvastatin significantly improved their intestinal uptake. Thereafter, pharmacokinetic studies were done in normal and diabetic rats to determine the presence of any change in the oral bioavailability of P-glycoprotein substrates with the progression of disease. The oral bioavailability of P-glycoprotein substrates decreased significantly with the progression of diabetes; however, co-administration of EGCG with P-glycoprotein substrates significantly improved their bioavailability in normal as well as in diabetic animals. In order to have a mechanistic insight, expression and activity of P-glycoprotein in intestinal segment of normal and diabetic animals were studied. The expression level of mdr1a and mdr1b genes that encoded for P-glycoprotein were determined by RT-PCR analysis whereas activity of P-glycoprotein was determined by quantifying the Na^{+}-K^{+}-ATPase enzyme activity in intestinal mucosal samples of normal and diabetic animals. It was observed that both expression and activity of P-glycoprotein was significantly higher in diabetic animals as compared to normal animals

and also increased with the progression of disease. It was also observed that intestinal oxidative stress and advanced glycation end-products (AGEs) levels, which are responsible for modulating expression of P-glycoprotein, was higher in diabetic animals as compared to normal. Treatment with EGCG significantly reduced the expression and activity of intestinal P-glycoprotein as well as intestinal oxidative stress and AGEs level in both normal and diabetic animals. It can be inferred from the obtained results that increased intestinal oxidative stress and AGEs level triggered the expression and activity of P-glycoprotein. This condition subsequently decreased the intestinal uptake and oral bioavailability of its substrates. Treatment with EGCG improved the intestinal uptake and oral bioavailability of P-glycoprotein substrates, by reducing the expression and activity of intestinal P-glycoprotein as well as intestinal oxidative stress and AGEs level. This study gave a mechanistic insight about the bioenhancement potential of EGCG. Hence, monitoring the enhanced expression and activity of P-glycoprotein in diabetes will be helpful in effective therapeutic drug monitoring and EGCG may be opted as an adjuvant therapy for overcoming P-glycoprotein mediated drug efflux.