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Hypoxia induces activity of both efflux and influx transporters in retinal epithelial cells

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Introduction: Hypoxia mediated signalingcauses a number of vascular retinal diseases. Their treatmentsremain challenging. To date, the effect of hypoxia onexpression of drug transporters (efflux and influx) in retinal cells has not been studied. Therefore, we have investigated molecular and functional expression of membrane transporters in human retinal pigmented epithelial (RPE) cells cultured under normoxic and hypoxic conditions.

Methods: RPE cells were cultured at 37°C in a hyoxia chamber using 1% O_2, 5% CO_2, and 94% N_2 in a Bactron Anaerobic Chamber. Quantitative real time polymerase chain reaction (qPCR), ELISA, immunoblot analysis and functional activity in both normoxic and hypoxic conditions were performed to examine the RNA, protein expression levels and uptake of various substrates respectively.

Results: Analysis of qPCR demonstrated elevated expression of efflux transporters (P-glycoprotein, multidrug resistant protein-2, breast cancer resistant protein) and influx transporters (folate receptor-α, cationic and neutral amino acid transporter, sodium dependent multivitamin transporter) in a time dependent manner. Immunoblot analysis further confirmed elevated expression of breast cancer resistant protein and sodium dependent multivitamin transporter. A decrease in the uptake of efflux transporter substrates (digoxin, lopinavir and abacavir) and enhanced uptake of influx transporter substrates (arginine, folic acid and biotin) in hypoxia relative to normoxia further confirmed elevated expression of transporters, respectively.

Conclusions: This study demonstrates that hypoxic conditions may alter expression of efflux and influx transporters in RPE cells. These findings suggest that hypoxia may alter disposition of ophthalmic drugs and overexpressed influx transporters can be exploited for drug delivery in retina.

Biography

Dhananjay Pal, Ph.D., MHA, is an Associate Research Professor, Division of Pharmaceutical Sciences, University of Missouri-Kansas City. Broadly, his research interests address the role of transporters in drug delivery, interplay of influx and efflux transporters, MDR- and CYP- mediated drug-drug/herbal interactions, and overcoming drug resistance in chemotherapy. He have over 20 years of experience performing in-vitro drug delivery, cellular drug transport, metabolism experiments, developing cell lines, biological assays and co-culture suitable for various pharmacological studies employing in vitro cellular models. He is the author/coauthor of several book chapters and over 100 research articles published in peer reviewed journals.

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