THE UNIVERSITY OF ARIZONA
COLLEGE OF MEDICINE TUCSON
Pharmacology

Presents

"Targeting Folate Transporters at Brain Barriers: Novel Therapeutic Approach for Cerebral Folate Deficiency"

BY

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Abstract: Folates are a family of B9 vitamins responsible for several biosynthetic processes collectively referred to as folate-mediated one-carbon metabolism. In mammals, folate transport primarily occurs through three major transport pathways: folate receptor alpha (FRα), proton-couple folate transporter (PCFT), and reduced folate carrier (RFC).1 In the brain, adequate folate supply is critical for normal neurodevelopment, with brain folate transport primarily mediated at the blood-cerebrospinal fluid barrier (BCSFB) by FRα and PCFT. Impairment in folate transport at the BCSFB can result in cerebral folate deficiency (CFD), a rare but devastating childhood neurological disorder which is characterized by suboptimal cerebrospinal fluid (CSF) folate levels. In addition, other neurological disorders have been associated with CFD, including autism spectrum disorder, Rett syndrome, and mitochondrial disorders. In disorders associated with CFD, the presence of neuroinflammation, brain oxidative stress, and mitochondrial dysfunction has also been described, however the contribution of folate deficiency in inducing these physiological abnormalities is not well understood. In an effort to identify novel treatment strategies for CFD, our group has uncovered the blood-brain barrier (BBB) as an alternate route for brain folate uptake, mediated by RFC. We have demonstrated the functional upregulation of RFC by vitamin D receptor (VDR) once activated by its specific ligand 1,25-dihydroxycholecalciferol (calcitriol), which resulted in significant increases in brain folate uptake in vitro2 and in vivo.3 More recently, we have identified the functional upregulation of RFC by the nuclear respiratory factor 1 (NRF-1) at the BBB once indirectly activated by the natural compound pyrroloquinoline quinone (PQQ).4 PQQ functions through activation of the PGC-1α signaling cascade and has been recognized for its neuroprotective effects by increasing mitochondrial function, and also eliciting anti-inflammatory and antioxidant effects5. Applying immunohistochemical analysis, we have also investigated the localization of FRα, RFC and PCFT at brain barriers and brain parenchyma in frozen brain slices of C57BL6/N mice utilizing specific antibodies and standard cell markers. We confirmed localization of the three transport pathways at the BBB, in brain microvessel endothelial cells, and at the BCSFB, in choroid plexus epithelial cells. We also demonstrated the localization of RFC and PCFT in the epithelial cells of the arachnoid barrier (AB), and in brain parenchyma cells, microglia, astrocytes and neurons6. Together our data demonstrate novel localization of folate transporters in brain parenchyma and at the AB and uncover an upregulation of RFC by transcriptions factors such as VDR and NRF-1 which increase folate delivery to the brain providing novel approaches for the treatment of CFD7. (supported by the Natural Sciences and Engineering Research Council of Canada)

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