Pharmaceutical Sciences Seminar Series

Wednesday, April 6, 2022
4:00pm
2548 NUB or Zoom

4th Allen J. Sedman Lecture

“Pathways for Folate Delivery to the Brain: Impact in Cerebral Folate Deficiency”

Presented by:

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Abstract: Folate derivatives (vitamin B9) are essential in regulating nucleic acid synthesis, fetal development, and brain metabolism. Low levels of folates in the brain are associated with cerebral folate deficiency, a rare but devastating pediatric neurological disorder affecting cognitive and motor skills. Folate uptake by mammalian tissues is primarily mediated by three transport mechanisms: folate receptor alpha (FRα), reduced folate carrier (RFC), and proton coupled folate transporter (PCFT). In the brain, folate uptake primarily occurs at the choroid plexus through the combined action of the folate receptor-alpha (FRα), the main folate transport pathway into the brain, and proton-coupled folate transporter (PCFT). Inactivation of FRα, through loss-of-function mutations or the presence of FRα autoantibodies, causes severe cerebral folate deficiency leading to inflammation, oxidative stress, mitochondrial dysfunction, and abnormal brain myelination. Although previous work has characterized folate transport at the level of the choroid plexus, transport at other brain barriers i.e., blood-brain barrier (BBB) or in brain parenchyma has not been extensively studied. This seminar presentation will address *in vitro* and *in vivo* work from our laboratory investigating the regulation of RFC by transcription factors i.e., the vitamin D receptor (VDR) or the nuclear respiratory factor-1 (NRF-1) at the BBB, and the potential role that RFC may play in enhancing folate uptake into the brain in the context of defective FRα function.

Modulating folate uptake at the BBB through the regulation of RFC functional expression may have clinical relevance in addressing the treatment of childhood neurodegenerative disorders caused by defective FRα and/or PCFT function. Our laboratory has shown that activation of VDR or NRF-1 by their specific ligands, calcitriol or pyrroloquinoline quinone, can upregulate RFC functional expression at the BBB and significantly increase brain folate delivery, implying that this transporter could potentially constitute a novel molecular target for the treatment of neurometabolic disorders caused by folate deficiency. (Supported by the Natural Sciences and Engineering Research Council of Canada)