BIOGRAPHICAL SKETCH
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NAME: Egleton, Richard

eRA COMMONS USER NAME (credential, e.g., agency login): regleton

POSITION TITLE: Associate Professor

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable.)*

INSTITUTION AND LOCATION	DEGREE (if applicable)	Completion Date MM/YYYY	FIELD OF STUDY
University of Hertfordshire, Hatfield, Hertfordshire	BS	05/1991	Applied Biology
St Thomas' Hospital, University of London, London	PHD	01/1995	Physiology
Kings College London, London	Postdoctoral Fellow	01/1997	Cell Physiology
University of Arizona, Tucson, AZ	Postdoctoral Fellow	03/2001	Pharmacology

A. Personal Statement

I have two roles in this COBRE application, which is focused on cellular transport physiology of obesity and obesity related disorders. My first role, as Co-Director of the Biomedical Sciences program, is to help mentor all of the junior investigators in graduate education. This includes guiding junior investigators through the various rules and regulations that govern graduate education, as well as being a resource for helping them develop mentoring plans and mentoring contracts with both undergraduate and graduate students that work in their laboratories.

The second role in this COBRE is as a mentor for junior investigator, Dr. Isabel Larre. My research over the last 20 years has focused on several aspects of barrier regulation during disease. This includes investigating the regulation of both transcellular transport and paracellular transport routes. My primary focus has been investigating tight junction regulation at the cerebrovascular barriers with around 20 papers on this research area. This has included a number of papers looking at regulation of both function and molecular properties of the tight junction during various aspects of metabolic syndrome, including diabetes and hypertension. As a mentor for Dr. Larre, I will mentor her with the studies of claudin function, especially for the in vivo studies in Specific Aim 3. We currently discuss tight junction regulation and her studies on a bi-weekly basis. These studies cover not only her work, but also were it fits into the general tight junction arena. Further, I have a considerable network of colleagues and collaborators who I can introduce to Dr. Larre to, to support expansion of her networking opportunities. Another area where I will provide support to Dr. Larre is in the non-research components of an academic career. As a current member of the Marshall School of Medicine, Promotion and Tenure Committee, I am very familiar with the requirements for tenure and can assist her in navigating the promotion and tenure process.

1. McCaffrey G, Staatz WD, Quigley CA, Nametz N, Seelbach MJ, Campos CR, Brooks TA, Egleton RD, Davis TP. Tight junctions contain oligomeric protein assembly critical for maintaining blood-brain barrier integrity in vivo. J Neurochem. 2007 Dec;103(6):2540-55. PubMed PMID: 17931362.
2. Hom S, Fleegal MA, Egleton RD, Campos CR, Hawkins BT, Davis TP. Comparative changes in the blood-brain barrier and cerebral infarction of SHR and WKY rats. Am J Physiol Regul Integr Comp Physiol. 2007 May;292(5):R1881-92. PubMed PMID: 17234953.
3. Hawkins BT, Ocheltree SM, Norwood KM, Egleton RD. Decreased blood-brain barrier permeability to fluorescein in streptozotocin-treated rats. Neurosci Lett. 2007 Jan 3;411(1):1-5. PubMed PMID: 17110033; PubMed Central PMCID: PMC1785293.
4. Hawkins BT, Lundeen TF, Norwood KM, Brooks HL, Egleton RD. Increased blood-brain barrier permeability and altered tight junctions in experimental diabetes in the rat: contribution of hyperglycaemia and matrix metalloproteinases. Diabetologia. 2007 Jan;50(1):202-11. PubMed PMID: 17143608.

B. Positions and Honors

Positions and Employment

1990 - 1991	Immunology Research Technician, Animal Health Trust, Newmarket
1992 - 1995	PhD Student, Sherrington School Of Physiology, United Medical and Dental School of Guys and St. Thomas, University of London, London
1995 - 1997	Post Doctoral Fellow, Physiology Group, Kings College London, London
1997 - 2001	Research Associate, Department of Pharmacology, University of Arizona, Tucson, AZ
2001 - 2007	Research Assistant Professor, Department of Pharmacology, University of Arizona, Tucson, AZ
2007 - 2010	Assistant Professor, Department of Pharmacology, Physiology and Toxicology, Marshall School of Medicine, Huntington, WV
2010 -	Associate Professor, Department of Pharmacology, Physiology and Toxicology, Marshall school of Medicine, Huntington, WV

Other Experience and Professional Memberships

2004 - 2004	Ad Hoc Member, NIH Study section Brain Injury and Neurovascular Pathologies study section (BINP)
2009 -	Grant Reviewer, European Commission's 7th Framework Program for Research
2009 -	Grant Reviwer Brain 1, American Heart Association
2012 -	Abstract Reviewer, American Heart Association International Stroke Conference
2014 -	Marshall's Representative, Coalition of Physician Education in Substance Use Disorders.
2015 -	Program Director, Graduate Studies Biomedical Sciences Marshall

C. Contribution to Science

1. My PhD studies focused on changes in the blood brain barrier during multiple sclerosis. During this time I used the Semliki forest virus to investigate optic nerve and brain demyelination and how this regulated BBB permeability to small molecular weight markers. These studies were some of the first to look at viral induced encephalomyelitis and brain demyelination.

    a. Egleton RD, Butt AM, Amor S, Segal MB. Biology and Physiology of the Blood-Brain Barrier, Advances in Behavioral Biology Volume 46 . Couraud P, Scherman D, editors. London: Springer; 1996. Blood-Brain Barrier Permeability Changes during Semliki Forest Virus-Induced Encephalomyelitis in the Balb/c Mouse; p.361-364.
    b. Butt AM, Kirvell S, Egleton RD, Amor S, Segal MB. Biology and Physiology of the Blood-Brain Barrier, Advances in Behavioral Biology Volume 46 . Couraud P, Scherman D, editors. London: Springer; 1996. Time-Course of Demyelination and Blood-Brain Barrier Disruption in the Semliki Forest Virus Model of Multiple Sclerosis in the Mouse.; p.353-359.

2. The Blood Brain Barrier Does transport peptides: For much of my time as a graduate student and my initial years as a postdoctoral fellow, there was a fairly significant debate within the blood brain barrier (BBB) field regarding the ability of peptides to cross the BBB. With the increased importance of biological drugs and their potential for therapeutic use to treat neurological disorders, an issue of considerable interest in the late 90's. During this time the group I was working with were investigating opioid peptides and potential for use in pain. My role was to characterize the transport of these peptides into the brain and how various modifications could regulate these changes. Since 1997, this has resulted in 12 research papers 3 reviews, 3 book chapters and a festschrift. In essence these studies which used a combination of in vitro and in vivo studies, coupled with metabolism and analytical studies showed that many peptides could indeed cross the BBB and in fact many have some specific mechanisms for this. Further those peptides that could not cross the BBB were often hindered by either metabolic stability or the presence of various multi-drug efflux transporters. These studies helped promote the idea that the brain is not as isolated as we had previously believed, but perhaps more importantly helped use truly start to define what the BBB really is. Selected publications out of 21 in this area.

a. Davis TP, Abbruscato TJ, Egleton RD. Peptides at the blood brain barrier: Knowing me knowing you. Peptides. 2015 Oct;72:50-6. PubMed PMID: 25937599; PubMed Central PMCID: PMC4627938.
b. Egleton RD, Mitchell SA, Huber JD, Palian MM, Polt R, Davis TP. Improved blood-brain barrier penetration and enhanced analgesia of an opioid peptide by glycosylation. J Pharmacol Exp Ther. 2001 Dec;299(3):967-72. PubMed PMID: 11714884.
c. Egleton RD, Mitchell SA, Huber JD, Janders J, Stropova D, Polt R, Yamamura HI, Hruby VJ, Davis TP. Improved bioavailability to the brain of glycosylated Met-enkephalin analogs. Brain Res. 2000 Oct 20;881(1):37-46. PubMed PMID: 11033091.
d. Egleton RD, Abbruscato TJ, Thomas SA, Davis TP. Transport of opioid peptides into the central nervous system. J Pharm Sci. 1998 Nov;87(11):1433-9. PubMed PMID: 9811502.

3. The BBB is a dynamic barrier. Almost since the concept of the BBB was theorized until relatively recently the BBB was considered by many to be a rigid barrier that would only be breached during major neurological events such as MS and stroke. However studies from my lab and others have shown that the BBB is an exquisitely controlled barrier with an almost constant fine tuning of properties by cells within the brain and also factors within the blood. Evidence of this dynamic interaction has led to the current concept of the Neurovascular unit. The initial studies that led us to this concept were rather serendipitous. We had decided to investigate if pain would regulate the transport of the opioid analgesic peptides into the brain. Our initial hypothesis was that pain would alter cerebral blood flow which would then alter the uptake of drugs that had flow dependent transport. Much to our surprise we discovered that peripheral pain would induce a response in the BBB that would induce changes in the molecular and functional properties of the barrier leading to altered permeability of morphine and codeine. Further these changes were time dependent and involved a combination of inflammatory mediators and nociceptive signaling. Subsequently we showed that there was a significant change in tight junction architecture and the expression and function of efflux transporters. These studies were truly ground breaking and demonstrated that the BBB was dynamic and could respond to signals from both the CNS and the periphery. Selected publications out of 9 in this area.

   a. Campos CR, Ocheltree SM, Hom S, Egleton RD, Davis TP. Nociceptive inhibition prevents inflammatory pain induced changes in the blood-brain barrier. Brain Res. 2008 Jul 24;1221:6-13. PubMed PMID: 18554577; PubMed Central PMCID: PMC2583462.
   b. McCaffrey G, Staatz WD, Quigley CA, Nametz N, Seelbach MJ, Campos CR, Brooks TA, Egleton RD, Davis TP. Tight junctions contain oligomeric protein assembly critical for maintaining blood-brain barrier integrity in vivo. J Neurochem. 2007 Dec;103(6):2540-55. PubMed PMID: 17931362.
   c. Seelbach MJ, Brooks TA, Egleton RD, Davis TP. Peripheral inflammatory hyperalgesia modulates morphine delivery to the brain: a role for P-glycoprotein. J Neurochem. 2007 Sep;102(5):1677-90. PubMed PMID: 17697052.
   d. Huber JD, Hau VS, Borg L, Campos CR, Egleton RD, Davis TP. Blood-brain barrier tight junctions are altered during a 72-h exposure to lambda-carrageenan-induced inflammatory pain. Am J Physiol Heart Circ Physiol. 2002 Oct;283(4):H1531-7. PubMed PMID: 12234806.

4. The BBB, metabolic syndrome and stroke. It has been known for some time that during a stroke the BBB is disrupted allowing edema and the entry of blood factors into the brain, which can then promote neurological damage. Until recently however the role of prior BBB disruption in the time course and severity of stroke was not considered important. The initial studies I was involved in for this area investigated how stroke models (in vitro) could disrupt barrier function. Though interesting, these studies are not particularly novel. Our focused turned to how the primary risk factors for stroke (diabetes and hypertension) could promote BBB dysfunction and thus increase stroke damage. Though I carried out some further studies on in vitro models and also on hypertension, my primary interest was diabetes. Our studies indicated that diabetes could regulate the function not only of the BBB, but also of the choroid plexus and could thus significantly regulate brain homeostasis. At the BBB in animal models of diabetes, we observed changes in junctional permeability, coupled with an increased expression of efflux transporters, thus permeability changes at the BBB were drug specific. This could have important consequences for therapeutic approaches in diabetes and may explain some of the issue seen in diabetic

anesthesia. These studies have since been confirmed by several other groups. Selected Papers out of 8 in this area.

a. Hom S, Fleegal MA, Egleton RD, Campos CR, Hawkins BT, Davis TP. Comparative changes in the blood-brain barrier and cerebral infarction of SHR and WKY rats. Am J Physiol Regul Integr Comp Physiol. 2007 May;292(5):R1881-92. PubMed PMID: 17234953.
b. Hawkins BT, Ocheltree SM, Norwood KM, Egleton RD. Decreased blood-brain barrier permeability to fluorescein in streptozotocin-treated rats. Neurosci Lett. 2007 Jan 3;411(1):1-5. PubMed PMID: 17110033; PubMed Central PMCID: PMC1785293.
c. Hawkins BT, Lundeen TF, Norwood KM, Brooks HL, Egleton RD. Increased blood-brain barrier permeability and altered tight junctions in experimental diabetes in the rat: contribution of hyperglycaemia and matrix metalloproteinases. Diabetologia. 2007 Jan;50(1):202-11. PubMed PMID: 17143608.
d. Egleton RD, Campos CC, Huber JD, Brown RC, Davis TP. Differential effects of diabetes on rat choroid plexus ion transporter expression. Diabetes. 2003 Jun;52(6):1496-501. PubMed PMID: 12765962.

5. Substance Abuse and endothelial function. Substance abuse is unfortunately a major issue in our region. The BBB as a dynamic barrier can have a significant role in substance use especially when you consider the potential pharmacokinetic role of the barrier in tolerance. My studies however have looked more at how drugs can regulate endothelial function and thus promote some of the pathophysiological components of addiction. My studies both in vivo and in vitro have shown that nicotine can induce significant changes in endothelial function in multiple capillary beds including brain and eye and in multiple endothelial cell types (brain, retinal, HUVEC). These changes are via an alpha-7 nicotinic receptor mediated modulation of VEGF function. In the brain, this induces a reduction of tight junction function and in eyes and cellular model promotes angiogenic mechanism. This is important with the advent and huge use of e-cigarettes. I have also carried out some studies on opioids and have seen that opioids can also regulate barrier function. Selected Papers out of 7 in this area.

a. Egleton RD, Abbruscato T. Drug abuse and the neurovascular unit. Adv Pharmacol. 2014;71:451-80. PubMed PMID: 25307226.
b. Dom AM, Buckley AW, Brown KC, Egleton RD, Marcelo AJ, Proper NA, Weller DE, Shah YH, Lau JK, Dasgupta P. The α7-nicotinic acetylcholine receptor and MMP-2/-9 pathway mediate the proangiogenic effect of nicotine in human retinal endothelial cells. Invest Ophthalmol Vis Sci. 2011 Jun 22;52(7):4428-38. PubMed PMID: 20554619; PubMed Central PMCID: PMC3175965.
c. Hawkins BT, Egleton RD, Davis TP. Modulation of cerebral microvascular permeability by endothelial nicotinic acetylcholine receptors. Am J Physiol Heart Circ Physiol. 2005 Jul;289(1):H212-9. PubMed PMID: 15708958.
d. Hawkins BT, Abbruscato TJ, Egleton RD, Brown RC, Huber JD, Campos CR, Davis TP. Nicotine increases in vivo blood-brain barrier permeability and alters cerebral microvascular tight junction protein distribution. Brain Res. 2004 Nov 19;1027(1-2):48-58. PubMed PMID: 15494156.

Complete List of Published Work in MyBibliography:
https://www.ncbi.nlm.nih.gov/sites/myncbi/1tmCEMskIn9kW/bibliography/48132830/public/?sort=date&direction=ascending

D. Additional Information: Research Support and/or Scholastic Performance

Ongoing Research Support

MU, Marshall Health Egleton (PI) 07/01/15-06/01/18
Directors Fund
A part of the new position as Director of graduate studies, I was given a research fund for my studies
Role: PI

MU-WVU, Marshall- WVU research grant Egleton, Richard (PI) 03/01/16-02/01/17
Using a whole exome sequencing approach to enhance the treatment of pregnant women with opioid use disorder and their neonates. This grant funds a clinical trial investigating the role of both maternal and neonate genetics on the incidence and course of neonatal abstinence syndrome in a substance abusing pregnant population. There is no overlap with this proposal
Role: PI

TI025957, SAMHSA Saunders, Amy (PI) 09/01/15-09/01/18
Marshall University SBIRT
The overall goal of this project is to train health care professionals and medical students in the use of SBIRT method (screening, brief intervention and referral to treatment) for substance use disorders.
Role: Co-Investigator