BIOGRAPHICAL SKETCH

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NAME: Richard D. Egleton, Ph.D.

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. Add/delete rows as necessary.)*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	Completion Date MM/YYYY	FIELD OF STUDY
Hatfield Polytechnic, Hertfordshire UK	BS	06/1991	Applied Biology
St Thomas' Hospital, University of London, UK	PhD	04/1995	Physiology
King's College London, UK	Post Doc	01/1997	Cell Physiology
University of Arizona, Tucson, AZ, USA	Post Doc	03/2001	Pharmacology

Please refer to the Biographical Sketch sample in order to complete sections A, B, C, and D of the Biographical Sketch.

A. Personal Statement

I have two main roles in the CoBRE application. My primary role as co-director of the Biomedical Sciences program is to help mentor the CoBRE mentees in graduate education. This includes guiding the CoBRE mentees 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. My secondary role in the grant is as another researcher with transport experience. My research over the last 20 years has focused on several aspects of transport and drug delivery during disease. This includes investigating the regulation of both transcellular transport and paracellular transport routes. Though these studies have largely been looking at the blood brain barrier, many of the core concepts (regulated ion transport, tight junctions) are common to other barrier tissues like the gut and kidney.

Hawkins BT, Abbruscato TJ, **Egleton RD** *et al.*: Nicotine increases in vivo blood-brain barrier permeability and alters cerebral microvascular tight junction protein distribution. *Brain research* 1027(1-2), 48-58 (2004).

Seelbach MJ, Brooks TA, **Egleton RD**, Davis TP: Peripheral inflammatory hyperalgesia modulates morphine delivery to the brain: a role for P-glycoprotein. *Journal of neurochemistry* 102(5), 1677-1690 (2007).

Dom AM, Buckley AW, Brown KC *et al.*: The alpha7-nicotinic acetylcholine receptor and MMP-2/-9 pathway mediate the proangiogenic effect of nicotine in human retinal endothelial cells. *Investigative ophthalmology & visual science* 52(7), 4428-4438 (2011).

Egleton RD, Abbruscato T: Drug abuse and the neurovascular unit. *Advances in pharmacology* 71, 451-480 (2014).

B. Positions and Honors

1990	Immunology Research Technician, Animal Health Trust, Newmarket, Suffolk, U.K.
1991- 1994	Ph.D. Student, Sherrington School Of Physiology, St. Thomas' Hospital, University Of London, London, U.K. Funded via the Medical Research Scholarship Program.
1995-1997	Post-Doctoral Fellowship, Physiology Group, Kings College London, London, U.K.
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.

2004	Ad Hoc Member of Brain Injury and Neurovascular Pathologies study section (BINP)
2007 – 2010	Assistant Professor, Department Of Pharmacology, Physiology and Toxicology, Marshall University School of Medicine, Huntington, WV.
2009	Reviewer for European Commission's 7th Framework Program for Research for the topic: HEALTH-2009-2.2.1-4: Understanding the blood brain barrier (BBB) to improve drug delivery to the brain
2009 -	Reviewer for American Heart Association Brain 1 study section
2010 –	Associate Professor, Department Of Pharmacology, Physiology and Toxicology, Marshall University School of Medicine, Huntington, WV.
2012 –	Abstract Reviewer for AHA International Stroke Conference
2014 –	Marshall's representative for region III meetings of the Coalition of Physician Education in Substance Use Disorders. Meetings organized by SAMHSA in Washington DC.
2014 –	Coordinator of Cardiovascular, Respiratory and Renal Medicine for Preclinical medical students.
2015 –	Co-Director of Graduate Studies for Biomedical Sciences Program at Marshall, with an emphasis on Research.

C. Contribution to Science:

I have a varied interest in research with four major research areas. These areas all focus on endothelial cell function and tissue barriers. Though my initial studies focused on transport, my current interest is how health care issues common in Appalachia (Diabetes, hypertension substance abuse) regulate brain endothelial function and what role this plays in psychiatric disorders. My studies have been funded via federal grants at both the PPG and RO1 level. This research has resulted in 43 publications with Pubmed IDs, three other research publications, four book chapters, and one book as an editor, as well as numerous abstracts to scientific conferences. The URL for my bibliography is:
http://www.ncbi.nlm.nih.gov/myncbi/browse/collection/48132830/?sort=date&direction=ascending

1. 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 Papers out of 20 in this area.

Egleton RD, Abbruscato TJ, Thomas SA, Davis TP: Transport of opioid peptides into the central nervous system. *Journal of pharmaceutical sciences* 87(11), 1433-1439 (1998).

Egleton RD, Mitchell SA, Huber JD *et al.*: Improved bioavailability to the brain of glycosylated Met-enkephalin analogs. *Brain research* 881(1), 37-46 (2000).

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. *The Journal of pharmacology and experimental therapeutics* 299(3), 967-972 (2001).

Egleton RD, Davis TP: Development of neuropeptide drugs that cross the blood-brain barrier. *NeuroRx : the journal of the American Society for Experimental NeuroTherapeutics* 2(1), 44-53 (2005).

2. 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 Papers out of 9 in this area.

Huber JD, Witt KA, Hom S, **Egleton RD**, Mark KS, Davis TP: Inflammatory pain alters blood-brain barrier permeability and tight junctional protein expression. *American journal of physiology. Heart and circulatory physiology* 280(3), H1241-1248 (2001).

Mccaffrey G, Staatz WD, Quigley CA *et al.*: Tight junctions contain oligomeric protein assembly critical for maintaining blood-brain barrier integrity in vivo. *Journal of neurochemistry* 103(6), 2540-2555 (2007).

Seelbach MJ, Brooks TA, **Egleton RD**, Davis TP: Peripheral inflammatory hyperalgesia modulates morphine delivery to the brain: a role for P-glycoprotein. *Journal of neurochemistry* 102(5), 1677-1690 (2007).

Campos CR, Ocheltree SM, Hom S, **Egleton RD**, Davis TP: Nociceptive inhibition prevents inflammatory pain induced changes in the blood-brain barrier. *Brain research* 1221, 6-13 (2008).

3. 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.

Egleton RD, Campos CC, Huber JD, Brown RC, Davis TP: Differential effects of diabetes on rat choroid plexus ion transporter expression. *Diabetes* 52(6), 1496-1501 (2003).

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* 50(1), 202-211 (2007).

Hawkins BT, Ocheltree SM, Norwood KM, **Egleton RD**: Decreased blood-brain barrier permeability to fluorescein in streptozotocin-treated rats. *Neuroscience letters* 411(1), 1-5 (2007).

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. *American journal of physiology. Regulatory, integrative and comparative physiology* 292(5), R1881-1892 (2007).

4. 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.

Hawkins BT, Abbruscato TJ**, Egleton RD** *et al.*: Nicotine increases in vivo blood-brain barrier permeability and alters cerebral microvascular tight junction protein distribution*. Brain research* 1027(1-2), 48-58 (2004).

Hawkins BT, **Egleton RD**, Davis TP: Modulation of cerebral microvascular permeability by endothelial nicotinic acetylcholine receptors*. American journal of physiology. Heart and circulatory physiology* 289(1), H212-219 (2005).

Egleton RD, Brown KC, Dasgupta P: Angiogenic activity of nicotinic acetylcholine receptors: implications in tobacco-related vascular diseases*. Pharmacology & therapeutics* 121(2), 205-223 (2009).

Egleton RD, Abbruscato T: Drug abuse and the neurovascular unit*. Advances in pharmacology* 71, 451-480 (2014).

D. Research Support

Current

Co-Directors fund

A part of the new position as co-director of graduate studies, I was given a research fund for my studies. $60,000 (July 2015 – July 2018)

Circulating miRNA and Vascular dysfunction in diabetes

PI on grant $40,000

A grant from WV Epscor

This grant investigate the role of circulating MiRNA in endothelial dysfunction reported in diabetes. My role on the grant was to coordinate the sampling and storage of plasma from diabetic patients.

Marshall Foundation School of Medicine Alzheimer's Research Fund

This is a charitable fund that was set up to investigate drug delivery and issues with the BBB during Alzheimer's disease, ~$200,000 (original donation)