Page 411 to 414

Volume 2 • Issue 2 • 2018

Scientia Ricerca

Editorial

Current Opinions in Neurological Science

ISSN: 2575-5447

Blood Brain Barrier Permeability and Neurodegenerative Diseases

Alain L Fymat*

International Institute of Medicine and Science, California, USA

***Corresponding Author:** Alain L Fymat, International Institute of Medicine and Science, California, USA.

Received: February 02, 2018; **Published:** February 06, 2018

Volume 2 Issue 2 February 2018

Bacteria, viruses, fungi, and other microbes are part of a growing list of pathogens found in the brains of patients with neurodegenerative diseases (NDD). Microbes in the brain may indicate meningitis or encephalitis, two diseases that are active infections with inflammation. For a disease like Alzheimer (AD) and other NDDs that were not thought to be infectious, finding pathogens in the brain is both surprising and concerning. Table 1 lists some of the various pathogens found in the brain [1,2]:

Pathogen	Origin/cause	Effects
Porphyromonas gingivalis (P. Gingivalis) bacterium (*)	Mouth	Some of the proteins made by this microbe have been found in brains
Fusobacterium nucleatum bacterium	Mouth	
Prevotella intermedia bacterium	Mouth	
Herpes simplex virus		Lives for years in nerve cells that supply the face and lips. Can migrate back up the same nerve and into the brain producing mild inflammatory response
Syphilis	Triponema pallidum (a spirochete type of bacterium)	Can live in the body for decades, eventually infecting the brain and causing dementia
Lyme disease	Borrelia burgdorferi carried by the deer tick Ixodes	
Ehrlichia		Infects white blood cells
Babesia (relative of the malaria parasite)		Infects red blood cells
Bartonella		Infects blood vessels
Alzheimer disease	Many different organisms. Also, by sterile inflammation not from invading pathogens	Also harbor fungi

Adapted from Reference (2).

***Table 1:** Pathogens in the brain.*

How do the organisms in Table 1, and others, get into the brain since it is protected by the blood brain barrier (BBB)? They do so when the barrier looses some of its impermeability. Other avenues for reaching directly the brain are intra-nasal and -sinus access, the gut (through the vagus nerve that connects it to the brain), and even through the eye.

The brain has five protective barriers (BPB) that hinder the delivery of therapeutic drugs. They describe the five main interfaces between the central nervous system (CNS) and the periphery. These include: the BBB that extends down the spinal cord; the brain cerebrospinal fluid B (CSF) B barrier; the brain-inner B (iCSF) B barrier; the brain-outer B (oCSF) B barrier; and the brain retinal barrier (BRB). All interfaces are physical and metabolic barriers that serve to regulate and protect the microenvironment of the brain. Composed of a monolayer of brain capillary endothelial cells, the barriers are formed by tight junctions.

In the case of the BBB proper, the tight junctions are between the *endothelial* cells of the primary vasculature with primary manifestation being the impermeability of the capillary wall due to the presence of the junctions and a low endocytic activity. There is a relative paucity of fenestrae and pinocytotic vesicles that restrict brain uptake of circulating molecules. For B (CSF) B, the tight junctions are between the *epithelial* cells of the choroid plexus. In the case of the B (iCSF) B, the junctions are between the *neuro-ependymal* cells lining the ventricular surfaces. As for b (oCSF) B, the junctions are between the *endothelial* cells of the arachnoid vessels (the pia arachnoid). Thus, the BBB limits access to the brain to small nonpolar molecules by passive diffusion or catalyzed transport of large and/or polar molecules. It hinders the delivery of most pharmaceuticals (diagnostic, therapeutic agents) to the brain.

Now, there are approximately 400 known neurological disorders (some of which classified as mental disorders). A number of these are due to a disruption or failure of the BBB [3] such as, for example: meningitis (an inflammation of the meninges or membranes surrounding the brain and spinal cord); epilepsy (chronic or acute seizures caused by inflammation), [4,5]; multiple sclerosis (MS, a disease of either the immune system or/and the breaking down of the BBB in a section of the brain or spinal cord); Alzheimer's disease (AD, a disease in which amyloid beta contained in blood plasma enters the brain and adheres to the surface of astrocytes); possibly prion and prion-like diseases such as Parkinson's disease (PD) [6] and AD [7]; HIV encephalitis (HIVE), a precursor of HIV-associated dementia (HIVAD) in which latent HIV can cross the BBB inside circulating monocytes in the blood stream; and systemic inflammation (sterile or infectious) that may lead to effects on the brain, cause sickness behavior and induce or/and accelerate brain diseases such as MS and PD. Table 2 summarizes for each disease the corresponding BBB factor [3].

Disease	BBB Factor	Disease	BBB Factor
Alzheimer	Disruption/Breakdown	Multiple sclerosis (immune system deficiency)	Breakdown
Brain abscess	Unknown mechanism	Neuromyelitis optica (Devic's disease)	Breakdown
Cerebral edema	Opening (due to hypoxia)	Prion and prion-like diseases (Parkinson and Alzeimer)	Unknown penetration mechanism
De vivo	Unknown mechanism	Progressive multi-focal leuko-encephalopathy	Disruption
Epilepsy	Disruption/Failure	Rabies	Increased permeability
HIV encephalitis (latent HIV crosses the BBB)	Damage (inflammatory)	Systemic inflammation (sterile, infectious)	Disruption?
Meningitis	Disruption	Tripanosomasis (sleep thickness)	Disruption

Reference (3): Fymat (2017).

Table 2: *Some brain diseases and their corresponding effects on the BBB.*

Notwithstanding the indications in Table 2, the convergence between BBB studies and clinical investigations has historically been limited. Thus, in the case of epilepsy, it has been limited to interactions between putative anti-epileptic drugs (AED) and the endothelium. These studies were based on the observation that many promising AEDs are excluded by the BBB. They are thus clinically unusable in spite of their significant potency and selectivity, as revealed by *in vitro* screening or animal models. More recently, it has become apparent that multiple drug resistance (MDR) is only one of the aspects in BBB research that may impact how we define, prevent and treat seizure disorders. A compromised BBB has been associated with seizures in a number of disorders. Not only congenital defects, such as GLUT1 deficiency, but acquired deficiencies, like those resulting from brain tumors, head trauma, etc., often result in seizure disorders. More recently systemic and immune triggers have been implicated in a leaky BBB and neuroinflammation.

Likewise, in the case of Parkinson's disease (PD), we know the following: Dopamine does not cross the BBB so it cannot be taken as a medicine to boost the brain's depleted levels of Dopamine. However a precursor of Dopamine, Levodopa, can pass through this barrier to the brain where it is readily converted to Dopamine. Administration of this drug temporarily diminishes the motor symptoms of PD. Unfortunately, only 5–10% of the drug crosses the barrier with much of the remainder being metabolized to Dopamine elsewhere in the body, where it causes a variety of side effects. Next, the immunotherapeutic strategy for PD therapy relies on the assumption that (a) alpha-synuclein is accessible in the extracellular space (trans-synaptic spreading), (b) antibodies against alpha-synuclein reach the brain in sufficient quantity, and (c) they trap alpha-synuclein aggregates when these are released ("spread") into the extracellular synaptic space.

However, one important limitation of active and passive immunotherapy is that the low amount of antibodies passing the BBB, may be overcome by coupling antibodies to the peptide penetratin, as has recently been reported in a mouse PD model. Lastly, modulating the aggregation of alpha-synuclein aims to block or reduce the aggregation of its monomers to oligomers or later on to fibrils. Three drugs are close to or under very early development (ANLE138b, NPT200-11, and NPT100-18a). The advantage of these small molecules is that, in variance to antibodies employed in immunotherapeutic attempts, they readily pass the BBB. Thus, being able to traverse or bypass the BBB while delivering therapeutic compounds at the right locations in the right dosage amounts would herald a new approach to the treatment of PD. This is what nanomedicine (NM) and nanotechnology (NT) promise to do. However, while the technology is now well known, its application to PD, and more generally ND, has not yet been undertaken.

Drug resistance and the possible role of the BBB obviously remain an important research focus. Further, understanding the nature of the role of the BBB in neurological disorders is imperative in their treatments, but the fundamental question of whether the compromised integrity of the BBB is a component of the etiology of the diseases or a consequence of it remains unanswered.

References

1. Poole S., *et al*. "Determining the presence of periodontopathic virulence factors in short-term post mortem Alzheimer's disease brain tissue". *Journal of Alzheimer 's Disease* 36.4 (2013): 665-677.
2. Bredesen D. "The end of Alzheimer's: the first programme to prevent and reverse the cognitive decline of dementia". Vermilion, London (2017): 308.
3. Fymat AL. "Nanoneurology: drug delivery across the brain protective barriers". *Journal of Nanomedicine Research* 5.1 (2017): 1-4.
4. Cornford EM and Oldendorf WH. "Epilepsy and the blood-brain barrier". *Advances in Neurology* 44 (1986): 787–812.
5. Oby E and Janigro A, "The blood brain barrier and epilepsy". *Epilepsia* 47.11 (2006): 1761-1774.
6. Fymat AL. "Neurological disorders and the blood brain barrier: 2. Parkinson and other movement disorders". *Current Opinions in Neurological Science* 2.1 (2018): 362-383.
7. Fymat AL (2018). "Neurological disorders and the blood brain barrier: 2. Alzheimer's disease". *Current Opinions on Neurological Science (in press).*