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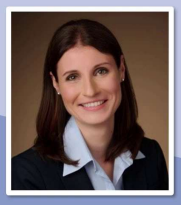
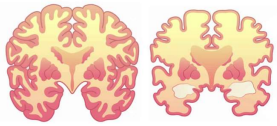
The Blood-Brain Barrier in Alzheimer's Disease



Dr. Anika Hartz
Associate Professor
University of Kentucky
Sanders-Brown Center on Aging

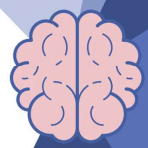
1

Outline



2

The blood-brain barrier



3

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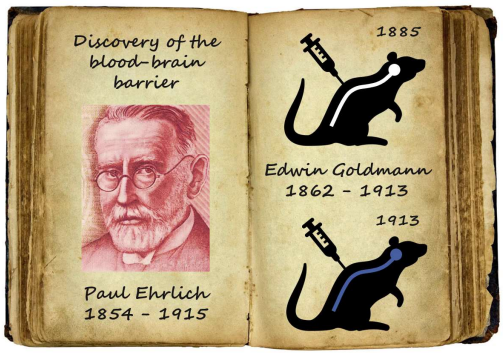
Blood-brain barrier – discovery

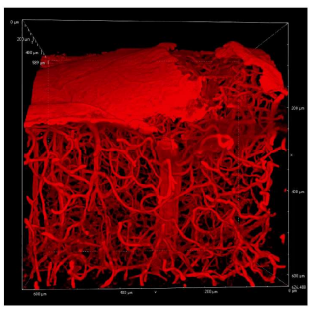


4

Blood-brain barrier – discovery

- Confirmed hypothesis that there is a barrier between the central nervous system and the periphery
- Provided evidence of compartments and a barrier between the brain and periphery
- Paul Ehrlich awarded Nobel Prize in 1908
- These experiments were the beginning of blood-brain barrier research
- The term 'Blood-brain barrier' was introduced in 1921

Capillaries of the blood-brain barrier



- Capillaries 5-7 microns in diameter
- Equipped with enzymes, receptor signaling molecules and transporters
- Protect and nurture the brain and remove waste
- Connected to astrocytes, pericytes and neurons
- Allows communication between the central nervous system and the periphery
- In Alzheimer's disease, changes in the blood-brain barrier contribute to disease pathology

5

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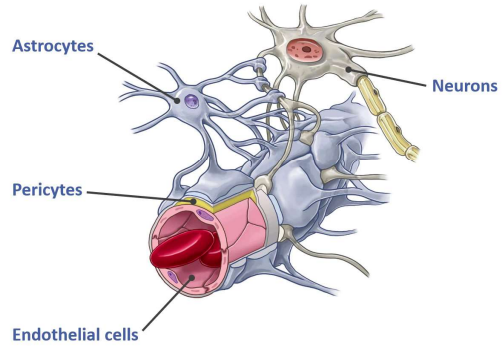
Neurovascular unit – anatomy



Custom-designed illustration by Rick Kollath, graphic designer, Duluth, MN, USA

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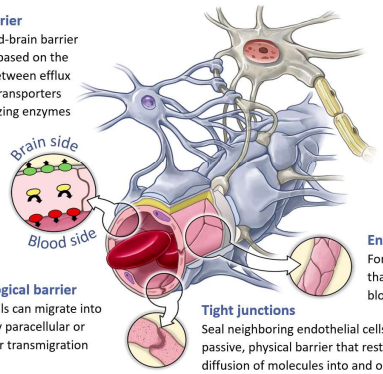
Neurovascular unit – function

Active barrier
Active blood-brain barrier function is based on the interplay between efflux and influx transporters & metabolizing enzymes



Endothelial cells
Form brain capillaries that comprise the blood-brain barrier

Immunological barrier
Immune cells can migrate into the brain by paracellular or transcellular transmigration

Tight junctions
Seal neighboring endothelial cells to form a passive, physical barrier that restricts free diffusion of molecules into and out of the brain

Custom-designed illustration by Rick Kollath, graphic designer, Duluth, MN, USA

7

Alzheimer's disease

8

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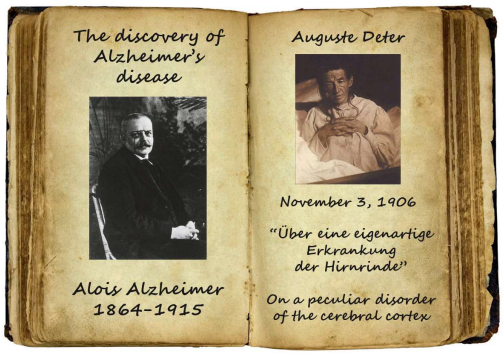
Alzheimer's disease – discovery



Alzheimer (1906) *Neurologisches Centralblatt*, **25**:1134
Alzheimer (1907) *Allgemeine Zeitschrift fur Psychiatrie und Psychisch-gerichtliche Medizin*, **64**:146–48

9

Alzheimer's disease – discovery

- Auguste started showing signs of memory loss, trouble sleeping and problems with language and writing when she was in her early 50's
- Her symptoms were characteristic of dementia, but she was very young
- She was originally diagnosed with presenile dementia
- Auguste's brain was found to contain senile plaques and tangles
- This disease was later named **Alzheimer's disease**

Alzheimer (1906) *Neurologisches Centralblatt*, **25**:1134
Alzheimer (1907) *Allgemeine Zeitschrift fur Psychiatrie und Psychisch-gerichtliche Medizin*, **64**:146–48

Alzheimer's disease – numbers and facts

Dementia

- Loss of cognitive function
- Problem solving
- Tension and memory
- Visual perception
- Communication
- Self management

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Alzheimer's disease – numbers and facts

Alzheimer's disease

- Most common type of dementia
- Irreversible and progressive
- 4th leading cause of death amongst elderly in developed nations
- 11% of diagnoses in people over 65 years old
- 50% of diagnoses over 85 years old
- 250 million patients expected in 2050 worldwide
- Early onset initiates between the ages of 30 and 60 and is often associated with genetic mutations
- Late onset (90% of patients) initiates after the age of 60 and is associated with numerous environmental and lifestyle-based factors

Alzheimer's disease – numbers and facts

Alzheimer's disease – early symptoms

- Decline in cognitive abilities
- Mood swings
- Agitation and anxiety
- Sleep disturbances
- Loss of appetite

Alzheimer's disease – numbers and facts

Alzheimer's disease – later symptoms

- Personality changes
- Memory loss
- Impaired spatial awareness
- Impaired movement
- Impaired planning skills
- Speech problems
- Lack of insight
- Problems with recognition
- Delusions and hallucinations

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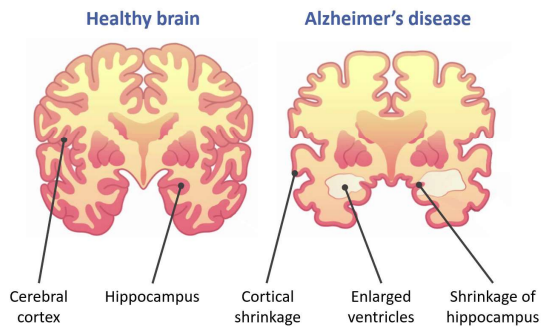
Alzheimer's disease - pathology



11

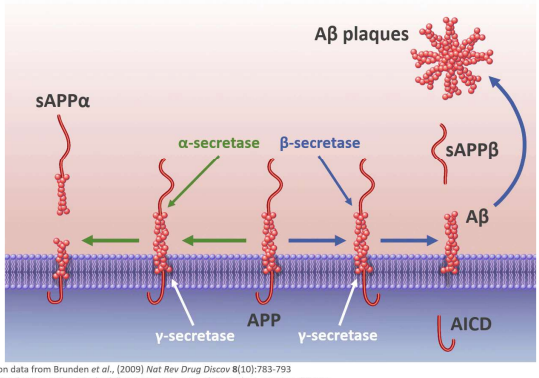
Based on data from Brunden *et al.*, (2009) *Nat Rev Drug Discov* 8(10):783-793

Alzheimer's disease – pathology

- Historically, plaques and tangles were observed in and around degenerating neurons and blood vessels in brain autopsy samples from AD patients
- Electron microscopy and diffraction studies enabled researchers to visualize that plaques are largely organized in β-sheets
- By the 1980's, multiple research groups had found that Aβ is the monomer that builds plaques, oligomers, protofibrils and fibrillar sheets

12

Alzheimer's disease – pathology



Based on data from Brunden *et al.*, (2009) *Nat Rev Drug Discov* 8(10):783-793
Illustration by Tom Dolan, Medical Illustrator, University of Kentucky, Lexington, KY, USA

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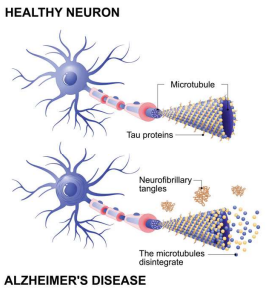
Alzheimer's disease - pathology

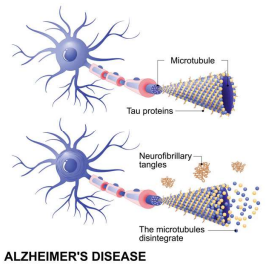


Neurofibrillary tangles are composed of paired helical filaments that contain the microtubule-associated protein 'tau' (50 kDa)

Brunden *et al.*, (2009) *Nat Rev Drug Discov* 8(10):783-793

13

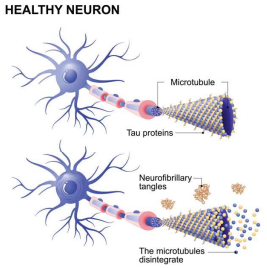
Alzheimer's disease - pathology



Tau is abnormally phosphorylated and forms tau oligomers and granular tau aggregates which accumulate in the brains of AD patients

Brunden *et al.*, (2009) *Nat Rev Drug Discov* 8(10):783-793

Alzheimer's disease - pathology



Tau peptides are composed of 31-32 amino acids, with 2-3 phosphate molecules per peptide

Brunden *et al.*, (2009) *Nat Rev Drug Discov* 8(10):783-793

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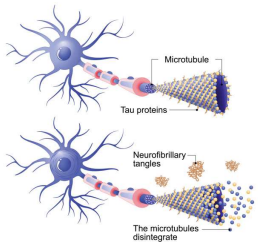
Alzheimer's disease - pathology

HEALTHY NEURON



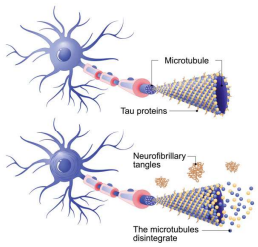
ALZHEIMER'S DISEASE

Tau peptides are maintained by tau-specific kinases and phosphatases in the brain

Brunden *et al.*, (2009) *Nat Rev Drug Discov* 8(10):783-793

Alzheimer's disease - pathology

HEALTHY NEURON



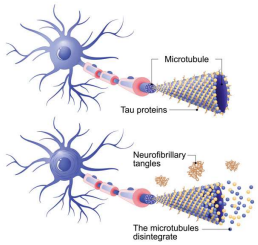
ALZHEIMER'S DISEASE

In AD, the levels of abnormally phosphorylated tau protein can be 4-8 fold higher than physiological tau levels in the brain

Brunden *et al.*, (2009) *Nat Rev Drug Discov* 8(10):783-793

Alzheimer's disease - pathology

HEALTHY NEURON



ALZHEIMER'S DISEASE

Accumulation of Aβ and tau in the brain causes pathophysiological changes that affect cognitive function

Brunden *et al.*, (2009) *Nat Rev Drug Discov* 8(10):783-793

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Diagnosis, prognosis and treatment

- Cognitive tests
- Imaging
- Lab assays
- Post mortem
- Clinical symptoms
- Neuropathological markers
- Plaques and tangles
- Symptoms worsen over time
- Disease progression varies by patient
- On average patients live 4-8 years after diagnosis
- No cure

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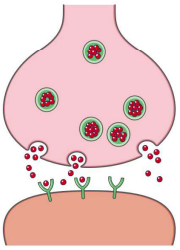
Diagnosis, prognosis and treatment

- 5 areas of drug development: neurotransmitters, Aβ pathology, neuroinflammation, tau pathology and cholesterol

Diagnosis, prognosis and treatment

- 5 areas of drug development: neurotransmitters, Aβ pathology, neuroinflammation, tau pathology and cholesterol
- There are currently only 4 FDA approved drugs available – all target synaptic activity



- Donepezil, Galantamine and Stigmine (cholinesterase inhibitors), Memantine (MDA receptor blocker)
- Modest effects. Lower symptoms in 40-70% patients
- Improvement subsides after 6-12 months of use
- Current approved drugs have no effect on the underlying pathophysiological causes of AD
- Experimental drugs that have a disease modifying effect show no significant improvement in cognition

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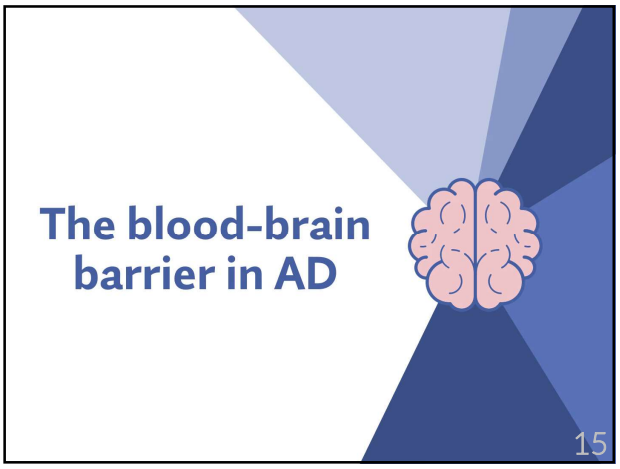

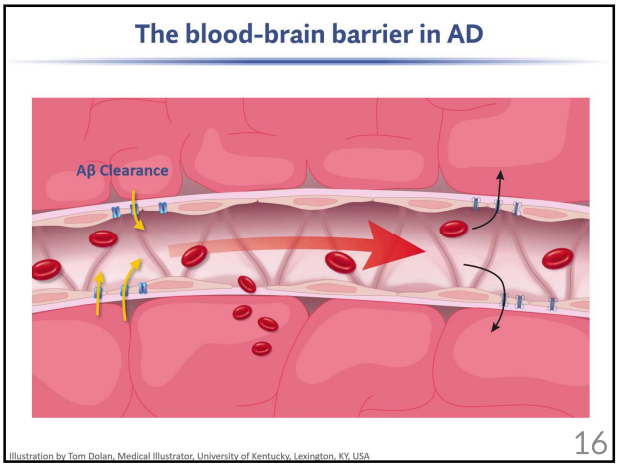

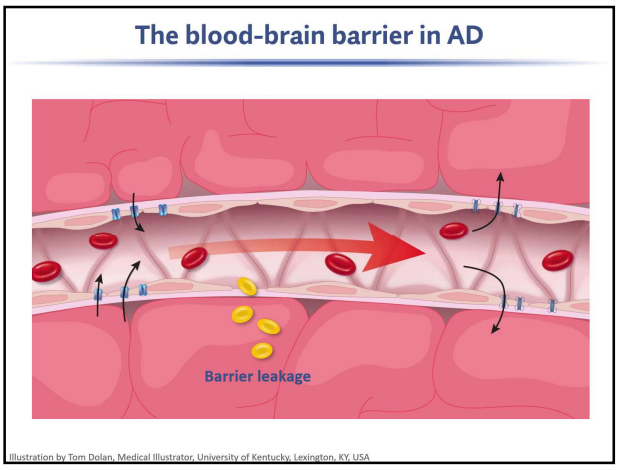

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The blood-brain barrier in AD

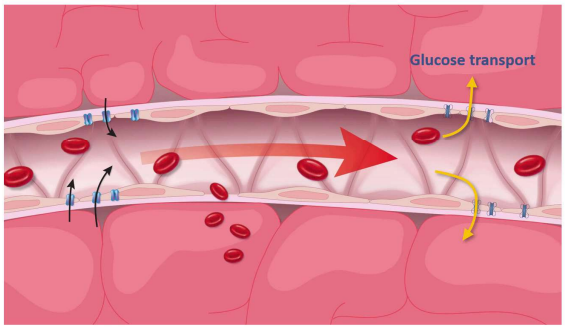


Illustration by Tom Dolan, Medical Illustrator, University of Kentucky, Lexington, KY, USA

The blood-brain barrier in AD

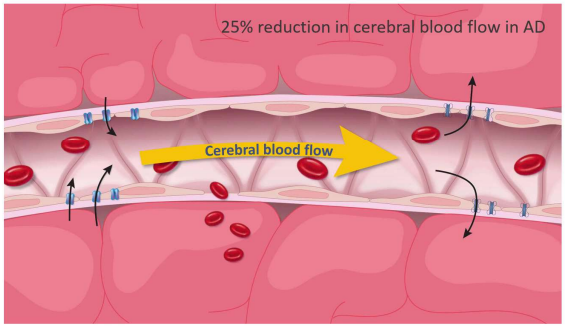
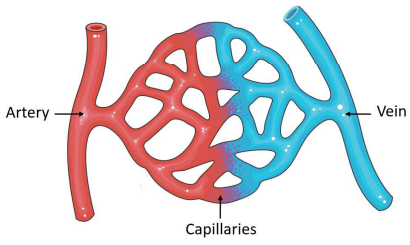


Illustration by Tom Dolan, Medical Illustrator, University of Kentucky, Lexington, KY, USA

The vascular hypothesis

"Alzheimer's disease is a vascular disorder with neurodegenerative consequences"



de la Torre JC and Mussivand T (1993) *Neurol Res*, **15**:146-153
de la Torre JC (2018) *Journal of Alzheimer's Disease*, **63**(1): 35-52

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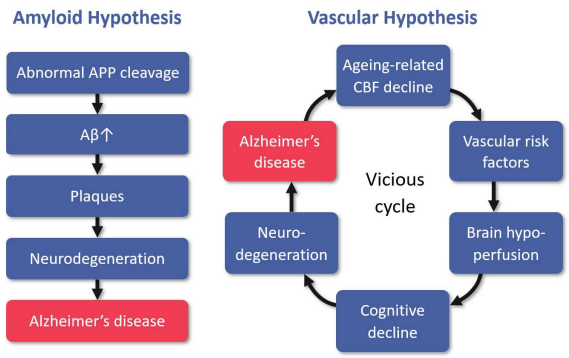
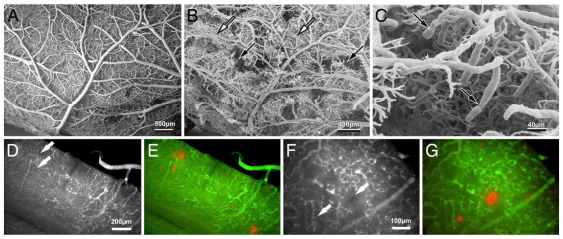
The vascular hypothesis



de la Torre JC and Mussivand T (1993) *Neurol Res*, **15**:146-153
de la Torre JC (2018) *Journal of Alzheimer's Disease*, **63**(1): 35-52

Cerebral blood flow

Vessel deformation and distortion



Meyer *et al.*, (2008) *PNAS* **105**(9):3587-3592

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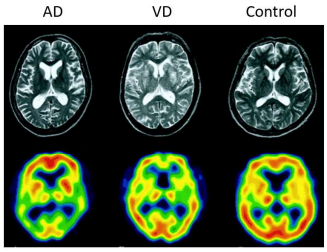
Cerebral blood flow



- Cerebral blood flow (CBF) is reduced in patients with Alzheimer's disease
- Changes in blood vessel architecture can alter CBF in different brain regions
- Reduced CBF leads to hypoperfusion and a reduced supply of oxygen and nutrients to the brain

Yoshikawa *et al.*, (2003) *AJNR*, **24**(7):1341-1347

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The blood-brain barrier in AD

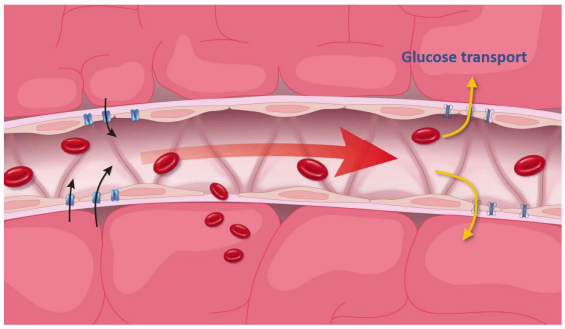
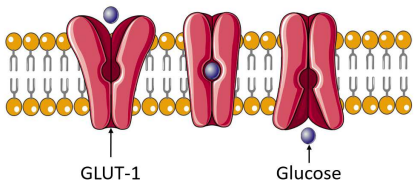


Illustration by Tom Dolan, Medical Illustrator, University of Kentucky, Lexington, KY, USA

20

Glucose transport – fuel for the brain



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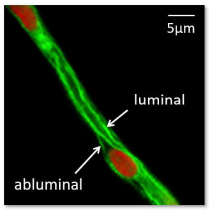
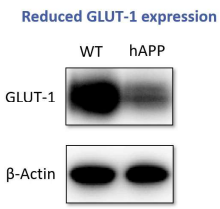
Glucose transport – fuel for the brain





Hartz *et al.*, unpublished data
Harik *et al.*, (1992) *Can J Physiol Pharmacol*, **70**: S113-117
Horwood and Davies (1994) *Virchows Arch*, **425**(1):69-72
Mooradian *et al.*, (1997) *Neurobiol Aging*, **18**(5):469-474
Winblad *et al.*, (2016) *The Lancet Neurology* **15**(5):455-532

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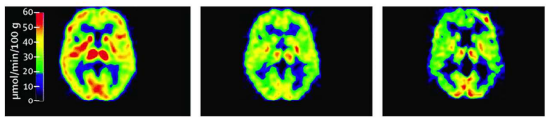
Glucose transport – fuel for the brain

Reduced glucose metabolism

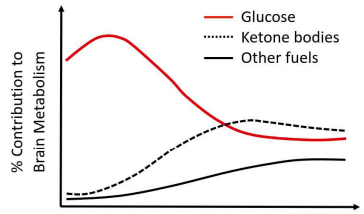


Alzheimer's disease MMSE 27/30 | Alzheimer's disease MMSE 21/30 | Alzheimer' disease MMSE 13/30

Regional cerebral glucose metabolism is significantly reduced during the progression of Alzheimer's disease compared with healthy participants

Hartz *et al.*, unpublished data
Harik *et al.*, (1992) *Can J Physiol Pharmacol*, **70**: S113-117
Horwood and Davies (1994) *Virchows Arch*, **425**(1):69-72
Mooradian *et al.*, (1997) *Neurobiol Aging*, **18**(5):469-474
Winblad *et al.*, (2016) *The Lancet Neurology* **15**(5):455-532

Glucose transport



- There is a bioenergetic shift towards the use of alternate fuels in AD
- Insulin resistance may promote this development
- What causes this shift? Is it an inherited defect? Is it caused by amyloid or tau?
- How do diseases of systemic metabolic dysfunction affect disease progression?

Modified from Neth and Craft (2017) *Front Aging Neurosci*, 9:345

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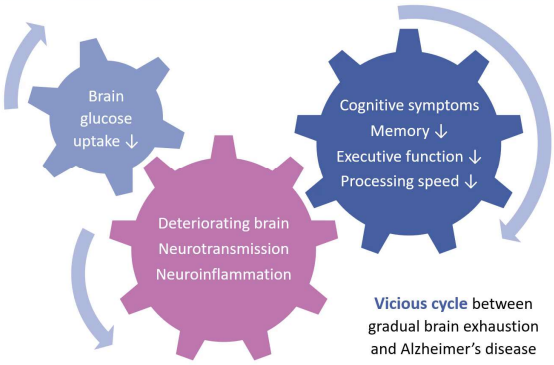
Glucose transport



Vicious cycle between gradual brain exhaustion and Alzheimer's disease

Modified from Cunnane *et al.*, (2016) *Front Mol Neurosci* 9:53

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The blood-brain barrier in AD

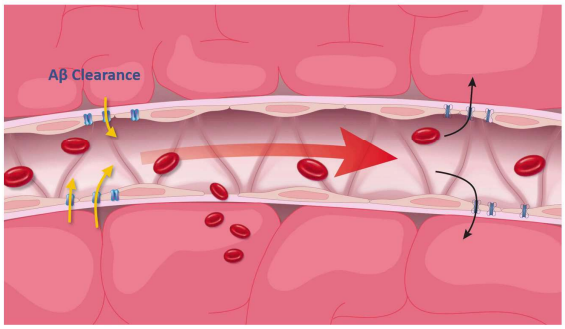

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Illustration by Tom Dolan, Medical Illustrator, University of Kentucky, Lexington, KY, USA

Aβ clearance

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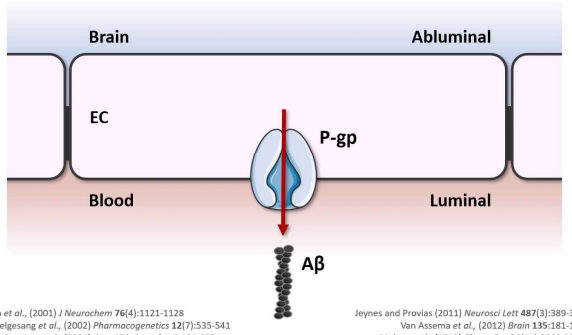
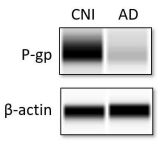


Lam *et al.*, (2001) *J Neurochem* **76**(4):1121-1128
Vogelgesang *et al.*, (2002) *Pharmacogenetics* **12**(7):535-541
Vogelgesang *et al.*, (2004) *Curr Alzheimer Res* **1**:121-125
Cirrito *et al.*, (2005) *J Clin Invest* **115**(11):3285-3290
Kuhnke *et al.*, (2007) *Brain Pathol* **17**(4):347-353
Wijesuriya *et al.*, (2010) *Brain Res* **1358**(28):228-238
Jeynes and Provias (2011) *Neurosci Lett* **487**(3):389-393
Van Assema *et al.*, (2012) *Brain* **135**:181-189
Mehta *et al.*, (2013) *Pharm Res* **30**(11):2868-2879
Deo *et al.*, (2014) *J Nucl Med* 1106-1111
Carrano *et al.*, (2014) *Neurobiol Aging* 565-575
Brückmann *et al.*, (2017) *Curr Alzheimer Res* **14**(6):656-667

Aβ clearance

UK-ADC Tissue Bank

n=10/group	CNI	AD
Age at Death [y]	86 ± 3.8	85 ± 2.6
PMI [h]	2.4 ± 0.8	2.8 ± 0.8
Braak	1.3 ± 0.3	5.3 ± 0.3
Final MMSE	29 ± 1.2	18 ± 7.3



- Simple western assay determines the P-gp levels found in isolated human capillaries
- Decreased P-gp levels found in capillaries of AD patients
- Protein quantification 10x higher sensitivity compared to western blot

Lam *et al.*, (2001) *J Neurochem* **76**(4):1121-1128
Vogelgesang *et al.*, (2002) *Pharmacogenetics* **12**(7):535-541
Vogelgesang *et al.*, (2004) *Curr Alzheimer Res* **1**:121-125
Cirrito *et al.*, (2005) *J Clin Invest* **115**(11):3285-3290
Kuhnke *et al.*, (2007) *Brain Pathol* **17**(4):347-353
Wijesuriya *et al.*, (2010) *Brain Res* **1358**(28):228-238
Jeynes and Provias (2011) *Neurosci Lett* **487**(3):389-393
Van Assema *et al.*, (2012) *Brain* **135**:181-189
Mehta *et al.*, (2013) *Pharm Res* **30**(11):2868-2879
Deo *et al.*, (2014) *J Nucl Med* 1106-1111
Carrano *et al.*, (2014) *Neurobiol Aging* 565-575
Brückmann *et al.*, (2017) *Curr Alzheimer Res* **14**(6):656-667

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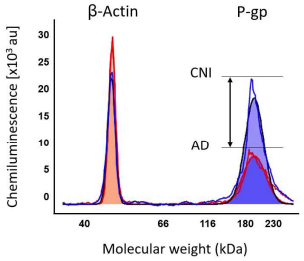
Aβ clearance



Lam *et al.*, (2001) *J Neurochem* **76**(4):1121-1128
Vogelgesang *et al.*, (2002) *Pharmacogenetics* **12**(7):535-541
Vogelgesang *et al.*, (2004) *Curr Alzheimer Res* **1**:121-125
Cirrito *et al.*, (2005) *J Clin Invest* **115**(11):3285-3290
Kuhnke *et al.*, (2007) *Brain Pathol* **17**(4):347-353
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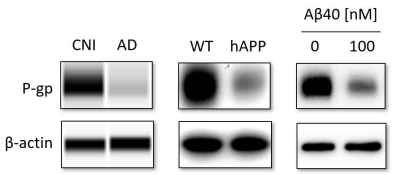
Jeynes and Provias (2011) *Neurosci Lett* **487**(3):389-393
Van Assema *et al.*, (2012) *Brain* **135**:181-189
Mehta *et al.*, (2013) *Pharm Res* **30**(11):2868-2879
Deo *et al.*, (2014) *J Nucl Med* 1106-1111
Carrano *et al.*, (2014) *Neurobiol Aging* 565-575
Brückmann *et al.*, (2017) *Curr Alzheimer Res* **14**(6):656-667

Aβ clearance

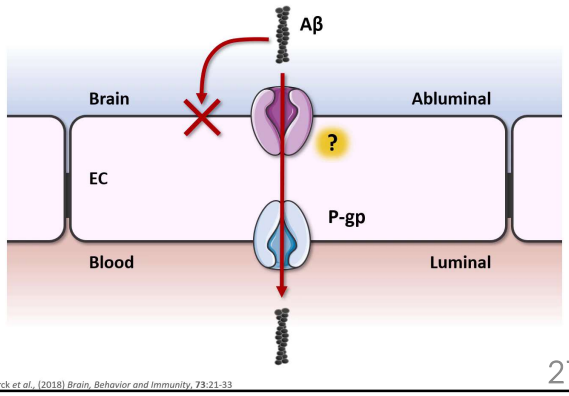


What came first? Aβ decrease or P-gp decrease?

Hartz *et al.*, (2018) *Front Aging Neurosci*, **10**:186
Hartz *et al.*, (2010) *Mol Pharmacol*, **77**(5):715-23
Hartz *et al.*, (2016) *J Neurosci*, **36**(6):1930-41

26

Aβ transport mechanism



Storck *et al.*, (2018) *Brain, Behavior and Immunity*, **73**:21-33

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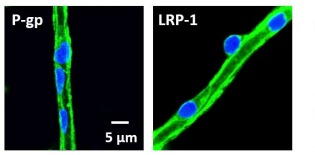
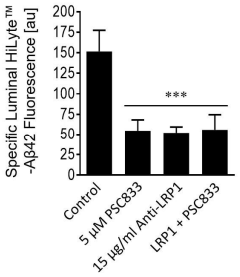
Aβ transport mechanism



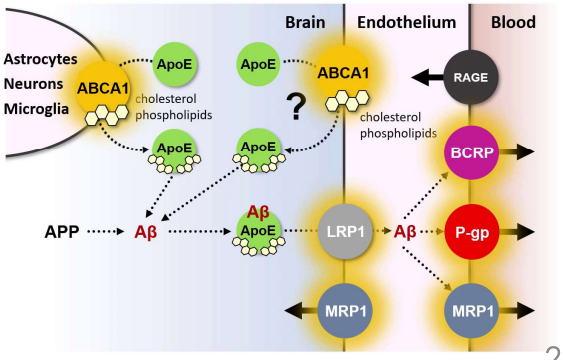


Simultaneous inhibition of P-gp and LRP-1 did not have an additive effect on Aβ transport

More studies are needed to determine whether both these proteins are involved in Aβ clearance

Storck *et al.*, (2018) *Brain, Behavior and Immunity*, **73**:21-33

Aβ clearance



Modified from Wolf *et al.*, (2012) *Front Psychiatry* 3(54):1-14

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The blood-brain barrier in AD

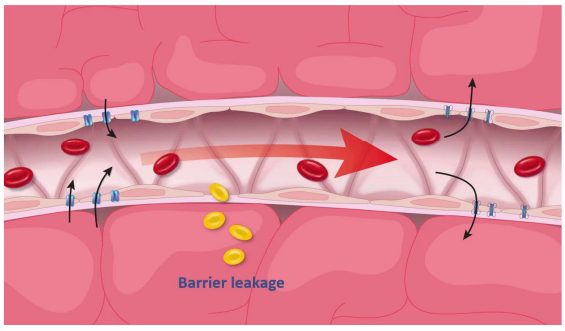

Illustration by Tom Dolan, Medical Illustrator, University of Kentucky, Lexington, KY, USA

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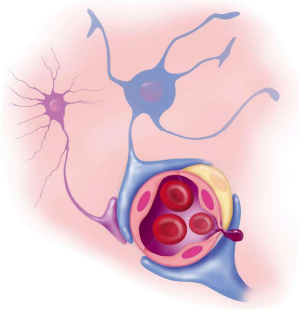
Blood-brain barrier leakage



- Blood-brain barrier leakage is well documented in patients with cerebral amyloid angiopathy (CAA)
- CAA is present in more than 80% of Alzheimer's disease patients
- CAA is a likely contributing factor to Alzheimer's disease pathology
- Significant Aβ build-up in capillaries

Hartz *et al.*, unpublished data
Hartz *et al.*, (2012) *Stroke*, **43**(2):514-523
Modified from Rempe *et al.*, (2016) *JCBFM*, **36**(9):1481-1508; illustration by Tom Dolan, Medical Illustrator, University of Kentucky

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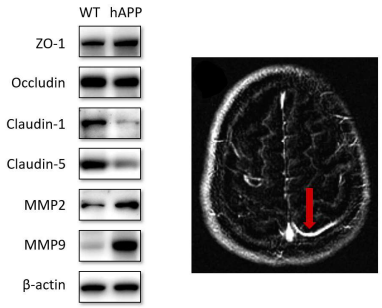
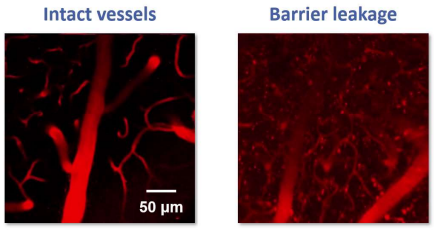
Blood-brain barrier leakage



Hartz *et al.*, unpublished data
Hartz *et al.*, (2012) *Stroke*, **43**(2):514-523
Modified from Rempe *et al.*, (2016) *JCBFM*, **36**(9):1481-1508; illustration by Tom Dolan, Medical Illustrator, University of Kentucky

Blood-brain barrier leakage



Hartz *et al.*, unpublished data
Hartz *et al.*, (2012) *Stroke*, **43**(2):514-523
Modified from Rempe *et al.*, (2016) *JCBFM*, **36**(9):1481-1508; illustration by Tom Dolan, Medical Illustrator, University of Kentucky

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Blood-brain barrier leakage

Barrier Leakage	Methods	Reference
Fibrinogen	IHC IHC SEM; ELISA ELISA IF	Hultman *et al.*, (2013) *J Cereb Blood Flow Metab*, **33**(8):1251-1258 Ryu *et al.*, (2009) *J Cell Mol Med*, **13**(9A):2911-2925 Cortes-Canteli *et al.*, (2010) *Neuron*, **66**(5):695-709 Miners *et al.*, (2018) *J Cereb Blood Flow Metab*, **38**(1):103-115 Sengillo *et al.*, (2013) *Brain Pathol*, **23**(3):303-310
Prothrombin	IHC, IF, ELISA	Zipser *et al.*, (2007) *Neurobiol Aging*, **28**(7):977-986
Albumin	IHC	Wisniewski *et al.*, (1982) *Ann N Y Acad Sci*, **396**:119-129
IgG	IF IHC	Halliday *et al.*, (2016) *J Cereb Blood Flow Metab*, **36**(1):216-227 Ryu *et al.*, (2009) *J Cell Mol Med*, **13**(9A):2911-2925
Hemosiderin	IHC	Cullen *et al.*, (2005) *J Cereb Blood Flow Metab*, **25**(12):1656-1667
Red blood cells	Auto-Fluorescence	Cullen *et al.*, (2005) *J Cereb Blood Flow Metab*, **25**(12):1656-1667
Contrast agent (gadolinium)	MRI MRI MRI	van de Haar *et al.*, (2016) *Radiology*, **281**(2):527-535 (CNI: n=17; AD: n=16) van de Haar *et al.*, (2016) *Neurobiol Aging*, **45**:190-196 (CNI: n=16; AD: n=14) van de Haar *et al.*, (2017) *Med Phys*, **44**(8):4112-4125 (CNI: n=17; AD: n=16)

Early findings were based on the detection of plasma proteins in Alzheimer's disease brains, suggesting protein extravasation through a leaky barrier

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Blood-brain barrier leakage

Barrier Leakage	Methods	Reference
Fibrinogen	IHC IHC SEM; ELISA ELISA IF	Hultman *et al.*, (2013) *J Cereb Blood Flow Metab*, **33**(8):1251-1258 Ryu *et al.*, (2009) *J Cell Mol Med*, **13**(9A):2911-2925 Cortes-Canteli *et al.*, (2010) *Neuron*, **66**(5):695-709 Miners *et al.*, (2018) *J Cereb Blood Flow Metab*, **38**(1):103-115 Sengillo *et al.*, (2013) *Brain Pathol*, **23**(3):303-310
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Albumin	IHC	Wisniewski *et al.*, (1982) *Ann N Y Acad Sci*, **396**:119-129
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Fibrinogen is a soluble glycoprotein complex that circulates in the blood. During vascular injury, it is converted to fibrin and forms clots

Blood-brain barrier leakage

Barrier Leakage	Methods	Reference
Fibrinogen	IHC IHC SEM; ELISA ELISA IF	Hultman *et al.*, (2013) *J Cereb Blood Flow Metab*, **33**(8):1251-1258 Ryu *et al.*, (2009) *J Cell Mol Med*, **13**(9A):2911-2925 Cortes-Canteli *et al.*, (2010) *Neuron*, **66**(5):695-709 Miners *et al.*, (2018) *J Cereb Blood Flow Metab*, **38**(1):103-115 Sengillo *et al.*, (2013) *Brain Pathol*, **23**(3):303-310
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Albumin	IHC	Wisniewski *et al.*, (1982) *Ann N Y Acad Sci*, **396**:119-129
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Hemosiderin	IHC	Cullen *et al.*, (2005) *J Cereb Blood Flow Metab*, **25**(12):1656-1667
Red blood cells	Auto-Fluorescence	Cullen *et al.*, (2005) *J Cereb Blood Flow Metab*, **25**(12):1656-1667
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In AD, fibrinogen levels increase in the blood and create large unregulated clots, inducing oxidative stress and inflammation

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Blood-brain barrier leakage

Barrier Leakage	Methods	Reference
Fibrinogen	IHC IHC SEM; ELISA ELISA IF	Hultman *et al.*, (2013) *J Cereb Blood Flow Metab*, **33**(8):1251-1258 Ryu *et al.*, (2009) *J Cell Mol Med*, **13**(9A):2911-2925 Cortes-Canteli *et al.*, (2010) *Neuron*, **66**(5):695-709 Miners *et al.*, (2018) *J Cereb Blood Flow Metab*, **38**(1):103-115 Sengillo *et al.*, (2013) *Brain Pathol*, **23**(3):303-310
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Prothrombin is a blood-borne protein that is converted to thrombin at the onset of coagulation, leading to vascular repair

Blood-brain barrier leakage

Barrier Leakage	Methods	Reference
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Hemosiderin	IHC	Cullen *et al.*, (2005) *J Cereb Blood Flow Metab*, **25**(12):1656-1667
Red blood cells	Auto-Fluorescence	Cullen *et al.*, (2005) *J Cereb Blood Flow Metab*, **25**(12):1656-1667
Contrast agent (gadolinium)	MRI MRI MRI	van de Haar *et al.*, (2016) *Radiology*, **281**(2):527-535 (CNI: n=17; AD: n=16) van de Haar *et al.*, (2016) *Neurobiol Aging*, **45**:190-196 (CNI: n=16; AD: n=14) van de Haar *et al.*, (2017) *Med Phys*, **44**(8):4112-4125 (CNI: n=17; AD: n=16)

95% of prothrombin resides in the blood. Less than 1% is present in the cerebral spinal fluid of healthy individuals

Blood-brain barrier leakage

Barrier Leakage	Methods	Reference
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Novel imaging techniques can be used to visualize barrier leakage in the brain

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Blood-brain barrier leakage

> Radiology. 2016 Nov;281(2):527-535. doi: 10.1148/radiol.2016152244. Epub 2016 May 31.

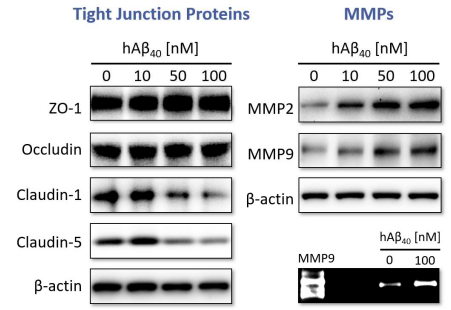
Blood-Brain Barrier Leakage in Patients with Early Alzheimer Disease

Harm J van de Haar [1], Saartje Burgmans [1], Jacobus F A Jansen [1], Matthias J P van Osch [1], Mark A van Buchem [1], Majon Muller [1], Paul A M Hofman [1], Frans R J Verhey [1], Walter H Backes [1]

- 5 fold leakage increase in AD compared to control individuals (M and F)
- Evidence of an inverse correlation between barrier leakage and cognition
- In AD, barrier leakage and memory decline may be mechanistically linked

Van de Haar *et al.*, (2016) *Radiology* **281**:527-615

Blood-brain barrier leakage



Hartz *et al.*, (2012) *Stroke* **43**(2):514-523

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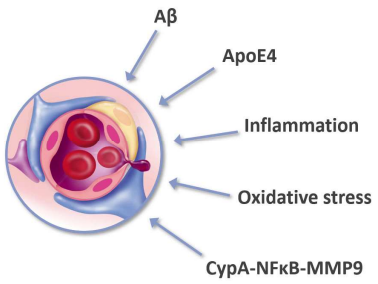
Blood-brain barrier leakage



Hartz *et al.*, (2012) *Stroke*, **43**(2):514-523
Bell *et al.*, (2012) *Nature*, **16**;485(7399):512-516
Kook *et al.*, (2012) *J of Neuroscience*, **32**(26):8845-8854
Marottoli *et al.*, (2017) *ASN Neuro*, **9**(4)
Lin *et al.*, (2017) *J Cereb Blood Flow Metab*, **37**(1):217-226
Nicolakakis *et al.*, (2008) *J Neurosci*, **28**(37):9287-9296
Modified from Rempe *et al.*, (2016) *JCBFM*, **36**(9):1481-1508; illustration by Tom Dolan, Medical Illustrator, University of Kentucky

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Summary

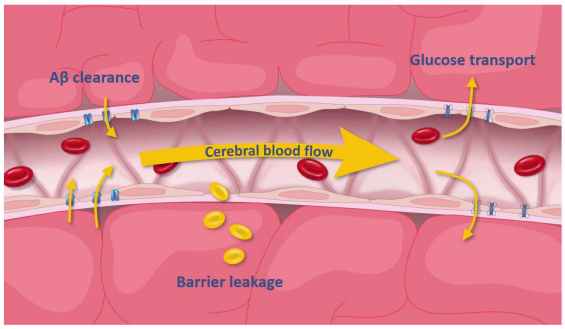

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Illustration by Tom Dolan, Medical Illustrator, University of Kentucky, Lexington, KY, USA

Blood-brain barrier repair

- Corrects pathophysiological cause
- Limited side effects
- Reverses cognitive decline
- Affordable
- Prevents disease onset
- Current therapies do not meet these criteria
- Effective in most patients

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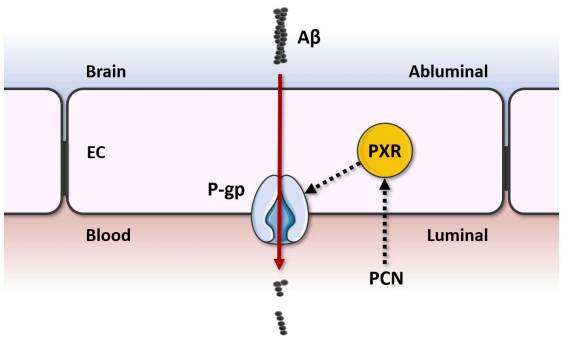
Blood-brain barrier repair



Hartz *et al.*, (2010) *Mol Pharmacol*, **77**:715-723
Bauer *et al.*, (2008) *J Cereb Blood Flow Metab*, **28**(6):1222-34
Bauer *et al.*, (2006) *Mol Pharmacol*, **70**(4):1212-9
Bauer *et al.*, (2004) *Mol Pharmacol*, **66**(3):413-9

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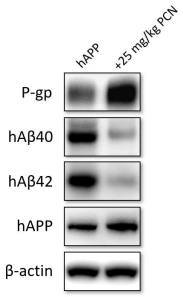
Blood-brain barrier repair



Hartz *et al.*, (2010) *Mol Pharmacol*, **77**:715-723
Bauer *et al.*, (2008) *J Cereb Blood Flow Metab*, **28**(6):1222-34
Bauer *et al.*, (2006) *Mol Pharmacol*, **70**(4):1212-9
Bauer *et al.*, (2004) *Mol Pharmacol*, **66**(3):413-9

Blood-brain barrier repair

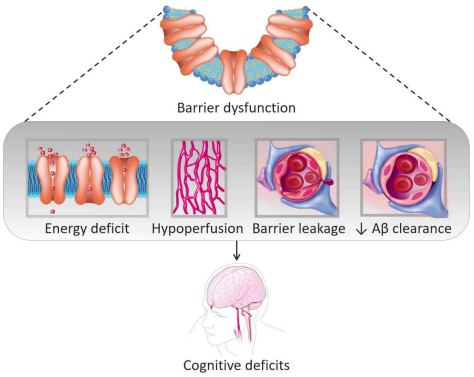


Illustration by Tom Dolan, Medical Illustrator, University of Kentucky, Lexington, KY, USA

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University of Kentucky

Anika Hartz, PhD
Sanders-Brown center on aging
anika.hartz@uky.edu

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