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New Understanding of BBB Impairments in Ageing and Neurodegenerative Diseases

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Abstract

Ageing is the major risk factor for neurodegenerative disorders such as Alzheimer's disease (AD). The impairments of the blood-brain barrier (BBB) have been frequently reported in numerous neurodegenerative diseases and may serve as an early marker of AD and dementia. Recently, new investigations have demonstrated that impairments of BBB during normal ageing is not simply breakage or leakage of the structure, but gradually loss of transcytosis and pericytes. Such interesting results are calling further investigations on the transportation capabilities of BBB and other barriers such as blood and cerebrospinal fluid barriers, refreshing our exploration of AD therapeutics, and may lead new drug delivery method.

Keywords: Blood-brain barrier; Alzheimer's disease; Transcytosis; Pericytes

Abbreviations: AD: Alzheimer's Disease; BBB: Blood-Brain Barrier; CNS: Central Nervous System.

Ageing is the major risk factor for neurodegenerative disorders such as Alzheimer's disease; however, it remains elusive about the exact processes that lead to age-related decline of brain structures and cognitive functions in both ageing and neurodegenerative disorders. The blood-brain barrier (BBB) is the physical boundary in the brain where the periphery and central system have been separated. BBB regulates the transportation of molecules between the brain and blood, prevents the neurotoxic elements in blood from entering the brain, and serves as a major impediment to drug delivery [1,2]. The impairments and breakdown of BBB have been frequently reported in numerous neurodegenerative diseases [1,2]. Although the report has shown in one AD mouse model there is no global BBB breakdown [3], more investigations have supported the conclusion that the severity of cognitive dysfunction of ageing and Alzheimer's disease (AD) in both animal models and human patients is correlated with the dysfunction of BBB [4-6]. Notably, the AD patients at an early stage have shown BBB leakage in both cortex and grey matter regions [5]. The BBB breakdown is promising to be an early diagnostic marker for human cognitive dysfunction [7]. Such results together point to the fundamental questions

1) What substance in the blood can cross the BBB?
2) To what extent the transportation impairments of BBB could be therapeutically targeted in neurodegenerative disorders?

Recently, Yang, et al. tried to answer the first question through specifically labelling the plasma substances in the blood [8]. They took advantage of the labelling of endogenous proteins and lipids in mammals but not the tracing of injected exogenous proteins/dyes. By comparing the young and aged mice, they found young mice are more capable to transport plasma proteins through transcytosis while the aged mice have no such capacity. Such results are somehow different from the previous conclusion that got from tracer studies. A step further, Yang and colleagues found the young mice have a bunch of receptors expressed by the endothelial cells which bind to the plasma proteins and form vesicles containing the plasma proteins. However, during the ageing process, receptors that expressed on the endothelial membranes are gradually decreased, thus the receptor-dependent transportation is gradually lost and the aged mice

transport non-protein substances in an unspecific manner. Moreover, Yang and colleagues have identified a list of genes which are perhaps crucial for maintaining the receptor-dependent transportation of plasma proteins in BBB. Such genes may serve as a hot spot for improving the efficiency of drug delivery into the central nervous system (CNS). Importantly, such impairments of the selective capabilities of blood endothelial cells are also contributed to the loss of pericytes [8]. Intriguingly, dysfunctions of pericytes have been shown contribute to neurodegenerative disorders such as AD [9]. Such interesting results are calling further research investigation on the transportation capabilities of BBB and other barriers such as blood and cerebrospinal fluid barriers (the choroid plexus of the ventricles and in the meninges that cover the brain) [10] during ageing. Besides, the exact proteins entering brains remains elusive [10], so does the proteins that exit the brain. For AD condition, different forms of Aβ and Tau are frequently found in the brains with a varied amount (which may point to the severity of AD), but the mechanisms of such BBB crossing remains largely unclear. Intriguingly, the accumulation of Aβ in human AD patients increases the release of endothelin-1 from blood endothelial cells and finally induces vasoconstriction since the activation of pericytes [11]. It is worthwhile to further unmask the exit of brain proteins into the blood and the pericytes alternation in the AD progress.

Collectively, impairments of BBB during normal ageing is not simply breakage or leakage of the structure, but gradually loss of transcytosis. Future research investigation may further broaden such knowledge in neurodegenerative disorders like AD. In the end, the BBB may serve both drug delivery targets and therapeutic chances for neurodegenerative disorders like AD. Notably, recent in vitro organ model has shown promise to elucidate the impairments of BBB in culture dish from AD patients [12]. Coincidently, such experiments have revealed the same pericytes loss and/or dysfunction in AD BBBs. Since the personalized manner and advantages for drug screening, future human blood-brain barrier in vitro will further speed up and strengthen the understanding of BBB impairments in both ageing and neurodegenerative disorders (Figure 1).

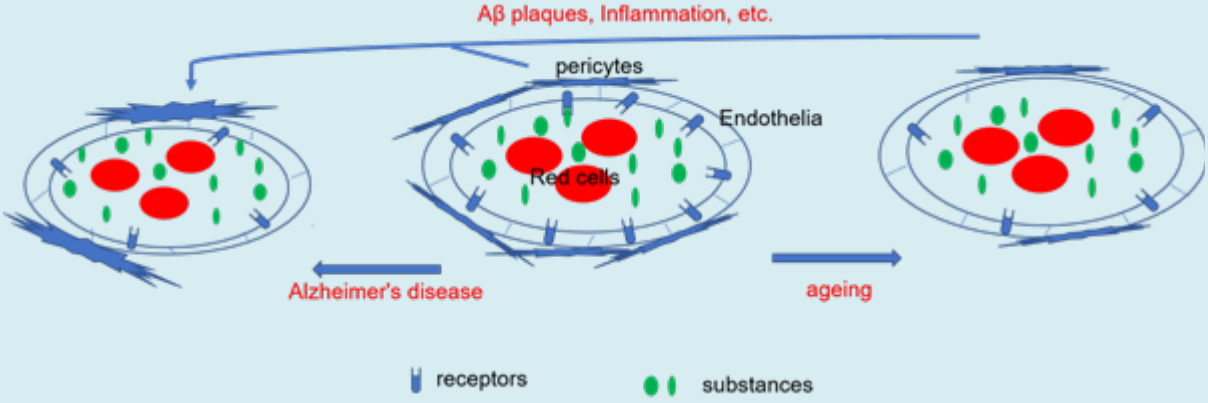

Figure1: Blood-brain barrier (BBB) ageing and Alzheimer's disease (AD).

In the Youngers, BBB transport substances from the blood to brain through receptor-dependent manner. In aged, both receptors and pericytes are decreased, so does the transportation capacity. Such loss of capacity may also occur in neurodegenerative disorders such as AD and become a therapeutic target.

References

1. Daneman R, Prat A (2015) The Blood–Brain Barrier. Cold Spring Harb Perspect Biol 7(1): a020412.

2. Sweeney MD, Zhao Z, Montagne A, Nelson AR, Zlokovic BV (2019) Blood-Brain Barrier: From Physiology to Disease and Back. Physiological Reviews 99(1): 21-78.

3. Bien-Ly N, Boswell CA, Jeet S, Beach TG, Hoyte K, et al. (2015) Lack of Widespread BBB Disruption in Alzheimer's Disease Models: Focus on Therapeutic Antibodies. Neuron 88(2): 289-297.

4. Montagne A, Barnes SR, Sweeney MD, Halliday MR, Sagare AP, et al. (2015) Blood-Brain Barrier Breakdown in the Aging Human Hippocampus. Neuron 85(2): 296-302.

5. van de Haar HJ, Burgmans S, Jansen JFA, van Osch MJP, van Buchem MA, et al. (2016) Blood-Brain Barrier Leakage in Patients with Early Alzheimer Disease. Radiology 281(2): 527-535.

6. Montagne A, Nation DA, Sagare AP, Barisano G, Sweeney

MD, et al. (2020) APOE4 leads to blood–brain barrier dysfunction predicting cognitive decline. Nature 581(7806): 71-76.

7. Nation DA, Sweeney MD, Montagne A, Sagare AP, D'Orazio LM, et al. (2019) Blood–brain barrier breakdown is an early biomarker of human cognitive dysfunction. Nat Med 25(2): 270-276.

8. Yang AC, Stevens MY, Chen MB, Lee DP, Stähli D, et al. (2020) Physiological blood–brain transport is impaired with age by a shift in transcytosis. Nature 583(7816): 425-430.

9. Brown LS, Foster CG, Courtney J-M, King NE, Howells DW, et al. (2019) Pericytes and Neurovascular Function in the Healthy and Diseased Brain. Front Cell Neurosci 13: 282.

10. Munji RN, Daneman R (2020) Unexpected amount of blood-borne protein enters the young brain. Nature 583: 362-363.

11. Nortley R, Korte N, Izquierdo P, Hirunpattarasilp C, Mishra A, et al. (2019) Amyloid β oligomers constrict human capillaries in Alzheimer's disease via signaling to pericytes. Science 365(6450): eaav9518.

12. Blanchard JW, Bula M, Davila-Velderrain J, Akay LA, Zhu L, et al. (2020) Reconstruction of the human blood–brain barrier in vitro reveals a pathogenic mechanism of APOE4 in pericytes. Nat Med 26: 952-963.