Neurovascular mechanisms in neurodegenerative diseases

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The neurovascular unit is comprised of vascular cells (i.e., endothelial cells pericytes, vascular smooth muscle cells), glial cells (i.e., astrocytes, microglia, oliogodendroglia) and neurons. The blood-brain barrier (BBB) is a highly specialized brain endothelial structure within the neurovascular unit. In concert with pericytes, astrocytes, and microglia, the BBB separates components of the circulating blood from neurons. Moreover, the BBB maintains the chemical composition of the neuronal ‘‘milieu’’ which is required for proper functioning of neuronal circuits, synaptic transmission, synaptic remodeling, angiogenesis and neurogenesis in the adult brain. Recent findings indicate that brain perfusion stress, from one hand, and the BBB breakdown with accumulation in brain of different proteinacious cytotoxic and neurotoxic macromolecules, from the other, may initiate and/or contribute to a loss of synapto-dendritic connections, neuronal dysfunction and neuronal loss in neurodegenerative diseases such as Alzheimer’s disease (AD), amyotrophic lateral sclerosis (ALS), multiple sclerosis (MS) and others. In addition, microbleeds have been observed AD, MS and animal models of ALS. Recent evidence suggests that pericytes control key neurovascuar functions that are necessary for normal neuronal structure and function. Pericytes degeneration can initiate vascular-mediated secondary neurodegenerative changes through either a chronic brain hypoperfusion and/or the BBB breakdown with a leakage of blood-derived endogenous neurotoxins and extravasation of red blood cells, and/or both. The double-hit vascular hypothesis for AD suggests that an initial vascular damage precedes the cerebrovascular and brain accumulation of Alzheimer’s toxin amyloid b-peptide (Aβ) (*hit 1*) which in turn amplifies the neurovascular dysfunction preceding neurodegenerative changes (*hit 2*). The role of brain vascular-specific genes relevant to AD and cerebrovascular receptors at the BBB in controlling the reductions in brain microcirculation, cerebral blood flow and a faulty amyloid b-peptide clearance at the BBB preceding neuronal loss will be discussed. Potential therapeutic approaches

with multiple-action multiple-target agents that could be developed for chronic neurodegenerative disorders based on the vascular concept of neurodegeneration will be also discussed.