Brain Angioplasticity: Microvascular Remodeling in the Mature Rodent Brain

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With the introduction of the concept of the neurovascular unit it became clear that neurons, glia and endothelial cells are capable of active reorganization throughout adult life. This plasticity has significant implications for brain function and pathophysiology. Capillary density is coupled to oxygen sufficiency. Consistently increased neuronal activity, for example during motor training exercises, leads to increased capillary density. Chronic hypoxic exposure, as occurs for example during sojourns at altitude also lead to increased capillary density. Important components of the capillary plasticity regulation mechanism are the HIF-1 and HIF-2 transcription factors that regulate vascular endothelial factor (VEGF), and cyclooxygenase-2 (COX-2) acting through prostaglandin E and angiopoietin-2 (ang-2). With age, the HIF-1 signalling pathway becomes attenuated due to increased prolyl hydoxylase activity due to increased reactive oxygen species, which changes the set point for tissue oxygen detection. Thus, plasticity becomes increasingly impaired with aging making learning more difficult and increasing the brain vulnerability to cerebrovascular challenges. The increased cerebrovascular vulnerability with age suggests a potential strategy for treating cerebrovascular diseases like stroke and dementia, i.e., agents that restore or augment HIF-1 function. Augmentation of HIF-1 may be the prime mechanism for pre-conditioning and neuroprotection. One such strategy is through a ketogenic diet that leads to HIF-1 accumulation due to inhibition of prolyl hydroxylase. Discovery of angioplasticity has opened up new areas for research that elucidates brain function, provides new explanations for the neuropathology following cerebrovascular injury and dementia, and suggests potential new therapeutic approaches to prevent or resolve these insults.