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ORAL PRESENTATIONS

Neurovascular risk factors and dysfunction in aging and dementia

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Plenary lecture

Brain function requires a finely regulated balance between the delivery of nutrients and the clearance of waste products through the blood flow.[1] If the blood flow delivery does not match the dynamic requirements for oxygen and glucose imposed by neural activity, brain dysfunction and damage may ensue. The cognitive alterations caused by vascular factors (vascular cognitive impairment, VCI) and neurodegeneration (Alzheimer's disease, AD) have traditionally been considered mechanistically distinct, but increasing evidence suggests previously unappreciated commonalities.[2] Clinical-pathological studies indicate that vascular lesions aggravate the deleterious effects of AD pathology and traditional stroke risk factors, such as hypertension, are also risk factors for AD, suggesting mechanistic overlap. Furthermore, disturbances of cerebral perfusion and/or energy metabolism occur early in the clinical course of AD suggesting a pathogenic role of vascular insufficiency.[3] Corroborating this clinical-epidemiological evidence, experimental data indicate that amyloid-beta, a key pathogenic factor in AD, alters the structure and function of cerebral blood vessels and associated cells (neurovascular complex), effects mediated by activation of innate immune cells leading to vascular oxidative stress and inflammation.[1] On the other hand, pathological tau suppresses glutamate-dependent production of nitric oxide, which, in turn, dampens the increase in blood flow produced by synaptic activity, but also leads to neuronal network dysfunction and increased excitability.[4] Aging and hypertension can also influence the production and clearance of amyloid-beta, promoting amyloid pathology. Furthermore, ApoE4 plays a critical role in the brain's susceptibility to vascular damage or neurodegeneration.[5] Injury to the neurovascular complex alters cerebral blood flow regulation, depletes vascular reserves, and reduces the brain's repair potential, effects that amplify the brain dysfunction and damage exerted by incident ischemia and coexisting neurodegeneration. These observations, collectively, indicate that vascular alterations are important both in vascular and neurodegenerative dementias, and suggest novel preventive and treatment modalities for these devastating and highly prevalent conditions. Therefore, in the absence of mechanism-based approaches to counteract dementia, targeting cerebrovascular function may offer the opportunity to mitigate the public health impact of one of the most disabling human afflictions.

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