Highly neurotoxic amyloid-bassemblies from Alzheimer's disease brain, amylospheroids, inhibit endothelial Na^+, K^+-ATPase α3 activity, resulting in the inhibition of eNOS activity in human brain microvascular endothelial cells.

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Vascular deposition of amyloid-bprotein (Aβ), known as cerebrovascular amyloid angiopathy (CAA), is associated with vascular dysfunction. In the previous meeting (WCP2018), we reported amylospheroids (ASPD, 30-mers highly neurotoxic Aβ assemblies in average isolated from Alzheimer's disease brain) suppressed the vasorelaxation via endothelial eNOS inactivation through mitochondrial ROS/PKC pathway. Neuronal toxicity of ASPD was reported to be exerted by impairing the activity of Na^+, K^+-ATPase α3 (NAKα3) via the direct binding (Ohnishi et al. *PNAS*2015). Here, we sought to elucidate whether NAKα3 was involved with the eNOS inactivation by ASPD. We first detected and found the protein and mRNA of NAKα3 in cerebrovascular endothelial cells. Furthermore, we found NAKα3 was expressed in innermost endothelial layer of vascular vessels. We then examined whether the eNOS inactivation by ASPD was abolished by siRNA transfection. Remarkably the knockdown of ASPD-binding target NAKα3 by ATP1A3-siRNA transfection blocked the eNOS inactivation by ASPD. Taken together, these results suggest the endothelial toxicity of ASPD was mediated by NAKα3.