Alzheimer's Disease & Dementia 2019: Novel pathophysiological roles of α-synuclein (SNCA) in age-related vascular endothelial dysfunction: Possible mechanistic link to the symptoms of dementia with Lewy bodies

Yoichi Takami, Yasushi Takeya, Shuko Takeda, Akane Oyama, Tsuneo Nakajima, Koichi Yamamoto, Ryuichi Morishita, Yasufumi Kaneda, Hironori Nakagami and Hiromi Rakugi
Osaka University, Japan
E-mail: takami@geriat.med.osaka-u.ac.jp

Abstract

Although SNCA is one of the well-known pathological molecules of Dementia with Lewy Bodies (DLB) in neurons, its physiological roles remain to be identified. We found SNCA was expressed in and secreted from endothelial cells by functional screening for anti-inflammatory molecules and detectable in circulating blood. Intriguingly, the human population study revealed serum SNCA levels decreased with aging and displayed inverse correlation with blood pressure and insulin sensitivity, which indicated protective properties of circulating SNCA on vascular endothelial function. Furthermore, we also found SNCA knockout mice displayed phenotypes of metabolic syndrome such as hypertension, impaired glucose metabolism and dyslipidemia. Based on these preliminary data, we sought to elucidate the physiological functions of endogenous and exogenous SNCA for vascular Endothelial Cells (ECs). Exogenous treatment with recombinant SNCA (rSNCA) promoted eNOS activation and nitric oxide production via Gab1/PI3K/Akt pathway in ECs, followed by cGMP production in cocultured vascular smooth muscle cells. Treatment with rSNCA also suppressed TNF-? induced NF-?B activation in ECs. As to endogenous SNCA, replicative senescence showed attenuation of SNCA expression in ECs and siRNA-mediated silencing of SNCA induced eNOS inactivation and cell senescence assessed by ??-gal activity along with decreased Sirt1 expression and increased p53 expression. SNCA overexpression displayed NF-?B inactivation in ECs. In ex vivo study, aortas from SNCA knockout mice showed impairment of acetylcholine-induced relaxation possibly due to eNOS dysfunction. In in vivo study utilizing atherosclerosis model of SNCA/ApoE double-knockout mice showed exaggerated expression of inflammatory genes which play important roles in atherogenesis. In conclusion, these results indicate exogenous and endogenous SNCA in ECs might physiologically maintain cerebral vascular integrity. Aging or aggregation-related loss-of-function of SNCA in ECs might be partially correlated with clinical features of DLB, especially fluctuating cognitive function and marked sensitivity of antipsychotic which could be modified by cerebral blood flow and vascular permeability.

Yoichi Takami is currently working at Osaka University, Japan. He has published numerous research papers and articles in reputed journals and has various other achievements in the related studies. He has extended his valuable service towards the scientific community with his extensive research work.

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