

OxLDL-induced endothelial exosomes drive axonal degeneration and cognitive impairment independent of Aβ

#3942

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OxLDL-injured endothelial cells induce axonal degeneration and cognitive impairment via the exosomal pathway, independent of Aβ.

INTRODUCION

Vascular risk factors are increasingly recognized as important contributors to cognitive impairment and dementia. Oxidized low-density lipoprotein (oxLDL), a key mediator of dyslipidemia-associated vascular injury, is strongly associated with endothelial dysfunction and cognitive decline. However, the mechanisms linking vascular injury to neuronal dysfunction remain poorly understood. We investigated whether oxLDL-induced endothelial exosomes (ox-LDL Exo) mediate vascular-to-neuronal communication and contribute to neurodegeneration.

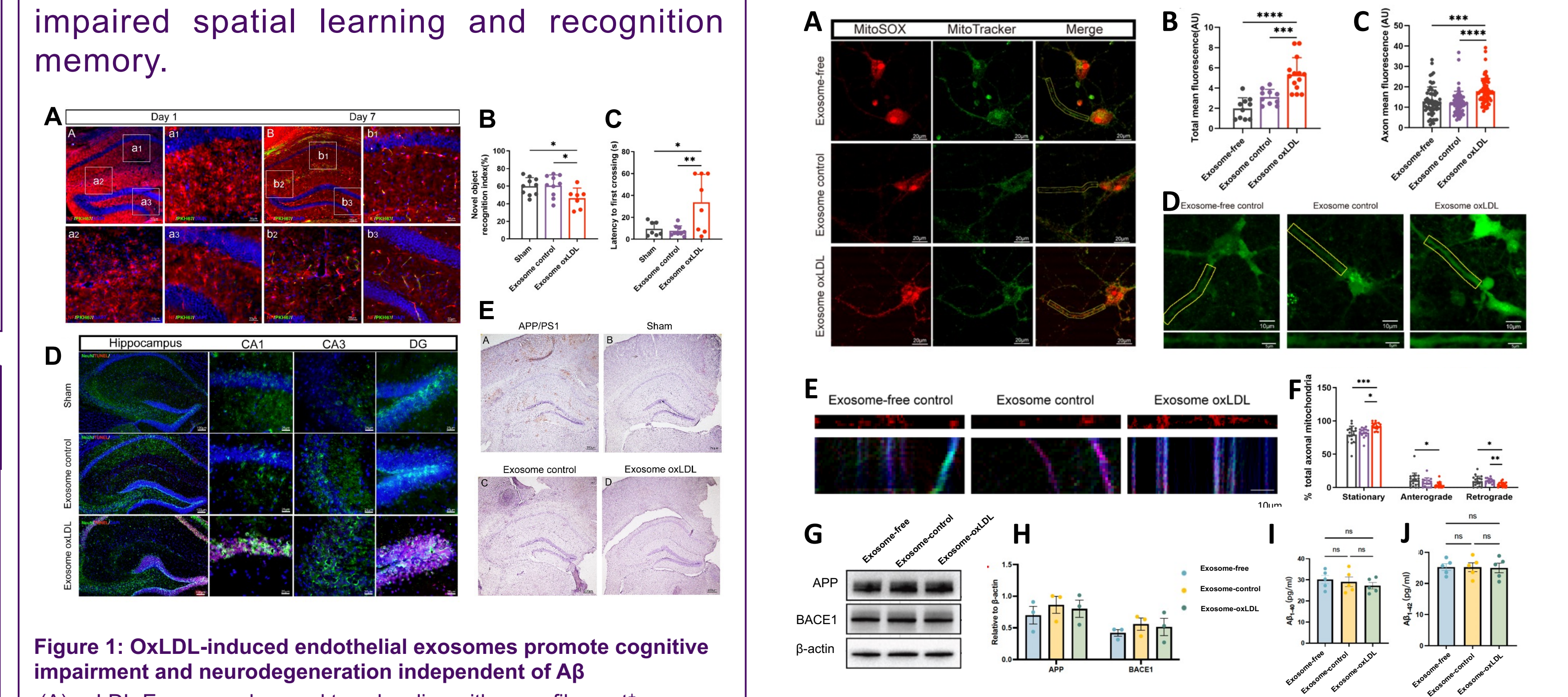
METHODS

Primary mouse brain microvascular endothelial cells (BMECs) were exposed to oxLDL, and ox-LDL Exo were isolated. ox-LDL Exo uptake, intracellular distribution, and functional effects were evaluated in primary neurons in vitro and following intracerebroventricular administration in vivo. Neuronal survival, axonal integrity, mitochondrial dynamics, and cognition were assessed using imaging, biochemical analyses, and behavioral testing.

RESULTS

1. OxLDL-Exo were taken up by hippocampal neurons and, upon in vivo administration, induced hippocampal neuronal apoptosis accompanied by impaired spatial learning and recognition memory.

2. OxLDL-Exo triggered axonal ROS and Ca²⁺ overload, and disrupted mitochondrial transport while leaving APP, β-secretase, and Aβ levels unchanged.



CONCLUSION

Our findings identify oxLDL-induced endothelial exosomes as a novel vascular neuronal communication pathway linking vascular injury to axonal degeneration and cognitive impairment. This mechanism operates independently of Aβ pathology and highlights endothelial exosome signaling as a potential therapeutic target for vascular cognitive impairment and dementia.

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Figure 2: OxLDL-Exo trigger axonal stress and disrupt mitochondrial dynamics without affecting Aβ

(A, B) OxLDL-Exo increased neuronal ROS production.

(C, D) OxLDL-Exo induced focal axonal Ca²⁺ accumulation.

(E, F) OxLDL-Exo reduced mitochondrial motility within axons.

(G–H) OxLDL-Exo did not affect APP, β-secretase levels, and Aβ levels in primary neurons.

*P<0.05, ***P<0.01, ****P<0.001. BACE1: β-secretase; PN: primary neuron.