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Cardiolipin-Incorporated Liposomes Carrying Curcumin and Nerve Growth Factor to Rescue Neurons from Apoptosis for Alzheimer's Disease Treatment

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Abstract : Curcumin (CRM) and nerve growth factor (NGF) were entrapped in liposomes (LIP) with cardiolipin (CL) to downregulate the phosphorylation of mitogen-activated protein kinases for Alzheimer's disease (AD) management. AD belongs to neurodegenerative disorder with a gradual loss of memory, yielding irreversible dementia. CL-conjugated LIP loaded with CRM (CRM-CL/LIP) and that with NGF (NGF-CL/LIP) were applied to AD models of SK-N-MC cells and Wistar rats with an insult of β-amyloid peptide (Aβ). Lipids comprising 1,2-dipalmitoyl-sn-glycero-3- phosphocholine (Avanti Polar Lipids, Alabaster, AL), 1',3'-bis[1,2- dimyristoyl-sn-glycero-3-phospho]-sn-glycerol (CL; Avanti Polar Lipids), 1,2-dipalmitoyl-sn-glycero-3-phosphoethanolamine-N- [methoxy(polyethylene glycol)-2000] (Avanti Polar Lipids), 1,2-distearoyl-sn-glycero-3-phosphoethanolamine-N-[carboxy(polyethylene glycol)-2000] (Avanti Polar Lipids) and CRM (Sigma–Aldrich, St. Louis, MO) were dissolved in chloroform (J. T. Baker, Phillipsburg, NJ) and condensed using a rotary evaporator (Panchum, Kaohsiung, Taiwan). Human β-NGF (Alomone Lab, Jerusalem, Israel) was added in the aqueous phase. Wheat germ agglutinin (WGA; Medicago AB, Uppsala, Sweden) was grafted on LIP loaded with CRM for (WGA-CRM-LIP) and CL-conjugated LIP loaded with CRM (WGA-CRM-CL/LIP) using 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide (Sigma–Aldrich) and N-hydroxysuccinimide (Alfa Aesar, Ward Hill, MA). The protein samples of SK-N-MC cells (American Type Tissue Collection, Rockville, MD) were used for sodium dodecyl sulfate (Sigma–Aldrich) polyacrylamide gel (Sigma–Aldrich) electrophoresis. In animal study, the LIP formulations were administered by intravenous injection via a tail vein of male Wistar rats (250–280 g, 8 weeks, BioLasco, Taipei, Taiwan), which were housed in the Animal Laboratory of National Chung Cheng University in accordance with the institutional guidelines and the guidelines of Animal Protection Committee under the Council of Agriculture of the Republic of China. We found that CRM-CL/LIP could inhibit the expressions of phosphorylated p38 (p-p38), p-Jun N-terminal kinase (p-JNK), and p-tau protein at serine 202 (p-Ser202) to retard the neuronal apoptosis. Free CRM and released CRM from CRM-LIP and CRM-CL/LIP were not in a straightforward manner to effectively inhibit the expression of p-p38 and p-JNK in the cytoplasm. In addition, NGF-CL/LIP enhanced the quantities of p-neurotrophic tyrosine kinase receptor type 1 (p-TrkA) and p-extracellular-signal-regulated kinase 5 (p-ERK5), preventing the Aβ-induced degeneration of neurons. The membrane fusion of NGF-LIP activated the ERK5 pathway and the targeting capacity of NGF-CL/LIP enhanced the possibility of released NGF to affect the TrkA level. Moreover, WGA-CRM-LIP improved the permeation of CRM across the blood–brain barrier (BBB) and significantly reduced the Aβ plaque deposition and malondialdehyde level and increased the percentage of normal neurons and cholinergic function in the hippocampus of AD rats. This was mainly because the encapsulated CRM was protected by LIP against a rapid degradation in the blood. Furthermore, WGA on LIP could target N-acetylglucosamine on endothelia and increased the quantity of CRM transported across the BBB. In addition, WGA-CRM-CL/LIP could be effective in suppressing the synthesis of acetylcholinesterase and reduced the decomposition of acetylcholine for better neurotransmission. Based on the in vitro and in vivo evidences, WGA-CRM-CL/LIP can rescue neurons from apoptosis in the brain and can be a promising drug delivery system for clinical AD therapy.

Keywords : Alzheimer's disease, β-amyloid, liposome, mitogen-activated protein kinase
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