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Linoleic Acid Derivative DCP-LA Sheds Light on Treatment of Alzheimer's Disease

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Abstract

Alzheimer's Disease (AD) is a really tragic disease in which a human being loses human dignity. AD is characterized by extensive deposition of Amyloid β (Aβ) and formation of NFT. To date, none of Aβ-directed drugs for AD therapy have been successful and therefore, a current target for AD therapy focuses on Tau. Glycogen Syntheses Kinase-3β (GSK-3β) is a key protein kinase to phosphorylated Tau. The linoleic acid derivative 8-[2-(2-pentyl-cyclopropylmethyl)-cyclopropyl]-octanoic acid (DCP-LA) with the cyclopropane ring instead of the cis-double bond selectively activates PKCε, that directly inactivates GSK-3β, leading to suppression of Tau phosphorylation (pTau). DCP-LA-induced PKCε activation, alternatively, directly activates Akt, followed by inactivation of GSK3β, leading to suppression of pTau. DCP-LA also inhibits PTP1B, thereby relatively activating Receptor Tyrosine Kinase (RTK) and Insulin Receptor Substrate 1 (IRS-1), followed by the sequential activation of PhosphoInositide 3-Kinase (PI3K), Phosphoinositide-Dependent Kinase 1 (PDK1), and Akt. Then, activated Akt inactivates GSK-3b, leading to suppression of pTau. DCP-LA bearing synchronous PKCe activation and PTP1B inhibition, thus, could become a promising and novel drug for prevention and treatment of AD.

Keywords: DCP-LA; PKCε; PTP1B; GSK-3β; Alzheimer's disease; Tau

Introduction

The number of Alzheimer's Disease (AD) patients is considerably mounting in association with prolongation of life span and AD is currently a major burden on society. No beneficial anti-AD drug, however, has been provided as yet. The most urgent issue, therefore, is to develop drugs for AD.

We have found that cis-unsaturated free fatty acids such as arachidonic, linoleic and linolenic acid, persistently facilitates hippocampal synaptic transmission by targeting presynaptic nicotinic ACh receptor under the control of PKC. *Cis*-unsaturated free fatty acids, however, are promptly metabolized and decomposed before arriving in the brain, even though the fatty acids are orally or intravenously taken into the body. To resolve this problem, we have synthesized a variety of derivatives of cis-unsaturated free fatty acids, that exhibit stable bioactivities, and obtained the most effective compound 8-[2-(2-pentyl-cyclopropylmethyl)-cyclopropyl]-octanoic acid (DCP-LA), a linoleic acid derivative with cyclopropane rings instead of *cis*-double bonds [1] (Figure 1).

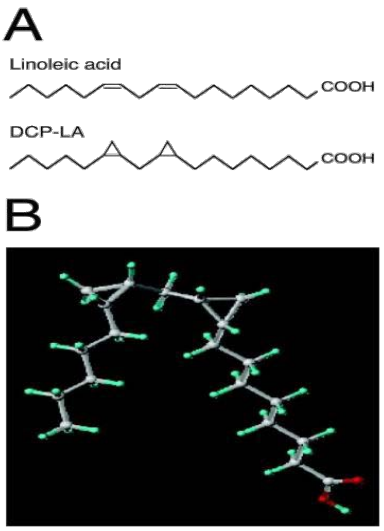

Figure 1: Chemical (A) and conformational structure (B) of DCP-LA.

Beneficial anti-AD drugs require protection of neuronal apoptosis and facilitation of synaptic transmission relevant to cognitive functions. I show here that DCP-LA has the actions of both anti-apoptosis and cognitive enhancement.

Tau Phosphorylation is a Critical Factor for AD

Tau, which is abundantly expressed in neurons of the central nervous system, stabilizes microtubules by interacting with tubulin. When phosphorylated excessively, Tau becomes a trigger for tauopathies [2]. Tauopathies are a class of neurodegenerative diseases associated with aggregation of hyperphosphorylated Tau in an insoluble form in the brain, referred to as Neurofibrillary Tangles (NFT), which include AD, frontotemporal dementia and parkinsonism linked to chromosome 17, progressive supranuclear palsy, Pick's disease, and corticobasal degeneration. AD is a really tragic disease in which a human being loses human dignity. AD is characterized by extensive deposition of amyloid β (A β) and formation of NFT. To date, none of Aβ-directed drugs for AD

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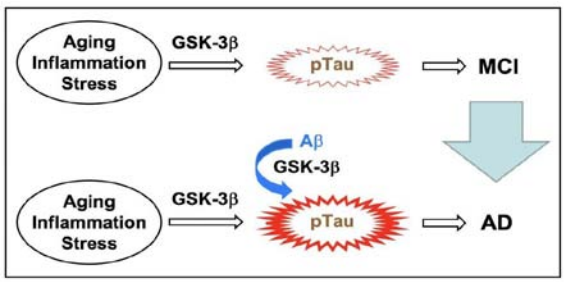

Figure 2: Pathogenesis of MCI and AD.

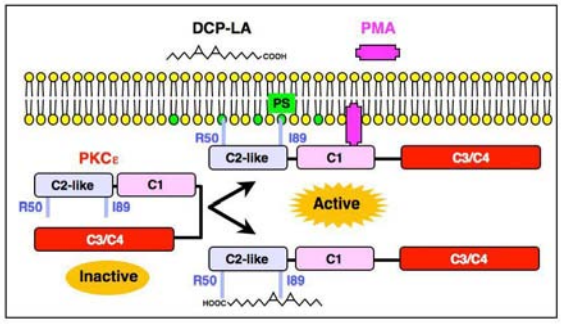

Figure 3: A schematic diagram for DCP-LA-induced PKCε activation.

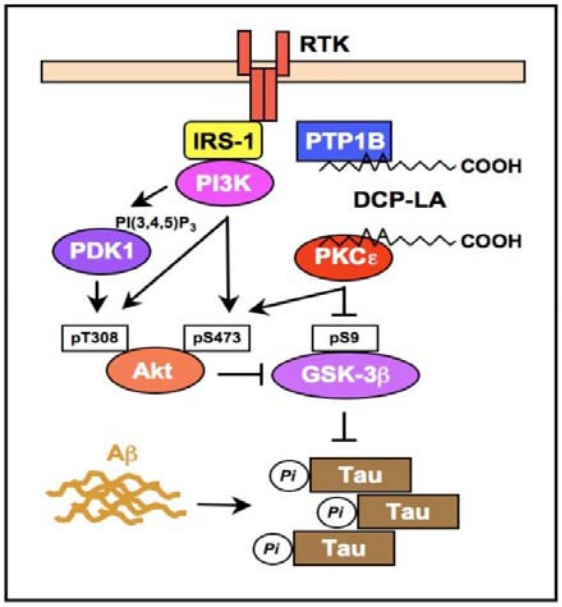

Figure 4: A schematic pathway underlying DCP-LA-induced Akt activation and GSK-3b inactivation.

therapy have been successful and therefore, a current target for AD therapy focuses on Tau. Of protein kinases proposed glycogen synthese kinase-3β (GSK-3β) is a central executioner to induce Tau phosphorylation (pTau).

Emerging evidence has shown that Aβ serves as an initiator of AD and that Tau acts as an executioner of AD. Mild Cognitive Impairment (MCI) is a preliminary group of AD. Aging, inflammation, and stress activate GSK-3β, to phosphorylate Tau, causing MCI (Figure 2). Then, participation of Aβ further activates GSK-3β and accelerates pTau, leading to progression to AD from MCI (Figure 2). Accordingly, pTau is a key factor both for MCI and AD.

Interaction of DCP-LA with Protein Kinases and Protein Phosphatases

PKCε

PKC includes the conventional PKC isozymes α, βI, βII, and ϒ, the novel PKC isozymes δ, ε, ŋ, and θ, the atyoical PKC isozymes ι/λ and ς, and the PKC-like isozymes μ and ν. Of PKC isozymes DCP-LA selectively and directly activates PKCε in a Ca^{2+}- and diacylglycerol-independent manner [3]. DCP-LA binds to PKCε at the Phosphatidylserine (PS) binding/associating sites Arg50 and Ile89 in the C2-like domain at the carboxyl-terminal end and the cyclopropane rings, respectively, which is distinct from the binding site (the C1 domain) of phorbol-12-myristate-13-acetate (PMA) [4] (Figure 3). Thus, the primary site of action of DCP-LA is PKCε.

Protein tyrosine phosphatase 1B (PTP1B) and protein phosphatase 1 (PP1)

DCP-LA inhibits PTP1B [5] and PP1 [6] through its direct interaction.

Akt

Akt1, which is preferentially expressed in neurons, is activated by being phosphorylated at Thr308 and Ser473. DCP-LA-induced PTP1B inhibition relatively activates Receptor Tyrosine Kinase (RTK) and Insulin Receptor Substrate 1 (IRS-1), followed by activation of Akt through a pathway along a RTK/IRS-1/phosphoinositide 3-kinase (PI3K)/phosphoinositide- dependent kinase 1 (PDK1)/Akt axis [7] (Figure 4). PKCe, activated by DCP-LA, directly activates Akt1 by phosphorylating at Ser473 [7] (Figure 4).

GSK-3β

GSK-3β is activated and inactivated by being phosphorylated at Tyr216 and Ser9, respectively. Akt, that is activated by PKCε or through a RTK/IRS-1/PI3K/PDK1/Akt pathway in association with PTP1B inhibition under the influence of DCP-LA, inactivates GSK-3β by phosphorylating at Ser9 [7] (Figure 4).

PKCε, activated by DCP-LA, inactivates GSK-3β by directly phosphorylating at Ser9 [7] (Figure 4).

DCP-LA Suppresses Tau Phosphorylation

Taken together, DCP-LA is capable of suppressing pTau by inactivating GSK-3β [7] (Figure 4). This indicates that DCP-LA has the potential to prevent and improve tauopathies including MCI and AD.

DCP-LA Protects Neuronal Cells from Apoptosis

Neuronal apoptosis in the neurodegenerative diseases such as AD and Parkinson's disease is caused by Endoplasmic Reticulum (ER) stress or oxidative stress. DCP-LA inhibits Nitric Oxide (NO) stress-induced activation of caspase-3/-9 and apoptosis of neuronal cells [8]. This indicates that DCP-LA could prevent or delay progression of AD.

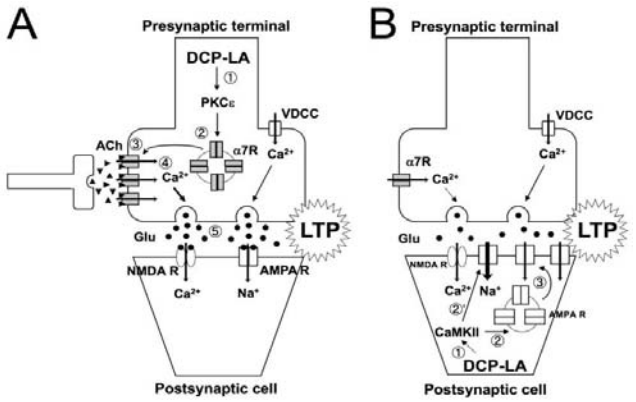

Figure 5: DCP-LA-induced LTP pathway.
NMDA R: N-Methyl-D-Aspartate Receptor; VDCC: Voltage-Dependent Calcium Channel.

DCP-LA Facilitates Synaptic Transmission

Long-term Potentiation (LTP) is an established cellular model of learning and memory. DCP-LA activates presynaptic PKCε (Figure 5A-①), which promotes vesicular transport of α7 ACh receptor (α7R) towards the cell surface from the cytosol (Figure 5A-②), to increase α7R on the plasma membrane at the presynaptic terminals (Figure 5A-③). An increase in the number of α7R allows greater deal of Ca^{2+} influx (Figure 5A-④), which stimulates glutamate release from presynaptic terminals (Figure 5A-⑤), thereby facilitating synaptic transmission, leading to LTP [1,9-11].

DCP-LA, alternatively, indirectly activates Ca^{2+}/calmodulin-dependent protein kinase II (CaMKII) due to PP1 inhibition (Figure 5B-①), which triggers vesicular transport of α-Amino-3-hydroxy-5-Methyl-4-isoxazolepropionic Acid (AMPA) Receptor (AMPA R) towards the plasma membrane from the cytosol (Figure 5B-②), to increase cell surface localization of AMPA R at the postsynaptic cells (Figure 5B-③). In addition, CaMKII potentiates AMPA R responses by phosphorylating AMPA R (Figure 5B-②). An increase in the number of AMPA R at the postsynaptic cells and potentiation of AMPA R responses enhance total excitatory postsynaptic conductance, leading to LTP [6]. DCP-LA, thus, could enhance cognitive functions by inducing LTP.

In addition, DCP-LA stimulates presynaptic release of ϒ-aminobutyric acid (GABA), serotonin, and dopamine by targeting α7R [12-14]. This implies that DCP-LA could tune not only cognitive functions but other brain functions.

DCP-LA Ameliorates Cognitive Impairment

Lines of evidence have shown that DCP-LA improves $A\beta_{1-40}$ - or mutant Aβ-induced spatial learning deficits in rats [15,16], scopolamine-induced spatial learning and memory disorders in rats [15], spatial learning and memory deterioration in senescence accelerated mice (SAMP8) [17,18], and spatial learning and memory impairment in 5xFAD transgenic mice, an animal model of AD [7].

Conclusion

DCP-LA is capable of efficiently suppressing Tau phosphorylation, responsible for MCI and AD. DCP-LA has the potential to inhibit oxidative stress-induced caspase activation and neuronal apoptosis, responsible for brain atrophy in AD. In addition, DCP-LA could ameliorate cognitive impairment in association with AD by facilitating synaptic transmissions. Consequently, DCP-LA must become a promising therapeutic drug of AD and relieve huge number of AD patients from despair.

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