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Short communication

DCP-LA neutralizes mutant amyloid β peptide-induced impairment of long-term potentiation and spatial learning

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ABSTRACT

Long-term potentiation (LTP) was monitored from the CA1 region of the intact rat hippocampus by delivering high frequency stimulation (HFS) to the Schaffer collateral commissural pathway. Intraventricular injection with mutant amyloid β_{1-42} peptide lacking glutamate-22 ($A\beta_{1-42}E22\Delta$), favoring oligomerization, 10 min prior to HFS, inhibited expression of LTP, with the potency more than wild-type amyloid β_{1-42} peptide. Intraperitoneal injection with the linoleic acid derivative 8-[2-(2-pentyl-cyclopropylmethyl)-cyclopropyl]-octanoic acid (DCP-LA) 70 min prior to HFS neutralized mutant $A\beta_{1-42}E22\Delta$ peptide-induced LTP inhibition. In the water maze test, continuous intraventricular injection with mutant $A\beta_{1-42}E22\Delta$ peptide for 14 days prolonged the acquisition latency as compared with that for control, with the potency similar to wild-type $A\beta_{1-42}$ peptide, and intraperitoneal injection with DCP-LA shortened the prolonged latency to control levels. The results of the present study indicate that DCP-LA neutralizes mutant $A\beta_{1-42}E22\Delta$ peptide-induced impairment of LTP and spatial learning.

1. Introduction

Accumulating studies have pointed to the implication of amyloid β (Aβ) peptide in the pathogenesis of Alzheimer disease. Lines of evidence have suggested that soluble Aβ oligomers, but not Aβ fibrils, play a critical role in synaptic and cognitive disorders for Alzheimer disease [1,3,7,13]. Indeed, Aβ oligomers decrease synaptic density [8,14], inhibit long-term potentiation (LTP), a cellular model of learning and memory, in the hippocampus [9,17,18], and impair memory function [2,10]. We have found a novel amyloid precursor protein mutation (E693Δ) to produce variant $A\beta_{1-42}$ lacking glutamate-22 ($A\beta_{1-42}E22\Delta$) in Japanese pedigrees showing Alzheimer-type dementia and Alzheimer disease [16]. Notably, $A\beta_{1-42}E22\Delta$ peptide, favoring oligomerization, inhibited expression of the *in vivo* hippocampal LTP [16].

In our earlier study, 8-[2-(2-pentyl-cyclopropylmethyl)-cyclopropyl]-octanoic acid (DCP-LA), a newly synthesized linoleic acid derivative, stimulated presynaptic glutamate release by enhancing activity of presynaptic α7 nicotinic acetylcholine (ACh) receptors through direct and selective activation of protein kinase C-ε (PKC-ε), thereby inducing an 'LTP-like' long-lasting facilitation of the *in vitro* and the *in vivo* hippocampal synaptic transmission [6,15,20]. In addition, DCP-LA ameliorated disorder of spatial learning and memory induced by intraperitoneal injection with scopolamine or continuous intraventricular injection with $A\beta_{1-40}$ peptide for rats [12] and improves age-related learning impairment for accelerated-senescence-prone mice 8 (SAMP8) [19].

The present study examined the effect of DCP-LA on LTP inhibition and spatial learning disorders induced by $A\beta_{1-42}E22\Delta$ peptide. The results show that DCP-LA neutralizes mutant $A\beta_{1-42}E22\Delta$ peptide-induced impairment of LTP and spatial learning.

2. Materials and methods

2.1. Animal care

All procedures have been approved by the Animal Care and Use Committee at Hyogo College of Medicine and were in compliance with the National Institutes of Health Guide for the Care and Use of Laboratory Animals.

2.2. Aβ peptides

Wild-type $A\beta_{1-42}$ peptide was purchased from American Peptide Company (Sunnyvale, CA, USA) and $A\beta_{1-42}E22\Delta$ peptide was synthesized based upon the results of mass spectrometry (American Peptide Company).

2.3. LTP monitoring

Under urethane (1.5 g/kg, intraperitoneal injection) anesthesia, field excitatory postsynaptic potentials (fEPSPs) were recorded from the CA1 region of the hippocampus of Wistar rats (male, 6w) by electrically stimulating the Schaffer collateral (0.033 Hz, 0.1 ms in duration). The parameters for high frequency stimulation (HFS) to induce LTP were four trains with an inter-train interval of 200 ms and each train consisted of ten 30-s 200-Hz pulses. Phosphate-buffered saline (PBS)

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or DCP-LA (1 mg/kg weight) was intraperitoneally injected 70 min before HFS and subsequently, PBS (2 μl), wild-type $A\beta_{1-42}$ peptide (10 ng in 2 μl PBS), or mutant $A\beta_{1-42}E22\Delta$ peptide (10 ng in 2 μl PBS) was injected in the right-sided lateral ventricle for 30 s using a Hamilton microsyringe 10 min before HFS.

2.4. Water maze test

PBS, wild-type $A\beta_{1-42}$ peptide (10 ng/day), or mutant $A\beta_{1-42}E22\Delta$ peptide (10 ng/day) was continuously injected in the right-sided lateral ventricle of Wistar rats (male, 6w) for 14 days using an osmotic pressure pump, and then PBS or DCP-LA (1 mg/kg weight) was intraperitoneally injected 30 min prior to water maze task.

A circular plastic water tank with 180 cm in diameter and 45 cm in deep was used for a water maze test. The entire inside of the pool was painted black, and the pool was filled up to 25 cm from the bottom with muddy water containing India ink at 22 °C. A platform (11 cm in diameter) painted black was placed into water, the top sinking 1 cm below water surface. The pool was put in a test room, where there were several marks those rats are able to see from the pool. The position of the marks remained unchanged throughout testing. A platform was located in the constant position, i.e., in the middle of one quadrant, equidistant from the center and edge of the pool. Rats facing the wall of the pool were placed into water at one of 5 positions selected at random, and time from start to escape onto the platform (acquisition latency) was measured. When succeeded, rats were allowed to stay on the platform for 10 s. Rats received the task for consecutive 16 days and the acquisition latency (time form the start to arrival onto the plate) was measured.

2.5. Statistical analysis

Statistical analysis was carried out using Fisher's Protected Least Significant Difference (PLSD) test.

3. Results

3.1. DCP-LA neutralizes mutant $A\beta_{1-42}E22\Delta$ peptide-induced LTP inhibition

We monitored fEPSPs from the CA1 region of the intact rat hippocampus by electrically stimulating the Schaffer collateral commissural pathway. For control, HFS enhanced fEPSP slopes to 170–250% of basal levels, being evident at 120 min after HFS (LTP) (Fig. 1A and B). Intraventricular injection with wild-type $A\beta_{1-42}$ peptide inhibited expression of LTP ($P < 0.001$ as compared with control LTP, Fisher's PLSD test), and DCP-LA (1 mg/kg, i.p.) significantly recovered the LTP inhibition to a level similar to control LTP ($P < 0.0001$ as compared with LTP for wild-type $A\beta_{1-42}$ peptide treatment, Fisher's PLSD test) (Fig. 1A). More marked inhibition of LTP was obtained with mutant $A\beta_{1-42}E22\Delta$ peptide (10 ng) ($P < 0.0001$ as compared with LTP for wild-type $A\beta_{1-42}$ peptide treatment, Fisher's PLSD test), and DCP-LA (1 mg/kg, i.p.) significantly improved the LTP disruption ($P < 0.0001$ as compared with LTP for mutant $A\beta_{1-42}E22\Delta$ peptide treatment, Fisher's PLSD test); conversely, DCP-LA enhanced LTP more than control LTP (Fig. 1B).

3.2. DCP-LA ameliorates mutant $A\beta_{1-42}E22\Delta$ peptide-induced spatial learning impairment

In the water maze test, intraventricular injection with wild-type $A\beta_{1-42}$ peptide prolonged the acquisition latency (Fig. 2A). A similar effect was obtained with mutant $A\beta_{1-42}E22\Delta$ peptide, with no significant difference in the latency between wild-type $A\beta_{1-42}$ and mutant $A\beta_{1-42}E22\Delta$ peptide (Fig. 2B). Intraperitoneal injection with DCP-LA (1 mg/kg, i.p.) significantly shortened the prolonged latency for both the treatment with wild-type $A\beta_{1-42}$ and mutant $A\beta_{1-42}E22\Delta$ peptide (each $P < 0.001$ as compared with the latency for wild-type $A\beta_{1-42}$ or mutant $A\beta_{1-42}E22\Delta$ peptide treatment without DCP-LA, Fisher's PLSD test), reaching the levels for control (Fig. 2A and B). This indicates that DCP-LA ameliorates spatial learning disorders induced not only by wild-type $A\beta_{1-42}$ peptide but mutant $A\beta_{1-42}E22\Delta$ peptide.

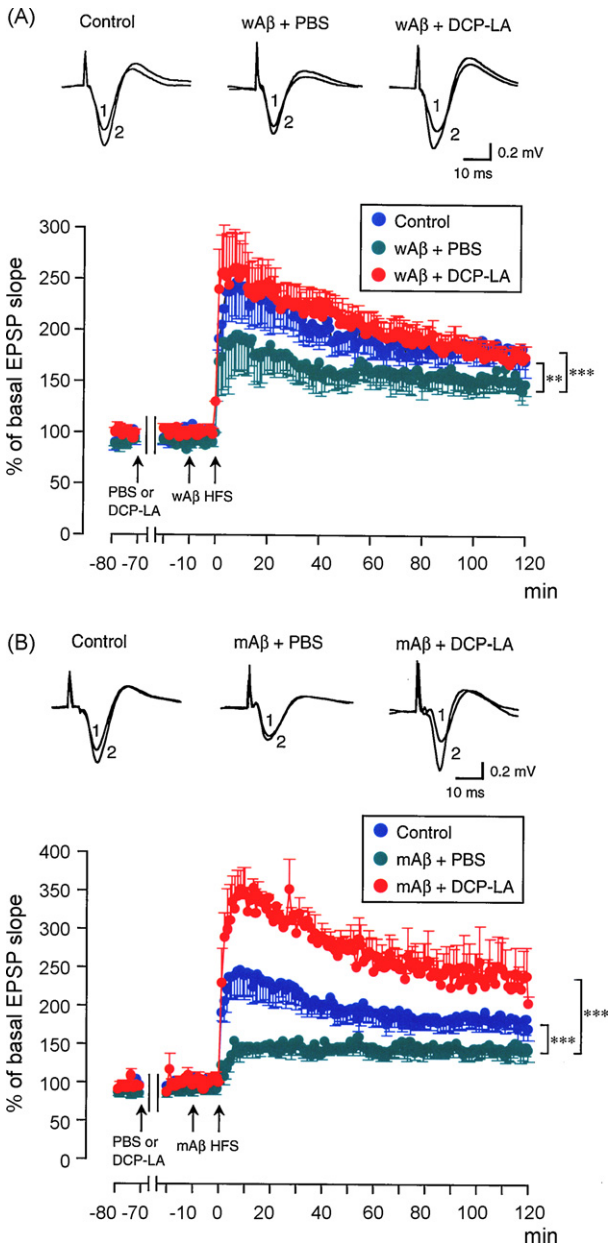

Fig. 1. Effect of DCP-LA on LTP inhibition induced by wild-type $A\beta_{1-42}$ and mutant $A\beta_{1-42}E22\Delta$ peptide. fEPSPs were monitored from the CA1 region of the intact rat hippocampus. DCP-LA (1 mg/kg) or PBS was intraperitoneally injected 70 min prior to HFS, to induce LTP, followed by intraventricular injection with wild-type $A\beta_{1-42}$ peptide (wAβ) (10 ng) (A) or mutant $A\beta_{1-42}E22\Delta$ peptide (mAβ) (10 ng) (B) 10 min prior to HFS. fEPSPs recorded at 0 (1) and 120 min (2) are superimposed. Control, intraventricular injection with PBS and intraperitoneal injection with PBS; wAβ + PBS, intraventricular injection with wild-type $A\beta_{1-42}$ peptide and intraperitoneal injection with PBS; wAβ + DCP-LA, intraventricular injection with wild-type $A\beta_{1-42}$ peptide and intraperitoneal injection with DCP-LA; mAβ + PBS, intraventricular injection with mutant $A\beta_{1-42}E22\Delta$ peptide and intraperitoneal injection with PBS; mAβ + DCP-LA, intraventricular injection with mutant $A\beta_{1-42}E22\Delta$ peptide and intraperitoneal injection with DCP-LA. In the graphs, each point represents the mean (±SEM) percentage of basal fEPSP slope (0 min) ($n = 5$). $^{**}P < 0.001$; $^{***}P < 0.0001$, Fisher's PLSD test.

4. Discussion

One might think that the effects of the linoleic acid derivative DCP-LA on synaptic transmission are similar to the effects of nicotine, an agonist of nicotinic ACh receptors including α7 receptors. DCP-LA, however, is not an agonist of nicotinic ACh receptors, distinct from nicotine, and therefore, DCP-LA does not