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Oxytocin reverses Aβ-induced impairment of hippocampal synaptic plasticity in mice

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ABSTRACT

Aim: Oxytocin, a peptide hormone synthesized in the hypothalamic paraventricular nucleus, has been reported to participate in the regulation of learning and memory performance. However, no report has demonstrated the effect of oxytocin on the amyloid-beta (Aβ)-induced impairment of synaptic plasticity. In this study, we examined the effects of oxytocin on the Aβ-induced impairment of synaptic plasticity in mice.

Methods: To investigate the effect of oxytocin on synaptic plasticity, we prepared acute hippocampal slices for extracellular recording and assessed long-term potentiation (LTP) with perfusion of the Aβ active fragment ($A\beta_{25-35}$) in the absence and presence of oxytocin.

Results: We found that oxytocin reversed the impairment of LTP induced by $A\beta_{25-35}$ perfusion in the mouse hippocampus. These effects were blocked by pretreatment with the selective oxytocin receptor antagonist L-368,899. Furthermore, the treatment with the ERK inhibitor U0126 and selective Ca^{2+}-permeable AMPA receptor antagonist NASPM completely antagonized the effects of oxytocin.

Conclusion: This is the first report to demonstrate that oxytocin could reverse the effects of Aβ on hippocampal LTP in mice. We propose that ERK phosphorylation and Ca^{2+}-permeable AMPA receptors are involved in this effect of oxytocin.

1. Introduction

Alzheimer's disease (AD) is the most frequent cause of dementia in the elderly, characterized in part by progressive memory loss and amyloid β (Aβ) peptide accumulation in the brain. Aβ peptides are 39-42-amino acid peptides produced as soluble metabolic products of the amyloid precursor protein. In AD, Aβ aggregates in the brain to form insoluble amyloid fibrils in senile plaques and cerebral vasculature. Thus, the connection between Aβ accumulation in the brain and the development of cognitive deficits has been an area of research focus.

Previous studies found that direct injections of synthetic Aβ into the brain cause learning and memory deficits in various animal models [1,2]. In addition, the perfusion of brain slices with the Aβ active fragment ($A\beta_{25-35}$) significantly inhibited the induction of long-term potentiation (LTP) without affecting the basal synaptic transmission and post-tetanic potentiation in the dentate medial perforant path, suggesting that sub-neurotoxic concentrations of Aβ peptides can strongly suppress long-term synaptic plasticity in the hippocampus [3]. Thus, the Aβ perfusion of brain slices has attracted attention as a model to analyze the underlying mechanisms of the memory deficits observed in AD before neuronal cell loss at early stages of Aβ accumulation is observed [3].

Oxytocin is a peptide hormone synthesized in the hypothalamic paraventricular nucleus. It is best known for its facilitatory roles in parturition and lactation. Oxytocin is also involved in the regulation of cognitive function, and its receptors exist in various brain regions, including the limbic forebrain in rodents [4,5]. For example, Tomizawa et al. reported that the intracerebroventricular injection of oxytocin in mice improved spatial learning and long-term memory performance in the radial maze test, and the perfusion of oxytocin into mouse hippocampal slices resulted in the long-

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lasting enhancement of field excitatory post-synaptic potential (fEPSP) slopes 3 h after stimulation [5].

Although oxytocin has been reported to participate in regulating learning and memory performance, no report has clarified its effects on the Aβ-induced impairment of synaptic plasticity. In this study, we demonstrated that oxytocin reversed the Aβ-induced impairment of LTP in mouse hippocampal slices and that MAPK and Ca^{2+}-permeable AMPA receptors are involved in this effect.

2. Methods

2.1. Animals

We used 5-7-week-old male ddY mice (Japan SLC Inc., Shizuoka, Japan). All animals had free access to food and water in an animal room with stable temperature (23 °C ± 1 °C) and relative humidity (55% ± 5%) under a 12-h/12-h light-dark cycle (lights were automatically switched on at 8:00 a.m.). All experimental protocols were approved by the Institutional Animal Care and Use Committee at Tokyo University of Science and were conducted in accordance with the guidelines of the National Institute of Health and Japan Neuroscience Society.

2.2. Hippocampal slice preparation and extracellular recordings

Hippocampal slice preparation and extracellular recordings were performed as previously described [6]. Briefly, mice were decapitated under isoflurane anesthesia, and the hippocampus of each animal was rapidly removed. Transverse slices (400-μm thick) were cut in ice-cold cutting solution containing (in mM) 124 NMDG-HCl, 3 KCl, 1.2 KH_2PO_4, 1.3 $MgSO_4$, 26 $NaHCO_3$, 10 glucose, and 2 $CaCl_2$, oxygenated with 95% O_2/5% CO_2 (pH 7.3-7.4) using a linear slicer, PRO7N (DOSAKA EM Co., Ltd., Kyoto, Japan). The slices were incubated artificial cerebrospinal fluid (aCSF) containing (in mM) 124 NaCl, 3 KCl, 1.2 KH_2PO_4, 1.3 $MgSO_4$, 26 $NaHCO_3$, 10 glucose, and 2 $CaCl_2$, oxygenated with 95% O_2/5% CO_2 at 37 °C at least for 30 min. Then, slices were additionally incubated at room temperature before use. A single slice was transferred to the recording chamber and perfused with aCSF at a rate of 2-3 mL/min (30 °C ± 2 °C). fEPSPs were recorded from the stratum radiatum of the hippocampal CA1 using a glass micropipette (0.8-1.5 MΩ) filled with aCSF. Electrical signals were amplified using an Axopatch 200B amplifier (Axon Instruments, Union City, CA, USA), filtered at 2 kHz, digitized at 10 kHz, and acquired using pClamp 9.2 software (Axon Instruments). A bipolar tungsten electrode was placed in the stratum radiatum to stimulate the Schaffer collateral pathway. In all experiments, the stimulus intensity was adjusted to produce a fEPSP that was 30-40% of the maximal amplitude. The strength of synaptic transmission was determined by measuring the slope of the fEPSP during the rising phase (20-80%). The stimulus duration was 0.1 ms, and the stimulus frequency was 0.05 Hz. To eliminate GABAergic activity, picrotoxin (100 μM) was included in the perfusate. LTP was induced by theta burst stimulation (TBS) (15 bursts of four pulses at 100 Hz, 200 ms interval). The average fEPSP slope during the 10 min before LTP induction was taken as baseline, and all values were normalized to this baseline (normalized fEPSP slope). The average normalized fEPSP slope from 35 to 40 min after LTP induction was calculated as a measure of the maintenance of LTP.

2.3. Drugs

Oxytocin (human) and $Aβ_{25-35}$ (human) were purchased from Peptide Institute Inc. (Ibaraki, Osaka, Japan). L-368,899 was purchased from R&D Systems Inc. (Minneapolis, MN, USA). U0126 was purchased from FUJIFILM Wako Pure Chemical Co., Ltd. (Chuo-ku, Osaka, Japan). NASPM was purchased from Cayman Chemical (Ann Arbor, MI, USA). Picrotoxin was purchased from Sigma-Aldrich (St. Louis, MO, USA). $Aβ_{25-35}$ (0.54 mg) was dissolved in 2.75 mL of 20% DMSO. Then, $AlCl_3$-$6H_2O$ (217 mg/L) was added to the Aβ solution. $Aβ_{25-35}$ was incubated for 4 days at 37 °C. L-368,899 and NASPM were dissolved in distilled water. U0126 was dissolved in DMSO. The drug concentration was adjusted as follows: oxytocin (2 μM), $Aβ_{25-35}$ (0.1 μM), L-368,899 (2 μM), U0126 (10 μM), and NASPM (10 μM). The final concentration of DMSO in the perfusate was 0.01%. DMSO (0.01%). $Aβ_{25-35}$ were perfused for 20 min before and after TBS. Oxytocin was perfused for 10 min before TBS and for 40 min after TBS. L-368,899, U0126, and NASPM were perfused as described for oxytocin. Hippocampal slices were preincubated in aCSF containing L-368,899 (2 μM) for 1 h before recording.

2.4. Statistical analysis

All data are presented as the mean ± SEM. The data were analyzed by one-way analysis of variance (ANOVA) for comparisons among three or more groups. If the ANOVA results were significant, then Bonferroni's multiple comparison tests were performed. The Mann-Whitney *U* test was used for statistical comparisons between two groups when the data were heteroscedastic. $P < 0.05$ was considered statistically significant.

3. Results

3.1. Oxytocin improves Aβ-induced impairment of hippocampal LTP

First, we confirmed the effect of $Aβ_{25-35}$ on hippocampal synaptic plasticity to investigate whether oxytocin reversed the $Aβ_{25-35}$-induced impairment of synaptic plasticity. In previous studies, $Aβ_{25-35}$ decreased hippocampal LTP [7–9]. In line with previous results, the perfusion of $Aβ_{25-35}$ (0.1 μM) resulted in a significant decrease of the potentiation of the fEPSP slope compared with the effects of vehicle (0.01% DMSO) ($P < 0.01$, Fig. 1a-b). The potentiation of the fEPSP slope in the last 5 min was significantly larger for the treatment with Aβ + oxytocin (2 μM) than for Aβ perfusion alone ($P < 0.001$, Fig. 1a-b). These results suggest that oxytocin can reverse the $Aβ_{25-35}$-induced impairment of synaptic plasticity.

To examine whether the observed effect of oxytocin is mediated by the oxytocin receptor, we recorded LTP in the presence of the oxytocin receptor antagonist L-368,899. The perfusion of L-368,899 failed to recover $Aβ_{25-35}$-induced impairment of synaptic plasticity. This result suggests that oxytocin improved the $Aβ_{25-35}$-induced impairment of synaptic plasticity via the oxytocin receptor ($P < 0.001$, Fig. 1c-d).

3.2. ERK phosphorylation is required for the effect of oxytocin on hippocampal LTP

Oxytocin facilitates ERK/CREB phosphorylation in the hippocampus [5,10] and ERK phosphorylation is important for LTP. We examined whether ERK phosphorylation is involved to improve $Aβ_{25-35}$-induced impairment of LTP. Oxytocin failed to restore $Aβ_{25-35}$-induced impairment of synaptic plasticity following the perfusion of the ERK/MEK inhibitor U0126 ($P < 0.001$, Fig. 2a-b). This result suggests that oxytocin restores $Aβ_{25-35}$-induced impairment of synaptic plasticity by inducing ERK phosphorylation.

3.3. Oxytocin revereses Ab-induced impairment of LTP through Ca^{2+}-permeable AMPA receptors in the hippocampus

$Aβ_{25-35}$ suppresses NMDA receptors located on synapses [11]. Ca^{2+} influx through synaptic NMDA receptors is essential for

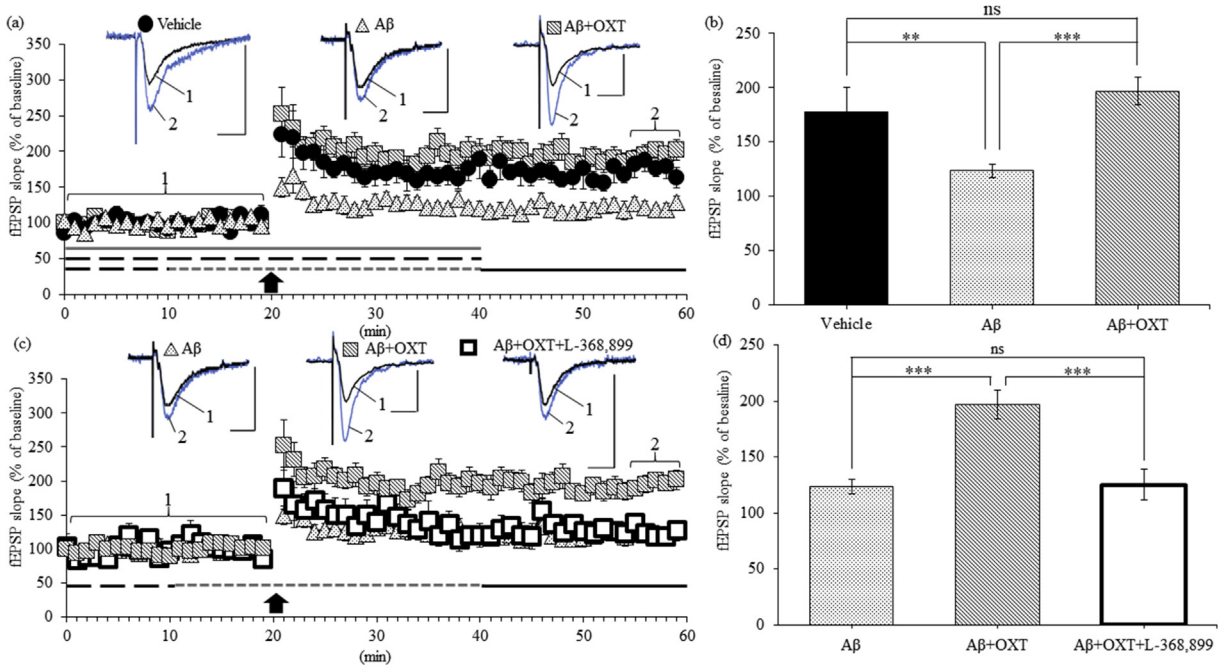

Fig. 1. (a-b) Effects of the amyloid β active fragment ($Aβ_{25-35}$) and oxytocin (OXT) on hippocampal long-term potentiation (LTP). (a) We recorded baseline for 20 min after field excitatory post-synaptic potential (fEPSP) became stable. LTP was induced by theta burst stimulation, and then EPSPs were continuously recorded for 40 min. Vehicle [DMSO (0.01%)] and $Aβ_{25-35}$ (0.1 μM) were perfused for 40 min. Aβ + OXT was perfused for 30 min. The perfusion of each drug is indicated as follows: gray line, Vehicle; dashed line, Vehicle + Aβ (0.1 μM); gray dashed line, Aβ + OXT; solid line, OXT. (b) LTP was recorded for 40 min. We analyzed the mean fEPSP over the last 5 min. Data are presented as the mean ± SEM ($n = 8$ for all). Vehicle = 177.26 ± 22.23%, Aβ = 123.3 ± 6.33%, Aβ + OXT = 196.0 ± 12.70%. $F(2,21) = 12.17$, $^{***}P = 0.0003$, one-way ANOVA; $^{**}P < 0.01$, $^{***}P < 0.001$, Bonferroni's multiple comparison test. (c-d) The oxytocin receptor antagonist L-368,899 blocked the recovery of LTP induced by oxytocin. (c) Slices were preincubated in the aCSF containing L-368,899 (2 μM) for 1 h. We recorded fEPSP following L-368,899 perfusion for 40 min. The gray dashed line indicates the perfusion of Aβ + OXT + L-368,899. (d) We analyzed the mean fEPSP over the last 5 min Data are presented as the mean ± SEM ($n = 6$ for OXT + L-368,899). L-368,899 = 125.2 ± 13.51%. $F(2,19) = 20.70$, $^{****}P < 0.0001$, one-way ANOVA; $^{***}P < 0.001$, Bonferroni's multiple comparison test.

memory formation and LTP. There is the possibility that the $Aβ_{25-35}$-induced impairment of synaptic plasticity is associated with decreased Ca^{2+} influx through synaptic NMDA receptors. In addition, oxytocin has been suggested to induce the expression of Ca^{2+}-permeable AMPA receptors in the medial prefrontal cortex [12]. Therefore, we examined whether Ca^{2+}-permeable AMPA receptors are involved in the effect of oxytocin on LTP impairment. The perfusion of the selective antagonist of Ca^{2+}-permeable AMPA receptor NASPM (10 μM) failed to improve $Aβ_{25-35}$-induced impairment of synaptic plasticity ($P < 0.001$, Fig. 2c-d). This result suggests that increased Ca^{2+} influx through Ca^{2+}-permeable AMPA receptors is involved in the beneficial effects of oxytocin on the $Aβ_{25-35}$-induced impairment of LTP.

3.4. Oxytocin itself produces no effect on LTP

We examined whether oxytocin (2 μM) alone affects LTP. The perfusion of oxytocin alone did not alter hippocampal LTP (Fig. 3). The dose of oxytocin was determined based on previous studies [5]. This result suggests that oxytocin itself has no significant effect on hippocampal synaptic plasticity.

4. Discussion

In the present study, we found that oxytocin reversed the impairment of LTP induced by $Aβ_{25-35}$ perfusion in the mouse hippocampus. Furthermore, these effects were recovered by the pretreatment with the selective oxytocin receptor antagonist L-368,899, suggesting that these effects were mediated by the oxytocin receptor. This is the first report to demonstrate that oxytocin receptors could mediate the recovery of LTP impaired by Aβ in the mouse hippocampus.

Previous reports showed that the perfusion of Aβ in hippocampal slices impaired LTP [7–9]. Vitolo et al. observed a strong inhibition of LTP generation in the rat CA1 hippocampal region when slices were exposed to $Aβ_{1-42}$ for 20 min before tetanic stimulation of the Schaffer collateral pathway [7]. In the present study, the perfusion of $Aβ_{25-35}$ produced significant decreases in the fEPSP slope for 40 min before the tetanic stimulation of the Schaffer collateral pathway, suggesting that Aβ could impair LTP in mouse hippocampal slice cultures. Our present results are consistent with previous findings.

A previous report demonstrated that the perfusion of oxytocin (1 μM) produced the long-lasting LTP (3 h after LTP-induction), but not early LTP (1 h after the induction) at the Schaffer collateral-CA1 synapses in hippocampal slices of female mice [5]. Similar with this report, we found that oxytocin itself produced no significant effect on LTP, however, oxytocin completely reversed the impaired LTP (1 h after the induction) produced by perfusion of $Aβ_{25-35}$ in the same synapses of male mice. Our results suggest that oxytocin has potential role to affect also on early LTP. Thus, we propose that oxytocin could exert a protective effect against Aβ-induced learning and memory impairment in mice. Further studies are necessary to examine whether oxytocin recovers impairment of cognitive behavior induced by Aβ in *in vivo* model.

Previous reports showed that Aβ has various effects on memory and synaptic plasticity. For example, Aβ suppresses the phosphorylation of ERK/CREB, which is essential for memory and synaptic plasticity [3,13]. Conversely, oxytocin facilitates ERK/CREB phosphorylation [5,10]. Lin et al. (2012) reported that oxytocin induces a significant increase in the phosphorylation of ERK1/2 in synaptosomes [10]. Tomizawa et al. noted that oxytocin facilitates CREB

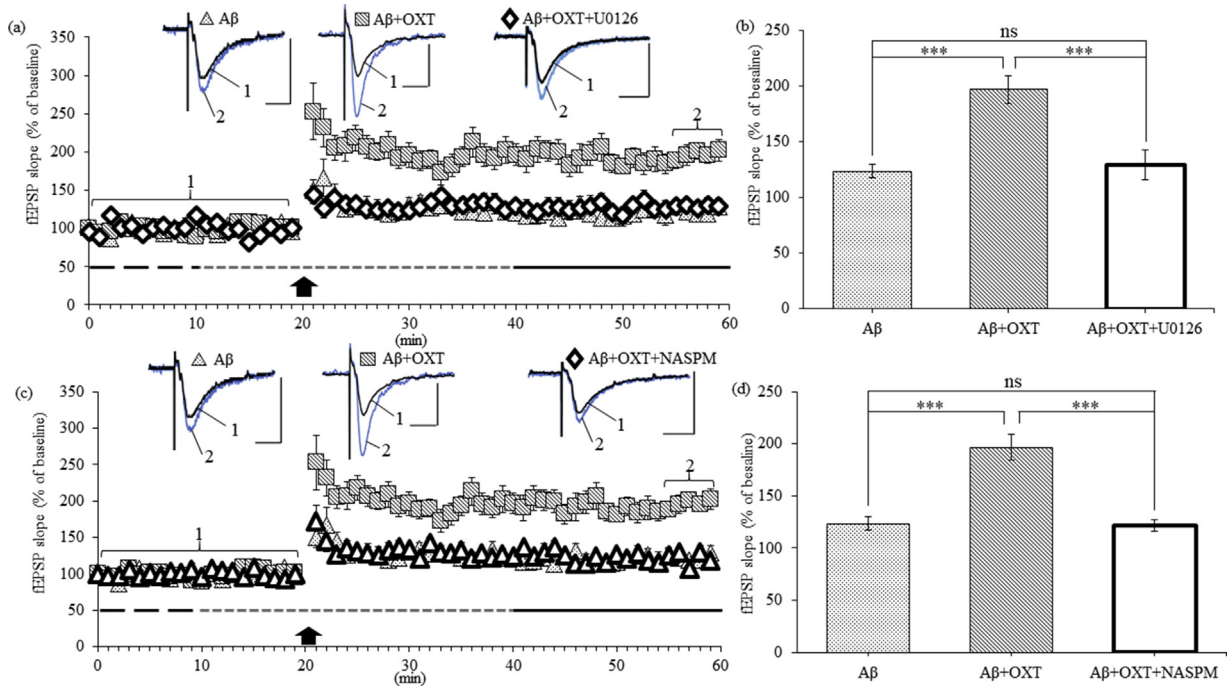

Figure 2. (a-b) Oxytocin (OXT) activated ERK signaling in the CA1 region. (a) The MAPK inhibitor U0126 blocked the effects of oxytocin on amyloid beta active fragment ($A\beta_{25-35}$)-induced inhibition of long-term potentiation. U0126 (10 μM) was perfused for 40 min. The perfusion of each drug is indicated as follows: dashed line, Vehicle [DMSO (0.01%)] + Aβ (0.1 μM); gray dashed line, Aβ + OXT + U0126; solid line, OXT. (b) We analyzed the mean field excitatory post-synaptic potential (fEPSP) over the last 5 min. Data are presented as the mean ± SEM ($n = 8$ for all). U0126 + Aβ + OXT = 129.3 ± 6.06%. $F(2,21) = 26.09$, $^{****}P < 0.0001$, one-way ANOVA; $^{***}P < 0.001$, Bonferroni's multiple comparison test. (c-d) Oxytocin induced the expression of Ca^{2+}-permeable AMPA receptors in the CA1 region. (c) The Ca^{2+}-permeable AMPA receptor antagonist NASPM (10 μM) was perfused for 40 min. The perfusion of each drug is indicated as follows: dashed line, Vehicle [DMSO (0.01%)] + Aβ; gray dashed line, Aβ + OXT + NASPM; solid line, OXT. (d) We analyzed the mean field excitatory post-synaptic potential (fEPSP) over the last 5 min. Data are presented as the mean ± SEM ($n = 8$ for all). NASPM + Aβ + OXT = 121.8 ± 5.781%. $F(2, 21) = 29.29$, $^{****}P < 0.0001$, one-way ANOVA; $^{***}P < 0.001$, Bonferroni's multiple comparison test.

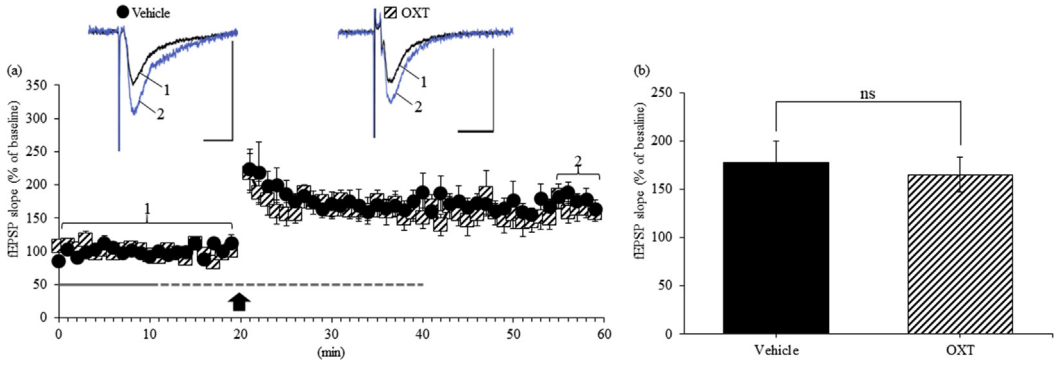

Fig. 3. Oxytocin alone had no effect on long-term potentiation (LTP). (a) We recorded field excitatory post-synaptic potential (fEPSP) following perfusion with oxytocin (OXT, 2 μM). The perfusion of each drug is indicates as follows: gray line, Vehicle [DMSO (0.01%)]; solid line, Vehicle + OXT. (b) We analyzed the mean fEPSP over the last 5 min. Data are presented as the mean ± SEM ($n = 8$ for each). OXT = 165.3 ± 18.37%. U = 25.0, $P = 0.5054$, Mann–Whitney U test.

phosphorylation in the mouse hippocampus [5]. In the present study, the selective MEK/ERK inhibitor U0126 inhibited oxytocin-induced LTP enhancement after Aβ perfusion, suggesting that oxytocin reversed $A\beta_{25-35}$-induced decreases in LTP by inducing ERK phosphorylation. Taken together, we suggest that oxytocin improves the Aβ-induced impairment of synaptic plasticity in the hippocampus by activating the oxytocin receptor-associated MEK/ERK signaling pathway.

In the present study, a selective antagonist of Ca^{2+}-permeable AMPA receptors, NASPM, reversed the oxytocin-induced enhancement of LTP after Aβ perfusion, suggesting that Ca^{2+}-permeable AMPA receptors are involved in the beneficial effects of oxytocin. Ca^{2+}-permeable AMPA receptors play important roles in synaptic plasticity [14,15]. A previous study suggested that oxytocin upregulates the expression of Ca^{2+}-permeable AMPA receptors in the medial prefrontal cortex [12]. Furthermore, phosphorylated ERK triggers the expression of Ca^{2+}-permeable AMPA receptors [15]. Thus, we propose that oxytocin can induce the upregulation of the Ca^{2+}-permeable AMPA receptors in the CA1 region of the hippocampus though ERK phosphorylation and the subsequent activation of ERK signaling (Fig. 4).

We suggest the interesting possibility that oxytocin may be a novel therapeutic modality for the treatment of memory loss associated with cognitive disorders, such as AD. However, oxytocin has poor blood–brain barrier permeability [17,18]. Thus, new approaches to selectively and effectively transduce oxytocin into the

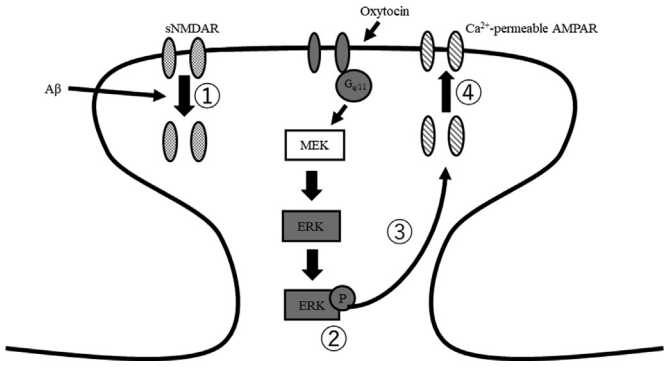

Fig. 4. Hypothetical Scheme.
①The amyloid beta active fragment ($A\beta_{25-35}$) depressed the expression of NMDA receptors located on synapses [11]. Ca^{2+} influx through synaptic NMDA receptors is essential for memory and long-term potentiation (LTP). Therefore, decreased Ca^{2+} influx through synaptic NMDA receptors is associated with $A\beta_{25-35}$-induced impairment of synaptic plasticity.
②Oxytocin facilitates ERK/CREB phosphorylation in the hippocampus. Oxytocin reverses $A\beta_{25-35}$-induced decrease in LTP by inducing ERK phosphorylation. Oxytocin improves the Aβ-induced impairment of synaptic plasticity in the hippocampus by inducing activation of the oxytocin receptor-associated MEK/ERK signaling pathway.
③Phosphorylated ERK triggers the expression of Ca^{2+}-permeable AMPA receptors [16].
④Oxytocin induces the upregulation of the Ca^{2+}-permeable AMPA receptors in the CA1 region of the hippocampus though ERK phosphorylation and the subsequent activation of ERK signaling. Therefore, increasing Ca^{2+} influx through Ca^{2+}-permeable AMPA receptors reverses $A\beta_{25-35}$-induced impairment of synaptic plasticity.

central nervous system are desired.

This is the first report to demonstrate that oxytocin can reverse Aβ-induced hippocampal LTP impairment in mice. We propose that ERK phosphorylation and Ca^{2+}-permeable AMPA receptors are involved in this effect of oxytocin.

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Declaration of competing interest

The authors have no conflict of interest to declare.

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