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Calcium/Calmodulin-dependent Protein Kinase II is a Ubiquitous Molecule in Human Long-term Memory Synaptic Plasticity: A Systematic Review

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ABSTRACT

Background: Long-term memory is based on synaptic plasticity, a series of biochemical mechanisms include changes in structure and proteins of brain's neurons. In this article, we systematically reviewed the studies that indicate calcium/calmodulin kinase II (CaMKII) is a ubiquitous molecule among different enzymes involved in human long-term memory and the main downstream signaling pathway of long-term memory.

Methods: All of the observational, case–control and review studies were considered and evaluated by the search engines PubMed, Cochrane Central Register of Controlled Trials and ScienceDirect Scopus between 1990 and February 2015. We did not carry out meta-analysis.

Results: At the first search, it was fined 1015 articles which included "synaptic plasticity" OR "neuronal plasticity" OR "synaptic density" AND memory AND "molecular mechanism" AND "calcium/calmodulin-dependent protein kinase II" OR CaMKII as the keywords. A total of 335 articles were duplicates in the databases and eliminated. A total of 680 title articles were evaluated. Finally, 40 articles were selected as reference.

Conclusions: The studies have shown the most important intracellular signal of long-term memory is calcium-dependent signals. Calcium linked calmodulin can activate CaMKII. After receiving information for learning and memory, CaMKII is activated by Glutamate, the most important neurotransmitter for memory-related plasticity. Glutamate activates CaMKII and it plays some important roles in synaptic plasticity modification and long-term memory.

Keywords: Calcium/calmodulin-dependent protein kinase II, long-term memory, synaptic plasticity, molecular mechanism

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INTRODUCTION

Memory is the information recording by selectively strengthening synapses in the brain.[1]

Biochemistry studies have shown long-term memory is based on the series of biochemical mechanisms as the synaptic plasticity.[2] Synaptic plasticity is the change in

the strength of synaptic transmission. It includes the alteration of the number of synaptic receptors, changes in the quantity of neurotransmitters and changes in respond to those neurotransmitters and action potential produced,[3] which can create long-term potentiation (LTP) caused by specific patterns of stimulation. LTP is a cellular correlate of memory that is produced by the increases in synaptic strength that can occur with high-frequency or paired stimulation.[1]

These changes in the efficiency of synaptic transmission are important for a number of aspects of neural function. A good candidate for the memory storage of information is Ca^{2+}/calmodulin-dependent protein kinase II (CaMK II). It's one of the most distinguished protein kinases that essentially presents in every tissue, but it has the most concentration in the brain.[4]

Two decades ago when CaMKII was identified as a major postsynaptic density protein, it was proposed a prominent role for it in the regulation of excitatory synaptic transmission.[5]

Holoenzyme CaMKII is a serine/threonine kinase with many substrates. In some brain regions such as the hippocampus that is a long-term memory location, it reaches to >2% of total protein. It can induce LTP in the hippocampus. Animals with the lack of the CaMKII isozyme have a deficit in LTP and then have impairments in spatial learning. CaMKII also has importance for synaptic plasticity. In mammals, this kinase has four isozymes, α, β, γ, and δ, that α and β are predominant in the brain. Although most catalytic molecules in the nervous system are relatively presented in low amounts, the high abundance of CaMKII makes it an unusual enzyme[6] and its molecular mechanism is the main type of synaptic plasticity in long-term memory.[4]

There are many studies about synaptic modification and memory, but its mechanism is still remained unclear then, finding and characterization of memory molecules are important.[4]

The studies indicated that in synaptic depression induced by Aβ – amyloids, CaMKII is a key target and enhancement drugs of CaMKII signaling may improve synaptic activity and cognitive function.[7]

Ca^{2+} influx during LTP activates CaMKII. It has autophosphorylation property in dendritic spines and can trigger an essential molecular switch mechanism for learning and memory.[8]

This review presents functions of CaMKII, as a major and ubiquitous enzyme of human long-term memory and learning.

METHODS

Identification of studies

All of the observational, case–control and review studies were considered and evaluated by the search engines PubMed, Cochrane Central Register of Controlled Trials and ScienceDirect Scopus between the years 1990 and February 2015. In addition to we searched the reference lists of related articles. This systematic review aimed to include all published studies that introduce CAMKII and its signaling pathway as the main and ubiquitous mechanism in long-term memory. Keywords including, "long-term memory," "remote memory," CAMKII that were selected by PubMed MeSH. We also used MeSH entry terms in the search strategy. Our search was restricted to English-language articles. We evaluated human and animal studies and selected the articles involved CAMKII as the main molecule in the molecular mechanism of long-term memory. Search strategies were explained in Table 1. After search, we reviewed the title

Table 1: Search strategies in PubMed, ScienceDirect Scopus and Cochrane Central Register of Controlled Trials using key words selected by MeSH and MeSH entry

PubMed
"Calcium/calmodulin-dependent protein kinase II" OR CaMKII AND "long-term memory": 74
"Calcium/calmodulin-dependent protein kinase II" OR CaMKII AND "synaptic plasticity" AND "long-term memory": 126
"Calcium/calmodulin-dependent protein kinase II" OR CaMKII AND "synaptic plasticity" OR "neuronal plasticity" OR "synaptic density" AND "long-term memory" OR "remote memory": 788
Science Direct Scopus
TITLE-ABSTR-KEY ("synaptic plasticity" OR "neuronal plasticity" OR "synaptic density" AND memory AND mechanism) (all sources [Biochemistry, Genetics and Molecular Biology]): 144
TITLE-ABSTR-KEY ("synaptic plasticity" OR "neuronal plasticity" OR "synaptic density" AND "long-term memory" AND mechanism) (all sources [Biochemistry, Genetics and Molecular Biology]): 14
TITLE-ABSTR-KEY ("synaptic plasticity" OR "neuronal plasticity" OR "synaptic density" AND memory AND "molecular mechanism") (all sources [Biochemistry, Genetics and Molecular Biology]): 22)]
Cochrane Central Register of Controlled Trials
"Ca^{2+}-calmodulin-dependent protein kinase OR CAMKII AND "long-term memory": 0
"Ca^{2+}-calmodulin-dependent protein kinase" OR CAMKII AND memory": 4
Title, abstract, keywords: Memory: 79
Title, abstract, keywords: "synaptic plasticity": 25
Title, abstract, keywords: "synaptic plasticity" OR "neuronal plasticity" OR "synaptic density" and "long-term memory": 6
Title, abstract, keywords: Memory AND mechanism: 5

CaMKII=Calcium/calmodulin kinase II

of articles, and eliminated duplicate articles, the articles that did not have original data and sufficient information, then we reviewed the abstracts of selected articles and have to exclude some papers following criteria including the articles that had no original data and sufficient information, and those which do not evaluate synaptic plasticity, and do not have interest in the outcome and do not apply key questions. Finally, all of the related human and animal studies with the key outcome of (CaMKII is a ubiquitous molecule memory synaptic plasticity) were included. We did not carry out meta-analysis.

RESULTS

A total of articles were found including "synaptic plasticity" OR "neuronal plasticity" OR "synaptic density" AND memory AND "molecular mechanism" as the keywords, a total of 788 article in PubMed, 144 in ScienceDirect Scopus and 83 in Cochrane Central Register of Controlled Trials [Table 1]. A total 335 articles were duplicated in the databases and were eliminated. A total of 680 title articles were evaluated and 600 articles that were not related, were excluded, then the abstracts of 80 articles were reviewed and 35 articles that had no original data and sufficient information and did not relate were excluded, then 45 articles were reviewed and the articles that did not have any original data and sufficient information, which did not evaluate synaptic plasticity, and did not have interest in the outcome and did not apply key questions also were excluded. Finally, 34 articles were selected as reference that 3 of them were about physiology and biochemistry of long-term memory, 8 articles about the role of synaptic plasticity in the memory formation and learning and 23 about molecular mechanism and effective downstream signals in long-term memory formation [Figure 1 and Table 2].

Quality of studies, cases, interventions, compared and output

In our study, there are 18 reviews and 16 experimental articles. About review articles we list the data include the number and the years of references. The cases of experimental studies include human (27, 11, 22), mice/rat (30, 19, 29, 31, 32, 33, 34, 7, 24, 25), cell (20), chick (20) and cricket (26). Interventions in the most of them are CAMKII, calcium and glutamate (11, 22, 27, 19, 31, 23, and 32) and in other studies, there are different intervention such as nitric oxide (NO) (30), naringin (7), rivastigmine (24), nefiracetam (25), cAMP and cGMP analogs (26), alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) (29) and without intervention (33, 34). In all of them, necessary changes of synaptic plasticity for long-term memory were compared with CAMKII and glutamate concentration after intervention [Table 2]. The outputs are shown in Table 2. These studies report information that improves the role of CAMKII as the most important molecule in long-term memory.

DISCUSSION

LTP is a short period of synaptic activity that can increase the size of the excitatory postsynaptic current (EPSC). Increasing of EPSC can enhance the strength of the synapse Longley. LTP includes two phases, an early phase that is without protein synthesis and late phase which is with protein synthesis.[9] In the earliest step, there is the N-Methyl-D-aspartate receptor (NMDAR) activation, calcium accumulation and calmodulin and CaMKII activation. The late stage of LTP that is more complex involves changing in gene expression, protein synthesis and synapse structure and number.[9] Studies have reported that CaMKII and protein synthesis are essential for long-term memory formation.[10] Among many of proteins involved in memory formation and the induction of synaptic potentiation, CaMKII is an abundant and critical synaptic signaling molecule.

CAMKII plays a key role during LTP induction by enhancing alternations in Hippocampal LTP that is the molecular basis of learning and memory.[11] Neuronal CaMKII can modulate important neuronal functions such as modulation of ion channel activity, cellular transport, neurotransmitter synthesis, neurotransmitter release, cell morphology and neurite extension, synaptic plasticity, gene expression, learning, and memory. This ubiquitous kinase triggers the molecular basis of learning and memory.[4]

The studies have shown that the most important neurotransmitter for memory-related plasticity is Glutamate.[12,13] AMPAR and NMDAR also are two main glutaminergic receptors in the postsynaptic membrane involved in long-term memory formation.[14] Cholinergic and GABA-ergic transmission may be regulated glutaminergic transmission.[15] Glutamate activates AMPAR and NMDAR after the release of presynaptic neuron excited by environmental stimulations and then some downstream signals that their most important is calcium-dependent signals, will be produced.[16]

Normal synaptic transmission is mediated mainly by AMPA receptors (AMPARs, whereas NMDARs become functional during repetitive synaptic activation.[17] By a weak stimulation of presynaptic neuron, glutamate releases from the axon terminal and binds to both NMDAR and AMPARs that are ion channels and can pass Na^+, K^+ and Ca^{2+} ions. But this weak stimulation normally activates only AMPARs and it can depolarize postsynaptic neuron slightly. At the slight depolarization, very few ions flow through N-Methyl-D-aspartate (NMDA) channel because a Mg^{2+} ion blocks it and does not permit to pass ions into the postsynaptic neuron. If there was strength or frequent stimulation, glutamate

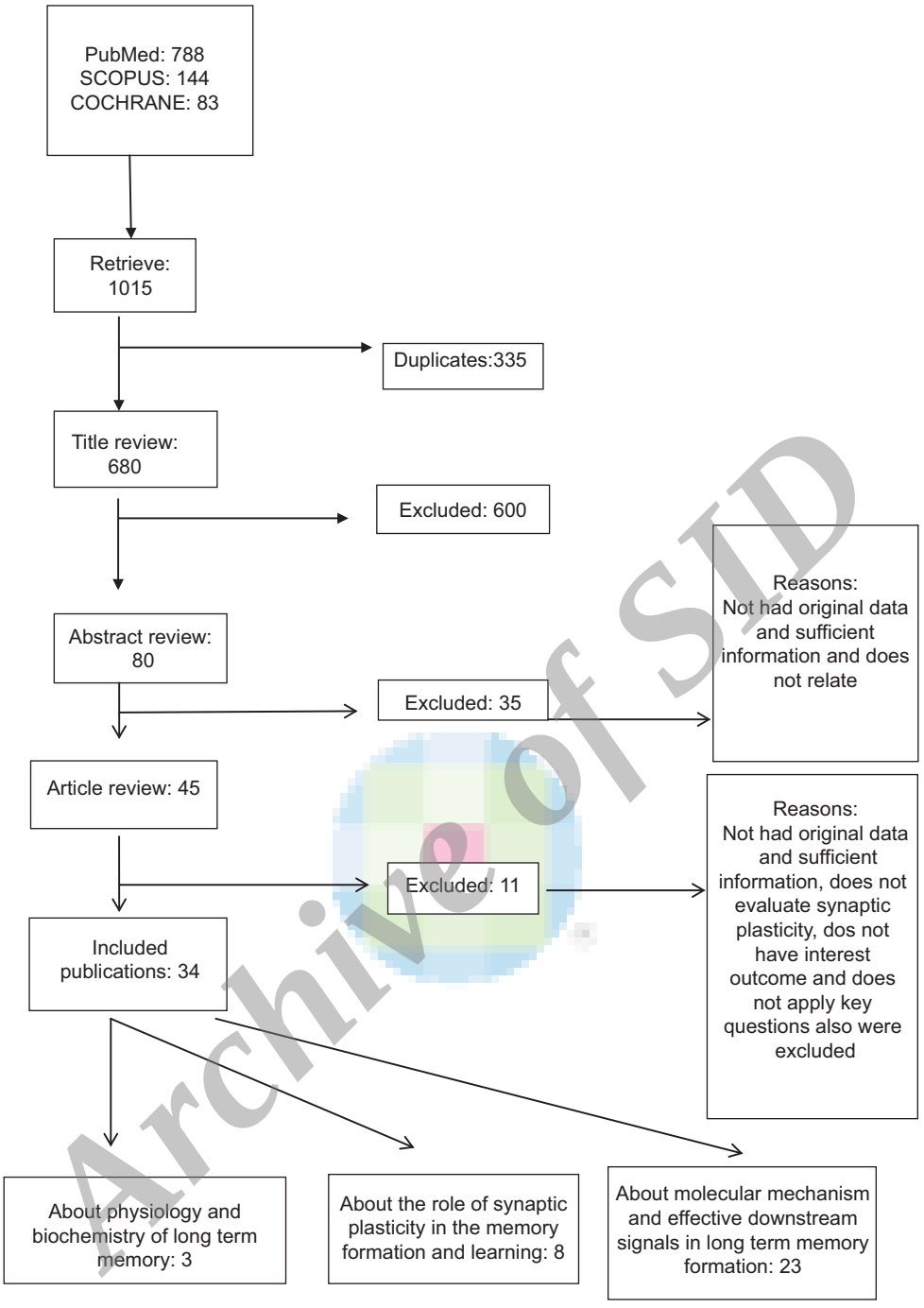

Figure 1: Study-flow diagram showing the number of studies screened, excluded and included in the review.

releasing increases and AMPAR can pass much more Na^+ and K^+ ions into the postsynaptic neuron and causes a sufficient depolarization. With effecting this depolarization, Mg^{2+} can expel from NMDAR and a large amount of Na^+, K^+ and also Ca^{2+} ion enter to the neuron. Ca^{2+} ion that acts as a second messenger and activates several intracellular signals[18] influxes into the postsynaptic neuron by NMDARs and it creates biochemical processes involved in synaptic plasticity such as LTP that is essential for memory formation in the hippocampus.[18]

Calcium binds calmodulin. Calmodulin is a major Ca^{2+} effector protein that after binding up to four Ca^{2+} ions it can activate at least six signaling enzymes in the neuron. Potentiation or depression of synapse after synaptic activity repetition is depending on amount and duration of calcium influx.[19]

Calcium/calmoduline complex can activate a kinase-dependent to calcium named CaMKII.[20] CaMKII can interact with NMDA glutamate receptors. The increasing of CaMKII auto phosphorylation and

Table 2: The summary of studies and comments on the role of CaMKII in long-term memory

First author	Publication year	Publication journal	Type of study	Population	Intervention	Significant outcome
Sophie	2007	Chem and Engine News	Review	12 articles 2007	-	Long-term memory is based on the series of biochemical mechanisms as the synaptic plasticity
Kimberly	2010	Curr Opi in Neurobio	Review	61 articles 2001-2010	-	Synaptic plasticity is the change in strength of synaptic transmission
Yamauchi	2007	Yakugaku Zasshi	Review	113 articles 1974-2005	-	A good candidate for the storage of information in the memory is CaMKII
Colbran	2004	Curr Opin in Neurobio	Review	84 articles 1997-2004	-	CAMKII has a prominent role in regulation of excitatory synaptic transmission
Leslie	2004	J of Neurosci	Mini-review	43 articles 1983-2004	-	The high abundance of CaMKII makes it an unusual enzyme
Fukunaga	1999	Jpn J Pharmacol	Review	39 articles 1989-1998	-	CAMKII plays a key role during LTP induction by enhancing alternations in synaptic efficiency
Coultrap	2012		Experimental and bioinformatics techniques	Human hippocampal pyramidal neurons	Calcium/CAMKII stimulatiom	CaMKII, PKA and protein synthesis are essential for long-term memory formation
Lucchesi	2011		Review	85 articles 1988-2010	-	CaMKII is an abundant and critical synaptic signaling molecule
Dudai	2002	Curr. Opin. Neurobiol	Review	61 articles 1984-2001	-	The most important neurotransmitter for memory-related plasticity is glutamate
Lamprecht	2004	Nat Rev Neurosci	Review	-	-	The most important neurotransmitter for memory-related plasticity is glutamate
Rongo	2002	Bioessays	Review	84 articles 1999-2001	-	AMPA and NMDA glutaminergic receptors of postsynaptic membrane involve in long-term memory formation
Moriguchi	2014	J Neurochem	Experimental	Mice	Rivastigmine	Cholinergic and GABA-ergic transmission may be regulated glutaminergic transmission
Oertner	2005	Cell Calcium	Review	42 articles 1977-2004	-	Glutamate activates some downstream signals that their most important is calcium-dependent signals will be produced
Manabe	2002	Brain Nerve	Review	-	-	NMDA receptors become functional during repetitive synaptic activation
Seok-Jin	2009		Experimental	Rat	Glutamate, calcium chelator (EGTA, BAPTA)	Postsynaptic calcium influx creates LTP and CaMKII transfers AMPA receptors from intracellular stores into the membrane
Shifman	2006	Proc Natl Acad Sci U S A.	Experimental	Cell	Different concentration of calcium, CAMKII, calmodulin	Ca^{2+}/calmodulin can activate at least six signaling enzymes in the neuron
Colbran	2008	A Comprehensive Reference	Review	84 articles 1997-2004	-	Calcium/calmoduline complex can activate CaMKII
Bayer	2001	Nature	Experimental	Human	Glutamate, CAMKII, calmodulin	CaMKII can interact with NMDA glutamate receptors and be auto phosphorylated or hyper phosphorylated
Solomonia	2013	Exp Brain Res	Experimental	Chick	P-GluA1 and T-GluA1 measurement after training	CaMKII can directly phosphorylate Ser831 AMPA receptors in the GluA1 subunit

Contd...

Table 2: Contd...

First author	Publication year	Publication journal	Type of study	Population	Intervention	Significant outcome
Kristensen	2011	Nat Neurosci	Experimental	Cultured hippocampal neurons, human embryonic kidney cells	Glutamate, mg^{2+}, CAMKII, AMPA receptor antagonist	Phosphorylation of AMPA receptors enhances ion conduction of AMPA receptors
Lisman	2001	Neuron	Review	Articles 1977-2001	-	Hyper phosphorylation of CaMKII can increase the interactions between NMDA and AMPA
Hayachi	2000	Science	Experimental	Rat hippocampal neurons	AMPA-Rs with an electrophysiological tag	Interactions between NMDA and AMPA, will be induced the insertion of AMPA receptors into the membrane
Bartus	2013	PLoS One	Experimental	Sprague Dawley rat and C57/Bl6/SV129 mice	NO-targeted guanylyl cyclase BAY 41-2272, NO donor DEA/NO	Calcium activates NO synthase and NO induces neurotransmitter release
Jourdain	2003	The Journal of Neuroscience	Experimental	Mice with the Gria1fl/fl, Gria2fl/fl, and Gria3fl/fl	CaMKII, calcium, calmodulin, mg^{2+}	CaMKII auto phosphorylation involves in production of new synapse
Granger	2013	Nature	Experimental	Mouse	Flip-isoform GluA1, GluA2	CaMKII auto phosphorylation promotes rapid growth of dendritic filo podia and dendritic spine formation
Engert	1999	Nature	Experimental	Rat	-	CaMKII auto phosphorylation promotes dendritic spine formation that is a type of synaptic plasticity and producing LTP
Sando	2012	Cell	Experimental	Mice	-	Calcium/calmodulin complex can phosphorylates HDAC4 in the cytoplasm of neuron. Phosphorylate HDAC4 cannot repressed the genes involved synaptic plasticity
Lachlan	2014	Ann Neurosci	Review	25 articles 2000-2014	-	Memory is the information recording by selectively strengthening synapses in the brain
Michael	2006	Curr Opini in Neurobiol	Review	62 articles 1992-2006	-	
Dong-Mei	2013	Int J Mol Sci	Experimental	Transgenic mouse	Naringin from pomelo peel	CaMKII is a key target and enhancement drugs of CaMKII signaling may be improve synaptic activity and cognitive function
Shonesy	2014	Prog Mol Biol Transl Sci	Review	215 articles 2000-2014	-	Ca^{2+} influx during LTP, activate CaMKII. It has autophosphorylation property in dendritic spines and can trigger an essential molecular switch mechanism for learning and memory
Lisman	2012	Nat Rev Neurosci	Review	154 articles 1994-2011	-	In the earliest steps of LTP, there are the NMDAR activation, calcium accumulation and calmodulin and CaMKII activation. The late stages of LTP is involve changes in gene expression, protein synthesis, and synapse structure and number
Moriguchi	2011	J Pharmacol Sci	Experimental	Rat	Nefiracetam	Nefiracetam, a pyrrolidine-related nootropic drug with a cognitive-enhancing effect, can increase LTP in hippocampus by CaMKII activation with increase in phosphorylation of postsynaptic CaMKII substrate which is Ser-831 AMPA-type glutamate receptor subunit 1 (GluA1)

Contd...

Table 2: Contd...

First author	Publication year	Publication journal	Type of study	Population	Intervention	Significant outcome
Mizunami	2014	PLoS One	Experimental	Male crickets	CaMKII inhibitor, cGMP analog, calcium ionophore, cAMP analog	Injection of a CaMKII inhibitor, could inhibit long-term memory but not short term memory and co-injection of CaMKII improved learning and memory

CaMKII=Calcium/calmodulin kinase II, LTP=Long-term potentiation, PKA=Protein kinase A, AMPA=Alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid, NMDA=N-Methyl-D-aspartate, GABA=γ-aminobutyric acid, NO=Nitric oxide, DEA=Diethylamine, HDAC4=Histone deacetylase4, NMDAR=N-Methyl-D-aspartate receptor

hyperphosphorylation are the results of this interaction.[21] By auto-phosphorylation, CaMKII can be autonomously active. There is an increasing of CAMKII activity 30 min after training of memory. It is interesting that CaMKII not only has auto-phosphorylation property, but it can directly phosphorylate Ser831 AMPARs in the glutamate receptor 1 (GluA1) subunit.[22] This phosphorylation enhances ion conduction of AMPARs.[23]

Some studies have proved these findings, for example Moriguchi *et al*. in 2014 have shown that in mice, rivastigmine treatment restores LTP in the hippocampus and phosphorylation of Ser831 AMPAR subunit glutamate receptor 1 (GluA1) and the stimulation of CaMKII activity in the hippocampus is critical for rivastigmine-induced memory improvement.[24] The results of the other study by Moriguchi in 2011 have indicated nefiracetam, a pyrrolidine-related nootropic drug with a cognitive-enhancing effect, can increase LTP in hippocampus by CaMKII activation with increase in phosphorylation of postsynaptic CaMKII substrate which is Ser-831 AMPA-type glutamate receptor subunit 1 (GluA1). It enhances NMDAR function and induces CaMKII activation. In conclusion, this drug can improve memory.[25]

Mizunami *et al*. suggested injection of a CaMKII inhibitor, could inhibit long-term memory but not short-term memory, and co-injection of CaMKII improved learning and memory.[26]

Wang *et al*. have shown naringin improved the long-term memory ability in an Alzheimer disease transgenic mouse model by Enhancement of CaMKII.[7]

The interactions between NMDAR and AMPARs may be increased by hyper-phosphorylation of CaMKII.[27] As a result of these interactions, the insertion of AMPARs will be induced in the membrane.[28]

CaMKII transfers AMPARs from intracellular stores into the membrane surface, and more receptors locate on the neuronal membrane.[18] Calcium also produces signals in the postsynaptic neuron that retrogrades and effects on a presynaptic neuron by NO synthesis. Calcium activates NO synthase in the postsynaptic neuron. NO retrogrades and activates the guanilate synthase enzyme to induce exocytosis of glutamate vesicles and release of more transmitter from presynaptic neurotransmitter.[29]

That is very interesting that CaMKII auto-phosphorylation involves in the production of the new synapse by the promotion of rapid growth of dendritic filopodia and dendritic spine formation. This phenomenon is a type of synaptic plasticity and producing LTP.[30-32] A histone deacetylase 4 (HDAC4) is a genomic control of synaptic plasticity and memory. It can shuttle between nucleus and cytoplasm. In the nucleus, HDAC4 affects synaptic structure and strength. In a strong or frequent potential, after NMDAR activation and calcium entering to the neuron, calcium/calmodulin complex can phosphorylate HDAC4 in the cytoplasm of the neuron. Phosphorylated HDAC4 cannot permeate to the nucleus. If HDAC4 enters to the nucleus, it can interact with some essential transcription factors for synaptic plasticity and then represses relative genes.[33,34]

CONCLUSIONS

The studies have indicated that CaMKII is an abundant and critical synaptic signaling molecule in learning and long-term memory. It plays a key role during LTP induction by enhancing alternations in synaptic efficiency. The high abundance of CaMKII in the hippocampus makes it an unusual enzyme in there, and its molecular mechanism is the main type of synaptic plasticity in long-term memory. In addition, stimulating drugs and agents of CaMKII can improve and increase long-term memory.

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