Function of the CaMK II on LTP of Exercise Learning

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I. INTRODUCTION

To make and store new memories is fundamental abilities for human. Unfortunately, many diseases such as Alzheimer’s disease impair memory formation. Long-term potentiation (LTP) in the CA1 region of the hippocampus has been the primary model by which to study the cellular and molecular basis of memory. It has been well documented that calcium/calmodulin-dependent protein kinase II (CaMKII) plays a key role in plasticity of glutamatergic synaptic transmission and is known to be important for memory formation [1]-[5].

CaMKII is an abundant kinase that regulates synaptic plasticity. It is central to the regulation of glutamatergic synapses. Particularly, it is critical for the induction of LTP, a candidate mechanism of memory formation. N-methyl-d-Aspartate (NMDA) receptors are ionotropic glutamate receptors’ these coincidence detectors of synaptic activity and induce LTP by mediating a postsynaptic Ca$^{2+}$/CaM entry into the postsynaptic cell. It is believed that Ca$^{2+}$ activates CaMKII through the NMDA receptor. Activated CaMKII can bind to NMDA receptor subunits and autophosphorylation at the Thr286 site of α CaMKII further enhances its binding affinity to Ca$^{2+}$/CaM and prolongs the association of CaMKII at PSD [2]-[4].

In addition to its essential role for LTP induction, CaMKII is also important for the formation of synaptic tags [6] and metaplasticity. Otherwise, it is persistently activated by stimuli that elicit LTP, and can, by itself, enhance the efficacy of synaptic transmission. Thus, the CaMKII’s persistent “on” state induced by LTP stimulation may allow the CaMKII autophosphorylation and dephosphorylation to serve as a memory device for information storage.

Physical exercise is a widely accepted to enhance overall health and it is well established that exercise can improve cognitive performance. It is well established that exercise regulates numerous molecular and signaling endpoints in the brain, providing multiple pathways by which exercise can modulate cognitive function and brain health. In particular, human studies have demonstrated exercise can reduce incidence of dementia attenuation of age-related loss of brain perfusion, reduced age-dependent brain atrophy [7].

We begin this review with a molecular description of CaMKII and its basic enzymatic function. We then discuss CaMKII activation occurs during LTP is necessary for memory and the important relationship between exercise and memory.

II. BIOLOGICAL COMPOSITION AND FUNCTION OF CAMKII

CaMKII is a Ca$^{2+}$-activated enzyme that is highly abundant in the brain where it constitutes 1–2% of the total protein. The kinase is enriched at synapses and is the main protein of the postsynaptic density (PSD).

CaMKII is a multifunctional serine/threonine kinas with a broad range of substrates. In mammalian cells CaMKII that is expressed from a family of four of 28 similar isoforms. They are derived from genes: α, β, γ and δ, each of which produces mRNA that can be alternatively spliced, giving rise to at least 30 different proteins [8]. Each isoform consists of a catalytic domain, an autoinhibitory domain, a variable segment and a self-association domain (Fig. 1) [9]. The catalytic domain is inherently capable of catalysing the phosphotransferase reaction. α and β isoforms are especially abundant in brain, constituting as much as 2% of total protein in the hippocampus whereas γ, and δ isoforms are ubiquitously expressed [10].

Manuscript received October 17, 2012; revised December 5,2012. This work is contributed equally by Dan Xu and Xiyan Xie as co-first authors. Lijuan Hou is with Beijing Normal University, majored in exercise physiology, Beijing China. (e-mail: houlij@bnu.edu.cn).
(PSD) protein and this isofrom has been studied extensively in relation to memory formation. In recent years, advances in genetic manipulation have allowed CaMKII knockout experiments. Mice lacking α CaMKII show numerous deficiencies in learning and neuronal plasticity [11,12], including blockage of hippocampal LTP and cortical experience-dependent plasticity.

Little is known about the function of βCaMKII in the brain and virtually nothing about the γ and δ isoforms [13]. βCaMKII is primarily neuronal, although the βM splice variant is found in skeletal muscle. The γ and δ isoforms are expressed throughout the body and important in smooth muscle.

Autophosphorylation is the main features of CaMKII. Each CaMKII protein is composed of an N-terminal catalytic domain, an auto-inhibitory regulatory domain, and an association domain with four variable regions inter-dispersed. CaMKII inactivation state when lack of Ca\(^{2+}\)/CaM that CaMKII inhibition area and catalytic structure combining domain curb the substrate protein and the catalytic combination. The molecular conformation changed when Ca\(^{2+}\)/CaM combination, each catalytic structure domain close to inhibition of the structure domain phosphor late itself at Ser, Thr sites. CaMKII becomes activation and phosphor-late other target protein in cells thus appears Ca\(^{2+}\)/CaM biological activity [1].

The second role of Autophosphorylation is promoting translocation of CaMKII to postsynaptic densities (PSDs), cytoskeletal scaffolds for the neurotransmitter receptor, ion channels, and their regulators. The target Thr286-auto-phosphorylated CaMKII to the PSD initially identified a 190-kDa binding activity, corresponding in size to the highly PSD-enriched NR2A and NR2B subunits of the NMDA receptor as a CaMKII-NMDA receptor complex from PSDs.

Recent studies have also shown that repeated electroconvulsive shock, an effective therapy for depression patients, disrupts CaMKII–GluN2B binding by causing phosphorylation of the latter at Ser1303, showing a modulation of glutamatergic transmission in depression like disorders and suggesting a reduction of GluN2B-Ser1303 phosphorylation in depression [14].

III. FUNCTION OF CAMK II IN LEARNING-MEMORY

The first study of the role of CaMKII in learning and memory was made in α-CaMKII knockout mice. These mice were deficient in LTP and hippocampus-dependent spatial learning tasks [15]. CA1 hippocampal synapses have served as a model system by which to understand synaptic plasticity. The study of LTP has been the demonstration that NMDA receptor can act as a detector of coincident activity in the pre- and postsynaptic cells. The channels formed by these receptors open efficiently only when glutamate is released from the presynaptic terminal and the postsynaptic cell is strongly depolarized. Channel opening produces a rise in Ca\(^{2+}\).

CaMKII is a family of ubiquitous with broad substrate specificity and regulates many physiological responses to Ca\(^{2+}\) mobilization [16]. It is major downstream effectors of Ca\(^{2+}\) signaling in eukaryotic cells. The passage of glutamate receptor coupling with Ca\(^{2+}\) open and Ca\(^{2+}\) into the cell that increased Ca\(^{2+}\) concentration in cells after nerve impulses caused glutamate receptor activated. A rise in intracellular Ca\(^{2+}\) concentration leads to binding of Ca\(^{2+}\) to calmodulin (CaM), which binds to and activates CaMKII. Upon activation, CaMKII becomes auto-phosphorylated at Thr286. This autophosphorylation mechanism of α CaMKII initiated by calcium influx into the postsynaptic cell prevents α CaMKII from reverting to its resting state even after calcium levels drop to baseline levels. It is this switch to a calcium independent state which allows signals to be potentiated for longer within the cell [2, 17].

CaMKII can bind to a wide variety of proteins in the postsynaptic density (PSD). These proteins include NMDA receptor subunits α-actinin 1 and 4, Densin-180, SynGap-β, Synapsin 1, Connexin36, L-Type Ca\(^{2+}\) channels. All NMDA receptor subunits have been shown to interact with CaMKII, although the results seem to be strongly dependent on the assay conditions and the phosphorylation status of CaMKII. This unique mechanism has been shown to play a special role in LTP formation, but not necessarily LTP storage [3, 18].

Without Ca\(^{2+}\) in vitro testing CaMKII activity, Fukunaga found that CaMKII activity increases after induction LTP in the slices of hippocampal and the active increase state could be lasting more than an hour[19].

It is not affect the synaptic transmission and activity of Ca\(^{2+}\)/CaM dependent kinases, but the induction of LTP out of control which mediated by NMDA receptors in CA1 area of hippocampus and emerge space learning disabilities when Knockout α CaMKII or gene mutations α CaMKII of normal mice[20].

The function of CaMKII in synaptic plasticity has been most extensively studied at excitatory synapses in adult hippocampal area CA1 [21]. In the absence of T286 autophosphorylation there is a complete block of NMDA receptor dependent LTP [22]. Behavioral studies with α CaMKII autophosphorylation-deficient mutant mice have shown that the T286 autophosphorylation is essential for induction of transcription during memory consolidation [23]. Recent studies in Lymnea suggest that intrinsic activation of CaMKII contributes to late memory consolidation [24].

IV. EFFECT OF EXERCISE ON CAMK II IN LEARNING-MEMORY

Physical exercise is a widely accepted behavioural strategy to enhance overall health. Human and animal studies demonstrate that exercise participation is a powerful behavioral intervention to improve cognitive function and brain health. In particular, human studies have demonstrated robust effects of exercise in the aged population, where higher physical activity is associated with improved cognitive scores on multiple aspects of cognition including executive function as well as with reduced incidence of dementia [25]. Rodent studies demonstrate that exercise can facilitate acquisition and/or retention in various hippocampal-dependent tasks including the Morris water maze, radial arm water maze and object recognition [26].

Alzheimer’s disease (AD) is a neurodegenerative disorder and Genetic factors are known to play a role in AD
vulnerability, yet less than 1% of incident AD cases are directly linked to genetic causes, suggesting that environmental variables likely play a role in the majority of cases. Several recent human and animal studies have examined the effects of behavioural factors, specifically exercise and psychological stress, on AD vulnerability. Some human studies suggest that psychological stress can increase the risk of developing AD, while other studies suggest that exercise can significantly reduce AD risk through multiple intracellular pathways, including cAMP response element binding protein (CREB), CaMKII, and mito-gen-activated protein kinase (MAPK) [27].

Regular and moderate exercise has been considered an interesting neuroprotective strategy [27] while there is controversial evidence showing brain mitochondrial dysfunction, oxidative damage and decreased neurotrophin levels after high-intensity exercise, which presumably worsens cognitive performance [28].

Long-term regular appropriate exercise could improve spatial learning-memory of rats and increased the expression of PSD-95, CaMKII, Synapsin signal transduction Pathway [29]. Other investigation found that the expression of CaMKII mRNA increased significantly in hippocampus of rats whose spatial learning and memory function were enhanced by regular aerobic exercise and proved CaMKII plays an important role in Learning-Memory [30].

V. CONCLUSION
A large number of studies show the role of CaMKII in LTP. There is thus little doubt that CaMKII is activated during LTP induction which is necessary and sufficient for LTP. It is also clear that CaMKII can strengthen synaptic transmission by multiple mechanisms. The recently discovered binding of CaMKII to NMDA receptors in the PSD could be an initial step in this structural process. PSD-specific receptor and scaffolding proteins, such as NR2B and densin-180, are attractive candidates for this role. However, further work is needed in order to understand the detailed mechanism of CaMKII translocation and high affinity PSD binding.

Several recent studies have proved that exercise plays an important role in Learning-Memory. Robust effects of exercise are good for aged population, AD and so on. CaMKII is central to the mechanism of hippocampal, NMDA receptor-dependent LTP. Also, CaMKII can be autonomously active and required for the formation of memory. Although the mechanisms by which physical exercise alters brain function are not really clear, it appears that neuroprotective properties of exercise could be related to synaptic remodeling. Lifestyle is an important factor which affects the level of the residents’ health. Maybe exercise not only keeps the residents’ health but improve Learning-Memory through CaMKII signaling on LTP during memory formation.

ACKNOWLEDGMENT
This research was supported by the Fundamental Research Funds for the Central Universities, China.

REFERENCES

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