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Modelling the dynamics of CaMKII–NMDAR complex related to memory formation in synapses: The possible roles of threonine 286 autophosphorylation of CaMKII in long term potentiation

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HIGHLIGHTS

- A mathematical model of the formation of CaMKII–NMDAR complex.
- A biologically meaningful probabilistic framework for the binding between CaMKII and NMDAR.
- The model suggests possible factors of the formation of CaMKII–NMDAR complex.
- The model provides understanding of the relationships among the autophosphorylation of CaMKII, CaMKII–NMDAR complex and E-LTP.

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ABSTRACT

A synaptic protein, Ca^{2+}/Calmodulin dependent protein kinase II (CaMKII), has complex state transitions and facilitates the emergence of long term potentiation (LTP), which is highly correlated to memory formation. Two of the state transitions are critical for LTP: (1) threonine 286 autophosphorylation of CaMKII; and (2) binding to N-methyl-D-aspartate receptor (NMDAR) in the postsynaptic density (PSD) to form CaMKII–NMDAR complex. Both of these state transitions retain the activity of CaMKII when the induction signal disappears which is very important for the long-lasting characteristics of LTP. However, the possible relationships between the state transitions in the emergence of LTP are not well understood. We develop a mathematical model of the formation of CaMKII–NMDAR complex with the full state transitions of CaMKII, including the autophosphorylation, based on ordinary differential equations. In addition, we formulate a probabilistic framework for the binding between CaMKII and NMDAR. The model gives accurate predictions of the behaviours of CaMKII in comparisons to the experimental observations. Using the model, we show that: (1) the formation of CaMKII–NMDAR complex is dependent not only on the binding affinity between CaMKII and NMDAR, but also on the translocation of CaMKII into PSD; and (2) the autophosphorylation is not a requirement for the formation of CaMKII–NMDAR complex, but is important for the rapid formation of CaMKII–NMDAR complex during LTP.

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1. Introduction

Recent research shows that memory is stored in a set of synapses as synaptic strength, which strongly correlates to the magnitude of the postsynaptic response to an environmental stimulus (see supplementary material (SI) for the details of synaptic structure and synaptic transmission). The memory is retrieved by recognising the stored synaptic response patterns that match or are most sensitive to the patterns of the environmental stimulus (Bear et al., 2007; Martin et al., 2000). The synaptic adaptation to the external stimulus is experimentally linked to the long term potentiation (LTP): LTP is a synaptic process that long-lastingly increases synaptic strength, through

Abbreviations: AMPAR, A-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid receptor; ATP, adenosine triphosphate; CaM, calmodulin; CaMKII, Ca^{2+}/CaM-dependent protein kinase II; cAMP, cyclic adenosine monophosphate; EPSP, excitatory postsynaptic potential; EPSC, receptor mediated current; HS, holoenzyme states of the whole CaMKII enzyme; HST, holoenzyme state transition of CaMKII based on the whole CaMKII enzyme; IS, inner states of CaMKII subunit; IST, inner state transition of CaMKII based on the individual subunit; LTD, long term depression; LTP, long term potentiation (E-LTP, early phase LTP; L-LTP, late phase LTP); NMDAR, N-methyl-D-aspartate receptor; PP1, protein phosphatase 1; PSD, postsynaptic density; pBS, potential binding sites; ST, state transition; *T286*, threonine 286 residue

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increasing the excitatory postsynaptic potential (EPSP) or receptor mediated current (EPSC) in vivo, in response to high frequency stimulations (Bliss and Collingridge, 1993; Bliss and Lømo, 1973; and see SI). LTP and memory formation are strongly correlated: (1) both the memory formation and LTP trigger formation of new synapses (Engert and Bonhoeffer, 1999; Morgado-Bernal, 2011); (2) blocking LTP diminishes spatial memory formation (Davis et al., 1992; Morris, 1989; Tsien et al.,1996); and (3) the disruption of LTP by mutations impairs memory formation (Abel et al., 1997; Bourtchuladze et al., 1994; Chang et al., 1999; Grant and Silva, 1994; Huang and Lee, 1995; Silva et al., 1992a, 1992b). Therefore, the elucidation of the mechanisms and the pathways underlying LTP is imperative to understand synaptic adaptation and memory formation. In this paper, we investigate a potential pathway and the associated mechanisms to adapt synaptic strength using a novel mathematical model. The model is centred around the conformational state transitions (STs) of the "memory molecule", Ca^{2+}/Calmodulin (CaM) dependent protein kinase II, CaMKII (Lisman et al., 2012).

LTP contains two distinct phases: (1) the early phase (E-LTP) occurs immediately after the transient (a few seconds) induction signal and rapidly potentiates synaptic strength; and (2) the late phase (L-LTP) follows E-LTP to maintain the potentiation by triggering gene expression pathways and may change the synaptic structure (Abel et al., 1997; Bliss and Collingridge, 1993; Frey et al., 1993). Our focus here is modelling mechanisms related to E-LTP as the mechanisms related to L-LTP are not well understood.

The consensus of the experimental studies of LTP in CA1 region of hippocampus (Bear et al., 2007; Bliss and Collingridge, 1993, Kandel, 2009) is that LTP is induced by a postsynaptic protein cascade (Isaac et al., 1995; Malenka and Bear, 2004; Sheng and Kim, 2002; Xia and Storm, 2005; see SI for the description of the cascade) initiated by N-methyl-D-aspartate receptor (NMDAR). Once the high frequency stimulation is applied, NMDAR triggers a Ca^{2+} influx to initiate the protein cascade, which leads to the changes in A-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid receptor (AMPAR)-mediated EPSC (Citri and Malenka, 2007; Kandel, 2009; Mayford et al., 2012).

CaMKII, a holoenzyme with 12 subunits (Lisman et al., 2012), phosphorylates AMPAR (see SI) to increase: (1) the conductance of the embedded ion channel of AMPAR (Derkach et al., 1999), and (2) the anchoring of AMPAR into the postsynaptic density (PSD) (Opazo et al., 2010; Tomita et al., 2005), where AMPAR becomes active; both of these increases will raise the AMPAR-mediated EPSC. Moreover, CaMKII can stay in PSD for more than 30 min (Fig. 2B, Bayer et al., 2006) that may be critical to cause the long-lasting increase in the EPSC and to link the two phases of LTP.

The binding between CaMKII and NMDAR serves a number of functions: (1) anchoring CaMKII in PSD (Gardoni et al., 1998; Leonard et al., 1999; Strack and Colbran, 1998); (2) targeting CaMKII to AMPAR since there is a linkage between NMDAR and AMPAR via A-kinase anchoring protein (Colledge et al., 2000; Robertson et al., 2009); and (3) longer sustaining periods of CaMKII in PSD (Bayer et al., 2006). Further, the formation of CaMKII–NMDAR complex is an essential component of LTP and memory formation (Barria and Malinow, 2005; Halt et al., 2012; Sanhueza et al., 2011; Otmakhov et al., 2004; Vest et al., 2007; Zhang et al., 2008; Zhou et al., 2007). Disparate experimental evidence exists on the significance of the autophosphorylation of CaMKII for the formation of CaMKII–NMDAR complex and for the induction of E-LTP. Some studies state that the formation of CaMKII–NMDAR complex does not require the autophosphorylation (Barcomb et al., 2013; Bayer et al., 2001, 2006): T286A mutant (Bayer et al., 2006), which lacks the autophosphorylation, and the autophosphorylation repressors (Barcomb et al., 2013) do not block the formation of CaMKII–NMDAR complex, although the strength of CaMKII and NMDAR binding decreases. On the other hand, another set of studies show that the autophosphorylation is required for LTP and spatial memory formation (Giese et al., 1998; Irvine et al., 2006), especially during E-LTP (Buard et al., 2010). Furthermore, a study reports that the autophosphorylation is irreversible in PSD that may have a critical role in LTP (Mullasseril et al., 2007).

Therefore, we hope to understand the role of the autophosphorylation and the relationships among the autophosphorylation, CaMKII–NMDAR complex and the LTP by developing a dynamic model of the processes involved in the STs of CaMKII and its binding to NMDAR in response to Ca^{2+} signals. The main contributions of this model development are the inclusion of the STs based on the conformation of CaMKII, the inclusion of translocation of the holoenzyme between dendritic spine and PSD, and the development of a probabilistic framework for the binding between NMDAR and CaMKII holoenzyme. The previous models either considered only the STs of single subunits of CaMKII or did not include the binding to NMDAR (Chao et al., 2011; Chiba et al., 2008; Dosemeci and Albers, 1996; Dupont et al., 2003; Hayer and Bhalla, 2005; Kubota and Bower, 2001; Lisman 1989; Lisman and Zhabotinsky, 2001; Miller et al., 2005; Pepke et al., 2010; Zhabotinsky, 2000). To the best of our knowledge, this is the first attempt to model the holoenzyme state transitions (HSTs) of CaMKII, including the binding to NMDAR. The modelling of HSTs is important to understand the dynamic nature of the formation of CaMKII–NMDAR complex as the experiments show (Strack et al., 2000) that the holoenzyme structure of CaMKII is crucial for its binding to NMDAR.

Our model provides insights into the formation of CaMKII–NMDAR complex which is regulated not only by the binding affinity between CaMKII and NMDAR as expected, but also by the rate of the CaMKII translocation into PSD. The model predicts well the alteration on the CaMKII translocation by T286A mutant in comparison to the experimental observation. In addition, the model predicts the formation of CaMKII–NMDAR complex under T286A mutant well: in particular, the model predicts that T286A mutant is not able to distinguish the frequency of tetanus; this prediction is consistent with the experimental observation. With regard to the autophosphorylation, the model shows that (1) the autophosphorylation amplifies the postsynaptic responses in reaction to the stimulation signals; (2) the autophosphorylation decodes the frequency of the stimulation to trigger appropriate postsynaptic response as reported frequently by previous modelling studies of CaMKII (Dosemeci and Albers, 1996; Kubota and Bower, 2001); and (3) the autophosphorylation can couple multiple trains of tetanus that are separated by relatively long inter-train intervals.

The paper is organised as follows: we briefly discuss the biochemical background needed for the model development in Section 2; Section 3 is about the previous models of ISTs; Section 4 is on the model development; and we discuss our results in Section 5, and we make concluding remarks in Section 6.

2. Biochemical background for modelling

A CaMKII subunit consists of a kinase domain, a regulatory domain, and a hub domain (see Lisman et al., 2002, 2012 for an in-depth review and Chao et al., 2011 for the structural images of CaMKII). Twelve subunits are folded into two hexametric rings and each ring contains six subunits with their hub domains attached one by one to form a central hub (Fig. 1A) (Chao et al., 2011). The functionality of CaMKII relies on the following critical sites (Fig. 1B): (1) the substrate binding site (S site) in the kinase domain (S site is crucial for the catalytic activity and can reversibly bind to NMDAR); (2) the pseudosubstrate segment in the regulatory domain which contains CaM footprint for Ca^{2+}/CaM complex binding (the pseudosubstrate segment is important for CaMKII

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