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Translational switch for long term maintenance of synaptic plasticity

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Introduction

Memory lasts a lifetime, yet the physiological substrate of memory, synaptic contacts, are composed of proteins that have much shorter lifetimes. A physiological analog of memory formation, long-term potentiation (LTP), has a late protein synthesis dependent phase (L-LTP) that can last for many hours in slices, or even days in vivo. Could the activity dependent synthesis of new proteins account for persistence of L-LTP and memory? Here, we examine the proposal that a self-sustaining regulation of translation can form a bistable switch that can persistently regulate the on-site synthesis of plasticity related proteins. We show that a αCaMKII-CPEB1 molecular pair can operate as a bistable switch. Our results imply that L-LTP should produce an increase in the total amount of αCaMKII at potentiated synapses. This paper also proposes an explanation for why the application of protein synthesis and αCaMKII inhibitors at the induction and maintenance phases of L-LTP result in very different outcomes.

Results

Previous experimental recordings have also shown that αCaMKII activity regulates the induction of L-LTP [1,2]. However, its role in maintenance of L-LTP is not very clear [3,4]. We simulate the application of αCaMKII activity inhibitors during the induction phase of L-LTP (Fig 1). We noted that outcome of αCaMKII activity blocking depends on the effectiveness of the activity inhibitor. Our results show that 73% of αCaMKII activity blocking during induction does not have any effect on L-LTP maintenance. However, as activity blocking levels are increased beyond 73% the L-LTP is compromised. Next we simulated the application of activity inhibitors starting 1 hr after the induction of L-LTP. We show that complete blocking of αCaMKII activity during the maintenance of L-LTP can completely abolish any increase in total αCaMKII. However, our results also indicate that partial blocking of activity during maintenance has no effect on total amount of αCaMKII, since blocking αCaMKII activity by less than 96% of αCaMKII does not lead to any significant change in total amount of αCaMKII, and only inhibition above 98% completely abolishes any change in total αCaMKII concentration.

Conclusion

This model, of a translational switch relies on the self sustained regulation of translation and can support both synaptic specificity and stability.

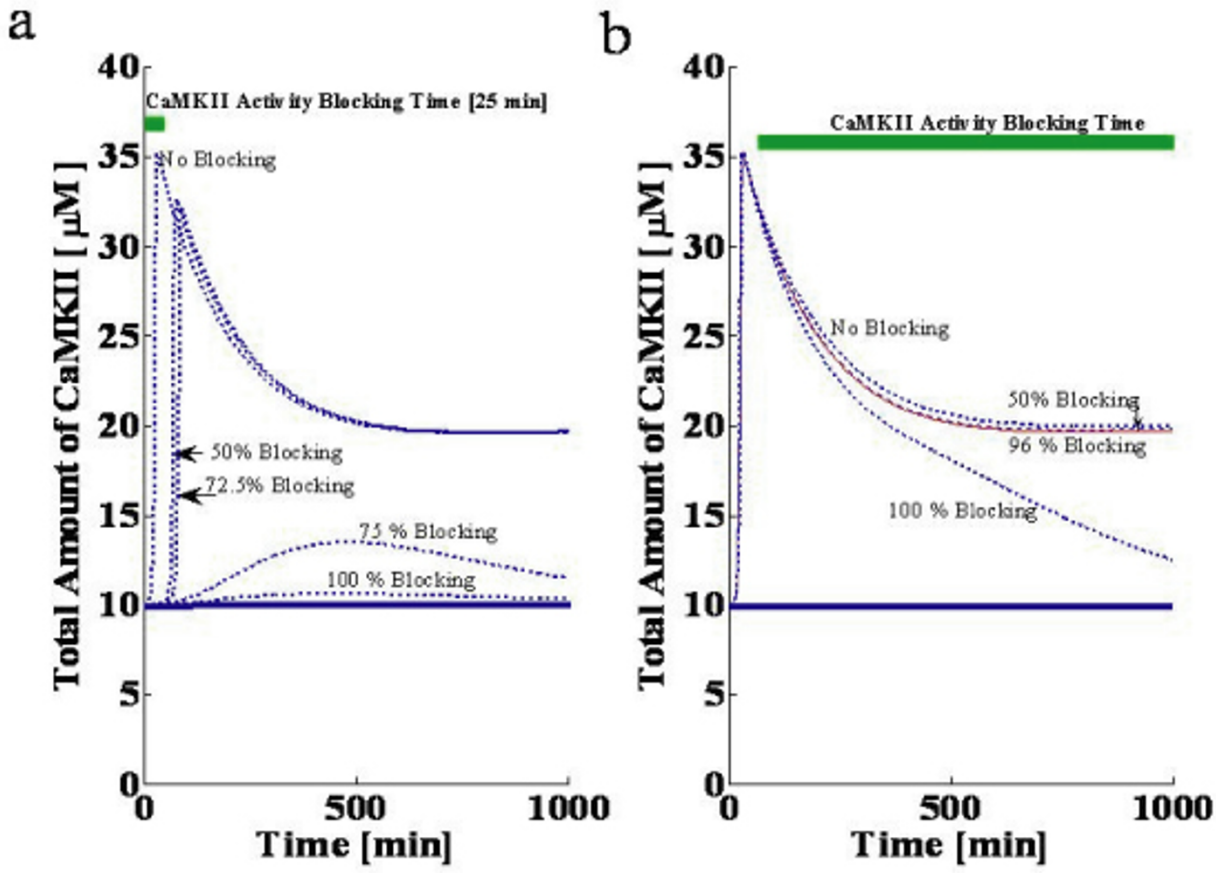

Figure 1
Blocking CaMKII activity.

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