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Calcium/calmodulin-dependent protein kinase II (CaM); its role in synaptic memory

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We have used biochemical, physiological and computational approaches to understanding how CaMKII gets activated during LTP and the mechanism by which this activation is sustained (longest measurements are 8 hours). In an initial project, we sought to better understand how many molecules of CaMKII would be required to form a stable molecular switch. Although previous work had shown that CaMKII could form a bistable switch, the modeling work had not taken into consideration the limits of stability imposed by stochastic fluctuations. To explore this issue, we undertook Monte-Carlo simulation, which individually modeled the phosphorylation of each site on each CaMKII molecule in the switch. This work revealed that a group of 10 CaMKII holoenzymes could form a switch that would be informationally stable for a human lifetime. However, in making these calculations, we had to crudely estimate the rate of the phosphatase action within the postsynaptic density (PSD) responsible for dephosphorylation of CaMKII. Because of the uncertainty of this number, we mounted a project to measure this directly. We used a phospho-specific antibody to the crucial Thr286-site that underlies the switching behavior of the molecule. Surprisingly we found that there was no dephosphorylation of this site. Previous work had shown dephosphorylation using ^{32}P labeling and we replicated this finding. It thus appears that the phosphatase (PP1) in the PSD is very specifically targeted to specific sites on CaMKII. Importantly, the dephosphorylation of Thr286, the reaction that limits stability of the "on" state of the switch, appears to be unmeasurably slow. We now realize that our previous understanding of how the switch works will have to be revised for two reasons. First, as indicated above, the phosphatase is slower that thought. Second, other experimental work in our laboratory has shown that LTP produces a translocation of CaMKII from the dendrite to the PSD and that this translocation is persistent. We are thus now developing the next generation model of CaMKII function that takes these new findings into consideration. The importance of this work is underscored by other recent findings in our laboratory that bear on the question of whether CaMKII is indeed responsible for synaptic memory. Although it has long been

clear that CaMKII is necessary for certain forms of LTP and memory, evidence for a role of persistent kinase in the maintenance of LTP has been lacking. Recent experiments have addressed this issue using a new generation of CaMKII inhibitor. We find that LTP can be saturated and then brought out of saturation by transient application of this inhibitor. Under these conditions, additional LTP can be induced. This indicates that synaptic memory can be reversed by CaMKII inhibitor, a critical requirement for demonstrating the molecular basis of synaptic memory.

PI Website

http://www.bio.brandeis.edu/faculty01/lisman.html

Publications

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