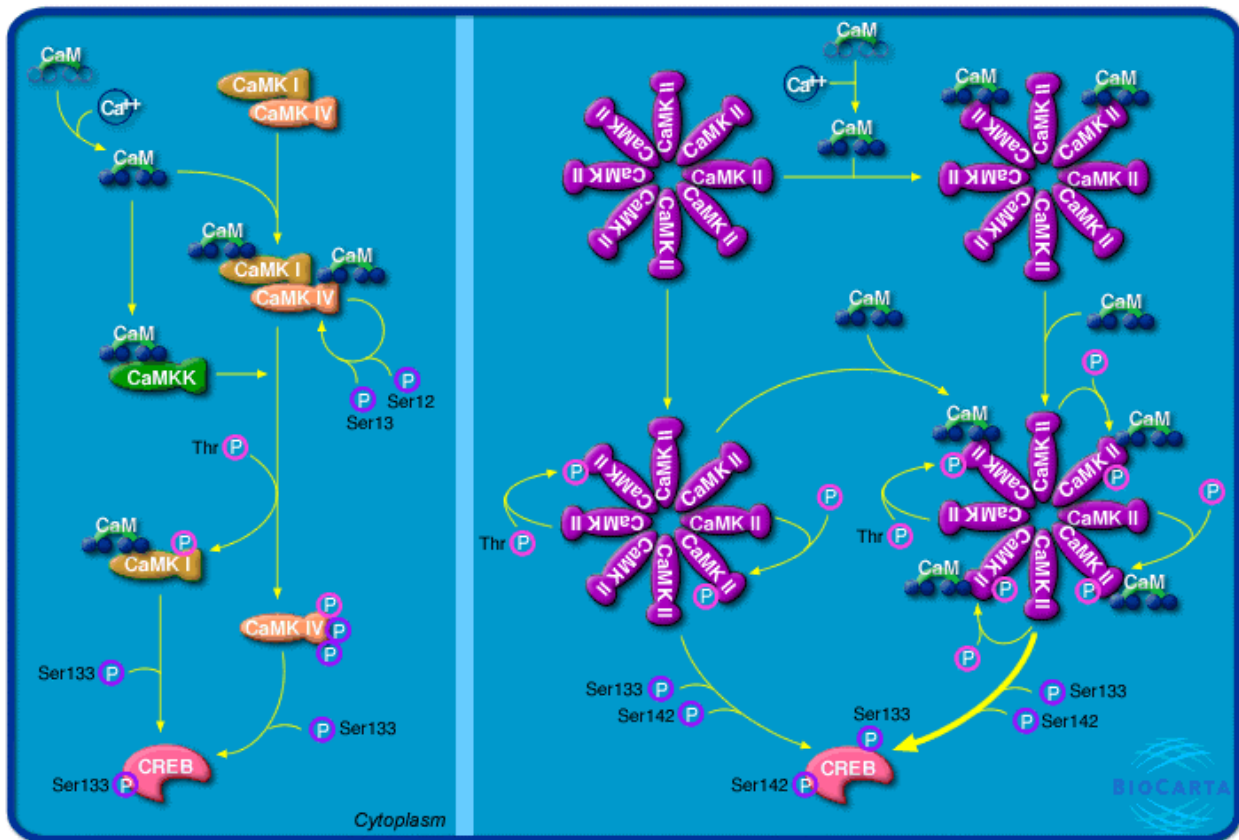


Calcium Signalling



The calcium/calmodulin-dependent kinases (CaMKs) are involved in a large number of cellular responses induced by hormones, neurotransmitters and other signalling. Elevation of calcium functions as a major second messenger, where the intracellular concentration of calcium can be maintained at extremely low levels and subsequently increased following specific calcium-mobilizing stimuli. There are many buffers to the calcium fluxuations including membrane pumps and calcium-binding proteins that create discrete spatial control of its effectors and their targets. The current family of multifunctional calcium/calmodulin (CaM)-dependent protein kinases (CaMKs) consists of CaMKI, CaMKII and CaMKIV. These kinases translate and co-ordinate the calcium fluxuations into the appropriate cellular responses via phosphorylation. These kinases are partially regulated by the intracellular calcium receptor calmodulin (CaM), have common as well as unique features in their structure, regulation and activation. CaMKII, CaMKI and CaMKIV, have an autoregulatory domain that restricts or inhibits enzymic activity in the absence of calcium/CaM.

Calcium/CaM binding alone produces maximal activity of CaMKII, whereas CaMKI and CaMKIV have an activation loop that requires phosphorylation of a threonine residue by CaMK kinase (CaMKK) for maximal activity. Two

genes (alpha and beta) for CaMKK, which is also regulated by CaM, have been identified. The highest expression of these isoforms occurs in the brain but the activity of the CaMKs has been identified in most cell types. CaMKIV has a post-calmodulin autophosphorylation step that is not observed in CaMKI. The CaMKII multimer can autophosphorylate either the autoregulatory domain or the CaM-binding domain, producing diverse effects in its regulation and sensitivity to Calcium/CaM. Autophosphorylation of CaMKII can produce Calcium/CaM- independent activity (autonomous activity), without affecting its maximal Calcium/CaM-stimulated activity. The CaMKII autophosphorylation involves a kinase cascade of sorts, with each subunit of the multimeric enzyme acting as both kinase and kinase kinase. Autophosphorylation establishes a 1000-fold increase in the affinity for its activator Calcium/CaM (also known as CaM trapping); however, autophosphorylation within the CaM-binding domain following CaM dissociation of activated/autophosphorylated enzyme restricts or prevents CaM from rebinding (CaM capping). The mechanisms and consequences of autophosphorylation are central to the CaMKII enzyme's complex regulatory behavior enabling it to become differentially activated at different frequencies and levels of calcium spikes.

The target proteins for the CaMKs are very similar. An example target of the CaMKs is the transcriptional activating protein CREB. The phosphorylation states of CREB after CaMK phosphorylation differ by the additional phosphorylation of CREB at serine 142 that functions as an additional inhibitory site. This difference appears to be the result of adjacent amino acids.