Mini-Review

Calcium/Calmodulin-Dependent Protein Kinase II: An Unforgettable Kinase

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The search for “memory molecules” and why CaMKII is an appealing candidate

Since the time neuroscientists first recognized that biochemical events inside neurons could influence the function of the brain, there have been people looking for “memory molecules.” This elusive ion, small molecule, protein, or nucleic acid would be the keystone on which memory was built; understanding the memory molecule would allow us to unlock the mysteries of cognition. Models of how this molecule could work abounded, but the idea of a memory molecule as a kinase/phosphatase-based molecular switch emerged as an important contender (Lisman, 1985). The discovery that there actually was an abundant neuronal protein kinase that had switch-like properties (Miller and Kennedy, 1986) was met with great enthusiasm, and the role of calcium/calmodulin-dependent protein kinase II (CaMKII) in learning and memory has been studied intensively. This series of reviews will cover recent advances in our understanding of the regulation of CaMKII and its autophosphorylation by phosphatases and localizing interactions, its involvement in synaptic plasticity, and the advent of mammalian genetic models for the study of CaMKII in behavior.

CaMKII is a ubiquitous, high-abundance signaling molecule

CaMKII is a serine/threonine kinase with a broad range of substrates. Since its activity was first described in the late 1970s (Schulman and Greengard, 1978), over 1200 papers have been published that feature the kinase in their title. These studies have provided a solid understanding of the gross structure and enzymatic properties of the kinase (for a recent review of the basic properties of CaMKII, see Hudmon and Schulman, 2002). CaMKII is found in most tissues, but it is present in especially high concentrations in neurons, in which it may be up to 2% of total protein in some brain regions (Erondu and Kennedy, 1985). In mammals, the kinase is encoded by four genes, α, β, γ, and δ, with the α and β isoforms predominant in the brain. Each of these isoforms has multiple splice variants. In invertebrate species in which the genome is sequenced, a single alternatively spliced gene encodes the kinase.

CaMKII monomers assemble into a large holoenzyme. Mone

mers of different isoforms are able to coassemble, allowing for a large number of possible holoenzyme compositions. Measurement of the Stoke’s radii and sedimentation coefficients of rat brain and Drosophila CaMKIIIs suggested a holoenzyme of 8–12 subunits (Bennett et al., 1983; Kuret and Schulman, 1984; GuptRoy and Griffith, 1996). Early electron microscopic studies of CaMKII purified from rat brain found some heterogeneity in holoenzyme size, reporting both 8 and 10 subunit particles (Kanaseki et al., 1991). More recent single-particle studies, using recombinant rat CaMKII, have provided much higher-resolution (21–25 Å) images (Kolodziej et al., 2000; Gaertner et al., 2004). These studies indicate that homomers of α, β, γ, and δ are capable of forming dodecamers that are dimers of hexameric rings, with the N-terminal catalytic domains extending off of a gear-like core made up of association domains. To date, no high-resolution x-ray structure is available for the CaMKII holoenzyme. An association domain fragment has been crystallized and was found to form a tetradecamer (Hoelz et al., 2003). The difference in subunit number between the single particle and x-ray structures is not understood but may indicate that the kinase has multiple possible holoenzyme configurations.

The high abundance of CaMKII in the nervous system makes it an unusual enzyme; most catalytic molecules are present in relatively low amounts. CaMKII is now recognized to inhabit many different subcellular structures and compartments. Neurons are complicated cells, and, as our knowledge of cell biology expands, the number of specialized subcellular domains that can be identified is increasing. Targeting of signaling molecules to particular structures within the cell can constrain their function. For CaMKII, localization is a dynamic process that is likely to be critical for the role of the kinase in synaptic plasticity. Recent advances in our understanding of the dynamic control of localization are presented in the mini-review by Schulman (2004).

The many modes of CaMKII activity regulation

The regulation of CaMKII activity has turned out to be much more than a simple function of the levels of Ca2+/CaM. Investigation of the localization of the kinase and its association with other proteins has led to the finding that CaMKII activity can be regulated by a subset of these binding interactions. Several CaMKII binding proteins have been found that can maintain the active state of the kinase in the absence of Ca2+/CaM, and one binding partner has been identified that inactivates the kinase by stimulating inhibitory autophosphorylation. The mechanisms of classical regulation of the kinase by Ca2+/CaM and more recently

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CaMKII is critical for synaptic and behavioral plasticity

The role of CaMKII in neuronal function has been studied at both cellular and behavioral levels using pharmacological and genetic manipulations. CaMKII activity is required for induction of long-term potentiation (LTP) in the CA1 region of the hippocampus (Malenka et al., 1989; Malinow et al., 1989; Silva et al., 1992a). LTP is a reflection of the increases in synaptic strength that can occur with high-frequency or paired stimulation and is believed to be a cellular correlate of memory (for a recent review, see Malenka, 2003). Defects in LTP often accompany impairments in spatial learning, and animals that lack the αCaMKII isoform do not learn normally in such tasks (Silva et al., 1992b, 1996; Elgersma et al., 2002). The switch-like features of CaMKII also appear to have importance for synaptic plasticity. Autophosphorylation of Thr286 is persistently increased after stimuli that induce LTP (Fukunaga et al., 1993, 1995; Barria et al., 1997; Ouyang et al., 1997), and knock-in of a T286A αCaMKII mutation prevents generation of autonomous activity blocks CA1 LTP and learning in the Morris water maze (Giese et al., 1998). Contextual fear conditioning can also induce autophosphorylation of αCaMKII (Atkins et al., 1998; Rodrigues et al., 2004).

Genetic manipulation of αCaMKII has led the way for use of engineered mice in neuroscience research. The depth of understanding of the biochemistry of the regulation of CaMKII has allowed very precise manipulations of regulatory aspects of the kinase to be performed by replacement of the wild-type gene with αCaMKII isoforms of CaMKII and CaMKII mutants. By crippling only a kinase to be performed by replacement of the wild-type gene with αCaMKII isoforms of CaMKII and CaMKII mutants, additional autophosphorylation sites within the CaM-binding domain become accessible and are autophosphorylated; these sites block rebinding of Ca2+/CaM. CaMKII autophosphorylation reactions have been studied quite extensively and are critical to regulation of the kinase by both Ca2+/CaM and other newly characterized protein regulators. The reversal of autophosphorylation by the activity of various cellular phosphatases is an important regulator of the lifetime of these autophosphorylated species. The influence of locally tethered phosphatase activity on plasticity is covered in the mini-review by Colbran (2004).

References


