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PERSPECTIVES

CaMKII: the Swiss army knife of synaptic plasticity

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Ca^{2+}/calmodulin-dependent protein kinase II (CaMKII) is known to play key roles in synaptic plasticity. It has a dodecameric structure composed of four different isoforms α–δ. Over the past decade or so, researchers have demonstrated that inhibition of CaMKII activity or ablation/down-regulation of CaMKII levels results in deficits in long-term potentiation (LTP), learning and memory. The study of CaMKII has primarily focused on the role of CaMKIIα in modulating LTP at excitatory synapses of the hippocampus and cortex. However, recent reports indicate that CaMKII is not only involved in the regulation of LTP, but that it is also required for hippocampal long-term depression (LTD) in a manner in which the specificity towards substrate changes depending on the induction protocol. In the cerebellum, CaMKII also regulates both LTP and LTD at parallel fibre–Purkinje cell synapses. In addition, growing evidence suggests that CaMKII is functionally heterogeneous, which is conferred by different isoforms.

In this issue of *The Journal of Physiology*, Nagasaki *et al.* show interesting results to indicate that CaMKIIα and -β, dominant isoforms in the brain, act differently to modulate rebound potentiation (RP), a specific form of plasticity at inhibitory synapses of cerebellar Purkinje cells (Kano *et al.* 1996; Nagasaki *et al.* 2014). RP is induced by strong climbing fibre excitation of Purkinje cells, which leads to an increase in intracellular Ca^{2+} via the activation of voltage-gated Ca^{2+} channels. Nagasaki *et al.* showed that α and β isoforms of CaMKII have opposing effects on RP, with CaMKIIβ being essential for RP induction whereas CaMKIIα is not only unnecessary for RP but also has a negative impact on it. Interestingly, it is the ratio between α and β that is more critical for RP, rather than the absolute levels. They monitored the activity of each isoform during RP using a Förster resonance energy transfer (FRET)-based CaMKII sensor, and showed that CaMKIIβ is persistently activated, whereas CaMKIIα is activated only transiently. Importantly, increasing the proportion of CaMKIIβ prolonged the activity, suggesting that it is the β isoform that determines the duration of CaMKII activity in RP.

Then how can two isoforms of CaMKII differently regulate synaptic strength? Nagasaki *et al.* focused on two well-documented differences between the two isoforms: the affinity for Ca^{2+}/calmodulin and F-actin-binding ability. CaMKIIβ has a higher affinity for Ca^{2+}/CaM than CaMKIIα. Also, through a specific sequence between regulatory and association domains, CaMKIIβ interacts with F-actin whereas the α isoform does not (Okamoto *et al.* 2007). In an elegant set of experiments, the authors provide evidence that the different roles of the CaMKII subunits in RP are attributed to a difference in their affinities for Ca^{2+}/CaM, rather than their F-actin-binding ability.

The study by Nagasaki *et al.* opens up new questions. First, their results indicate that the ratio of α and β isoforms is sufficient to regulate synaptic plasticity. It is therefore extremely interesting and important to see the α/β ratio changes in any form of synaptic plasticity in a physiological context in Purkinje cells. In a hippocampal dissociated culture, the treatment of cells with tetrodotoxin or bicuculline regulates CaMKIIα and -β expression in opposing directions, leading to opposite effects on synaptic strength (Thiagarajan *et al.* 2002). Interestingly, CaMKIIα mRNA is found in the dendrite as well as in the cell body. This enables the rapid expression of CaMKIIα near synaptic sites, which may cause a local increase in the α/β ratio. In this way, modulation of the α/β ratio may be mechanistically important for homeostatic plasticity in hippocampal neurons.

During development, the α/β ratio changes differentially in different brain regions. At birth, CaMKIIβ levels are higher than CaMKIIα throughout the brain. However, CaMKIIα expression in the forebrain increases by ~10-fold during the second postnatal week, reaching an α/β ratio of ~3:1 in adult brain. In contrast, CaMKIIα levels are much lower in the cerebellum giving an α/β ratio of 1:3–4. In line with this, it is interesting that CaMKIIα and -β knockout mice show different phenotypes at the parallel fibre–Purkinje cell synapse, with intact LTP and impaired LTD being exhibited by CaMKIIα knockout mice, while the direction of plasticity was reversed in the CaMKIIβ knockout (van Woerden *et al.* 2009). Combined with the results from Nagasaki *et al.*, this suggests that small changes in intracellular Ca^{2+} concentration have a greater effect on the cerebellum than the hippocampus, and CaMKIIβ with its higher sensitivity for Ca^{2+} may play a more important role in regulating plasticity than CaMKIIα.

Second, what determines the decay time of CaMKII activity? The authors used chimera and deletion mutants to show that the decay time correlates with the affinity for Ca^{2+}/calmodulin. However, whether the interaction between Ca^{2+}/calmodulin and CaMKII is maintained for the duration of enhanced CaMKII activity has not been demonstrated. It is still formally possible that CaMKIIα and -β have different sensitivities to phosphatases. CaMKII can be dephosphorylated by broad-spectrum PPP family phosphatases as well as by CaMKII-specific phosphatase (CaMKIIPase/PPM1F). The relative contribution of different phosphatases in determining the time window of CaMKII activity during synaptic plasticity is a vastly underexplored area of study.

Finally, using a similar FRET construct to that used by Lee et al. (2009), it was demonstrated in hippocampal CA1 pyramidal cells that the α isoform shows transient activation in single spine stimulation. This basically changed our view of CaMKII as a long-standing memory molecule. However, Nagasaki *et al.* demonstrated that CaMKIIβ is persistently activated in Purkinje cells. It would be interesting to see how the β isoform behaves in the hippocampus.

The type of synaptic plasticity that takes place at a given time and place relies on a wide range of factors including brain region, developmental stage, neuronal activity, and source/intensity/duration of Ca^{2+}. Even in a given neuron, the strength and direction of synaptic plasticity can

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vary at different synapses. By modulating the expression level of different isoforms, Ca^{2+}/calmodulin sensitivity and association with other proteins, CaMKII may play a critical role in maintaining this diversity.

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Additional information

Competing interests

None declared.

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