CaM You Remember?

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WHAT IS CALMODULIN?

According to the Alzheimer's Association, more than 5 million Americans are living with Alzheimer's. One in three seniors die with this disease or another type of dementia. The potential to eliminate this painful disease lies within calmodulin, an intra-cellular receptor protein that is found throughout the body but functions in the brain to affect learning and memory. Calmodulin (CaM) plays a role in cell growth, proliferation and movement of electrons within the electron-transport chain. Calcium enters from the pre-synaptic side of the spine of a dendrite within the brain and binds to calmodulin causing a conformational change of the calmodulin itself. Calcium binds to the EF hand motif (a conserved helix–loop-helix sequence) found in calmodulin. The action of the calcium binding induces a conformational change to calmodulin, which forms a calmodulin-complex. An enzyme, calcium/calmodulin-dependent protein kinase II (CaMKII) binds to and activates the calmodulin-complex. Activation causes an influx in the amount of α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptors (AMPAR), which increases the amount of calcium entering the cell. Researchers believe that an increase in calcium absorbed directly impacts the durability and stability of the brain. The West Bend SMART (Students Modeling A Research Topic) modeled CaM using 3-D printing technology. Further calmodulin studies could prove to be the key to developing therapeutic treatments for mental illness, as well as finding ways to increase mental function.

THE STORY OF CALMODULIN

In 2013, Alzheimer's cost the nation $203 billion, according to the Alzheimer's Association. This number is expected to rise to $1.2 trillion by 2050. It is crucial that a solution be developed not only to save people from this terrible disease but also to save the nation trillions of dollars. The possible answer could be found in calmodulin (CaM), a protein that can be found in various cell types throughout the body. It aids in the calcium binding and sensing of other cellular proteins. Specifically in neurons, it allows for the binding of calcium and subsequent activation of other proteins that will ultimately result in more efficient neuron function and increased short and long term memory formation and retention. Current research has shown that increased calmodulin activity can lead to better overall brain function. Future research could potentially shed light into how calmodulin could be used therapeutically in the fight against Alzheimer's and other forms of dementia.

Healthy Brain

Brain with Alzheimer's

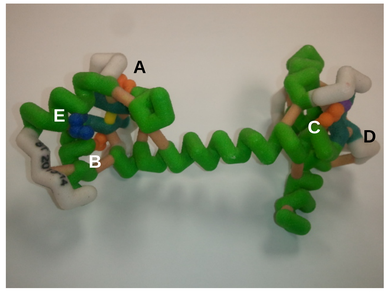
Courtesy of the University of MN Nun Study

According to the University of Minnesota Nun study, an Alzheimer's patient's brain will experience observable shrinkage as the disease progresses.

STRUCTURE OF CALMODULIN

The structure of calmodulin is shown here. Highlighted in this model are five critical binding sites. A-D shown in orange represent the glutamic acids that serve as the calcium binding sites. E shown in blue represents methionine where CaMK binds.

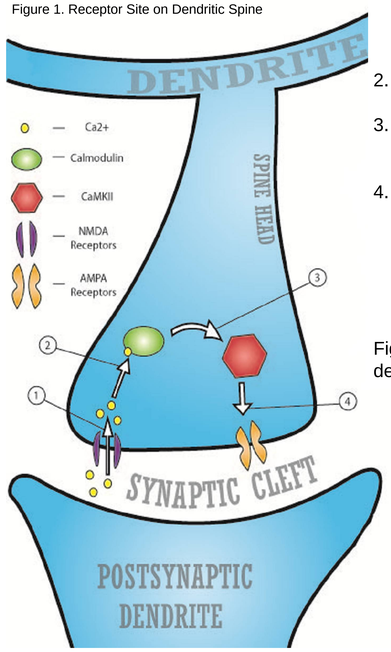
- Lime green- alpha helices
- Blue- Met 124
- Orange- Glu 31, 67, 104 and 140
- Teal- beta sheets
- Yellow- hydrogen bonds
- Grey- structural supports
- Purple- calcium ion
- White- alpha carbon backbone



3CLN.pdb

HOW DOES CALMODULIN WORK?

Figure 1. Receptor Site on Dendritic Spine



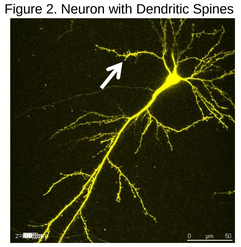
Courtesy of Nick Sanfelippo

Figure 1 models a close up view of a receptor site on the dendritic spine of a neuron.

1. Calcium is shown entering the dendrite from the synaptic cleft through the NMDA receptor (NMDAR).
2. Once calcium is inside the cell it binds with calmodulin.
3. After the calcium and calmodulin bind, this activates calcium/calmodulin-dependent protein kinase II (CaMKII).
4. This activation causes an increase in AMPA receptors (AMPAR) migrating to the membrane. This increased receptor insertion allows for more efficient neuron firing and memory formation.

Figure 2 shows a micrograph of the dendrites on a neuron.

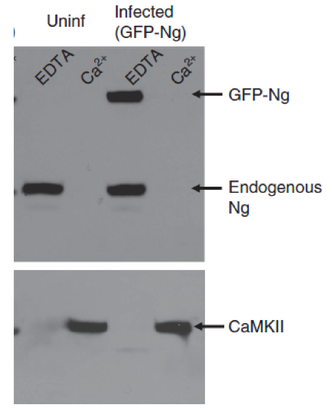
Figure 2. Neuron with Dendritic Spines



Courtesy of Audra Kramer

DATA ANALYSIS

The western blot shown here examines calcium-dependent binding of CaM to two proteins, neurogranin (Ng) and CaMKII. When CaM is calcium-bound it undergoes a conformational change. CaM-binding proteins generally only bind to either the calcium-free CaM or calcium-bound complex, not both. The presence of a band in the blot (shown bottom right) signifies protein that bound complex, not both. The presence of a band in the blot (shown top right) signifies protein that bound to CaM in either the calcium condition or EDTA, calcium free condition. Ng, both endogenous and infected, only bound CaM in the EDTA condition. CaMKII on the other hand, only bound CaM in the calcium condition. This demonstrates the reciprocal relationship between Ng and CaMKII in regards to calcium-dependent binding. This study gives insight into the function of CaM within the dendritic spine.



Courtesy of Zhong, et. al. 2009.

WHAT'S NEXT?

Calmodulin is a current focus in neuroscience research, especially in the area of cognitive disorders and memory capacity. Calmodulin activity increases neuron membrane receptors in the brain that help increase learning and memory. In addition, research suggests that the close proximity of calmodulin to the cell membrane is key for increasing neuron efficiency and that the intracellular protein neurogranin helps to maintain this localization. Not only does the activity of calmodulin matter, but its positioning within the cell as well.

Current and future research should seek to find mechanisms of shifting calmodulin localization closer to the cell membrane or to even bypass the protein altogether and still affect downstream processes, such as receptor insertion. As a result of such research, the therapeutic use or treatment of calmodulin could become an effective and efficient method by which to treat Alzheimer's and other forms of dementia. While there are countless possibilities for treatment of mental disorders, calmodulin is a relevant and current target in this field of study.

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