Cracking brain memory code

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(Medical Xpress) -- Despite a century of research, memory encoding in the brain has remained mysterious. Neuronal synaptic connection strengths are involved, but synaptic components are short-lived while memories last lifetimes. This suggests synaptic information is encoded and hard-wired at a deeper, finer-grained molecular scale.

In an article in the March 8 issue of the journal PLoS Computational Biology, physicists Travis Craddock and Jack Tuszynski of the University of Alberta, and anesthesiologist Stuart Hameroff of the University of Arizona demonstrate a plausible mechanism for encoding synaptic memory in microtubules, major components of the structural cytoskeleton within neurons.

Microtubules are cylindrical hexagonal lattice polymers of the protein tubulin, comprising 15 percent of total brain protein. Microtubules define neuronal architecture, regulate synapses, and are suggested to process information via interactive bit-like states of tubulin. But any semblance of a common code connecting microtubules to synaptic activity has been missing. Until now.

The standard experimental model for neuronal memory is long term potentiation (LTP) in which brief pre-synaptic excitation results in prolonged post-synaptic sensitivity. An essential player in LTP is the hexagonal enzyme calcium/calmodulin-dependent protein kinase II (CaMKII). Upon pre-synaptic excitation, calcium ions entering post-synaptic neurons cause the snowflake-shaped CaMKII to transform, extending sets of 6 leg-like kinase domains above and below a central

domain, the activated CaMKII resembling a double-sided insect. Each kinase domain can phosphorylate a substrate, and thus encode one bit of synaptic information. Ordered arrays of bits are termed bytes, and 6 kinase domains on one side of each CaMKII can thus phosphorylate and encode calcium-mediated synaptic inputs as 6-bit bytes. But where is the intra-neuronal substrate for memory encoding by CaMKII phosphorylation? Enter microtubules.

Using molecular modeling, Craddock et al reveal a perfect match among spatial dimensions, geometry and electrostatic binding of the insect-like CaMKII, and hexagonal lattices of tubulin proteins in microtubules. They show how CaMKII kinase domains can collectively bind and phosphorylate 6-bit bytes, resulting in hexagonally-based patterns of phosphorylated tubulins in microtubules. Craddock et al calculate enormous information capacity at low energy cost, demonstrate microtubule-associated protein logic gates, and show how patterns of phosphorylated tubulins in microtubules can control neuronal functions by triggering axonal firings, regulating synapses, and traversing scale.

Microtubules and CaMKII are ubiquitous in eukaryotic biology, extremely rich in brain neurons, and capable of connecting membrane and cytoskeletal levels of information processing. Decoding and stimulating microtubules could enable therapeutic intervention in a host of pathological processes, for example Alzheimer's disease in which microtubule disruption plays a key role, and brain injury in which microtubule activities can repair neurons and synapses.

Hameroff, senior author on the study, said: "Many neuroscience papers conclude by claiming their findings may help understand how the brain works, and treat Alzheimer's, brain injury and various neurological and psychiatric disorders. This study may actually do that. We may have a glimpse of the brain's biomolecular code for memory."

More information: Craddock TJA, Tuszynski JA, Hameroff S (2012) Cytoskeletal signaling: Is memory encoded in microtubule lattices by CaMKII phosphorylation? *PLoS Computational Biology*, doi10.1371/journal.pcbi.1002421

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