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Creating the Unforgettable: The Short Story of Mapping Long-Term Memory

Bicentennial Symposium

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Memory is a binary process relying on a short-term form lasting minutes to forge and communicate with a long-term form lasting years. Yale's Bicentennial Symposium opened with a lecture elucidating the obscure process of long-term memory formation. From his decades of research, Nobel Laureate Eric Kandel offered insight into the molecular framework that is long term-memory.

The adult human brain holds more than 100 billion neurons. In both our waking and sleeping states, a fraction of them are engaged in recalling, storing, and consolidating experiences. This process of storing, retaining, and recalling information is "memory" — a nebulous process up until only a few decades ago, when the crossroads of neuroscience and cognitive psychology pieced together a molecular and clinical appreciation. At Yale School of Medicine's Bicentennial Symposium, Eric Kandel presented his Nobel prize-winning research on long-term memory, delineating its reliance on short-term memory, its molecular make up, and its synapse-specific storage.

One form of memory — short-term memory — lasts from a few flickering seconds to several hours at most. The limited duration of short-term memory suggests a process that is not sustained or decays over time. Kandel began his lecture with an overview of his early studies into short-term memory and learning: short-term sensitization in the model organism, *Aplysia* [1]. He explored the gill-withdrawal reflex in short-term sensitization, making use of the elementary synaptic connection between motor and sensory neurons. A stim-

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†Abbreviations: cAMP, cyclic adenosine monophosphate; PKA, protein kinase A; MAPK, mitogen-activated protein kinase.

ulus applied to *Aplysia* triggers this reflex, leading to gill and siphon withdrawal from noxious stimuli. In Kandel's studies, providing a single electrical shock to the tail led to short-term sensitization, and a heightened response was noticed when he reapplied the same noxious stimuli. Furthermore, Kandel studied the direct effects of applying serotonin — a facilitating transmitter released by tail shocks — to the monosynaptic connection between motor and sensory neurons. Synaptic transmission was increased by minutes, with a spike in cyclic adenosine monophosphate (cAMP†) in the abdominal ganglion responsible for motor withdrawal. This initial ground-breaking work demonstrated that short-term memory was not contingent on new protein synthesis, but instead on phosphorylation and dephosphorylation modifications controlled through cAMP mediated pathways [2].

The possibility that such transient signaling events could give rise to long-term memories did not escape Kandel. Harnessing his previous works' findings, he applied multiple pulses of serotonin to the monosynaptic connection between sensory and motor neurons and realized that long-term facilitation — seen as an increase in cAMP levels — could be demonstrated by applying four or more serotonin pulses and would last more than 24 hours [3]. When he applied a selective protein synthesis inhibitor, rapamycin, to a dissociated cell culture of the monosynaptic motor and sensory neurons, the same long-term facilitation was blocked. This result suggested that long-term memory is transcription and translation dependent — a marked contrast from short-term memory. Interestingly, applying transcription and translation inhibitors two hours after stimulation led to no change in facilitation or sensitization. The characteristics of long-term memory were beginning to be fleshed out: Novel protein synthesis is required within a narrow window of time [4].

Nevertheless, the precise genes and transcription factors activated in long-term memory needed to be expounded. Kandel ventured into discussing how in the last decade, an accumulating body of research suggests that the cAMP response element-binding protein family (CREB) of transcription factors is integral for long-term facilitation [5,6].

Long-term facilitation requires the activation of cAMP-inducible genes through CREB transcription factors [7], which is dependent on the activation of protein kinase A (PKA) and mitogen-activated protein kinase (MAPK). Yet, a single pulse of serotonin will not stimulate CREB-mediated gene expression; four or more pulses of serotonin, however, will stimulate it [8]. It is the repeated serotonin pulses that will promote the translocation of the PKA catalytic subunit into the nucleus to activate CREB [9]. Furthermore, long-term facilitation entails the growth of new synapses [10].The exciting realization that the molecular machinery of long-term facilitation renders new synaptic connections suggests that memory is synaptically stored.

Kandel's opening lecture succinctly illustrated that long-term memory necessitates intracellular protein synthesis, extracellular changes in neurotransmitter volume, and intercellular interactions between sensory and motor neurons. Our most memorable experiences stored in our long-term memory once communicated with our short-term memory to facilitate neuron-wide transcriptional events that led to localized synaptic change. The experience of Kandel's talk were captured in his words: "You will leave with an entirely different brain than the one you entered with."

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