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cAMP and memory: A seminal lesson from *Drosophila* and *Aplysia*

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BACKGROUND

Uncovering the molecular and cellular nature of learning and memory is perhaps one of the most far reaching, yet, realistic, goals for neuroscience in the next century. This quest originates more than 30 years ago in studies of two invertebrate model systems that continue to play a central role in molecular neuroscience: *Aplysia* and *Drosophila*. The startling facet of this story is that independently—and despite using fundamentally different approaches and techniques—the studies of *Aplysia* and *Drosophila* both revealed that activation of the cyclic adenosine monophosphate (cAMP) signaling pathway played a critical role in learning and memory processes.

Because molecular neurobiology currently permeates almost every aspect of neuroscience research, it is difficult for many to imagine a time when molecular mechanisms were thought to have no direct role in cognitive processes such as learning and memory. However, even within the last 5 years, there have been several opinion papers published in top neuroscience journals deriding molecular studies of behavior, dismissing them as naïve misguided reductionism. Similarly, the very idea that specific molecular events underlie different aspects and phases of memory, and therefore that the manipulation of single genes and proteins could affect memory in specific and revealing ways, has been the subject of great debate until only recently. In the not too distant past, learning and memory was viewed as the exclusive property of complex and mysterious circuit events. In contrast, molecules were though to have a general role in memory, analogous to the role of silicon in computer chips: required because of their physical properties, but possessing no specific computational function. However, the seminal experiments outlined below changed this viewpoint forever and opened the door for much of the learning and memory research that is being conducted today.

HIGHLIGHT

In an elegant series of studies that began in the early 1970s, Eric Kandel and his colleagues at Colombia University captured in a reduced cellular preparation the essential properties of a simple form of non-associative form of learning in *Aplysia* known as sensitization (see [5]; for a more contemporary review see [2]). One key aspect of this preparation is that it is amenable to pharmacological and electrophysiological studies that were simply not possible in most other systems (see also studies in *Hermissenda* [1]).

Mild tactile stimulation of the siphon of this marine mollusc triggers a defensive withdrawal reflex that includes the retraction of the gill and siphon for a few seconds. However, after a single sensitizing stimulus (e.g., head/tail shock), the same mild tactile stimulation produces a siphon and gill withdrawal reflex that lasts significantly longer. Pharmacological and electrophysiological studies have shown that the sensitizing stimulus activates a group of modulatory interneurons (some of which are serotonergic) that in turn activate G-protein coupled receptors on the siphon sensory neurons mediating the withdrawal response. Activation of these receptors stimulates adenylate cyclase, an enzyme that synthesizes cAMP. The resulting increase in cAMP activates another enzyme (cAMP-dependent protein kinase) which phosphorylates a number of substrates that mediate both short- and long-term sensitization. Amazingly, an unbiased screen for Pavlovian conditioning mutants in *Drosophila*, initiated in the laboratory of Seymour Benzer at the California Institute of Technology in the mid-1970s, also revealed evidence for the involvement of cAMP signaling in learning and memory. In fact, three out of the four learning and memory mutations found to date in genetic screens *Drosophila* code for members of the cAMP-signaling pathway. For example, the first mutant to be discovered by Benzer and colleagues named *dunce* [4], lacks a phosphodiesterase that degrades cAMP [3]. Importantly, these findings have recently been extended into vertebrates, where electrophysiological and behavioral studies have confirmed the critical importance of cAMP signaling to learning and memory (for recent review see [6]).

SIGNIFICANCE

The elegant experiments in *Aplysia* and *Drosophila* mentioned above demonstrated that molecular explanations of memory could not be summarily dismissed. It is important to note that these pioneering studies, and the work that has followed in *Aplysia* and *Drosophila* (as well as a number of other model organisms) do not demonstrate that memory can be explained solely by molecular

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interactions. Instead, the visionary work of Kandel and Benzer cleared the way for current investigations that have already demonstrated that specific properties of memory indeed can be captured in molecular and cellular interactions.

So far, memory is the only higher cognitive function that has been extensively studied in animal systems. If memory has fallen within the tenacious embrace of reductionism, it is only a question of time before language, love and even consciousness follow. In the next 100 years, our children will bear witness to the greatest revolution mankind has ever witnessed—we will finally understand what it means to be human. Our poets may no longer have to look in dark Dostoyevskian undergrounds for the seats of our souls. They may look instead into the gentleness of *Aplysia* swaying in ancient seas and into the fluttering of *Drosophila* wings.

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