CHAPTER

1

Beyond the Cellular Alphabet of Learning and Memory in Invertebrates

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INTRODUCTION

In 1984, Hawkins and Kandel published a seminal paper titled "Is There a Cell-Biological Alphabet for Simple Forms of Learning?".[1] Based on their early findings of the cooperative regulation of adenylyl cyclase in sensory neurons of *Aplysia*, an overarching concept was presented which opened our mind to molecular mechanisms of experience-dependent neural plasticity. Several basic forms of nonassociative and associative learning (habituation, sensitization, and classical conditioning) were explained on the level of rather simple molecular reaction cascades in specific neurons. At that time, these were radical ideas, and even today we struggle with the question whether cognitive faculties such as learning and memory formation can be reduced to ubiquitous cellular functions, and what such a reduction might mean. The concepts presented in this paper were also radical in the sense that they broke with the speculation that the information of acquired memories is stored in molecules like RNA. Meanwhile, it is well accepted in neuroscience that neural circuits acquire new information by changing network properties on the level of specified neurons and their synaptic connections. Multiple key elements contribute to these adaptations, and it is the task of today's neuroscience to unravel the complex hierarchies of interactions from the molecular to the systems level in solving the problem of predicting future behavior from experience in the past.

Invertebrate nervous systems, because of their relative simplicity, offer significant advantages for multidisciplinary molecular, cellular, genetic, and behavioral investigations of the mechanisms underlying learning, memory formation, and memory retrieval. Memory formation in invertebrates occurs within small circuits containing a few hundred neurons rather than the millions of the mammalian brain, and it is often possible to study the role of individual neurons that play a key role in these adaptive neural processes. Because of this tractability of invertebrate model systems, many important discoveries have been made in invertebrates (e.g., the role of second messengers such as cAMP, protein kinases, and transcription factors such as CREB (Chapters 15−18, 20, 27, 31, and 35); the role of neural plasticity in addition to and separate from synaptic plasticity (Chapters 14, 15, 19, 20, and 35); the function of identified neurons in the evaluating pathways (examples in many chapters in Section 4); and the differential role of circuits in storing and retrieving memory (Chapters 27, 29, and 31)) that have been found to be generally applicable to higher organisms. The discovery that synaptic plasticity involves both pre- and postsynaptic interactive processes characteristic of Hebbian long-term potentiation in vertebrates again emphasizes the general importance of the results from invertebrate systems (Chapters 17 and 24). Furthermore, a good deal of information is emerging on the molecular and neural mechanisms underlying the different phases of memory consolidation (from short-term to intermediate-term and long-term memory). Training triggers a cascade of molecular events with phase-dependent requirements for protein kinases (Chapters 16−18, 27, 31, and 35) and neuropeptides (Chapter 17). A fascinating recent discovery is that a self-sustaining prion-like protein ApCPEB (*Aplysia* cytoplasmic polyadenylation element binding protein) is involved in memory maintenance promoting persistent facilitation of synaptic transmission (Chapter 17).

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BEYOND THE CELLULAR ALPHABET: CIRCUIT AND NETWORK LEVELS OF ANALYSIS, THE NECESSARY STEP

The previous cellular studies emphasized changes at a single locus. However, there is increasing evidence that most forms of learning in invertebrates involve changes at multiple sites in the brain (e.g., Chapters 14, 19, 25, 27, and 29). The identification of these multiple sites of plasticity requires a systems approach to the analysis of learning and memory, which makes it important to first identify the electrical changes that result from training and then attempt to relate these changes to behavioral plasticity. The role of individual neurons and their synaptic connectivity can then be investigated in the context of behavior in a 'top-down' approach. The ability to identify changes in sensory, interneuronal, and motoneuron pathways contributing to the learning process has been one of the successes of this systems approach to invertebrate learning and memory. From this work, it is realized that we cannot hope to understand the nature of the 'engram' without a knowledge of the electrical and cellular changes at all levels of the networks involved in establishing and retrieving the engram (Chapters 14, 19, 29, and 36). This systems analysis is far from complete, especially in the more complex behaviors of social insects and cephalopod mollusks, but considerable progress has been made. Computational modeling of learning networks is an important component of the systems approach (Chapter 7), and links to robotics (Chapter 8) are providing a complementary type of approach to understanding adaptive behavior in invertebrates.

Will it be ever possible to "read" the content of the memory trace, the engram? This question requires a shift from the analysis of mechanisms to that of processes. Finally, we want to understand where and how particular memory contents are stored, and how they are activated for behavioral control. A helpful but rather simple-minded approach is to visualize the changes of neural functions in the course of learning. Such an approach is manifested in the search for structural plasticity as induced during long-term memory formation (Chapter 31) or in the calculation of changes of patterns in neural activity before and after learning (Chapters 14, 20, and 29). These patterns of changes, both in time and in space, should constitute the engram as read by the complete nervous system of the respective animal, and may be even accessible to the human mind for elementary forms of learning that lead to memory traces in restricted parts of the nervous system. However, even in invertebrates the engram will usually involve several to many circuits distributed throughout the nervous system, making it very difficult to relate stored information to neural circuits. The conceptual and experimental problems should not demotivate us to hunt for the engram by shifting our attempts from single neuron analysis to network analyses. Indeed, such a shift appears achievable with molecular-genetic techniques in *Caenorhabditis elegans* (Chapters 9—13) and *Drosophila* (Chapters 5 and 27).

DO INVERTEBRATES HAVE COGNITIVE ABILITIES?

Despite having small brains, invertebrates show a remarkable ability to carry out complex tasks in their natural environment, to learn and to form long-term memory through stepwise consolidation processes. Suggesting that invertebrate animals have cognitive abilities implies that they have sophisticated behavioral capabilities that transcend the elementary forms of adaptive responses to environmental changes. It requires the selection of different options from a repertoire of learned behaviors that allows an animal to respond selectively to novel external stimuli. It is clear that insects, particularly social insects, have this kind of capability (Chapter 3) but also cephalopod mollusks (Chapters 23 and 25) and perhaps terrestrial slugs (Chapter 22). It is interesting that all three groups of animals have special learning 'centers' in the brains (mushroom body in insects, vertical lobes in octopus, and procerebral lobes in terrestrial slugs) with intricate interneuronal organization that would be required for complex information processing at the neural level. Cognitive behavior is suggested by examples of exploration, instrumental and observation learning, expectation, learning in a social context, and planning of future actions (Chapters 3, 23, and 25). In some examples, such as second-order conditioning, it is possible to suggest neural network mechanisms derived from the neural network models of simple forms of first-order conditioning (Chapter 14), but in most examples we have little or no knowledge of the neural mechanisms involved. Computational modeling where explicit mechanisms have to be proposed may be useful here (Chapters 7 and 8). Until we have more detailed information on the mechanisms and processes involved in examples of cognitive behaviors, it will be difficult to know whether cognitive mechanisms have unique information processing compared with 'noncognitive' adaptive behaviors. Could it be that the most complex forms of invertebrate cognitive behavior represent a loop too difficult to close in terms of neural mechanisms? As in other disciplines, cognitive neuroscience advances depend on new methods and new concepts, probably in this order. Invertebrate neuroscience works at the forefront of both aspects, methods and concepts (Chapters 5, 6, and 8). Transgenic or transfected animals will offer opportunities particularly when combined with recording techniques. We are facing an exciting future of invertebrate neuroscience, and we hope this volume will help to prepare for these endeavors.

Reference

1. Hawkins RD, Kandel ER. Is there a cell-biological alphabet for simple forms of learning? *Psychol Rev*. 1984;91:375–391.