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Associative learning and monoamine signaling in the sea anemone Nematostella vectensis

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The nervous system is an essential feature of most animals, allowing for remarkable adaptive capacities, as well as complex behavioral and cognitive abilities. Although this complex network of specialized cells – neurons – plays a crucial role in animals, numerous intriguing questions persist regarding its origin and evolution. To address such questions, one approach relies on the comparison of features of distantly related clades in order to make assumptions on their last common ancestor. Cnidarian species, such as sea anemones and jellyfish, possess a nerve net, but lack centralization. As the sister group to bilaterian animals, they are particularly well-suited for studying the evolution of neurons and nervous systems. However, whilst progress has been made in describing the development of nerve nets, the molecular mechanisms underlying behavior remain poorly understood.

Here, we implemented methods to track and analyze the behavior of the sea anemone *Nematostella vectensis* to further probe its capacity to form associative memories. By showing that this brainless sea anemone can learn using an aversive conditioning approach, we not only shed light on a novel aspect of cnidarian behavior, but also root associative learning before the emergence of central nervous systems in bilaterians.

Monoamines, like dopamine or serotonin, are essential neuromodulators required for cognitive functions such as learning and memory formation, as well as fundamental homeostatic processes such as sleep and feeding. Similarly, the evolutionary origin of the genes required for monoaminergic modulation is uncertain. Using a phylogenomic approach, we showed that most of the genes involved in monoamine production, modulation, and reception originated in the bilaterian stem group. Despite this assertion, we uncover the expression of a key dopamine synthesis enzyme, as well as two putative dopamine receptors, in the nervous system and pharyngeal cells of *Nematostella vectensis* polyps. Thus, our results suggest that some elements may be present and expressed in cnidarian neurons, drawing a complex picture on the evolution of the role of monoamines in animals.

Altogether, this work highlights the unexpected complexity of the "simple" nerve nets of these brainless animals, and provides valuable insights on the ancestral characteristics of the first nervous systems.

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