·Minireview·

Molecular control of memory in nematode *Caenorhabditis elegans*

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Abstract: Model invertebrate organism *Caenorhabditis elegans* has become an ideal model to unravel the complex processes of memory. *C. elegans* has three simple forms of memory: memory for thermosensation, memory for chemosensation, and memory for mechanosensation. In the form of memory for mechanosensation, short-term memory, intermediate-term memory, and long-term memory have been extensively studied. The short-term memory and intermediate-term memory may occur in the presynaptic sensory neurons, whereas the long-term memory may occur in the postsynaptic interneurons. This review will discuss the recent progress on genetic and molecular regulation of memory in *C. elegans*.

Keywords: memory; molecular mechanism; *Caenorhabditis elegans*; model invertebrate organism

Memory, one of the important properties of central nerve system (CNS), is defined as encoding, storage and retrieval of learned inputs. However, many complex processes of memory still need further scientific explanations. Invertebrate animals have been already widely accepted as successful organisms for the study of neuroscience, and many important discoveries on behavioral cognitive science were made in the model invertebrate animals[1,2]. Model invertebrate organisms such as *Caenorhabditis elegans* and *Drosophila melanogaster* have provided powerful genetic approaches to a series of central questions concerning neural development, learning and memory, and the cellular and molecular substrates of behaviors[3-4]. In this review, we will discuss the recent progress on the molecular control of memory based on the studies of model organism *C. elegans*, via different paradigms in which diverse environmental clues are involved.

C. elegans has become an ideal organism model to unravel the complex processes of learning and memory[5]. Besides its extensively anatomical knowledge, the neural circuit of the worm can be analyzed by the technique of laser ablation for identified neurons. Its entire genome has been mapped and sequenced, which allow us to use the methods of systematic forward or reverse genetic screen to elucidate the molecular mechanisms of memory. Especially, *C. elegans* displays simple forms of memory, such as thermotaxis, chemotaxis and mechanotransdution[5].

1 Memory for thermosensation

C. elegans depends on environmental temperature to sense and search food. Therefore thermotaxis may be the most powerful behavioral paradigm for elucidating the memory mechanism underlying this behavioral plasticity. That model gives an association between the temperature encoded into memory and the nutritional state, and the temperature-food association can be kept for a long period[6]. This thermosensory system exhibits properties of exquisite temperature sensitivity [storage of the thermotactic set-point (T_s)], long-term plasticity (comparison of current temperature with the T_s), and the ability to transform thermosensory input into different patterns of motor neurons (measurement of thermal gradients during movement). In brief, the animals adjust a stored set-point of thermotactic memory to their cultivation temperature (T_{cult}) and the AFD (a sensory neuron)-AIY (an

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interneuron, the major postsynaptic partner of AFD)-AIZ (an interneuron, the major postsynaptic partner of AIY) neuron circuit: the AFD and AIY neurons specify the thermophilic components of the circuit, driving movement to higher temperatures in a thermal gradient; the AIY and AIZ neurons specify the cryophilic components of the circuit, driving movement to lower temperatures in a thermal gradient[7].

The time-course assay of thermotaxis suggested that a new temperature encoding is a relative long process, and which appears to be independent of cultivation temperature[6]. In addition, starvation can accelerate the memory formation for new temperature, and the memory formation for temperature and for feeding state are discrete processes[6]. Nevertheless, the long-term plasticity for isothermal tracking does not involve association between temperature and food, and the thermotactic set-point reflects a simple integration over temperature history[8].

Genetic analyses have identified a number of genes involved in thermosensation control. Among these genes, the functional neuron-specific calcium sensor-1 (*ncs-1*) appears to be very crucial for memory maintenance. The *ncs-1* knockout animals performed an irregular IT behavior[4] and a defect of faster extinction (Wang *et al*., personal communication). This abnormal thermotactic phenotype could be rescued by recopy wild type *ncs-1* into AIY interneurons, and *ncs-1* over-expression could largely slowed the extinction[4].

The memory of cultivation temperature can be reset by cultivating adult animals at one temperature and then shifting them to a new temperature for a sustained period. Recently, Biron *et al*. found that diacylglycerol kinase 3 (DGK-3) modulated the rate of adaptation to new temperatures by observing animals' ability to reset the thermal memory after sustained exposure to new temperatures[8]. The *dgk-3* mutants showed a lower thermotactic set-point (T*c*) than wild-type animals, and set-point shifts were more slowly or faster relative to wild-type animals when *dgk-3* mutants were transferred from 15 °C to 25 °C or from 25 °C to15 °C, respectively. The transgenic animals which had high DGK-3 activity due to deletion of calcium-binding motifs exhibited altered rate of themotactic set-point resetting. DGK-3 was identified as a thermal molecule that regulates the rate of thermotactic resetting by modulating the temperature range of synaptic output, but not temperature sensitivity, of the AFD thermosensory neurons. Therefore, the enzymatic activity levels of DGK-3, in particular the levels of diacylglycerol (DAG) in the AFD neurons, control the rate of thermal memory resetting, which provide the first mechanistic insight into the basis of experience-dependent plasticity in this complex behavior.

C. elegans senses and remembers its T*c*, and this memory modulates animal's behaviors on specific thermal gradients. Satterlee *et al*. revealed an additional possible mechanism for sensation and/or memory of the T*c* of AFD neurons[9]. Ca^{2+}/calmodulin-dependent protein kinase I (CMK-1) and abnormal chemotaxis (TAX-4) cyclic nucleotide-gated channel regulate gene expression, morphology, and functions of AFD neurons at different growth temperatures. The authors raised a hypothesis that the sensation and/or store of T*c* is through CMK-1 and TAX-4 to activate distinct programs of gene expression in the AFD neurons at different temperatures during development. Besides, additional mechanisms may also play roles in setting or maintaining the T*c* memory, since the T*c* can be reset by shifting adult animals to different temperatures for short periods or by starvation.

The memory could last for hours, which suggests that dynamic changes may occur on neuronal activity and synaptic strength. The small size and transparency make the nematode an ideal system for noninvasive, optical measurements of neuronal activity. Clark *et al*. (2007) used a high signal-to-noise version of cameleon, a fluorescent calcium-binding protein, to quantify the activity of AFD thermosensory neurons and found that AFD activity is directly coupled to the worm's exploratory movements in spatial thermal gradients[10]. Kimura *et al*. examined the changes in intracellular Ca^{2+} concentration in AFD neuron and found that Ca^{2+} concentration increased responding to warming[11]. Thus, a major part, if not all, of the transient $[Ca^{2+}]_i$ increase in AFD neuron depends on the temperature-sensing molecular pathway including TAX-4. It was for the first time to indicate that the temperature memory is stored within a thermosensory neuron as a threshold temperature to the thermal stimuli. Of course, it is also likely that it may require the activity of other neurons such as downstream neurons of the thermotaxis circuit. Samuel *et al*. also measured the synaptic release of AFD in worms cultivated at temperatures between 15 °C and 25 °C by monitoring fluorescence of the pH-sensitive green fluorescent protein localized to synaptic vesicle. They found

that the rate of AFD synaptic release was high when ambient temperature was not equal to cultivated temperature, but low when the two temperatures were close, suggesting that AFD may encode a direct comparison between ambient temperature and the memory of cultivation temperature[12].

2 Memory for chemosensation

Memory components involve the chemosensory plasticity as well. Starvation can increase the olfactory adaptation to odorant benzaldehyde, and this effect of starvation maintained for at least 3 h after the animals had returned to be fed[13]. In addition, starvation can enhance olfactory memory, because starvation inhibits worms' recovery from adaptation to a different odorant, 2-methylpyrazine[13]. The effect of starvation is also antagonized by exogenous serotonin[13]. Moreover, pre-exposure to calcium chelator induced a deficit in olfactory adaptation, indicating that calcium influx plays a crucial role for animals to remember previous odorant exposure[14]. A putative ion channel with structural similarity to the fly transient receptor potential (TRP) channel may mediates this process[13].

Olfactory imprinting is a process that exposure of animals to olfactory cues during specific and restricted time windows will leave a permanent memory, occurring in contexts as diverse as homing behavior in salmon and neonatal mammals. Remy and Hobert found that *C. elegans* exhibited a form of olfactory imprinting by assaying the odorant attraction in the adult animals who exposed to a specific odorant over defined developmental time windows[15]. That is, exposure of juvenile animals to benzaldehyde results in enhanced memory of the odor in adult stage. Moreover, pre-exposure of worms to the odorant of benzaldehyde at a specific developmental stage significantly improves the ability of adult worms to migrate toward a benzaldehyde source presented at moderately attractive concentrations. Addition of exogenous serotonin, which can mimics the presence of food in various sensory paradigms, into the food-free agar plates can restore olfactory imprinting; whereas another monoamine, octopamine, can not compensate for food deprivation. If animals were starved and exposed to benzaldehyde and serotonin at adult stage, no improvement could be observed in the subsequent odorant attraction assay. Therefore, a potential function of olfactory imprinting is to memorize their favorable growth conditions. Furthermore, olfactory imprinting requires a single interneuron pair (AIY) that is postsynaptic to olfactory neurons such as AWC (The AWC and AIY neurons specify the olfactory behaviors to benzaldehyde). It is only functioned in AIY interneuron as confirmed by abnormal thermotaxis (*ttx-3*) mutant which is lack of AIY function. The serpentine receptor class A (alpha) gene (*sra-11*) which encodes an orphan G-protein-coupled seven-transmembrane receptor is specifically required for this imprinting behavior. The SRA-11 may have a role in determining aspects of AWC-AIY connectivity that may be modulated upon olfactory imprinting. These studies provided insight into the cellular and molecular basis of olfactory imprinting and revealed a function for a chemosensory receptor family member in AIY interneuron.

3 Memory for mechanosensation

C. elegans can sense tactile (head and tail touch) and vibrational (tap) stimuli. The neuronal circuit for "head-touch", including the anterior mechanosensory neurons (two ALMs and AVM), drives the reversal response; while the neuronal circuit for "tail-touch", including the posterior mechanosensory neurons (two PLMs), drives the acceleration response. Habituation includes the sensitivity to intensity, stimulation frequency, and spontaneous recovery. *C. elegans* shows short-term memory in the form of habituation, shows long-term memory in the form of retention of the habituated response for at least 24 h after training, and shows intermediate memory in the form of retraining of habituated response. Works on mechanotransduction have shed new light on molecular control of memory in *C. elegans*.

3.1 Short-term memory for habituation Short-term memory can be studied by analyzing the kinetics of worms' habituation to tap stimuli presented at different interstimuli intervals (ISI). To measure short-term memory, animals are given a series of taps at a predetermined ISI; and then three test taps at the same time points following the end of training (30 s, 10 min, and 20 min) are given to determine the rate of spontaneous recovery from habituation. Short-term memory can be determined by the rate of habituation and recovery speed. Short ISI training exhibits a rapid habituation and spontaneous recovery, whereas long ISIs training produces a slower but longer habituation.

Rankin and Wicks (2000) found that *eat-4* (eating) mutant animals habituated more rapidly and recovered more

slowly than wild-type animals at all tested ISI, and did not show dishabtuation[16]. The *eat-4* mutation did not affect the response to a single tap; however, it had a significant effect on the responses to repeated stimulation. EAT-4 is a glutamate transporter, and may be required for glutamatergic neurotransmission in *C. elegans*. The results suggest that the neurotransmitter glutamate may play an important role in short-term memory. EAT-4 may be involved in regulating the amount of neurotransmitter available at the sensory neuron terminals, and the synapse between tap sensory neurons and interneurons might be the site of mechanosensory habituation and spontaneous recovery.

Steidl *et al*. also have obtained interesting preliminary results from mutations in an inhibitory glutamate receptor, altered avermectin sensitivity-14 (*avr-14*). The *avr-14* null mutants trained at a short ISI (10 s) showed enhanced habituation with a greater decrease in responding compared with wild type controls, whereas animals trained at a long ISI (60 s) appeared to exhibit habituation similar to wild type[17]. Therefore, there may be separate genetic mechanisms underlying different types of short-term memory.

3.2 Intermediate memory for habituation The intermediate form of memory in *C. elegans* is called retraining memory, which has been observed in two types of behavioral experiments: context-conditioning experiments and long-term memory experiments. If animals were habituated in presence of a distinctive environmental cue such as a chemical taste (contextual cue) and then were rehabituated in presence of that cue an hour later, there was greater retention of the habituation training than if they were tested without the context cue being present[19]. These experiments showed that retraining memory was present at both a 10-s and a 60-s ISI and can be enhanced by context. The retraining memory for habituation depends neither on protein synthesis, since heat shock had no effect on the accumulation of habituation across blocks of training; nor on glutamate transmission, since distributed training blocks for *eat-4* and *glr-1* (glutamate receptor family) animals showed normal or even enhanced accumulation of short-term habituation[18]. The greater retention of habituation training in the worms that have been habituated in presence of contextual cue will disappear when animals are exposed to the context cue for the 1 h prior to training or exposed to the cue for the 1 h rest period between habituation training and testing[19]. Therefore, the retraining memory for habituation can be described as a separate process that occurs at both short and long ISIs. It reflects a non-protein (glutamate)-synthesis dependent form of memory and is enhanced by the context in *C. elegans*[20]. Nevertheless, the relationship between retraining memory and short-term memory remains largely unknown.

3.3 Long-term memory for habituation Long-term memory, the retention of learning for more than 24 h, is mediated by cellular processes that engaged during or soon after the training. Beck and Rankin found that memory consolidation was disrupted by heat shock (32 °C, 45 min) during but not before or after training, and demonstrating that long-term memory for habituation training is protein synthesis dependent, and heat shock can be used as a fine-grained tool to investigate the dynamics of memory consolidation in *C. elegans*[18, 21]. Similarly, a pretraining cold shock in the 30 min before conditioning and a posttraining cold shock in the 30 min after conditioning both disrupt the memory processes tested short after conditioning[22].

For the molecular control of long-term memory, glutamate release from the sensory neurons has been proved to have an important role in the formation of long-term memory for habituation[18]. Although *eat-4* mutant animals showed enhanced short-term habituation[16], they had no 24-h retention of habituation training when trained with taps[18]. Nevertheless, if a stronger stimulus was used for training and testing, long-term memory for training could be seen, suggesting that long-term memory does rely on glutamate transmission. That is, when a strong enough stimulus is used for training, it may lead to sufficient glutamate release, and result in long-term memory.

The hypothesis that glutamate transmission is required for long-term memory formation is further supported by the study from Rose *et al.* (2003). Mutation of *glr-1* caused no long-term memory for distributed training regardless of whether a tap or a train of taps was used as the habituation training stimulus[23]. Trained animals had less GLR-1::GFP expression than untrained animals[23]. Heat shock during training blocked both the behavioral expression of long-term memory and the changes in GLR-1::GFP expression, demonstrating that long-term memory is dependent on GLR-1 and likely involves changes of the expression or localization of glutamate receptors.

Consolidated memories can return to a labile state when

a process of re-storage termed reconsolidation is reactivated. Rose and Rankin demonstrated that adult worms retained reliable memory 48 h later after habituation training[24]. Response magnitudes of trained animals matched response levels of untrained animals when heat shock was administered immediately after a reminder, suggesting that the inhibitory effects of heat shock on protein synthesis disrupt memory reconsolidation. Pharmacological blockade of non-NMDA (*N*-methyl-D-aspartic acid) type glutamate receptors with 6, 7-dinitroquinoxaline-2,3-dione (DNQX) during reminder also eliminated the 48-h retention. Furthermore, the expression level of specific glutamate receptor subunit (GLR-1) decreased significantly in trained animals compared with untrained controls, and the effect of training on GLR-1 levels was reversed if the trained animals were given a reminder immediately followed by heat shock[24]. Therefore, both the behavioral expression of long-term memory for habituation and a cellular correlation of that memory can be altered after retrieval in *C. elegans*[24]. In addition, similar mechanisms are involved in the control of memory consolidation and memory reconsolidation, since conditions that impair memory consolidation similarly disrupt memory reconsolidation[24]. These findings also confirm the previous observation that GLR-1 cluster density was closely correlated with the expression of memory for habituation.

Because recall of a memory can return it to a labile state and make it sensitive to some of the same initial consolidation factors, inhibiting this reconsolidation process by blockade of transcription or translation would abolish the memory. Ebrahimi and Rankin tested the response depression in 5-day-old worms and found that it was sensitive to reconsolidation blockade, suggesting that the recall of the memory to tap stimulus returned it to a labile state and it is thus sensitive to elimination[25]. Moreover, this sensitivity could be observed even when the time interval between initial stimulus and reminder tap delivery increased, suggesting that the older memories are also sensitive to reconsolidation blockade[25].

4 Conclusion

The phases of memory have been systematically studied by behavioral, neural circuit, and genetic analyses in *C. elegans*. In this review, we summarized the recent progresses as shown in Fig. 1. From these progresses, the short-term memory in *C. elegans* can be considered as a number of processes activated differentially by the temporal characteristics of training; the intermediate-term memory or retraining memory can be seen as the effects of previous habituation training on later training; while the long-term memory is a glutamate-mediated, protein synthesis dependent memory produced by distributed training and lasts for at least 24 h. Short-term memory and retraining memory may occur in the presynaptic sensory neurons, while long-term memory may occur in the postsynaptic interneurons.

Thus far, some important events underlying the control of short-term memory and long-term memory have been revealed in nematodes. However, the molecular mechanisms of memory in *C. elegans* are still largely unclear, and some more questions are still waiting for answering. First, we have not obtained a relatively complete network pathway controlling the short-term memory and long-term memory. Second, whether the memory behaviors are also under the epigenetic control? Third, what are the exact roles of synaptic activity in the regulation of short-term memory and long-term memory? Fourth, what's the possible relationship between the regulation of synaptic assembly or synaptic function with memory control? Fifth, what are the possible effects on the memory behaviors in animals with mutations on the synthesis, transportation, or receptor functions of different neurotransmitter? Sixth, which neurons are directly involved in the control of memory behaviors? Seventh, what are the possible upstream or downstream molecules of identified important proteins involved in the memory control, such as the NMDA-receptor? The systematic analysis of genetic interactions and physical interactions corresponding to the genes constituting the relative key and conserved signaling pathways will largely help us answer these questions.

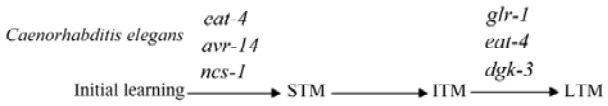

Fig.1 Molecular control of memory in *Caenorhabditis elegans*. Genes involved in the control of short-term memory (STM), intermediate memory (ITM), and long-term memory (LTM) are listed, respectively.

Although invertebrate model organisms have simple nervous systems, referring to fewer neurons or simple neuronal structure, worms can also exhibit similar behavior to

vertebrate. Moreover, invertebrates and vertebrates can share many similar cellular and molecular mechanisms in neuronal control, such as neurotransmission and behavioral plasticity. The very similar functions and regulation mechanisms in nematodes would give contributions to our understanding for the molecular control of memory in vertebrates. Memory is a complex and integrated process involving many aspects, and many problems await full understanding. The two classical invertebrate model systems, such as worm and fly, will provide powerful approaches to cognitive neuroscience, and the extensive studies from these two organisms have already brought light to this field. With the progresses on genetic and genomic strategies, it is conceivable that a comprehensive understanding of the cellular and molecular complexity of memory could be dissected.

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秀丽线虫记忆的分子调控机制

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摘要：模式无脊椎动物秀丽线虫已经成为揭示记忆复杂行为的理想研究模型之一。线虫具有三种简单的记忆形式：对温度感知的记忆、对化学物质感知的记忆以及对于机械刺激感知的记忆。在对机械刺激感知的记忆研究中，短时程、中时程与长时程记忆均得到了系统的分析。其中短时程与中时程记忆可能定位于感觉神经元的前突触，而长时程记忆可能定位于中间神经元的后突触。本文针对线虫中记忆的遗传与分子调控机制近些年的研究进展进行了总结与讨论。

关键词：记忆；分子机制；秀丽线虫；无脊椎模式动物