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Behavioral plasticity, learning, and memory in *C. elegans*

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Caenorhabditis elegans exhibits behavior plasticity that appears to correspond to non-associative and associative learning, and short-term and long-term memory. Recent finding revealed that evolutionally conserved molecules such as insulin, monoamines, and neuropeptides are required for the plasticity. We propose the concept of human brain operation from the *C. elegans* studies.

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Introduction

Learning and memory are fundamental biological properties that appeared to be acquired in the early era of animal evolution. Because of simple neuronal circuits and easy access to experiments, invertebrates have played an important role in understanding the biological basis of learning and memory. Studies on *Aplysia* and *Hermissenda* revealed the essential mechanism of synaptic plasticity [1,2]. Similarly, the behavioral molecular genetics in *Drosophila* and *Caenorhabditis elegans* greatly advanced our knowledge on the nervous system [3–5]. Invertebrate studies found neural logic commonly used throughout evolution [1,4,6,7].

Much of neurotransmitters and neuronal modulators used in *C. elegans* such as acetylcholine, glutamate, dopamine, serotonin, GABA, and neuropeptides are amazingly similar to those used in mammals [8]. Genome project revealed that genes required for neuronal development and function are also highly homologous to mammalian genes [9,10]. Rapidly advanced technologies such as calcium imaging and optogenetics are particularly accessible to the *C. elegans* nervous system, thereby enabling the worm researchers to extensively study dynamics of neurons and circuits. Classical forward and reverse genetics became much more powerful, with help of whole genome sequencing and RNAi knockdown experiments. These advantages of *C. elegans* allow comprehensive and high-resolution studies for understanding human brain and neuronal disorders.

C. elegans apparently exhibits behaviors that reflect learning and memory (Figure 1) [11–19]. In this review, we focus on some of the recent works on behavioral plasticity, learning and memory in *C. elegans*.

Associative learning between salt and food

C. elegans eats bacteria as nutriment [5]. Presence or absence of food is a determinant that largely affects behavior of *C. elegans*. Hence, various behavioral strategies had been evolved to obtain food effectively [11–22].

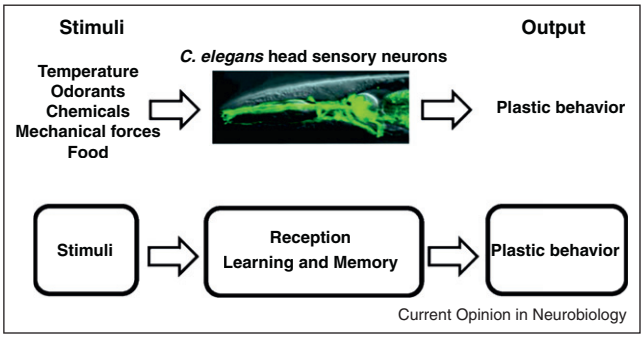
C. elegans exhibits chemotaxis to water-soluble attractant NaCl that is sensed by ASE neurons. Two ASE neurons are developmentally and functionally asymmetric: the ASER preferentially detects Cl^- and is stimulated by decreases in NaCl concentration (OFF cell), while the ASEL preferentially detects Na^+ and is stimulated by increases in NaCl concentration (ON cell) [16,23–25]. *C. elegans* subjected to prolonged exposure to NaCl under starvation condition showed a dramatic reduction of chemotaxis to NaCl and eventually a negative chemotaxis against NaCl [26]. Exposure to NaCl in the presence of food does not lead to a reduction of chemotaxis, suggesting that salt chemotaxis learning occurs between NaCl and starvation [26]. G-protein, Ca^{2+}, and cGMP pathway are involved in similar gustatory plasticity [27,28].

Insulin/PI3-kinase pathway also regulates salt chemotaxis plasticity. INS-1, an insulin-like peptide, is secreted from AIA interneuron and feeds back to salt receptor neuron ASER. INS-1 then activates phosphoinositide 3-kinase (PI3K) pathway in ASER through insulin receptor DAF-2, thereby modulating the neural activity of ASER, further leading to determine the final orientation of salt chemotaxis learning (Figure 2) [29].

CASY-1, an ortholog of calsyntenins (alcadeins) that is associated with episodic memory performance in human, is essential for salt chemotaxis learning [30••]. CASY-1 is a transmembrane protein carrying two tandem cadherin domains and LG/LNS domain in the ectodomain. The expression of CASY-1 in ASER and the ectodomain released by cleavage of CASY-1 are required for salt chemotaxis learning (Figure 2) [30••].

HEN-1, a secreted protein with an LDL receptor motif involved in integration processing between copper ion and odorants, is also known to control salt chemotaxis learning [31].

Figure 1



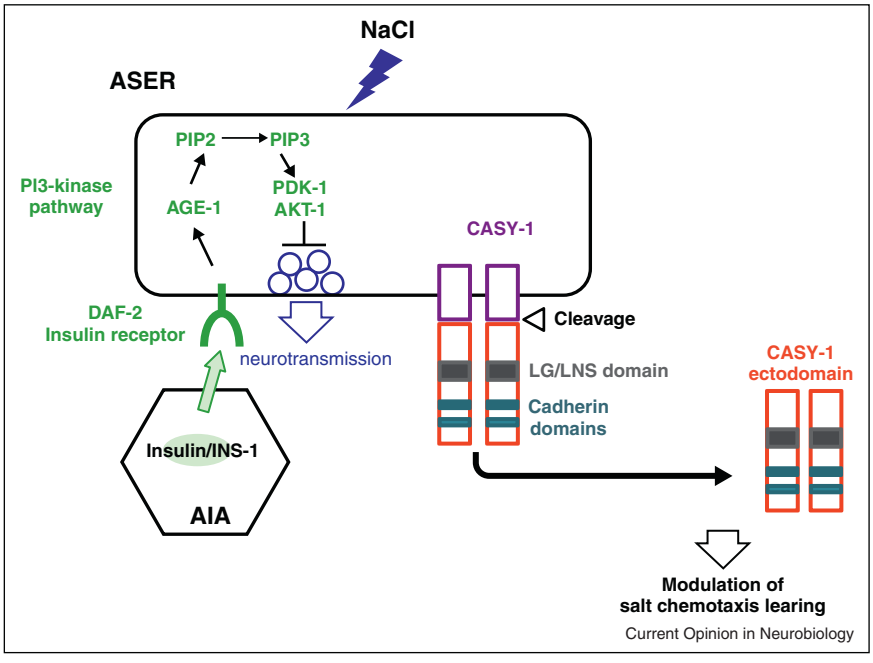
Conceptual scheme for learning and memory-based plastic behavior. A variety of behavioral plasticity is observed. Animals sense different environmental stimuli through sensory system. Multi information is processed and integrated in the nervous system. On the basis of learning and memory, plasticity in behavior is generated. Photograph shows the *C. elegans* head sensory neurons visualized with GFP. Cell bodies of sensory neurons, such as olfactory, taste, and thermosensory neurons make ganglia. They extend the dendrites to the tip of head and project axons to the nerve ring where synaptic connections to other neurons are formed.

Associative learning between temperature and food

C. elegans associates past cultivation temperature with food. After animals were cultivated with food at a certain temperature ranging from 15°C to 25°C and placed on agar surface with a temperature gradient, they migrate and move isothermally near the past cultivation temperature. When animals were recultivated at a new temperature with food for two to four hours, they migrate to that new cultivation temperature [32]. Dynamic alternation of temperature preference is also observed in the absence of food. Cultivation without food at a certain temperature for several hours induces animals to disperse or avoid the past cultivation temperature [32–35]. The neural circuit that critically regulates thermotaxis is quite simple and ideal for dissecting neural plasticity (Figure 3) [18,22].

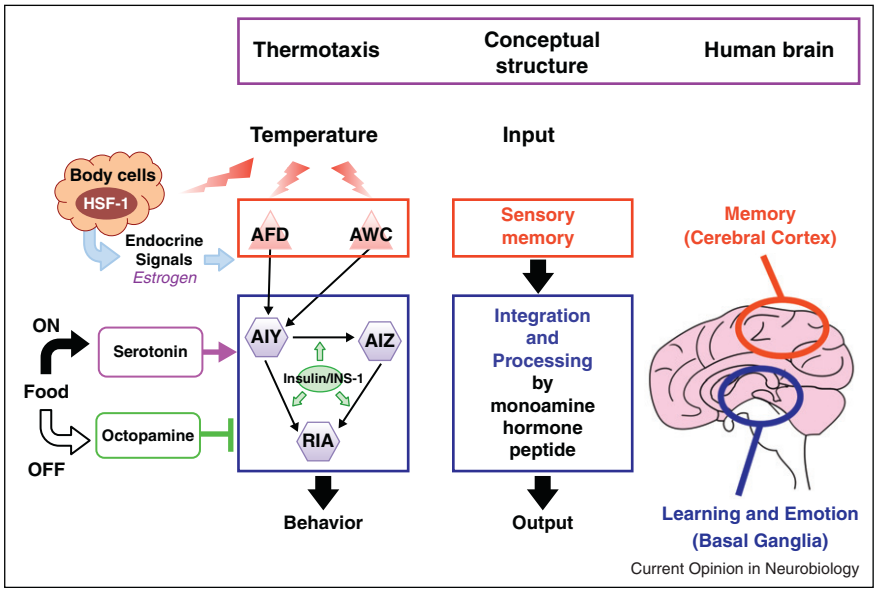
Molecular genetic analysis identified several molecules required for food associated thermotactic plasticity. For example, an ortholog of human calcineurin alpha subunit TAX-6 is required in two pairs of interneuron, AIZ, and RIA [36]. Similarly, a novel hydrolase AHO-3 is required in AWC neurons for food associated thermotactic plasticity [35]. A human homolog of AHO-3, FAM108B1 expressed in brain, restored the defect in *aho-3* mutants, which suggests that this novel type of hydrolase is functionally conserved from *C. elegans* to human. Although the role of AHO-3 remains to be further elucidated, palmitoylation of N-terminal cysteine cluster was found to be essential for the food associated thermotactic plasticity. Since ABHD12, an AHO-3 related protein in *C. elegans*

Figure 2



Proposed model for the regulation of salt chemotaxis learning by insulin-like signaling and *casy-1*. Insulin-like peptide INS-1 is secreted from AIA interneurons and insulin-like signaling pathway is activated in ASER through insulin receptor DAF-2. DAF-2 activates PI3-kinase AGE-1 that converts PIP2 to PIP3, which leads to activation of downstream signal components, Ser/Thr kinases PDK-1 and AKT-1. Then, the activation of this pathway negatively regulates neuronal activity of ASER, thereby generating plasticity in salt chemotaxis [29]. CASY-1/Calsyntenins expressed in ASER is cleaved and the ectodomain is released. Released ectodomain acts on either ASER itself or others to modulate salt chemotaxis learning [30].

Figure 3



Analogy between the thermotaxis neural circuit in *C. elegans* and human brain. In *C. elegans*, temperature is sensed and thermal information is stored in AFD (and probably in AWC). Stored information is transmitted to the thermotaxis core interneurons AIY, AIZ, and RIA. Thermal information and food state are integrated and processed in interneurons by monoamines and insulin to generate output behavior [18,22]. In human brain, working memory is coded in cerebral cortex. The coded information is conveyed to basal ganglia, where learning and emotion proceed with modulation through monoamines.

was suggested to hydrolyze endocannabinoid 2-arachidonoylglycerolendocan, it is likely that AHO-3 hydrolyzes some type of endocannabinoid [35].

The *aho-2* mutant was isolated as severely defective mutants in food associated thermotactic plasticity. The *aho-2* gene was identical to *ins-1* gene, which encodes a homolog of human insulin. INS-1 acts cell non-autonomously, and antagonizes insulin receptor DAF-2 and its downstream PI3-kinase AGE-1 in food associated thermotactic plasticity. The defects of *age-1* mutants were rescued by expressing *age-1* gene in any of three interneurons, AIY, AIZ or RIA, all of which are major component neurons in the neural circuit for thermotaxis (Figure 3) [37]. These results suggest that in contrast to salt-food association where INS-1 acts to salt sensing neuron ASE [29], INS-1 acts to interneurons of thermotaxis circuits. Consistent with the notion that integration of food and temperature information occurs within interneurons, the absence of food did not affect the response of AFD thermosensory neurons [37].

Exogenous serotonin mimicked the presence of food, whereas exogenous octopamine mimicked the absence of food in food associated thermotactic plasticity [34]. This result suggests that the balanced regulation by two monoamines in interneurons is a key process for the thermotactic plasticity (Figure 3).

Memory of temperature information

AFD functions as not only temperature-sensing neuron but also a temperature memory device. The memory function of AFD was revealed by Ca^{2+} imaging experiments, where AFD neurons began to respond in warming to a temperature that nearly corresponded to the cultivation temperature [38,39]. cAMP-response element binding protein (CREB) is a transcriptional factor that regulates neural plasticity from invertebrates to mammals [1]. The mutants in *crh-1* gene encoding a *C. elegans* homolog of CREB showed abnormal thermotaxis and the expression of *crh-1cDNA* only in AFD almost completely rescued the defects [40]. CREB may be required for memory in AFD or pre-synaptic plasticity in AFD. Isothermal tracking near the past experienced temperature is suited to directly observe memory process [18,32,33]. *dgk-3* mutants lacking diacylglycerol kinase DGK-3 showed poorer isothermal tracking. The expression of DGK-3 in AFD rescued the defect, suggesting that DGK-3 mediated lipid signaling is important for Isothermal tracking [41].

After temperature is received and assessed with memorized temperature in AFD, thermal information is flowed to AIY interneurons (Figure 3). The regulation of information flow from AFD to AIY may be a critical step for thermotactic plasticity, and recent works partly dissect this regulation. *eat-4* gene encodes a vesicular glutamate

transporter (VGLUT). EAT-4-dependent glutamatergic transmission from AFD down-regulates the activity of AIY through a glutamate-gated chloride channel GLC-3 [42••]. Besides EAT-4 mediated inhibitory signal, peptides mediated excitatory signal from AFD to AIY is predicted [43]. The balance between excitatory and inhibitory signals from AFD to AIY as well as the amplitude control of both signals is important for allowing *C. elegans* to migrate from low to high temperature [22,39,42–44].

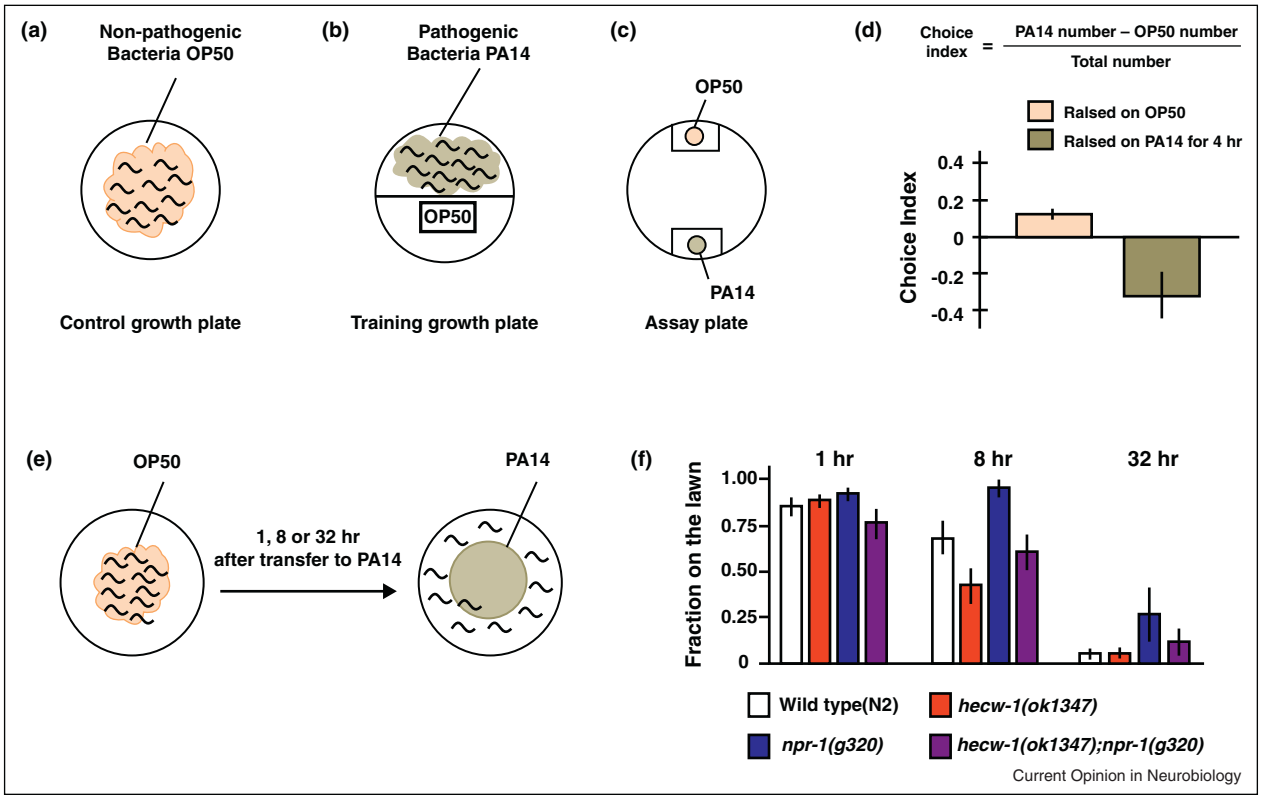
Temperature is also sensed by non-neuronal body cells such as intestine and bodywall muscle cells through heat shock transcription factor HSF-1 [45•]. HSF-1 mediated thermosensation cell non-autonomously regulates the activity of AFD through estrogen signaling [45•] (Figure 3). Thus, neurohormonal modulation of hard-wired neural circuits also contributes to behavioral plasticity in *C. elegans*.

Pathogenic bacteria induce olfactory aversion

Some pathogenic bacteria proliferate in the intestine and release toxin, resulting in death of the infected animal after several days. To protect from pathogenic bacterial infection, *C. elegans* has behavioral strategy to judge food quality and leave from pathogenic bacteria by associative learning. While an odor of pathogenic bacteria attracts *C. elegans*, actual contact with pathogenic bacterial for four hours causes *C. elegans* to avoid them (Figure 4a–d) [46–48]. Prolonged exposure to pathogenic bacteria elevates serotonin content in ADF chemosensory neuron. Serotonin acts to a serotonin-gated chloride channel MOD-1 that is expressed in AIZ and AIY interneurons and is a key molecular basis for the plasticity [48]. Neuronal circuits regulating the learned aversion to pathogenic bacteria have been investigated [49•]. Olfactory sensory neurons AWB and AWC with their downstream interneurons, AIY, AIZ, and AIB, are needed for animals to display naïve olfactory preference to food. ADF serotonergic neurons with downstream interneurons and motorneurons, RIA, SMD, and RIM, are required for associative learning to pathogenic food. Interplay between these two neuronal pathways is important for aversive olfactory learning [49•].

Recent studies showed that a neuropeptide Y receptor and E3 ubiquitin ligase are required for pathogen

Figure 4



Pathogenic bacteria induce aversion behavior. **(a)** and **(b)** *C. elegans* cultivates on non-pathogenic bacteria OP50 (control growth plate) or on pathogenic bacteria PA14 (training growth plate). In order to avoid death from infection, OP50 is contained on training growth plate. **(c)** and **(d)** Two-choice olfactory preference assay. Cultivation on OP50 showed positive choice index, whereas cultivation on PA14 showed negative choice index [48]. **(e)** Another assay system to evaluate the aversion from pathogenic bacteria. Animals were transferred to plates containing a lawn of PA14. **(f)** PA14 occupancy of each *C. elegans* strains was counted 1, 8, or 32 hours after transfer. *hecw-1* mutants showed the enhanced avoidance behavior. *npr-1* mutants were defective in avoidance behavior. *hecw-1* mutation suppress the phenotype of *npr-1* mutants [51••].

avoidance behavior [50•,51••]. The *npr-1* gene encodes a G-protein-coupled receptor related to the mammalian neuropeptide Y receptor. The 215V *npr-1* allele in N2 (Bristol strain) causes increased NPR-1 activity relative to the 215F allele in CB4856 (Hawaiian strain). The polymorphism of *npr-1* gene results in many different food-related behaviors, such as aggregation, aerotaxis, and locomotion [15,52–54]. By spending more time on bacterial lawn, CB4856 strain and loss of function mutants of *npr-1* gene in Bristol strain receive an increased dose of the pathogenic bacteria, leading to higher mortality [50•]. The long staying phenotype on pathogenic bacterial lawn in the 215F *npr-1* allele was suppressed by alleles of *hecw-1* gene that encodes conserved HECT domain-containing E3 ubiquitin ligase. *hecw-1* null mutants in Bristol strain exhibited early leaving phenotype from pathogenic bacterial lawn (Figure 4e,f). The expression of *hecw-1cDNA* in OLL neurons of *hecw-1* null mutants was sufficient to rescue early leaving phenotype, whereas laser-ablation of OLLs neurons in wild type animals induced early leaving phenotype. The function of HECT-1, E3 ubiquitin ligase, in OLL neurons inhibits the pathogen avoidance behavior through negative regulation of NPR-1(215F) [51••].

The regulation of plasticity by monoamines and peptides

Neuromodulators, monoamines, and peptides affect many aspects of *C. elegans* behavior [11–17,20,21,55–58]. A G-protein-coupled catecholamine receptor TYRA-3 is activated by tyramine and octopamine, which are equivalent to vertebrate epinephrine and norepinephrine, respectively [59,60]. Octopamine affects locomotion, arousal and aggregation in invertebrates, and norepinephrine is important for decision-making behavior in mammals [61,62]. Different strains of *C. elegans*, Bristol and Hawaiian, vary in their tendency to leave or remain on a small lawn of bacterial food [52,63••]. Polymorphisms in noncoding region of *tyra-3* gene cooperated with polymorphisms in *npr-1* gene, regulate whether *C. elegans* leaves or remains on the food that is regarded as decision-making behavior. Accordingly, catecholamines seem to be ancient in origin in the modulation of behavioral plasticity [63••].

After exposure to the odor in the absence of food, *C. elegans* stops approaching to otherwise attractive odor and disperse from it [64]. This olfactory plasticity is correlated to the density of animals. The high density enhances dispersion from the odor. *C. elegans* recognizes the density of animals through crude pheromone [57]. When crude pheromone was given, the expression of SNET-1, a neuropeptide homologous to L11 peptide in *Aplysia*, is down-regulated in ASI pheromone sensing neurons [65••]. Consistently, the loss of SNET-1 enhanced and overexpression of SNET-1 weakened the olfactory plasticity, respectively. The *nep-2* gene encoding an extracellular peptidase neprilysin negatively regulates the *snet-1* gene. These results suggest that population density of animal is transmitted through the external pheromone and endogenous peptide activity is a key modulator for plastic behavior [65••].

Association of odorant and alkaline

Food is a strong unconditional stimulus (US) in any conditioning paradigm, because any animal species devoid of food cannot live and reproduce. Some studies therefore avoided using food as US and instead used two different chemical cues [66]. Recently, a new classic conditioning with 1-propanol as CS and HCl (pH 4.0) as US has been developed [67]. In this protocol, spaced training consists of repeated training sessions with an inter-trial interval (ITI), and massed training comprises repeated trials without ITI. The memory after the spaced training was retained for 24 hours, whereas the memory after the massed training lasted only three hours. In addition, *C. elegans* also possesses both long-term memory and short-term memory like other organisms. *C. elegans* mutants defective in *nmr-1* encoding an NMDA receptor subunit fail to form both long-term and short-term memory, while mutations in *crh-1* encoding the CREB transcription factor only affect long-term memory [67]. These results implicate a quite similar molecular mechanism underlying short and long-term memory between *C. elegans* and mammals.

Enhancement of odor repulsion by pre-exposure

C. elegans avoids repulsive odors such as 2-nonanone and 1-octanol [16]. Pre-exposure to a stimulus usually attenuates behavioral responses [68,69]. Nevertheless, the avoidance behavior against 2-nonanone is enhanced by pre-exposure [70•]. Enhancement of avoidance is also observed in pain sensation in mammals, implicating the importance of avoidance may be important for animals to defend themselves from deleterious stimuli. The enhancement of avoidance to 2-nonanone is independent of feeding status during pre-exposure period, suggesting that this behavior is not associated with food. Interestingly, dopamine signaling is involved in this plasticity. The function of D2-like dopamine receptor, DOP-3, in a single pair of interneuron RIC is crucial for enhancement of avoidance to 2-nonanone. RIC neurons intensively synapse onto AVA neurons that mediate forward or backward movement [15,69,71]. Dopamine modulation of RIC likely regulates AVA neuronal activity, thereby controlling the enhancement of avoidance and acute movement [70•].

Long lasting memory in *C. elegans*

In behavioral plasticity described so far, memory is mostly maintained in the order of minutes or hours. The intriguing question is whether long lasting memory exists in *C. elegans* as clearly observed in human. Several lines of

evidences suggest that *C. elegans* indeed possesses long lasting memory. *C. elegans* shows olfactory imprinting, where exposure to attractive odors at the first larval stage in the presence of food leads to enhancement of attractive responses to the experienced odors at the adult stage. A G-protein-coupled receptor SRA-11 expressed in interneurons AIY is required for olfactory imprinting [72].

Bringing up dramatically influences human personality. The importance of bringing up condition is also observed in *C. elegans*. Colony-grown animals exhibited much stronger response to the mechanical stimulus than solitary-grown animals at adult stage. This enhancement may be generated by activity dependent process during development, where colony-grown animals collided with each other, leading to strength the response to the touch. Consistent with this notion, the application of mechanosensory stimulation to solitary-grown animals during mid point of larval development resulted in enhancement of response to the extent of colony-grown animals [73].

Two types of non-associative plasticity exist for mechanosensory (tap) habituation, short-term, and long-term habituation [69]. Short-term habituation is thought to occur in the sensory neurons, whereas long-term habituation that lasts as long as 48 hours is CREB dependent. The gene expression changes in interneurons by CREB are required for long-term habituation [17,74]. The involvement of CREB in long-term memory and not in short-term memory was also observed in other behavioral platforms in *C. elegans* [67,75]. The relationship between long-term memory and CREB requirement is likely to be tight.

Conclusion

Recent studies revealed that *C. elegans* shows a variety of behavioral plasticity as exemplified in this review. Food availability and pathogenicity in the past experience influence behavioral responses to odorants. Salt chemotaxis learning is also affected by the past food condition. These studies should facilitate the understanding of the mechanisms on learning and memory at molecular and cellular levels. Intriguingly, the neural circuit of thermotactic plasticity represents dramatic conceptual analogy to the human brain (Figure 3). The memorized temperature information stored in AFD (and probably AWC) is transmitted to the interneurons, AIY, AIZ, and RIA, where the temperature information is associated with the feeding and/or starvation signals to generate associative learning (Figure 3). We propose that the neural circuit for thermotactic plasticity is analogous to two functional parts of the human brain, cerebral cortex, and basal ganglia. Cerebral cortex encodes working memory that is required for a temporal storage of information. Similarly, sensory neuron AFD (and probably AWC) acts as a memory storage device. Basal ganglia play an important role in learning, emotion and motivation. Likewise, three interneurons AIY, AIZ, and RIA, which likely receive neuromodulatory monoamines in response to feeding state, play a part in learning (Figure 3). Hence, further study of the neural circuit underlying thermotactic plasticity should help unveil the basic principle of the human mind.

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- •• of outstanding interest

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