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The Neuroethology of *C. elegans* Escape

Jennifer K. Pirri and Mark J. Alkema*

Abstract

Escape behaviors are crucial to survive predator encounters. Touch to the head of *C. elegans* induces an escape response where the animal rapidly backs away from the stimulus and suppresses foraging head movements. The coordination of head and body movements facilitates escape from predacious fungi that cohabitate with nematodes in organic debris. An appreciation of the natural habitat of laboratory organisms, like *C. elegans*, enables a comprehensive neuroethological analysis of behavior. In this review we discuss the neuronal mechanisms and the ecological significance of the *C. elegans* touch response.

Introduction

“Eat but don’t get eaten” is a prevailing motto that guides animal behavior. However, this principle presents a dilemma since foraging often increases the risk of predation. Animals can offset part of these risks by trying to survive an confrontation with a predator. Run, dart, jump, fly, burrow and hide can all improve the prey’s odds in these life or death encounters. Time is of the essence so the animal needs to quickly translate sensory information into action. As a consequence, these escape responses are typically robust, use dedicated neuronal structures and have a clear evolutionary purpose, making them favorite subjects for laboratory study [1]. The tail-flip escape in the crayfish [2], the C-start escape in goldfish [3] and the mollusk withdrawal response [4] have provided crucial insights into fundamental neuronal processes as diverse as synaptic transmission, sensory transduction, decision making, and learning and memory. The study of these relatively simple circuits has provided some of the rare examples where we know the complete path from sensory input to a motor output. However, genetic analyses in these organisms are difficult, leaving the molecular coding of these behaviors relatively unexplored. Studies in genetically tractable organisms, like the fruit fly *Drosophila melanogaster* and the roundworm *Caenorhabditis elegans*, have provided some insight into the molecular basis of escape behaviors. In the fly, the giant fiber (GF) neurons coordinate leg extension and wing depression, which are critical for fast flight initiation when a fly is startled by a strong visual stimulus [5] (See review G. Card, this issue). A number of genes have been identified from genetic screens which play a role in the development of the giant fiber circuit, identifying molecular mechanisms that control outgrowth of GF axons, and the formation and maturation of synapses [6]. The neuronal pathway from the GF to motor neurons is well defined, but relatively little is known about its sensory inputs.

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*Corresponding author: Mark J. Alkema, Department of Neurobiology, LRB 717, University of Massachusetts Medical School, 364 Plantation Street, Worcester, MA 01605, U.S.A., Tel: 508 856 6158, Fax: 508 856 6266, mark.alkema@umassmed.edu.

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The *C. elegans* touch response

The complete wiring diagram of the *C. elegans* nervous system is known [7]. This framework is a tremendous asset for understanding sensory processing, including the escape response. *C. elegans* moves on its side by propagating a sinusoidal wave of dorsal ventral flexures along the length of its body [8]. Locomotion is accompanied by exploratory head movements, where the head of the animal sways rapidly from side to side (Figure 1). Head and body movements are controlled independently by distinct classes of motor neurons and muscles. While body bends are restricted to the dorsal-ventral plane, the animal can flex its head in three dimensions. Head movements most likely allow the animal to explore its immediate environment and aid in the search for food, as the tip of worms nose contains the sensory endings that smell, taste and sense touch. Gentle touch to the body of the animal induces an escape response where the animal moves away from the stimulus. Touch to the tail of the animal causes the nematode to speed up, while touch to the anterior half of the animal induces a quick reversal during which foraging head movements are suppressed [9], [10]. Much like the coordination of leg extension and wing depression during a fly escape, the worm coordinates backward locomotion with the suppression of foraging head movements in response to anterior touch.

The neural circuit of escape

In the worm, gentle touch to the body is sensed by six mechanosensory neurons; the ALM and AVM neurons sense touch to the anterior half, while the PLM and PVM neurons sense touch to the posterior half (Figure 2) [11]. Optogenetic activation of the ALM/AVM or PLM/PVM neurons in transgenic animals that express the light activated channelrhodopsin in the mechanosensory neurons induces a reversal or a forward acceleration, respectively [12], [13]. All six neurons send anteriorly directed processes that run close to the cuticle and can sense touch over their entire length. Touch reception is mediated by a DEG/ENAC channel complex that can sense the application and removal of forces as small as 100 nN with a latency of less than 5 ms, allowing the animal to quickly respond to even the lightest of touches [14], [15]. The touch sensory neurons make chemical synapses and electrical gap junctions with a set of command like interneurons that control locomotion. The PVC and AVB locomotion command neurons provide inputs into the VB and DB motoneurons which synapse onto body wall muscles and drive forward movement; the AVD and AVA neurons provide inputs into the VA and DA motor neurons that drive backward locomotion [7]. Laser ablation studies and genetic perturbations indicate that the activity of the interneurons establishes the direction of locomotion [9], [16]. Recent calcium imaging studies support this notion, indicating that the reciprocal activation of AVB and AVA command neurons correlates with forward and backward locomotion respectively [17], [18], [19].

Activation of the anterior touch sensory neurons inhibits command neurons that drive forward locomotion (PVC, AVB) and activates those, which promote backward locomotion (AVD, AVA), causing the animal to back away from the stimulus (Figure 2). During this reversal, the animal also suppresses foraging head movements. Animals that lack tyrosine decarboxylase (*tdc-1*), the biosynthetic enzyme that makes tyramine, or animals in which the single pair tyramineric RIM neurons are ablated fail to suppress these head movements and back up less far in response to touch [10]. The RIM neuron is connected to the backward locomotion circuitry via a gap junction with the AVA command neuron. Optogenetic activation of the RIM neurons causes an increase in intracellular calcium in the AVA [20], suggesting that the AVA and RIM are coactivated during a backing response. The RIM has synaptic outputs onto the forward locomotion command neuron, AVB, as well as the motor neurons and neck muscles that facilitate foraging head movements. The identification of the

tyramine-gated chloride channel, LGC-55 [21], [•22] demonstrated that tyramine can act as a classical neurotransmitter. LGC-55 is expressed post-synaptically to the RIM, consistent with a model where activation of LGC-55 by tyramine release in response to anterior touch induces hyperpolarization of neck muscles and the AVB leading to the suppression of head movements and sustained backward locomotion [•22]. The role of tyramine in the *C. elegans* escape response illustrates how biogenic amines can coordinate the output of independent motor programs in the generation of complex behaviors.

***C. elegans* ecology**

What does *C. elegans* need to escape from? Natural populations of *C. elegans* are found world wide in decomposing organic material such as compost, decaying leaves and rotting fruit [23], [•24]. *C. elegans*, can survive less favorable conditions as a dauer larvae, an alternative developmental stage that is long lived. Dauer larvae can climb onto protrusions, stand on their tail and wave in the air, a process known as nictation. This behavior may promote dispersal to new more favorable habitats. Dauer larvae have been found in association with insects and snails [25], and have been shown to hitch a ride on fruit flies in the laboratory [26]. Once a favorable habitat is found, a viable evolutionary option is to produce many offspring quickly. *C. elegans* reaches adulthood in 3 to 4 days and under laboratory conditions produces approximately 300 offspring. The prolific nature of *C. elegans* was one of the genetic selection criteria that eased its transition from English compost in the 1950s to luscious laboratory life [27]. The laboratory strain N2 spends its life on agar plates with abundant amounts of *E. coli* as a food source. The domestication of *C. elegans* has brought a different set of selective pressures. Laboratory strains of *C. elegans* have different preferences for oxygen [• 28], [• 29], foraging behavior [30], and response to dauer pheromone [•• 31] than animals recovered from the wild, indicating an adaptation to laboratory life. These behavioral adaptations to changing environmental conditions emphasize the importance of the natural history of the animal. Its natural habitat, with fluctuating temperature, humidity and osmotic pressure and other microbes, presents a plethora of behavioral challenges to *C. elegans*. It needs to forage for bacteria and slime molds that compose a majority of its diet [32], [33]. It also needs to be selective in its dietary choices, since some bacteria and fungi can infect and kill the animal [34]. Knowing what has been on the menu helps *C. elegans* make healthy choices, since it can learn to avoid eating bacteria that are hard to digest or are pathogenic [35], [36].

While nourishment is essential for the animal's survival and reproduction, foraging behavior incurs costs that extend beyond the energy used for finding food. Foraging can expose *C. elegans* to encounters with natural predators. Nematophagous mites [37], springtails [38], water bears [39] and other predacious nematodes like *Pristionchus pacificus* [40] can actively kill and eat nematodes. Nematodes face another lurking foe in their habitat: predacious fungi. These carnivorous fungi, from the family of Orbiliales (Ascomycota), possess hyphal structures to trap nematodes in the soil and decaying organic debris [41], [42]. One method of capturing nematodes employs adhesive branches, knobs or hyphal nets that stick to, and entangle nematodes. By far the most sophisticated trapping mechanism is the constricting ring. When a worm crawls through the ring gentle friction induces the ring to rapidly inflate and lasso its prey (Figure 3). Predacious fungi form few, if any traps in the absence of nematodes. Trap formation is induced by the presence of nematodes, including *C. elegans* [43], and stimulates the growth of a variety of hyphal traps. Once a nematode is caught by a hyphal trap, death does not come quickly. A prolonged struggle usually only ends when fungal hyphae perforate the cuticle, and absorb the contents of the nematode.

Out of the jaws of death

Since the *C. elegans* mechanosensory neurons are very sensitive, the touch of a mite, a sticky hyphae or a tightening fungal noose could provide enough force to trigger an escape response. An acceleration or quick reversal may allow the worm to survive such an encounter with a predator. The wide array of available mutants in *C. elegans* provides unique opportunities to directly test if behavioral traits contribute to the odds of surviving predator encounters. Studies of predator-prey relationships between *C. elegans* and the constricting ring fungus *Drechlerella doedycoides* showed that the fungus is most efficient in entrapping the early larval stages with a diameter similar to that of the ring [••44]. Young larvae are small enough to move far into the ring and wide enough to wedge themselves and trigger trap inflation. There is a delay between the animal moving into a trap and trap closure allowing some nematodes to enter and withdraw from the ring before getting caught. While wild-type animals survive most encounters with the hyphal noose, mutants that fail to sense touch or that cannot reverse, are trapped more frequently. Moreover, mutants that fail to suppress the foraging head movements in response to touch are caught more often than the wild type. The ability to tag different genotypes with transgenic fluorescent markers allows one to test whether coordination of a touch-induced reversal with the suppression of swaying head movements provides a selective advantage. Animals that fail to suppress foraging head movements are caught more efficiently by the fungus than the wild type animals in direct competition experiments in with mixed populations of wild-type and mutant animals. Thus, the coordination of motor programs in the *C. elegans* escape response is vitally important to evade fungal predation.

Other soil nematodes from the Eurhabditis clade, close relatives of *C. elegans*, display a similar escape response. Interestingly, several species from the Pleiorhabditis clade, which have been found in association with insects, fail to coordinate head and body movements in their escape response (J.K.P and M.J.A unpublished observation). This may indicate that the touch-induced suppression of head movements has evolved from selective pressures imposed by predacious fungi. Nematodes and predacious fungi that use rings as trapping devices have been found in 100 million year old amber indicating an ancient predator-prey relationship [45]. The phylogeny of predacious fungi and morphology of their trapping devices suggest that constricting rings have evolved from non-constricting rings [46]. This raises the tantalizing possibility that constricting rings and the suppression of head movements are the result of an evolutionary arms race. An extensive analysis of the ecology of predatory fungi and cohabitating nematodes is required to fully comprehend the dynamics of this predator-prey relationship. Since we know the molecular and neuronal basis of the escape response in *C. elegans*, comparative studies with other nematodes should allow us to find selection pressures that shape behavioral adaptation.

Conclusions

While escape responses have been a favorite subject for neuroethological studies of behavior, it has been hard to unify the analysis of proximate and ultimate causes of behavior. A renewed appreciation for the natural history of laboratory animals may allow us to bridge a gap between the molecular “how” and behavioral “why”. Furthermore, even though genomic approaches have been instrumental in studies of genotypic selection, our understanding is largely correlative. The experimental manipulation of behavioral traits provides unique inroads to define causative forces of natural selection. The ability to connect the path from molecule to neuron to neural circuit to behavior, ecology, and evolution fulfils the true goals of neuroethology set out by Niko Tinbergen half a century ago [47].

Highlights

- *C. elegans* coordinates head and body movements during a touch induced escape response.
- The complete sensory-motor circuit that controls the *C. elegans* escape response is known.
- Predacious fungi catch nematodes using hyphal trapping devices.
- The *C. elegans* escape response increases its odds of surviving encounters with predacious fungi.
- Study of the natural habitat of genetic model organisms allows for a comprehensive neuroethological analysis of behavior.

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Figure 1. Escape responses

Silhouettes of animal escape responses. Arrows indicate the direction of the threatening stimulus. Crayfish tail-flip (top): Tail touch in the crayfish induces powerful abdominal flexures that are spatially and temporally controlled to propel the animal through the water away from the stimulus. Time from first to last frame is approximately 15 ms [2] [48].

Tritonia swim reflex: Upon touch to the body, *Tritonia* initiates a series of coordinated dorsal and ventral body flexures to swim away from predators. Time from first to last frame is approximately 5 s [49].

Goldfish C-start: Lateral stimulation causes the animal to coordinate both the strength and the timing of agonist and antagonist muscle contractions on either side of the body to quickly change direction to move away from the stimulus. Time

from first to last frame is approximately 50 ms [50]. *Drosophila* startle response: A strong visual stimulus induces fast flight initiation, where the fly couples leg extension and wing depression to quickly fly away. Time from first to last frame is approximately 25 ms [5]. *C. elegans* anterior touch response: Gentle touch to the anterior of the body of the worm induces a reversal coupled with the suppression of foraging head movements followed by a deep ventral bend (omega turn) and a 180° change in the direction of locomotion. Time from first to last frame is approximately 10s [10].

Figure 2. Neural circuit of the *C. elegans* escape response

C. elegans moves its head rapidly from side to side during forward locomotion as indicated by the outline. The relative cell body position and neuronal process of neurons responsible for sensing touch (purple: anterior touch; red: posterior touch) are depicted. The circuit diagram illustrates the connections between the sensory neurons and those that control locomotion and head movements. Synaptic connections (arrows) and gap junctions (spheres) are as described by White, et al. (1986). Sensory neurons are shown as triangles, command neurons required for locomotion are shown as hexagons, and motor neurons as circles. Excitatory (+) and inhibitory (–) connections involved in the anterior touch escape response are noted. Anterior touch activates the AVA backward locomotion command neuron, which

in turn activates the tyraminerpic RIM motor neuron. Tyramine release from the RIM neurons activates the tyramine gated chloride channel LGC-55, which is expressed in the AVB forward locomotion command neuron and cells of the head movement circuit: RMD, SMD, and neck muscles. Activation of LGC-55 causes hyperpolarization of neck muscles and the AVB neuron inducing the suppression of head movements and sustained backward locomotion in response to anterior touch [9], [10], [•22].

Figure 3. *C. elegans* caught by a constricting ring of a nematophagous fungus
Scanning electron micrograph of *C. elegans* L2 larvae caught in the constricting rings of the nematode trapping fungi, *Drechslerella doedycoides*. Image Sean M. Maguire.