Metabolic Modulation of Neuroinflammatory Responses and Behavior of Caenorhabditis Elegans: Implications for Neuronal Resilience and Function

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Abstract: - This project looks at how diet changes may affect inflammation in the nervous system, using the nematode *Caenorhabditis elegans* as a model. The goal was to explore whether nutrients such as fats, vitamins, and plant compounds can alter brain-related processes like those seen in neurodegenerative diseases. The hypothesis was that altering metabolism through diet would lead to measurable changes in inflammation and behavior. To test this, worms were given food supplemented with omega-3 fatty acids, vitamin E, or curcumin, and their movements were tracked through thrashing and locomotion assays. Interestingly, worms exposed to omega-3 moved slightly less than the control group, and those that received vitamin E showed a clearer reduction in activity. Curcumin caused a moderate effect that fell between the two. These patterns suggest that diet can meaningfully shape how the nervous system reacts to inflammation. In short, nutrition seems to play a major role in linking metabolism with neural function. What we learn from these simple organisms might help clarify how diet affects brain health in humans, where inflammation and nutrition are deeply connected.

Key-Words: - *C. Elegans*, Curcumin, Omega-3, Vitamin E, Behavior, Thrashing, Neuroinflammation, Locomotive

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1 Introduction

There has been increasing interest in understanding how diet can influence inflammation in the nervous system and, in turn, affect behavior. Nutrition is not only linked to general health but also plays a direct role in regulating brain function and disease progression. In this project, it was explored how specific nutrients such as omega-3 fatty acids, vitamin E, and curcumin might influence neuroinflammatory signaling and behavior in the well-studied model organism *Caenorhabditis elegans* (C. elegans).

The goal was to see whether targeted dietary changes could lead to measurable shifts in neural activity and movement. To test this, *C. elegans* were fed diets enriched with these nutrients, and their behavior was evaluated using two standard methods named the thrashing assay and the locomotion assay. These experiments helped reveal how altering diet changes metabolic activity, which then affects movement patterns and possibly inflammation in the nervous system.

Overall, the study suggests that nutrients can have a tangible impact on neurobehavioral outcomes in *C. elegans*. While this is a simple organism, the findings may reflect broader biological patterns that connect diet, inflammation, and brain function offering clues that could one day inform approaches to preventing or treating neurodegenerative diseases.

2 Background Research

This research explores the intricate relationship between metabolic status, neuroinflammation, and behavior in the nematode *Caenorhabditis elegans*. While the broader context frames neuroinflammation as a pathological driver in neurodegenerative disease—arising from immune activation within the central nervous system parenchyma—the focus here is on how metabolic inputs, through dietary interventions, can modulate neuroimmune signaling and behavior (Moyse et al., 2022). By employing a non-vertebrate model with highly conserved pathways such as p38-MAPK/PMK-1, DAF-16/FOXO, and SKN-1/Nrf we can isolate the effects of diet on neural inflammation and function in a simplified yet translationally relevant system (Wu et al., 2019; Xu et al., 2023). As overnutrition itself induces neuroinflammation in vertebrate hypothalami, linking metabolism to neural degeneration (Cai et al., 2013), working in *C. elegans*

offers an ideal platform to dissect conserved mechanisms. The outcomes have the potential to offer mechanistic insights into how lifestyle and nutrient status could impact neurodegenerative processes in more complex organisms, including humans.

2.1 Defining Neuroinflammation in *C. elegans*

Neuroinflammation generally refers to an immune-like response within neural tissue, classically studied in vertebrates where glial cells respond to infection or injury with the release of cytokines (IL-1β, TNF-α, IL-6), chemokines, and reactive oxygen/nitrogen species (Moyse et al., 2022). While an acute inflammatory response can be protective, when chronic it contributes to neurodegenerative diseases such as Alzheimer's, Parkinson's, and ALS (Lyman et al., 2014;Kwon et al., 2020).

Overnutrition-induced metabolic inflammation similarly activates hypothalamic IKKβ/NF-κB signaling and impairs neurogenesis (Cai, 2013), reinforcing inflammation's role in neural dysfunction. In *C. elegans*, although Neuroinflammation generally refers to an immune-like response within neural tissue, classically studied in vertebrates where glial cells respond to infection or injury with the release of cytokines (IL-1β, TNF-α, IL-6), chemokines, and reactive oxygen/nitrogen species (Moyse et al., 2022). While an acute inflammatory response can be protective, when chronic it contributes to neurodegenerative diseases such as Alzheimer's, Parkinson's, and ALS (Lyman et al., 2014; Kwon et al., 2020). Overnutrition-induced metabolic inflammation similarly activates hypothalamic IKKβ/NF-κB signaling and impairs neurogenesis (Cai, 2013), reinforcing inflammation's role in neural dysfunction. In *C. elegans*, specialized glial cells are absent and conserved molecular pathways such as PMK-1/p38-MAPK perform immune functions similar to those in more complex organisms. These pathways regulate defense genes, oxidative stress resistance, and general stress responses all within a simplified framework that avoids the complexity of vertebrate nervous system structures (Wu et al., 2019). Because of this, *C. elegans* provide a clear way to examine how metabolic changes, like those introduced through diet, trigger neuroimmune activity and alter behavior (Kaletta & Hengartner, 2006).

2.2 Caloric/Dietary Restriction (DR)

Caloric restriction (DR) in *C. elegans*, achieved either through eat-2 mutants or bacterial dilution, consistently extends lifespan and improves stress resilience. Mechanistic studies show that DR activates the NSY-1 → SEK-1 → PMK-1 (p38-MAPK) signaling cascade, which leads to activation of ATF-7 and downstream immune effectors even when no pathogens are present (Wu et al., 2019). Loss of pmk-1, sek-1, or nsy-1 reduces the lifespan benefits of DR, while alternative pathways such as JNK only partly compensate (Wu et al., 2019; Steinbaugh et al., 2020). From a behavioral perspective, DR increases locomotion and foraging through DAF-7/TGF-β signals from ASI neurons. However, this improvement is absent in pmk-1 mutants, showing that a coordinated link between metabolism, immunity, and behavior is required. In addition, DR boosts the production of omega-3 polyunsaturated fatty acids, especially EPA and linoleic acid, which act as natural signals to strengthen PMK-1-driven protective gene expression (Steinbaugh et al., 2020). Together, these findings illustrate how nutrient scarcity engages neuroimmune pathways that ultimately shape both lifespan and behavior.

2.3 Omega-3 Polyunsaturated Fatty Acids (PUFAs)

Omega-3 PUFAs—such as eicosapentaenoic acid (EPA)—are recognized for their anti-inflammatory and neuroprotective roles in vertebrates, where they suppress NF-κB signaling and elevate IL-10 and pro-resolving mediators (Gómez-Pinilla et al.). In *C. elegans*, exposure to DR significantly increases endogenous PUFA synthesis, activating PMK-1 to regulate a suite of xenobiotic detox and stress resilience genes (Steinbaugh et al., 2020). Manipulating PUFA levels—whether through fat-1 desaturase mutants or specialized bacterial diets—modulates PMK-1 activity and yields clear behavioral outcomes: delayed paralysis in amyloid/tau neurodegeneration models, improved locomotion, and enhanced survival under oxidative or thermal stress (Steinbaugh et al., 2020; PubMed 32978396). These findings reinforce the concept of PUFAs as metabolic-immune messengers that bridge diet and behavior, supported by similar evidence in human and rodent systems (Cai et al., 2013).

2.4 Curcumin

Curcumin, the primary bioactive polyphenol found in turmeric, is known for its antioxidative, anti-inflammatory, and neuroprotective effects. In *C. elegans*, supplementation at ~25 μM extends median lifespan by approximately 15%, significantly reduces reactive oxygen species, and enhances survival under

heat and paraquat exposure—without adversely impacting reproduction or motility (Xu et al., 2023; PMC 10279890). On a molecular level, curcumin downregulates components of the MAPK pathway (nsy-1, sek-1, pmk-1) while upregulating cytoprotective genes (sod-1, sod-2, sod-3, gst-4), indicating a switch from inflammatory signaling to antioxidant defense (Xu et al., 2023). These life- and health-extending effects require intact SEK-1, PMK-1, SKN-1, and DAF-16 functions; their absence nullifies curcumin's benefits (Xu et al., 2023). Behaviorally, curcumin rescues locomotor deficits and neural morphology in tauopathy worm models without reducing aggregate load (Zhang et al., 2022), consistent with its broader anti-inflammatory action in vertebrates (Moyse et al., 2022), underscoring its status as a potent dietary neuroimmune regulator.

2.5 Vitamin E

Vitamin E, particularly its α-tocopherol isoform, is a lipid-soluble antioxidant that plays a crucial role in protecting membranes from oxidative stress and regulating immune responses. In *C. elegans*, vitamin E supplementation has been shown to reduce reactive oxygen species (ROS) levels, delay age-associated decline in motility, and extend lifespan under oxidative challenge (Ishii et al., 2004; Adachi & Ishii, 2000). Mechanistically, vitamin E enhances stress tolerance by upregulating antioxidant defense genes through the SKN-1/Nrf2 pathway and by preserving mitochondrial integrity under metabolic stress (Honda & Honda, 2002; Ishii et al., 2011). In addition, tocopherol treatment mitigates neurodegenerative phenotypes in worm models of amyloid toxicity, decreasing paralysis and improving locomotor resilience without altering aggregate load (Yatin et al., 2000; Fukui et al., 2012). These findings demonstrate that vitamin E supports neuronal function primarily through its antioxidative and membrane-stabilizing effects, underscoring its role as a dietary modulator of neuroimmune balance and neurobehavioral health.

3 Methodology

3.1 Worm Strain and Maintenance

Wild-type *Caenorhabditis elegans* strain N2 (Bristol) was obtained from the Caenorhabditis Genetics Center (CGC, University of Minnesota, USA) and maintained at 20 °C on standard nematode growth medium (NGM) plates seeded with *E. coli* OP50. All experiments used synchronized day-1 adult worms obtained via bleaching protocol.

3.2 Dietary Interventions

For nutrient supplementation, each compound—omega-3 fatty acids (EPA; 50 μM), vitamin E (α-tocopherol; 50 μM), or curcumin (25 μM)—was first dissolved in DMSO and added directly to lysogeny broth (LB) cultures of *E. coli* OP50. The supplemented bacterial cultures were grown overnight at 37 °C with shaking, then seeded onto NGM agar plates and allowed to grow for 24 hours at room temperature before use. Control plates were prepared using LB broth with 0.1% DMSO only.

3.3 Exposure Duration

Worms were exposed to each diet for 48 hours prior to behavioral testing. During this period, they were transferred daily to fresh treatment plates to maintain compound stability and prevent bacterial overgrowth.

3.4 Behavioral Assays

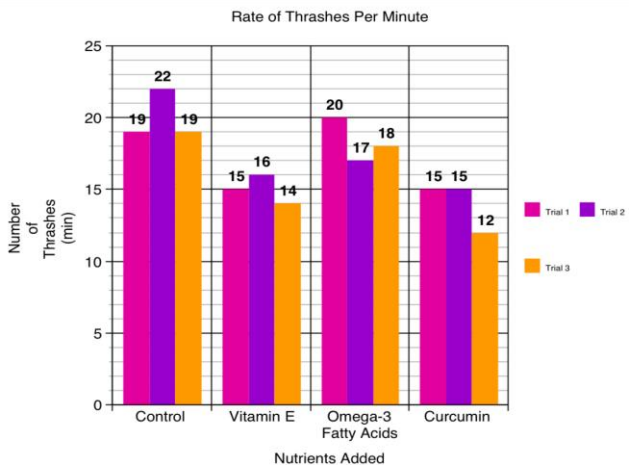
Thrashing Assay: Worms (n = 30 per treatment, 3 independent biological replicates) were transferred to 50 μL M9 buffer drops on glass slides. Thrashes were counted for 1 minute under a stereomicroscope, with one thrash defined as a complete change in bending direction.

Locomotion Assay: Worms (n = 30 per treatment, 3 biological replicates) were placed on unseeded NGM plates, and the number of forward body bends was recorded for 1 minute.

4 Thrashing Assay

This assay measures spontaneous body bends and thrashes, indicates motor function and coordination, and impacted by neuroinflammation: reduced thrashing may signal nervous system dysfunction.

The control group exhibited an average of 20 thrashes, while vitamin E supplementation resulted in a slightly reduced average of 15 thrashes. Omega 3 supplementation increased thrashing with an average of 18.33, and curcumin showed an intermediate effect with an average of 14 thrashes (Figure 1). These findings suggest that omega 3 may enhance locomotor activity, while vitamin E and curcumin may have potential inhibitory effects on thrashing behavior.

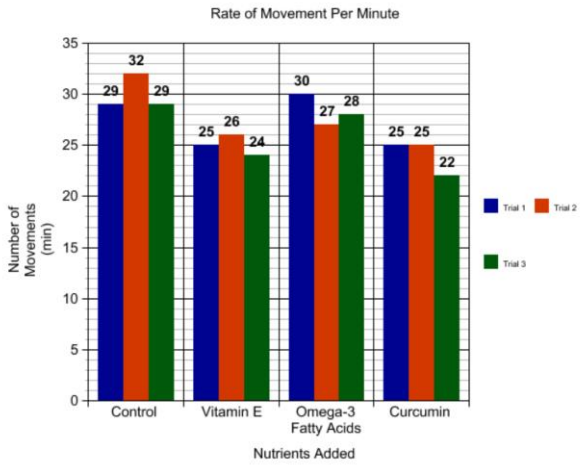


(Figure 1) This graph shows the results of the thrashing assay conducted on the C. elegans including the rate of thrashes per minute and the results of three trials for each nutrient.

5 Locomotion Assay

Measures overall movement and displacement, indicates speed and coordination, sensitive to neuroinflammation: altered locomotion may signal nervous system dysfunction.

Control worms displayed an average of 30 movements, while vitamin E-supplemented worms exhibited a reduced average of 25 movements. Omega 3 supplementation increased locomotion with an average of 28.33, and curcumin resulted in a lower average of 24 movements as (Figure 2). The locomotive assay results align with the thrashing assay, suggesting that omega 3 may enhance overall movement, while vitamin E and curcumin may have inhibitory effects on locomotive behavior.



(Figure 2) This graph shows the locomotion assay results which summarize how C. elegans moved per minute under each nutrient condition, based on three separate trials.

6 Discussion

The thrashing assay, a standard approach for evaluating neuromuscular and behavioral function in *C. elegans*, provided useful insight into how different dietary components affected locomotor activity. The control group exhibited an average of 20 thrashes per unit time, which served as the baseline for comparison, while worms supplemented with omega-3 fatty acids showed a slightly lower average of 18.33 thrashes. Although slightly lower than the control, this value was still higher than those observed in the other nutrient groups, suggesting that omega-3 may support motor circuit function. This finding is consistent with the well-established anti-inflammatory and neuroprotective roles of omega-3 PUFAs, which have been shown to enhance synaptic activity and reduce inflammation in the nervous system (Gómez-Pinilla et al.). By contrast, supplementation with vitamin E and curcumin reduced thrashing rates to averages of 15 and 14, respectively. These reductions may indicate a dampening of neural activity or movement capacity, potentially through either direct effects on motor neurons or indirect changes in neuroimmune signaling that influence neuronal excitability.

The locomotion assay offered complementary data by measuring overall movement. Control worms displayed an average of 30 body bends, while omega-3 supplemented worms recorded a slightly lower but still comparable average of 28.33.In contrast, worms exposed to vitamin E and curcumin again demonstrated decreased locomotion, with averages of 25 and 24, respectively. The concordance of results across these two distinct behavioral assays reinforces the notion that omega-3 fatty acids support neuromuscular health and behavioral vigor, while vitamin E and curcumin may exert suppressive influences on locomotor activity. Notably, the reduction in movement observed with vitamin E and curcumin contrasts with some vertebrate studies where these compounds have anti-inflammatory roles; this discrepancy may reflect species-specific responses or dosage-dependent effects requiring further mechanistic elucidation.

However, this study has limitations, including its small sample size and reliance on behavioral assays. These factors constrain the mechanistic interpretation of the results and may limit the generalizability of the findings.

Future work should integrate quantitative imaging of neural morphology, gene expression analysis of inflammation-related pathways, and computational modeling to predict nutrient–pathway interactions.

7 Conclusion

Taken together, these behavioral data suggest that omega-3 supplementation produced a slight, non-significant reduction in locomotor activity compared to controls, rather than enhancing neural function. Conversely, the observed decrease in thrashing and locomotion following vitamin E and curcumin treatment may indicate impaired neural circuitry or increased neuroinflammatory activity, potentially disrupting normal motor outputs. These findings highlight the complex and nuanced influence of dietary components on neurobehavioral responses and underscore the importance of dissecting the underlying molecular mechanisms. Future studies should investigate how these nutrients modulate conserved signaling pathways such as PMK-1/p38-MAPK, DAF-16/FOXO, and SKN-1/Nrf, which are known to regulate both immune responses and neuronal function in *C. elegans*. Additionally, understanding these interactions in a simple model organism may provide translational insights into the dietary modulation of neuroinflammation and behavior in higher organisms, including humans, where dietary factors significantly impact neurodegenerative disease progression and cognitive health.

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