



Modulation of stress responses in *C. elegans*: Sex differences and neuronal control

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The effect of stress on an organism can be diverse and systemic, impacting cell physiology, development and behaviour. Here, I review the molecular mechanisms by which stressors (noxious stimuli) negatively impact all these aspects of animal biology and some of the mechanisms employed by the organism to combat damage by such insults. I focus on research carried out in the nematode *Caenorhabditis elegans* and the stress response pathways that enhance the core proteostasis network, a collection of molecular chaperones and degradation factors that refold or remove damaged proteins. Insults are often sensed by the nervous system, which then triggers stress response pathways systemically in distal tissues. Inter-tissue communication for cell nonautonomous regulation of stress responses by the nervous system involves many different neurotransmitters and modulators in an insult-specific manner. Sex-specific differences in stress sensitivity and proteostasis strategies also exist, with males generally being more resilient than hermaphrodites. However, male reproductive development and behaviour remain particularly vulnerable to stress.

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Through their lives, organisms are constantly exposed to physiological stressors that negatively impact their health and survival rate. Stressors are diverse in nature and include environmental insults, such as changes in temperature and contact with toxic chemicals, as well as biological interactions, such as exposure to conspecifics and pathogen infection. While a myriad of cellular processes and macromolecules are negatively impacted by

these stressors, a major consequence is the misfolding and aggregation of proteins (commonly referred to as a “loss of protein homeostasis (proteostasis)”), which this review will focus on. To combat this threat, organisms have evolved the proteostasis network (PN), a collection of interacting pathways involved in biogenesis, trafficking and degradation of proteins. At the heart of the PN, is a pool of molecular chaperones and degradation factors (such as the ubiquitin proteasome system (UPS) and autophagy factors) that sense and respond to misfolded or damaged proteins by either refolding or removing them [1]. I will refer to this collection of chaperones and degradation proteins as the core PN in this review. Crucially, the composition and activity of the core PN can be rapidly enhanced through the activation of highly conserved stress response pathways [1]. These pathways are controlled by transcription factors that sense protein folding stress within specific compartments and regulate the expression of core PN components in a compartment-specific manner. The three best studied stress response pathways are the cytosolic heat shock response (HSR), which is controlled by the transcription factor HSF1 [2], the endoplasmic reticulum unfolded protein response (UPR^{ER}), which is controlled by the transcription factors XBP1, ATF6 and PERK [3] and the mitochondrial unfolded protein response (UPR^{mito}), which is controlled by the transcription factors ATFS-1, HSF1, CHOP, ATF4 and ATF5 [4]. Additionally, the oxidative stress response (OxSR) is triggered upon reactive oxygen species (ROS) accumulation to prevent protein damage. OxSR consists of antioxidant enzymes such as superoxide dismutases (SODs), glutamate cysteine ligases (GCLs) and glutathione S-transferases (GSTs) and is controlled by the transcription factor NRF2 [5].

The nematode *Caenorhabditis elegans* has significantly advanced the mechanistic understanding of organismal stress responses due to its genetic tractability, transparency and short life cycle. Furthermore, tissue-specific reporter transgenes allow precise assessment of stress response activation upon different stressors and conditions. Key insights have emerged, including notable sex differences in stress susceptibility and the central role of the nervous system in regulating stress responses across tissues. In this review, I will primarily focus on sex differences and the neuronal regulation of proteostasis stress responses. Given the pronounced

sexual dimorphism in nervous system function, I will also discuss how broader forms of stress influence neural development and behaviour.

The influence of social interactions on stress and longevity

Social interactions in *C. elegans* influence stress responses and lifespan. In short, growth in the presence of other males is detrimental for both hermaphrodites and males [6–10]. Males reared in isolation live longer than those grown in same-sex groups, while hermaphrodites also experience increased lifespan when reared in same-sex groups compared to mixed-sex groups. No lifespan difference is observed between hermaphrodites raised in isolation versus same-sex groups [6].

The negative effects of male presence on other males stem from both mating behaviors—*C. elegans* males attempt to mate with one another—and male secretions such as pheromones [6,7]. Male pheromones trigger toxicity rather than accelerated ageing in other males and both the production and reception of this toxicity require the nervous system to be genetically specified as a male [7]. The mechanisms underlying male toxicity involve the upregulation of lipase-related hydrolases, leading to decreased fat storage, as well as increased expression of vitellogenin (normally used for egg production in hermaphrodites) and the transcription factor PQM-1, which regulates stress responses [7] and promotes cross-tissue responses to protein folding stress [11].

Male-induced hermaphrodite demise, on the other hand, does not require copulation but male secretions such as seminal fluid and pheromones [8,9]. Although copulation is not required for male-induced demise, a contributing role cannot be ruled out since spicule prodding has been shown to exert physical damage [9,12]. The effect of male-induced demise occurs, amongst other pathways, through upregulation of neuronally expressed peptides such as *ins-11* and *ins-7* as well as Rab family GTPases involved in vesicular trafficking [8,9]. Interestingly, *ins-11* is also involved in mediating intermale toxicity [7]. The lifespan-reducing effects of male pheromones on hermaphrodites appear to be a trade-off for reproductive benefits. Male pheromones accelerate hermaphrodite development and sexual maturation while delaying germline progenitor cell loss [10]. They also enhance gamete survival under stress and improve sperm guidance toward oocytes [13].

Sex differences in stress response pathways

When social interactions are removed, males generally live longer than hermaphrodites [6]. However, the relationship between sex and stress resistance is more complex. While males demonstrate greater

resistance—measured by survival rates—to osmotic, heat and juglone-induced oxidative stress [14], they are more sensitive to ROS generated by sodium arsenite, paraquat, or hydrogen peroxide [15].

Unfolded protein and antioxidant stress responses

The mechanisms behind these sex differences remain unclear. Males exhibit higher basal levels of the canonical UPR^{ER} and HSR genes, *hsp-4/BiP* and *hsp-16.2/HSPB1*, respectively, suggesting that males may possess greater XBP-1 and HSF-1 activity than hermaphrodites. Furthermore, males exhibit a SKN-1/NRF2-dependent increase in the expression of oxidative stress and detoxification genes. However, this does not translate to an enhanced response to heat shock or oxidative stress [14].

A potential evolutionary explanation for males' greater stress resistance may be their prevalence in harsh environments and their need to search for mates. However, it should also be noted that anatomical differences between the sexes complicate direct comparisons.

In contrast, sensitivity to oxidative stress induced by sodium arsenite, paraquat, or hydrogen peroxide, is regulated by the DMD transcription factor MAB-3, which is involved in sex determination [15]. One of the tissues where *mab-3* is expressed is the intestine, where it suppresses *elt-2*, a global regulator of intestinal transcription. Since the intestine plays a major role in stress responses, *mab-3* may make males more vulnerable to oxidative stress by downregulating *elt-2* [15]. Additionally, male sensitivity to paraquat (an inhibitor of the mitochondrial respiratory chain complex I) maybe due to their inability to mount a systemic cell nonautonomous UPR^{mito} [16].

The sex determination pathway also contributes to differences in vulnerability to loss of *PTEN/DAF-18*, a protein and lipid phosphatase that acts upstream of target of rapamycin (TOR) and reduces insulin signalling. Males and hermaphrodites use distinct strategies to cope with the stress caused by *PTEN* loss. Hermaphrodites experience global protein aggregation and activate the UPR^{ER}, whereas males upregulate *unc-23/BAG2*, leading to activation of the UPS and increased protein degradation, which results in survival advantage [17].

Caloric restriction

Since the intestine and insulin signalling play key roles in stress regulation, diet is also a major factor in longevity. Dietary restriction has been shown to extend lifespan in nearly all organisms studied [18] except for *C. elegans* males [19]. In hermaphrodites, dietary restriction extends lifespan via the *FOXO* transcription factor *DAF-16*, which translocates to the nucleus in response to fasting and regulates stress resistance and longevity genes [20]. In males, however, *DAF-16* fails to

translocate to the nucleus during dietary restriction [19]. Furthermore, starvation induces strikingly different transcriptional profiles in males and hermaphrodites: while hermaphrodites suppress reproductive programs and invest in longevity, males upregulate genes related to reproduction and cell division. Males' prioritisation of reproduction at the expense of caloric intake is also reflected in behaviour [21]. Males will leave a source of food in search of mates [22] and will navigate towards cues that predict the encounter of mates at the expense of food [23–25]. One key regulator of both male mate-searching behaviour and hermaphrodite longevity which acts downstream of the sex determination pathway is DAF-12, a homologue of vitamin D and liver X receptors [26]. The regulator *daf-12* is more highly expressed in males than in hermaphrodites and contributes to males' unresponsiveness to dietary restriction [19].

In addition to the insulin pathway and FOXO/DAF-16, several other factors regulate lifespan in response to caloric restriction. These include AMP-activated protein kinase AMPK/AAK-2, the FOXA/PHA-4 transcription factor and the innate immunity pathway regulators p38 and the ATF-7 [18,27]. Whether any of these pathways acts in a sexually dimorphic manner remains an open question.

Pathogen infection

Exposure to pathogens and infection is another major source of stress to which males have consistently been shown to be more resistant than hermaphrodites. The basal transcriptional profile of males is most similar to that of bacteria-infected hermaphrodites, indicating that genes associated with immunity, stress responses and pathogen resistance are already highly expressed in noninfected males [28]. In particular, genes involved in autophagy, such as *atg-2* and the transcription factor HLH-30/TFEB are required for male resistance, and conversely, overexpression of *hlh-30* (but not *atg-2*) confers hermaphrodites with resistance to bacterial infection.

Resistance to other pathogens such as the fungus *Cryptococcus Neoformans* and the Orsay virus is also increased in males [29,30]. Viruses, unlike bacteria, are intracellular pathogens and infection induces the intracellular pathogen response (IPR) as well as RNA interference against the viral genome. IPR expression appears constitutively high in males which may confer resistance to infection [30]. Of note, sexual dimorphism in viral resistance is observed in Bristol N2 but not in other wild isolates such as Hawaiian CB4856 or JU1580 (which are particularly susceptible because of a deficiency in the RNAi pathway) [30]. Fungal resistance on the other hand is higher in males for all *C. elegans* wild isolates tested and it depends on DAF-16 [29].

Neuronal control of stress responses

The nervous system plays a crucial role in mediating systemic stress responses. Given the overlap in gene expression between stress and ageing [29,31], early evidence suggesting neural regulation of stress response pathways came from findings that mutations in *syntaxin/unc-64*, *CAPS/unc-31*, or *unc-13* increased lifespan [6,32,33]. Subsequent studies demonstrated a direct role for motor neuron communication in maintaining muscle protein homeostasis [34] and for the thermo-sensory neuron AFD in triggering the somatic heat shock response via HSF-1 activation and increased expression of HSP70 chaperones [35]. These discoveries paved the way for uncovering a network of stress pathways regulated nonautonomously and independently of each other by the nervous system (Figure 1).

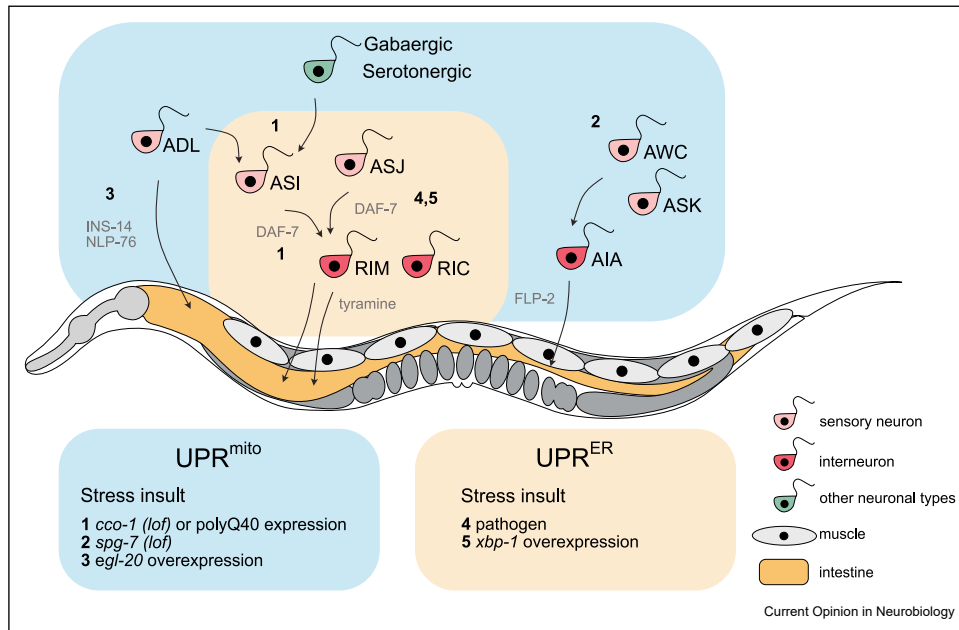
Proteostasis and protein quality control

Sensory neurons coordinate protein quality control across tissues. The UPS in the intestine depends on AWC neurons, while the HSR requires AFD neurons [35,36]. These communication pathways employ distinct mechanisms: AFD utilises dense core vesicles, while AWC enhances proteostasis through inhibition of the toll-like receptor protein TIR-1 by microRNA mir-71 [36,37]. The systemic HSR triggered by AFD activation is relayed through serotonergic neurons and the serotonin receptor SER-1 and serotonin signalling suppresses neurotoxicity of polyglutamine aggregates [38,39].

The endoplasmic reticulum unfolded protein response (UPR^{ER}) is another key stress pathway that, once activated in neurons or glia, triggers its induction in distal tissues [40,41]. Neural induction of distal UPR^{ER} requires synaptic transmission through small clear vesicles, whereas glial induction of distal UPR^{ER} depends on neuropeptide signalling [40,41]. Inter-tissue UPR^{ER} signalling from neurons is mediated by acetylcholine and by tyramine from RIC and RIM interneurons (Figure 1) [42]. UPR^{ER} activation in these neurons is sufficient to trigger distal UPR^{ER}, enhance proteostasis and extend lifespan. Neuronal UPR^{ER} activation also altered food-related exploratory behaviour in a tyramine-dependent manner suggesting that neuronal UPR^{ER} serves as an integrated hub for coordinating physiological and behavioural responses to stress [42].

Neurons also control systemic stress pathways in response to pathogenic bacteria. Exposure to *Pseudomonas* odour activates HSF-1 transcription in a serotonin-dependent manner [43] and intestinal UPR^{ER} via DAF-7/TGF- β signalling from sensory neurons ASI and ASJ to RIM and RIC interneurons [44] (Figure 1). Systemic HSF-1 upregulation and recruitment to the vicinity of RNA polymerase II enriched regions of the genome primes the animal with protection against

Figure 1



Cell nonautonomous regulation of proteostasis stress responses by neurons. Different insults engage distinct neural circuits and UPR responses. With the exception of systemic UPR^{mito} regulation, which does not occur in males, sexual dimorphism in inter-tissue regulation of UPR has not been explored. ASI-RIM communication through DAF-7 is involved in cell non-autonomous regulation of both UPR^{mito} and UPR^{ER}. Neuron names are indicated in black. Neuropeptides (INS-14, NLP-76, FLP-2), neurotransmitters (tyramine) and hormones (DAF-7/TGF-β) in grey. UPR, unfolded protein response.

subsequent encounters with *Pseudomonas* [43], whereas DAF-7 promotes bacterial avoidance and, by enhancing enhances distal UPR^{ER}, improves proteostasis [44].

Mitochondrial stress response networks

DAF-7 signalling from ASI to RIM is also upregulated upon mitochondrial stress and it triggers UPR^{mito} in distal tissues [45]. Neuronal mitochondrial stress can be induced through various manipulations, each of which regulates inter-tissue UPR^{mito} through distinct pathways. Expression of the aggregating polyQ40 protein or knock down of the electron transport chain component cytochrome c oxidase subunit IV (CCO)-1 in the sensory neurons ASI or ADL, in serotonergic neurons or in GABAergic neurons, triggers intestinal UPR^{mito} in a DAF-7 dependent manner (Figure 1). This inter-tissue communication requires synaptic transmission but is independent of neuropeptide communication and the dense core vesicle regulator UNC-31 [45]. In contrast, cell nonautonomous induction of UPR^{mito} in the intestine by neuronal knock-out of the mitochondrial protease SPG-7 requires neuropeptide communication [46]. The neuropeptide gene *flp-2* becomes upregulated in the interneuron AIA, induced by signalling from sensory neurons AWC and ASK [46] (Figure 1). The gene *flp-2*, however, is not required if neuronal mitochondrial stress is induced by expression of the ROS-generating killer red protein [46]. Systemic induction of UPR^{mito} upon

overexpression of the Wnt ligand EGL-20 also requires neuropeptide genes *ins-14* and *nlp-76* from ADL [47] (Figure 1). For further reading on UPR^{mito} regulation in *C. elegans* and mammals, see a recent review by Ref. [48]. Although all aforementioned UPR^{mito} manipulations stated above are lab-based treatments, systemic UPR^{mito} in *C. elegans* is triggered by exposure to pathogenic bacteria and it constitutes an important and advantageous process that increases immunity and lengthens life span [49,50]. Not surprisingly, therefore, many neuron types have the ability to trigger peripheral UPR^{mito} [51]. What neuron type may be the most susceptible to a particular mitochondrial stressor may determine what neurotransmitter will play a bigger role in engaging distal UPR^{mito} in each condition. Mitochondrial stress caused by loss of function in the mitofusin gene *fzo-1* may impact the nervous system broadly as inter-tissue UPR^{mito} requires multiple neurotransmitters and neuropeptides [51]. However, not all manipulations that trigger neuronal mitochondrial stress result in distal UPR^{mito} activation. Uncoupling the electron transport chain from ATP production through overexpression of UCP-4 leads to UPR^{mito} activation only cell autonomously [46]. Another puzzling question that warrants further investigation is what determines stress pathway specificity during inter-tissue signalling given the considerable overlap in neurons and chemokine signalling that exists between stress pathways

(Figure 1). One possibility is that the signals that have been identified to be released by particular neurons during inter-tissue stress response regulation are only a part of a more complex and heterogeneous cocktail of molecules whose composition has pathway specificity. Another possibility, particularly when encountering naturally occurring stressors, is that the receiving tissues are primed to respond with stress pathway specificity upon receiving the neural signals.

Effects of stress on nervous system remodelling and behaviour

The effects of stress on an organism extend beyond cellular physiology and protein homeostasis, influencing nervous system development and behaviour. In this context as well, inter-tissue regulation of the proteostasis network and stress response pathways plays a mechanistic role. During sexual maturation, significant neurite remodelling occurs in certain tail neurons, involving both developmentally programmed, sex-specific pruning and experience-dependent neurite outgrowth. Sex-specific pruning of PHB synapses establishes sexually dimorphic connectivity, which is essential for efficient male mating behaviour [52]. Developmental starvation prevents this pruning, disrupting the formation of male-specific circuitry. As a result, males retain juvenile behaviours and exhibit impaired mating performance [53]. This starvation-induced effect is mediated by octopamine released from RIC neurons, which suppresses serotonin release from ADF neurons—an essential factor for PHB synapse pruning [53]. Additionally, starvation impairs experience-dependent remodelling of the male-specific GABAergic neuron DVB, leading to inappropriate spicule protrusion [54,55]. Aberrant DVB neurite remodelling requires the synaptic components neuroligin and neuroligin, as well as the transcription factors DAF-16/FOXO and HSF-1 [54,55].

Sublethal temperature increases trigger heat stress responses that reduce fertility in both males and hermaphrodites. This reduction is partly due to defects in sperm production in both sexes [56,57] and malformations of the male tail [58]. Additionally, heat stress impacts male reproductive behaviour, particularly motivation [59]. Exposure to heat stress at early larval stages impairs mate-searching behaviour at adulthood. This is consistent with observed developmental defects in tail neurons and reduced expression of the olfactory receptor *odr-10*, both of which regulate male mate-searching behaviour [60–63]. Whether any of these effects induced by heat stress are regulated by the heat stress response pathway and HSF-1 is not known.

Beyond developmental effects, acute stress can directly suppress male sex drive. Acute exposure to high-intensity blue light stimulation disrupts mating behaviour, though tolerance to blue light increases as males

approach ejaculation [64]. Tolerance is enhanced by gain-of-function mutations in *seb-3*, a corticotropin-releasing factor family-like receptor, which lead to a constitutively active stress response system. The receptor SEB-3 enhances excitability in a hub neuron that is reciprocally connected to mating circuits, thereby influencing stress-related disruption of reproductive behaviour [64]. Mating behaviour is also disrupted by acute osmotic stress and this may be why males display enhanced behavioural avoidance compared to hermaphrodites despite males being physiologically more resistant to osmotic stress [65].

Stress also impacts learning in a sexually dimorphic manner. Physiological stress such as mitochondrial disruption (often caused by pathogen infection) results in aversive learning and avoidance of those stress-inducing stimuli [66]. In males, however, previous exposure to pathogenic bacteria does not result in learned avoidance [67], perhaps because of their inability to mount a systemic cell nonautonomous UPR^{mito} [16]. Learned avoidance is regulated by dopamine, serotonin and octopamine released from the mechanosensory neurons CEP and ADE, the pharyngeal neurons NSM and the RIC interneurons, respectively [66,68,69]. Serotonin from NSM modulates the responses of RIB interneurons to stress-inducing bacterial cues [66], whereas octopamine from RIC acts through the receptor SER-6 on AIY interneurons to shape aversive behaviour [66]. These monoamine releasing neurons (such as RIC) receive information about mitochondrial damage in non-neuronal tissues through sphingolipid signalling and the G protein-coupled receptor SPHR-1 [70].

Ageing and cognitive decline

As organisms age, their ability to maintain protein homeostasis (proteostasis) and respond to stress deteriorates, leading to impaired nervous system function. In *C. elegans*, cognitive-like abilities such as learning and memory decline more rapidly in males than in hermaphrodites [31]. In males, ageing is associated with neuronal metabolic decline, morphological abnormalities and a shift in transcriptional profiles from genes related to mitochondrial metabolism and synaptic function to enrichment in proteolysis and proteasome genes. In contrast, aged hermaphrodite neurons are enriched for X-linked, neuronally expressed genes, which may contribute to their greater neural resilience against ageing [30].

Concluding remarks

Organisms respond to stress through diverse and complex mechanisms that integrate genetic, environmental and physiological factors. While the nervous system serves as a global regulator of systemic, cell nonautonomous stress responses, inter-tissue communication remains highly

pathway-specific and insult-specific. Lastly, significant sex differences exist in stress vulnerability, yet the underlying mechanisms remain poorly understood, highlighting an important area for future research.

Declaration of competing interest

The author declares no conflict of interest.

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Data availability

No data was used for the research described in the article.

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