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Neuromodulators: an essential part of survival

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Abstract

The coordination between the animal's external environment and internal state requires constant modulation by chemicals known as neuromodulators. Neuromodulators, such as biogenic amines, neuropeptides and cytokines, promote organismal homeostasis. Over the past several decades, *Caenorhabditis elegans* has grown into a powerful model organism that allows the elucidation of the mechanisms of action of neuromodulators that are conserved across species. In this perspective, we highlight a collection of articles in this issue that describe how neuromodulators optimize *C. elegans* survival.

Keywords

Octopamine; tyramine; dopamine; serotonin; FMRFamide-like peptides; insulin-like peptides; non-FLP; non-ILP neuropeptides; *C. elegans*; neuromodulators; survival; homeostasis

An animal receives multiple environmental stimuli, some of which have the potential to disrupt metabolism and overall physiology. To survive environmental stressors, an animal must transition between a range of internal states and behaviors to identify new set points at which its physiological processes function optimally, thereby regaining homeostasis. One mechanism by which all organisms, including *Caenorhabditis elegans*, integrate changes in their external environments with their internal states is through the secretion of chemicals known as neuromodulators, which allow the animal to best exploit its niche and prioritize survival. This perspective introduces a series of articles in this collection that highlight the role of these chemicals in survival programs, aging and disease.

What are neuromodulators?

Neuromodulators were discovered as brain chemicals that transform a neuron's intrinsic excitability or synaptic dynamics (see Bargmann, 2012; Bargmann & Marder, 2013; Marder, 2012; Taghert & Nitabach, 2012, for excellent reviews on neuromodulator function). In contrast to classical neurotransmitters, diverse members of this class of chemicals, such as

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monoamines, neuropeptides, and cytokines, can be released extrasynaptically from neural sources (Bargmann, 2012; Bargmann & Marder, 2013; Bentley *et al.*, 2016; Marder, 2012; Taghert & Nitabach, 2012). They can also be released from non-neural sources (Marder, 2012; Taghert & Nitabach, 2012). Neuromodulators act locally in a paracrine manner or act hormonally at neural or non-neural targets far from their site of release (Bargmann, 2012; Bargmann & Marder, 2013; Hobert, 2013; Marder, 2012; Schafer, 2006; Taghert & Nitabach, 2012). They can modify the outputs of anatomically defined neural circuits or alter the composition of these circuits to generate entirely different outputs (Bargmann, 2012; Bargmann & Marder, 2013; Marder, 2012; Taghert & Nitabach, 2012). To add to their complexity, a neuromodulator may promote one response by enhancing one cell's activity and/or repressing the activity of another (Bargmann & Marder, 2013; Marder, 2012). Then, due to a change in local cell environments, that same neuromodulator may promote a second or opposite response by affecting the activities of other cells that now express the appropriate receptors (Bargmann & Marder, 2013; Di Giovangiulio *et al.*, 2015; Marder, 2012; Schafer, 2006). This multiplicity of effects by neuromodulators has made their study particularly challenging.

Neuromodulators in *C. elegans* survival

Thanks to the pioneering work of Brenner, Sulston, and others, the worm *C. elegans* has grown into a powerful experimental system to study the effects of neuromodulators on all aspects of animal physiology. *Caenorhabditis elegans* expresses all the major classes of neuromodulators, which include the biogenic amines (serotonin, dopamine, octopamine, and tyramine; Bentley *et al.*, 2016), neuropeptides (short peptides that are processed post-translationally from precursor proteins; reviewed by Hobert, 2013; Li & Kim, 2008), and cytokines [such as TGF-β and the interleukin IL-17 (Bargmann, 2012; Chen *et al.*, 2017)]. The worm's extra-ordinary tractability to forward and reverse genetics allows the easy manipulation of neuromodulators and their receptors in specific cells and visualization of the subsequent changes in cellular properties, behavior, and physiology. The secretion of neuromodulators by neural or non-neural tissues into the worm pseudocoelomic cavity also facilitates the study of the systemic effects of these chemicals—how they mediate communication between neural and non-neural cells. The above advantages of *C. elegans* has yielded a wealth of information that allows us to understand the impact of neuromodulators on its biology. Indeed, the worm's food choices, its decision to forage, mate, or reproduce, its metabolism or responses to threats and competition, its developmental programs and longevity are but some processes influenced by neuromodulators and amenable to experimental manipulation (Aprison & Ruvinsky, 2019; Banerjee, Bhattacharya, Gorczyca, Collins, & Francis, 2017; Beets, Temmerman, Janssen, & Schoofs, 2013; Bhattacharya & Francis, 2015; Cermak *et al.*, 2020; Ezcurra, Walker, Beets, Swoboda, & Schafer, 2016; Ghosh *et al.*, 2016; Ishita, Chihara, & Okumura, 2020; Kagawa-Nagamura, Gengyo-Ando, Ohkura, & Nakai, 2018; Ringstad, 2017; Schafer, 2006; Wu *et al.*, 2019; Zang, Ho, & Ringstad, 2017).

A common thread throughout this issue

The profound influence of neuromodulators on behavior, metabolism, and overall physiology is a common thread throughout this issue (Cheon, Hwang, & Kim, 2020; Honer *et al.*, 2020; Kim & Flavell, 2020; Kim, Lee, Kim, & Lee, 2020; Liang, McKinnon, & Rankin, 2020; Liu & Zhang, 2020; Muirhead & Srinivasan, 2020; Prahlad, 2020; Srinivasan, 2020; Takeishi, Takagaki, & Kuhara, 2020; Yang, Lee, Yim, & Lee, 2020). In this perspective, we will focus on the roles of monoamines and neuropeptides in *C. elegans* survival.

Monoamine modulators—*Caenorhabditis elegans* synthesizes four monoamine neuromodulators—octopamine (OA), tyramine (TA), dopamine (DA), and serotonin (5-HT)—but lack histamine, epinephrine, and norepinephrine, which are found in vertebrates (Bentley *et al.*, 2016; Chase & Koelle, 2007). The major source, and, in some cases, the only source, of these monoamine modulators are neurons. *Caenorhabditis elegans* mutants that lack key biosynthetic enzymes for each of the bioamine neuromodulators are viable, allowing *C. elegans* to serve as a powerful discovery platform to understand neuromodulator function. These bioactive monoamine synthesis mutants exert pleiotropic effects on *C. elegans* internal states, thereby affecting behavior (see, *e.g.*, Cermak *et al.*, 2020; Ghosh *et al.*, 2016; Schafer, 2006).

Octopamine and tyramine.: OA and TA are considered the functional equivalent of epinephrine and norepinephrine in invertebrates (Li *et al.*, 2017). OA and TA are best characterized in orchestrating the transition between the foraging state, which is elicited by lack of food, and the dwelling state, which denotes food availability. TA is present in low abundance and is synthesized by the enzyme tyrosine decarboxylase (TDC-1) in the RIM-1 motor neurons, gonadal sheath cells, and the uv1 neuroendocrine cells (Alkema, Hunter-Ensor, Ringstad, & Horvitz, 2005; Chase & Koelle, 2007). OA is synthesized from TA by the enzyme tyramine β-hydroxylase (TBH-1) in RIC interneurons and the gonadal sheath cells (Alkema *et al.*, 2005; Chase & Koelle, 2007; Horvitz, Chalfie, Trent, Sulston, & Evans, 1982). Food deprivation results in the release of OA by the RIC neurons (Churgin, McCloskey, Peters, & Fang-Yen, 2017; Roeder, 2020; Suo, Culotti, & Van Tol, 2009). The released OA acts via the G protein-coupled receptors (GPCRs) SER-3 and SER-6 in SIA neurons to promote roaming behaviors that increase the probability of finding food (Churgin *et al.*, 2017; Suo *et al.*, 2009). When food becomes available, TA promotes reduced locomotion to allow feeding (Churgin *et al.*, 2017).

Caenorhabditis elegans is a bacterivore, and the bacteria encountered by the animal range from highly nutritious to poorly nutritious and outright pathogenic (see Kim & Flavell, 2020; this issue). Interestingly, OA also suppresses aversive behaviors (Guo *et al.*, 2015; Mills *et al.*, 2012) to prioritize feeding. OA allows *C. elegans* to tolerate low-quality or detrimental bacterial food sources by modulating bacteria-elicited innate immune responses (Sellegounder, Yuan, Wibisono, Liu, & Sun, 2018; Suo *et al.*, 2009). Consequently, OA mediates a shift towards attraction to a greater range of foods, like altering the valence of the response to CO_2 levels that typically signify food (Rengarajan, Yankura, Guillermin, Fung, & Hallem, 2019). In this issue, Srinivasan (2020) discusses how RIC neuron-secreted OA

coordinates food availability with lipolytic activity by signaling through intestinal SER-3 receptors to activate the intestinal lipases LIPS-6 and ATGL-1.

Remarkably, *C. elegans* is subject to signaling not only from its self-synthesized OA, but also from OA or OA-like compounds secreted by certain bacteria or other *C. elegans*, respectively. In this issue, Kim and Flavell (2020) highlight the recent findings from the Sengupta lab (O'Donnell, Fox, Chao, Schroeder, & Sengupta, 2020) on how OA produced by commensal bacteria alters *C. elegans* behavior and internal state. Cheon *et al.* (2020; this issue) and Muirhead and Srinivasan (2020; this issue) also review how starved larvae produce the OA-like small molecule osas#9, an ascaroside component of the worm-secreted pheromone blend, which is then sensed by nociceptive ASH neurons in adults to initiate their avoidance behavior (Chute *et al.*, 2019).

Dopamine.: The DA neurons in *C. elegans* were initially identified by Sulston and coworkers (Sulston, Dew, & Brenner, 1975), using the catecholamine-specific technique of formaldehyde-induced fluorescence (FIF). DA is synthesized in eight neurons (ADEL/R, CEPDL/R, CEPVL/R, and PDEL/R) in hermaphrodites and in six additional neurons (R5AL/R, R7AL/R, R9AL/R) in males by the tyrosine hydroxylase CAT-2, which catalyzes the rate-limiting step in dopamine synthesis (Lints & Emmons, 1999; Sulston, Dew, & Brenner, 1975). As in other animals, *C. elegans* DA plays key roles in coordinating motor programs with the reward system during foraging, feeding, and egg laying (Ardiel *et al.*, 2016; Bettinger & McIntire, 2004; Chase & Koelle, 2007; Cermak *et al.*, 2020; Qin & Wheeler, 2007; Rivard *et al.*, 2010; Sanyal *et al.*, 2004; Sawin, Ranganathan, & Horvitz, 2000; Suo *et al.*, 2019). DA is released upon sensing food (Oranth *et al.*, 2018) to initiate the slowing of movement in the presence of food (Sawin *et al.*, 2000). Thus, DA counteracts OA-induced hyperactivity (Luedtke, O'Connor, Holden-Dye, & Walker, 2010; Rengarajan, Yankura, Guillermin, Fung, & Hallem, 2019). Similarly, DA works antagonistically to OA in switching the responses to CO_2: DA promotes aversion to CO_2 in the fed state and OA promotes attraction in the starved state (Rengarajan *et al.*, 2019). As in mammalian neurodegenerative models, *C. elegans* DA neurons appear more susceptible to degeneration upon expression of disease-associated aggregation-prone proteins, such as α-synuclein (Mor *et al.*, 2017). In this collection, the Rankin lab focuses on how *C. elegans* serves as a powerful model in which to study neurodegeneration (Liang, McKinnon, & Rankin, 2020).

Serotonin.: The rate-limiting enzyme tryptophan hydroxylase, TPH-1, synthesizes 5-HT in eight to ten neurons in hermaphrodites (ADFL/R, NSML/R, HSNL/R, ASGL/R upon hypoxia, and rarely in AIM and RIH) and in more neurons in males (CP0 to CP06 and the B-type ray neurons R1BL/R, R3BL/R, and R9BL/R; Hare & Loer, 2004; Loer & Kenyon, 1993; Loer & Rivard, 2007; Pocock & Hobert, 2010; Serrano-Saiz *et al.*, 2017). Release of 5-HT from each of these neurons performs different functions, either because of its co-release with other neurotransmitters (Srinivasan, 2020; this issue) or because the acute versus chronic availability of 5-HT exerts different effects on target tissues (Prahlad, 2020; this issue). In the worm, 5-HT can mimic food and favorable conditions or signal stress, based upon the duration and site of release (Avery & You, 2012; Chase & Koelle, 2007; Cruz-Corchado, Ooi, Das, & Prahlad, 2020; Curran & Chalasani, 2012; Ishita, Chihara, &

Okumura, 2020; Rankin, 2006). For instance, 5-HT can promote recovery from the developmental arrest known as dauer that forms in response to early life stress (Cassada & Russell, 1975; Mylenko *et al.*, 2016; see also Yang, Lee *et al.*, 2020), by mimicking food signals that promote growth and differentiation (Srinivasan, 2020; this issue). Alternatively, 5-HT can activate behavioral avoidance responses or stress-responsive transcription programs (Prahlad, 2020; this issue). Notably, these opposing effects resemble what is observed during the administration of 5-HT modulators for the treatment of neuropsychiatric disorders in humans: an acute increase in 5-HT availability causes increased anxiety; chronic treatment leads to anti-depressant effects (Sharp & Cowen, 2011).

Neuropeptides—The *C. elegans* genome contains more than 120 genes that encode neuropeptide precursor proteins, and these proteins are processed to more than 250 neuropeptides. Most of their receptors belong to the large GPCR family but can also include ion channels and receptor kinases (for more extensive reviews on neuropeptides and their receptors, see Hobert, 2013; Li & Kim, 2008). *Caenorhabditis elegans* has the FMRFamide-like peptides (FLPs; Li, Kim, & Nelson, 1999), insulin-like peptides (ILPs; Pierce *et al.*, 2001), and the non-FLP, non-ILP neuropeptides called NLPs (Nathoo, Moeller, Westlund, & Hart, 2001). Like the biogenic amines, neuropeptides have also been extensively studied in *C. elegans* and are implicated in behaviors and physiological mechanisms that modulate homeostasis and survival.

FMRFamide-like peptides.: A prominent example of a worm FLP-dependent pathway is neuropeptide Y signaling, which is represented by the FLP-21 peptide ligand and its associated GPCR, NPR-1 (Rogers et al., 2003). FLP-21 and NPR-1 are required for avoidance responses to noxious stimuli and loss of pathway activity compromises survival (Glauser *et al.*, 2011; Reddy, Andersen, Kruglyak, & Kim, 2009; Styer et al., 2008). In this issue, Kim and Flavell (2020) review how this pathway can alter *C. elegans* behavior in response to bacterial metabolites in the animal's natural environment. Other FLP genes also modulate longevity and metabolism. In this collection, Kim *et al.* (2020) describe the role of *flp-6* in increasing survival at high temperatures, but *flp-6* also intriguingly exhibits an opposite role in survival at lower temperatures (Chen *et al.*, 2016). Srinivasan (2020; this issue) discusses how FLP-17 coordinates environmental oxygen levels with intestinal fat metabolism. Yang *et al.* (2020; this issue) refer to findings by the Sternberg lab (Lee *et al.*, 2017), where peptides encoded by two *flp* genes, *flp-10* and *flp-17*, facilitate a dispersal behavior adopted by dauers in migrating to environments that support better survival.

Insulin-like peptides.: ILP signaling has long been associated with survival (see Kenyon, 2010; and references therein). The worm ILP receptor DAF-2, which is a receptor tyrosine kinase (Kimura, Tissenbaum, Liu, & Ruvkun, 1997), promotes reproductive growth and inhibits dauer arrest (Riddle, Swanson, & Albert, 1981). The downregulation of DAF-2 activity doubles *C. elegans* lifespan (Kenyon, Chang, Gensch, Rudner, & Tabtiang, 1993), a discovery that ushered the birth of a field—the genetics of aging. Like DAF-2 (Gems *et al.*, 1998), at least some of the worm ILPs (Hobert, 2013; Li & Kim, 2008) have pleiotropic functions (Fernandes de Abreu *et al.*, 2014), which might be a consequence of their ILP-to-ILP network organization, where one ILP regulates multiple ILPs (Fernandes de Abreu *et*

al., 2014). Many of the ILP functions typify neuromodulator functions. For example, there are ILPs that sometimes behave like the DAF-2 receptor in one context and opposite from DAF-2 in another context (Fernandes de Abreu *et al.*, 2014). The articles in this collection discuss the roles of ILPs in temperature-sensing (see Takeishi, Takagaki, & Kuhara, 2020), in context-dependent avoidance behaviors (see Cheon, Hwang, & Kim, 2020; Kim & Flavell, 2020), in neuroprotection (see Liang, McKinnon, & Rankin, 2020), the dauer program (see Yang *et al.*, 2020), and longevity (see Kim *et al.*, 2020).

Non-FLP, non-ILP neuropeptides.: NLPs comprise a heterogeneous group of neuropeptides, but are again involved in diverse physiological processes (Li & Kim, 2008; Hobert, 2013), from sleep behaviors (see Honer, Buscemi *et al.*, 2020; this issue) to neurodegeneration (Lezi *et al.*, 2018) and longevity (Park, Link, & Johnson, 2010). Similar to FLPs and ILPs, NLPs can amplify or dampen signaling at specific synapses (Chalasani *et al.*, 2010; Hapiak *et al.*, 2013; Macosko *et al.*, 2009), thereby shaping circuit connectivities and behaviors. The three classes of neuropeptides, the FLPs, ILPs, and NLPs, are also known to work together through feedforward or feedback mechanisms to maintain homeostasis at both the circuit level and the organismal level (Chalasani *et al.*, 2010; Chen, Chen *et al.*, 2016).

Coda

The dysregulation of neuromodulator activities can lead to disease. Indeed, numerous studies in mammalian systems implicate neuromodulator dysfunction in neurodegenerative diseases, such as Alzheimer's disease, Huntington's disease and Parkinson's disease, where impaired neuromodulator signaling often preempt disease symptoms (Du, Pang, & Hannan, 2013; Elsworthy & Aldred, 2019; Ohno, Shimizu, Tokudome, Kunisawa, & Sasa, 2015; Politis & Niccolini, 2015). *Caenorhabditis elegans* expresses many orthologs of neurodegenerative disease-associated genes and their study in the worm have contributed to our understanding of the above human diseases (see Liang, McKinnon, & Rankin, 2020; this issue). Understanding the role of neuromodulators in worm neurodegeneration will likely add to our understanding of human neurodegenerative disorders.

To conclude, we would like to highlight an important question. How does a neuromodulator modify a physiological response to a stimulus? This question circles back to experiments performed in the 1960s. Injection of an abdominal ganglion extract from one *Aplysia* into another *Aplysia* elicited the cessation of locomotor and feeding behavior, followed by the stereotyped head-waving behavior that facilitated egg laying in the second animal (Kupfermann, 1967; Strumwasser, Jacklet, & Alvarez, 1969; Toevs & Brackenbury, 1969). These experiments demonstrated that diverse modulatory substances could act centrally and peripherally to change the physiological state of an animal completely. It would be interesting to learn the rules and constraints by which different cocktails of neuromodulators achieve such a dramatic switch in physiological responses to environmental stimuli. Ultimately, the complete identification of the interacting modulators, their receptors and sites of action should allow us to address this question. We posit that *C. elegans* is an ideal system to achieve this goal.

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