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## Dopamine manages locomotion in *Caenorhabditis elegans* by modulating motor neurons

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### Abstract

Dopamine is a crucial neurotransmitter in the brain that regulates the coordination of movement and cognition by modulating synaptic activity through two kinds of G protein-coupled receptors. It has also been demonstrated that these two receptor classes can have either positive or negative effects on neurotransmission. Although the pharmacology of mammalian dopamine receptors has been extensively defined, less is known about the molecular pathways that work downstream of the receptors. *Caenorhabditis elegans*, which requires two types of dopamine receptors to regulate brain activity, can be used as a genetic tool to pinpoint the molecular processes by which dopamine receptors influence neurotransmission.

**Keywords:** Dopamine, neurotransmitter, *Caenorhabditis elegans* and brain activity

### Introduction

Dopamine is a neuromodulator that is widely known for controlling direct and indirect circuits of the basal ganglia that generate excitatory D1 and inhibitory D2 receptors, respectively, in vertebrates. It is well known that dopamine plays a crucial role in controlling neuronal activity in the mammalian brain. To affect neurotransmission in mammals, dopamine binds to five or seven transmembrane heterotrimeric G-protein coupled receptors. Based on biochemical and pharmacological criteria, these five mammalian dopamine receptors have also been divided into two classes: D1-like and D2-like [1-4]. For instance, high concentrations of dopamine released during phasic cell firing stimulate lower affinity excitatory D1 receptors, which in turn promote locomotor activity, while low concentrations of dopamine released during tonic activity stimulate higher affinity inhibitory D2 receptors, which in turn reduce motor output.

It appears that its function in plants is that of a potent antioxidant, protecting against the lipid peroxidative damage brought on by the extreme heat and sunlight of the tropics. Dopamine appears to be present wherever it is needed in bacteria, fungi, protozoans, cnidarians, nematodes, arthropods, mollusks, annelids, and vertebrates [5, 6]. Dopamine is widely used across taxa and within species, where it may influence a variety of processes thanks to a multitude of specific receptors. This diversity might have developed by bacterial gene duplication and horizontal gene transfer pathways [7, 8]. One of dopamine's primary functions in animals is to serve as a behavioural switch in the change from quicker to slower motor behaviours. The clearest examples of this have been found in carefully monitored electrophysiological studies of fictive rhythmic locomotion in reduced (semi-intact) preparations. Dopamine, for instance, slows snails' movement. Dopamine suppresses swimming and encourages crawling in sea slugs and leeches, while slowing locomotor rhythms in lamprey, zebrafish, and crabs. However, it hasn't been shown that dopamine plays a part in regulating locomotion in these systems in naturally behaving animals [9-11].

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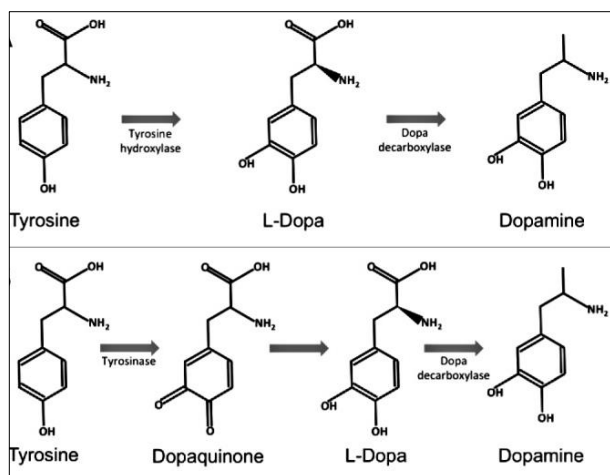


Fig 1: Synthesis pathway for dopamine

### Dopamine Signaling in *C. elegans*

Motoneuron classes in the head ganglia and the ventral nerve cord, which are characterised by transmitter, dorso-ventral innervation, and functions in forward or backward locomotion, are used by *C. elegans* to carry out movement. Premotor interneurons (PINs), which directly innervate and "gate" motoneurons to coordinate forward or backward states, give instructions to this fundamental machinery. Proprioceptive input is necessary to transmit undulatory body waves [12]. PINs combine sensory data from the head and body to react to signals that are either repellent or enticing. Head motoneurons and interneurons regulate more advanced locomotor behaviours like directional changes and navigation. Neuropeptides and transmitters like serotonin, tyramine, octopamine, and dopamine (DA) are involved in modulating behavioural switches, long-term behavioural states, and strategies for long-range locomotion, such as finding (and remaining at) a food source. Finding nourishment necessitates sharp actions like slowing down [13-15].

In some subsets of cholinergic motoneurons, *C. elegans* coexpresses D1-like (DOP-1) and D2-like (DOP-3) receptors. DOP-1 and DOP-3 act antagonistically to control movement when animals come across food. DVA and AVK interneurons are deeply innervated by dopaminergic PDE neurons. Body bending triggers a response from DVA, which then feeds back to moto- and interneurons to affect body posture [16, 17]. DVA reacts to body bending and transmits feedback to interneurons and moto-neurons, which affects body posture. DVA signals to motoneurons via NLP-12 neuropeptides and the G-protein-coupled receptor CKR-2 to control locomotion by integrating mechanosensory information (from PDE neurons, via the DOP-1 receptor) about the presence of food. The production of NLP-12 peptides, which are connected to cholecystokinin and are involved in motivated behaviour and movement in animals and are also controlled by DA signalling, for example, in reward-associated behaviour such as feeding. FLP-1 FMRFamide-like neuropeptides are expressed by AVK neurons, and *flp-1* deletion causes hyperactive locomotion [18-20].

It has been demonstrated that mutations in the molecular elements essential for limiting locomotion in response to dopamine are resistant to these paralytic effects when high doses of exogenous dopamine are administered to *C. elegans*. Therefore, utilising exogenous dopamine resistance

as a selective criterion, forward genetic techniques can be employed to uncover additional dopamine signalling pathway components in *C. elegans*. These prior screenings were successful in discovering some elements of dopamine transmission in *C. elegans* that are preserved in mammal. Given the significance of the DOP-3 receptor in the exogenous dopamine response and the fact that dop-3 mutants were not isolated in these screens, we hypothesised that there may be other dopamine signalling components that are still unknown. Consequently, a modified genetic screen was carried out to identify new elements of the exogenous dopamine response. Our screening revealed that two opposing dopamine receptor signalling pathways exist inside a single cell, and that dopamine regulates the excitability of the cholinergic motor neurons to control the release of acetylcholine [21].

### Rab GTPases role in dopamine signaling

Rab activity can be altered by a number of other proteins. Rab GTPases are significant molecular switches that control the transit, docking, and fusion of vesicles in many cellular processes. A Rab protein's affinity for vesicular membranes is improved by guanine nucleotide exchange factors (GEFs), and a Rab protein's intrinsic GTPase activity is boosted by Rab GTPase activating proteins (Rab GAPs), which causes the Rab protein to separate from the membrane to which it is bound [22]. RAB-3 (a homolog of mammalian Rab3A) and AEX-6, two Rab GTPases, have been found to be localised to the pre-synaptic terminals of cholinergic motor neurons in *C. elegans* (homolog of mammalian Rab27A). In *C. elegans*, it has been demonstrated that RAB-3 and AEX-6 both play significant roles in synaptic transmission.

Genetic search for mutants resistant to exogenous dopamine led us to the discovery of a mutation in the *tbc-4* gene, which in *C. elegans* is believed to encode a Rab GAP. Since the TBC-4 protein is predicted to include a single TBC domain and all known Rab GAPs include this highly conserved TBC domain, it is plausible that the *tbc-4* gene encodes a Rab GAP in *C. elegans*. Furthermore, the resistance of a *tbc-4* mutant to exogenous dopamine implies that dopamine signalling may have an impact on the regulation of Rab GTPase activity, and this regulation may offer a method by which dopamine regulates acetylcholine release.

The fact that mutations in both TBC-4 and RAB-3 restore the SWIP phenotype in *dat-1* mutants is also unexpected, as it suggests that both RAB-3 and TBC-4 are necessary to inhibit acetylcholine release. This finding is supported by TBC-4's functional role as a Rab GAP but goes against what one would expect of a Rab GTPase. However, it has been shown that Rab3A can inhibit neurotransmitter release in the mammalian nervous system under specific circumstances, so this observation is not new [23].

### DOP-3 signalling inhibits acetylcholine release

The cAMP-dependent processes in the mammalian brain are inhibited by D2-like receptors, and the *C. elegans* D2-like receptor DOP-3 has also been demonstrated to suppress neurotransmission. In addition to playing an obvious function in controlling locomotor activity, DOP-3's expression pattern in ventral cord motor neurons also implies that communication via the DOP-3 receptor decreases acetylcholine release. These findings provide strong evidence that DOP-3 receptor signalling prevents

acetylcholine release from cholinergic motor neurons, supporting mammalian research on the regulation of striatal cholinergic interneurons by D2-like receptors [24]. Although it is well recognised that D1- and D2-like dopamine receptors can influence neurotransmission either antagonistically or synergistically, the underlying mechanism(s) for these interactions is (are) poorly unclear. Even though there is growing evidence for the co-expression of D1- and D2-like receptors in particular cell types, it has been widely observed that the antagonistic or synergistic interactions between these two receptor signalling pathways occur between different cells that express only one class of receptor at detectable levels [25].

### Dopamine Mediates Movement

Recent research on *C. elegans* movement has heavily relied on modelling methods to quantify the physical interactions between this microscopic organism and its surroundings. In fact, a complete comprehension of movement requires an awareness of the physical characteristics of the animal and its surroundings [26-28]. Dopamine has been found to modify the so-called basal-slowing behaviour, in which worms slow down when they enter a patch of food, in *C. elegans*. When dopamine neurons are activated in water using D1-like signalling, the animal immediately changes from swimming to a form of the worm's feeding crawl. In both situations, velocity is decreased by dopamine neuron activity, but the consequences are reverse when dopamine signalling is lost. In particular, after entering a feeding patch, worms with reduced dopamine signalling continue to travel fast as if there is no food present, but when moving from the water to land, the same worms with reduced dopamine signalling stop all movement. Additionally, the basal-slowing response utilises D2-like dopamine signalling as opposed to the D1-like signalling route that we identified to be necessary for the transition from swimming to crawling. Dopamine thus appears to have context-dependent effects on locomotion, delaying crawling on land through a D2-like pathway and inducing crawling as animals escape water through a D1-like pathway.

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