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# Dopamine Controls Locomotion by Modulating the Activity of the Cholinergic Motor Neurons in C. elegans



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Document Type
Open Access

Degree Program
Biochemistry

Degree Type
Master of Science (M.S.)

Year Degree Awarded
2009

Month Degree Awarded
May

Keywords
dopamine receptor elegans acetylcholine GAP neurotransmission

Abstract
Dopamine is an important neurotransmitter in the brain, where it plays a regulatory role in the coordination of movement and cognition by acting through two classes of G protein-coupled receptors to modulate synaptic activity. In addition, it has been shown these two receptor classes can exhibit synergistic or antagonistic effects on neurotransmission. However, while the pharmacology of the mammalian dopamine receptors have been characterized in some detail, less is known about the molecular pathways that act downstream of the receptors. As in mammals, the soil nematode Caenorhabditis elegans uses two classes of dopamine receptors to control neural activity and thus can serve as a genetic tool to identify the molecular mechanisms through which dopamine receptors exert their effects on neurotransmission. To identify novel components of mammalian dopamine signaling pathways, we conducted a genetic screen for C. elegans mutants defective in exogenous dopamine response. We

screened 31,000 mutagenized haploid genomes and recovered seven mutants. Five of these mutants were in previously-identified dopamine signaling genes, including those encoding the Ga proteins GOA-1 (ortholog of human Gao) and EGL-30 (ortholog of human Gaq), the diacylglycerol kinase DGK-1 (ortholog of human DGK0), and the dopamine receptor DOP-3 (ortholog of human D2-like receptor). In addition to these known components, we identified mutations in the glutamate-gated cation channel subunit GLR-1 (ortholog of human AMPA receptor subunits) and the class A acetycholinesterase ACE-1 (ortholog of human acetylcholinesterase). Behavioral analysis of these mutants demonstrates that dopamine signaling controls acetylcholine release by modulating the excitability of the cholinergic motor neurons in C. elegans through two antagonistic dopamine receptor signaling pathways, and that this antagonism occurs within a single cell. In addition, a mutation in the putative Rab GTPase activating protein TBC-4 was identified, which may suggest a role for this Rab GAP in synaptic vesicle trafficking. Subsequent behavioral and genetic analyses of mutants in synaptic vesicular trafficking components implicate RAB-3-mediated vesicular trafficking in DOP-3 receptor signaling. These results together suggest a possible mechanism for the regulation of dopamine receptor signaling by vesicular trafficking components in the cholinergic motor neurons of C. elegans.

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