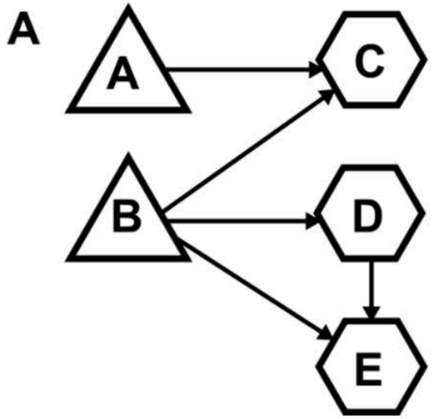
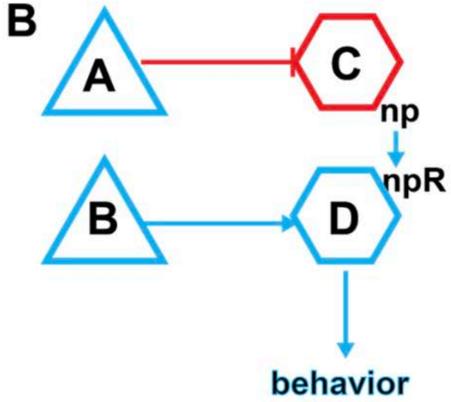
The Goal *Model organism neural circuit knowledge graph*

NOT-OD-21-094





Connectome data (physical connections between neurons)

Functional data (activity of neurons by ephys or Ca+2)

Link Neurons to Behavior

Gene expression data (e.g., neuropeptides, receptors, ion channels)

Optogenetic data: neuronal activation and silencing

Compute on knowledge graph to predict circuits, effects of genetic variants, etc.

Sharan Prakash, Kimberly Van Auken, Nick Stiffler, Raymond Lee, Markus Meister, David Hill, PWS

NIH National Human Genome Research Institute

NIH National Library of Medicine

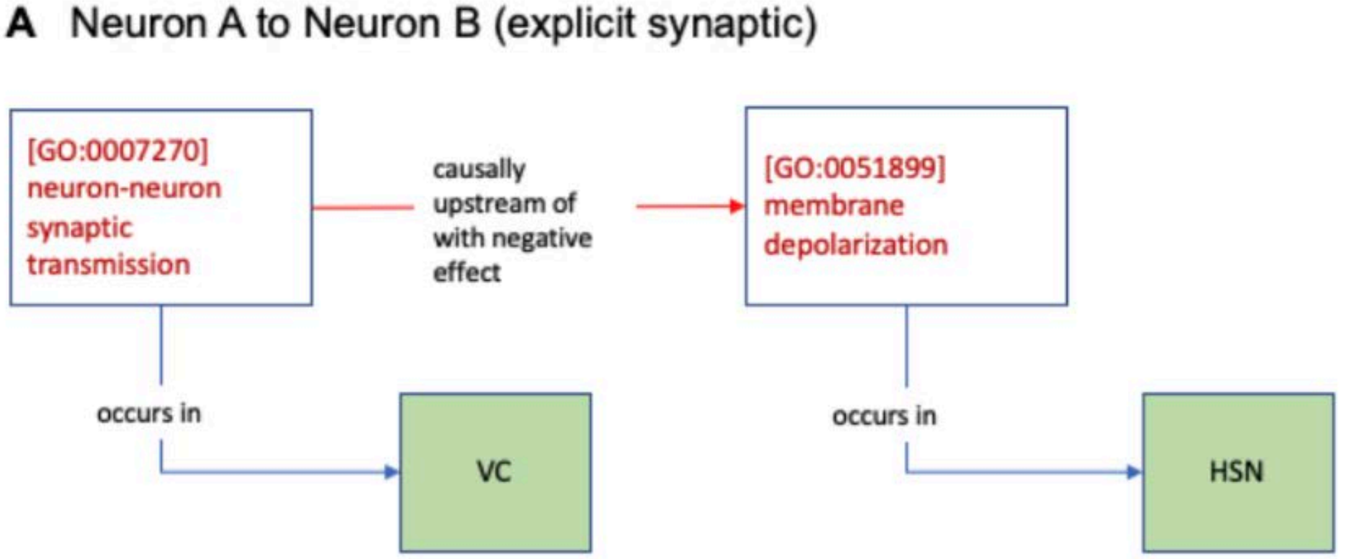
ALLIANCE of GENOME RESOURCES

ACKnowledge Author Curation to Knowledgebase

The Problem

Convert author statements to assertions

"To determine whether VC synaptic transmission regulates egg laying via HSN, we recorded HSN Ca2+ activity in WT and transgenic animals expressing TeTx in the VCs (Fig. 6A). During the egg-laying active state, the HSNs drive egg laying during periods of increased Ca2+ transient frequency in the form of burst firing (Fig. 6B) (Collins et al., 2016; Ravi et al., 2018a). We observed a significant increase in HSN Ca2+ transient frequency when VC synaptic transmission was blocked compared with nontransgenic control animals (Fig. 6C). WT animals spent ~11% of their time exhibiting high-frequency burst activity in the HSN neurons, whereas transgenic animals expressing TeTx in the VC neurons spent ~21% of their time exhibiting HSN burst firing activity (Fig. 6D). These results are consistent with the interpretation that VC neurotransmission is inhibitory toward the HSNs, such as proposed in previous studies (Bany et al., 2003; Zhang et al., 2008)."

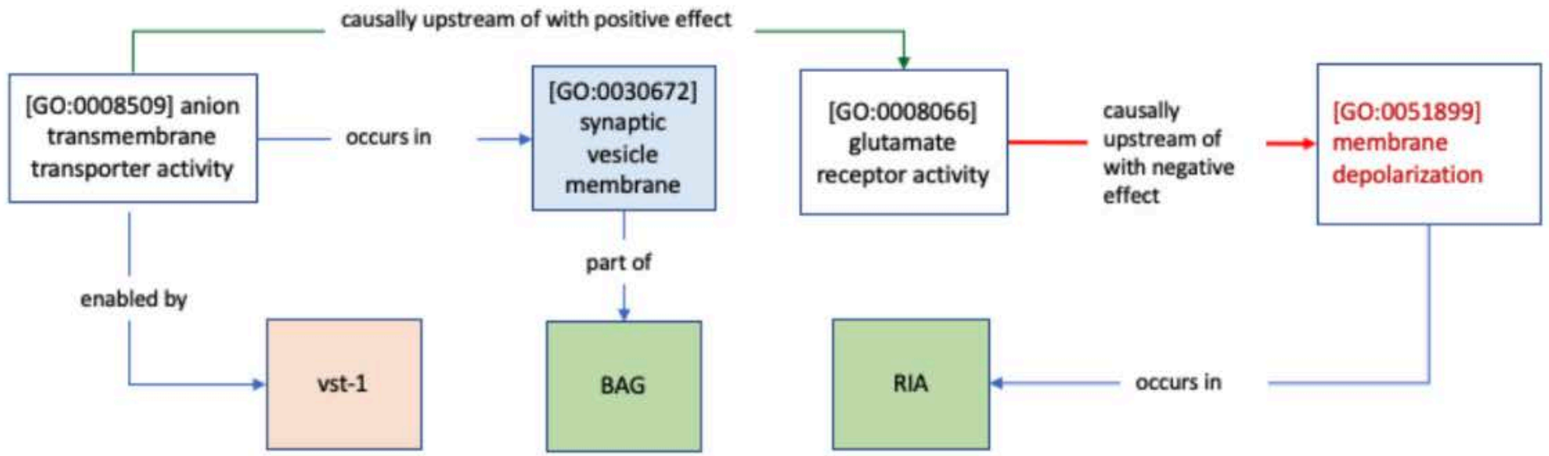


Progress

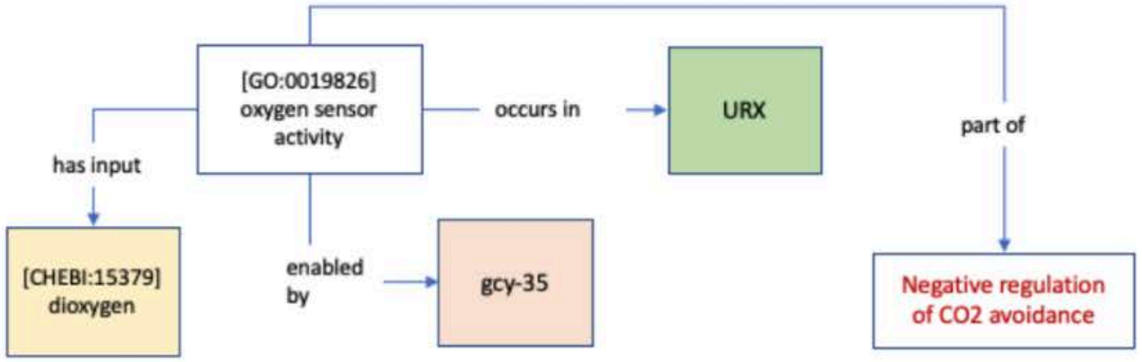
Model types of connections between neurons

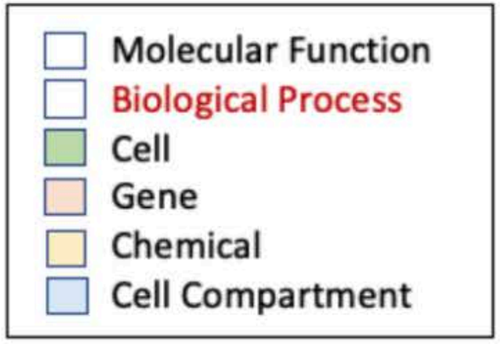
Use GO-CAM approach

C Gene Activity Affecting Synaptic Transmission



D Sensing of environmental stimuli by receptor within neuron





Progress

Model types of connections between neurons

Categories of Neurobiological Phenomena Modelled with GO-CAM

Neuron-neuron interaction

Activity of Neuron A regulates activity of Neuron B (explicit synaptic)

Neurotransmitter activity regulates behaviour or cell activity

Neurotransmitter regulates behaviour via specific receptor (cell agnostic)

Neurotransmitter regulates behaviour via specific receptor in identified neuron

G-protein pathway activity regulates behaviour or cell activity

G protein activity in specific neuron regulates behaviour

Ion channel activity regulates behaviour or cell activity

Neurotransmitter regulates neuronal activity via ion channel

Environmental influence on behaviour or cell activity

Environmental condition regulates neuronal activity

Neuron regulates behaviour

Neuron regulates cellular activity

Neuronal activity regulates peptide secretion.

Mechanical regulation

Mechanical stimulation of Neuron A regulates activity of Neuron B

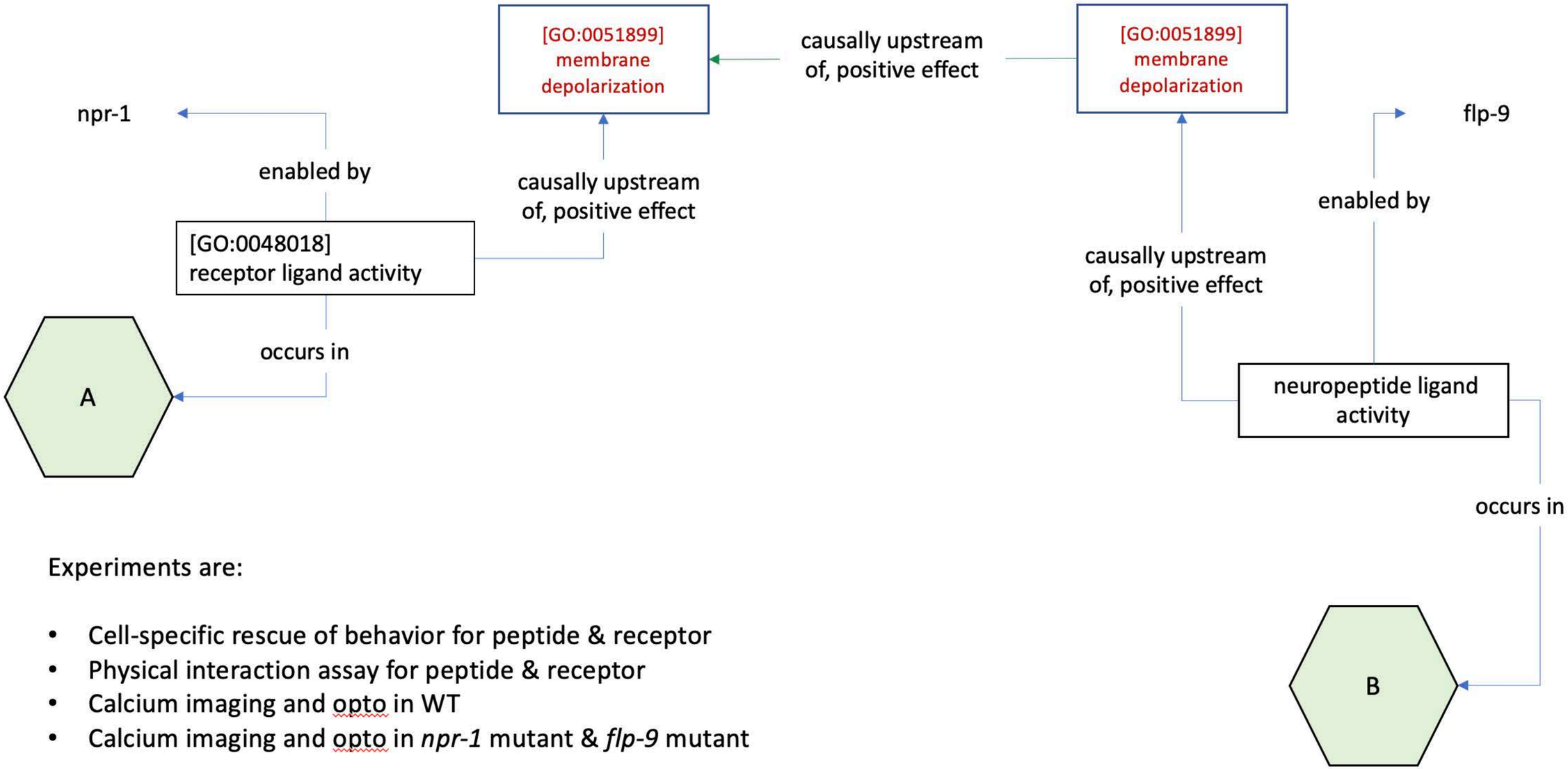
Neuromodulation

Neuromodulation of specific neuron by ion channel activity (cell agnostic)

Etc.

Progress

Model neuropeptidergic signaling



Experiments are:

- Cell-specific rescue of behavior for peptide & receptor
- Physical interaction assay for peptide & receptor
- Calcium imaging and opto in WT
- Calcium imaging and opto in *npr-1* mutant & *flp-9* mutant

Progress

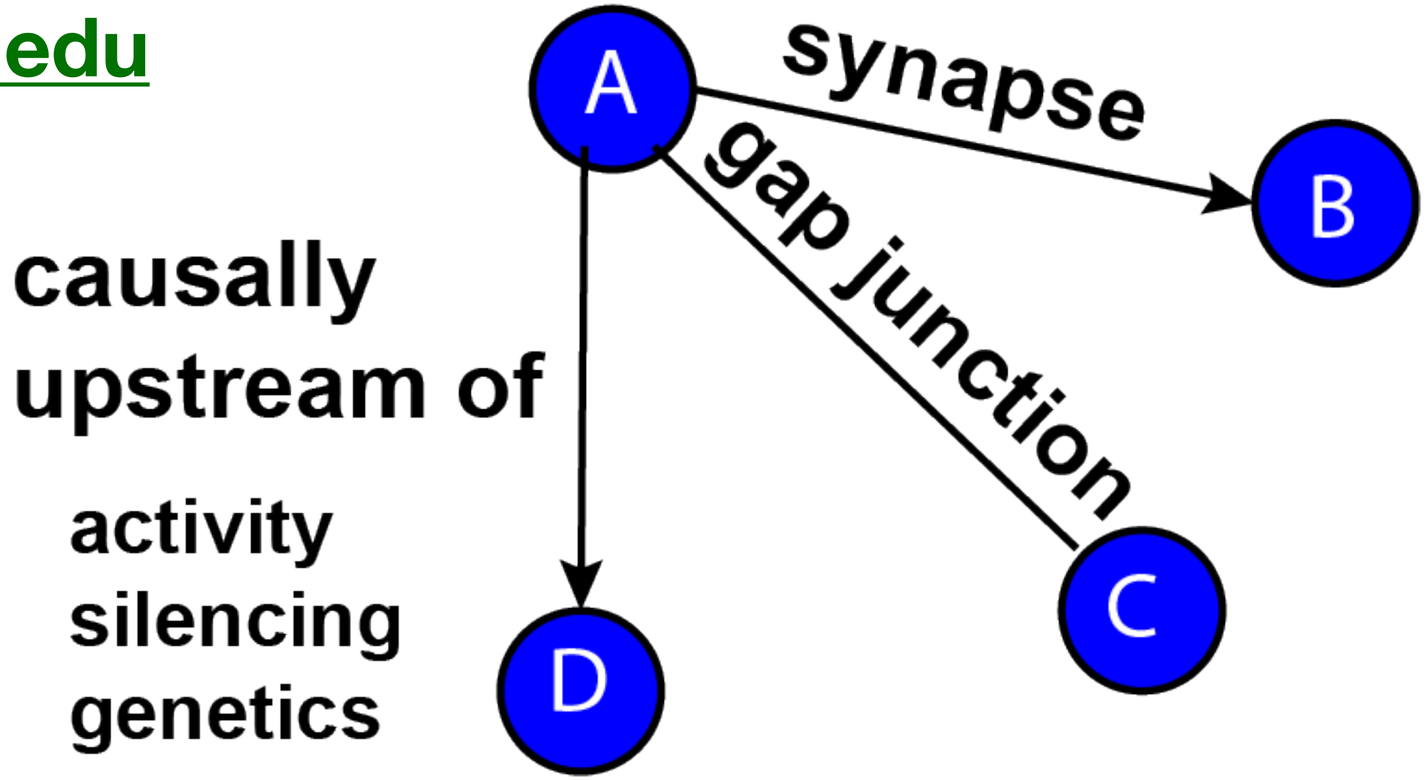
Ontology development: add to existing ontologies

Category	Proposed Novel or Modified Class	Notes, Definitions or Proposed Modification
Biological Process	Neuromodulation	Any process that regulates the excitability, dynamic response, synaptic connectivity or output (electrical or molecular) of a neuron.
Biological Process	CO2 avoidance	Locomotory behavior directed away from a source or gradient of carbon dioxide.
Biological Process	Membrane depolarization (frequency)	Any process that modulates the frequency of membrane depolarization. Membrane depolarization is the process in which membrane potential changes in the depolarizing direction from the resting potential, usually from negative to positive.
Molecular Function	Chloride Ion Export	The directed movement of chloride ions out of a cell or organelle.
Molecular Function	CO2 sensor activity	Binding to and responding, e.g. by conformational change, to changes in the cellular level of carbon dioxide (CO2) or its dissociation products in water.
ECO Evidence Classes	Neuron Chemical Inhibition Assay	A type of experimental phenotypic evidence arising from experiment in which neuronal activity is manipulated using genetically encoded, chemical activated inhibitors of neural activity.
ECO Evidence Classes	Synaptic Transmission Inhibition Assay	A type of experimental phenotypic evidence arising from experiment in which neuron-to-neuron synaptic transmission is manipulated using genetically encoded inhibitors of synaptic transmission.
ECO Evidence Classes	Long-term Exposure or Conditioning Assay	A type of experimental phenotypic evidence arising from experimental treatment involving sustained exposure of an organism to one or more environmental conditions.
Environmental Inputs	Nutrition	Exposure to a source of nutrition such as a naturally-occuring food source or specific supplemental nutrition e.g. amino acids
Environmental Inputs	Increasing	Exposure to an input whose intensity or frequency is increasing over time or space.

Progress

Visualization logic & design

Use nemanode.org
funcoNN.princeton.edu



Thanks to Mei Zhen (Toronto) and Andy Leifer (Princeton)

Progress

Training sets for NLP

Towards Automated generation of first-pass semantic models

Biological Category	PMID	Author	Author Statement	ECO evidence 1	ECO evidence 2	ECO evidence 3	PROCESS 1	Relation 1a	GENE	CELL/CC	INPUT/OUTPUT	Relation 1b	GENE	CELL/CC	INPUT/OUTPUT	Relation 1c	GENE	CELL/CC	INPUT/OUTPUT	Relation 1d	PROCESS 2	Relation 2a	GENE	CELL/CC	INPUT/OUTPUT	Relation 2b	GENE	CELL/CC	INPUT/OUTPUT
G protein activity regulates gene expression + G protein activity regulates neurotransmitter biosynthesis		Tanis et al 2008	"Mutations in goa-1 caused a twofold increase in ex- pression of fluorescent transgenes driven by the tph-1 promoter in the HSNL (Figure 5, A–C), suggesting that GOA-1 signaling reduces expression from the tph-1 pro- moter. A sixfold decrease in fluorescence intensity in the HSNL was observed in egl-30 mutants, indicating that EGL-30 signaling stimulates expression from the tph-1 promoter (Figure 5, A, B, D, and E). The opposing effects of GOA-1 and EGL-30 on tph-1 expression were reproduced using five independent chromosomally in- tegrated transgenes (data not shown). Each consisted of the tph-1 promoter and 23 bp of the tph-1 5′ untranslated region, followed by coding sequences for a variety of DsRed2 or GFP proteins and the unc-54 3′ untranslated region. An analogous GFP transgene in which the tph-1 promoter was replaced by the unc-86 promoter was also expressed in the HSNs (Adler et al. 2006) but no changes in expression levels were observed in goa-1 and egl-30 mutant animals compared to the wild type (Figure 5A). These results show that GOA-1 and EGL-30 antagonistically regulate expression from the tph-1 pro- moter, presumably by regulating	Mutant visible phenotype evidence used in manual assertion [ECO:0007118]			[GO:0003925] G protein activity	enabled by	goa-1			occurs in		HSN						causally upstream of with negative effect	[GO:0010468] regulation of gene expression	has input			tph-1				
G protein activity regulates gene expression + G protein activity regulates neurotransmitter biosynthesis		Tanis et al 2008	"Mutations in goa-1 caused a twofold increase in ex- pression of fluorescent transgenes driven by the tph-1 promoter in the HSNL (Figure 5, A–C), suggesting that GOA-1 signaling reduces expression from the tph-1 pro- moter. A sixfold decrease in fluorescence intensity in the HSNL was observed in egl-30 mutants, indicating that EGL-30 signaling stimulates expression from the tph-1 promoter (Figure 5, A, B, D, and E). The opposing effects of GOA-1 and EGL-30 on tph-1 expression were reproduced using five independent chromosomally in- tegrated transgenes (data not shown). Each consisted of the tph-1 promoter and 23 bp of the tph-1 5′ untranslated region, followed by coding sequences for a variety of DsRed2 or GFP proteins and the unc-54 3′ untranslated region. An analogous GFP transgene in which the tph-1 promoter was replaced by the unc-86 promoter was also expressed in the HSNs (Adler et al. 2006) but no changes in expression levels were observed in goa-1 and egl-30 mutant animals compared to the wild type (Figure 5A). These results show that GOA-1 and EGL-30 antagonistically regulate expression from the tph-1 pro- moter, presumably by regulating transcription."	Mutant visible phenotype evidence used in manual assertion [ECO:0007118]			[GO:0003925] G protein activity	enabled by	egl-30			occurs in		HSN						causally upstream of with positive effect	[GO:0010468] regulation of gene expression	has input			tph-1				
G protein activity regulates gene expression + G protein activity regulates neurotransmitter biosynthesis		Tanis et al 2008	"We tested whether GOA-1 and EGL-30 act cell au- tonomously in the HSNs to have their opposing effects on tph-1 expression. We crossed the chromosomally integrated transgenes that had previously been used to manipulate GOA-1 and EGL-30 function in the HSNs into one of the tph-1 promoterTDsRed2 transcriptional reporter strains. Expression of PTX specifically in the HSNs to inactivate GOA-1 caused a threefold increase in fluorescence intensity (Figure 5F). This effect was greater than that observed using the goa-1 mutation (Figure 5A), likely because PTX causes more complete inactivation of GOA-1 than the partial loss-of-function goa-1 mutation used. Expression of GOA-1Q205L in the HSNs of the goa-1 mutant caused a 2.5-fold reduction in expression levels of the tph-1 reporter transgene (Figure 5G). EGL-30Q205L expression in the HSNs of the egl-30 mutant caused a 2.3-fold increase in expression levels of the tph-1 reporter transgene (Figure 5H). A 1.5- fold increase in expression levels of the tph-1 reporter transgene was also observed when wild-type EGL-30 was expressed in the HSNs of the egl-30 mutant (1311 6 90 fluorescence intensity units compared to 888 6 83 fluorescence intensity units in the egl-30 mutant con- trol). These results show that GOA-1 and EGL-30 act cell autonomously to regulate tph-1 expression in the HSNs."	Mutant visible phenotype evidence used in manual assertion [ECO:0007118]			[GO:0003925] G protein activity	enabled by	goa-1			occurs in		HSN						causally upstream of with negative effect	[GO:0010468] regulation of gene expression	occurs in		HSN		has input			tph-1
G protein activity regulates gene expression cell autonomously + G protein activity regulates neurotransmitter biosynthesis cell autonomously	18202365	Tanis et al 2008	"GOA-1 and EGL-30 signaling may affect serotonin levels in all serotonergic neurons, or this phenomenon could be HSN specific. Thus, we analyzed the effects of G-protein mutations on serotonin levels in two other pairs of C. elegans serotonergic neurons, the ADFs and NSMs. In the ADFs, the G proteins affected serotonin levels and tph-1 transcription as observed in the HSNs. Antiserotonin staining increased 1.3-fold in the goa-1 mutant and decreased 1.6-fold in the egl-30 mutant (Figure 6F), and analogous changes in tph-1 reporter transgene expression were also seen in the ADFs (data not shown). However, the G proteins caused different effects in the NSM neurons compared to those seen in the HSNs. Antiserotonin staining decreased 1.4- to 1.6- fold in the NSMs of both the goa-1 and the egl-30 mutants (data not shown). These results indicate that there is cell-type specificity in G-protein regulation of tph-1 ex- pression, demonstrating that this phenomenon must be studied in specific identified neurons."	Mutant visible phenotype evidence used in manual assertion [ECO:0007118]			[GO:0003925] G protein activity	enabled by	goa-1			occurs in		ADF						causally upstream of with negative effect	[GO:0010468] regulation of gene expression	occurs in		HSN		has input			TPH-1
G protein activity regulates gene expression cell autonomously + G protein activity regulates neurotransmitter biosynthesis cell autonomously	18202365	Tanis et al 2008	"GOA-1 and EGL-30 signaling may affect serotonin levels in all serotonergic neurons, or this phenomenon could be HSN specific. Thus, we analyzed the effects of G-protein mutations on serotonin levels in two other pairs of C. elegans serotonergic neurons, the ADFs and NSMs. In the ADFs, the G proteins affected serotonin levels and tph-1 transcription as observed in the HSNs. Antiserotonin staining increased 1.3-fold in the goa-1 mutant and decreased 1.6-fold in the egl-30 mutant (Figure 6F), and analogous changes in tph-1 reporter transgene expression were also seen in the ADFs (data not shown). However, the G proteins caused different effects in the NSM neurons compared to those seen in the HSNs. Antiserotonin staining decreased 1.4- to 1.6- fold in the NSMs of both the goa-1 and the egl-30 mutants (data not shown). These results indicate that there is cell-type specificity in G-protein regulation of tph-1 ex- pression, demonstrating that this phenomenon must be studied in specific identified neurons."	Mutant visible phenotype evidence used in manual assertion [ECO:0007118]			[GO:0003925] G protein activity	enabled by	egl-30			occurs in		ADF						causally upstream of with positive effect	[GO:0010468] regulation of gene expression	occurs in		HSN		has input			TPH-1
G protein activity regulates gene expression cell autonomously + G protein activity		Tanis et al 2008	"We tested whether GOA-1 and EGL-30 act cell au- tonomously in the HSNs to have their opposing effects on tph-1 expression. We crossed the chromosomally integrated transgenes that had previously been used to manipulate GOA-1 and EGL-30 function in the HSNs into one of the tph-1 promoterTDsRed2 transcriptional reporter strains. Expression of PTX specifically in the HSNs to inactivate GOA-1 caused a threefold increase in fluorescence intensity (Figure 5F). This effect was greater than that observed using the goa-1 mutation (Figure 5A), likely because PTX causes more complete inactivation of	Mutant visible phenotype evidence used in manual assertion			[GO:0003925] G protein activity	enabled by	egl-30			occurs in		HSN						causally upstream of with positive effect	[GO:0051899] Membrane depolarization	occurs in		HSN		has output			tph-1

Plans

Publish method: use of GO-CAM semantic modeling for neural circuits

Adopt ACKnowledge systems for neural circuit assertions

Author Curation to Knowledgebase

Incentivize experts via microReviews

Visualize connectome, activity, and circuit assertions

Compute on knowledge graph to predict circuits, effects of genetic variants, etc.

Apply method to rmouse retina

pws@caltech.edu
@wormraiser