More Than Conventional Synaptic Transmission.

孙梦实 彭琼琳 马铭泽

2020 年 5 月 28 日

15:00-15:30 孙梦实 Neuropeptides and Their Cytoplasmic Signaling Pathways.

15:30-16:00 彭琼琳 The Use of Multiple Neurotransmitters at Synapses

16:00-16:30 马铭泽 Neuron-glial Cell Interaction in Drosophila

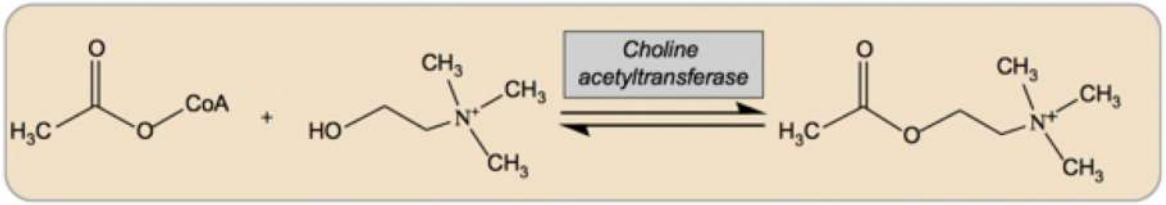
1. The difference between neurotransmitter and neuropeptides.

2. The signaling within neuropeptide receptors.

1. Precursor molecules and synthesis

Neurotransmitter: Various precursors available within the axon terminal.

For example 1. Acetylcholine (Ach): choline and acetyl CoA



the unique synthetic enzyme

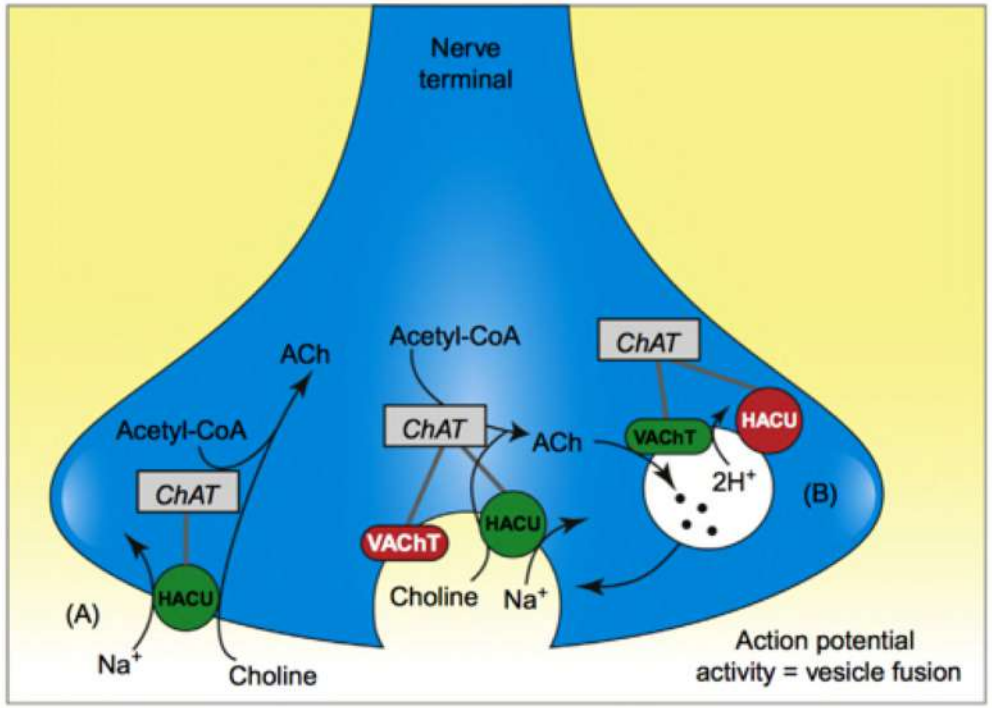
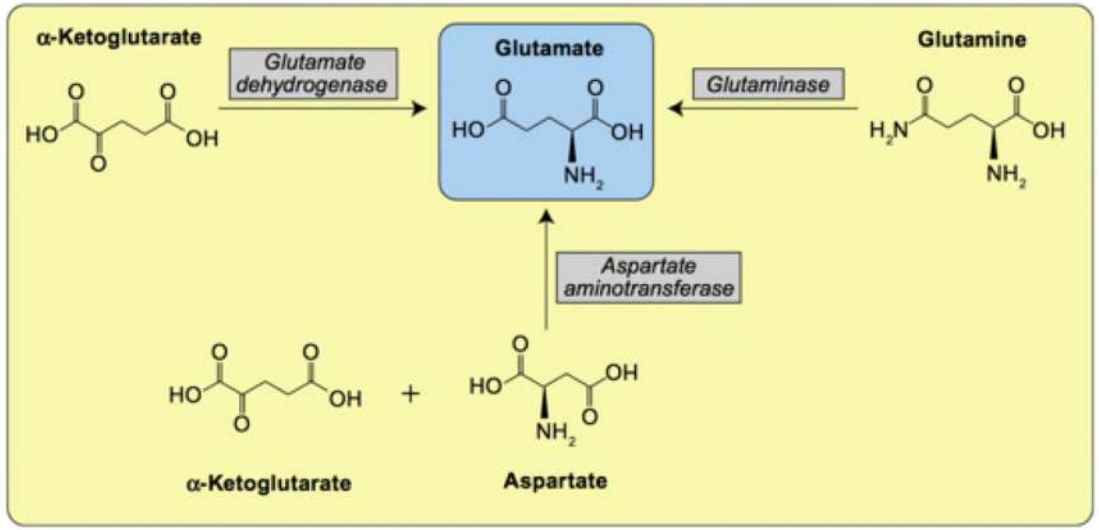


FIGURE 16.10
Physiological regulation of acetylcholine synthesis.

Stephen D. Meriney, *Synaptic Transmission* . 1e (2019)

For example 2. Glutamate



None of the synthesis pathways described here is unique to glutamatergic cells.

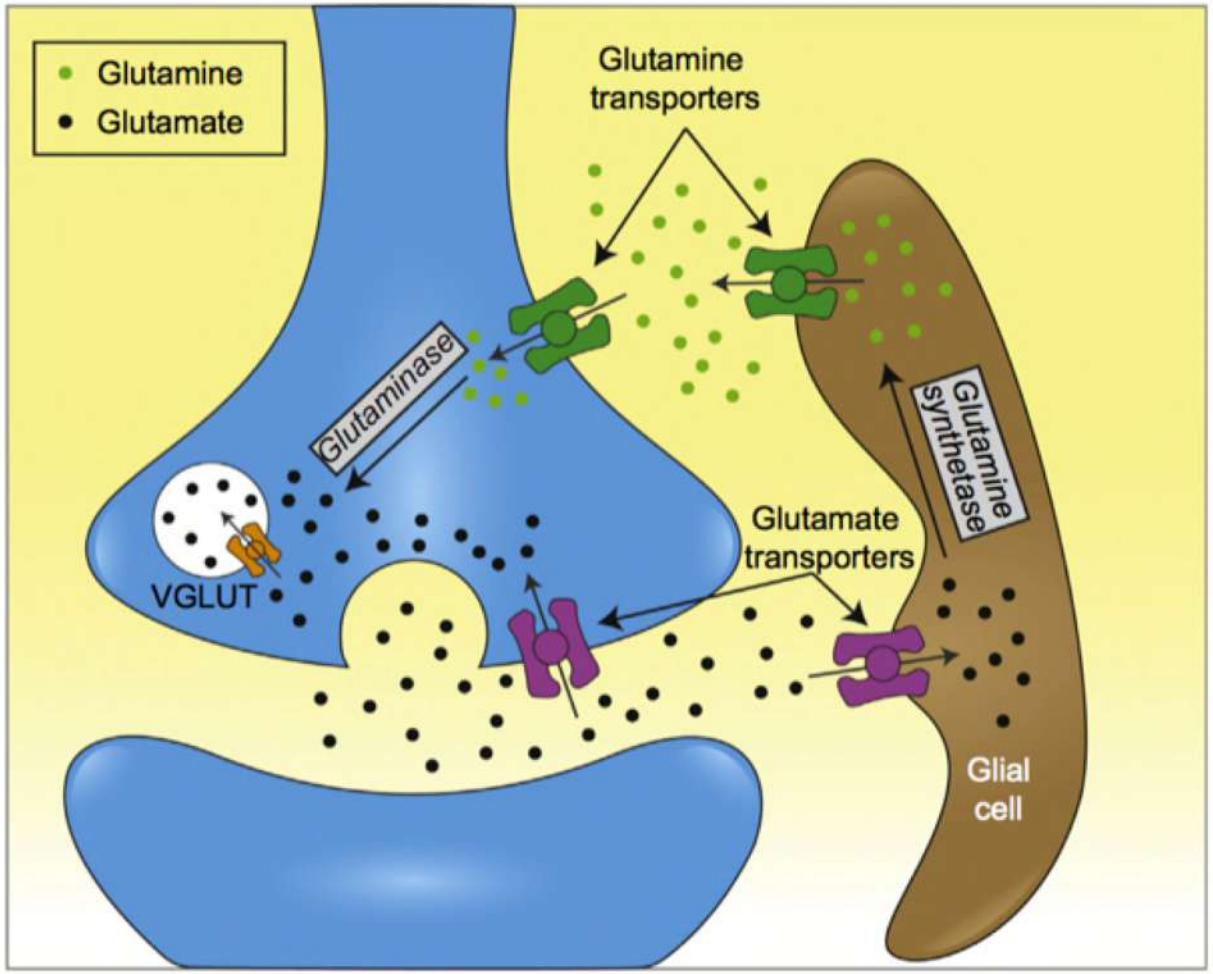
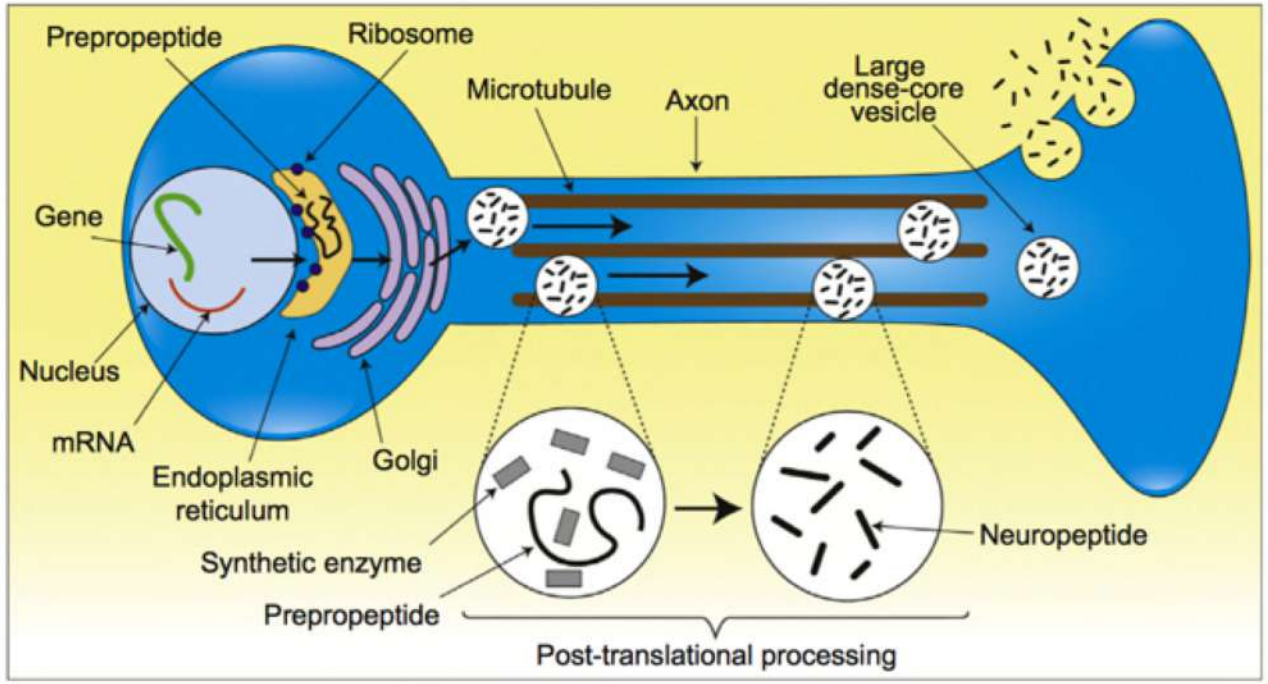


FIGURE 18.6 The glutamate cycle.

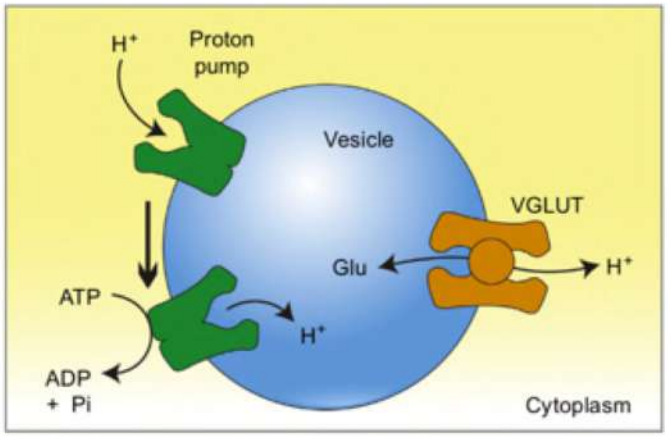
The vesicular glutamate transporter (VGLUT) is uniquely expressed in the vesicular membranes of glutamatergic cells.

Neuropeptide: formed from amino acids on ribosomes on the rough ER in the cell body.

Gene → mRNA → prepropeptide → propeptide → peptide



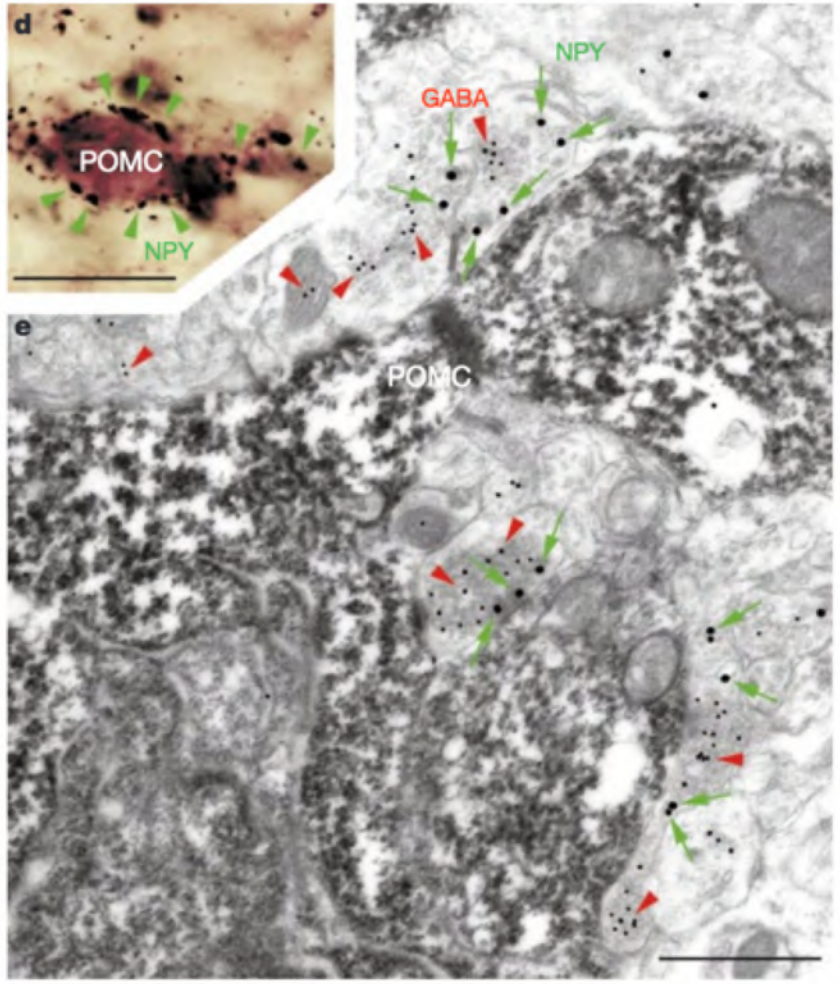
2. Vesicles:



Neurotransmitters – small clear synaptic vesicles (SSVs)
SCSVs are initially formed in the Golgi apparatus and then travel down the axon to the nerve terminal.
Neurotransmitters are pumped into SCSVs by energy-driven vesicular transporters in the presynaptic terminal.

Neuropeptides – large dense-core vesicles (LDCVs)
Prepropeptides are packaged into large dense-core vesicles in the Golgi apparatus.
Post-translational processing happens in LDCVs with specific synthetic enzymes.

Expression of GABA and NPY in nerve terminals synapsing onto POMC neurons in the ARC



Neuropeptides – large dense-core vesicles (LDCVs)

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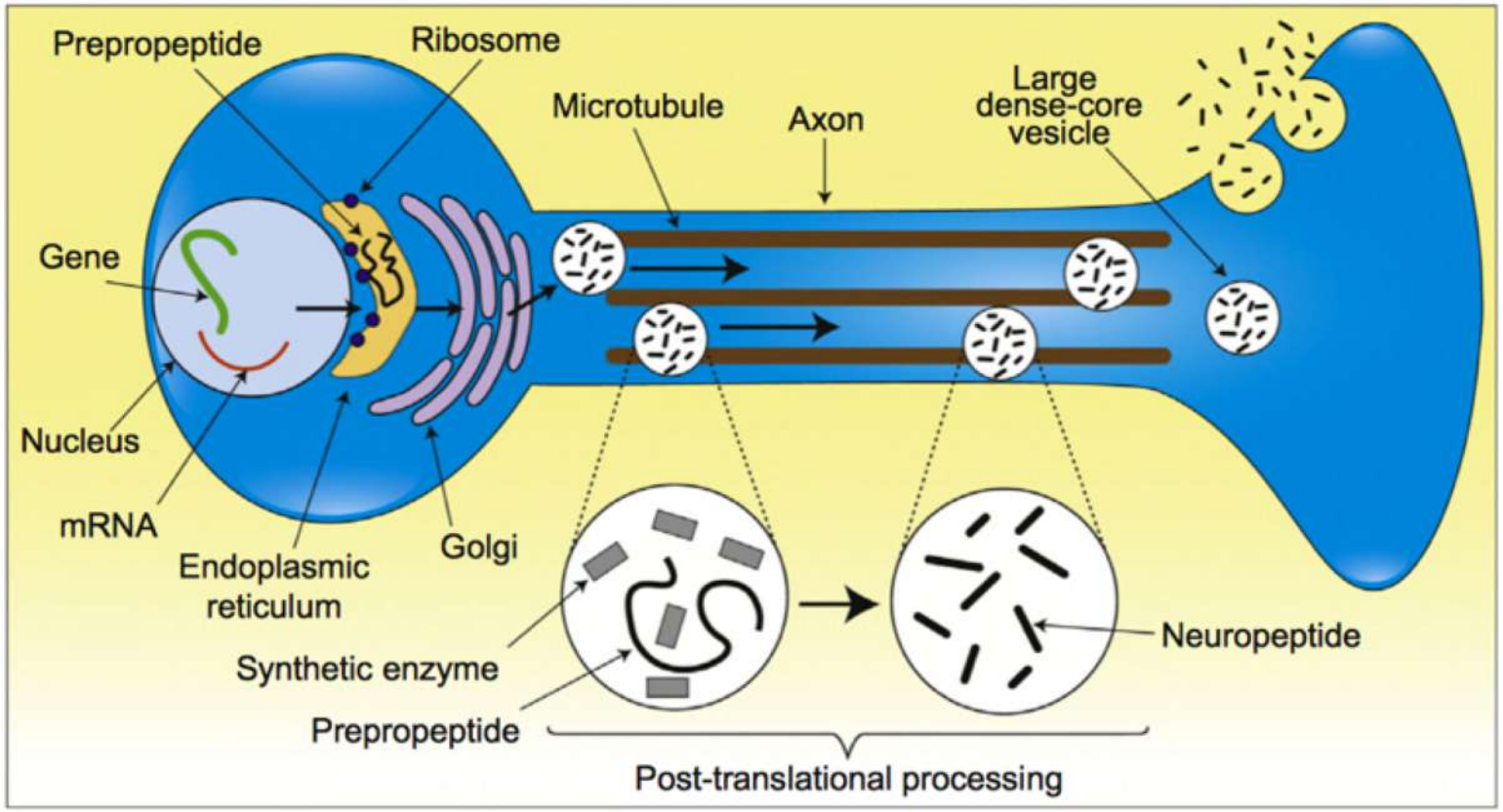
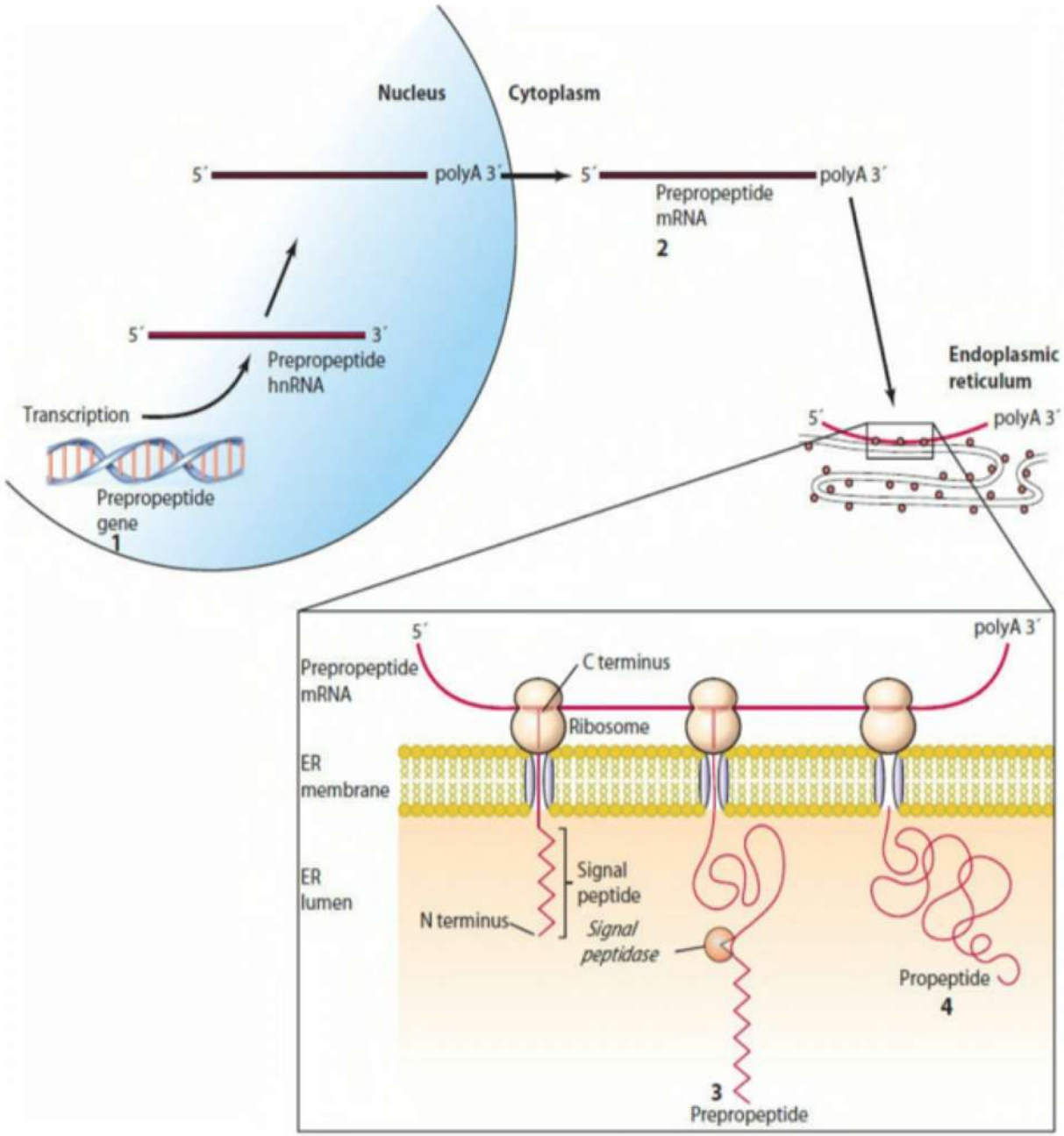
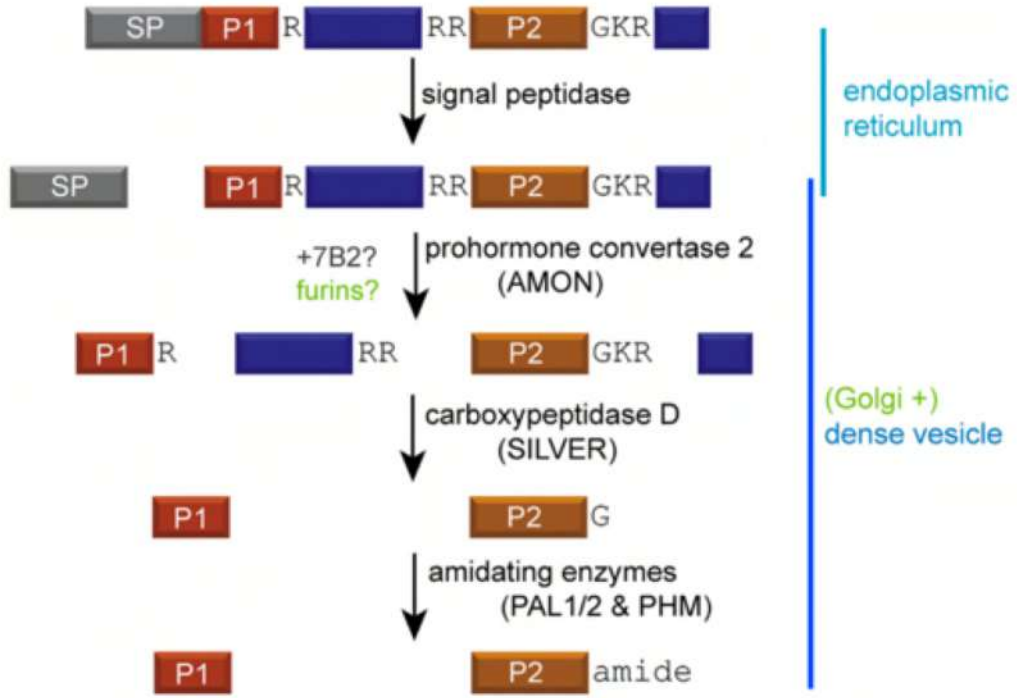


Prepropeptides are packaged into large dense-core vesicles in Golgi.



Eric J. Nestler, *Molecular Neuropharmacology: A Foundation for Clinical Neuroscience*, 3e (2015)



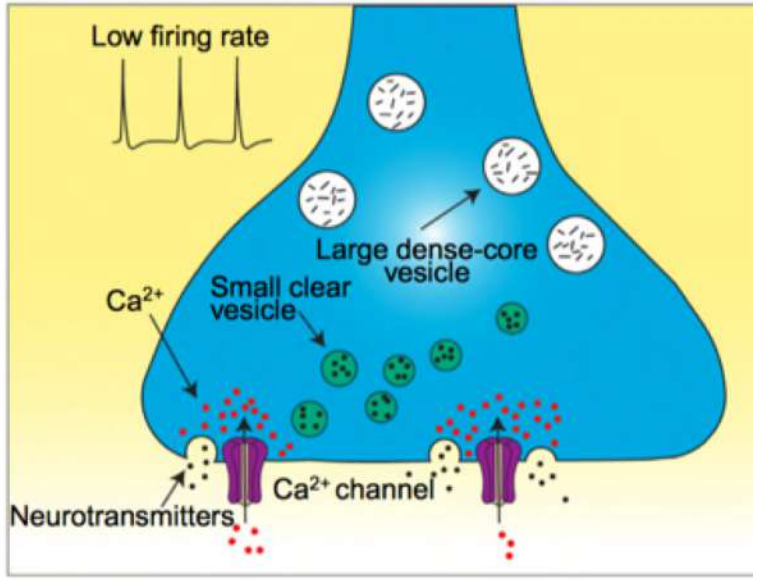
D. Pauls *et al.*, *Eupa Open Proteom*. **3**, 114–127 (2014).

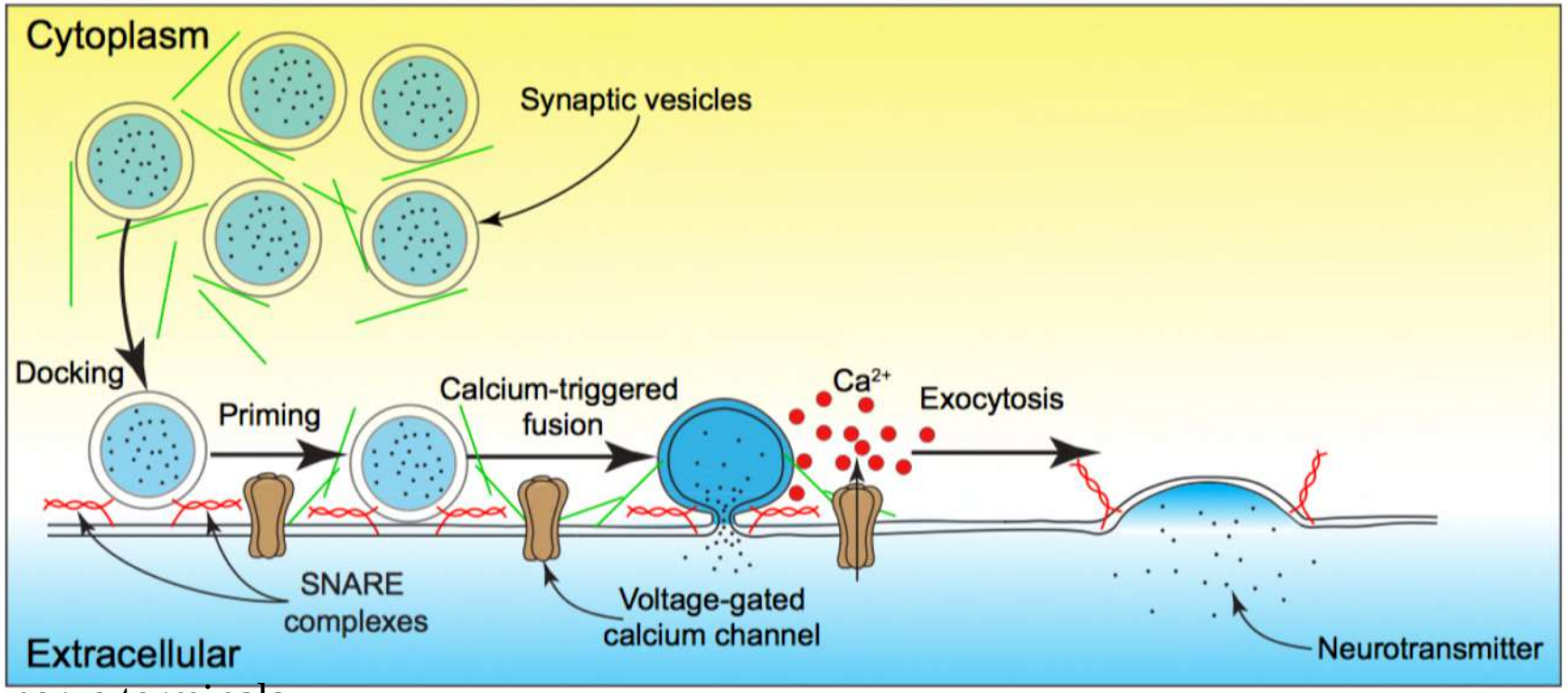
3. Vesicular Release

Neurotransmitter:

SSVs response to large, transient increase in intracellular Ca^{2+} .

A single action potential can cause SSVs to fuse with the cell membrane.





SSVs are released within active zones at nerve terminals,

FIGURE 8.8 The regulated process by which synaptic vesicles fuse with the plasma membrane.

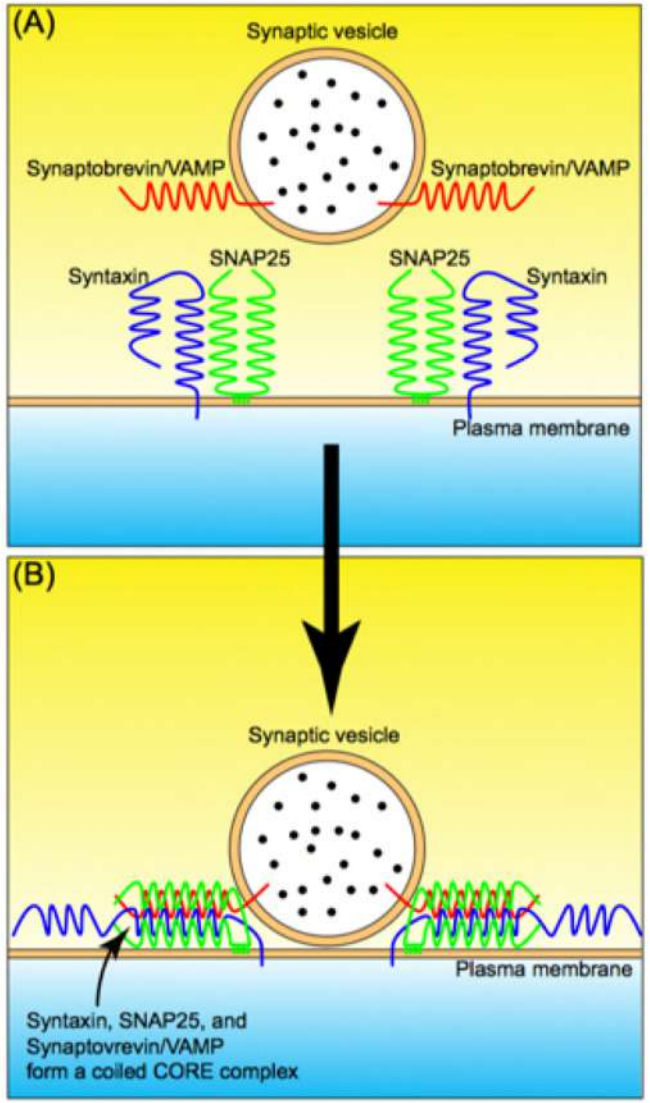


FIGURE 8.11
CORE complex proteins are associated with the attachment of a synaptic vesicle in close proximity to the plasma membrane.

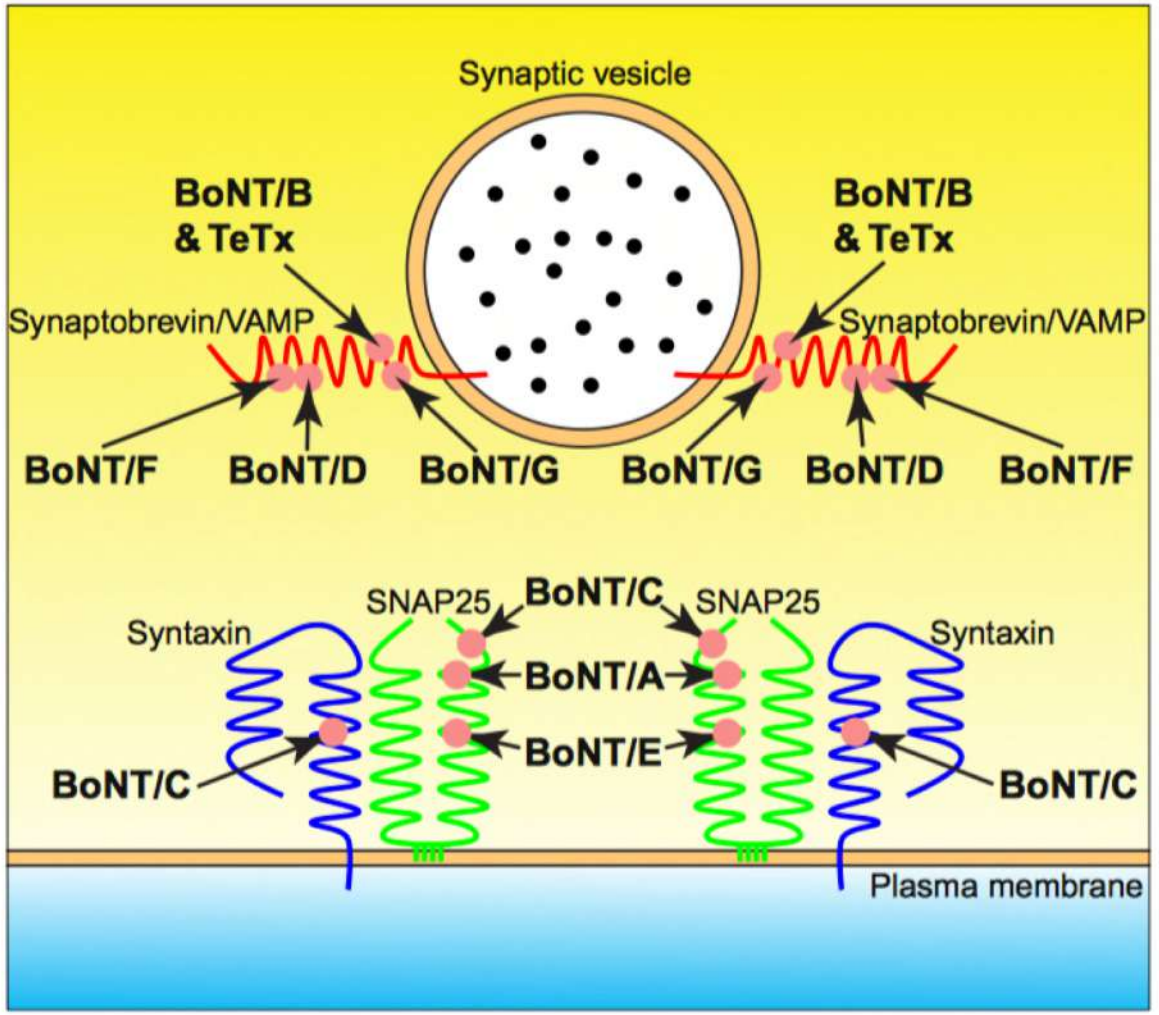
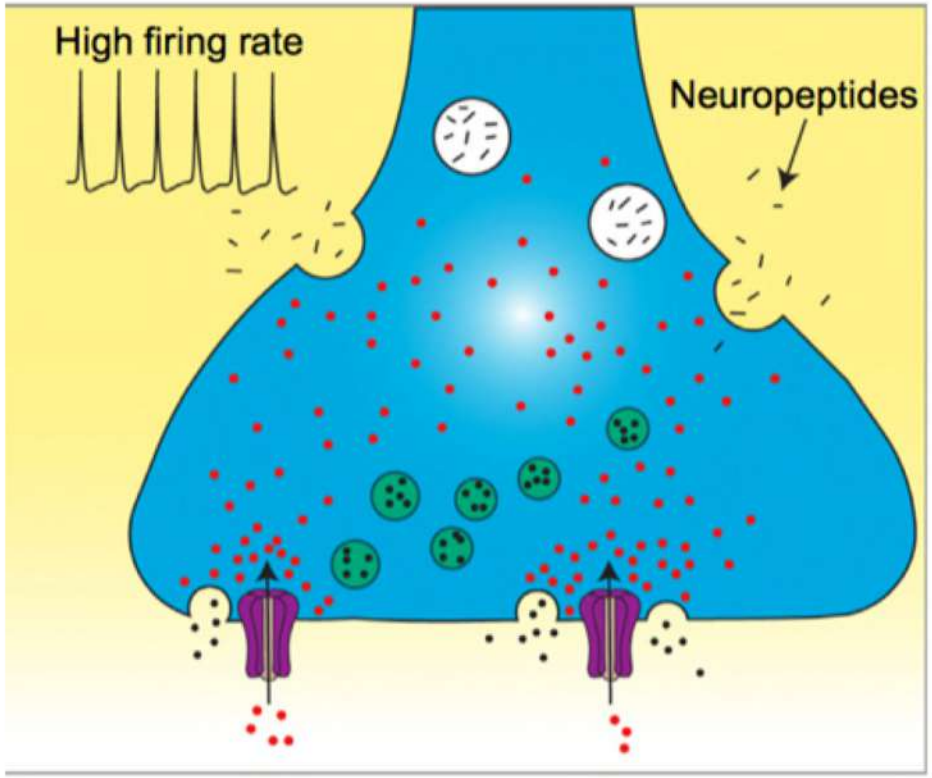


FIGURE 8.12
Selective targeting of particular SNARE proteins by each serotype of botulinum toxin (BoNT/A-G) or by tetanus toxin (TeTx). The pink dots represent cleavage sites on each SNARE protein for the labeled toxin.

Neuropeptides:

LDCVs requires increases in ca2+ of lesser magnitude but longer duration so that the ca2+ can diffuse in adequate concentration to reach these vesicles.



LDCVs are released in a paracrine and extrasynaptic fashion.

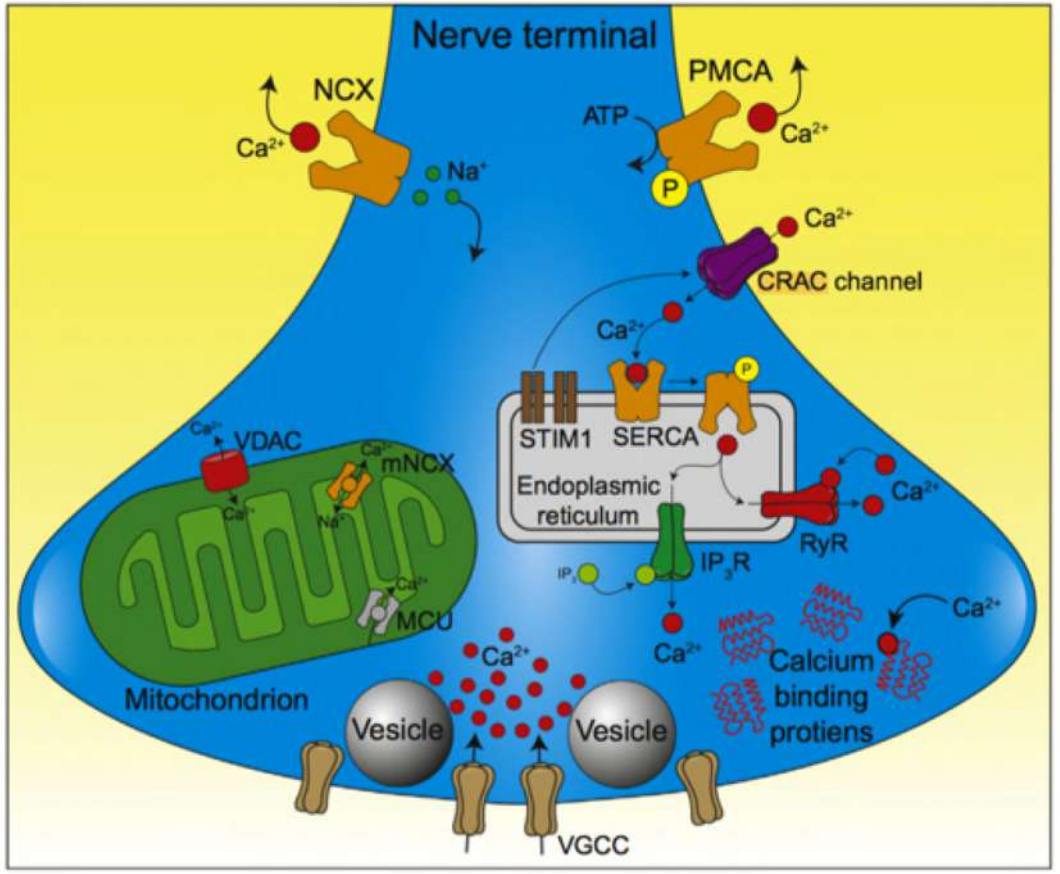
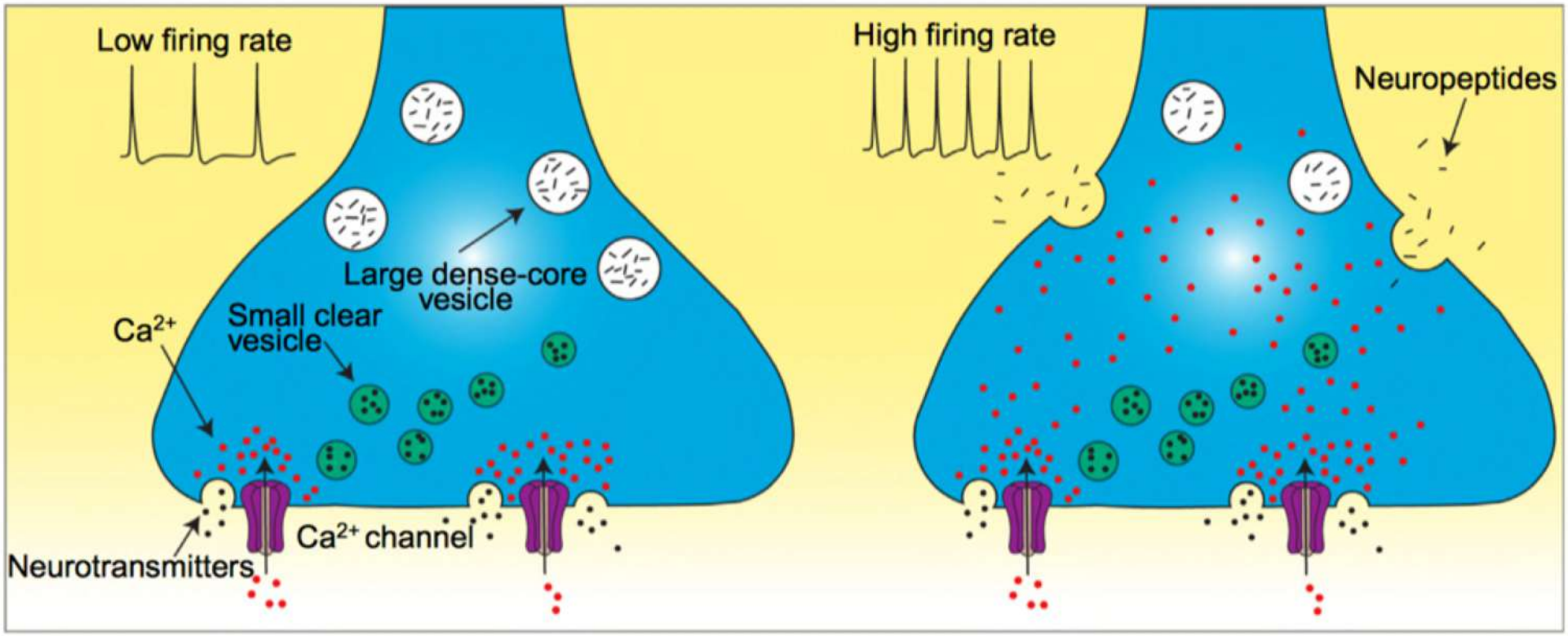


FIGURE 7.7 Summary of calcium buffering and handling mechanisms in the nerve terminal.

Specific patterns of electrical activity in a neuron may lead to the preferential release of a neuropeptide or a small molecule neurotransmitter.



4. Concentrations and affinities:

neurotransmitters (in small clear vesicles): ~100mM
receptor affinities: low

neuropeptides (in large dense-core vesicles): – 3-10mM
receptor affinities: very high

For example, acetylcholine binds to its receptors in the 100uM to 1 mM range, whereas some neuropeptides can bind with nanomolar affinity.

5. Termination/recycling:

Neurotransmitters

Either undergo reuptake into the presynaptic terminal or glial cells, or are degraded by enzymes.

The neurotransmitter molecules themselves, or their breakdown products, can be reused.

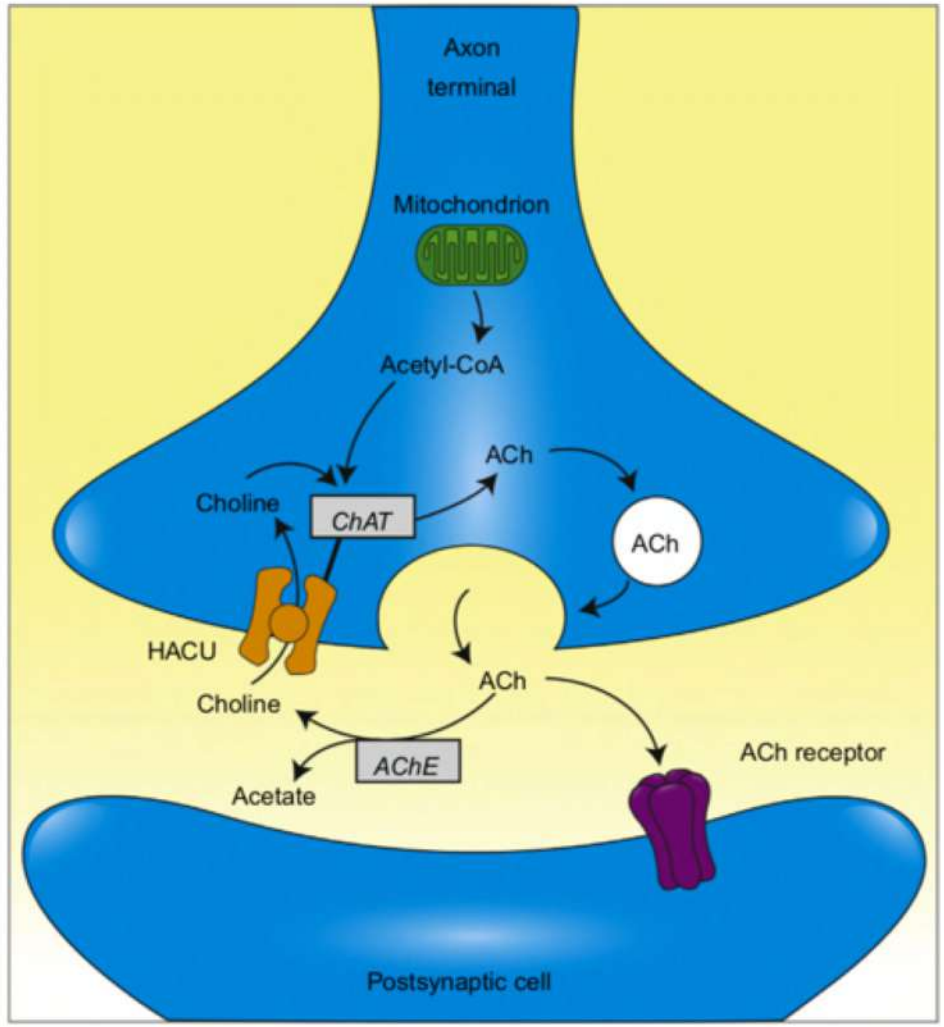
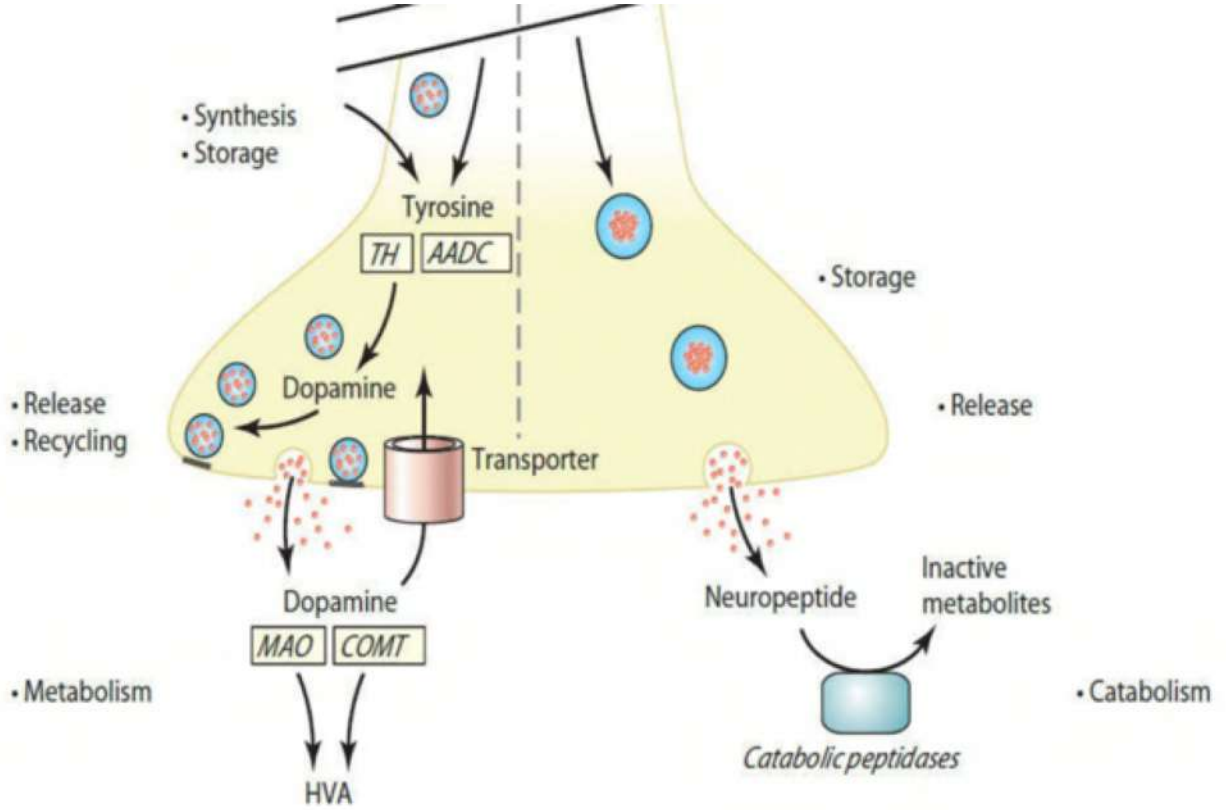


FIGURE 16.6 The synthesis and breakdown of acetylcholine at a synapse.

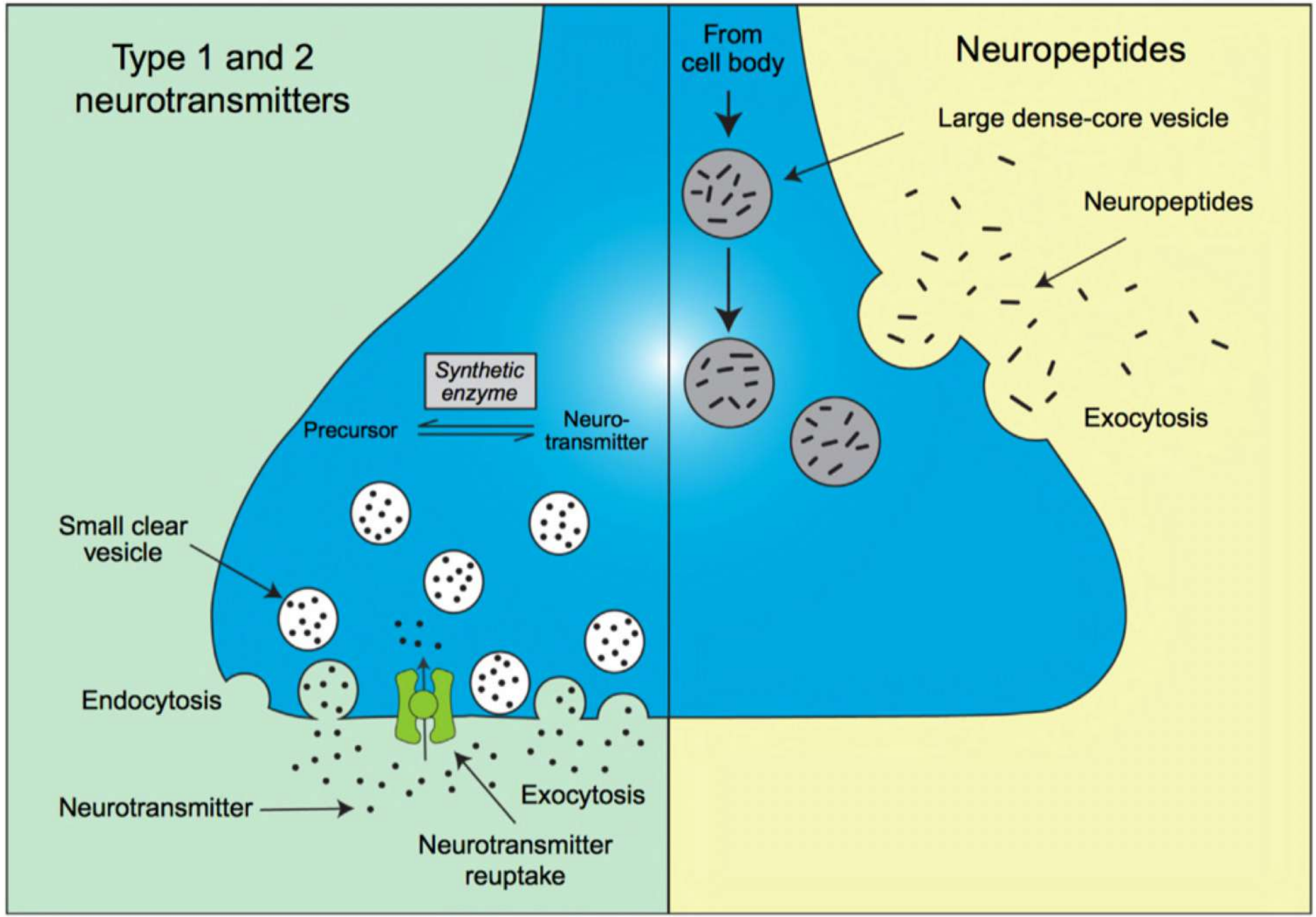
Neuropeptides

Their action is terminated by endopeptidases and exopeptidases that cleave peptide bonds.

Neuropeptides are not recycled and need to be synthesized anew from raw materials in the cell body.



Eric J. Nestler, Molecular Neuropharmacology: A Found for Clinical Neuroscience, 3e (2015)

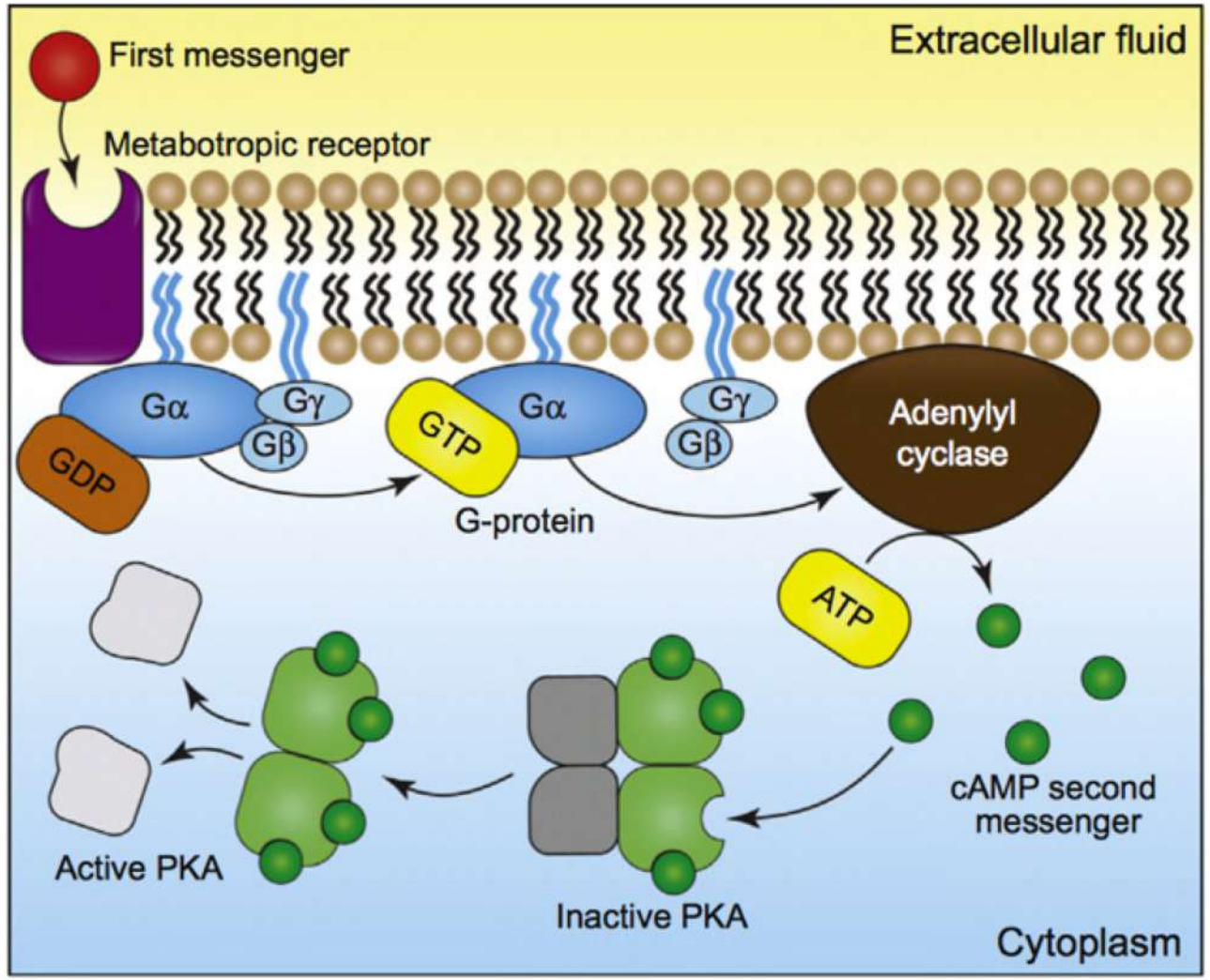

Type 1 and 2
neurotransmitters
Synthetic
enzyme
Precursor
Neuro-
transmitter
Small clear
vesicle
Endocytosis
Neurotransmitter
Exocytosis
Neurotransmitter
reuptake
From
cell body
Neuropeptides
Large dense-core vesicle
Neuropeptides
Exocytosis

1. The difference between neurotransmitter and neuropeptides.

2. The signaling within neuropeptide receptors.

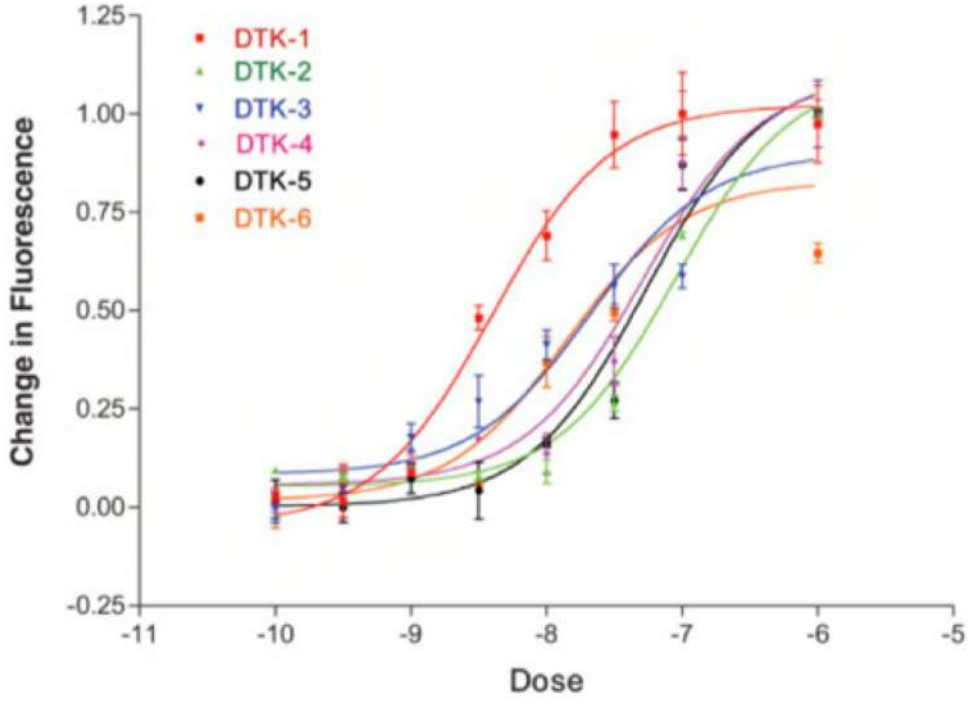
GPCR cAMP Pathway

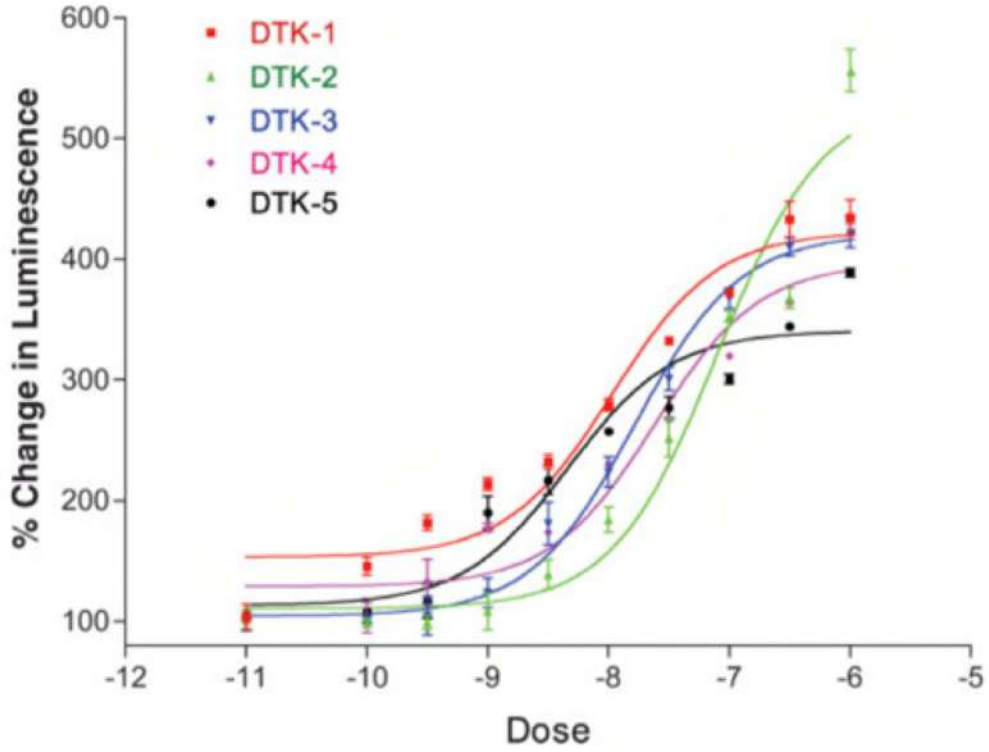
cAMP-PKA Pathway



PKA phosphorylates a wide variety of targets, including many receptors and ion channels that govern the excitability of neurons.

DTK receptor





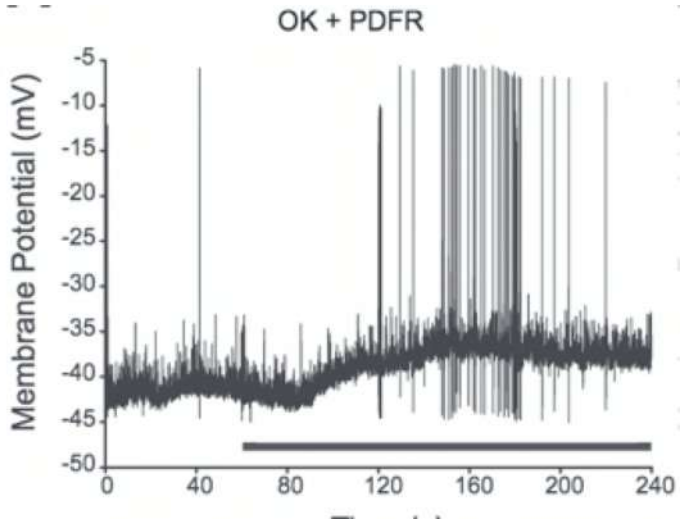
J Neurophysiol 111: 1033–1045, 2014.
First published December 18, 2013; doi:10.1152/jn.00712.2013.

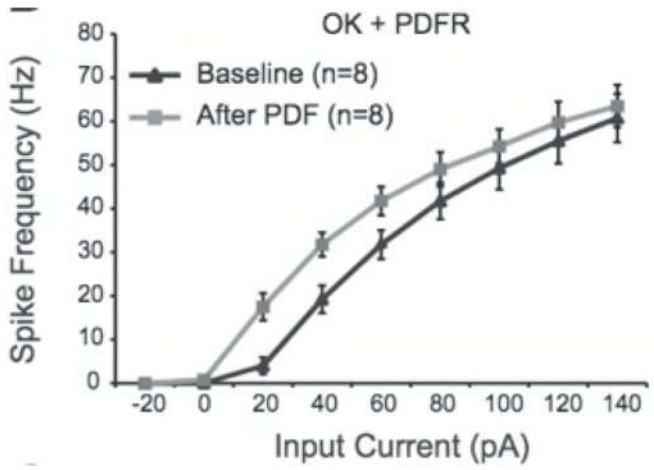
The *Drosophila* neuropeptides PDF and sNPF have opposing electrophysiological and molecular effects on central neurons

Christopher G. Vecsey, Nicolás Pírez, and Leslie C. Griffith
National Center for Behavioral Genomics, Volen National Center for Complex Systems and Department of Biology, Brandeis University, Waltham, Massachusetts

Submitted 3 October 2013; accepted in final form 12 December 2013

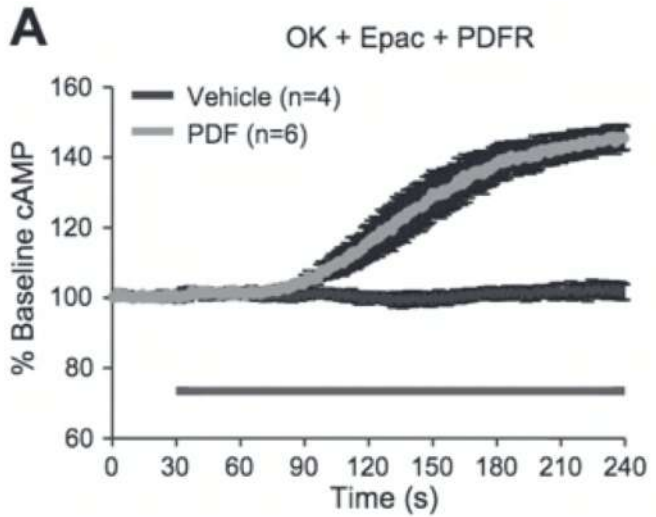
PDF causes excitation of larval motor neurons expressing the PDFR

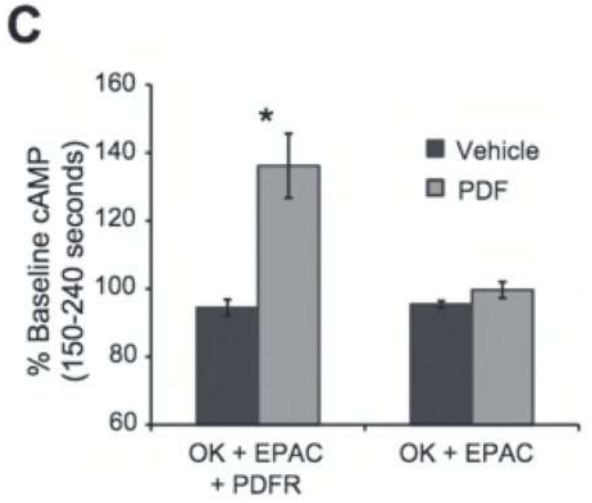




PDF increases cAMP levels in both motor neurons and muscle cells expressing the PDFR

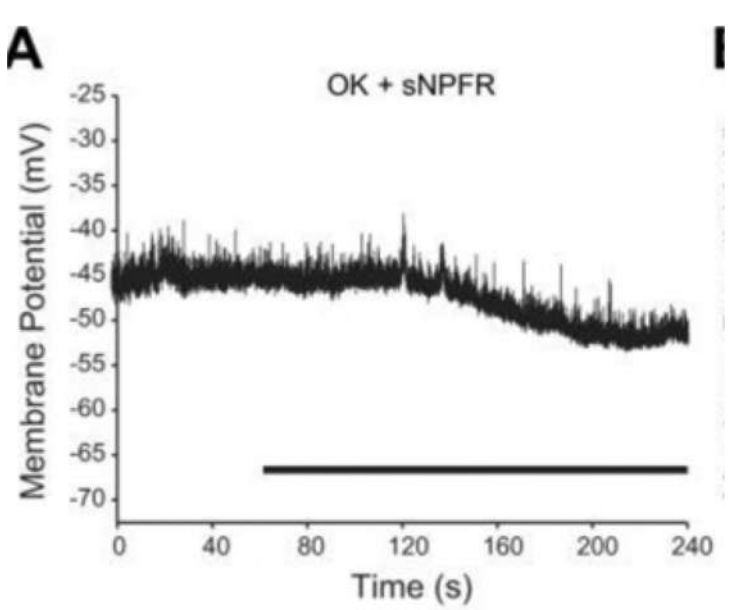
UAS-Epac-cAMPs:
the FRET-based cAMP sensor

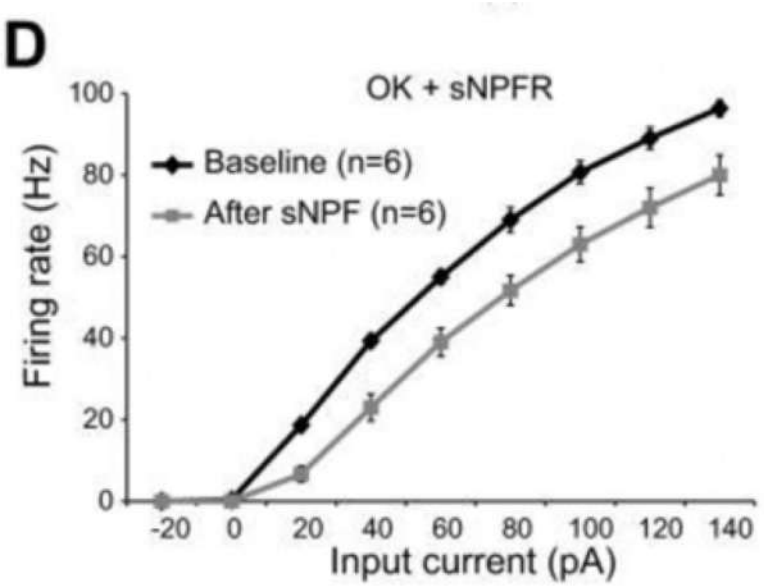




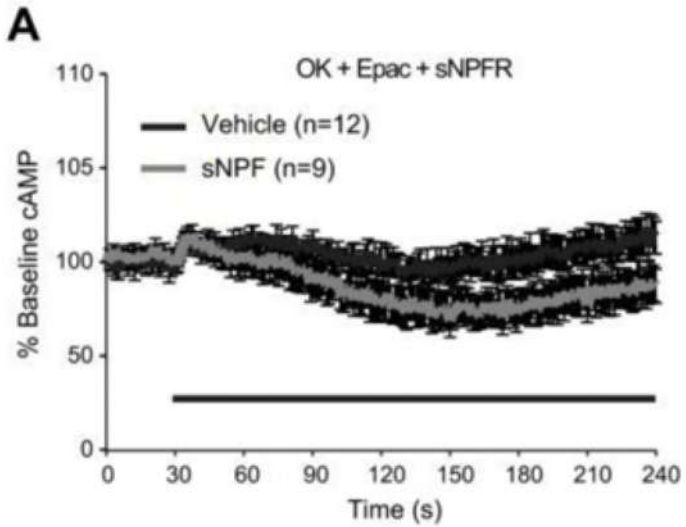
C. G. Vecsey, N. Pírez, L. C. Griffith, The Drosophila neuropeptides PDF and sNPF have opposing electrophysiological and molecular effects on central neurons. J Neurophysiol. 111, 1033–45 (2013).

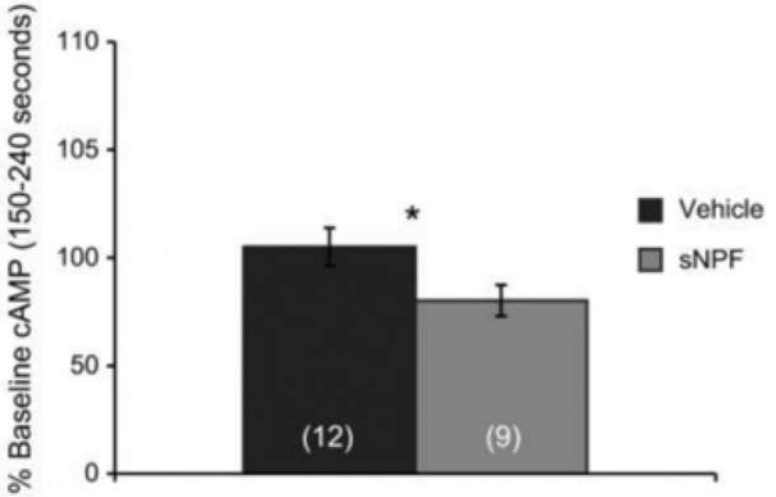
sNPF inhibits larval motor neurons expressing the SNPFR.

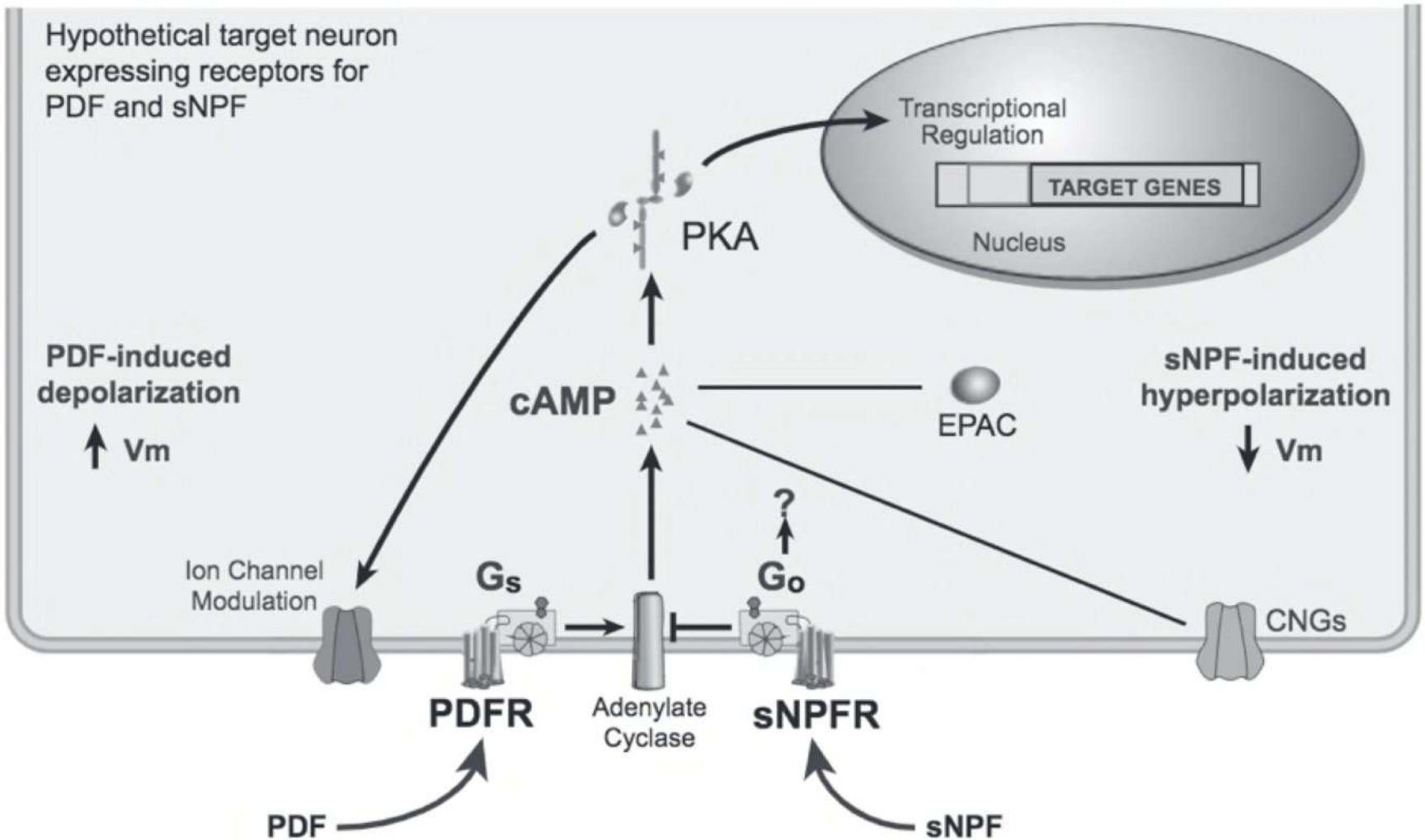




sNPF causes a slight reduction in cAMP and suppresses spontaneous calcium waves in motor neurons expressing the sNPFR.






Hypothetical target neuron
expressing receptors for
PDF and sNPF
Transcriptional
Regulation
TARGET GENES
Nucleus
PKA
PDF-induced
depolarization
Vm
cAMP
EPAC
sNPF-induced
hyperpolarization
Vm
?
Ion Channel
Modulation
Gs
Go
CNGs
PDFR
Adenylate
Cyclase
sNPFR
PDF
sNPF

GPCR Phosphoinositol Pathway

PLC-PKC pathway

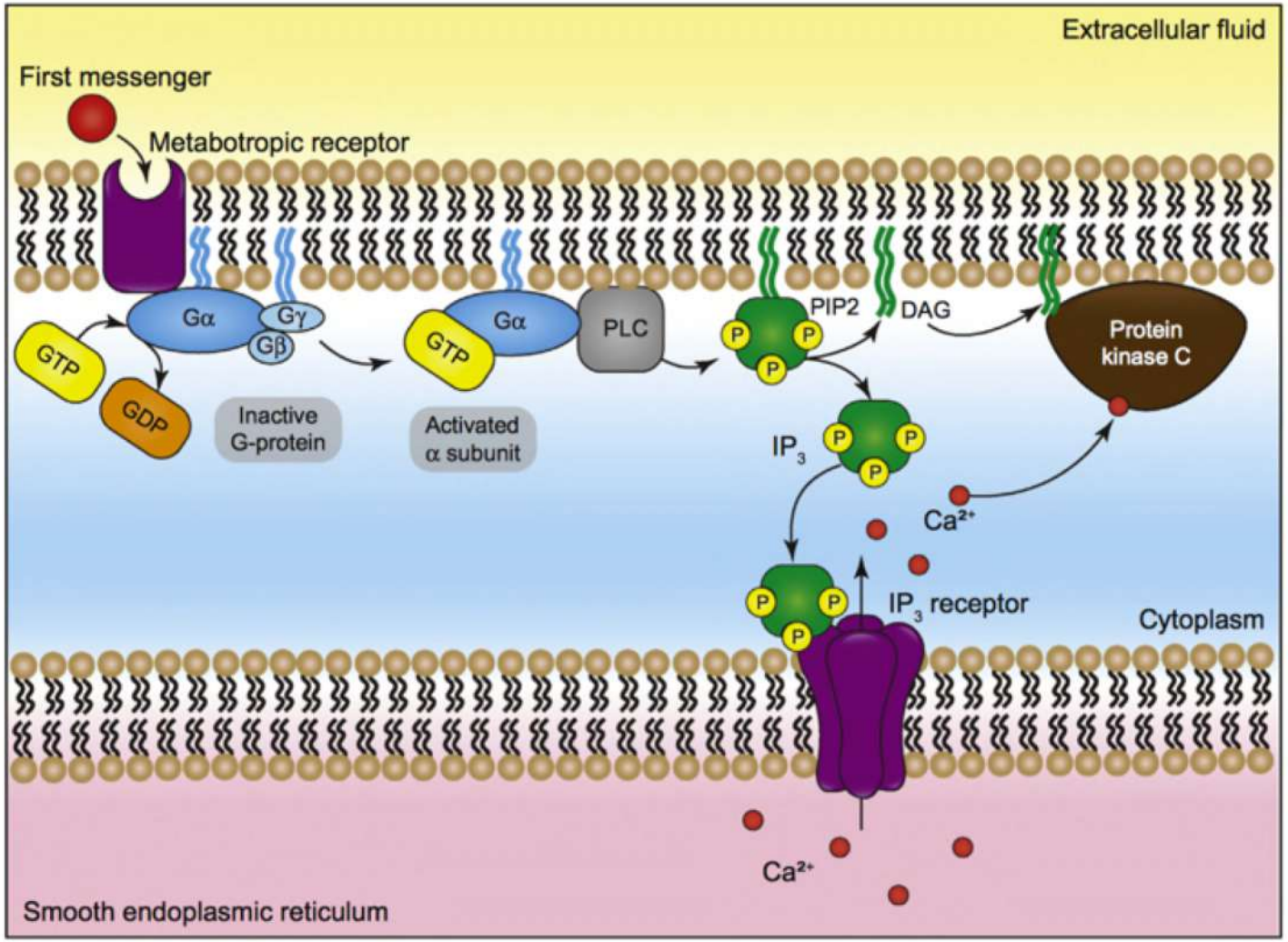
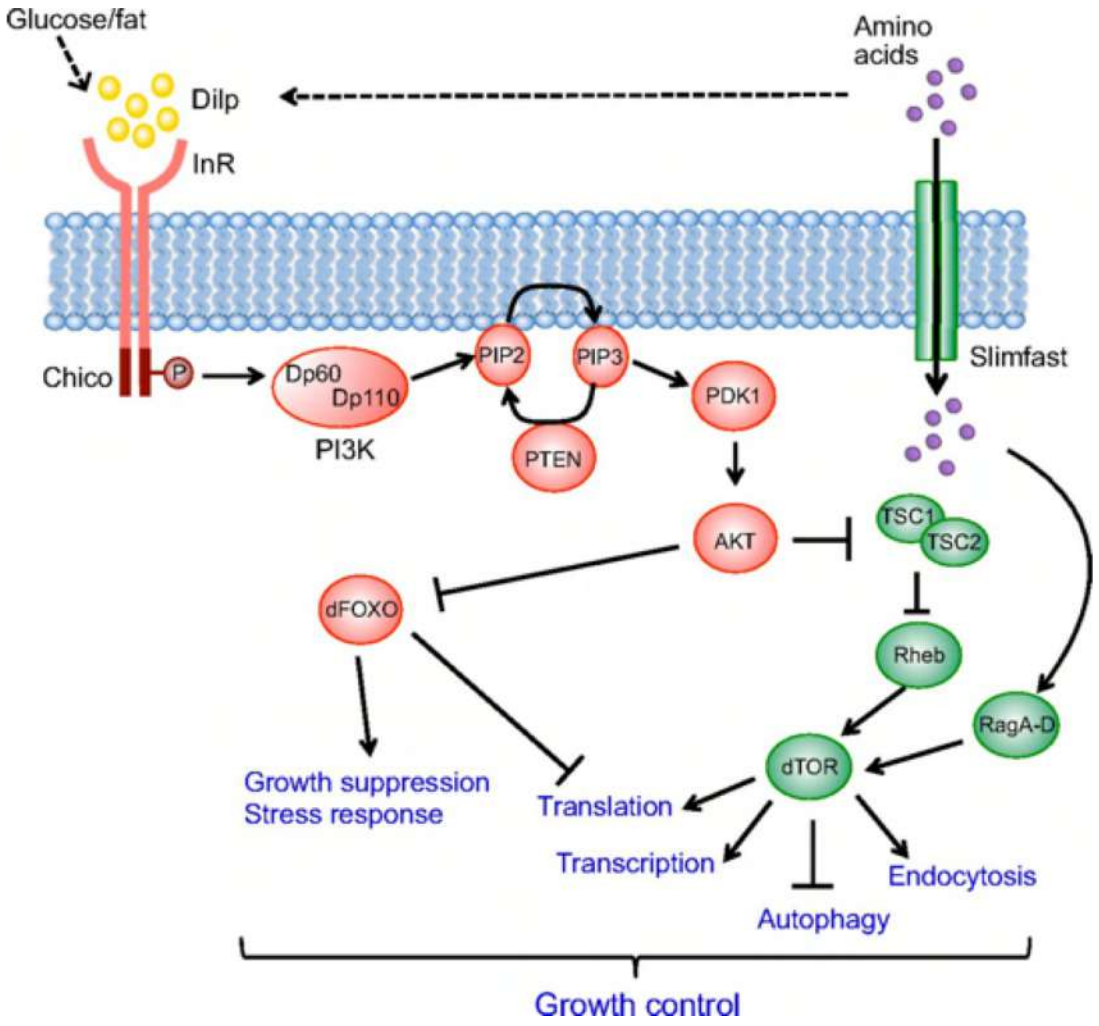


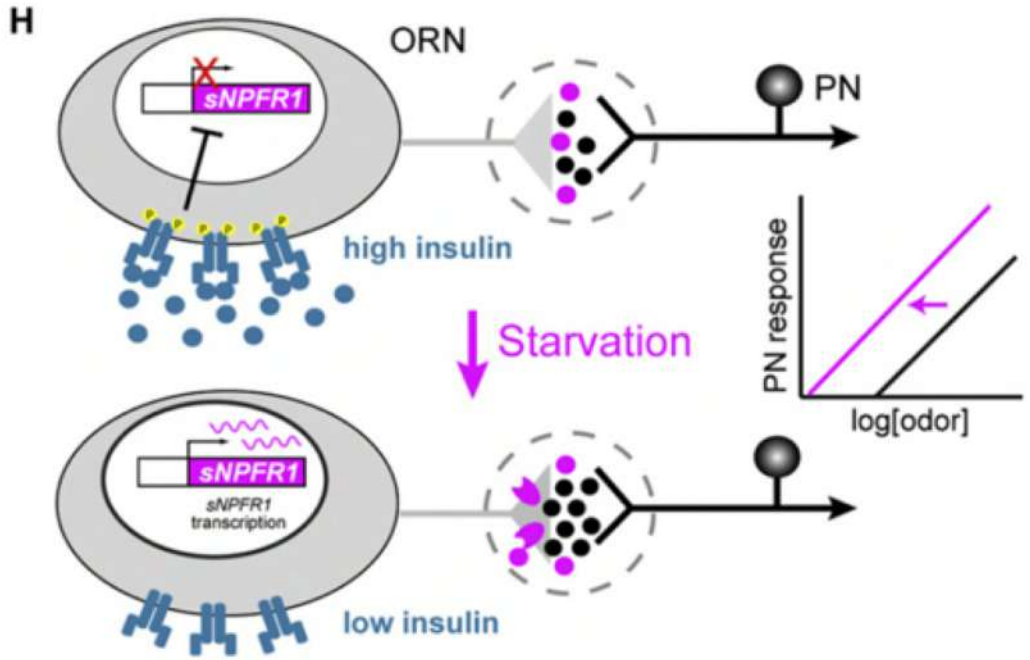
FIGURE 12.13 The phosphoinositol (PI) pathway.

Enzyme-Linked Receptors: receptor tyrosine kinases



J. Shim, S. Gururaja-Rao, U. Banerjee. Dev Camb Engl. 140, 4647–56 (2013).

Insulin Signaling Modulates Expression of sNPFR1



C. M. Root, K. I. Ko, A. Jafari, J. W. Wang, Cell. 145, 133–44 (2011).

The use of multiple neurotransmitters at synapses

PQL 2020-5-28

The “one neuron, one neurotransmitter” doctrine

Henry Hallett Dale

John C. Eccles

“Dale’s Principle”

1. Each neuron expresses exactly one neurotransmitter.
2. A neuron’s neurotransmitter phenotype (the set of neurotransmitters that it releases) is fixed and unchangeable.
3. A neuron releases the same neurotransmitter at each of its synapses.

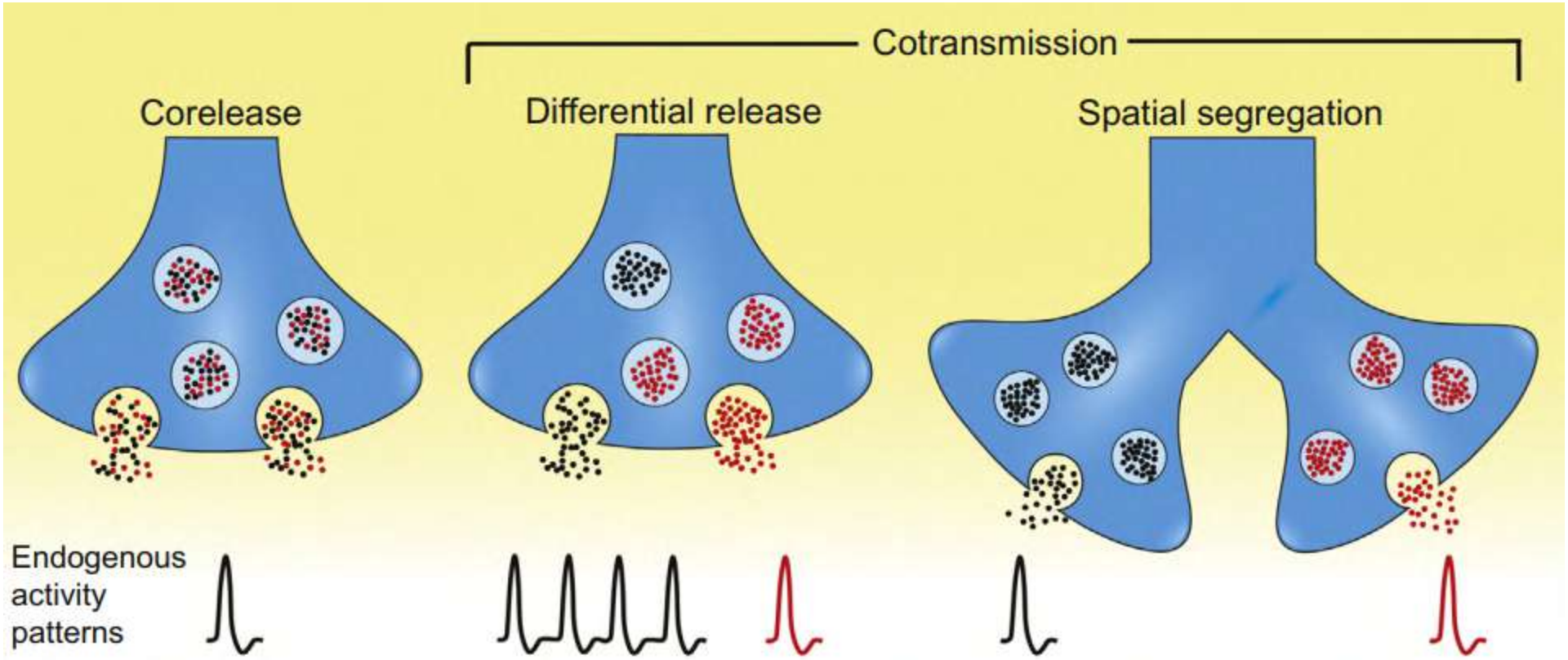
For his study of acetylcholine as agent in the chemical transmission of nerve impulses (neurotransmission) he shared the 1936 Nobel Prize in Physiology or Medicine with Otto Loewi.

Do some nerve cells release more than one neurotransmitter?

We now know that:

1. Most or all neurons express multiple neurotransmitters.
2. A neuron’ s neurotransmitter phenotype can change.
3. Some neurons release different neurotransmitters at different synapses.

Different mechanisms of cotransmission



Peptidergic Cotransmission

- Neuropeptides are packaged into large dense-core vesicles
- Small-molecule transmitters are packaged separately into small clear vesicles

- Neuropeptides tend to mediate slower, longer-lasting changes in cells than small-molecule neurotransmitters do

The neurotransmitter phenotype of a synapse can change during development

- **Neurotransmitter switching**

Neurons can switch from expressing one neurotransmitter to expressing another, gain expression of an additional neurotransmitter, or lose expression of one or more of their multiple neurotransmitters

Neurotransmitter switching

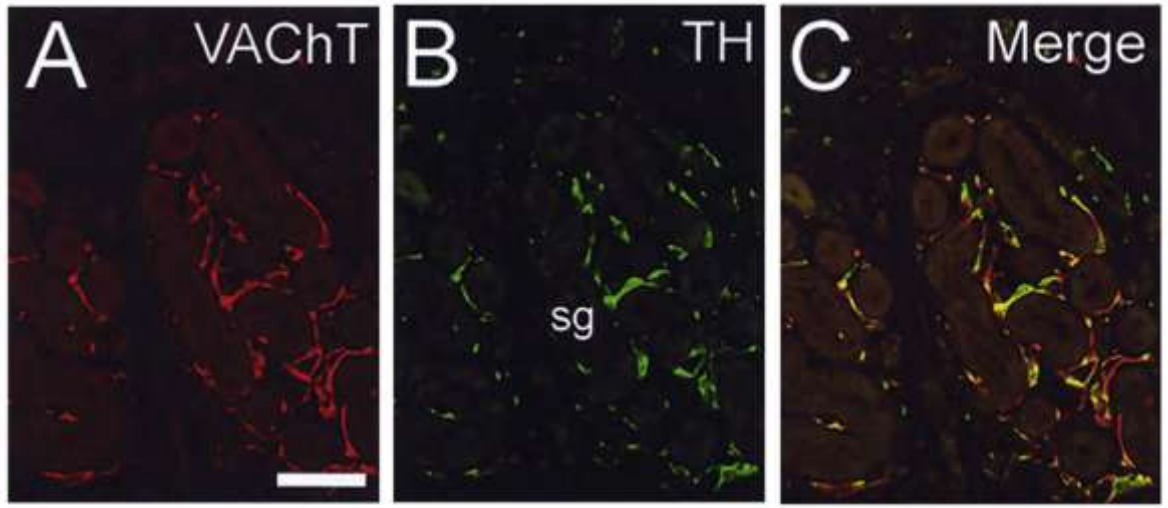
- Neurotransmitter switching in the developing nervous system
- Neurotransmitter switching in the adult nervous system

Developmental neurotransmitter switching:
The noradrenergic-to-cholinergic switch in sympathetic neurons

"Cholinergic switch" *in vivo*

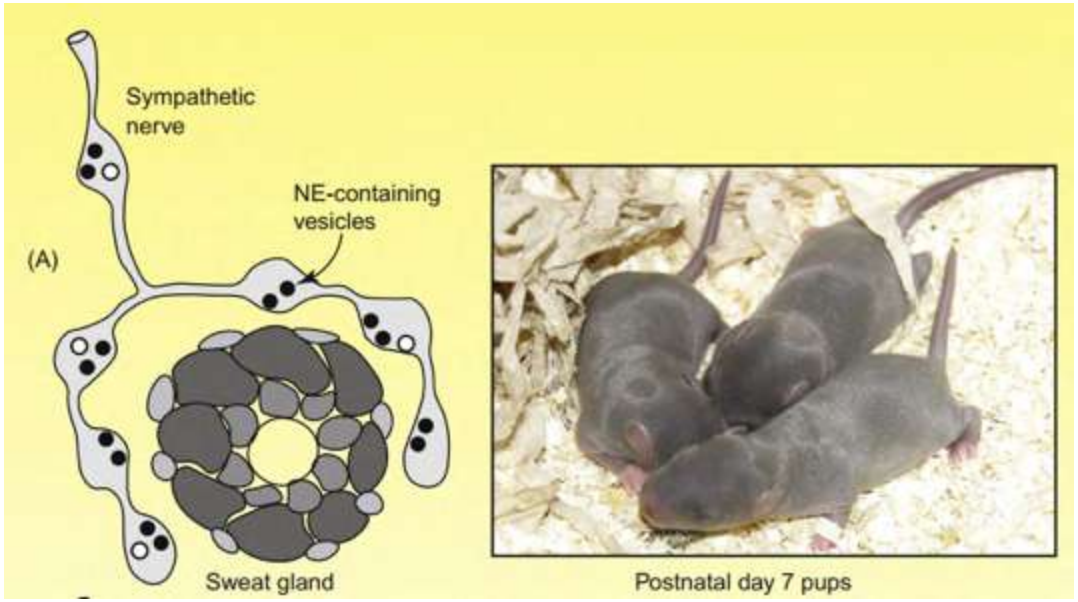
Does neurotransmitter phenotype ever change in living organisms?

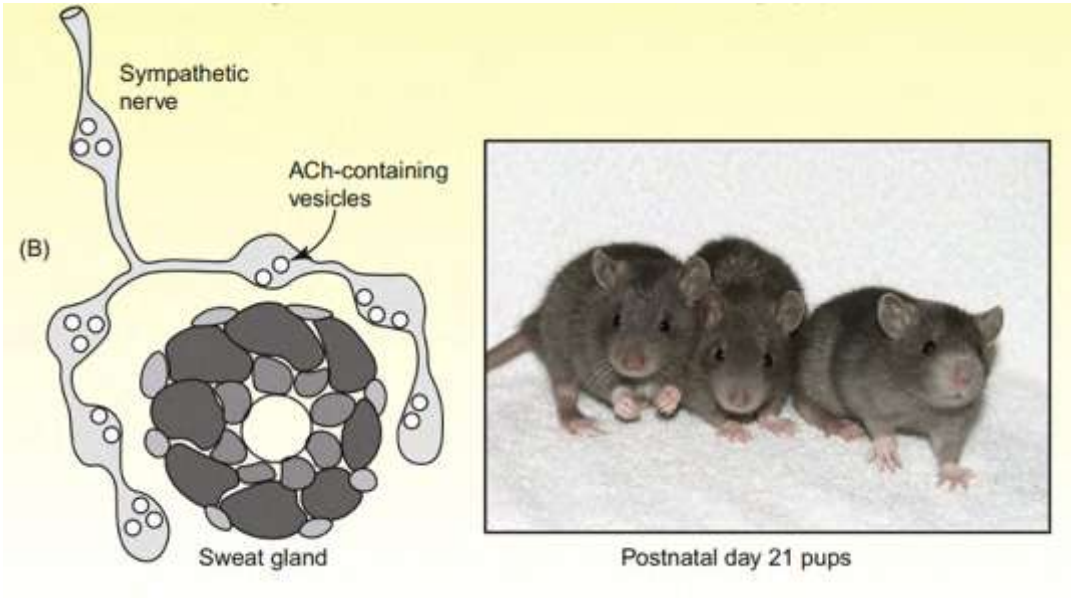
The cultured superior cervical ganglion (SCG) neurons that normally release norepinephrine as their neurotransmitter can undergo a developmental switch to acetylcholine.



Cholinergic and noradrenergic 胆碱能和去加肾上腺素能 markers are coexpressed in mouse sudomotor nerve terminals even after cholinergic switch

Developmental neurotransmitter switching:
The noradrenergic-to-cholinergic switch in sympathetic neurons

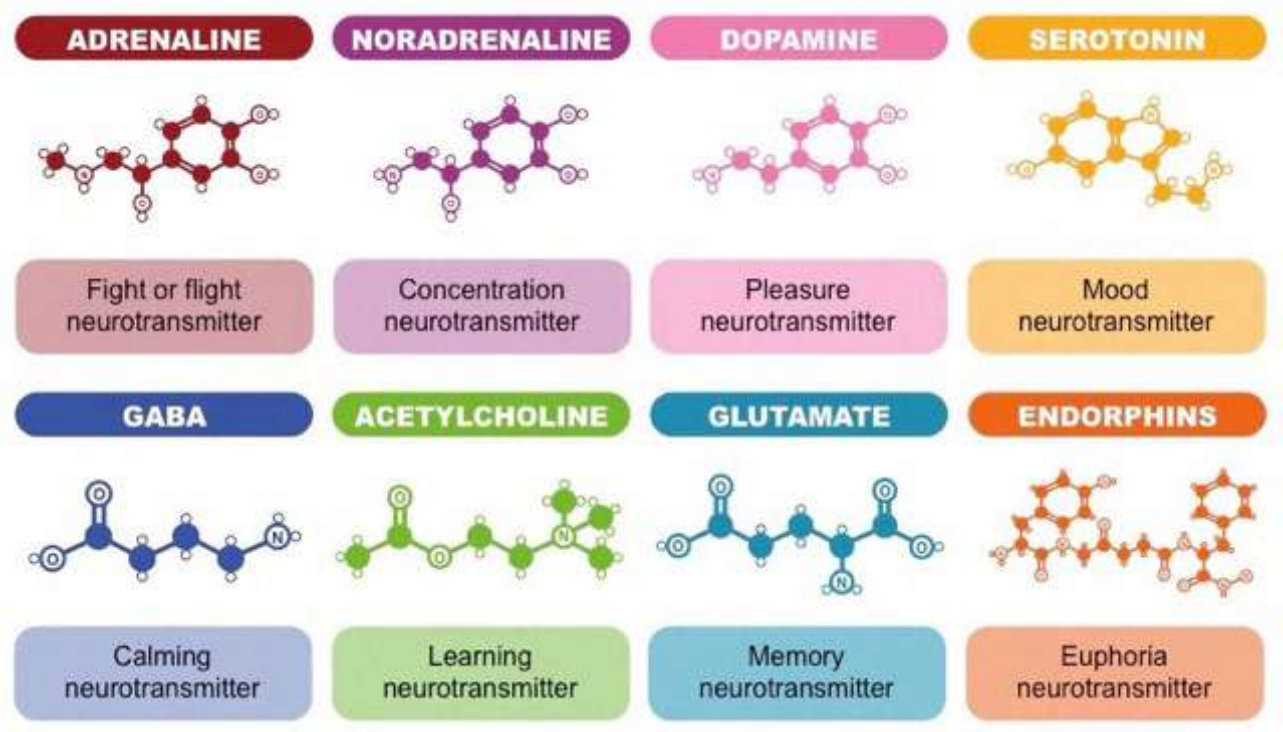




Rat sudomotor nerve terminals contain many catecholamine (norepinephrine)-containing vesicles for several days after birth, but these vesicles disappear by postnatal day 21.

Spontaneous electrical activity drives neurotransmitter switching

Developmental neurotransmitter differentiation

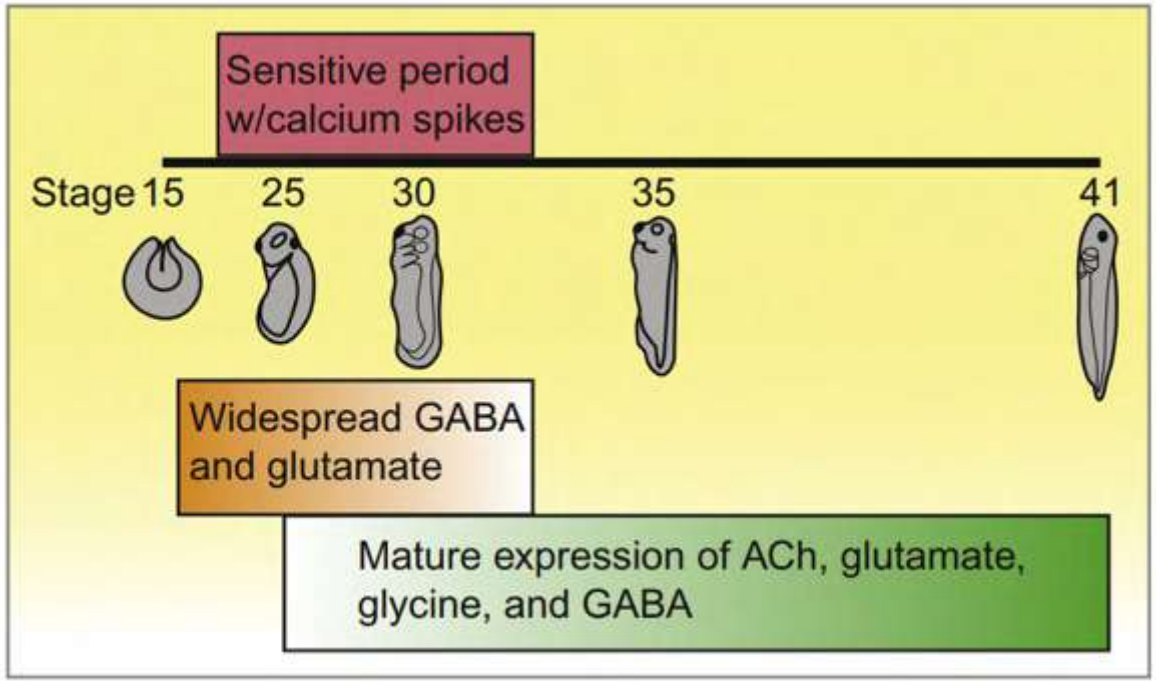


How does each type of neuron "know" the correct neurotransmitter phenotype to switch to?

- **voltage-gated calcium channels**

Spontaneous electrical activity drives neurotransmitter switching

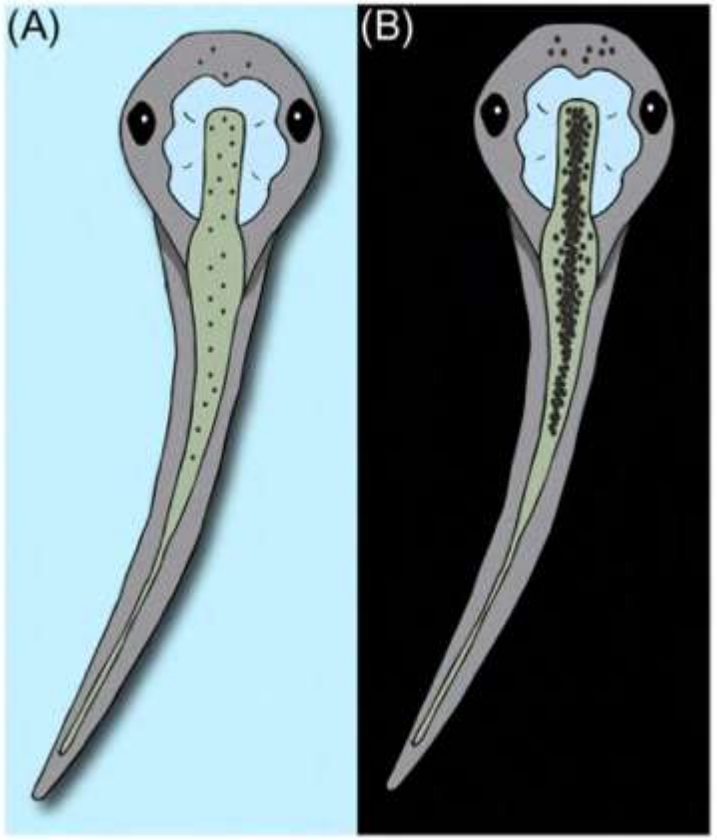
- **In mature neurons**, action potentials are sodium-dependent
- **In immature neurons**, action potentials are often calcium-dependent
- Calcium spiking activity causes immature neurons to release paracrine factors that induce surrounding cells to undergo changes in neurotransmitter phenotype



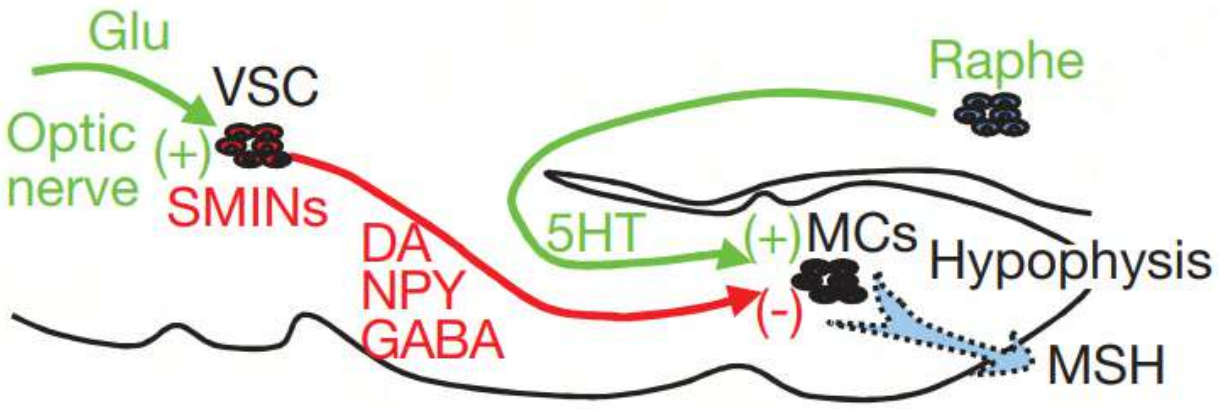
Timing of activity-dependent neurotransmitter switching in the *Xenopus laevis* spinal cord

Whether natural environmental stimuli specify transmitter expression in a neuronal population ?

Sensation-Mediated Neurotransmitter Switching



***Xenopus tadpole* pigmentation changes in response to surrounding light levels**



Vol 456|13 November 2008|doi:10.1038/nature07569 nature

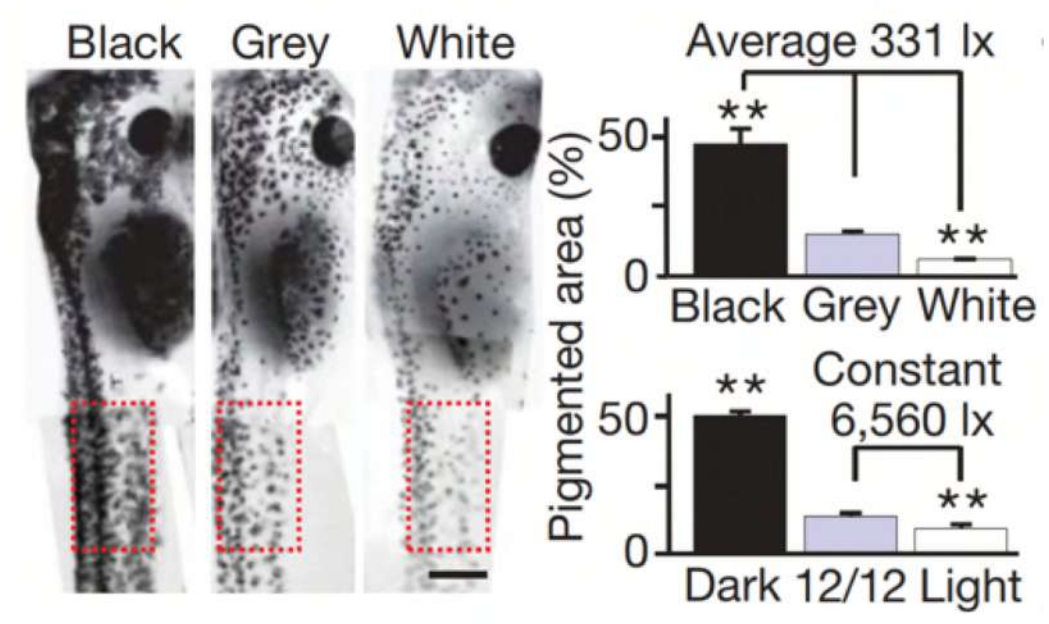
ARTICLES

Illumination controls differentiation of dopamine neurons regulating behaviour

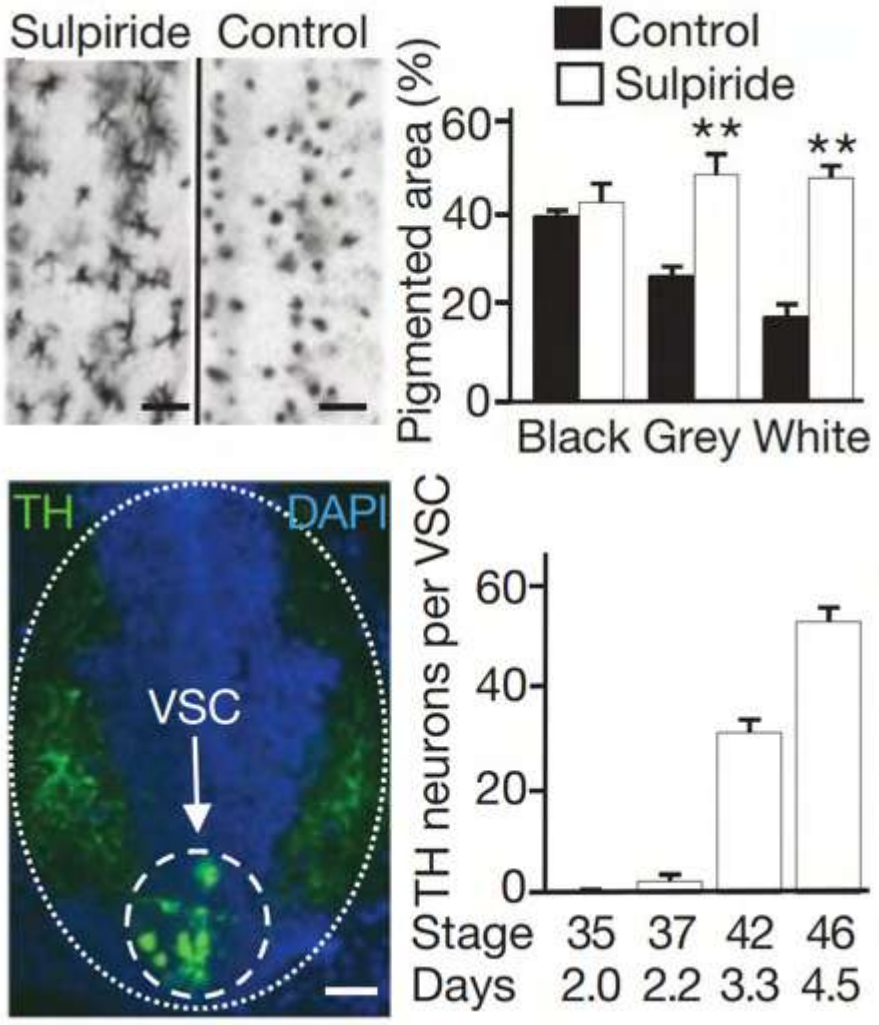
Davide Dulcis[1] & Nicholas C. Spitzer[1]

Specification of the appropriate neurotransmitter is a crucial step in neuronal differentiation because it enables signalling among populations of neurons. Experimental manipulations demonstrate that both autonomous and activity-dependent genetic programs contribute to this process during development, but whether natural environmental stimuli specify transmitter expression in a neuronal population is unknown. We investigated neurons of the ventral suprachiasmatic nucleus that regulate neuroendocrine pituitary function in response to light in teleosts, amphibia and primates. Here we show that altering light exposure, which changes the sensory input to the circuit controlling adaptation of skin pigmentation to background, changes the number of neurons expressing dopamine in larvae of the amphibian *Xenopus laevis* in a circuit-specific and activity-dependent manner. Neurons newly expressing dopamine then regulate changes in camouflage colouration in response to illumination. Thus, physiological activity alters the numbers of behaviourally relevant amine-transmitter-expressing neurons in the brain at postembryonic stages of development. The results may be pertinent to changes in cognitive states that are regulated by biogenic amines.

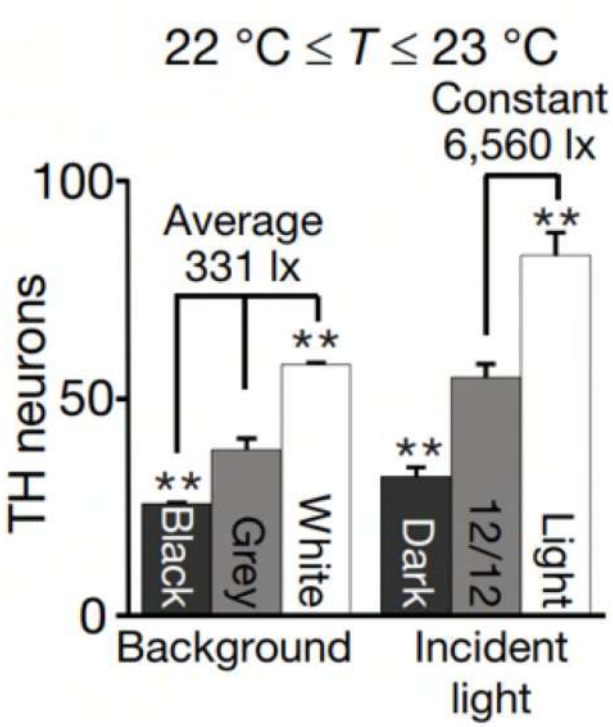
Dopaminergic VSC neurons regulate skin pigmentation



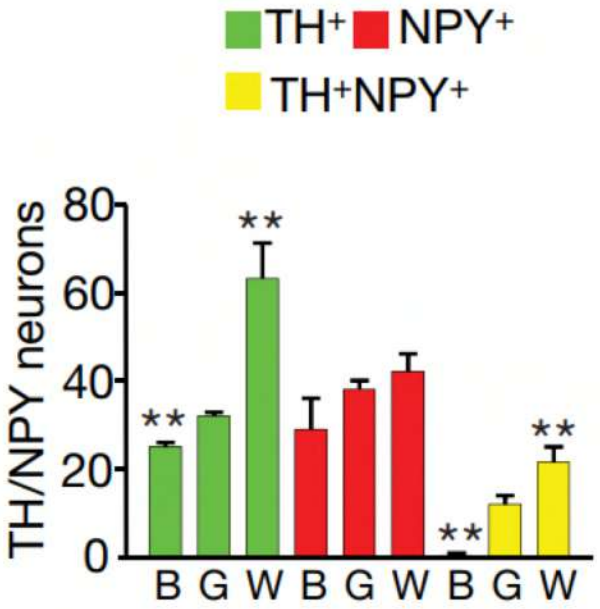
Raising animals in different light levels changes pigmentation



Illumination changes the number of dopaminergic neurons selectively in the VSC

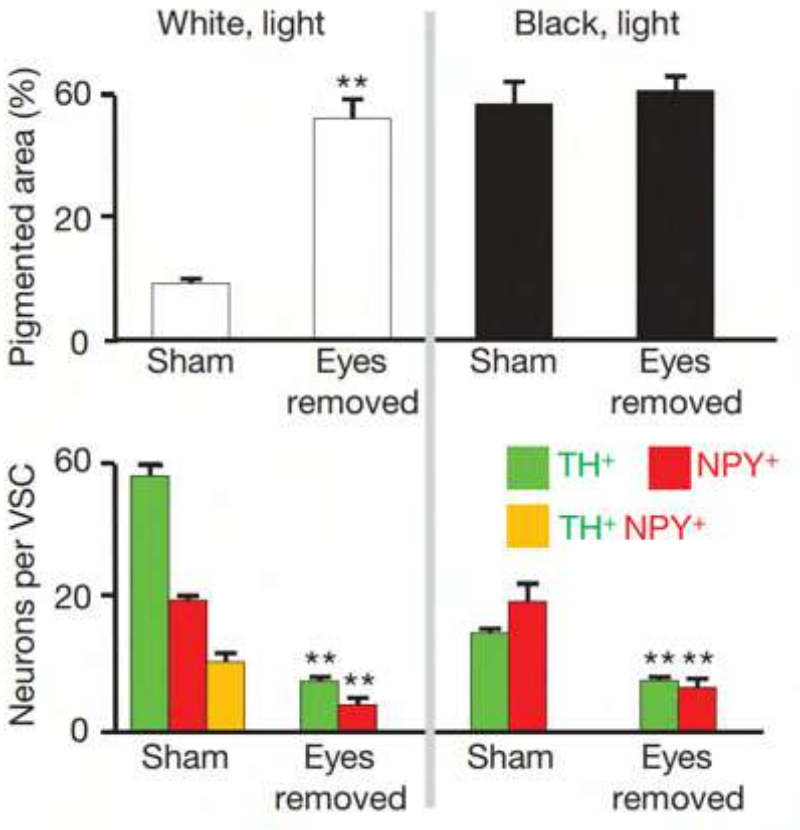


Raising animals in different light levels changes the number of VSC TH neurons

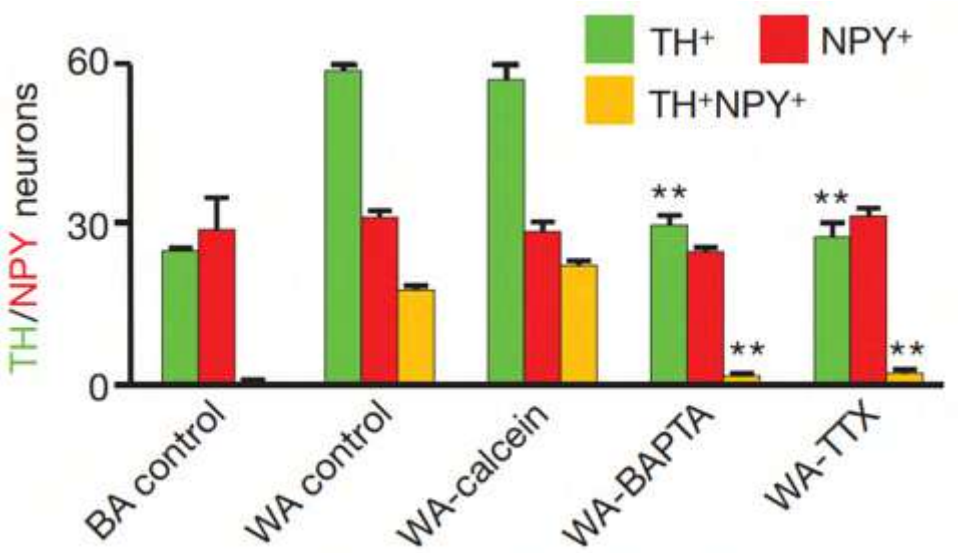


Two hour exposure to different background illumination changes the number of TH/NPY neurons in the VSC

Blocking physiological activity eliminates illumination dependent changes in the number of dopaminergic VSC neurons

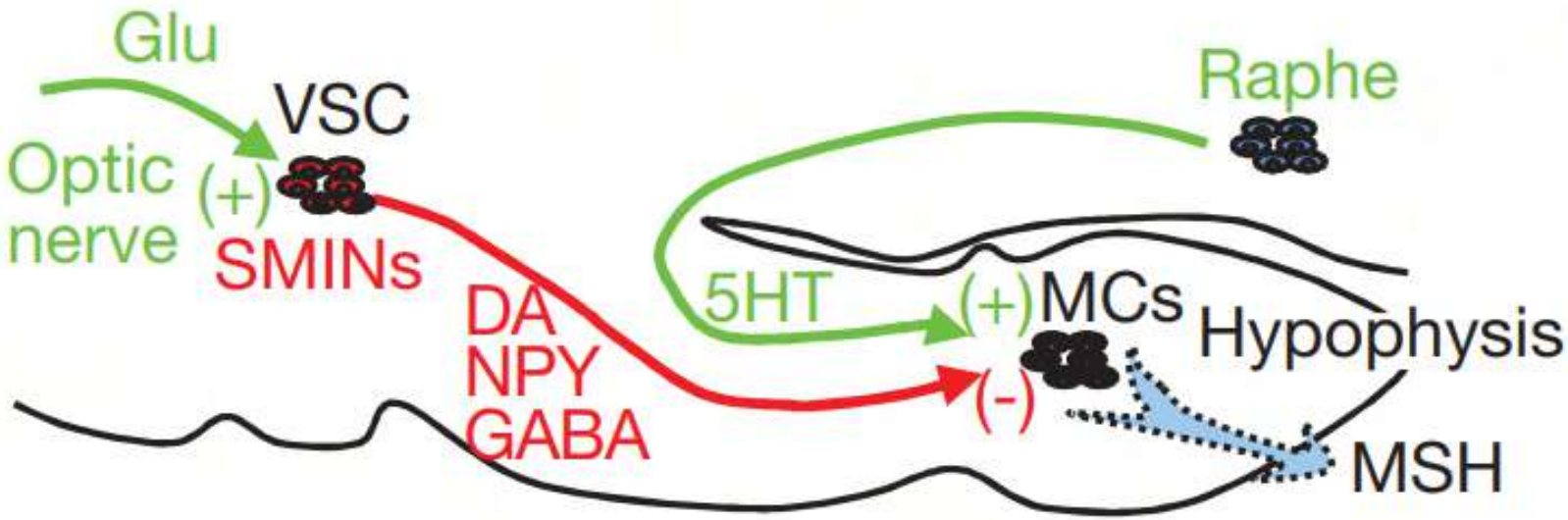


Binocular eye enucleation abolishes white-adaptation- and background-illumination-dependent changes in numbers of TH neurons



TH and NPY identify VSC neurons in the WA control and black-adapted (BA) control and after suppression of activity

The neuronal circuit controlling skin pigmentation



Glu: glutamate 谷氨酸

VSC: ventral suprachiasmatic nucleus 腹侧视交叉上核

MC: melanotrope cells 脑垂体中生成促黑激素的细胞

MSH: melanocyte-stimulating-hormone 促黑激素

Neurotransmitter switching

- Neurotransmitter switching in the developing nervous system
- Neurotransmitter switching in the adult nervous system

“Stimulus-mediated” Neurotransmitter Switching in Mature Neurons

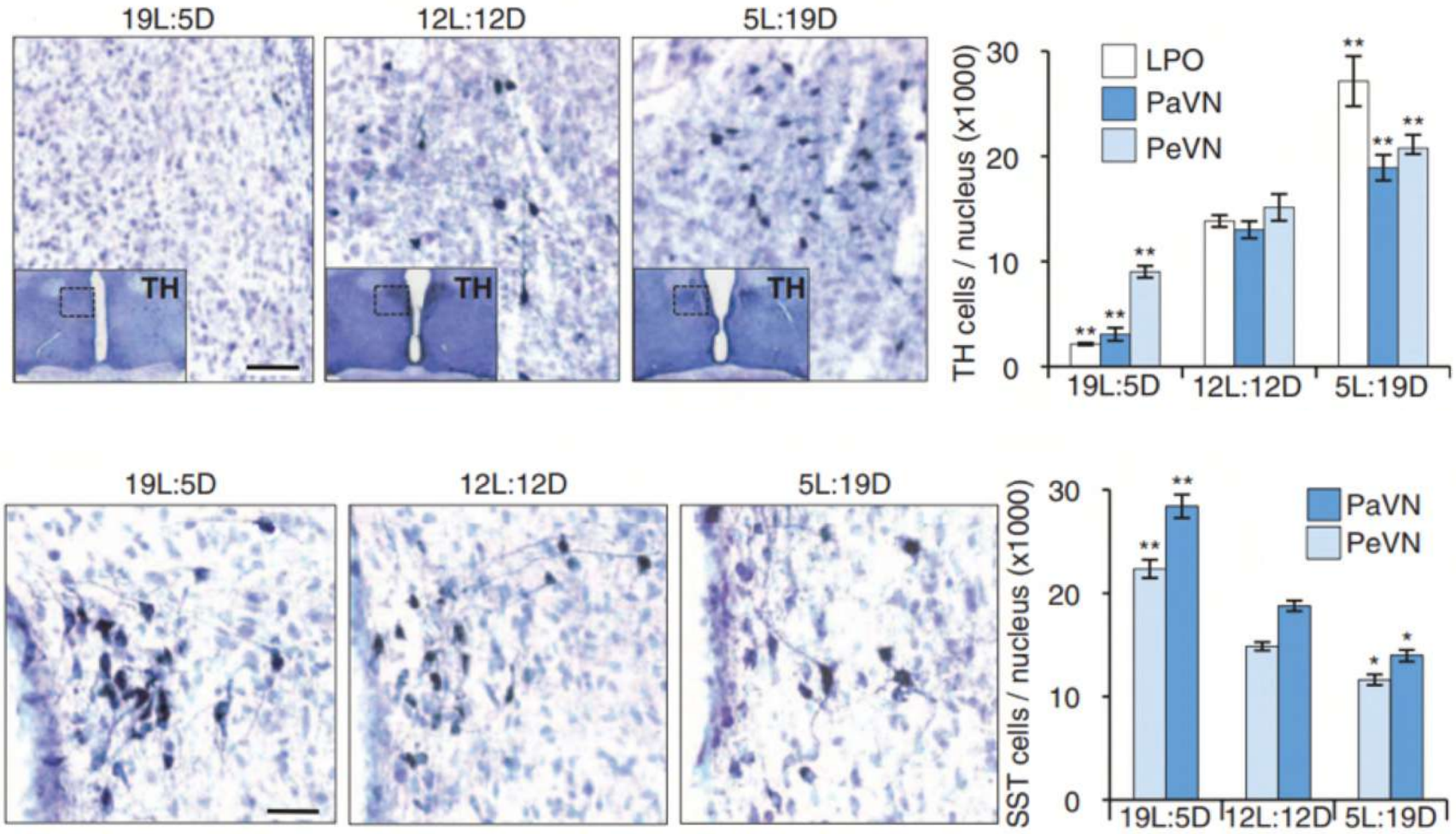
During winter, when the hours of daylight are shorter, many people suffer from a form of depression called seasonal affective disorder (SAD).

Neurotransmitter Switching in the Adult Brain Regulates Behavior

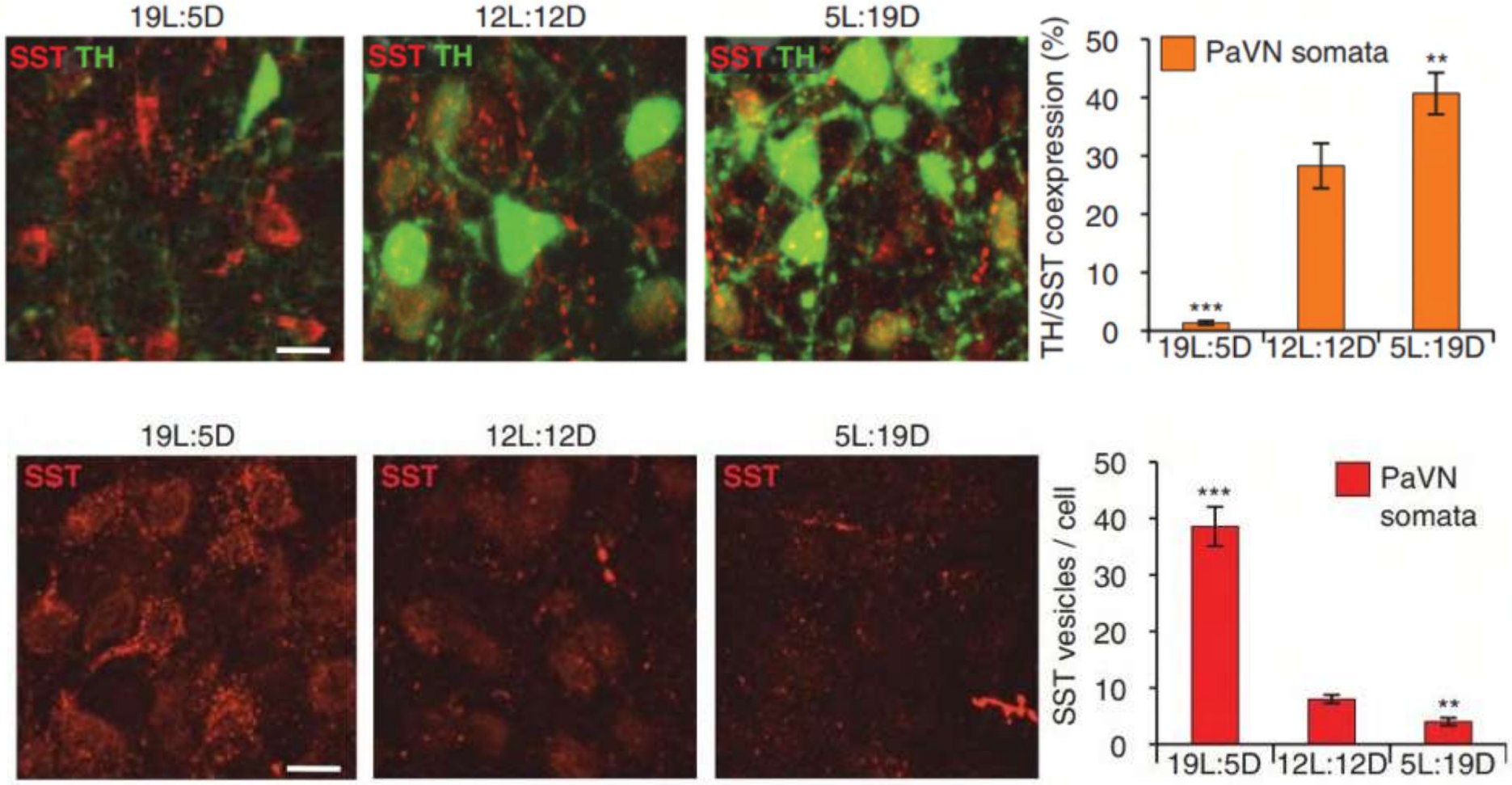
Davide Dulcis,[1,2]*† Pouya Jamshidi,[1]†‡ Stefan Leutgeb,[1,2] Nicholas C. Spitzer[1,2]

Neurotransmitters have been thought to be fixed throughout life, but whether sensory stimuli alter behaviorally relevant transmitter expression in the mature brain is unknown. We found that populations of interneurons in the adult rat hypothalamus switched between dopamine and somatostatin expression in response to exposure to short- and long-day photoperiods. Changes in postsynaptic dopamine receptor expression matched changes in presynaptic dopamine, whereas somatostatin receptor expression remained constant. Pharmacological blockade or ablation of these dopaminergic neurons led to anxious and depressed behavior, phenocopying performance after exposure to the long-day photoperiod. Induction of newly dopaminergic neurons through exposure to the short-day photoperiod rescued the behavioral consequences of lesions. Natural stimulation of other sensory modalities may cause changes in transmitter expression that regulate different behaviors.

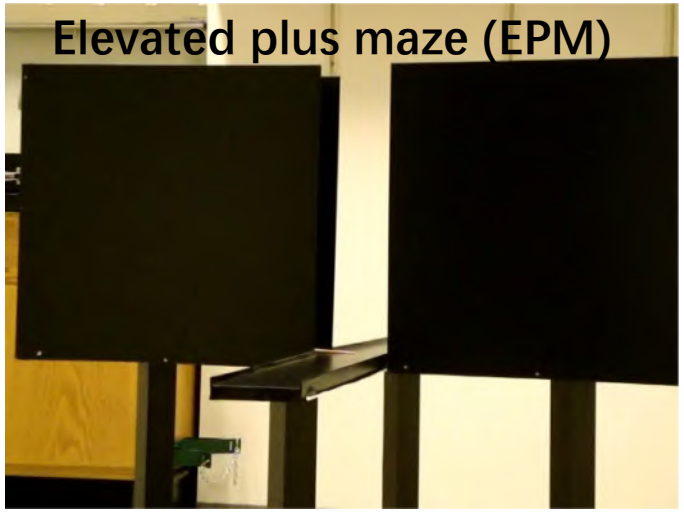
Photoperiods regulate numbers of dopaminergic neurons and SST-IR neurons

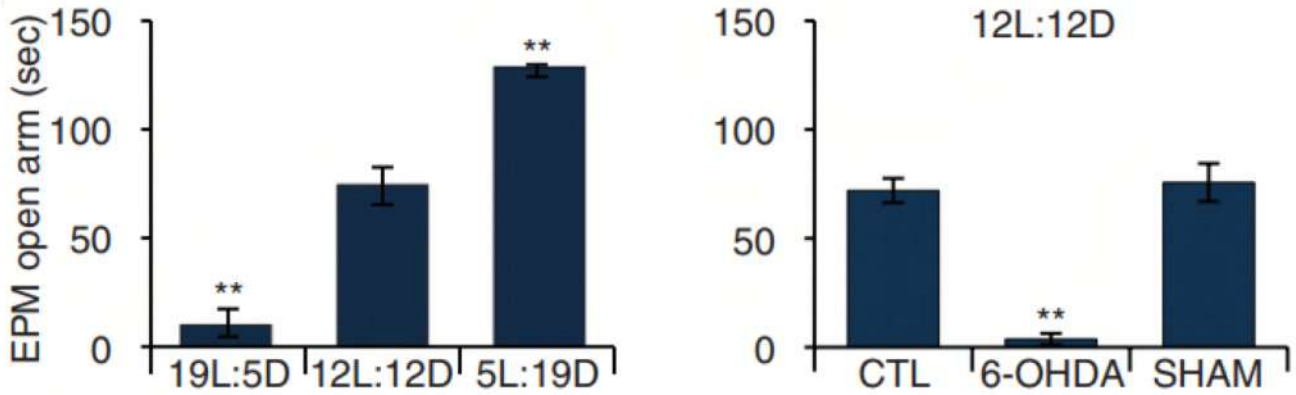


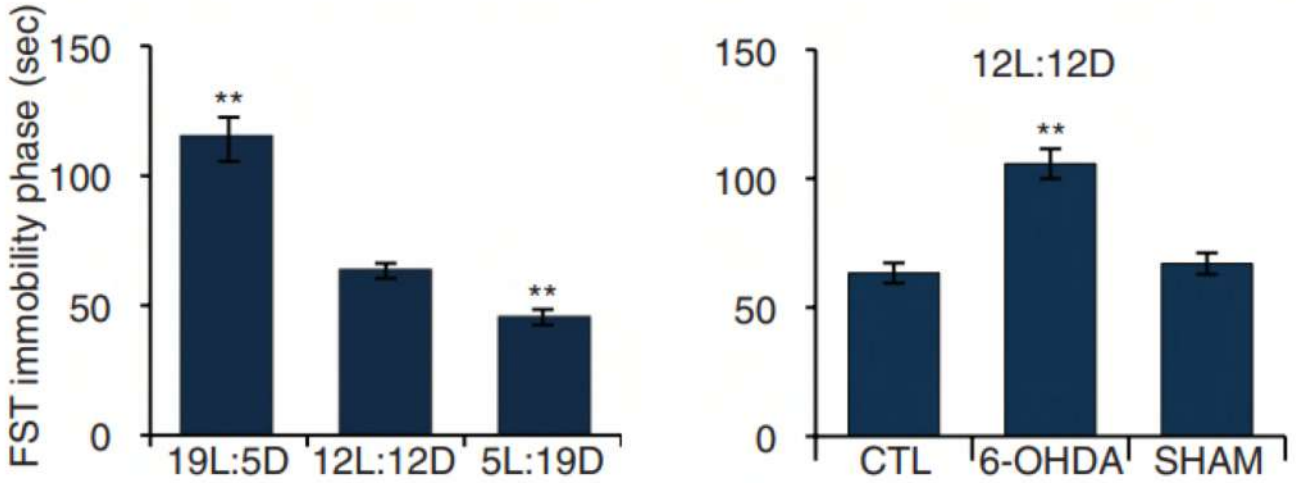
Photoperiods drive neurotransmitter switching between dopamine and somatostatin



Photoperiod-dependence of behaviors







Neurotransmitter switch

A switch in the type of neurotransmitter released in the brain underlies changes in mammalian behavior associated with day-night cycles.

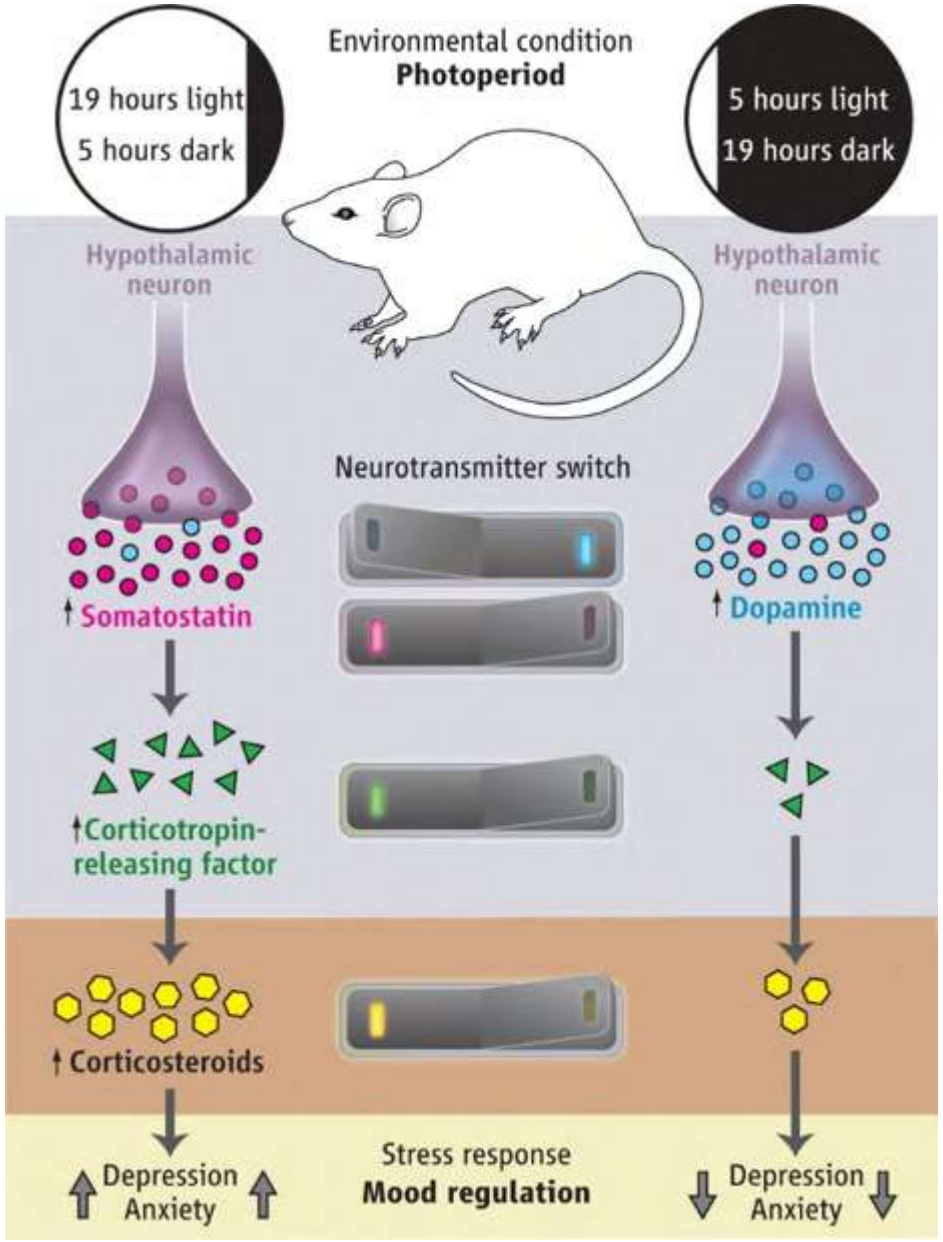
Hypothalamic neuron 下丘脑神经元

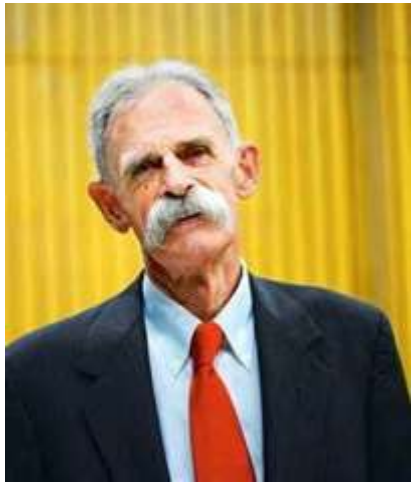
Somatostain 生长激素抑制素

Dopamin 多巴胺

Corticotrophin-releasing factor 促肾上腺皮质激素释放因子

Corticoteroids (肾上腺)皮质激素





Nicholas C. Spitzer
University of California, San Diego

Research

We study neurotransmitter switching, a newly appreciated form of neuroplasticity in which neurons change the transmitters that they make and release in response to sustained sensory or motor activity. Transmitter identity shifts from excitatory to inhibitory or vice versa, with matching changes in postsynaptic receptors, both in the developing amphibian nervous system and in the adult rodent brain. Perhaps unsurprisingly the reversal of the sign of synaptic transmission is accompanied by changes in the animals' behavior.

Summary

- Many neurons make and release two or more neurotransmitters including small-molecules and neuropeptides.

- Neurotransmitters can elicit a variety of different actions on their neuron targets to alter neuronal excitability or synaptic transmission.

Discussion

- How does the transient expression of specific neurotransmitters in developing neurons aid in refining circuits ?
- How do maturing neurons adopt a neurotransmitter phenotype appropriate for their target tissue or environment ?

Neuron-glial Cell Interactions in *Drosophila*

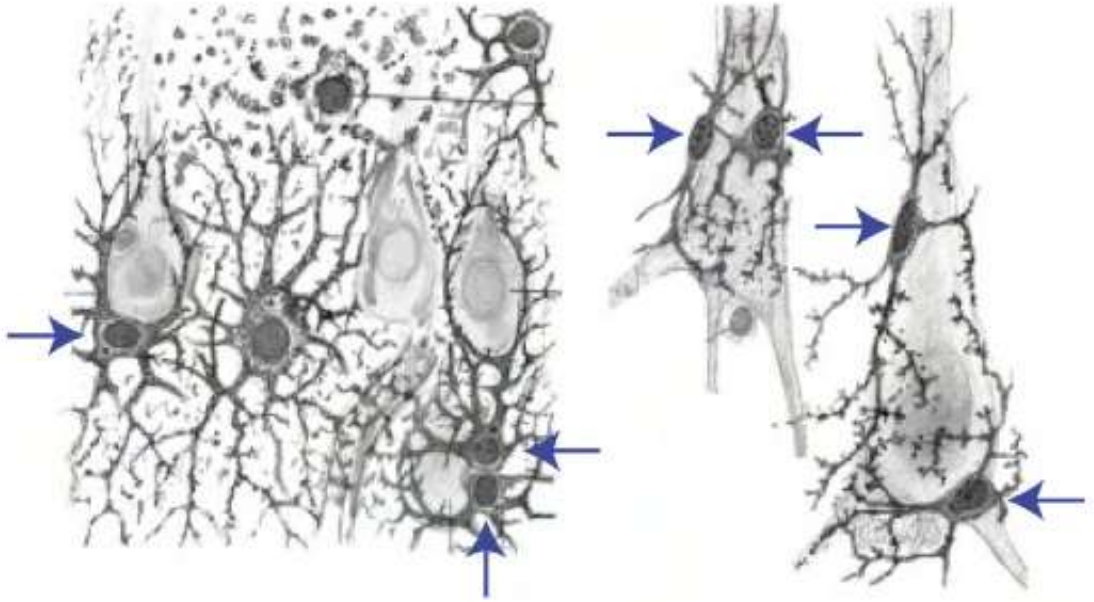
Ma Mingze

2020/05/28

Composition of nerve tissue

Nervous Tissue
- neuron: Receive, integrate, and transmit nerve impulses
- glial cell: support neurons

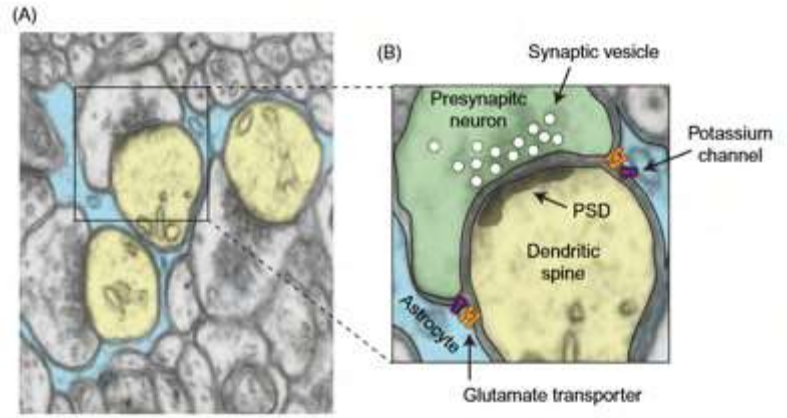
Do glial cells affect the activity of neurons?



García-Marín et al., 2007.

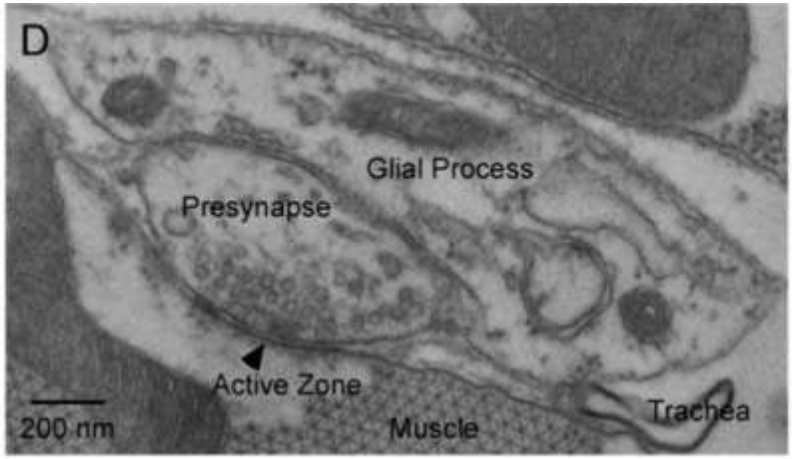
Synapse structure

Tripartite Synapse
- presynaptic terminal
- postsynaptic cell
- surrounding glial cells



Atlas of Ultrastructural Neurocytology
http://synapseweb.clm.utexas.edu/atlas

Do glial cells regulate the transmission of nerve impulses?



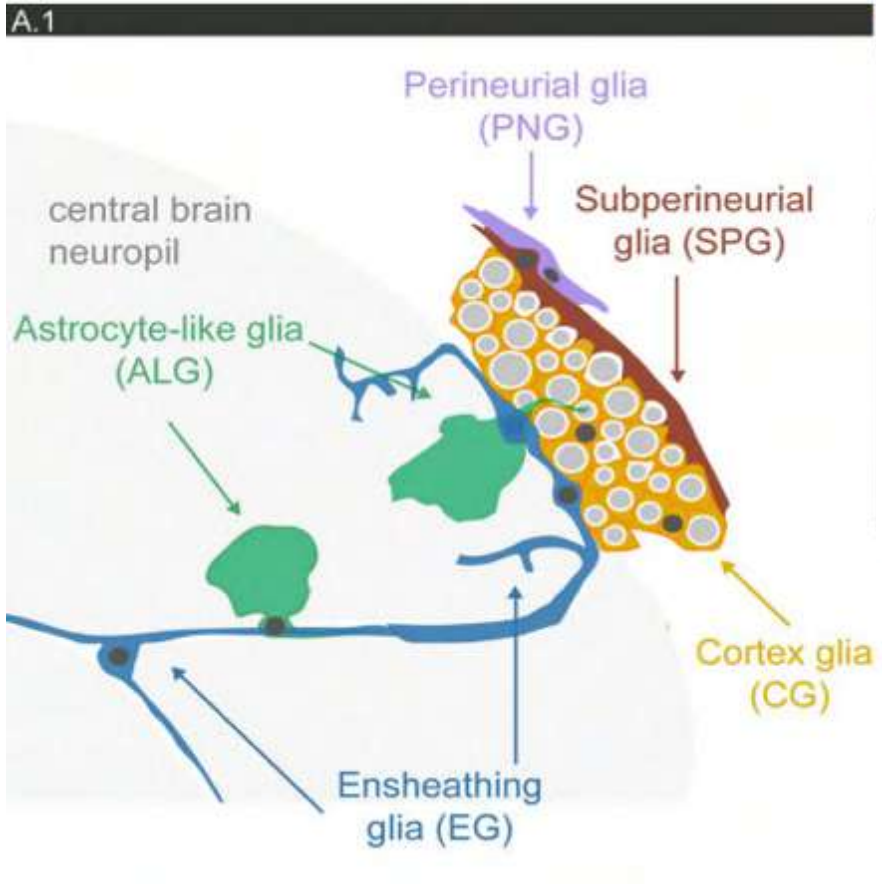
Rie Danjo et al., *PLoS One*, 2011.

- Glia in *Drosophila*
- Glial cells regulate rhythmic behavior
- Glial cells regulate other behaviors

Glia in *Drosophila*

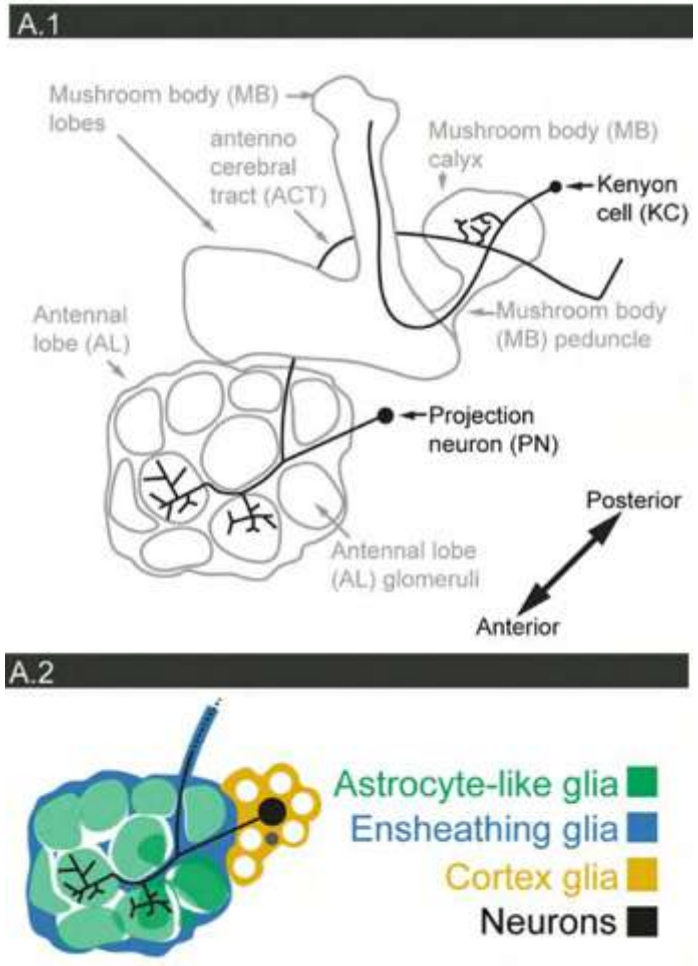
Glia in *Drosophila*

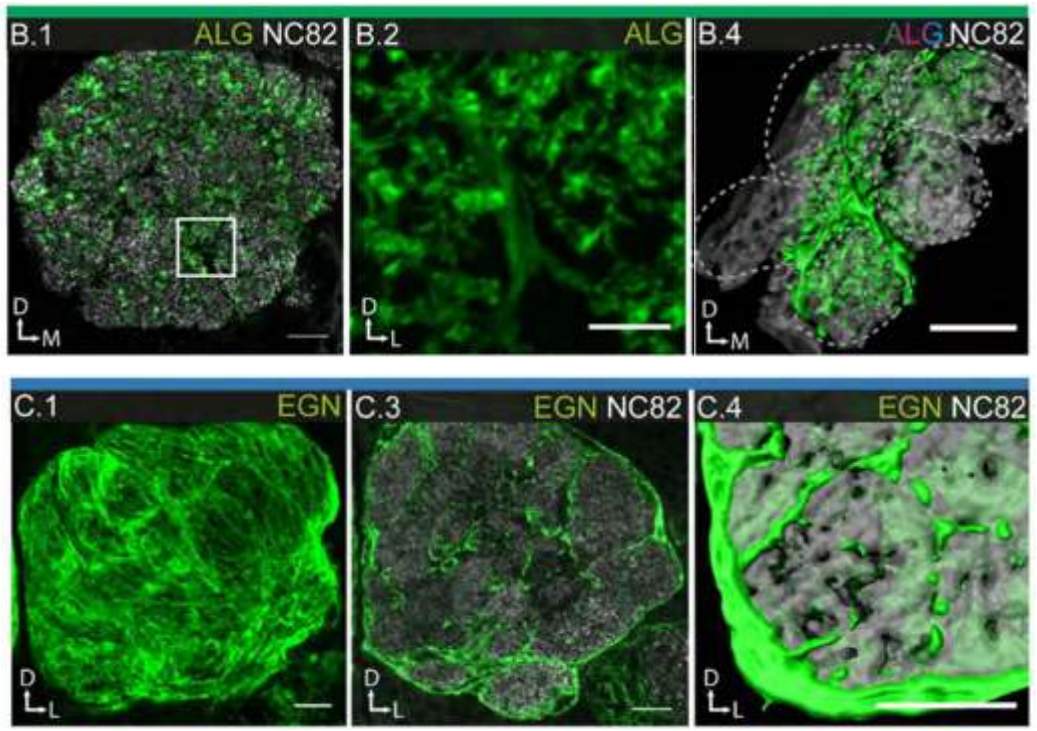
- Glia
  - surface glia
    - perineurial glia (PNG)
    - subperineurial glia (SPG)
  - cortex glia (CG)
  - neuropil glia
    - astrocyte-like glia (ALG)
    - ensheathing glia (EG)



Malte C. Kremer et al., 2017

ALG and EG in antennal lobe

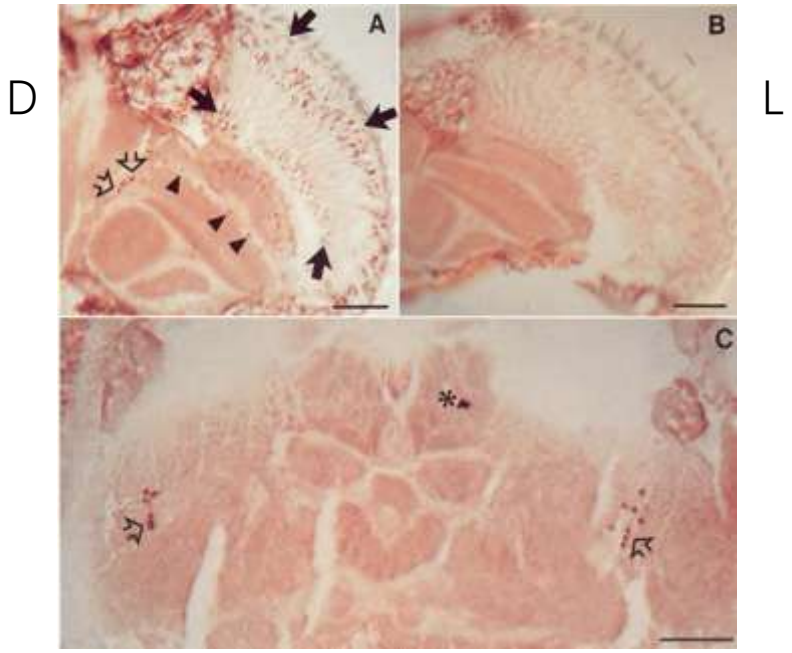


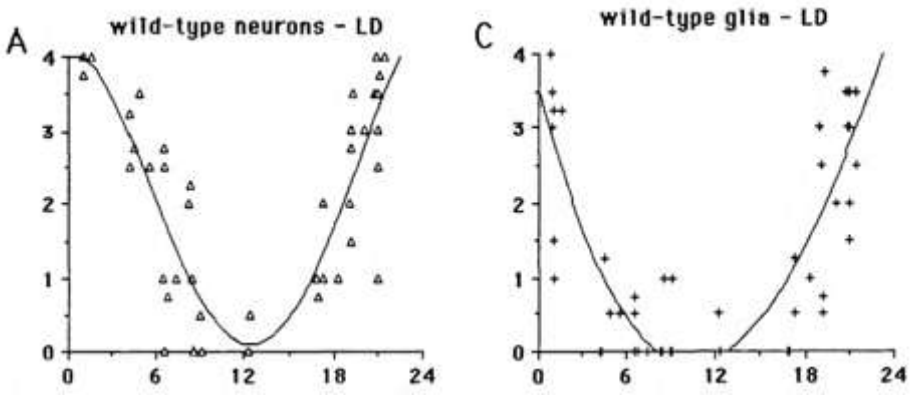


Malte C. Kremer et al., 2017

Glial cells regulate rhythmic behavior

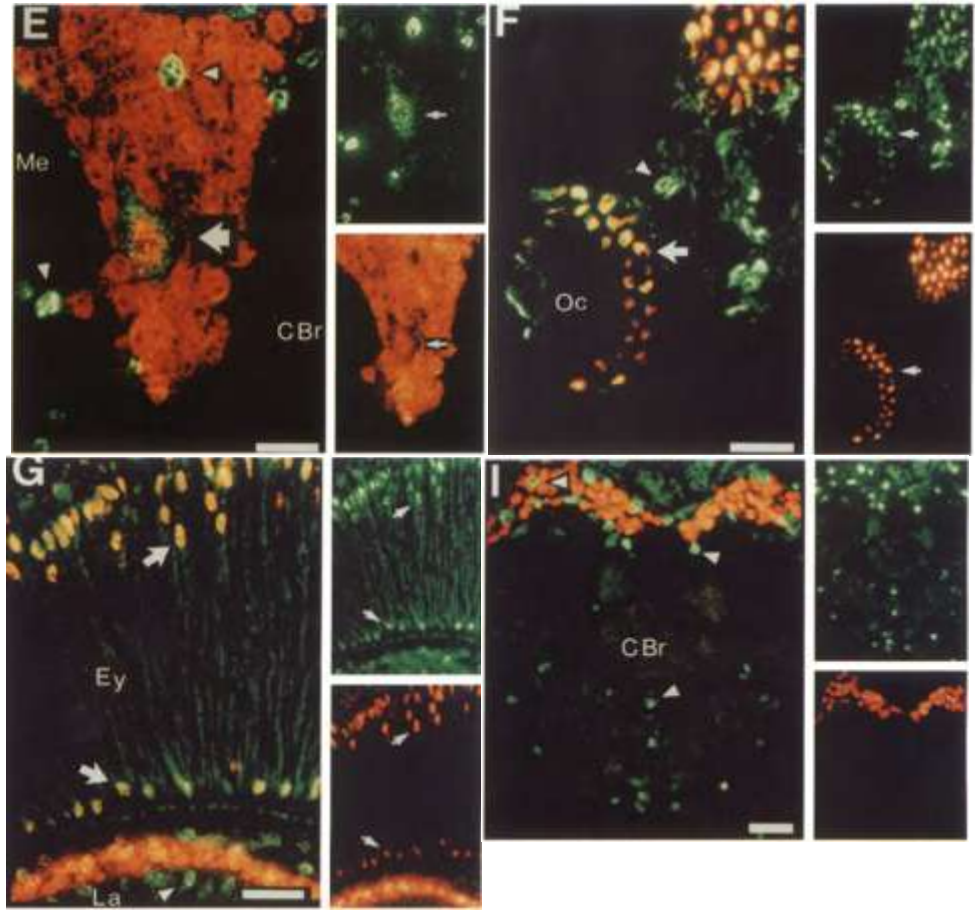
Expression of the period gene within different cell types





Zerr et al., 1990

PER-βgal Elav



J Ewer et al., 1992

The Rob Jackson Lab

- Cell Type-Specific Expression Profiling of Clock Cells and Glia
- Brain Glial Cells and Behavior

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Neuron. 2007 August 2; 55(3): 435–447.

Drosophila Ebony Activity is Required in Glia for the Circadian Regulation of Locomotor Activity

Joowon Suh and **F. Rob Jackson***
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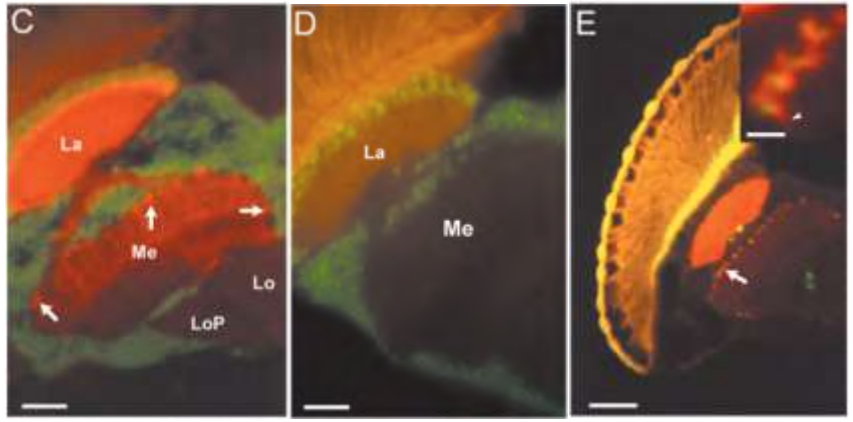
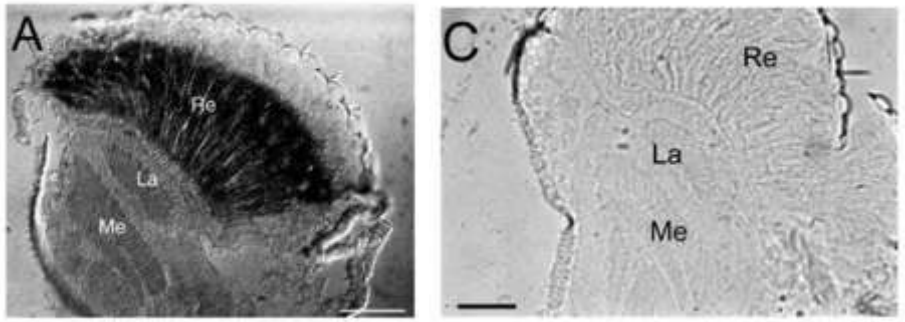
Ebony in glia may be involved in histamine circulation of photoreceptors

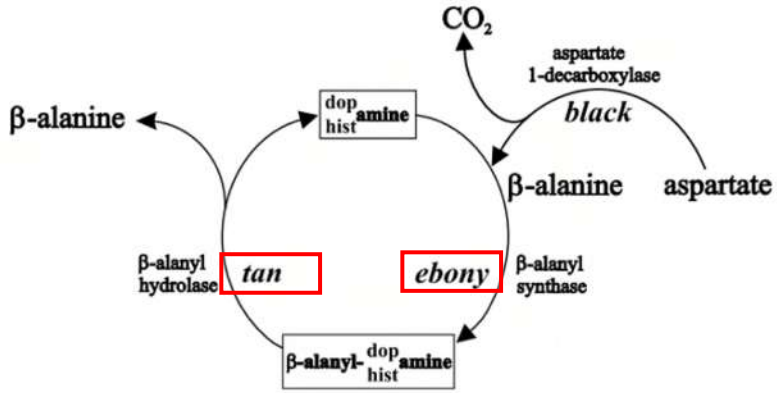
Ebony Elav Ebony Elav Ebony Glia

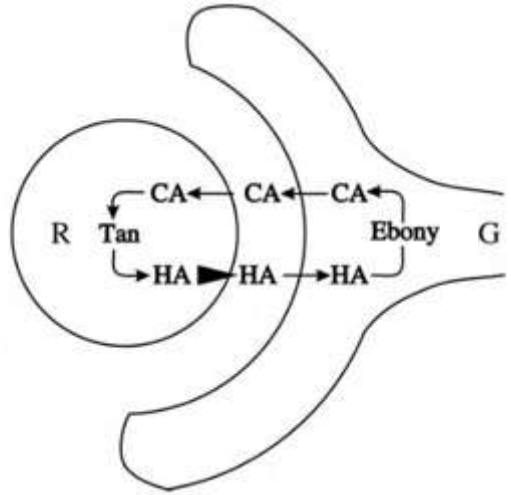


ebony-

tan

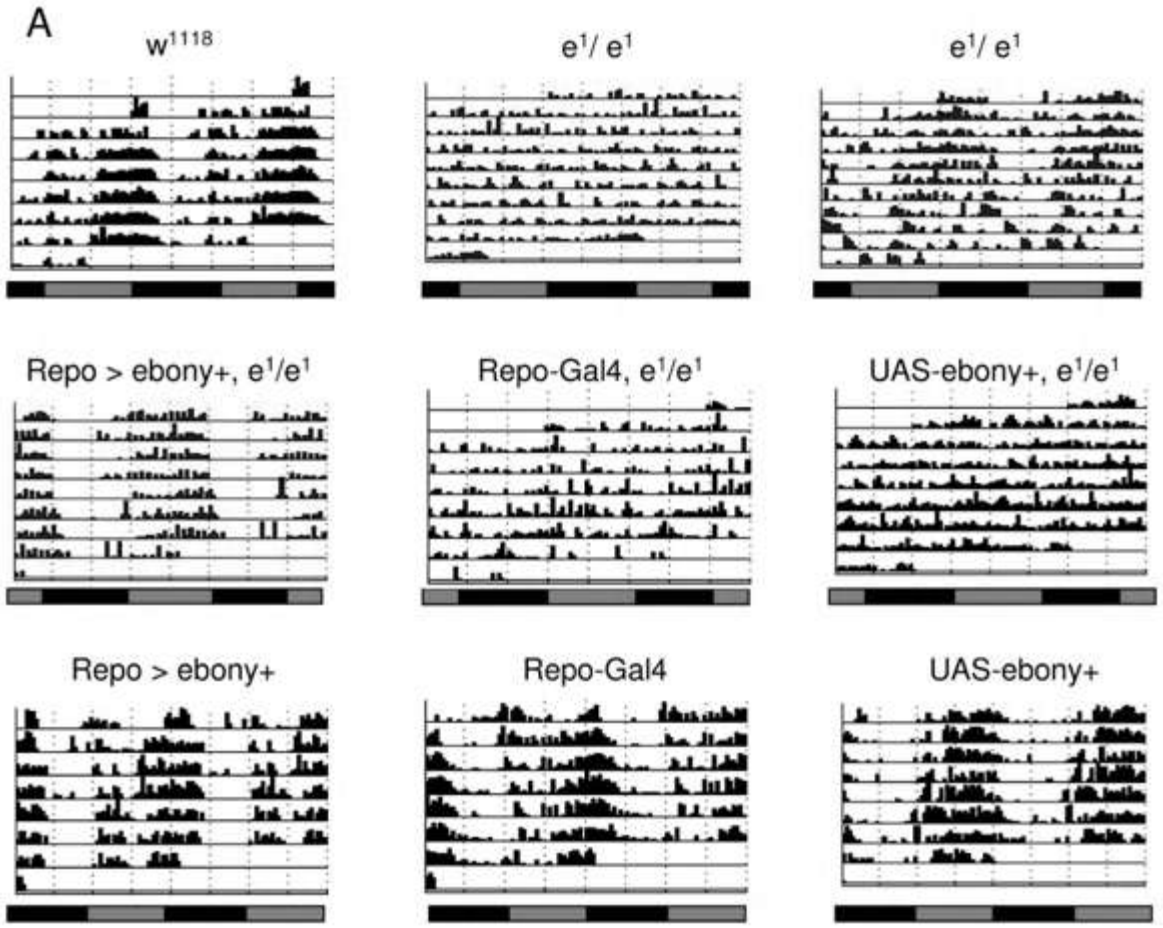






Borycz, et al., 2002
J Ewer et al., 1992
True, J.R. et al., 2005

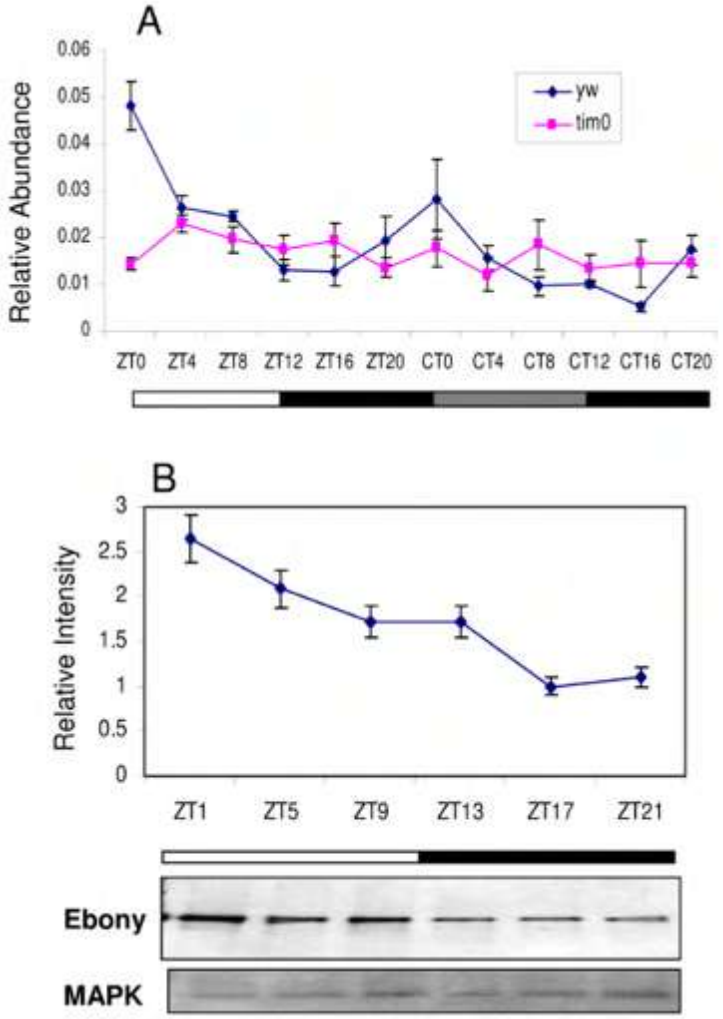
Ebony in glia plays an important role in maintaining normal rhythm

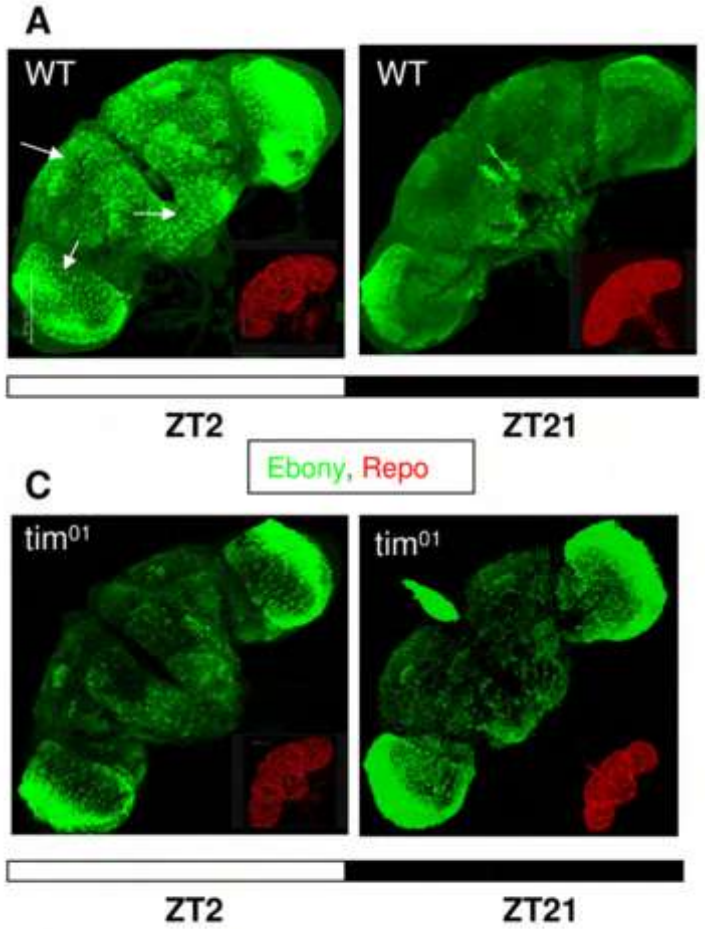


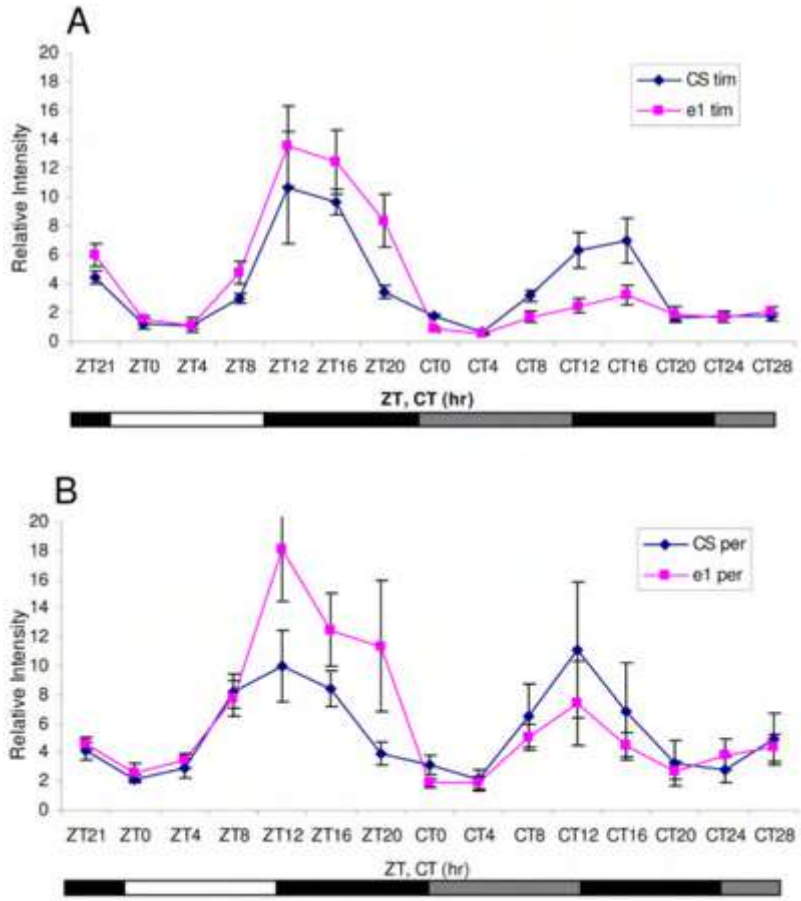
Genotype	Period*	Std. err.	% Rhythmicity	RI	RI std. err.	n
w^{1118}	24.1	0.1	96	0.57	0.02	80
yw	23.8	0.2	88	0.53	0.03	41
CS	23.8	0.06	92	0.42	0.08	22
CS e^1/+	23.3	0.11	90	0.49	0.04	27
CS e^1/e^1	23.9	0.07	35	0.27	0.03	26
e^1/e^1	23.4	0.3	28	0.17	0.02	28
yw e^1/e^1	23.5	0.24	20	0.12	0.01	24
Rescue						
w;+;repo-Gal4,e^1/UAS-e^+,e^1	23.9	0.1	81	0.40	0.02	70
w;+;repo-Gal4,e^1/TM6,e^1	24	0.2	23	0.22	0.03	22
w^{1118};+;repo-Gal4.e^{AFA}/UAS-e^+.e^{AFA}	24.1	0.04	95	0.46	0.03	23
w^{1118};+;UAS-e^+.e^{AFA}/TM6,e^1	24.1	0.08	39	0.26	0.03	28
w^{1118};actin-Gal4/+;e^{AFA}/UAS-e^+.e^{AFA}	24.2	0.03	92	0.51	0.02	31
w^{1118};actin-Gal4/+;e^{AFA}/e^{AFA}	24.3	0.05	33	0.25	0.03	27
elav-Gal4/y;+;UAS-e^+,e^1/e^1	23.7	0.01	59	0.42	0.03	32
elav-Gal4/y;+;TM6,e^1/e^1	23.8	0.1	41	0.26	0.03	60

Suh & Jackson, 2007

Ebony may under clock protein control

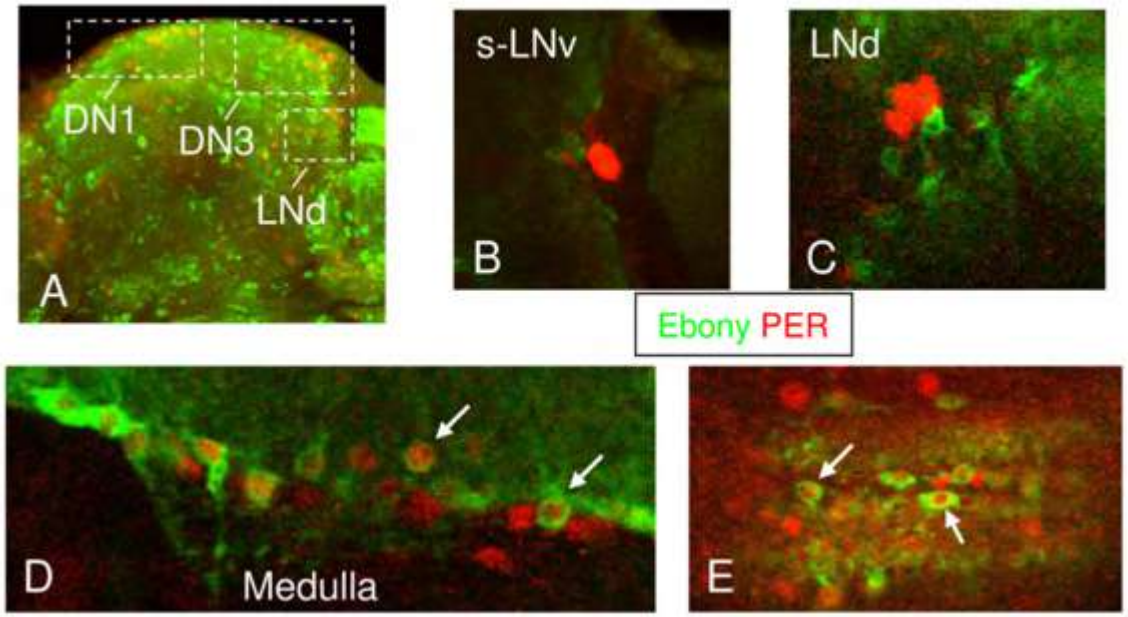


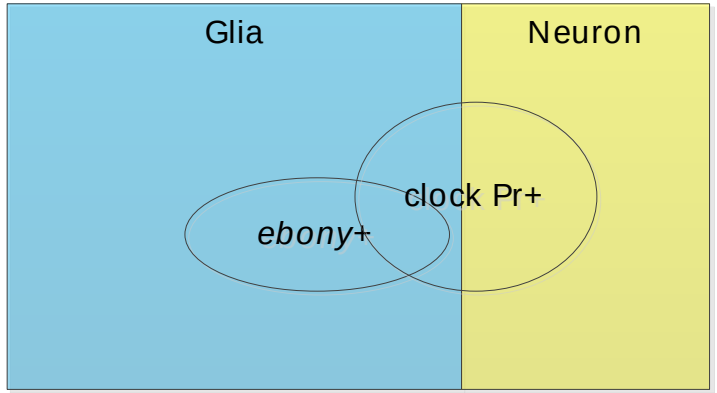




Suh & Jackson, 2007

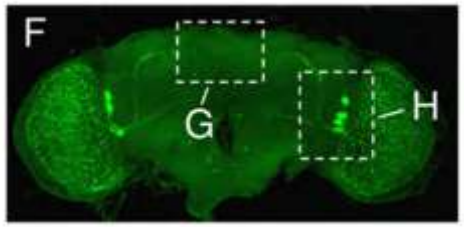
Not all ebony+ cells have clock protein expression

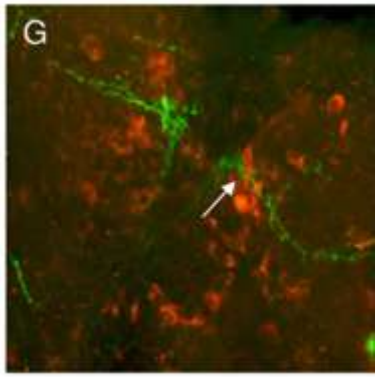




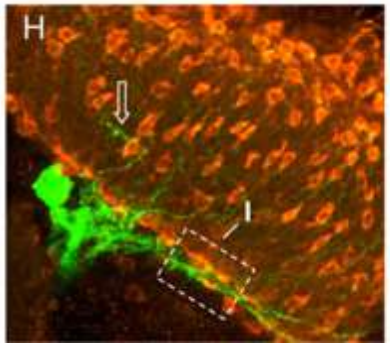
Suh & Jackson, 2007

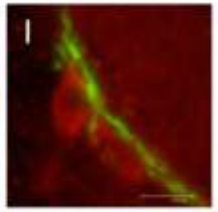
Ebony regulates rhythm through PDF-independent pathway



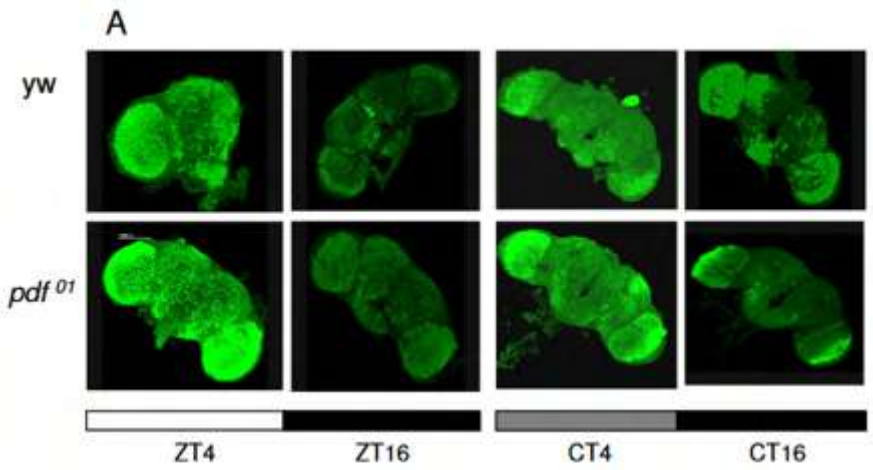


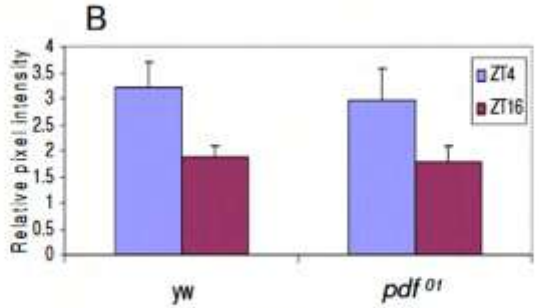
Ebony PDF





Ebony





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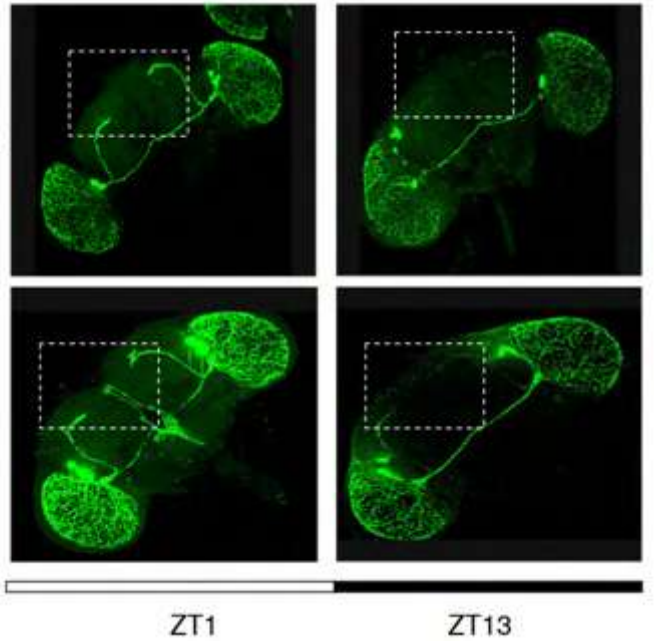
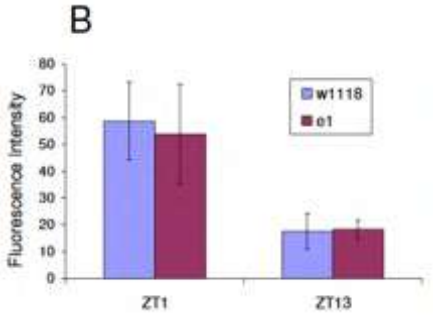
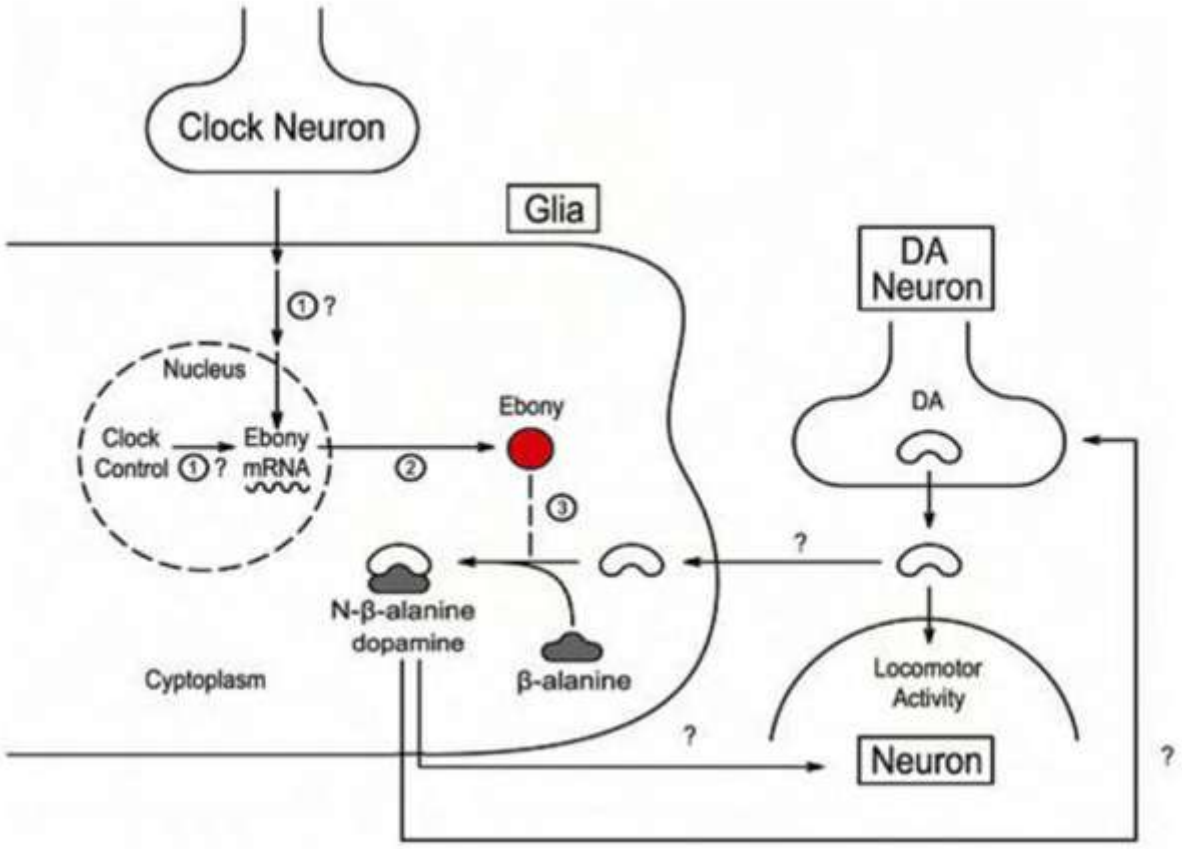
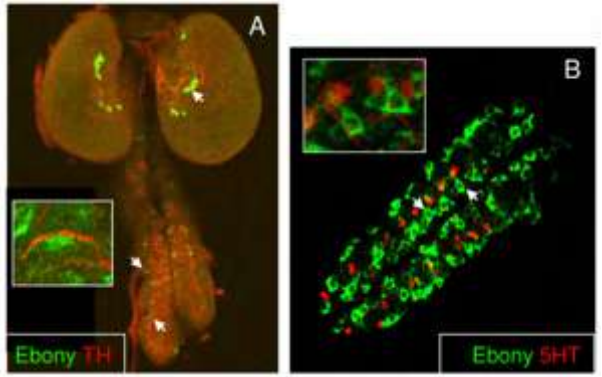


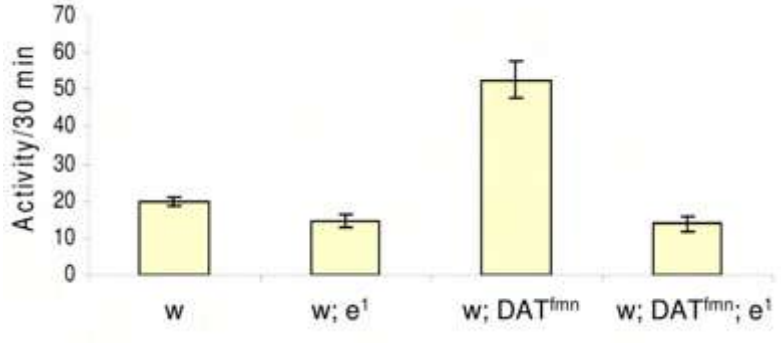


Suh & Jackson, 2007

A model for the control of the Ebony molecular rhythm and locomotor activity







Suh & Jackson, 2007

Published in final edited form as:
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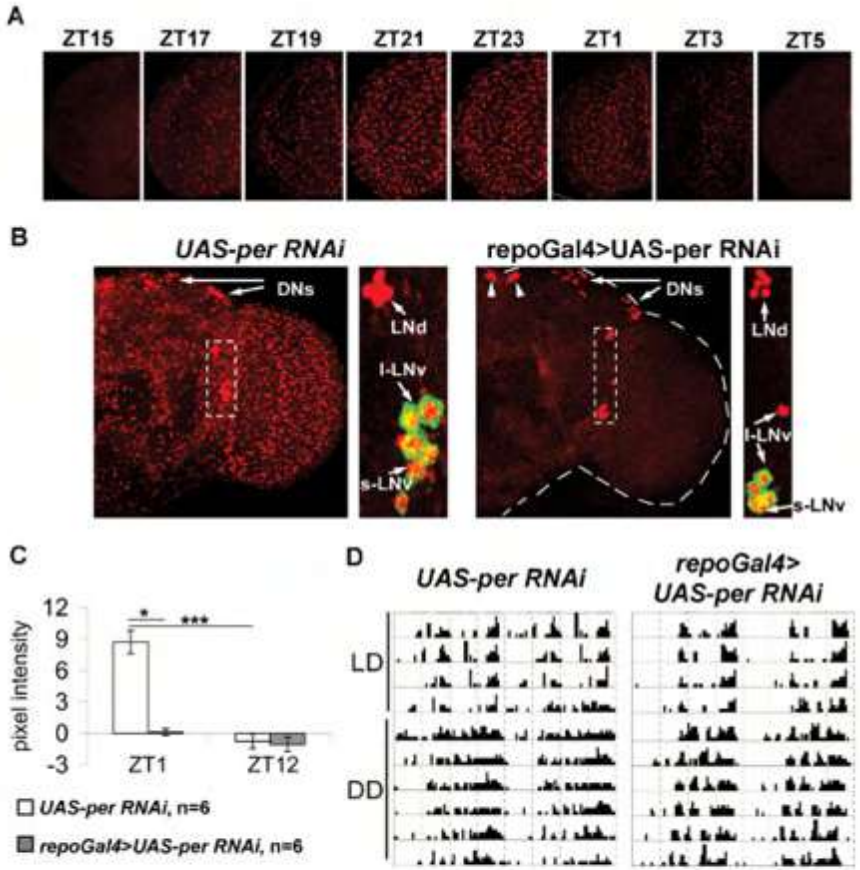
Glial cells physiologically modulate clock neurons and circadian behavior in a calcium-dependent manner

Fanny S. Ng, **Michelle M. Tangredi**, and **F. Rob Jackson**[1]
Department of Neuroscience, Center for Neuroscience Research Tufts University School of Medicine, 136 Harrison Avenue, Boston, MA 02111

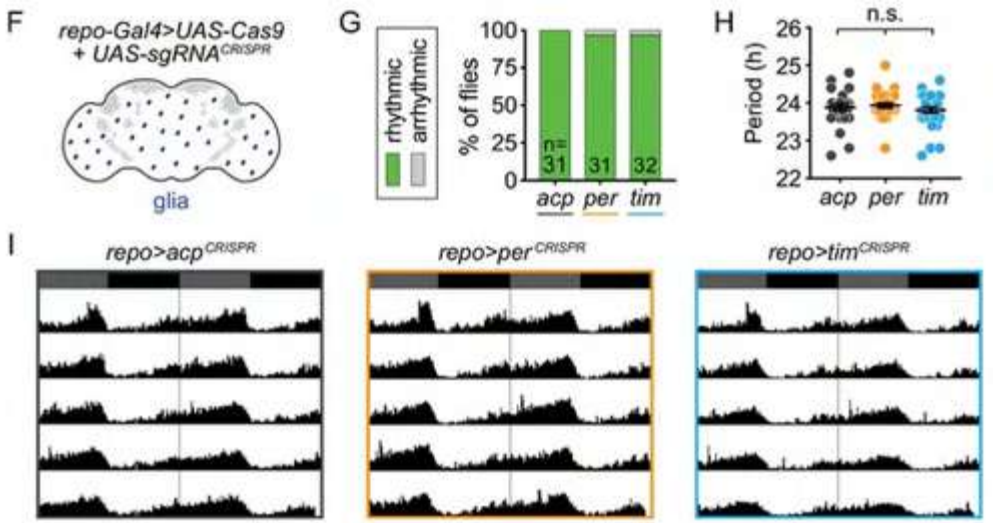
Clock proteins in glia have no significant effect on rhythm



E

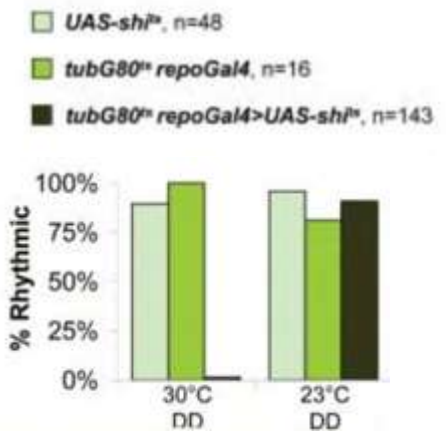
Genotype	DD (23°C)				
	N	Mean activity ± SEM	Tau (h) ± SEM	RI ± SEM	%R
UAS-per RNAi	28	19.92 ± 1.40	23.66 ± 0.1	0.46 ± 0.02	96
repoGal4	12	21.58 ± 1.31	23.76 ± 0.06	0.53 ± 0.02	92
repoGal4>UAS-per RNAi	60	17.06 ± 5.08	23.44 ± 0.09	0.46 ± 0.11	98
timGal4	12	29.39 ± 1.71	24.07 ± 0.05	0.47 ± 0.04	88
timGal4>UAS-per RNAi	20	21.31 ± 1.23	26.35 ± 0.09 *	0.30 ± 0.03 **	55

Ng et al., 2011

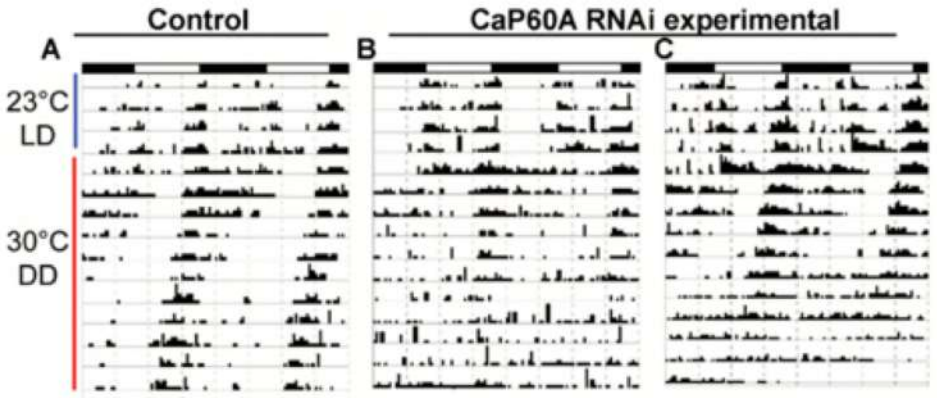


Rebecca Delventhal et al., 2019

Glial cells may be involved in regulating neurotransmitter concentration



Glial class driver	Genotype	N	% Rhythmic
Perineurial	Control- *NP6293*	44	93
	NP6293 > UAS-shi^{ts}	27	100
Subperineurial	Control- *tubG80^{ts} NP2276*	22	95
	tubG80^{ts} NP2276 > UAS-shi^{ts}	48	87
Cortex	Control- *NP577*	45	96
	NP577 > UAS-shi^{ts}	52	92
	Control- *tubG80^{ts} NP2222*	18	89
	tubG80^{ts} NP2222 > UAS-shi^{ts}	44	85
Ensheathing	Control- *NP6520*	28	100
	NP6520 > UAS-shi^{ts}	62	84
	Control- *tubG80^{ts} MZ0709*	22	100
	tubG80^{ts} MZ0709 > UAS-shi^{ts}	54	98
Astrocyte	Control- *tubG80^{ts} alrm Gal4*	10	100
	tubG80^{ts} alrm Gal4 > UAS-shi^{ts}	53	**40**
	Control- *tubG80^{ts} Eaat1 Gal4*	19	95
	tubG80^{ts} Eaat1 Gal4 > UAS-shi^{ts}	51	**14**



D

Genotype	DD (Day5 to Day 13 at 30°C) N	RI ± SEM (R)	RI ± SEM (AR)	Tau (h) ± SEM	Mean Activity ± SEM	%R
tubG80ts repoGal4> UAS-Dicer2	10	0.47 ± 0.01	N/A	23.39 ± 0.06	29.16 ± 2.15	80
UAS-CaP60A RNAi	30	0.51 ± 0.02	N/A	23.71 ± 0.07	23.88 ± 1.20	94
tubG80ts repoGal4> UAS-Dicer2/UAS-CaP60A RNAi	68	0.39 ± 0.02	0.27 ± 0.02 **	23.71 ± 0.05	17.23 ± 0.58 ***	**43**

** p <0.01, *** p<0.001 compared with the control strains and the rhythmic sibling

Ng et al., 2011

frontiers in Cellular Neuroscience

ORIGINAL RESEARCH
published: 03 July 2015
doi: 10.3389/fncel.2015.00256

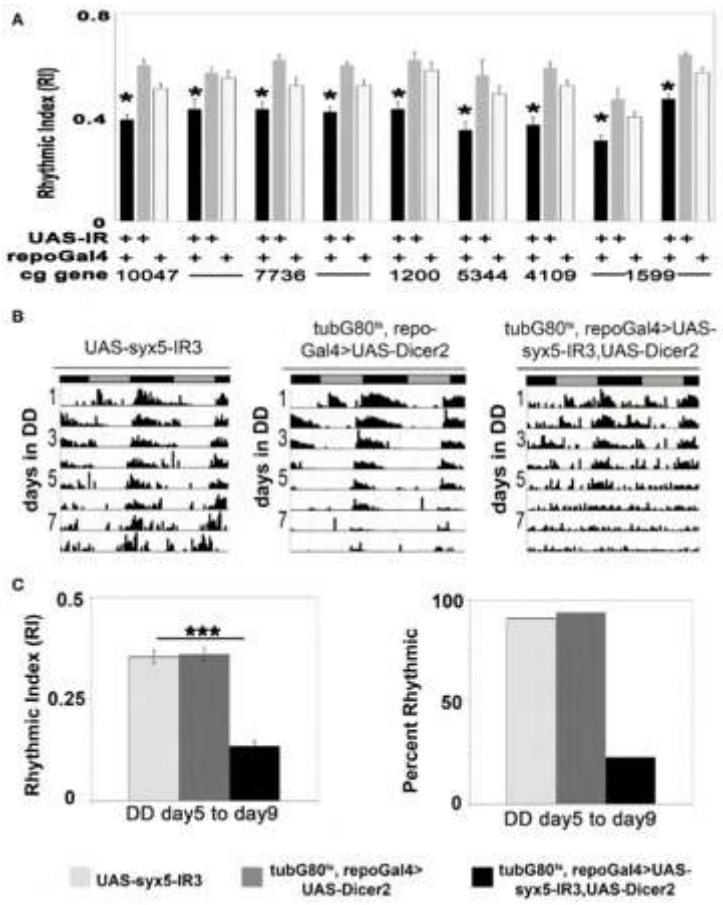
The ROP vesicle release factor is required in adult Drosophila glia for normal circadian behavior

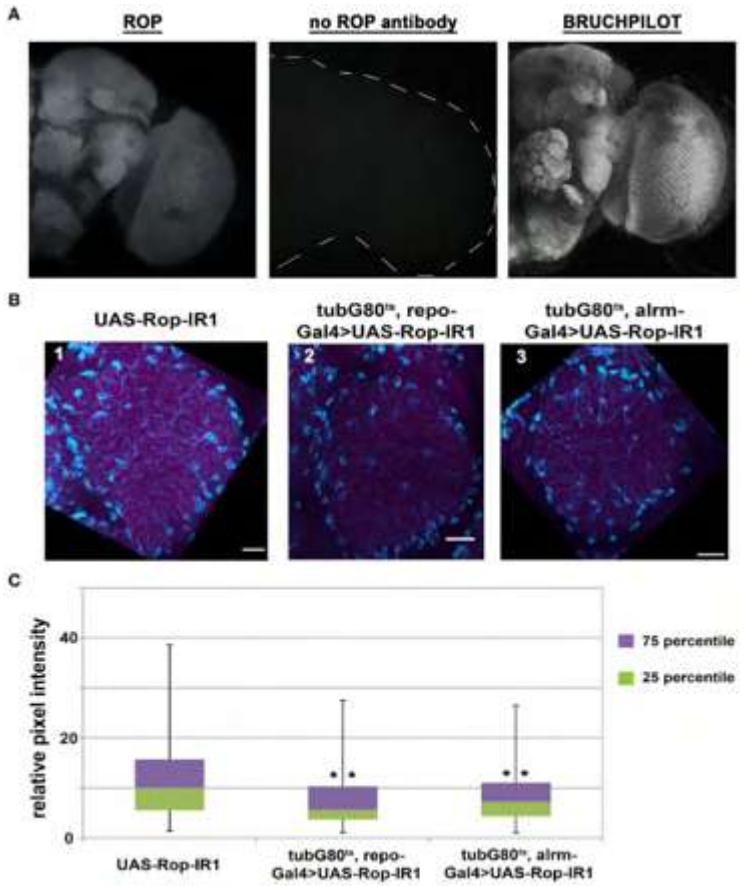
Fanny S. Ng and F. Rob Jackson *

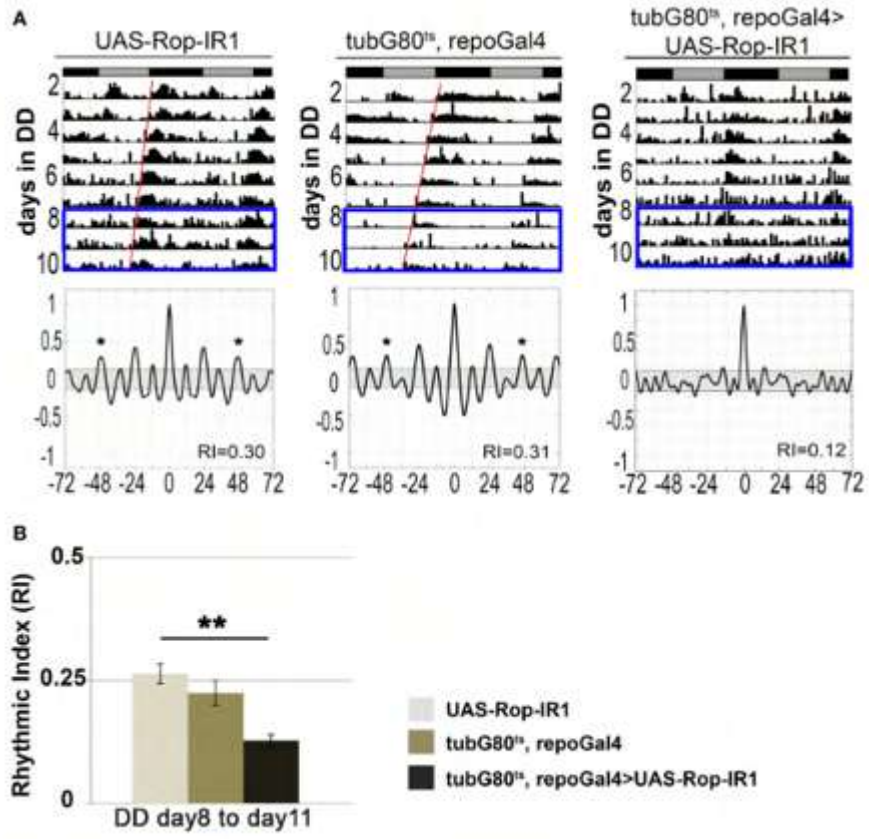
Department of Neuroscience, Sackler School of Biomedical Sciences, Tufts University School of Medicine, Boston, MA, USA

Vesicle transport genes in glial cells that affect rhythm

tub-G80ts, repoGal4>UAS-IR





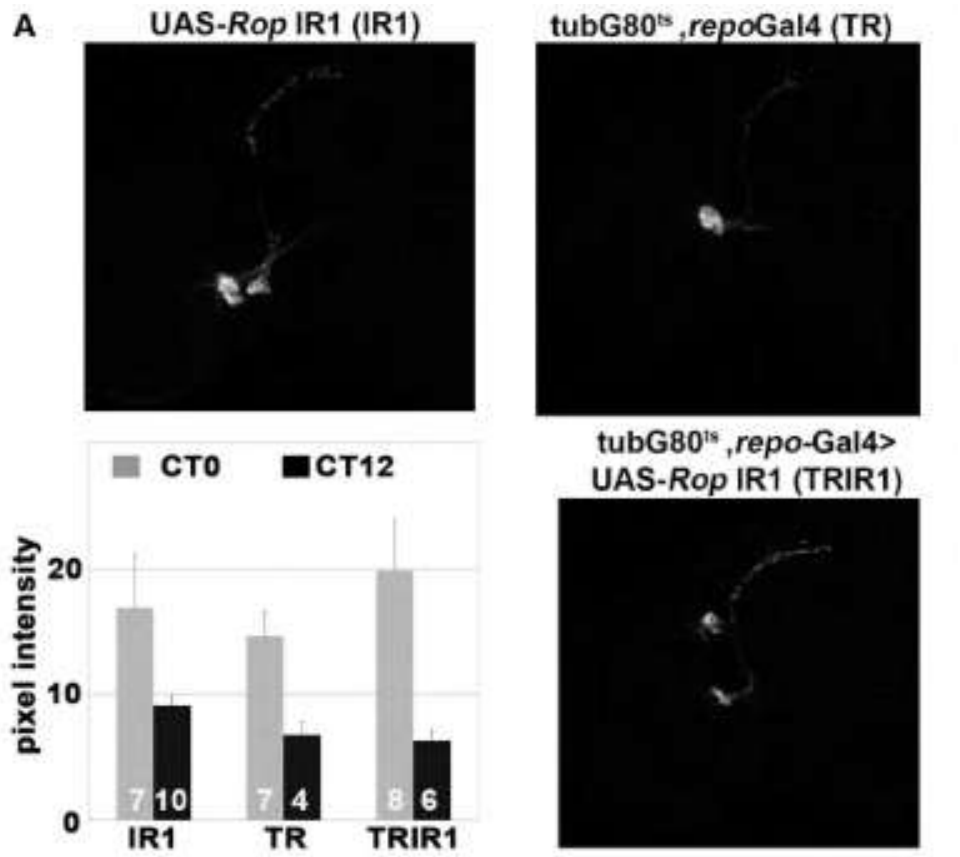


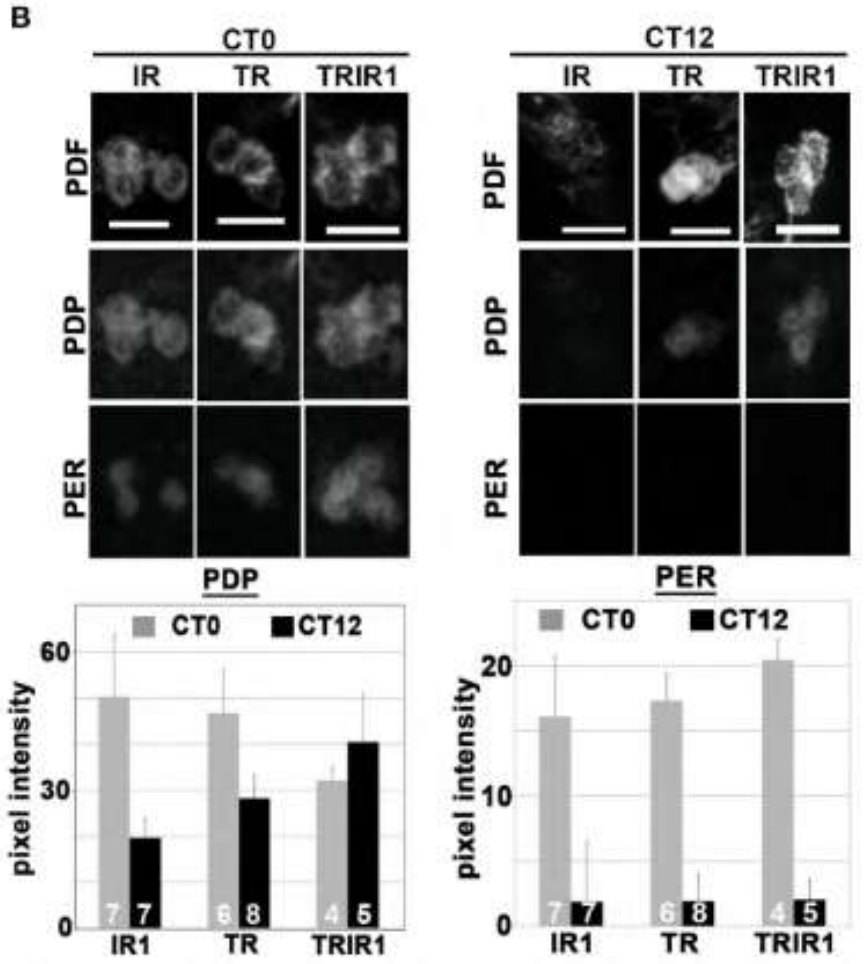
syt4 syx6 aplil1 wkd syx8 vamp7

Ng et al., 2015

Glia regulates rhythm may through PDF-independent pathway

PDF





Ng et al., 2015

frontiers in Molecular Neuroscience

ORIGINAL RESEARCH
published: 22 December 2016
doi: 10.3389/fnmol.2016.00146

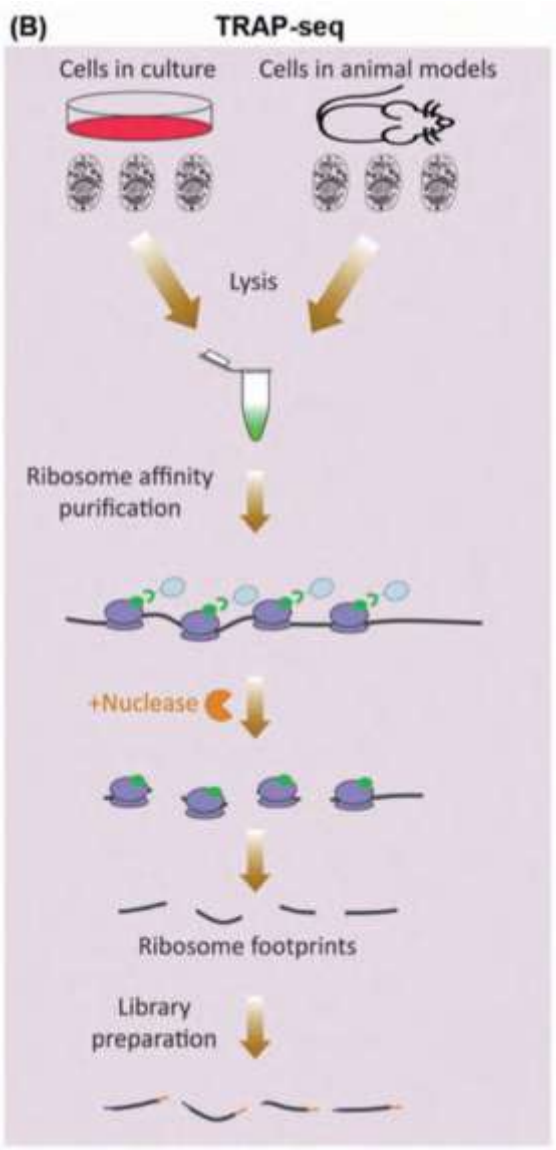
Check for updates

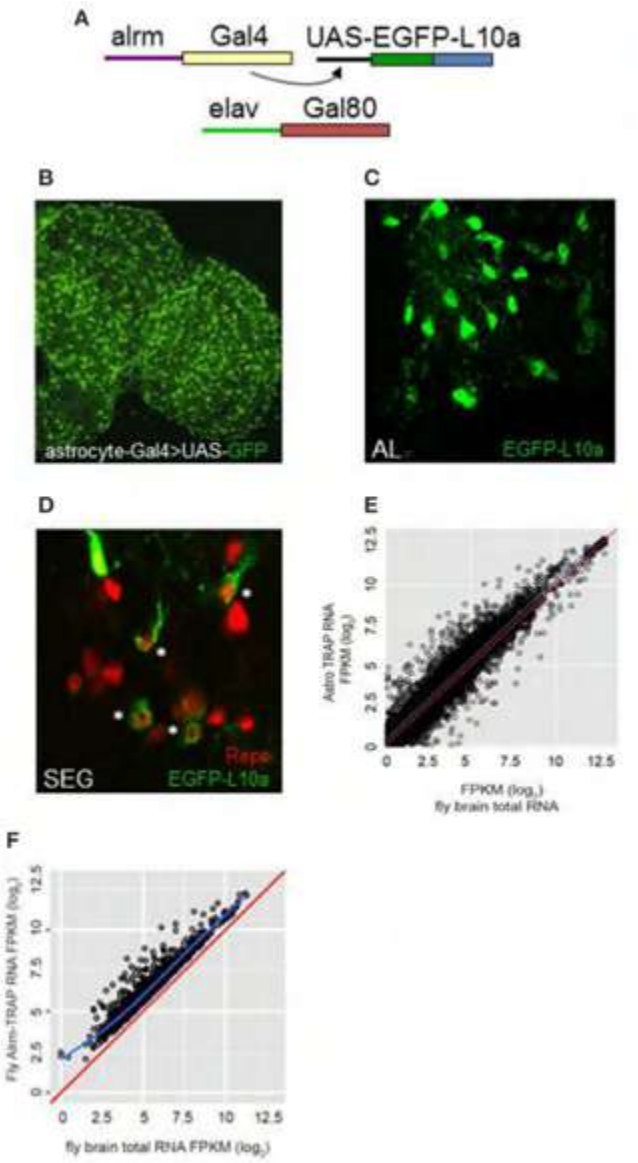
TRAP-seq Profiling and RNAi-Based Genetic Screens Identify Conserved Glial Genes Required for Adult Drosophila Behavior

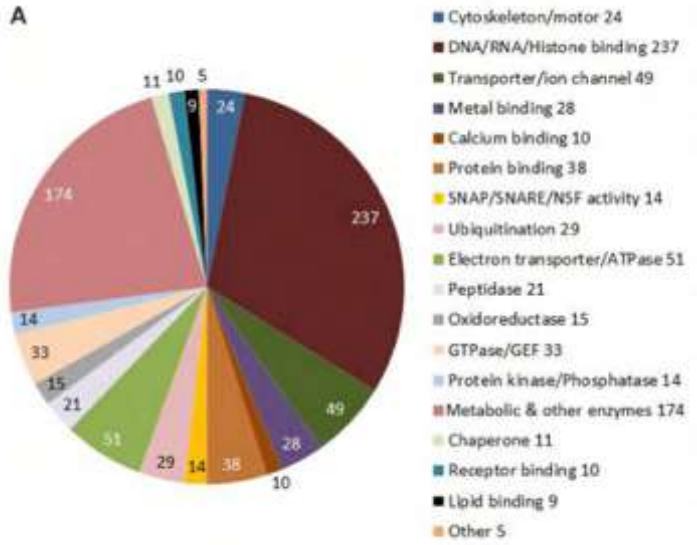
*Fanny S. Ng †, Sukanya Sengupta †, Yanmei Huang, Amy M. Yu, Samantha You, Mary A. Roberts, Lakshmanan K. Iyer, Yongjie Yang and F. Rob Jackson **

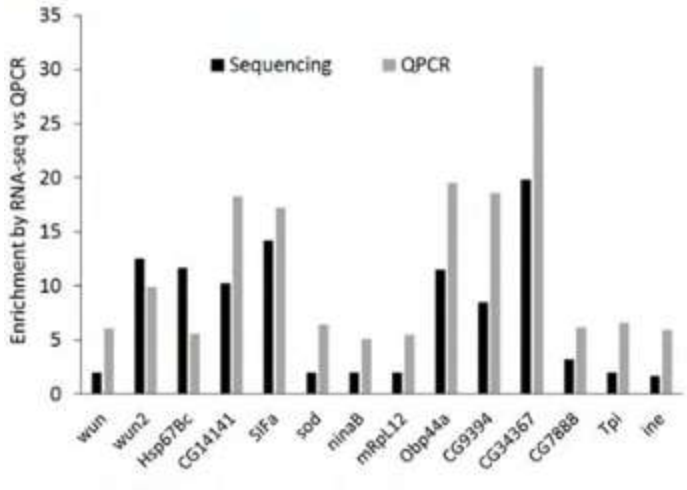
Department of Neuroscience, Sackler Program in Biomedical Sciences, Tufts University School of Medicine, Boston, MA, USA

TRAP-seq profiling identify glial genes required for adult *Drosophila* behavior







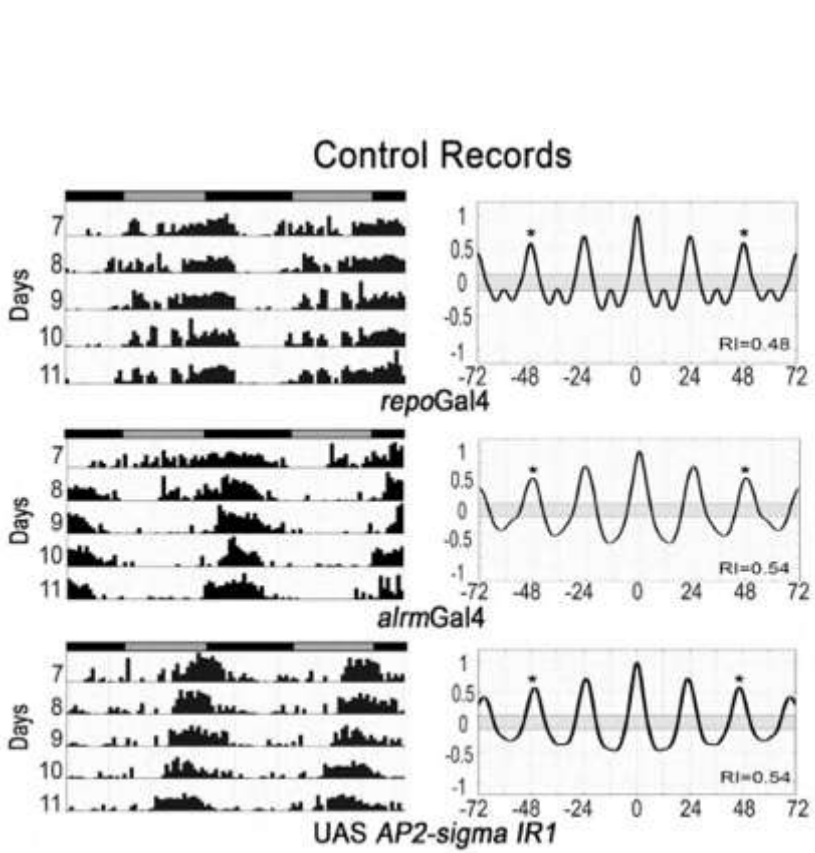


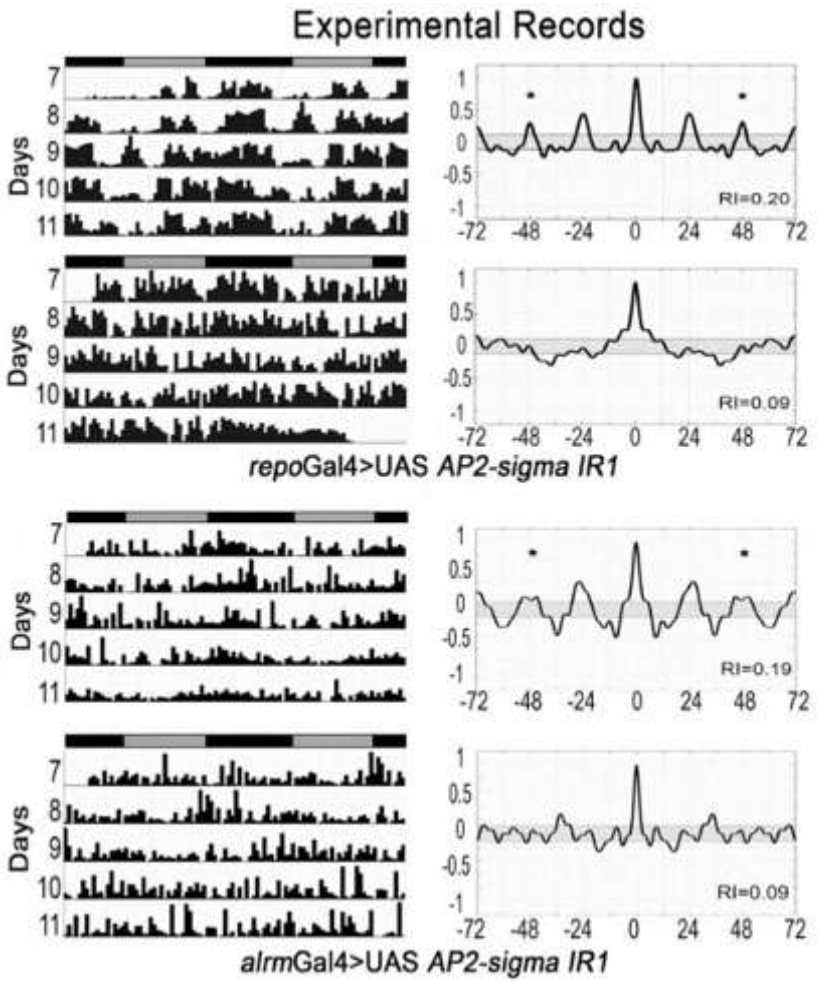
Ng et al., 2016

- **Factors Relevant for Secretion**: AP-2σ; Spase25, Tsp, CG1552, CG14141, and CG1537
- **Potential Metabolic Support Proteins**: Treh, Npc2g, CG9657
- **Glial Transporters**: CG9657 and nrv2, Ncc69

Factors Relevant for Secretion

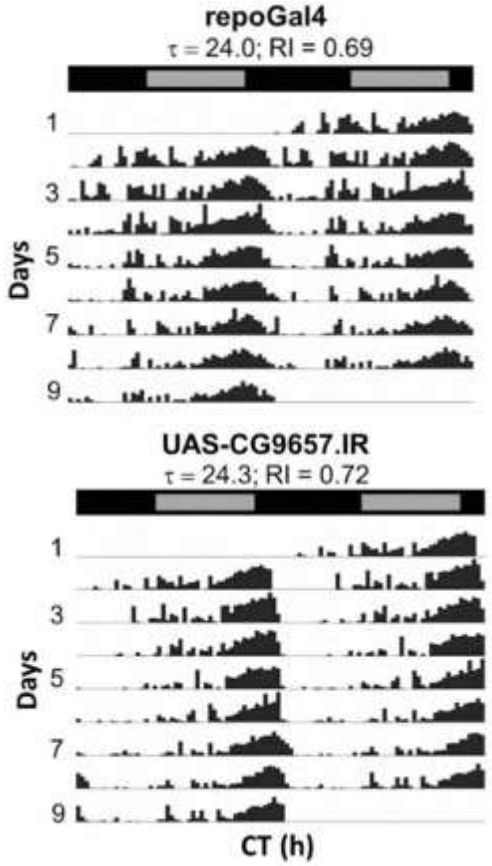
AP2-σ



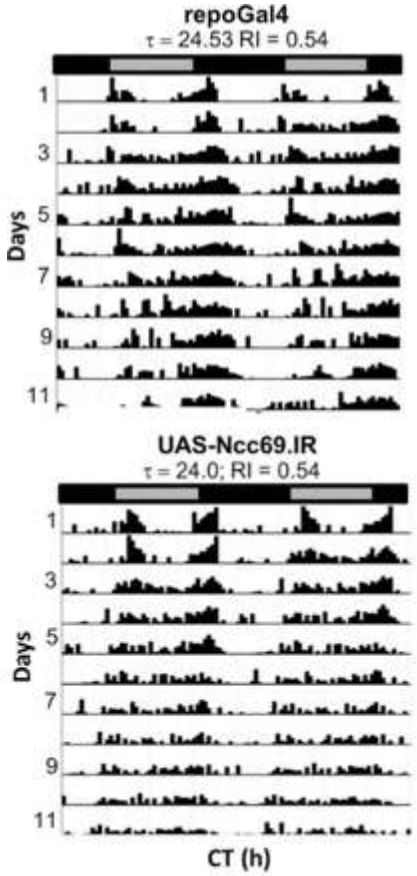


Ng et al., 2016

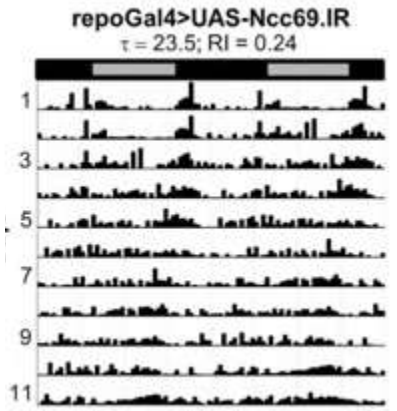
Potential metabolic support proteins and glial transporters



CG9657



Ncc69



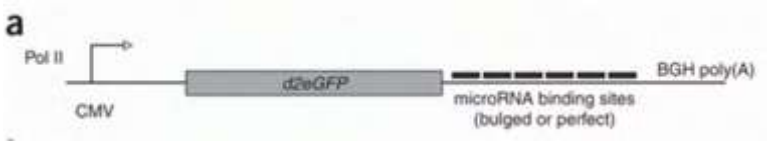
Ng et al., 2016

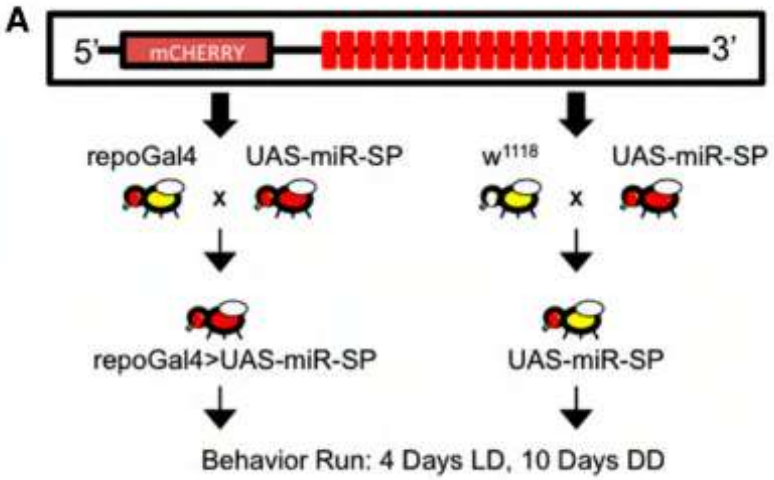
HIGHLIGHTED ARTICLE
GENETICS | INVESTIGATION

Regulation of Circadian Behavior by Astroglial MicroRNAs in *Drosophila*

Samantha You,* Tudor A. Fulga,†,1 David Van Vactor,† and F. Rob Jackson*,2
*Department of Neuroscience, Sackler Program in Biomedical Sciences, Tufts University School of Medicine, Boston, Massachusetts 02111 and †Department of Cell Biology, Harvard Medical School, Boston, Massachusetts 02115
ORCID ID: 0000-0002-3679-1495 (F.R.J.)

miRNA affecting rhythm in glia

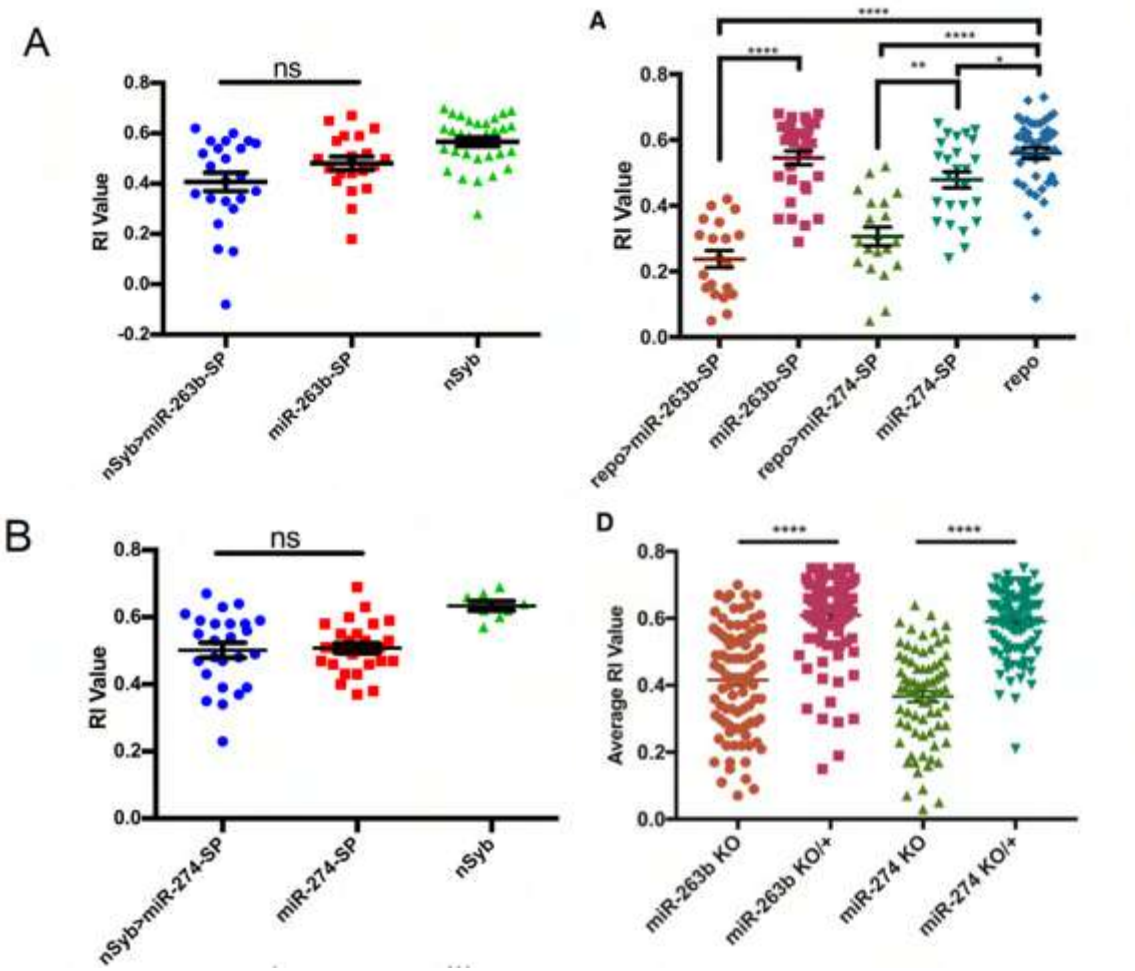




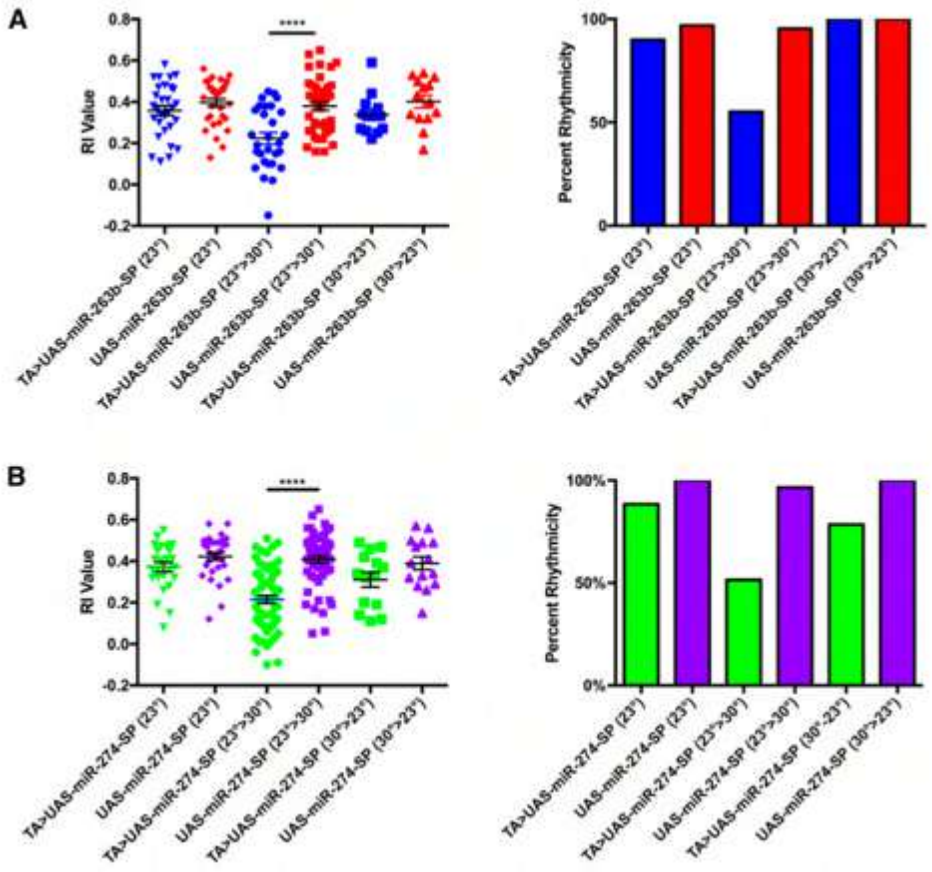
	Experimental			Control			
Genotype	RI ± SEM	*n*	Percent rhythmic	RI ± SEM	*n*	Percent rhythmic	*P* value
miR-79-SP	0.25 ± 0.03	18	50.00	0.47 ± 0.04	20	80.00	<0.0001
miR-79-SP (2)	0.25 ± 0.02	16	50.00	0.44 ± 0.03	26	84.62	0.0002
miR-210-SP	0.28 ± 0.02	25	44.00	0.51 ± 0.02	32	90.63	<0.0001
miR-263b-SP	0.24 ± 0.03	20	60.00	0.55 ± 0.02	31	96.77	<0.0001
miR-274-SP	0.31 ± 0.03	20	65.00	0.48 ± 0.02	25	96.00	<0.0001
miR-281-1-SP	0.30 ± 0.03	23	60.87	0.53 ± 0.03	30	96.67	<0.0001
miR-285-SP	0.32 ± 0.02	21	52.38	0.49 ± 0.03	27	92.59	<0.0001
miR-304-SP	0.28 ± 0.02	31	51.61	0.50 ± 0.02	30	96.67	<0.0001
miR-305-SP	0.27 ± 0.02	44	54.41	0.51 ± 0.02	44	90.00	<0.0001
miR-309-SP	0.28 ± 0.02	35	57.14	0.51 ± 0.02	44	97.73	<0.0001
miR-310-SP	0.26 ± 0.03	34	57.14	0.50 ± 0.02	39	94.74	<0.0001
miR-317-SP	0.29 ± 0.03	22	57.14	0.51 ± 0.02	37	100.00	<0.0001
miR-927-SP	0.27 ± 0.03	28	53.57	0.51 ± 0.02	36	97.22	<0.0001
miR-963-SP	0.28 ± 0.03	26	53.85	0.49 ± 0.02	30	96.67	<0.0001
miR-967-SP	0.25 ± 0.03	25	56.00	0.45 ± 0.02	45	93.33	<0.0001
miR-971-SP	0.28 ± 0.04	23	60.87	0.51 ± 0.02	31	100.00	<0.0001
miR-981-SP	0.32 ± 0.02	41	67.39	0.50 ± 0.02	41	95.65	<0.0001
miR-990-SP	0.28 ± 0.04	13	60.00	0.47 ± 0.02	29	92.50	<0.0001
miR-992-SP	0.34 ± 0.02	67	67.16	0.52 ± 0.01	75	96.00	<0.0001
miR-994-SP	0.24 ± 0.02	28	32.14	0.45 ± 0.02	30	100.00	<0.0001
miR-iab-4-3p-SP	0.31 ± 0.03	26	65.38	0.45 ± 0.02	30	96.67	0.0002
miR-33-SP	0.39 ± 0.04	14	92.86	0.40 ± 0.03	13	92.31	NS
miR-315-SP	0.49 ± 0.03	14	100.00	0.52 ± 0.02	16	100.00	NS
Scramble-SP	0.49 ± 0.02	45	97.78	0.54 ± 0.02	32	100.00	0.0009
repoGal4[a]				0.52 ± 0.03	14	100.00	NA

Samantha You et al., 2018

miR-263b and miR-274 are necessary and sufficient for the rhythm in glia

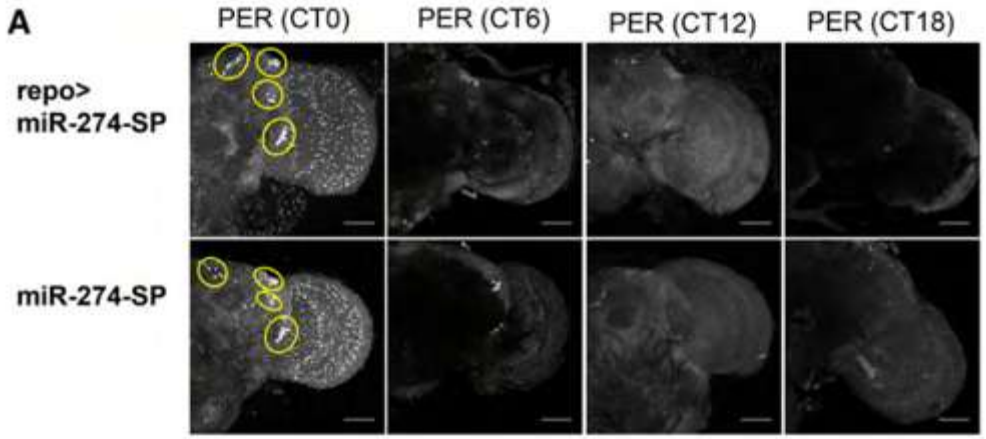


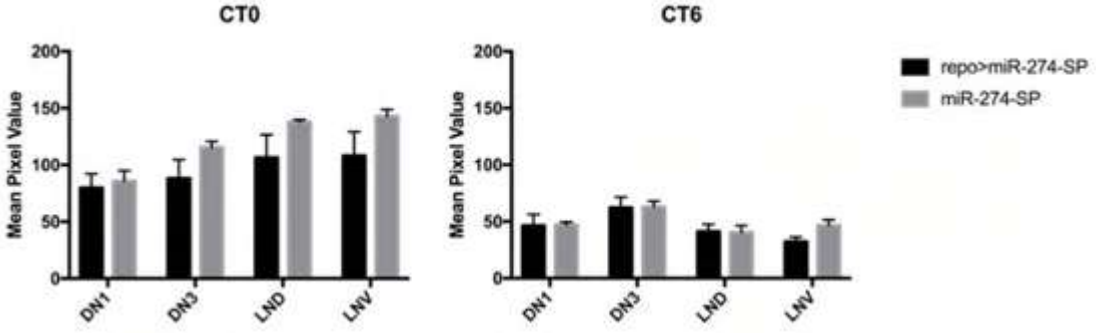
tubGal80^{ts},alrm-Gal4>2× UAS-miR-SP

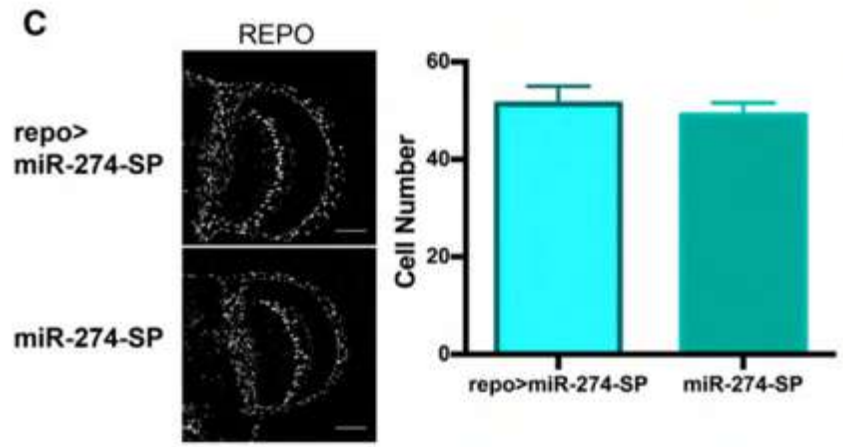


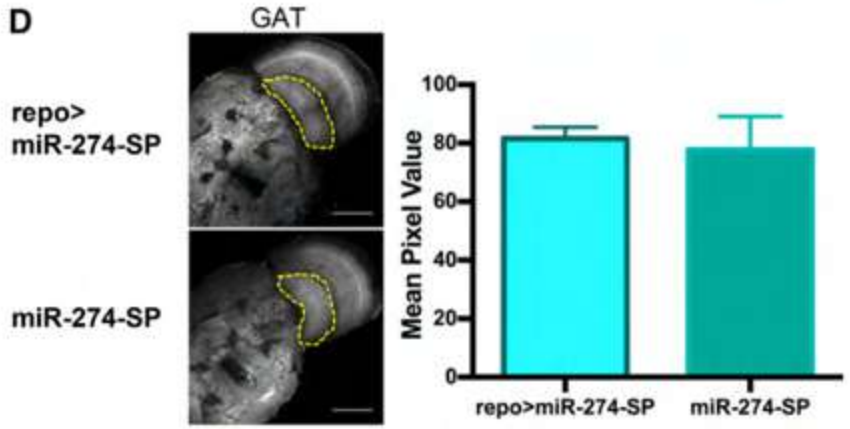
Samantha You et al., 2018

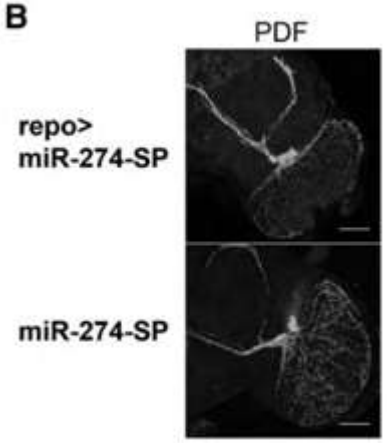
miR-274 does not affect the size of glial cells





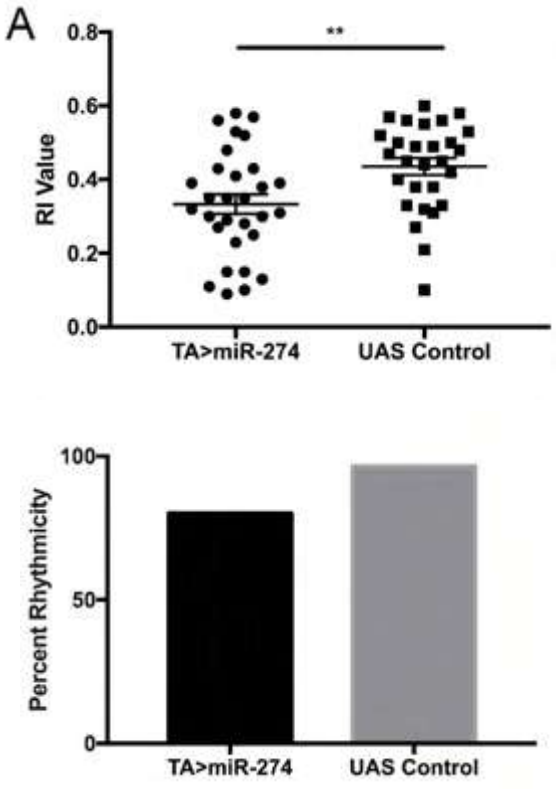


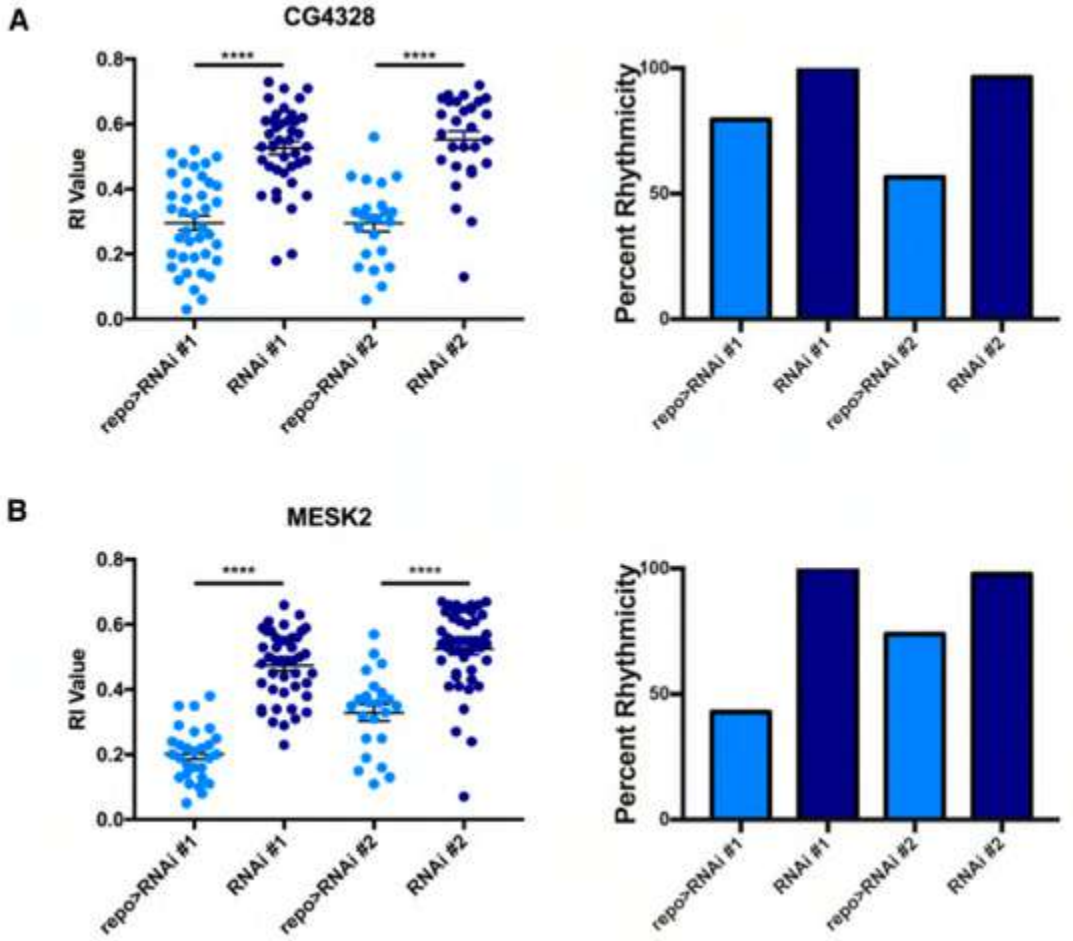


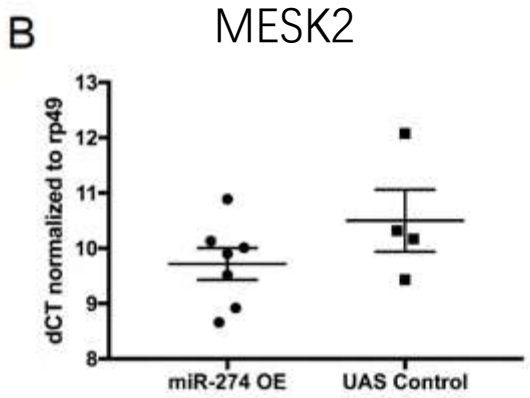


Samantha You et al., 2018

Potential target genes of miR-274







Samantha You et al., 2018

Summary

- Glial rhythm is regulated by clock neurons.
- Glial cells may transport and recover synaptic neurotransmitters through vesicle transport.
- Glial regulatory rhythm may not depend on PDF.
- Some diseases may cause abnormal behavior by affecting the function of glial cells.

Glial cells regulate other behaviors

(chemotaxis, startle responses)

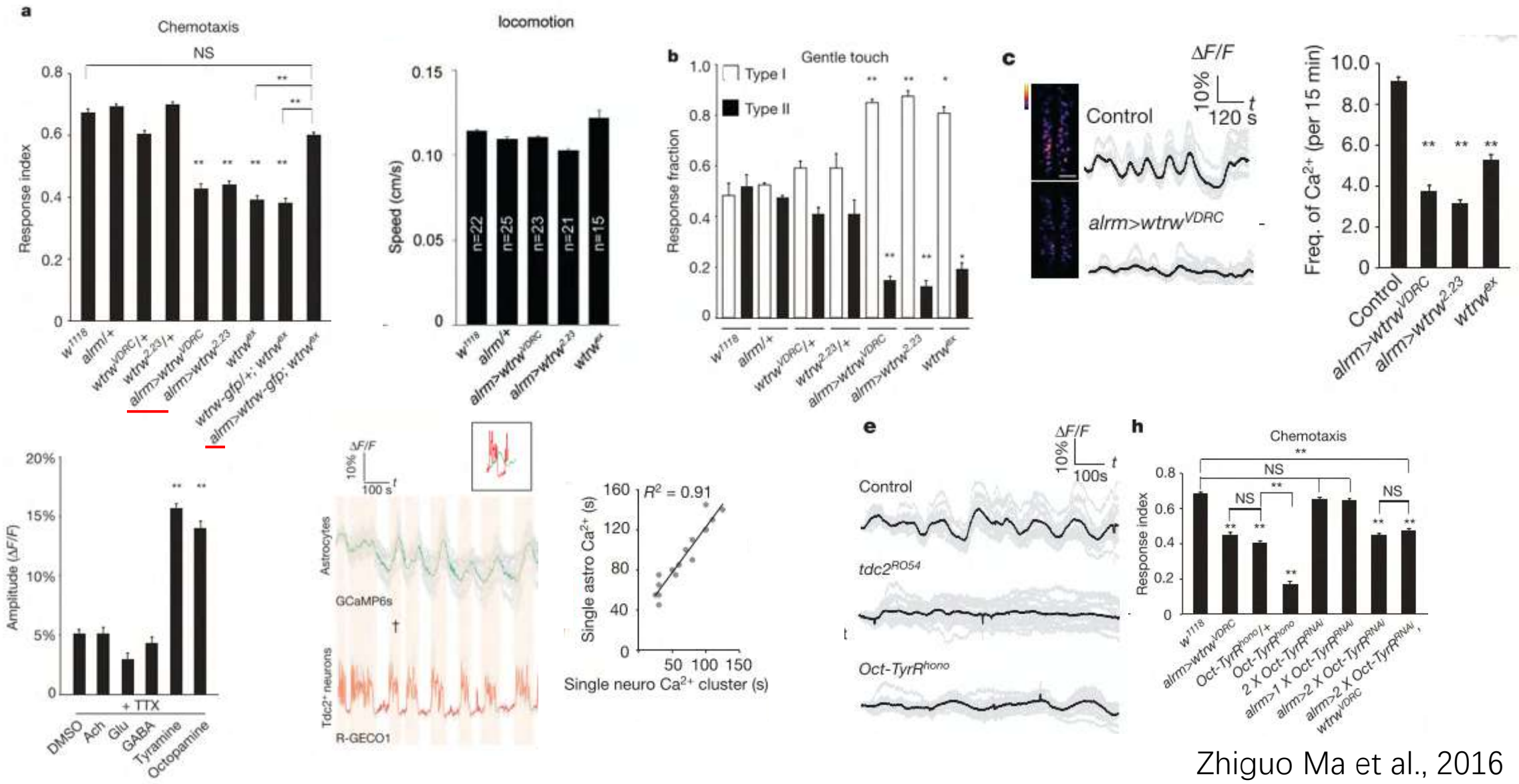
LETTER

doi:10.1038/nature20145

Neuromodulators signal through astrocytes to alter neural circuit activity and behaviour

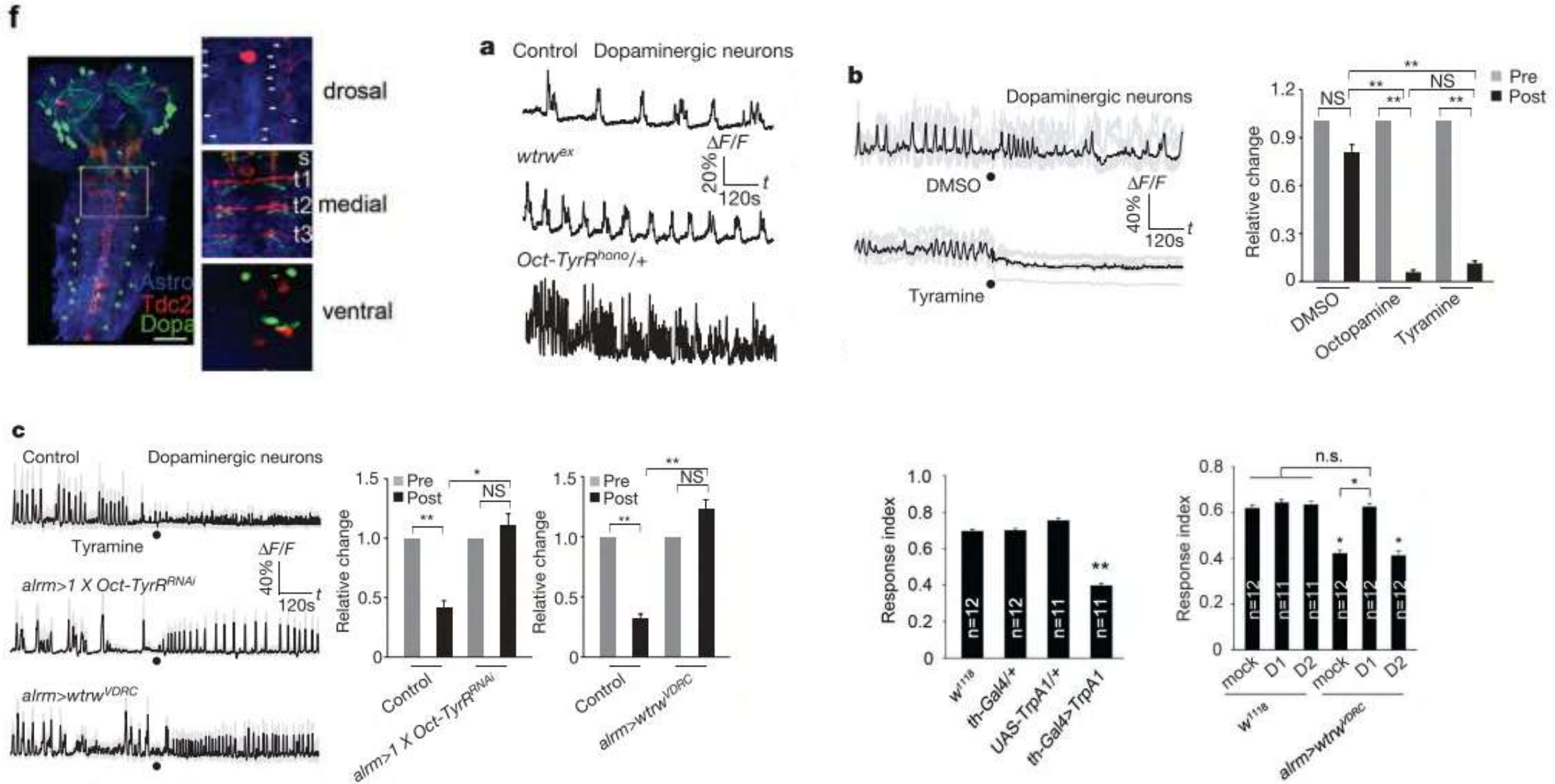
Zhiguo Ma[1], Tobias Stork[1], Dwight E. Bergles[2] & Marc R. Freeman[1]†

Tdc2+ neuron activation causes calcium-wave in astrocytes



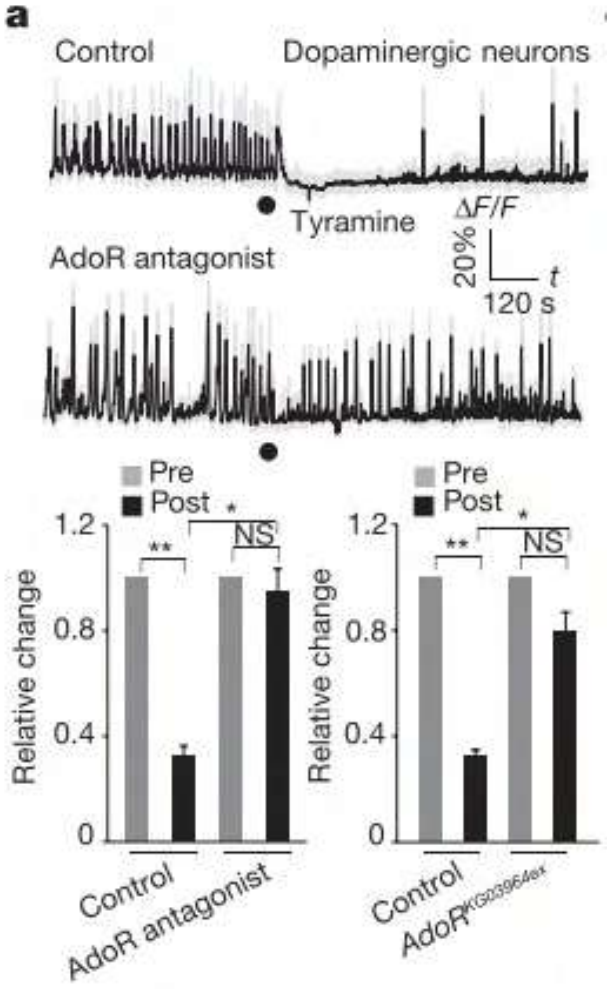
Zhiguo Ma et al., 2016

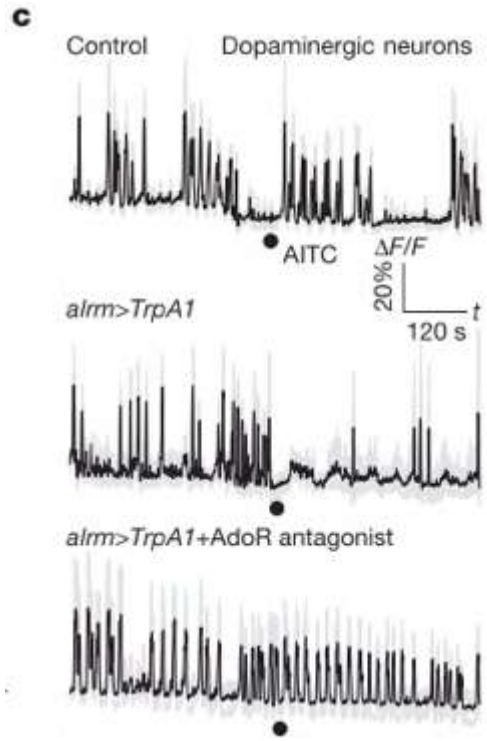
Tyr/Oct signals through astrocyte to inhibit dopaminergic neuron activity

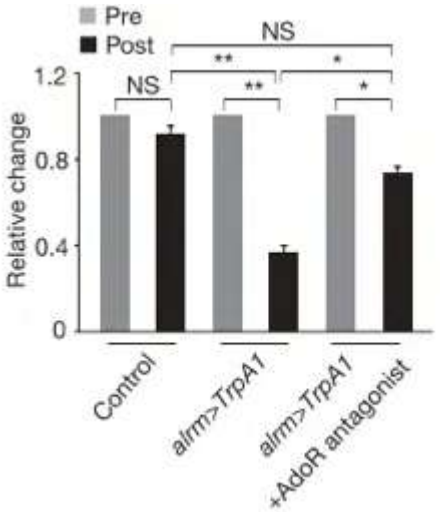


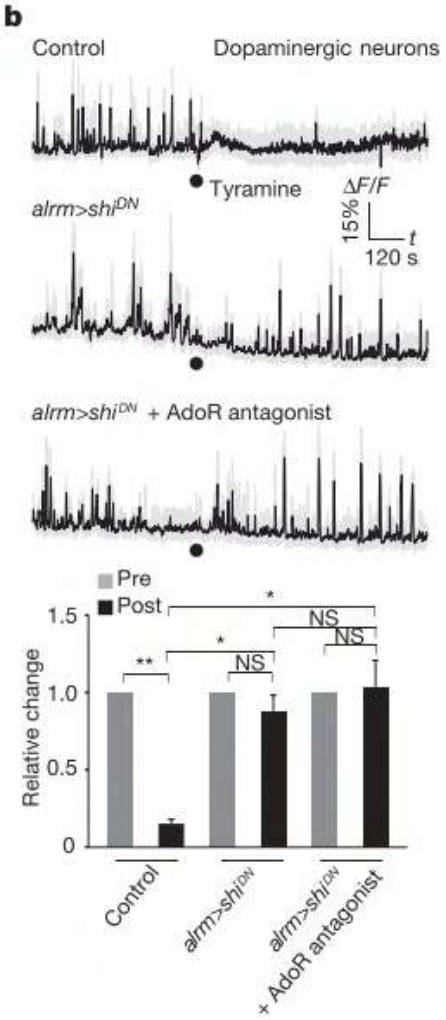
Zhiguo Ma et al., 2016

Astrocytes regulate dopaminergic neurons activation through purinergic signals



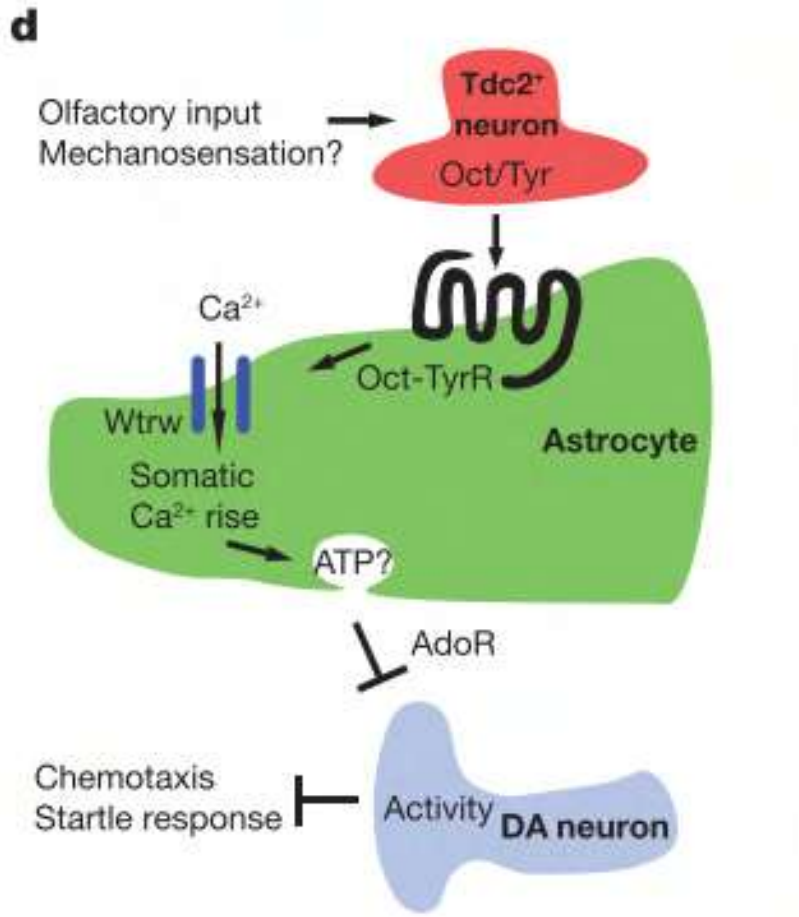






Zhiguo Ma et al., 2016

Summary



Zhiguo Ma et al., 2016

Take home message

- Glial cells are involved in tripartite synapses.
- Astrocytes may be excitable.
- Difficulties in studying the role of glia in neural circuits

Thanks