Hormone : The Only Way to Maturation in *Drosophila*

王　林

朱　寰

李小龙

2021/4/29

What is the definition of maturation?

1. Physical growth has stopped and fully developed.
2. Various organs reach the average adult level, especially the development of the nervous system.
3. The maturity of sexual function.

What Are Hormones?

- Classical definition

1. Hormones are chemical substances produced by specialized tissues(gland) and secreted into blood, in which they are carried to target organs

2. Slower, More long-term reposes and Blood-borne

Ecdysteroid **Juvenile Hormone** **Neuropeptide Hormone**

Assignments:

1.General Introduction for Research Progress of Hormone -王林

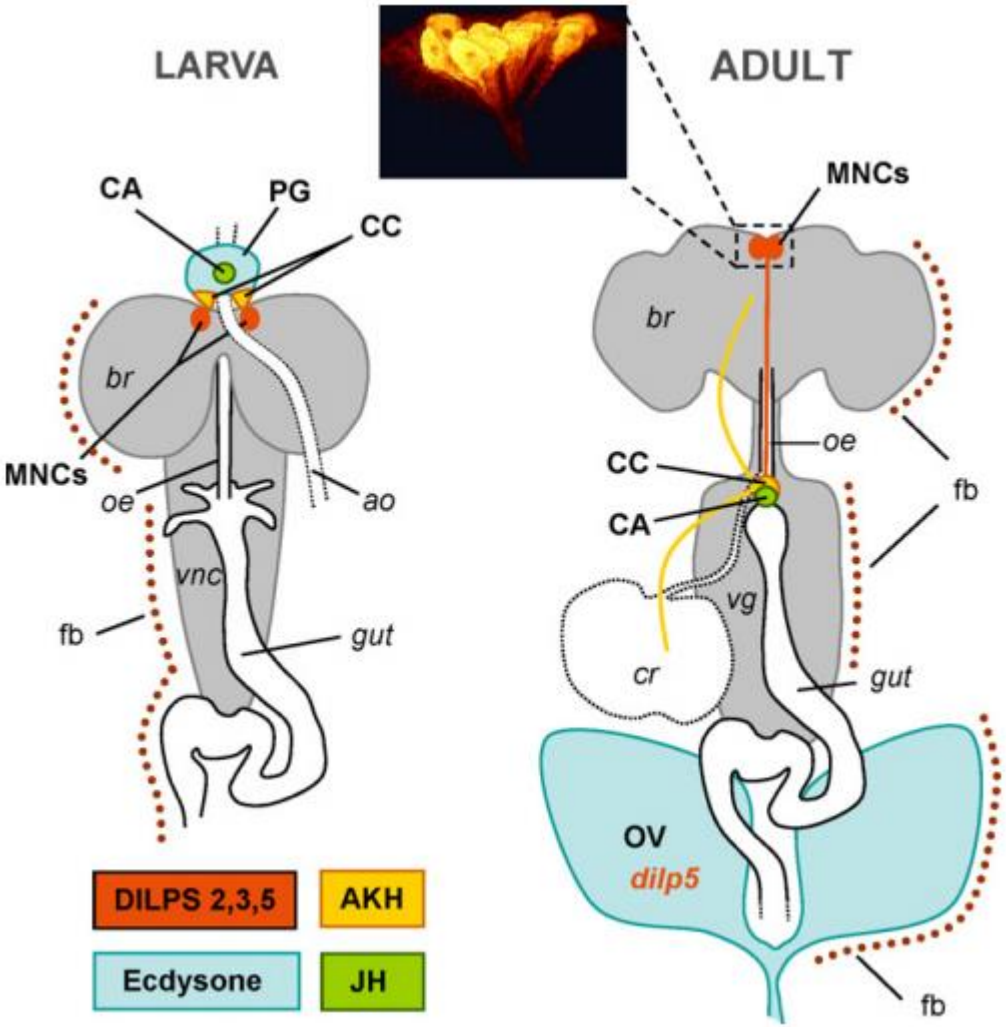
2.Functions of Hormone on Growth and Maturation in Development –李小龙

3. Juvenile and Ecdysteroid: the Reproduction Related-朱寰

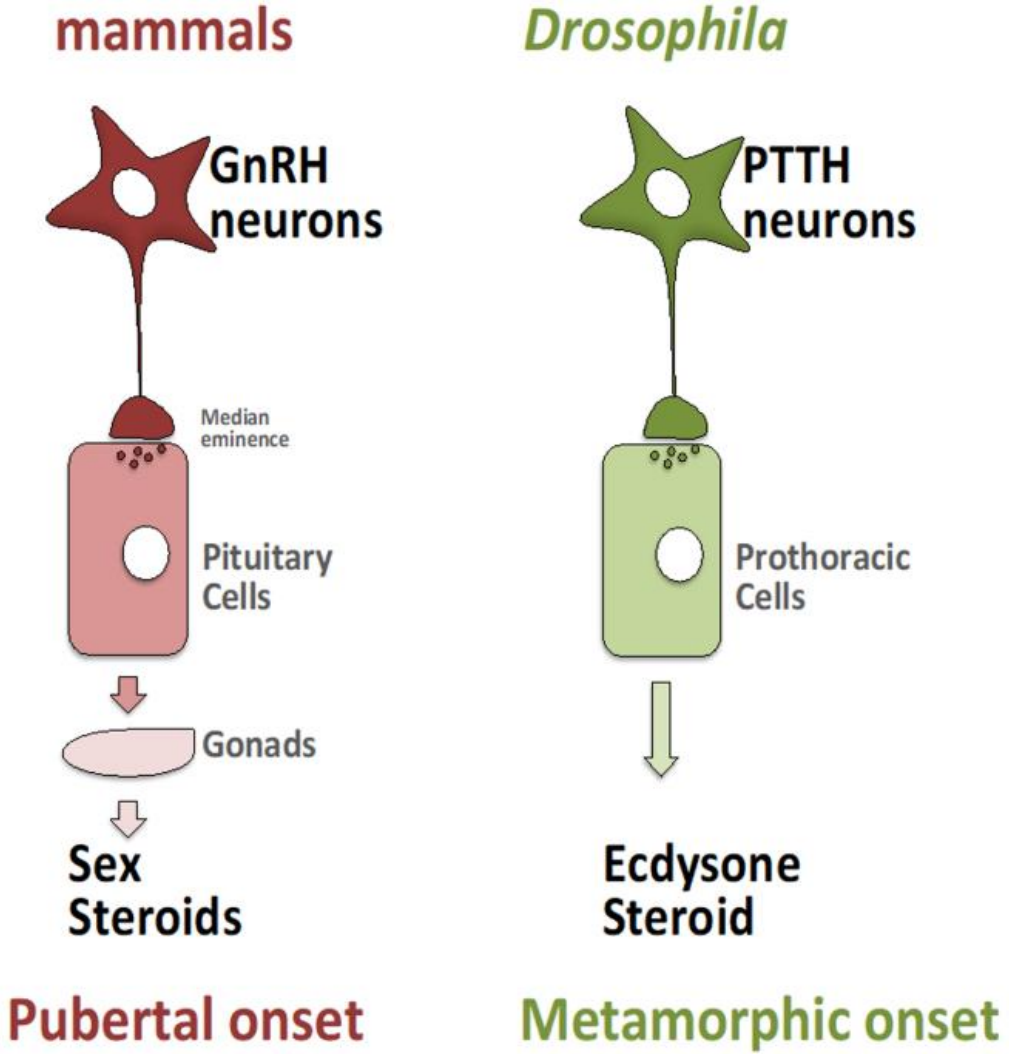
PART 1:

General Introduction for Research Progress of Hormone

Schematic representation of endocrine tissues in *Drosophila*

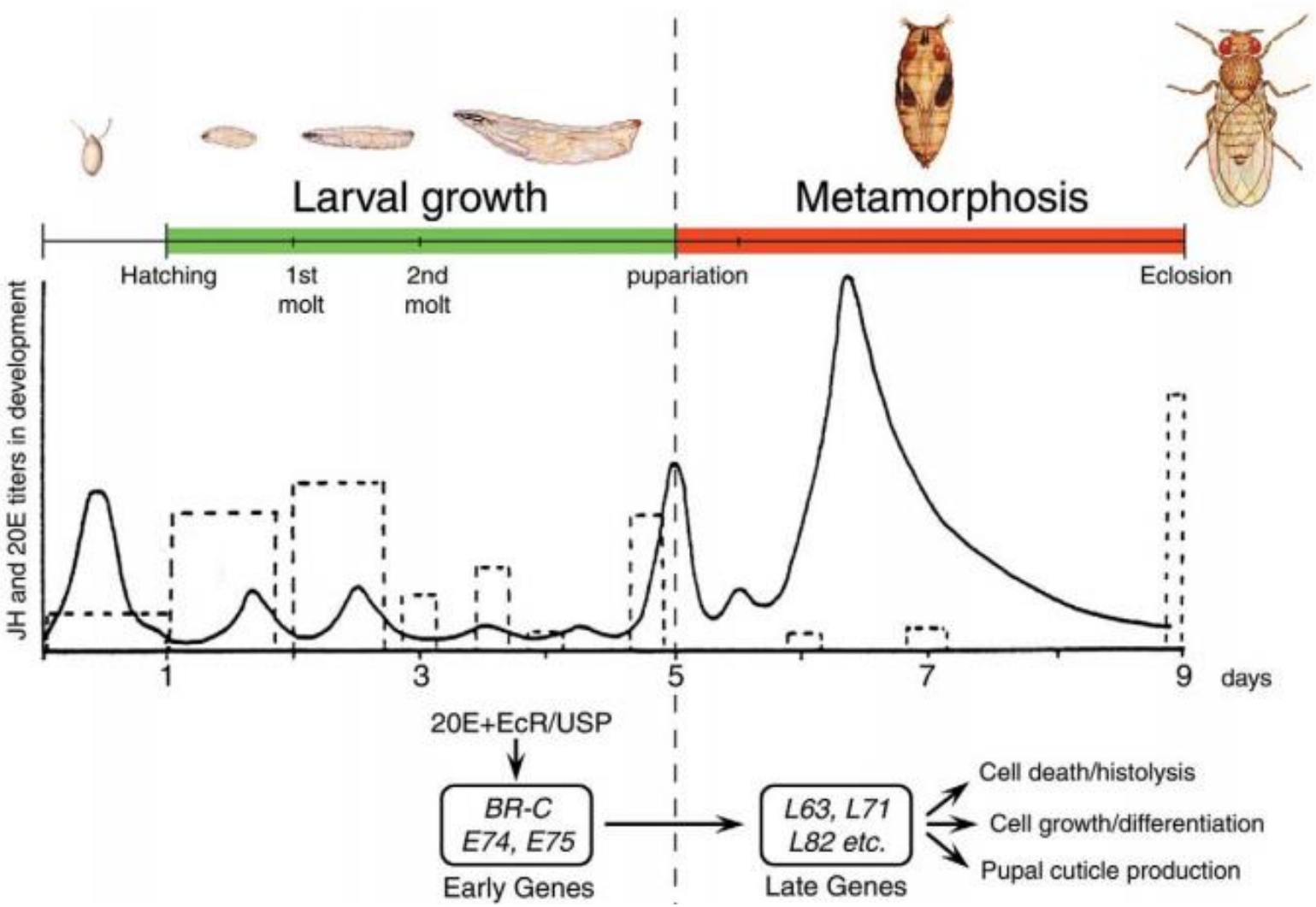


(Toivonen and Partridge, *Mol Cell Endocrinol*, 2009)

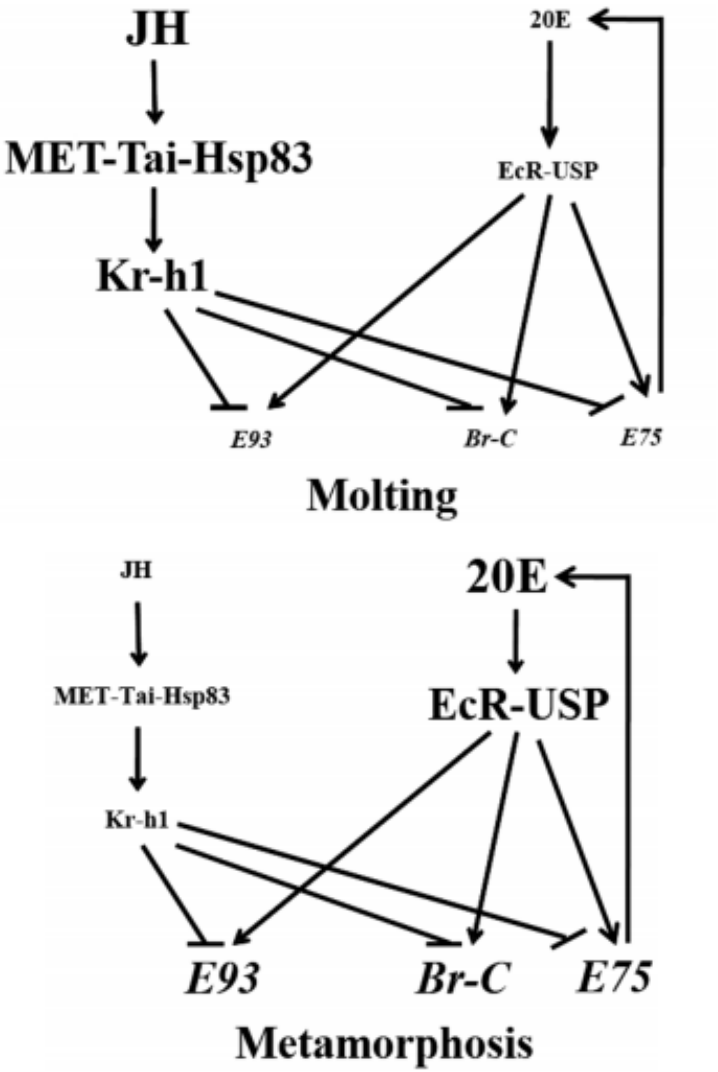


Renald Delanoue,*et al.*,*Int. J. Mol. Sci.* **2020**

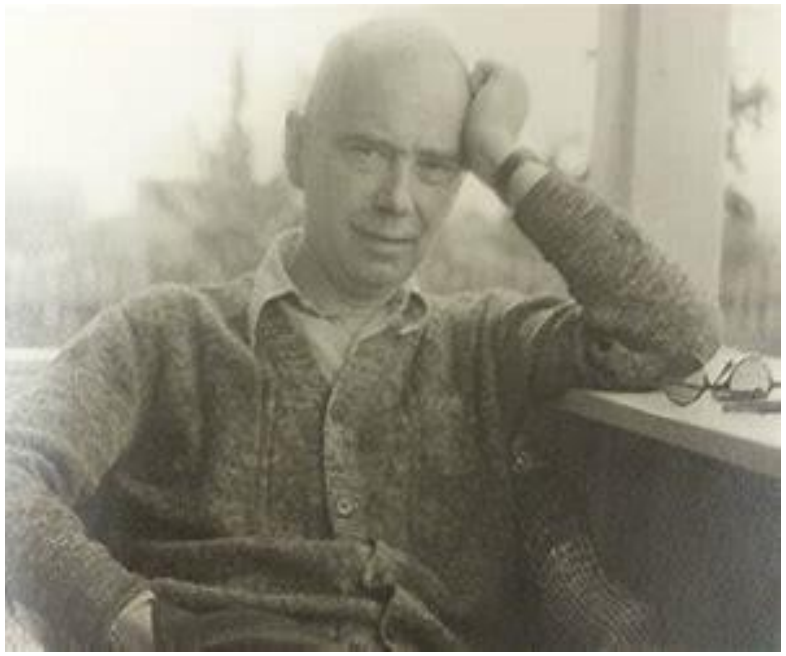
- Juvenile hormone (JH) and 20-hydroxyecdysone (20E) coordinate to regulate molting and metamorphosis



(Dubrovsky, Trends Endocrinol Metab, 2005)

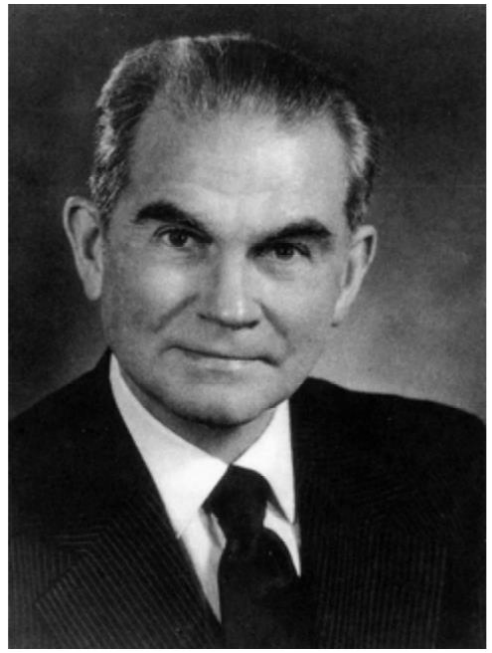


(Li et al., Insect Sci, 2019)



In 1912,Classical study of Stefan Kopec on the metamorphosis of the gypsy moth, *Lymantria dispar*

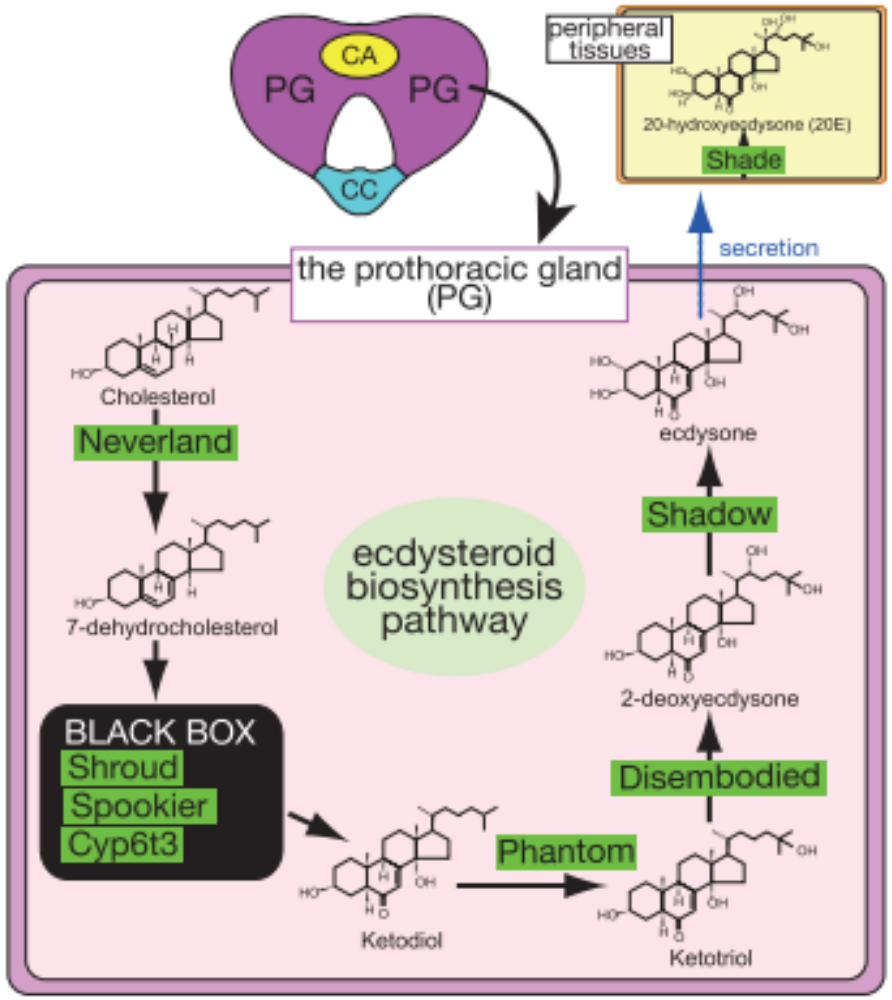
In 1936,Vincent B. Wigglesworth was the first to show that there was a hormone prevented metamorphosis.



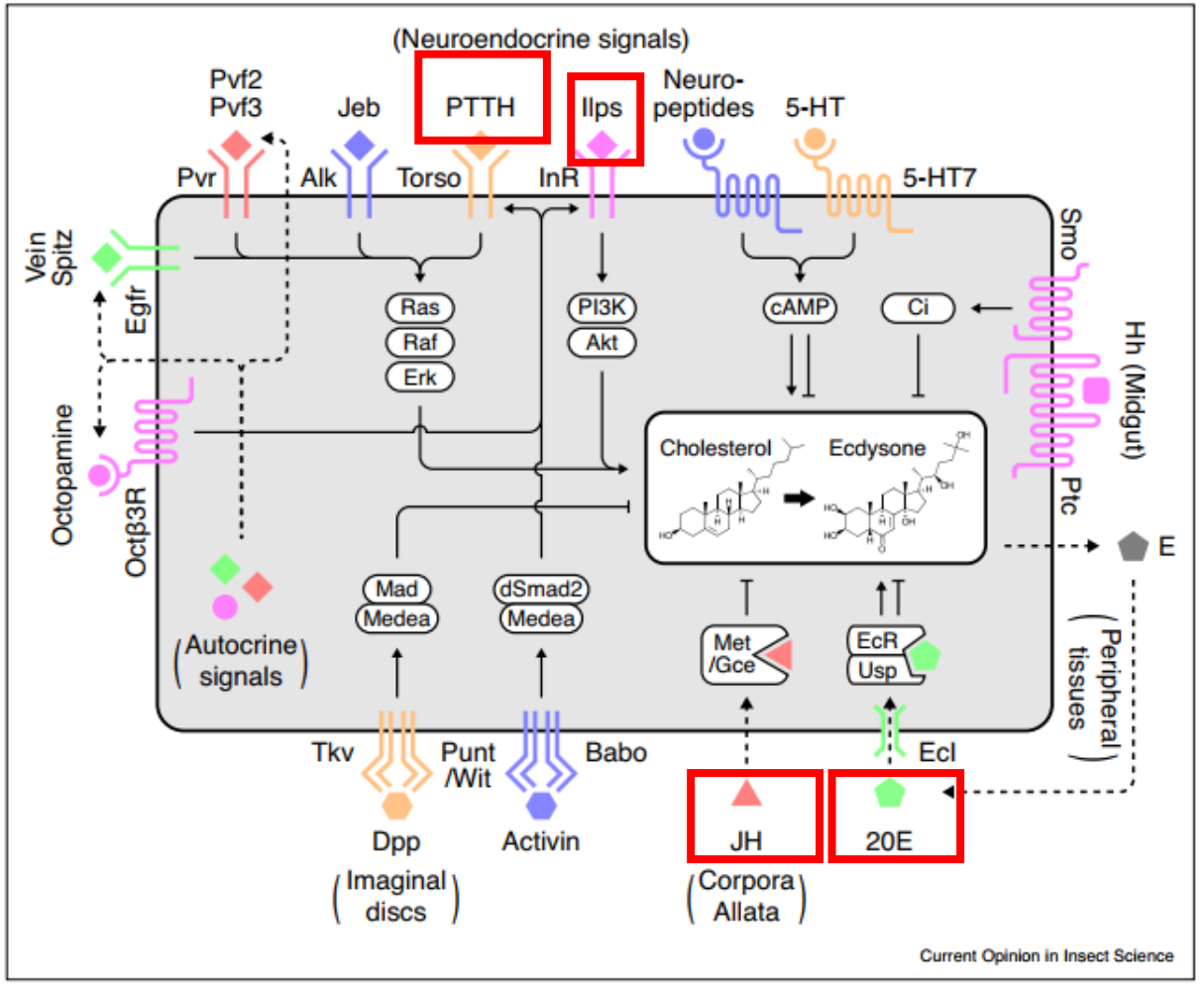
In 1947,C.M.Williams showed that a substance from the brain can activate the prothorax and produce a hormone that stimulates the larvae to molt

I.Biosynthesis pathway and Regulation of ecdysteroid

The ecdysteroid biosynthetic pathway and Extracellular signals regulating



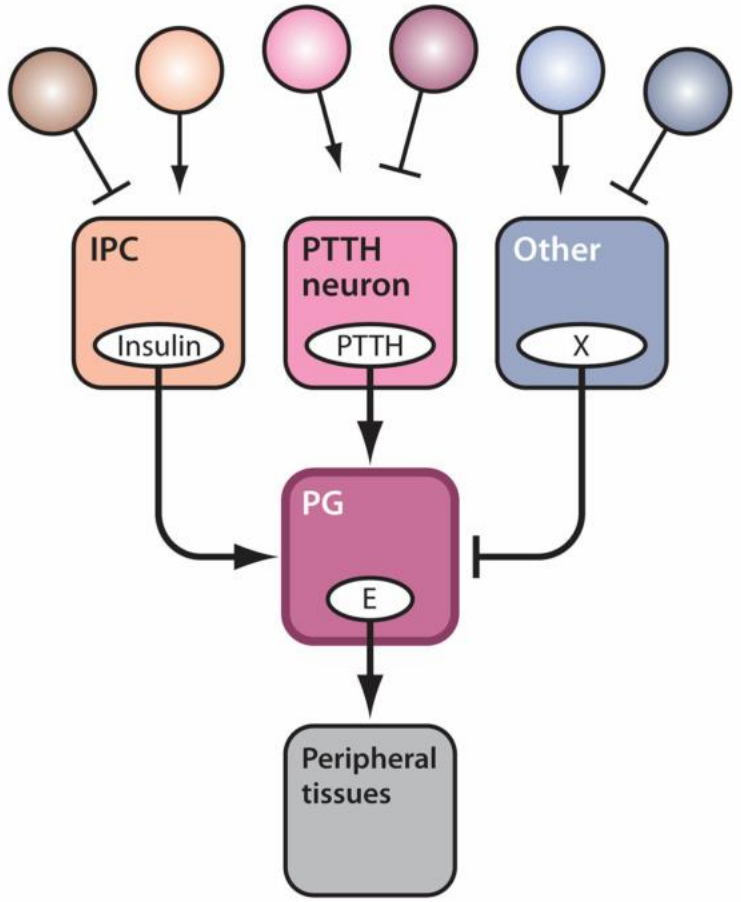
Niwa and Niwa,*Genes Genet Syst*, 2014



Elisabeth Marchal,et al.,*Current Opinion in Insect Science*,2019

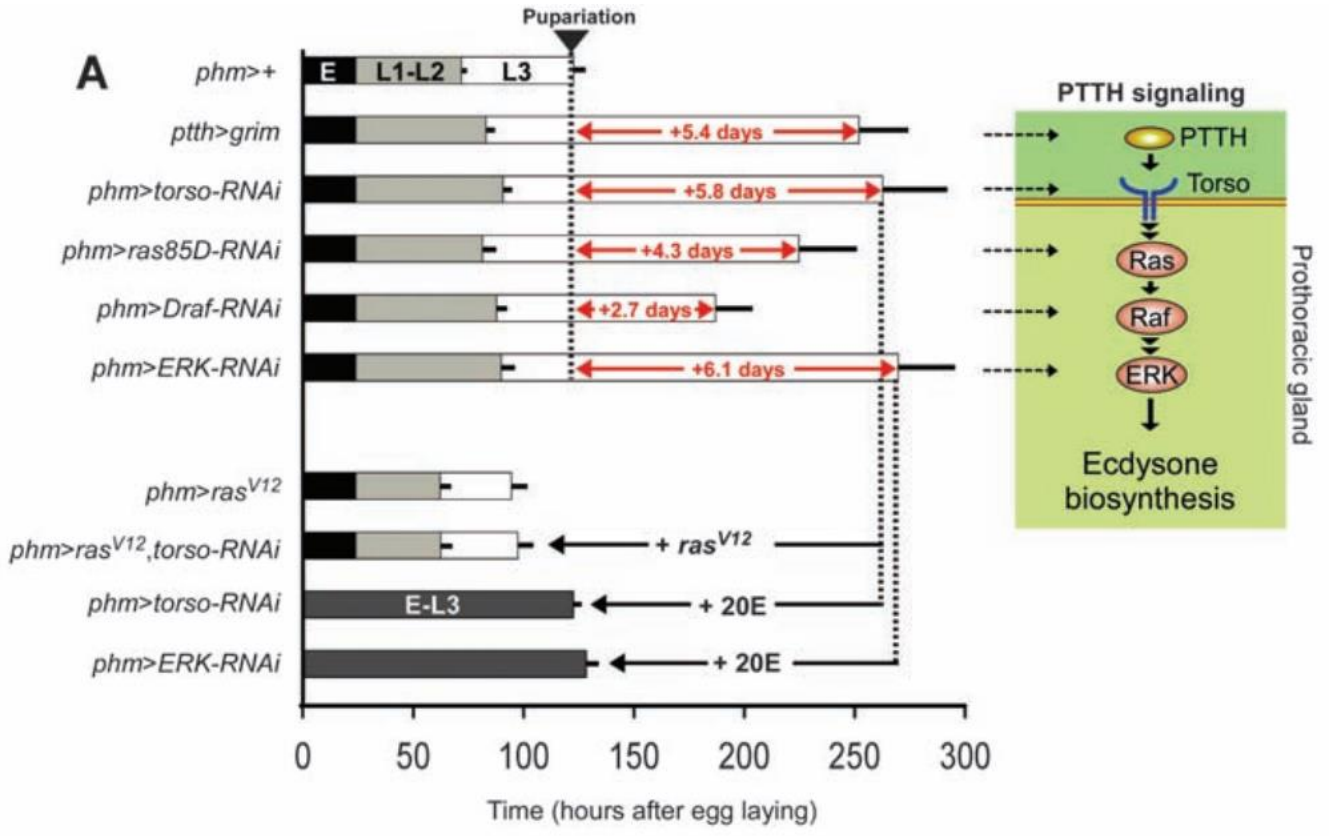
- Extracellular signals regulating ecdysteroid synthesis in the PG

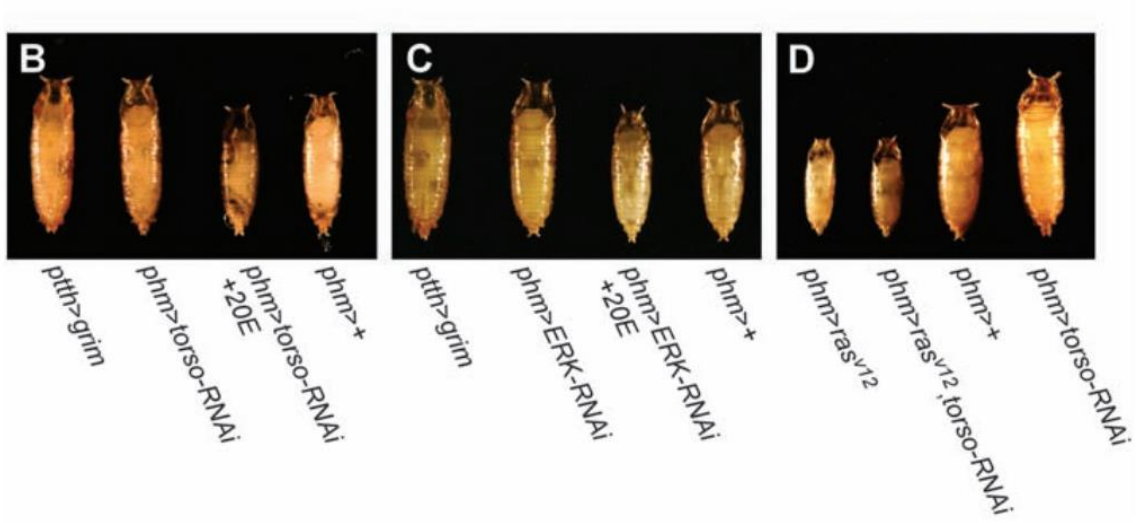
  - Prothoracicotropic hormone (PTTH)
  - Insulin/insulin-like growth factors
  - Juvenile hormone
  - Ecdysone



Naoki Yamanaka,et al.,*Annu Rev Entomol*.2013

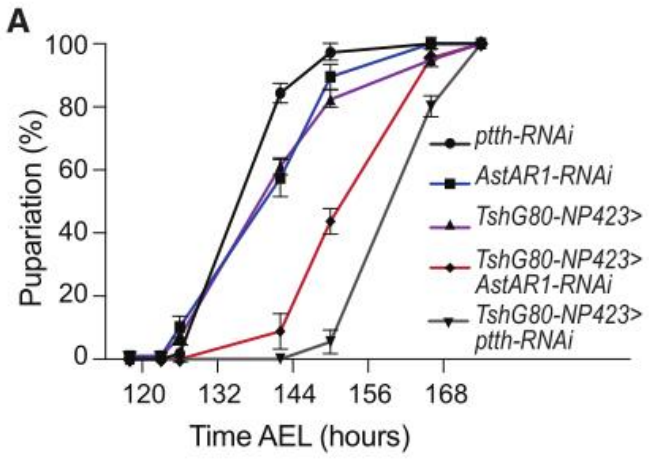
Prothoracicotropic hormone (PTTH)

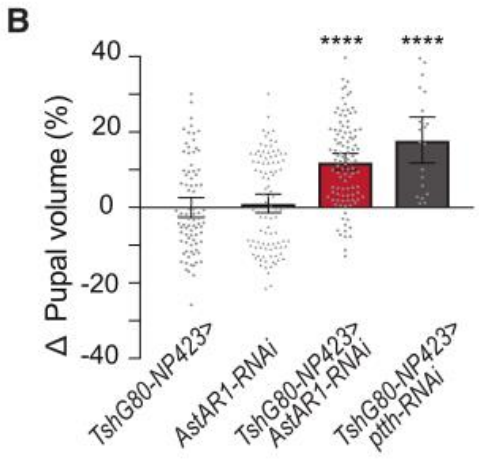


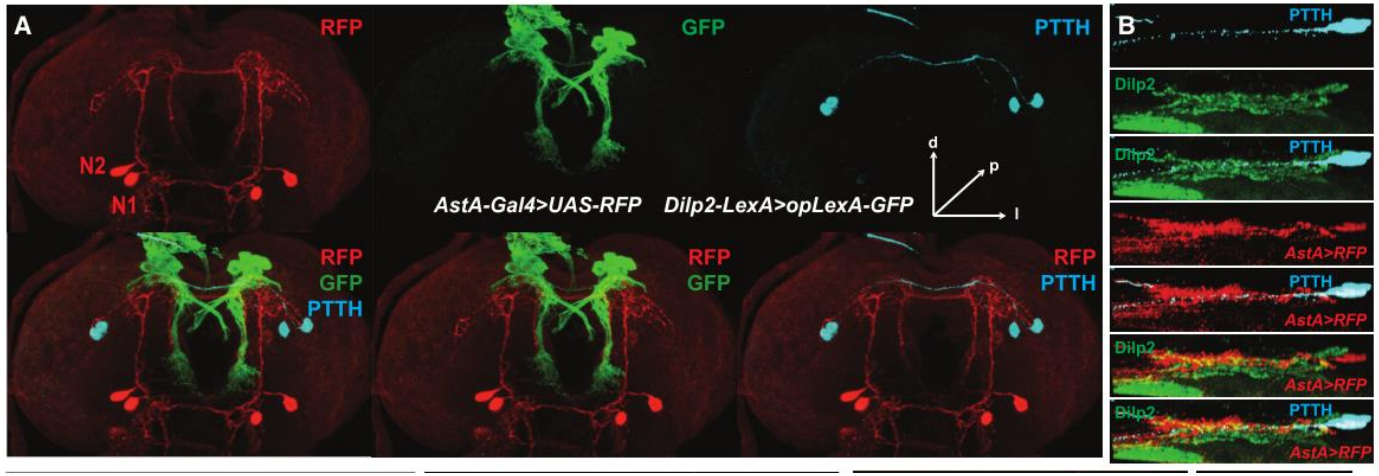


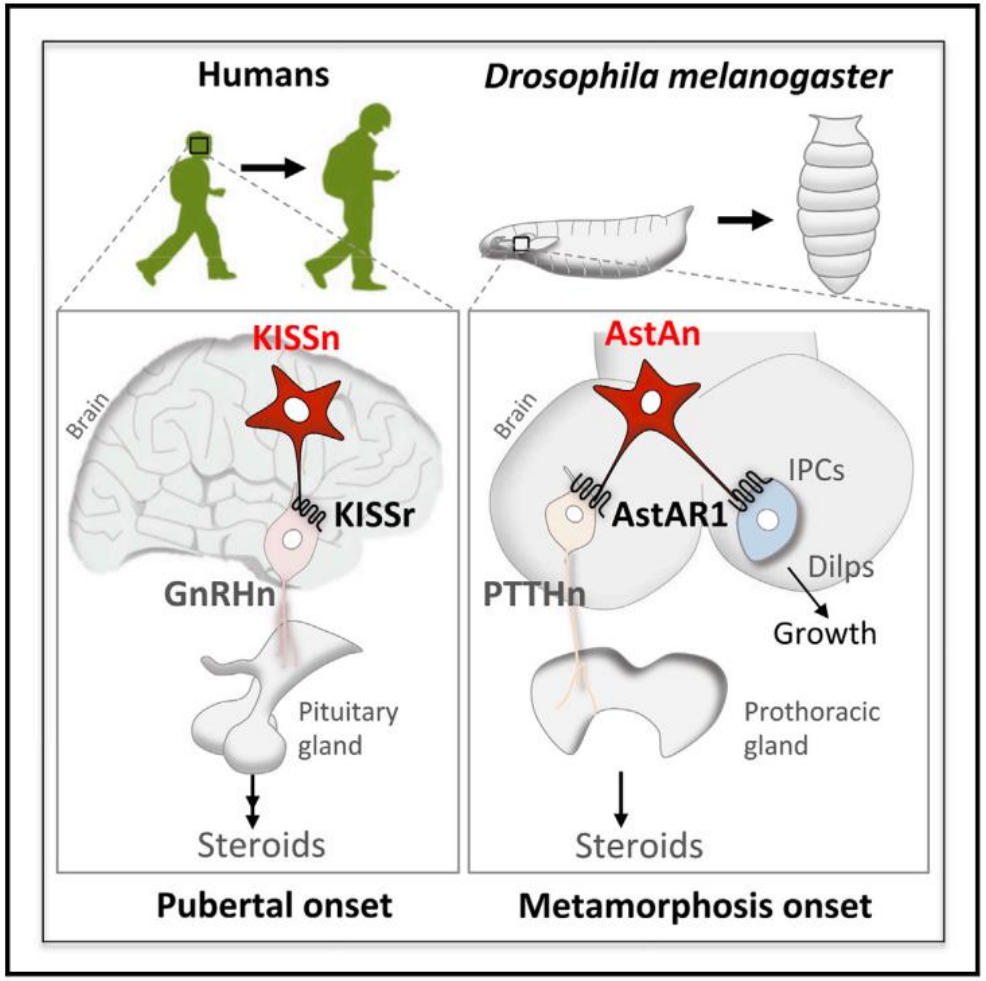
Kim F. Rewitz,.et.cl.,*Science*,2009

- AstA/AstAR1 signaling times the onset of maturation by promoting PTTH secretion



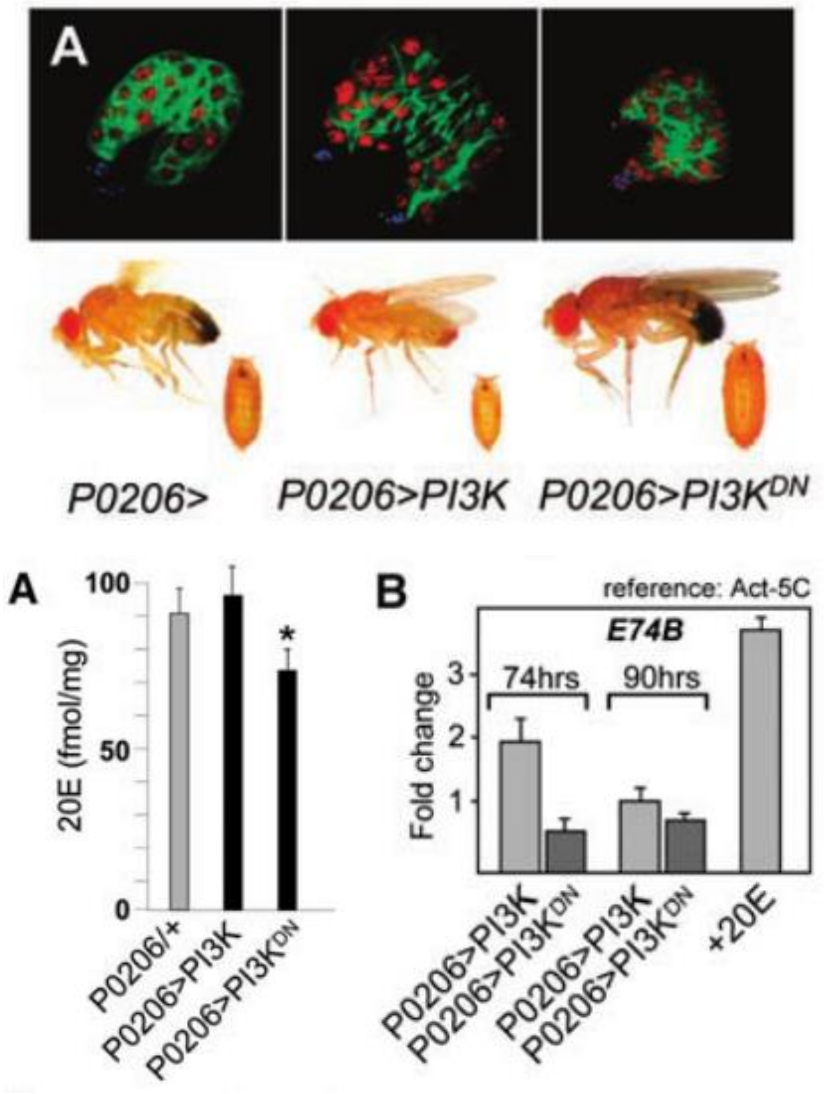




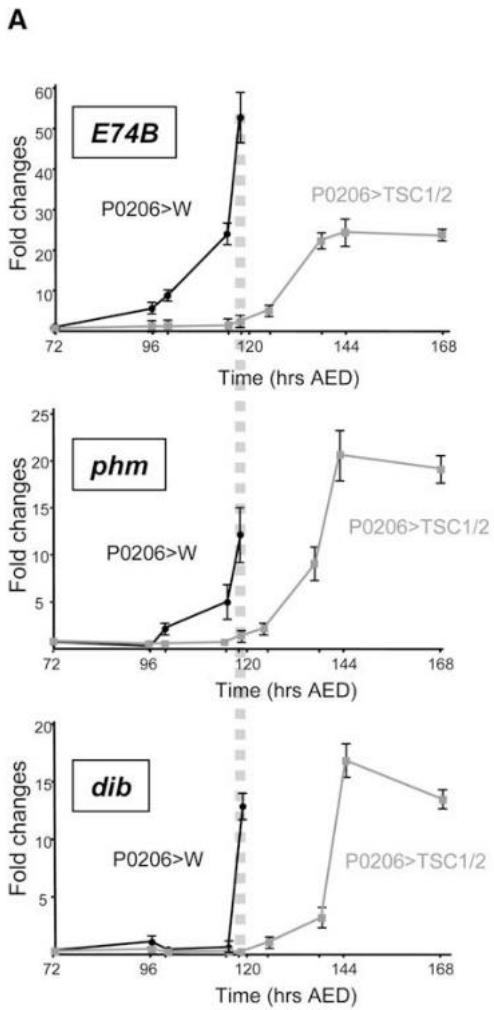


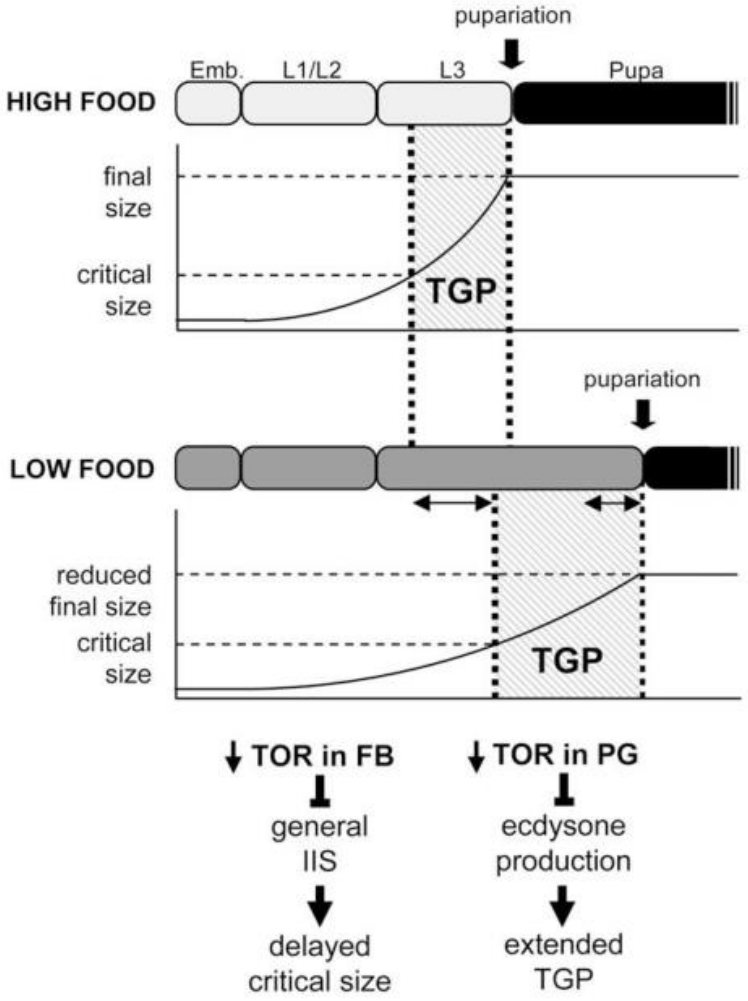
Derya Deveci,.et al.,*Current Biology*,2019

- Insulin/insulin-like and mTOR signaling



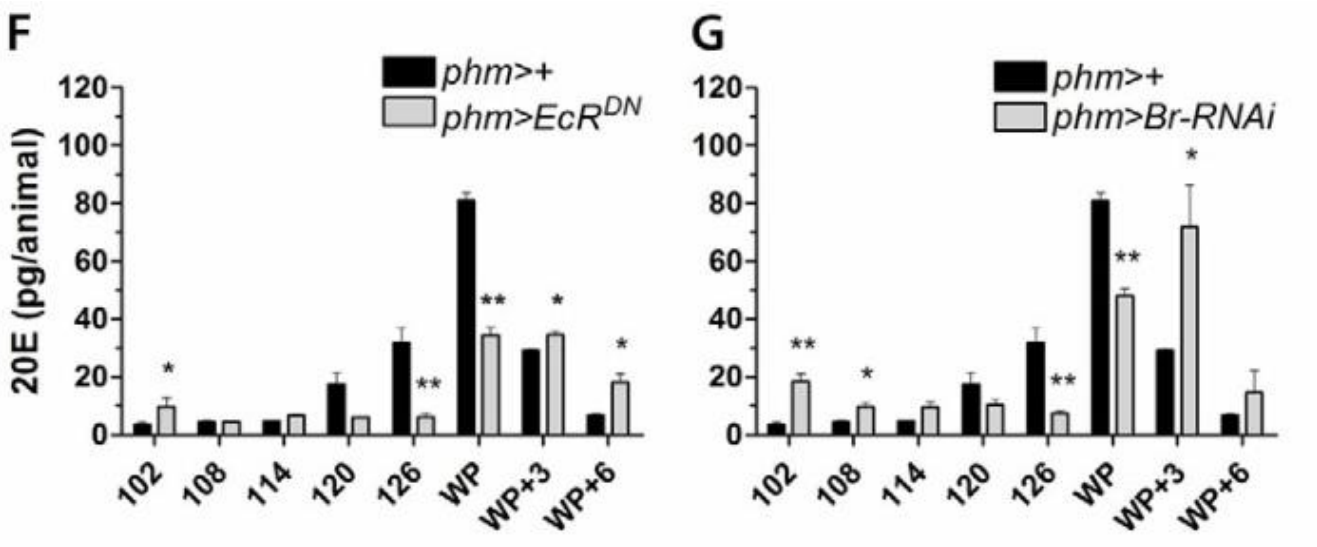
Colombani J,et al.,*Science*,2005

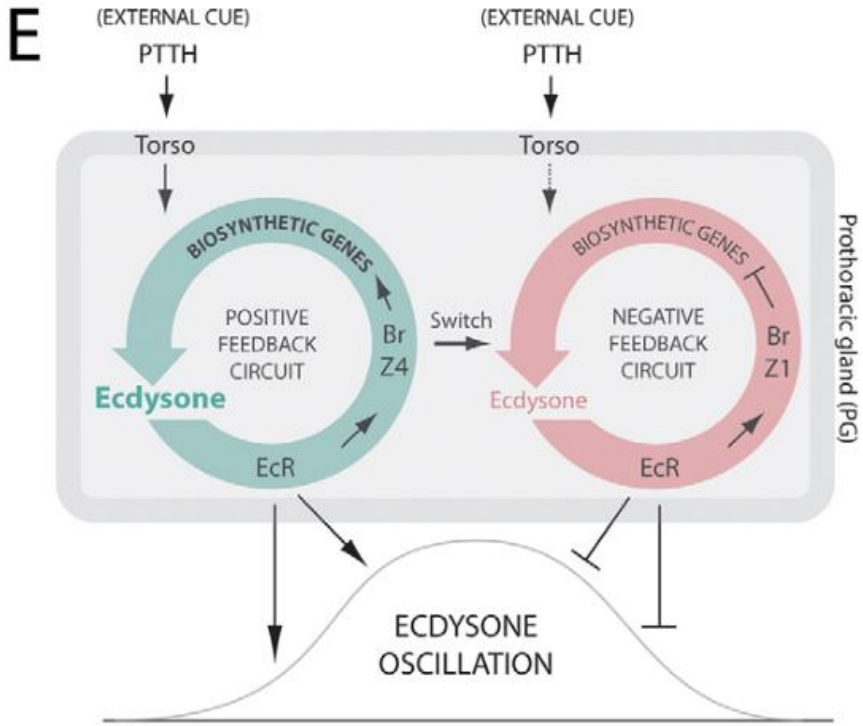




. Layalle S,et al.,*Dev Cell*,2008

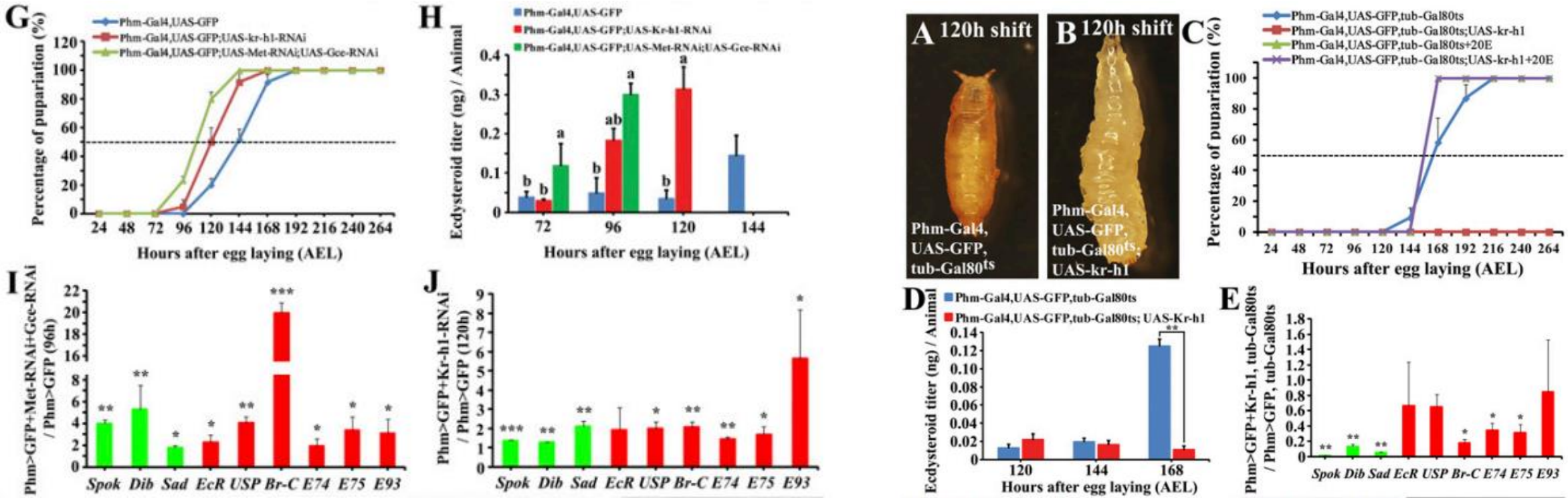
- Feedback regulation of Ecdysone





Morten E. Moeller,et al.,*Develoment*,2013

- Juvenile hormone



(Liu et al., PNAS, 2018)

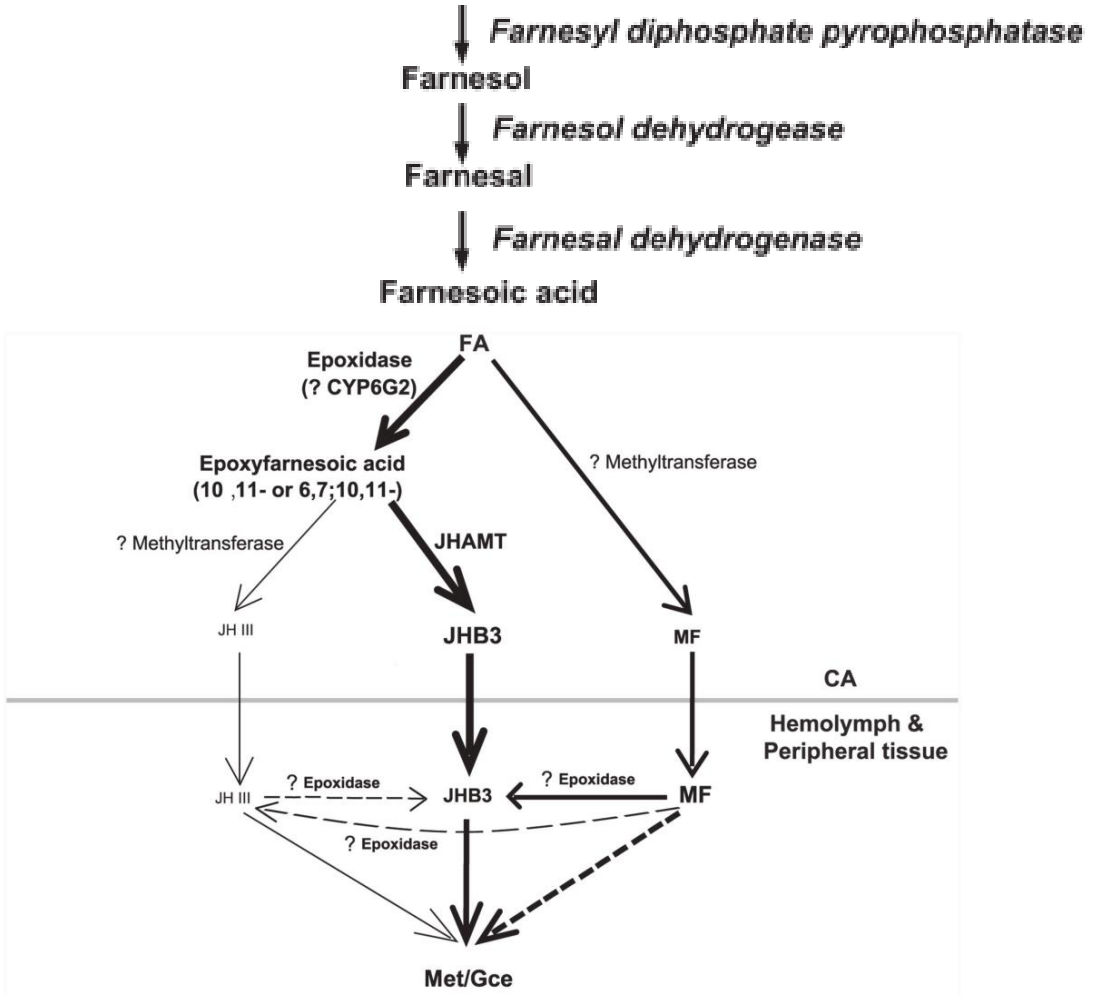
II.Biosynthesis pathway and Regulation of Juvenile hormone

- JH biosynthesis pathway in *Drosophila*

Early mevalonate pathway (MVAP)甲羟戊酸途径

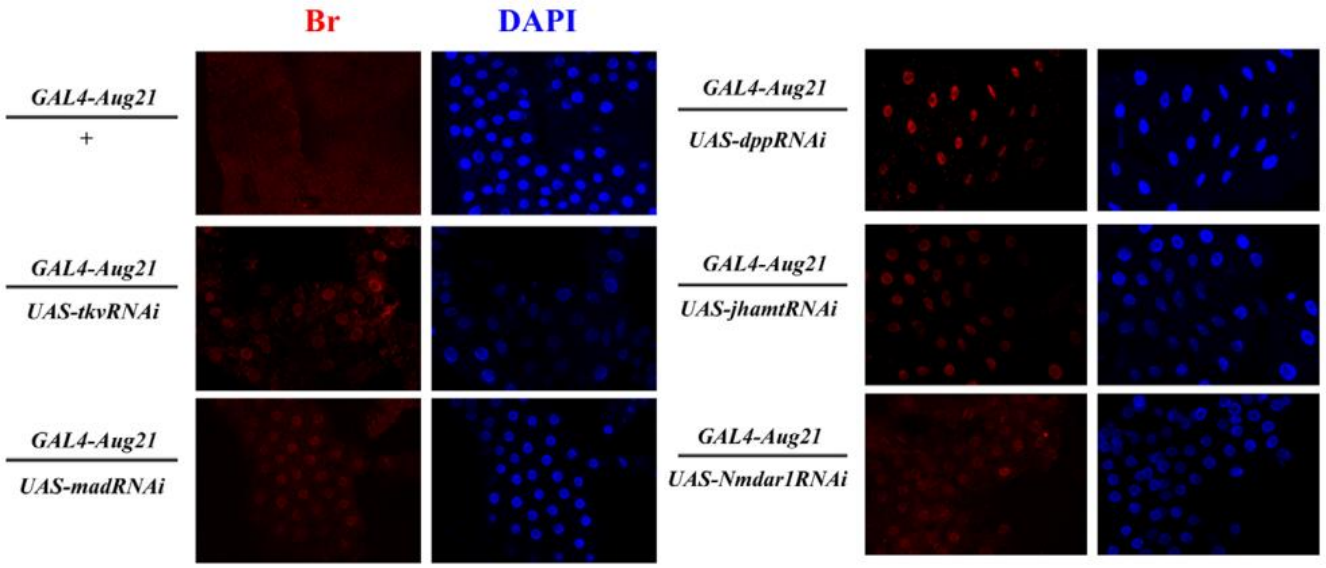
Acetyl CoA
↓ *Acetoacetyl-CoA thiolase*
Acetoacetyl CoA
↓ *3-Hydroxy-3-mehylgutaryl-CoA synthase* (HMGS)
Hydroxymethylglutharyl CoA
↓ *3-Hydroxy-3-methylglutaryl-CoA reductase* (HMGCR)
Mevalonate
↓ *Mevalonate kinase*
Mevalonate-5-P
↓ Phosphomevalonate kinase
Mevalonate-5-PP
↓ *Diphosphomevalonate decarboxylase*
Isopentenyl-PP ⟷ Dimethylallyl-PP
↓
Geranyl-PP
↓ *Farnesyl diphosphate synthase* (FPPS)
Farnesyl-PP

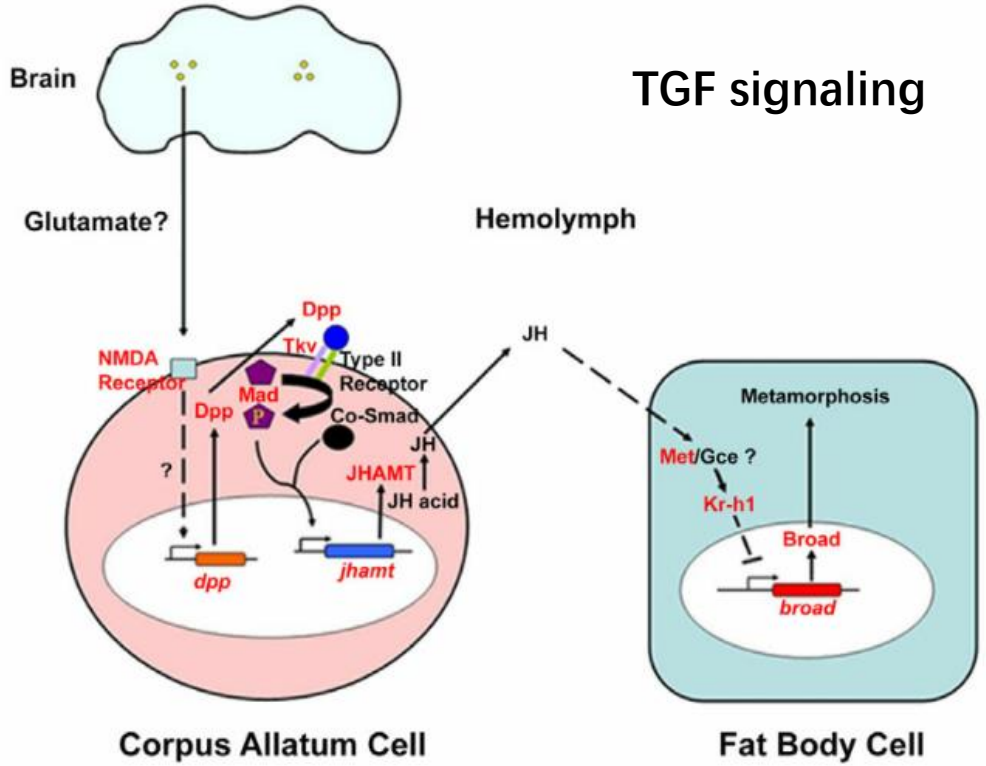
Late JH-branch



(Wen et al., PLOS Genetics, 2015)

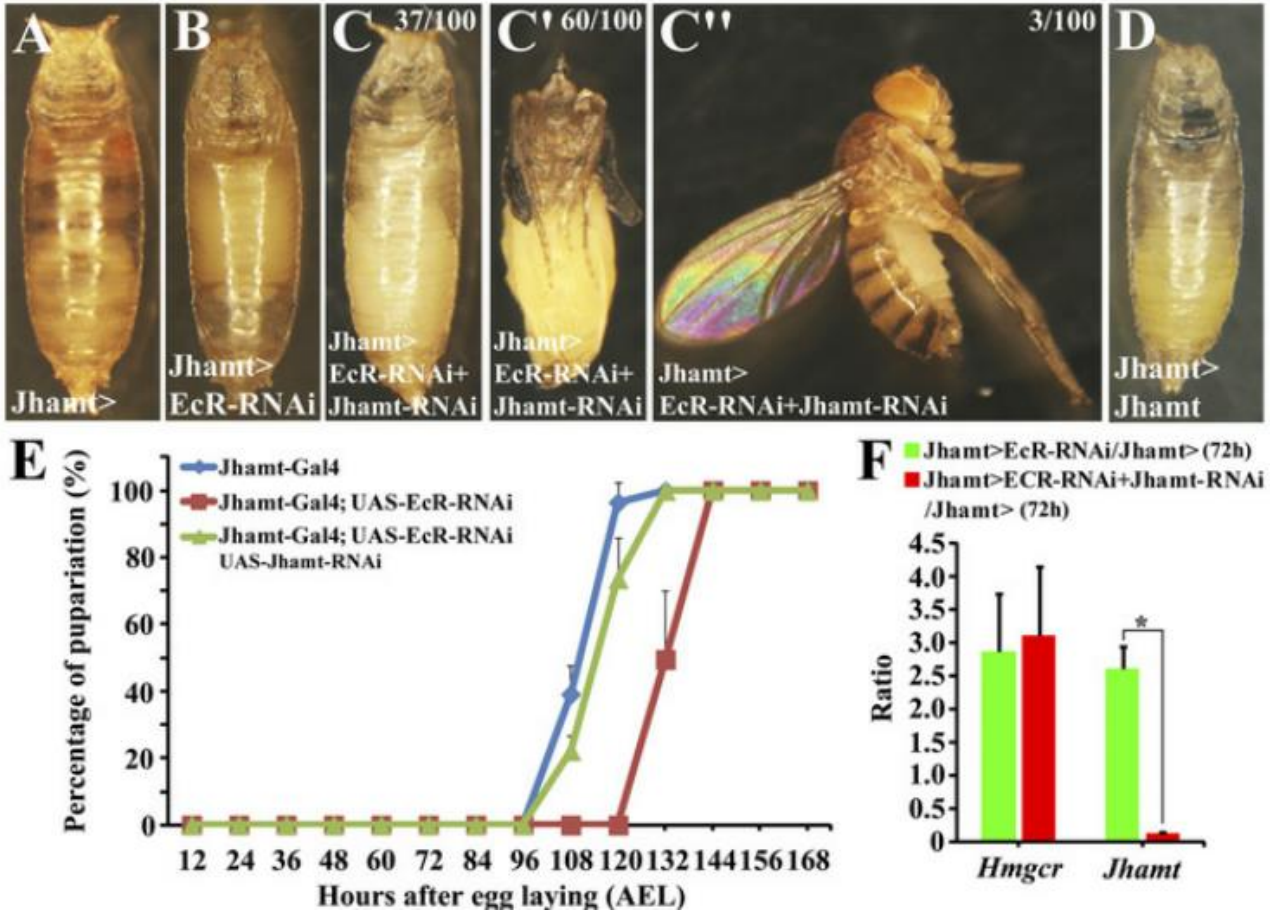
- Regulation of JH biosynthesis





(Huang et al., Development, 2011)

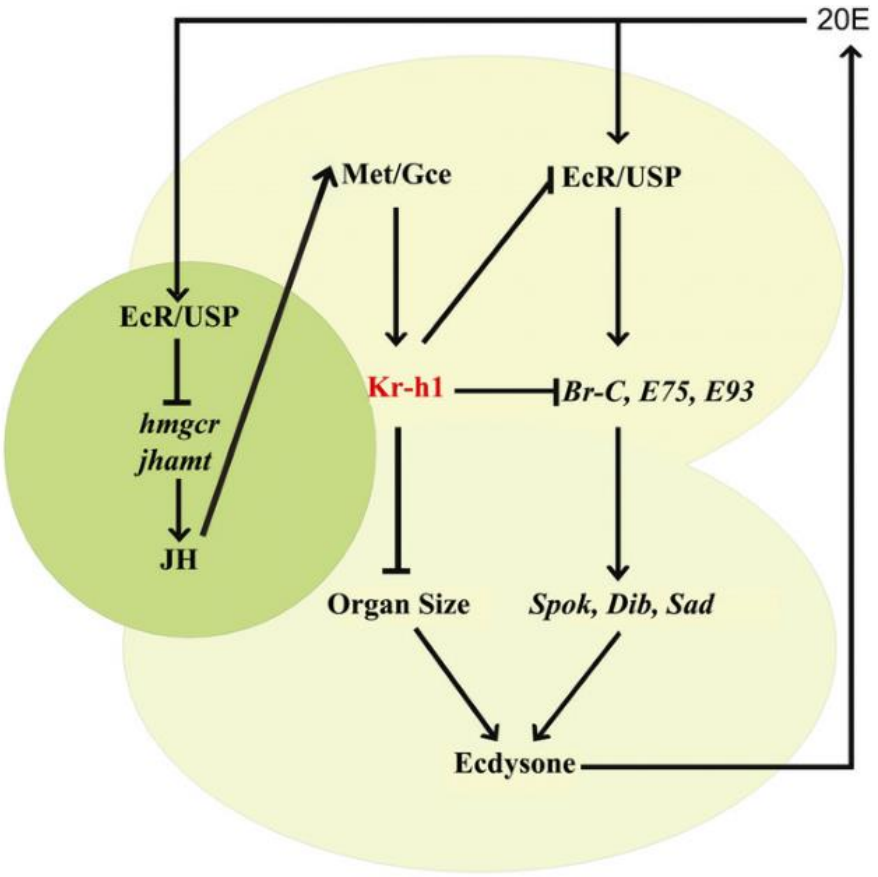
- 20E Prevents JH Biosynthesis



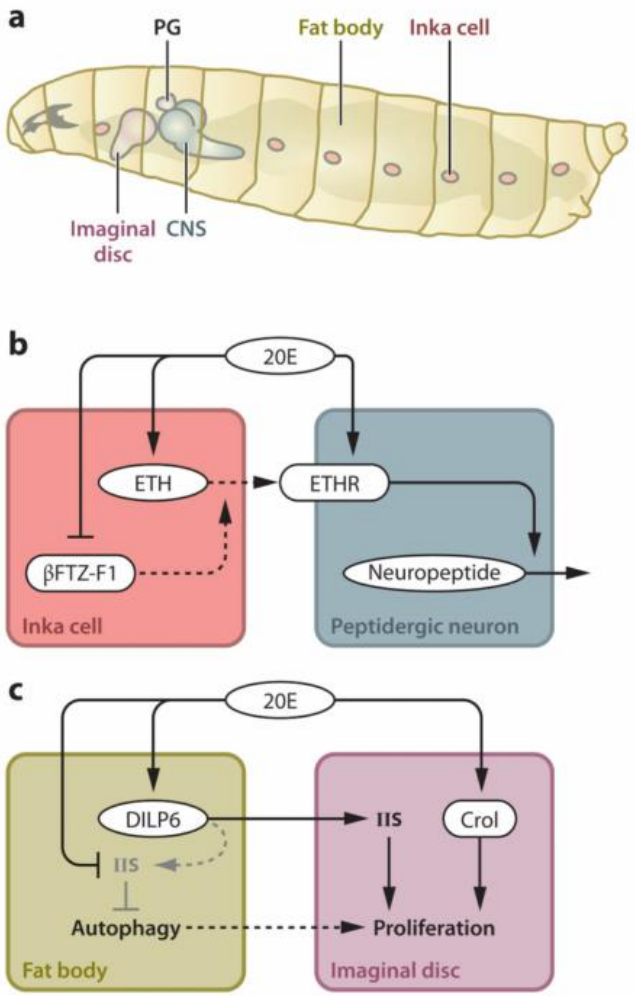
(Liu et al., PNAS, 2018)

III. Functions of ecdysteroid and JH in development

- JH and 20E coordinate to regulate molting and metamorphosis

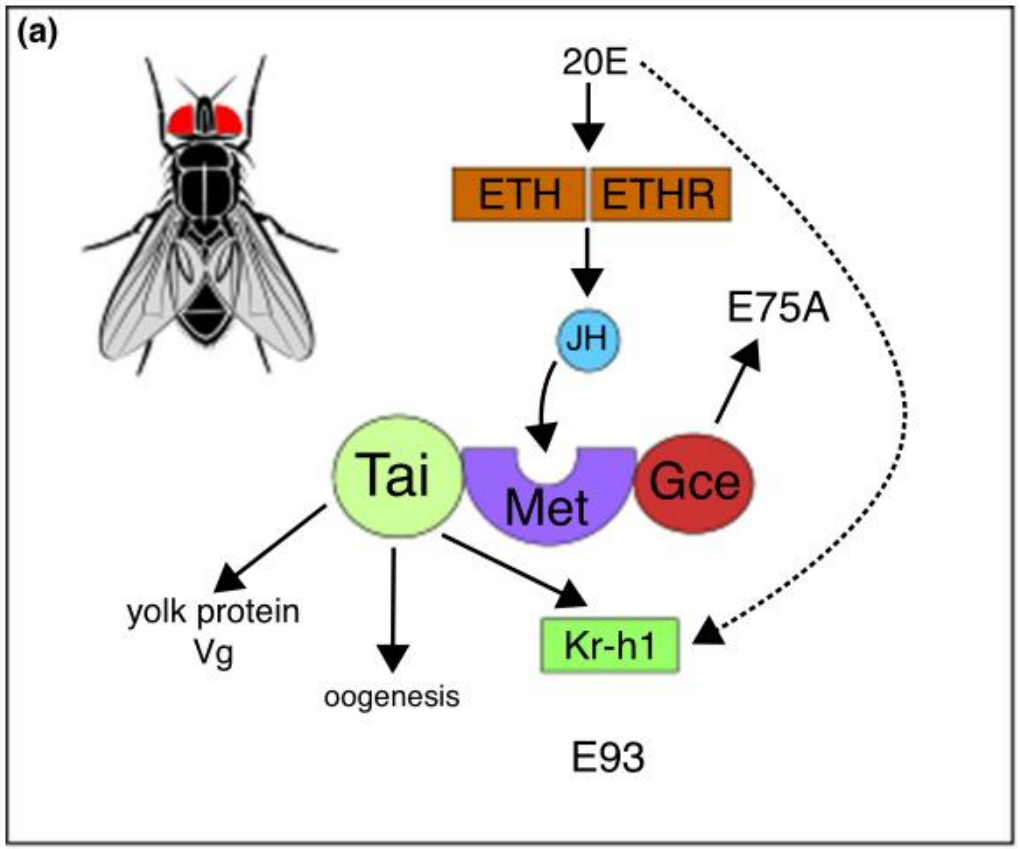


(Liu et al., PNAS, 2018)



Yamanaka, et al., *Annu Rev Entomol*. 2014

- JH and 20E coordinate to regulate reproductive maturation of the ovaries

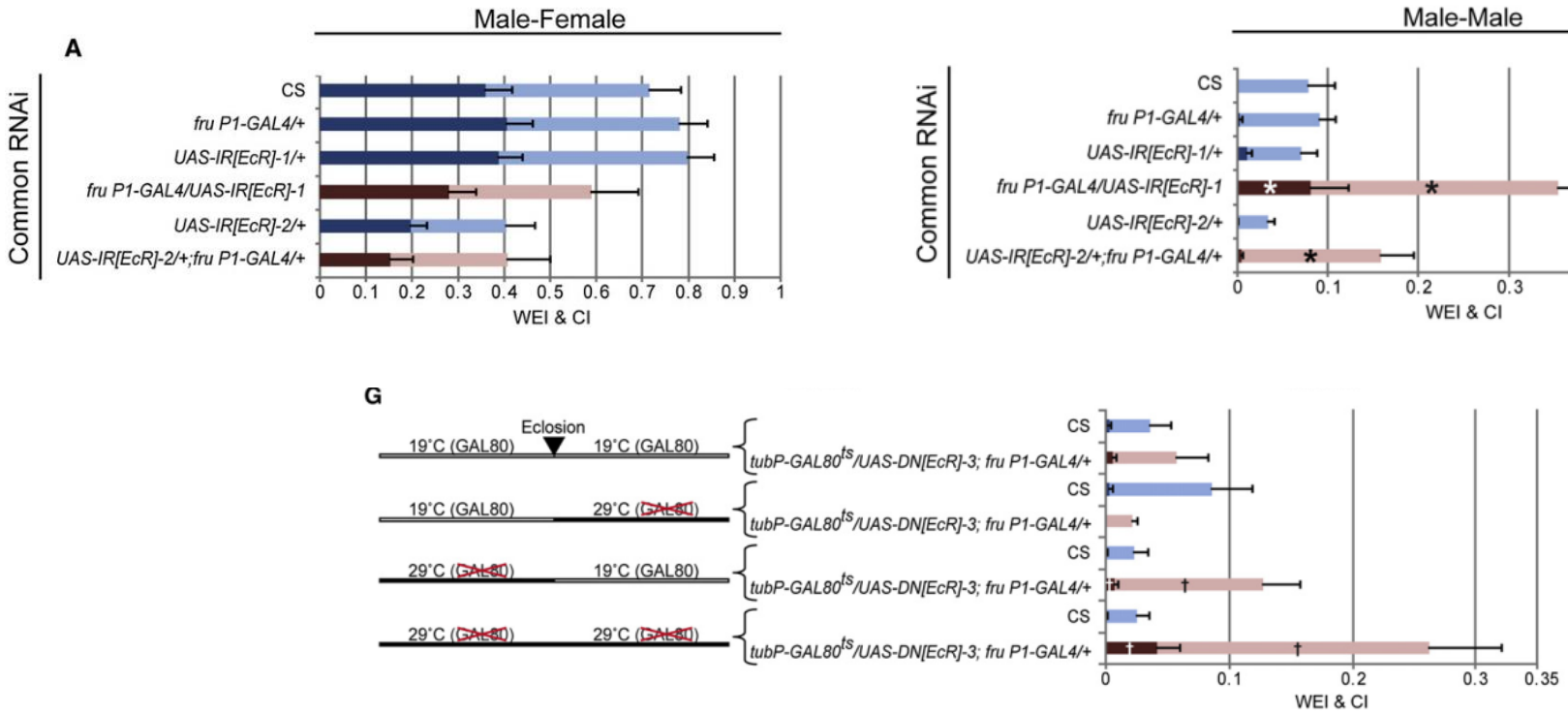


- 20E is critical for the expression of ETH and ETHR in the maintenance of high JH levels.
- ETH functions as an obligatory allatotropin to promote juvenile hormone (JH) production and reproduction.
- The JH receptor (Met or Gce) forms a transcription complex with Taiman (Tai), coordinating yolk protein synthesis and its uptake by the ovary.

III. Functions of ecdysteroid and JH in instinctive behaviors

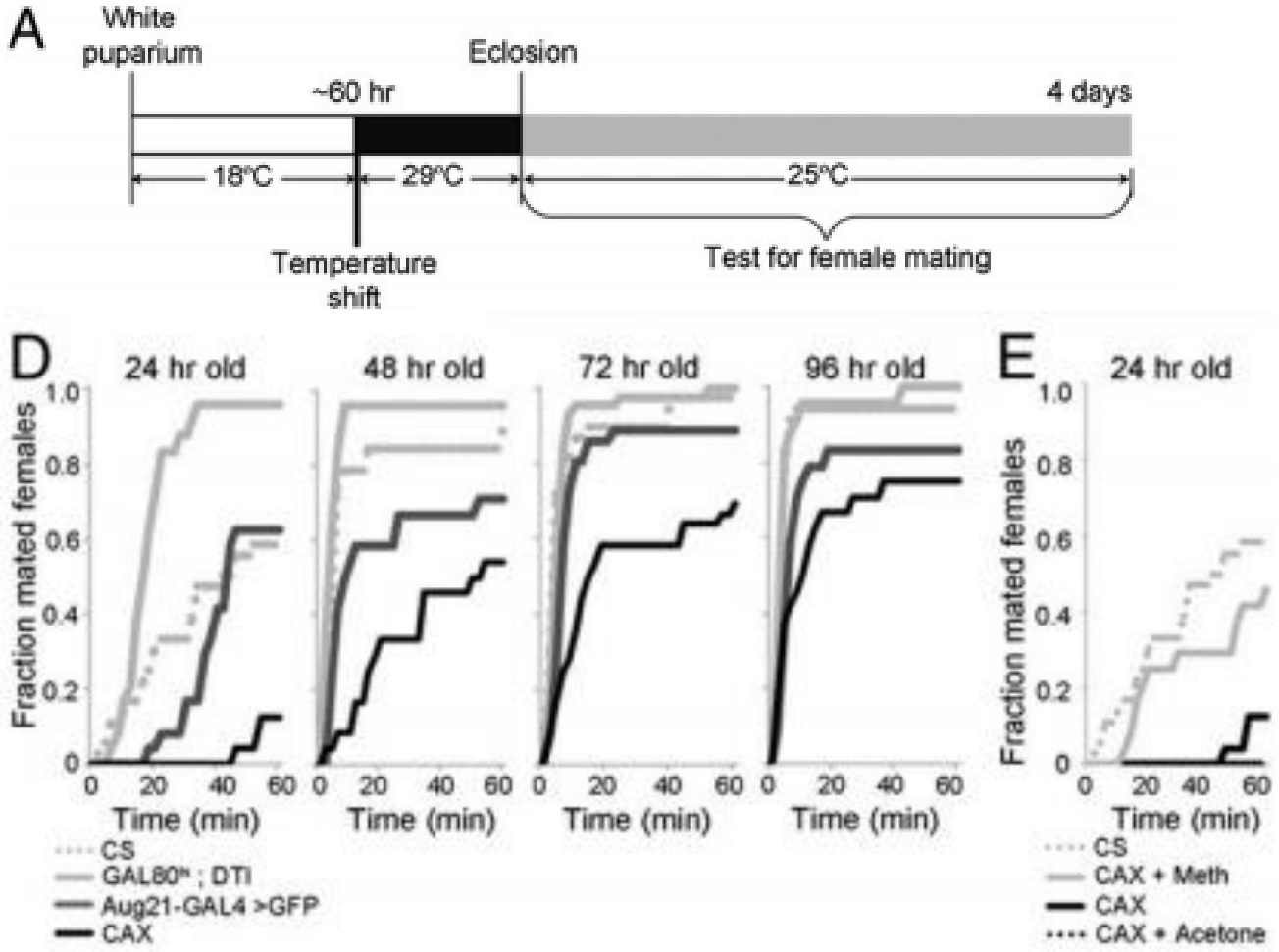
- Sexual behavior (ecdysone and JH: male and female)
- Sleep(ecdysone and JH: male and female)
- Aggression

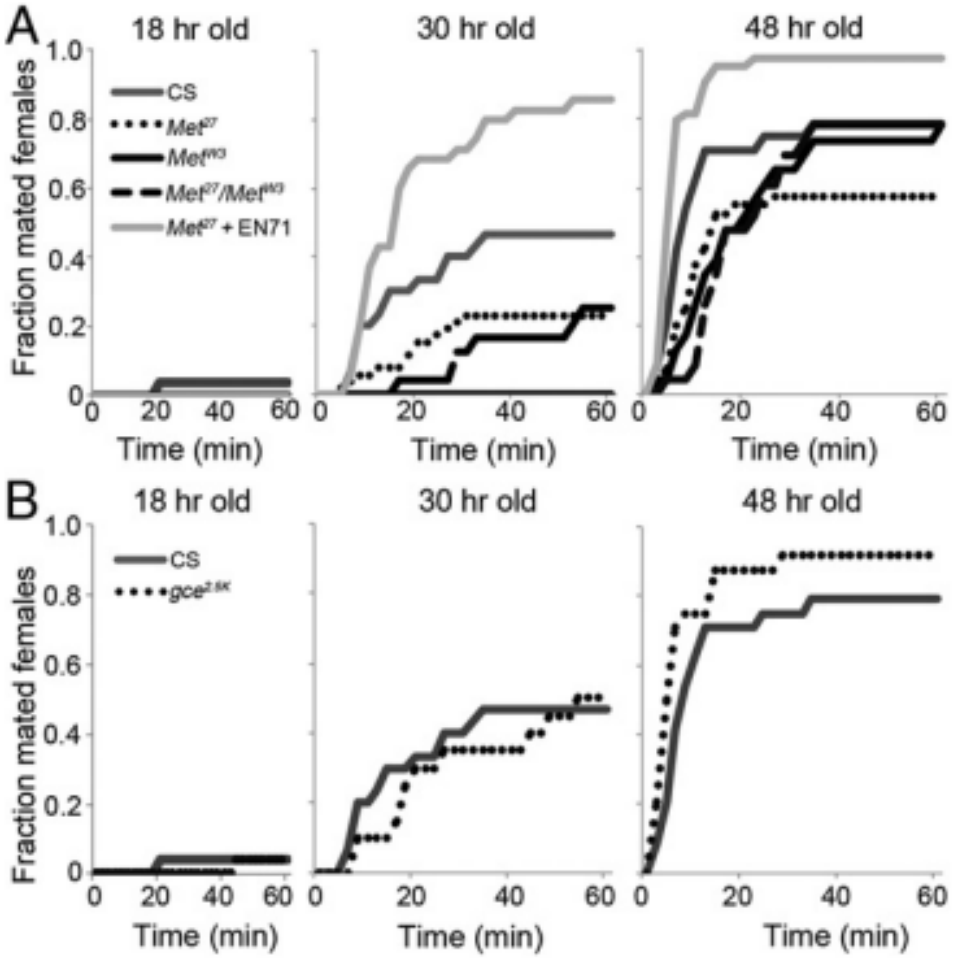
- Regulation of 20E to courtship behavior



Justin E. Dalton, et al., *Current Biology*,2009

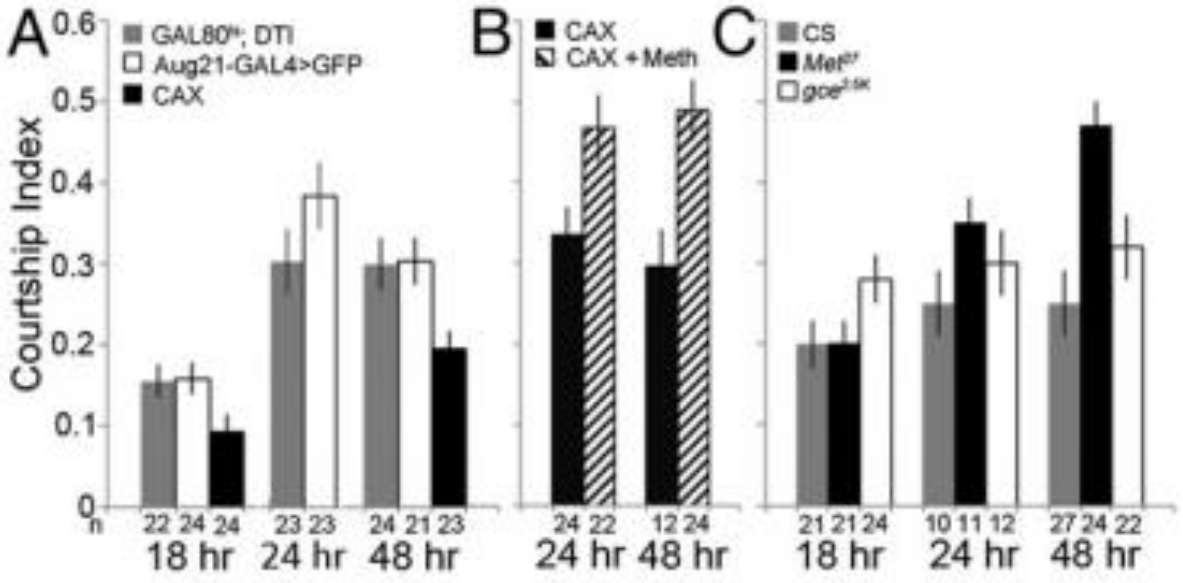
- JH acts primarily via *Methoprene tolerant* (*Met*) to modulate mating in females

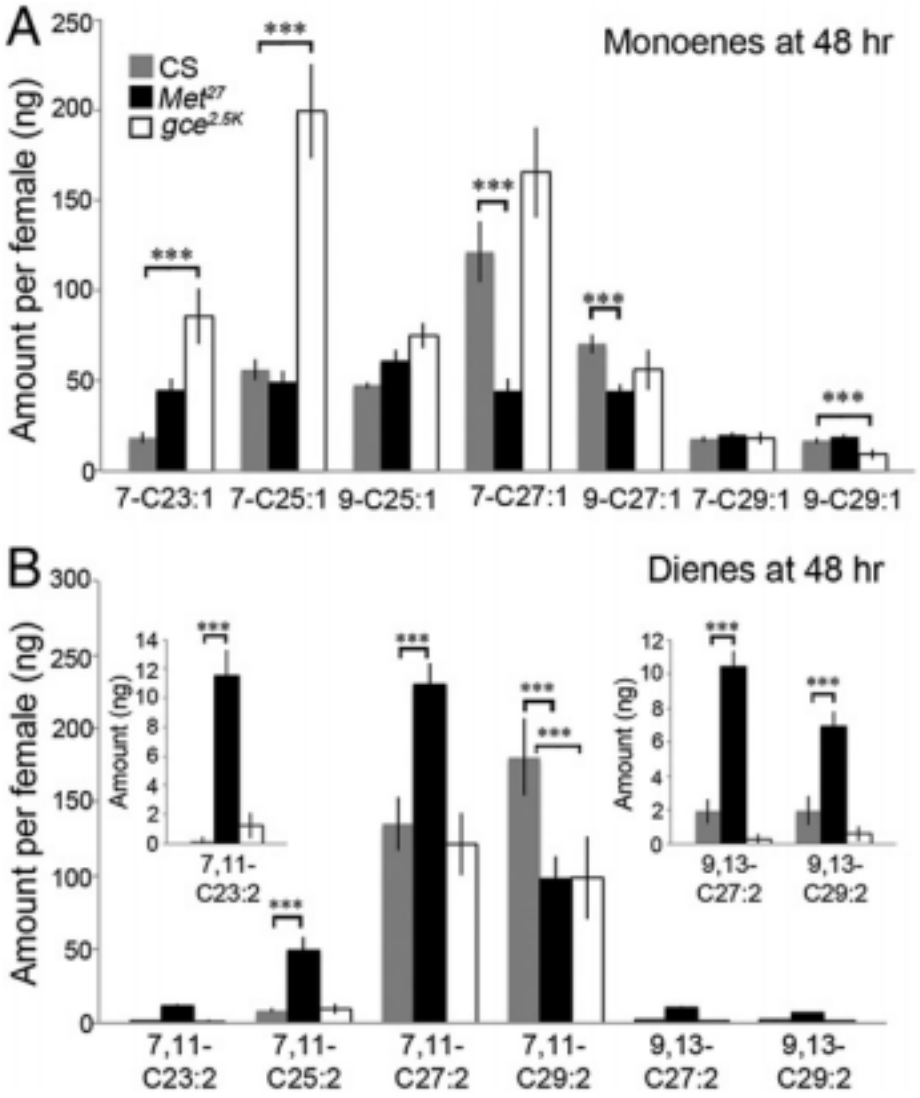




(Bilen et al., PNAS, 2013)

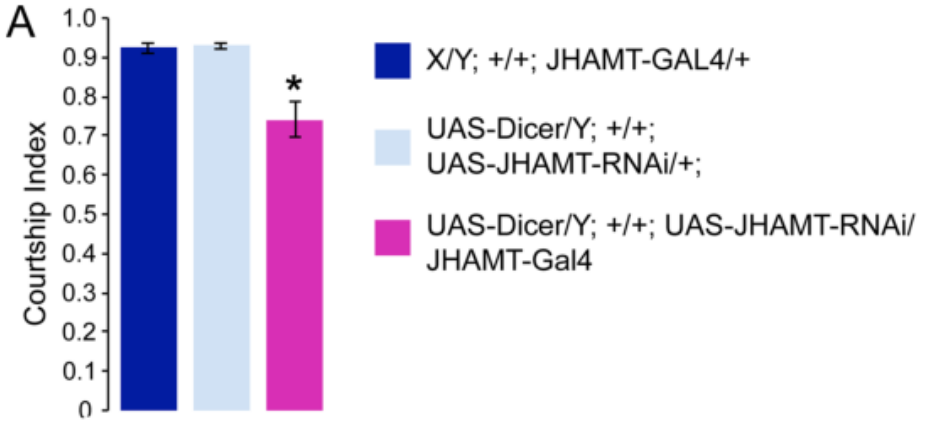
- JH signaling modulates the attractiveness females through altered CHS

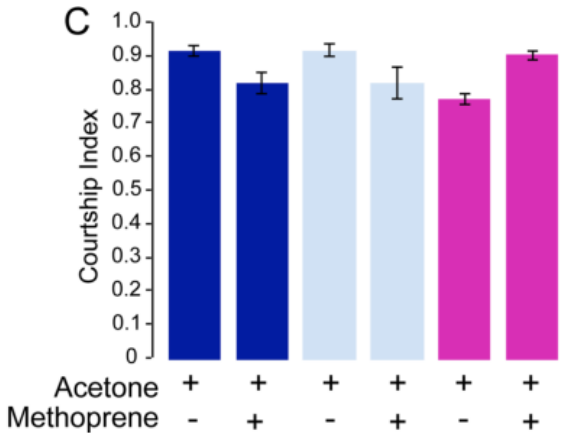


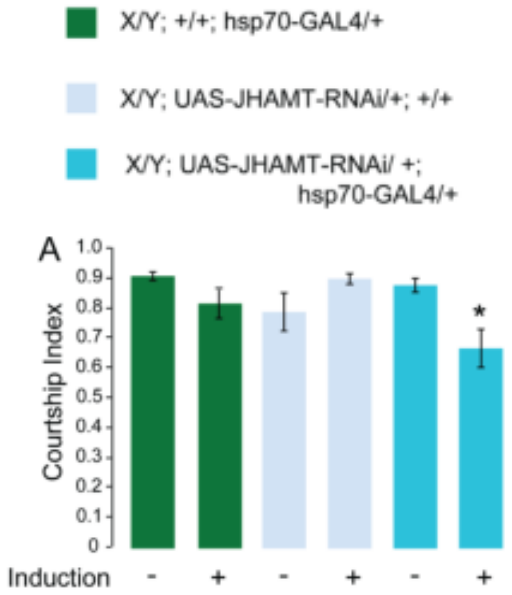


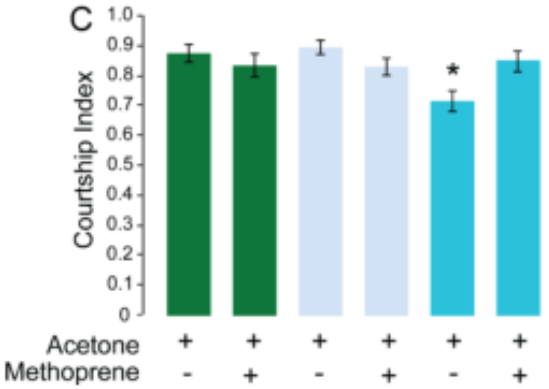
(Bilen et al., PNAS, 2013)

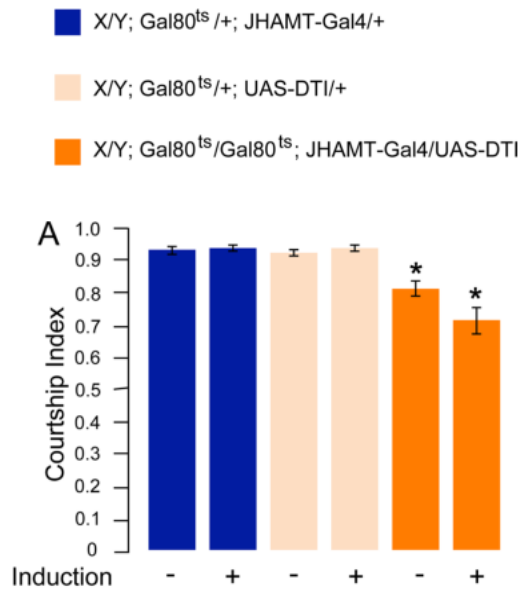
- Males with reduced levels of JHAMT showed a reduction in courtship

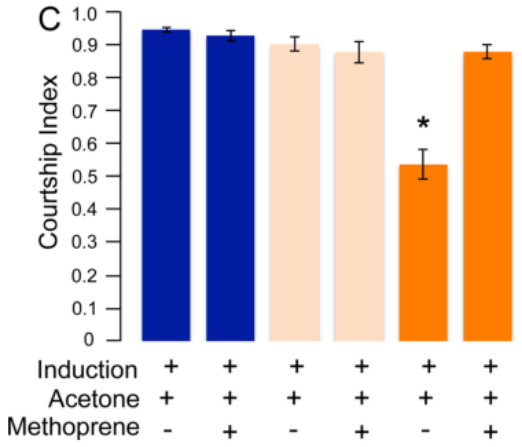






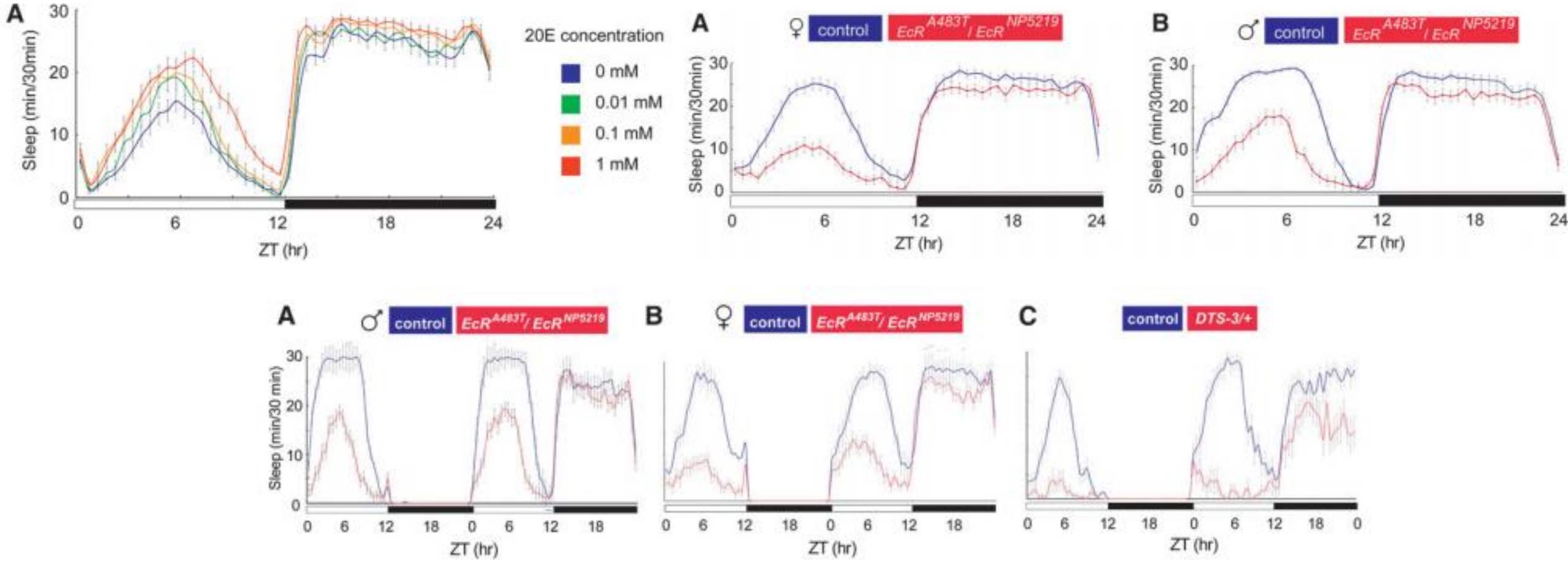






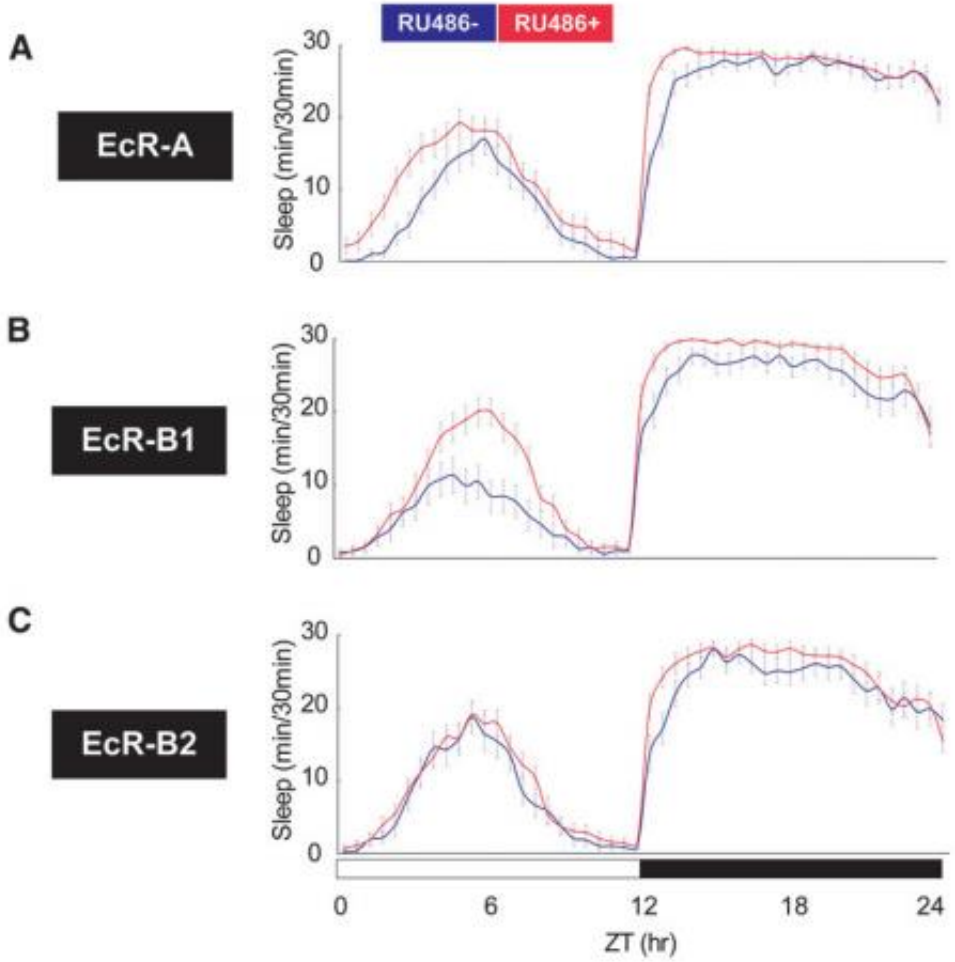
(Wijesekera et al., PLOS ONE, 2016)

- Ecdysone regulates sleep in adult *Drosophila*



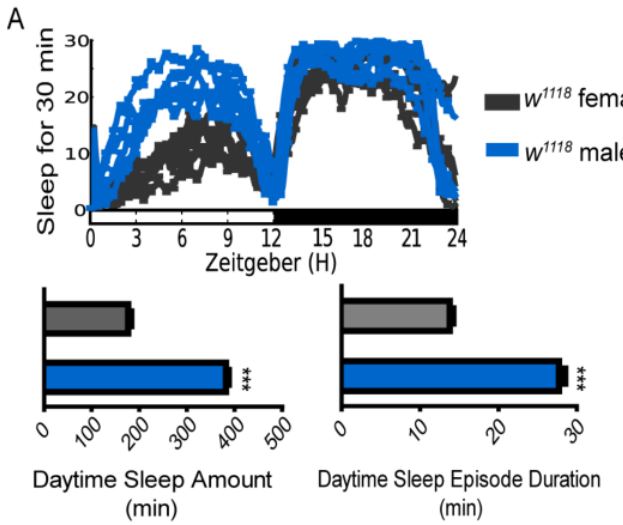
(Ishimoto and Kitamoto, Genetics, 2010)

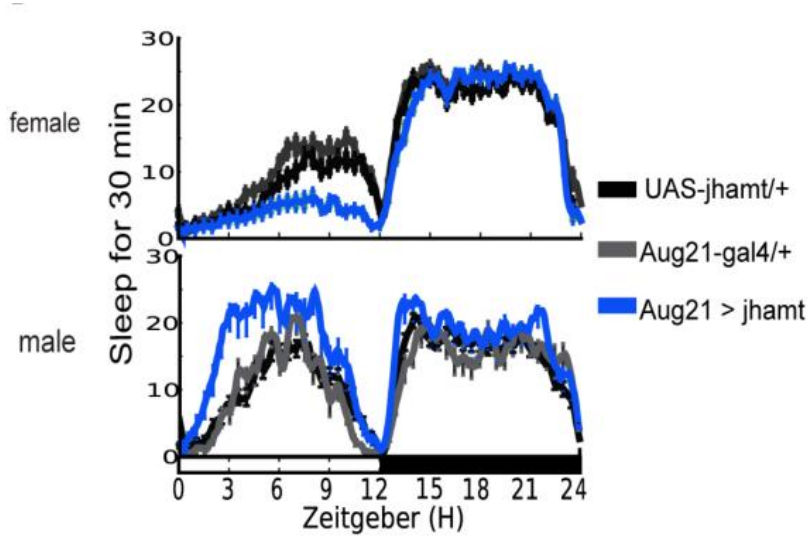
- Sleep is promoted by the conditional expression of certain EcR subtypes in the mushroom bodies

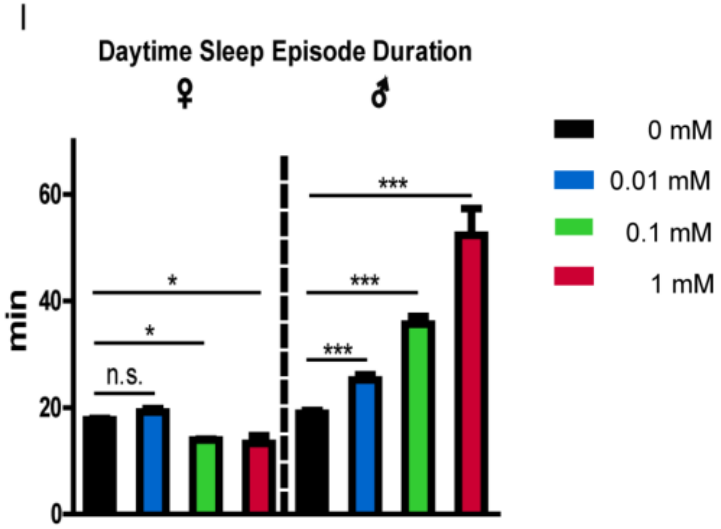


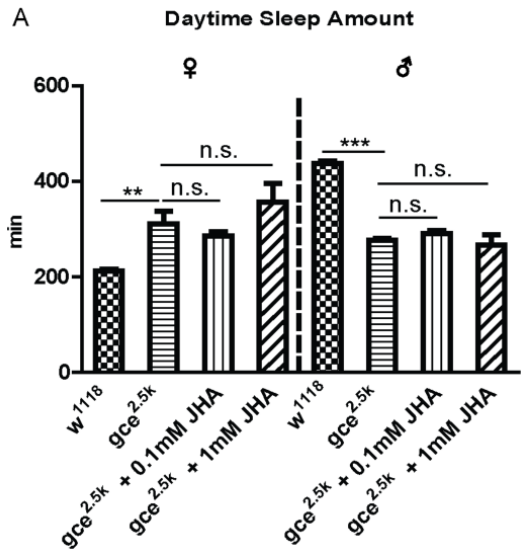
(Ishimoto and Kitamoto, Genetics, 2010)

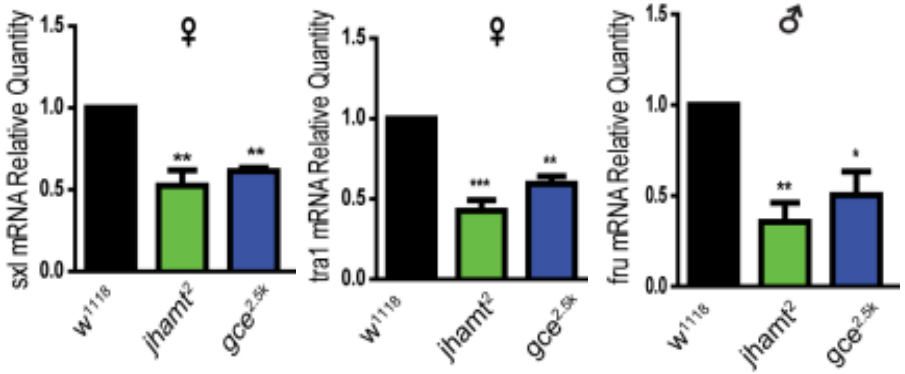
- JH regulate sexual dimorphism of sleep











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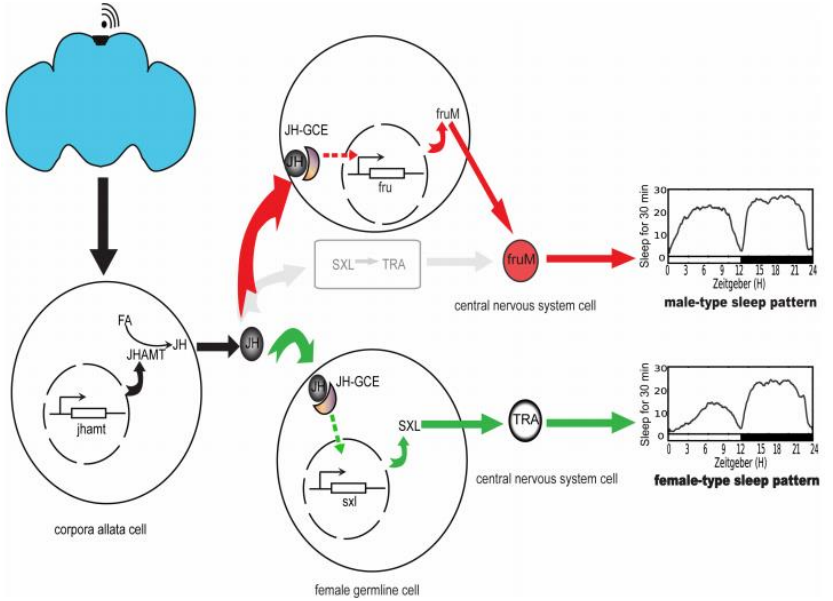


(Wu et al., *PLOS Genetics*, 2018)

Influence of JH on aggression in honey bees

- Older bees, which have higher JH levels (Huang et al., 1994), are generally more aggressive than younger bees with lower JH levels (Breed, 1983).
- Bees treated with a JH analog exhibited an earlier response to alarm pheromone (Robinson, 1987), and the proportion of bees acting as guards also increased (Sasagawa et al., 1989).
- Workers reared in isolation showed higher levels of aggressiveness toward other bees (Breed, 1983), and recently Huang and Robinson (1992) found that isolated bees have elevated JH levels compared to bees reared in groups or in a colony

Summary:

- The steroid hormone ecdysone is the **central regulator** of insect developmental transitions.

- The PG functions as a central node to **integrate diverse physiological and environmental signals** and converts them into E pulses that trigger molting and the metamorphic transition

- 20E, coordinates with JH regulating **molting and metamorphosis** and **reproductive maturation of the ovaries**

- 20E and JH are involved in regulating **instinctive behavior**

Thank You!

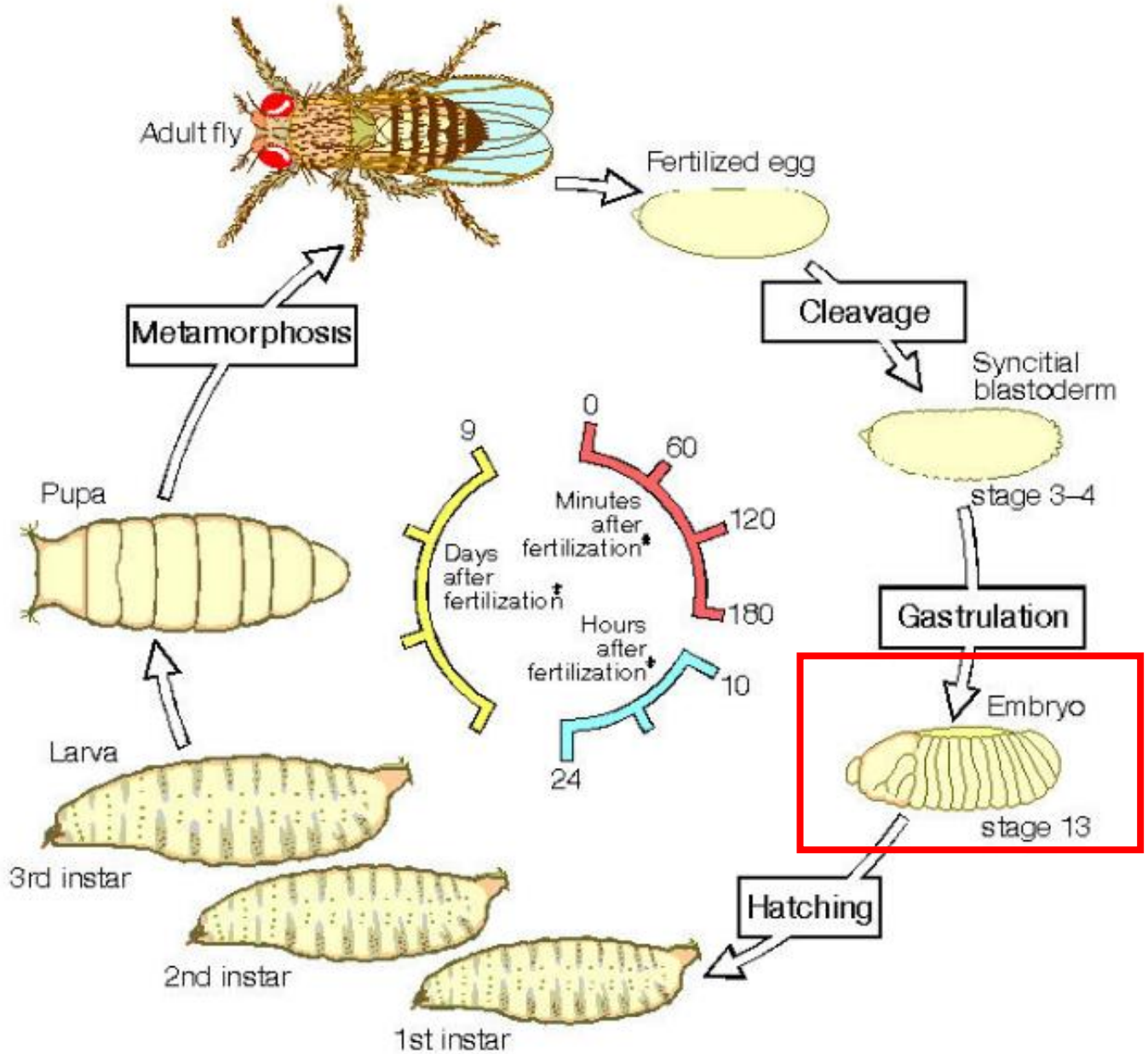
PART 2:

Functions of Hormone on Growth and Maturation in Development

Functions of hormone on growth and maturation in development

汇报人：李小龙

2021.4.29


Adult fly
Fertilized egg
Cleavage
Syncitial blastoderm
stage 3–4
Gastrulation
Embryo
stage 13
Hatching
1st instar
2nd instar
3rd instar
Larva
Pupa
Metamorphosis
0
60
120
180
Minutes after fertilization*
10
24
Hours after fertilization*
9
Days after fertilization*
*At 25°C incubation

Contents

1. Prothoracicotropic Hormone(PTTH)

2. Ecdysteroid(20E)

3.Juvenile Hormone(JH)

Contents

1. Prothoracicotropic Hormone(PTTH)

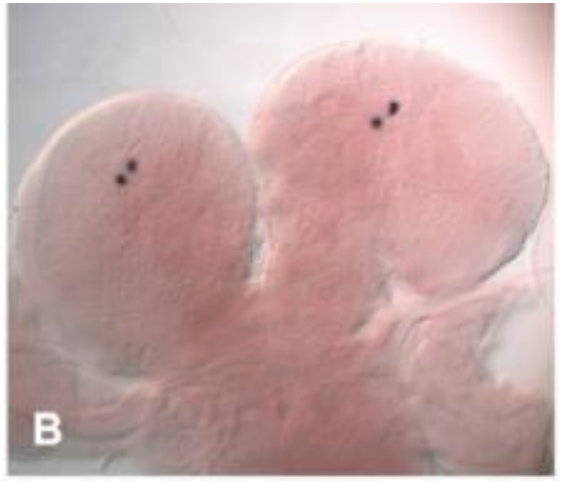
2. Ecdysteroid(20E)

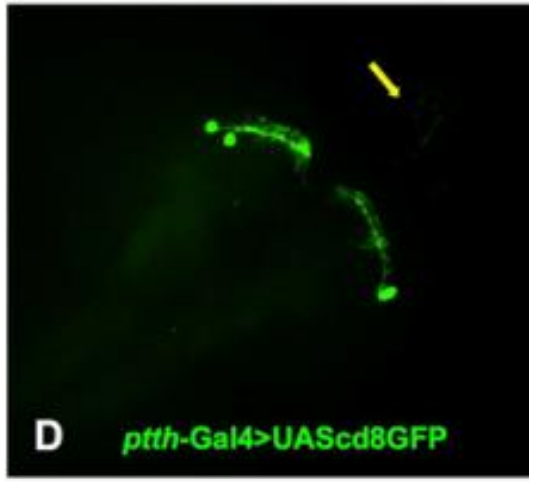
3.Juvenile Hormone(JH)

Concept:

- Critical weight: the weight after attainment of which the time course to metamorphosis initiation can no longer be delayed by starvation.
- Final adult size：depend on two parameters，the speed of growth and the overall duration of the growth period.

Drosophila PTTH Is Produced in the PG Neurons





Stage-17 of embryo

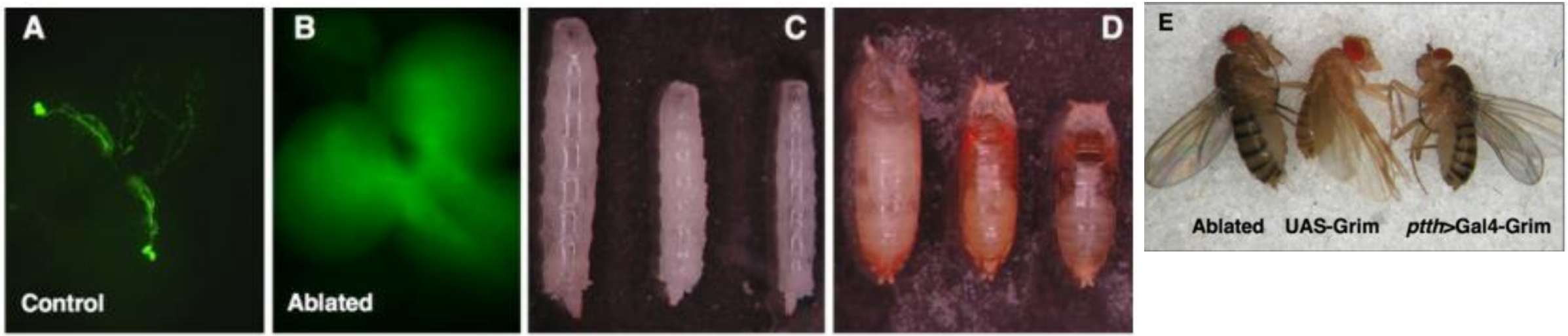
Brain of L3

Brain of L3

PTTH RNA in situ hybridization

Zofeyah McBrayer et al., 2007, Developmental Cell

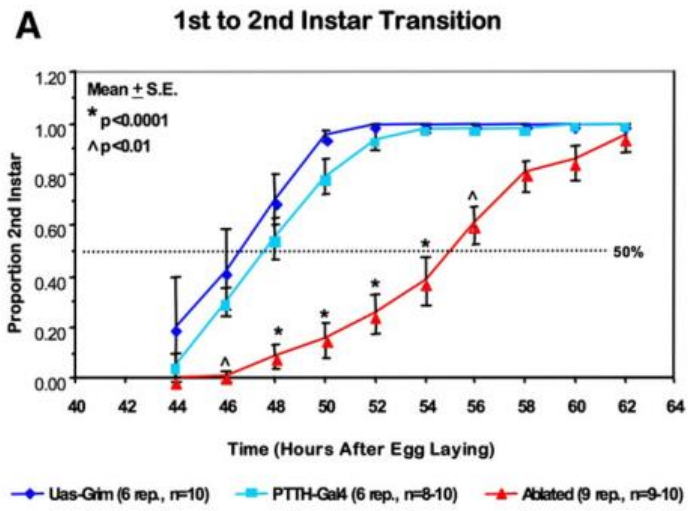
Ablation of PG Neurons Produces Developmental Delay and a Prolonged Duration of Feeding

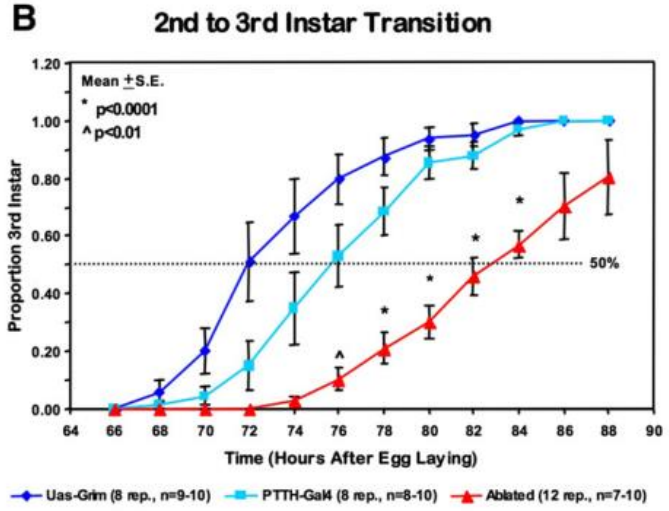


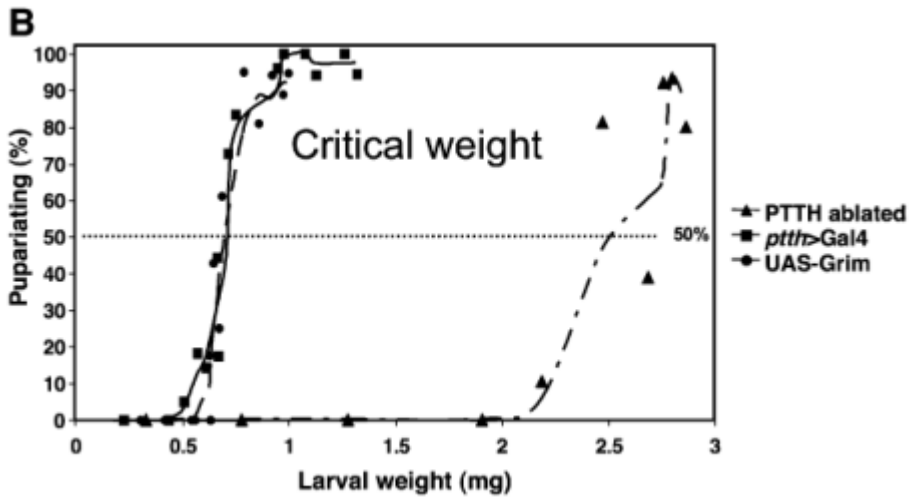
PTTH - Gal4
UAS-Grim

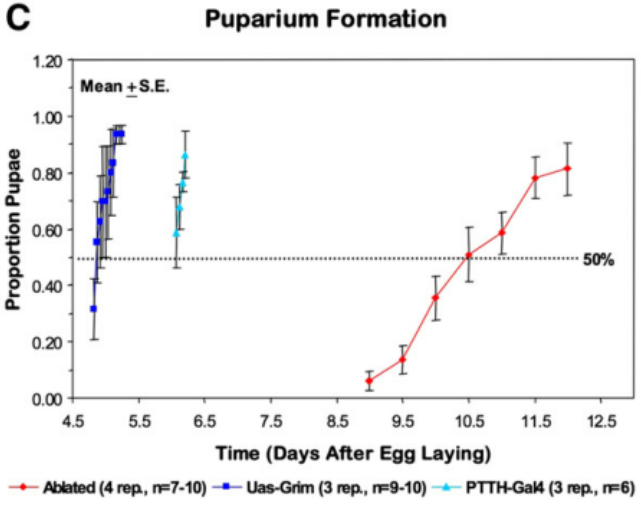
Zofeyah McBrayer et al., 2007, Developmental Cell

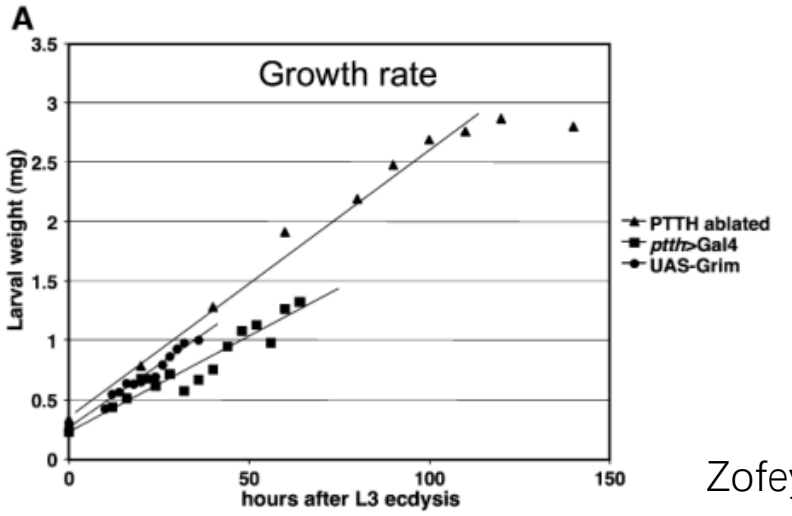
Ablation of PG neurons primarily affects the duration of feeding and not the rate of weight gain.











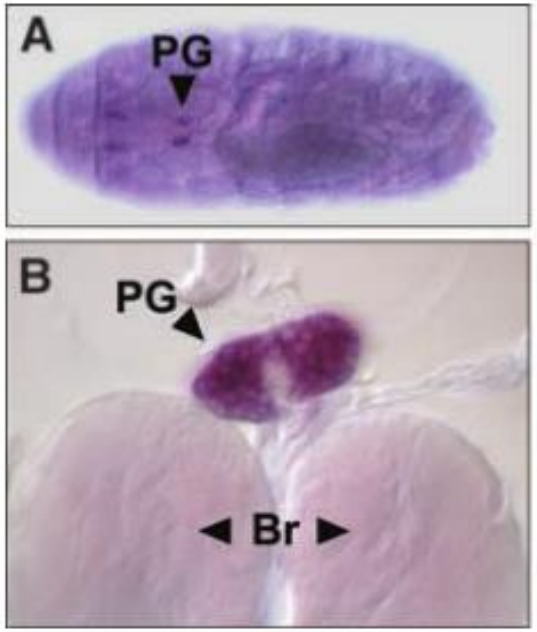
Zofeyah McBrayer et al., 2007, Developmental Cell

Conclusion

1. PTTH is not absolutely required for metamorphosis, but rather it regulates the timing of metamorphosis and thereby controls the final body size.

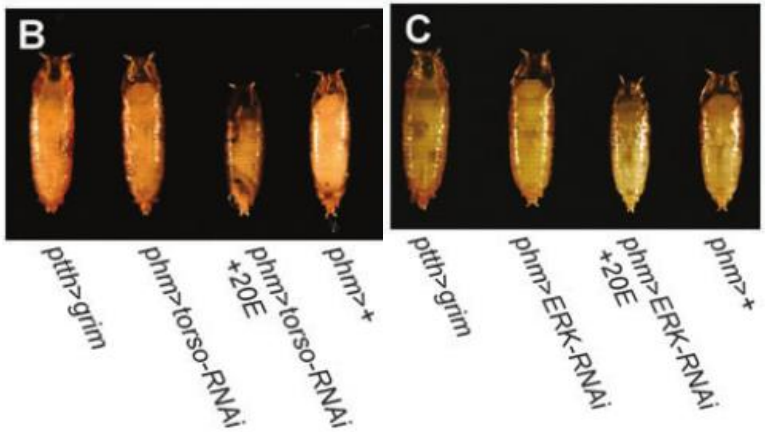
PTTH acts on Torso receptor to activate MAPK signaling pathway

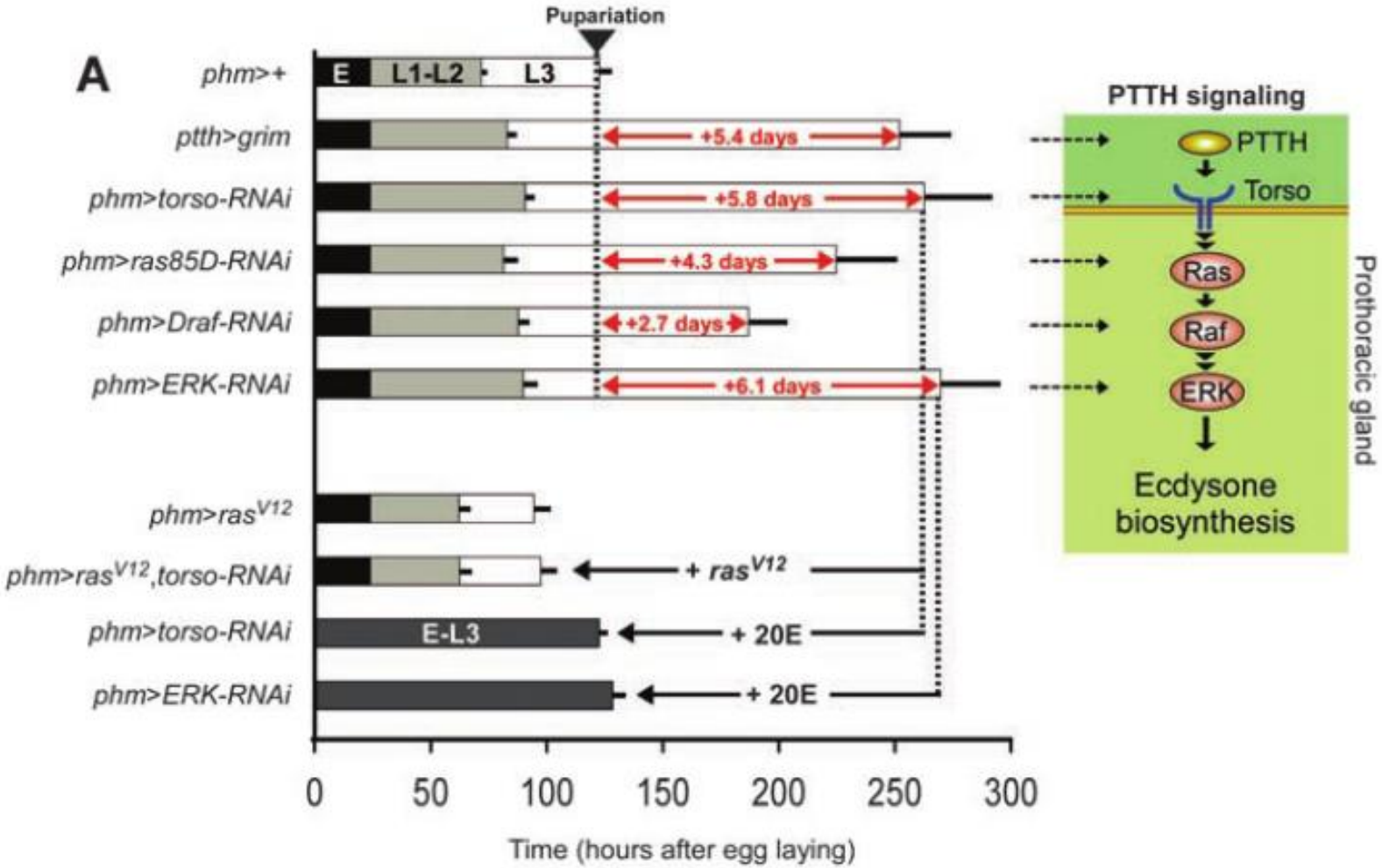
Torso RNA in situ hybridization



Stage-17 of embryo

Brain of L3





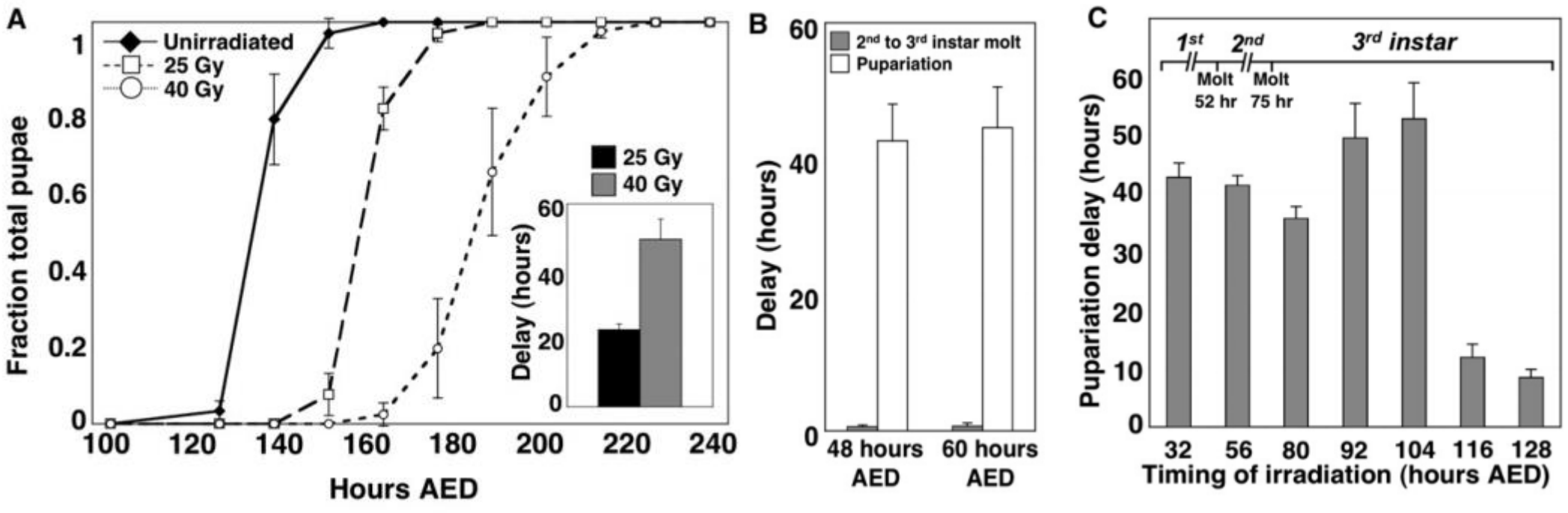
Rewitz KF et al., 2009, Science

Conclusion

1.PTTH is not absolutely required for metamorphosis, but rather it regulates the timing of metamorphosis and thereby controls the final body size.

2. PTTH acts on Torso receptor to activate MAPK signaling pathway, thereby promoting the expression of ecdysone.

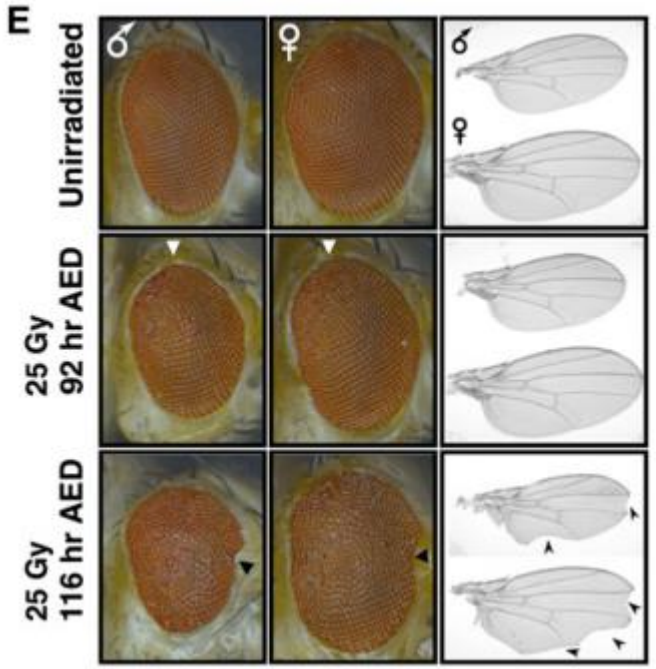
A checkpoint-like mechanism operates after tissue damage.

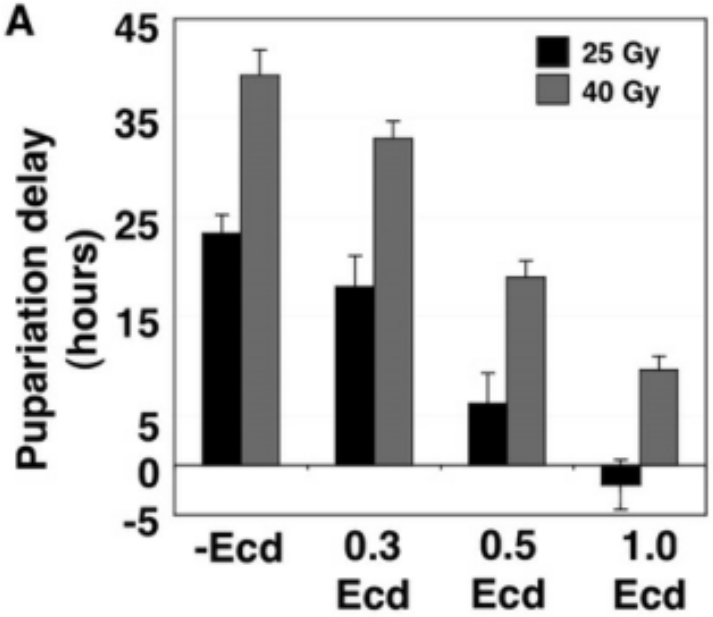


92h(AED)

Halme A et al., 2010, Curr. Biol.

A checkpoint-like mechanism after tissue damage.

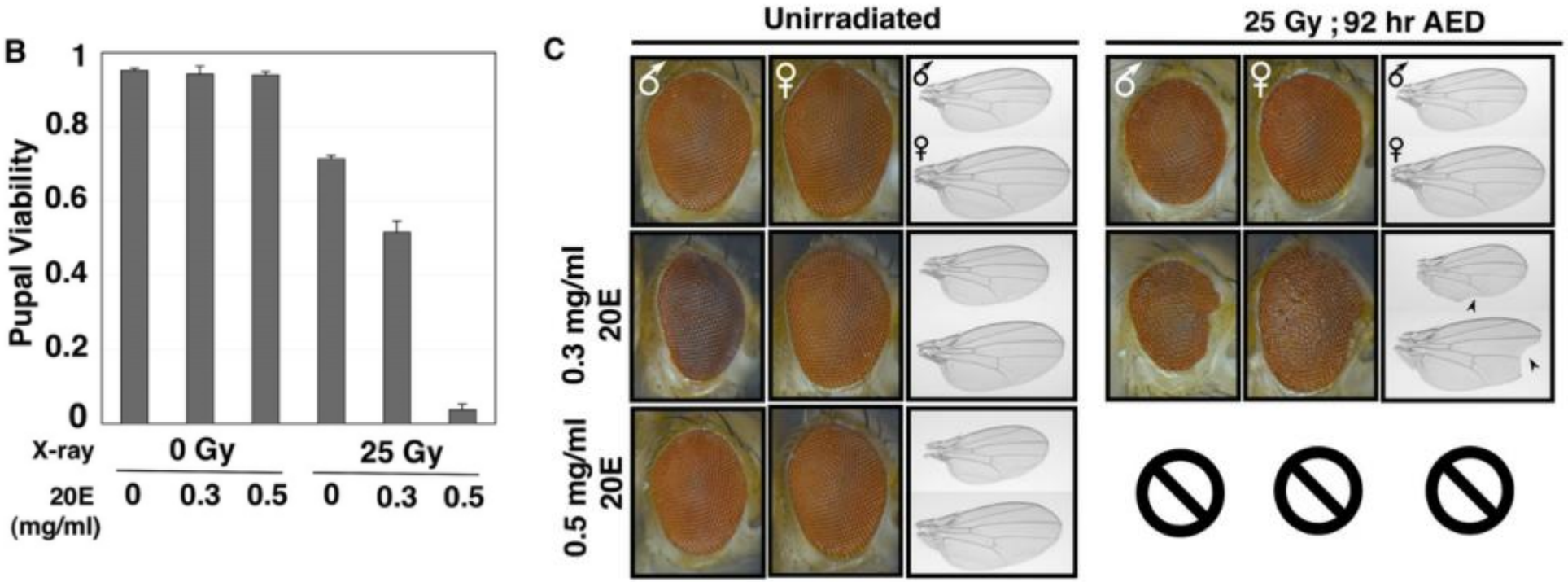




92h(AED)

Halme A et al., 2010, Curr. Biol.

A checkpoint-like mechanism after tissue damage.

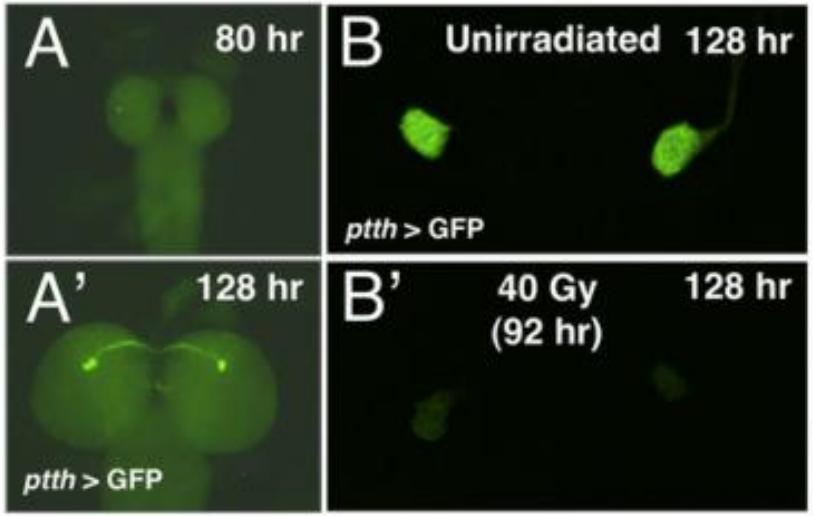


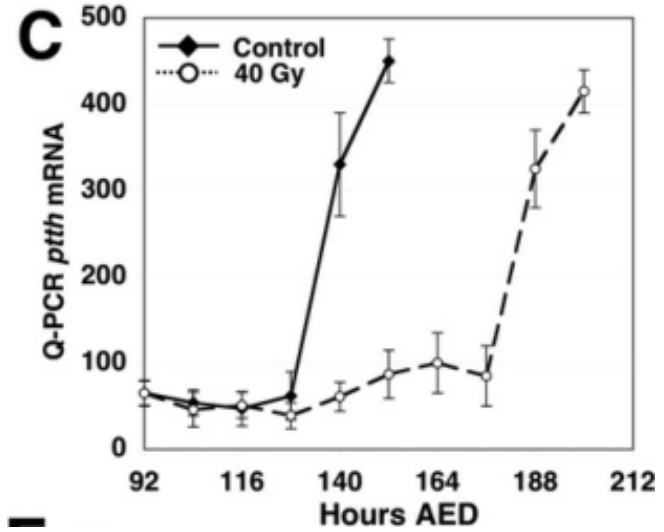
Halme A et al., 2010, Curr. Biol.

Conclusion

1. PTTH is not absolutely required for metamorphosis, but rather it regulates the timing of metamorphosis and thereby controls the final body size.
2. PTTH acts on Torso receptor to activate MAPK signaling pathway, thereby promoting the expression of ecdysis hormone.
3. Increasing the level of 20E limits the larvae's ability to regenerate X-ray-damaged tissues and overcome checkpoint-induced delays.

A checkpoint-like mechanism after tissue damage.





Halme A et al., 2010, Curr. Biol.

Conclusion

1. PTTH is not absolutely required for metamorphosis, but rather it regulates the timing of metamorphosis and thereby controls the final body size.
2. PTTH acts on Torso receptor to activate MAPK signaling pathway, thereby promoting the expression of ecdysis hormone.
3. Increasing the level of 20E limits the larvae's ability to regenerate X-ray-damaged tissues and overcome checkpoint-induced delays.
4. PTTH expression is downregulated when larval imaginal tissues are either physically or genetically damaged.

Contents

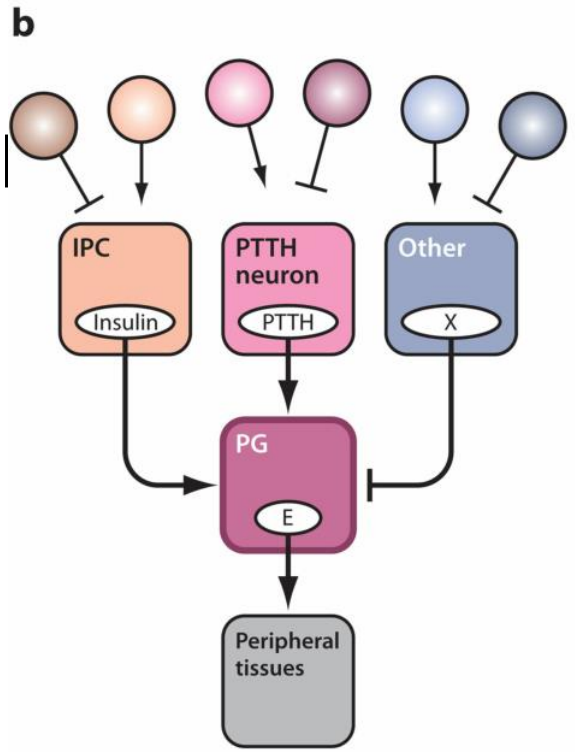
1. Prothoracicotropic Hormone(PTTH)

2. Ecdysteroid(20E)

3.Juvenile Hormone(JH)

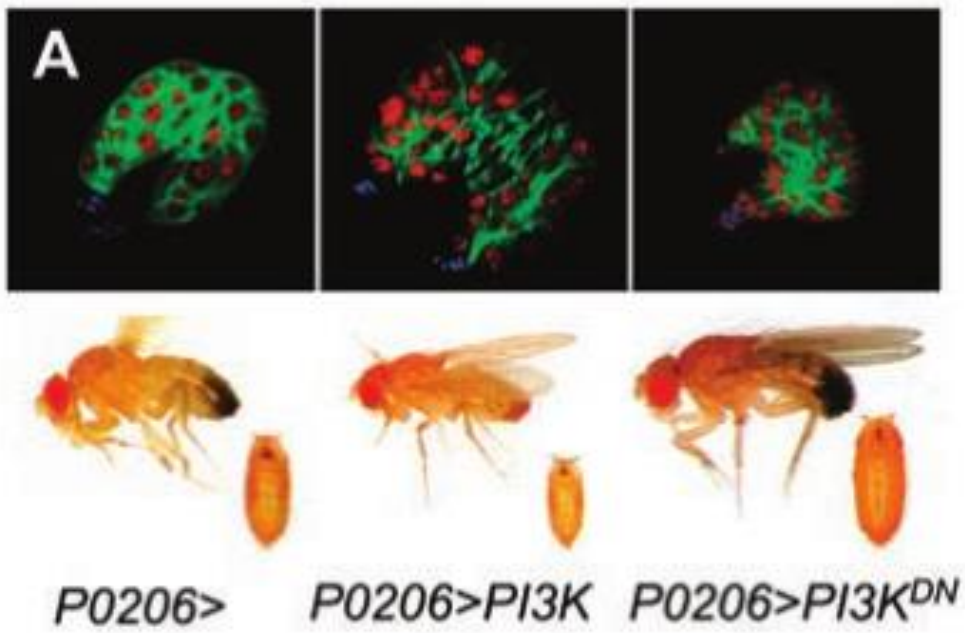
Brief Introduction of Ecdysteroid

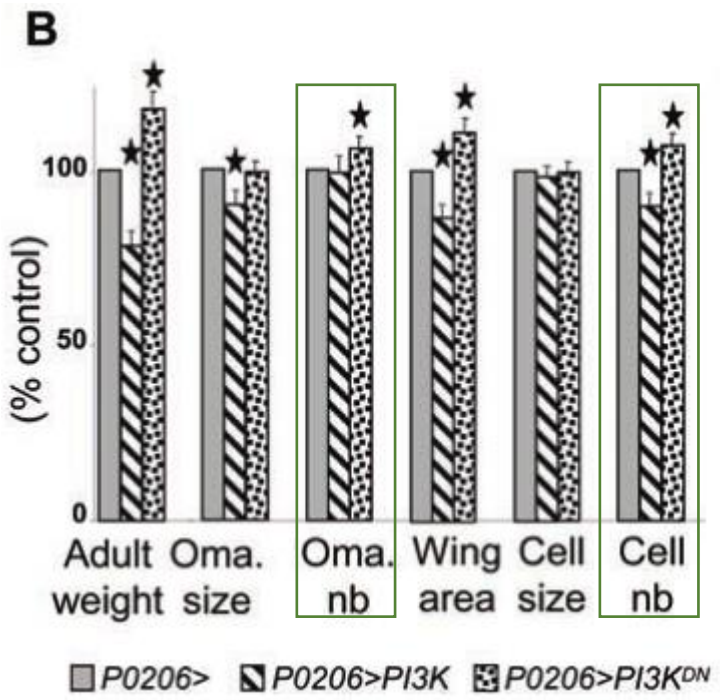
- Ecdysone（E）： a steroid hormone that stimulates molting and metamorphosis.
- 20- hydroxyecdysone（20E）： active form of E， which is the main ecdysone.
- Transduce the 20E signal is a l o nuclearreceptors, EcR and Ultraspiracle (USP) .

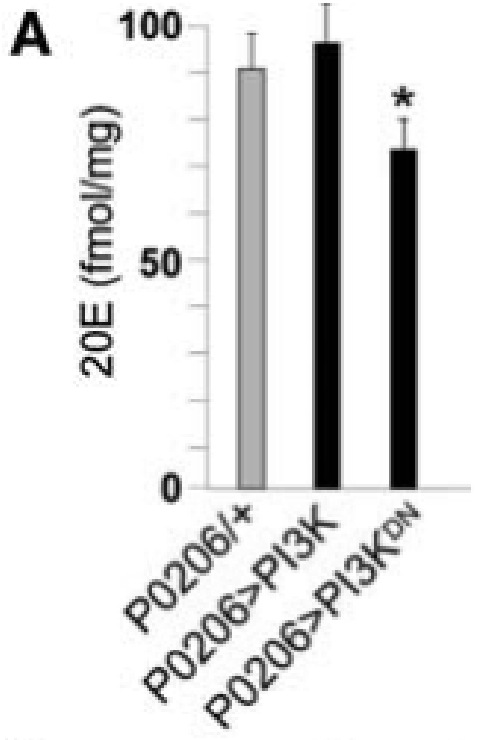


Naoki Yamanaka et al., 2013, PMC

High levels of 20E cause the flies to become smaller







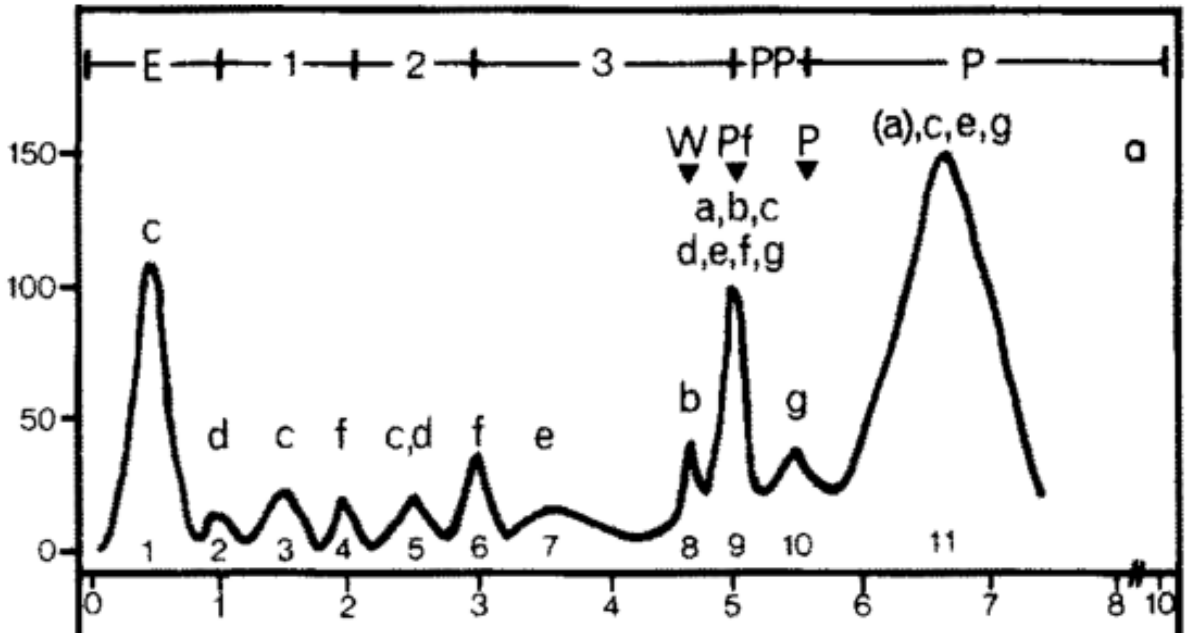
90hAED

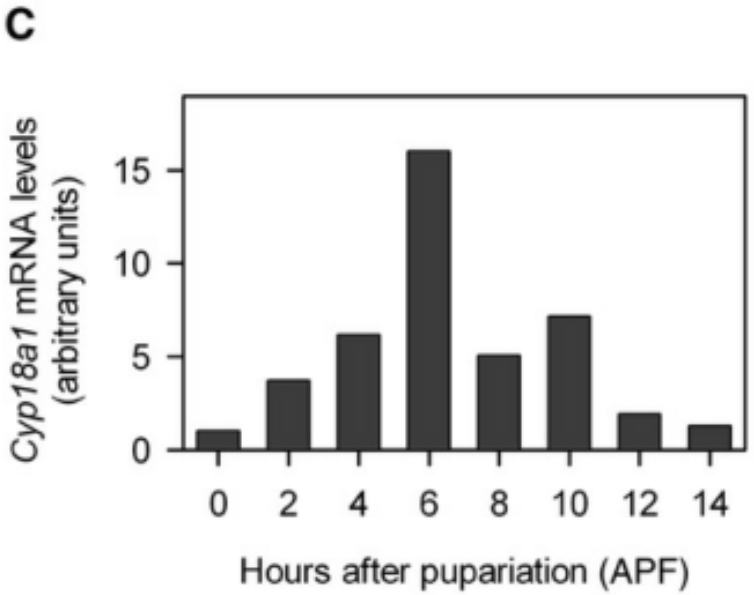
Julien Colombani et al., 2005, Science

Conclusion

1.In fruit fly larvae, the levels of 20E can control the size of flies.

Cyp18a1-Mediated Inactivation of 20E Is Required for Metamorphic Development





RT-PCR

Rewitz KF et al., 2010, Dev. Cell

Conclusion

1.In fruit fly larvae, high levels of 20E cause the flies to become smaller, meaning early emergence.

2.Cyp18a1-Mediated Inactivation of 20E Is Required for Metamorphic Development.

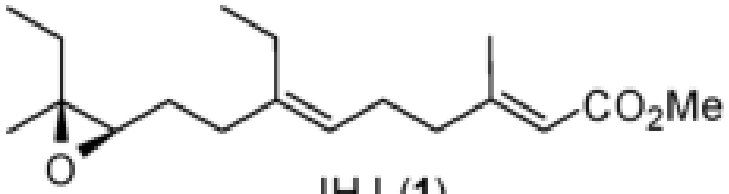
Contents

1. Prothoracicotropic Hormone(PTTH)

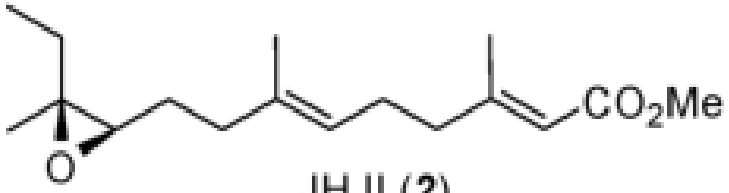
2. Ecdysteroid(20E)

3.Juvenile Hormone(JH)

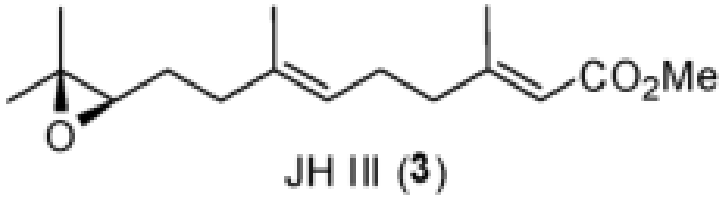
The type of juvenile hormones



JH I (**1**)



JH II (**2**)

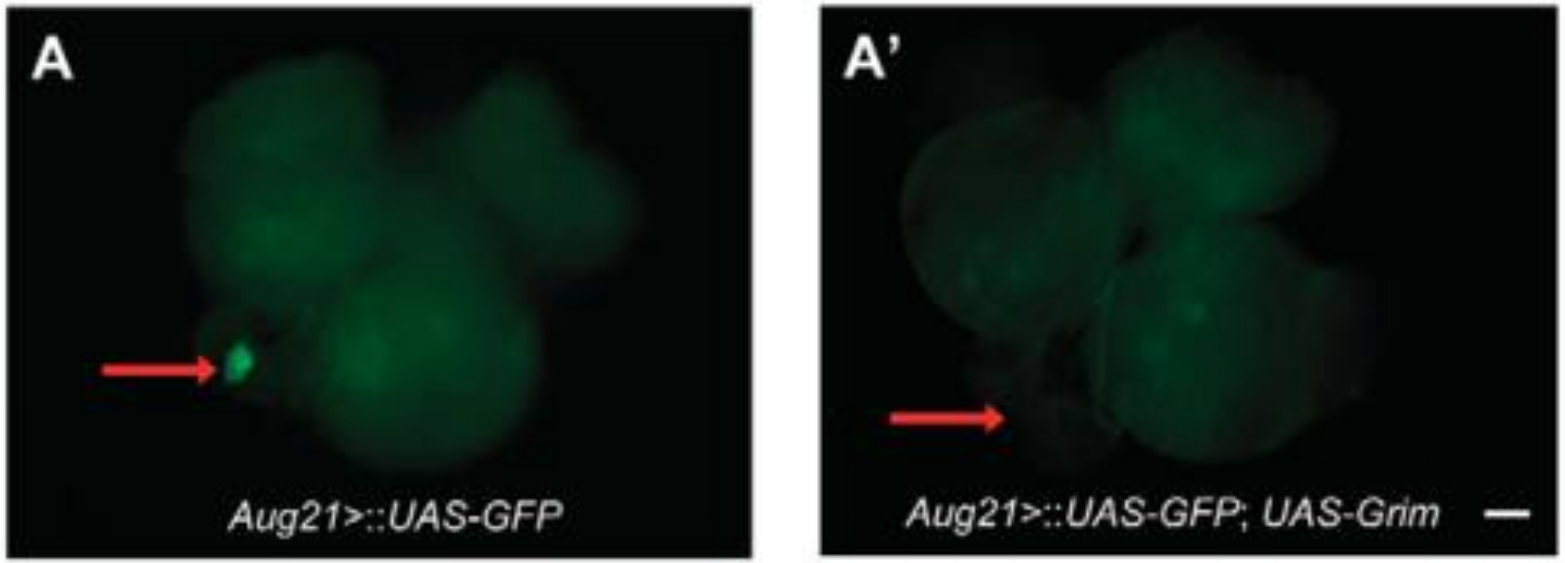


JH III (**3**)

JHB_3 (**6**)

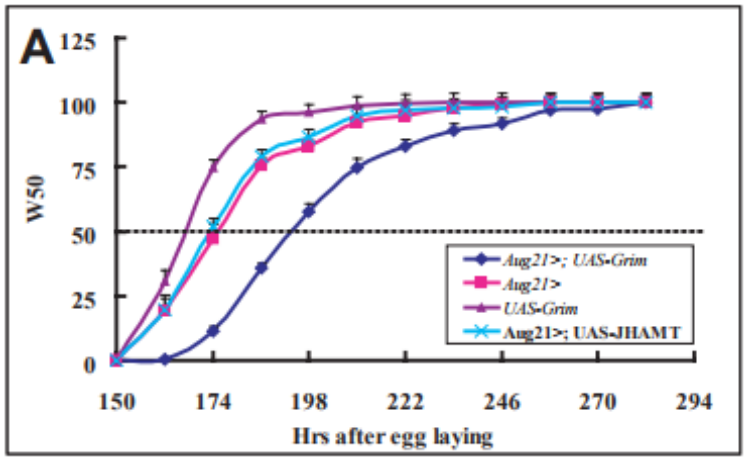
Toyomi Kotaki et al.， 2009， Organic Letters

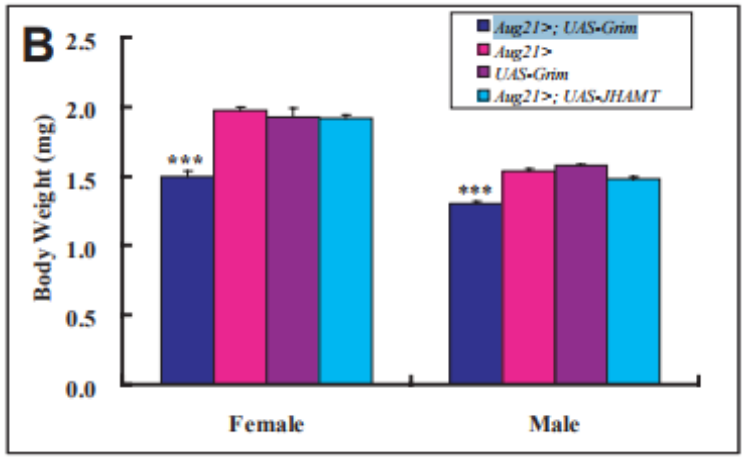
Ablation of the corpus allatum results in JH deficiency leading to pupal lethality

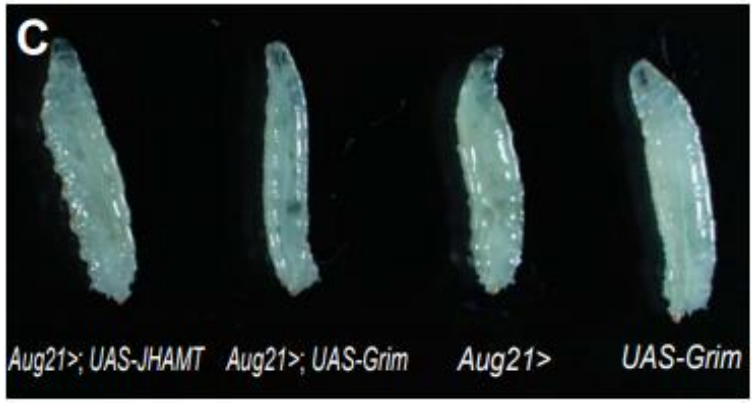


Liu Y et al.，2009，Development

Ablation of the corpus allatum results in JH deficiency leading to pupal lethality

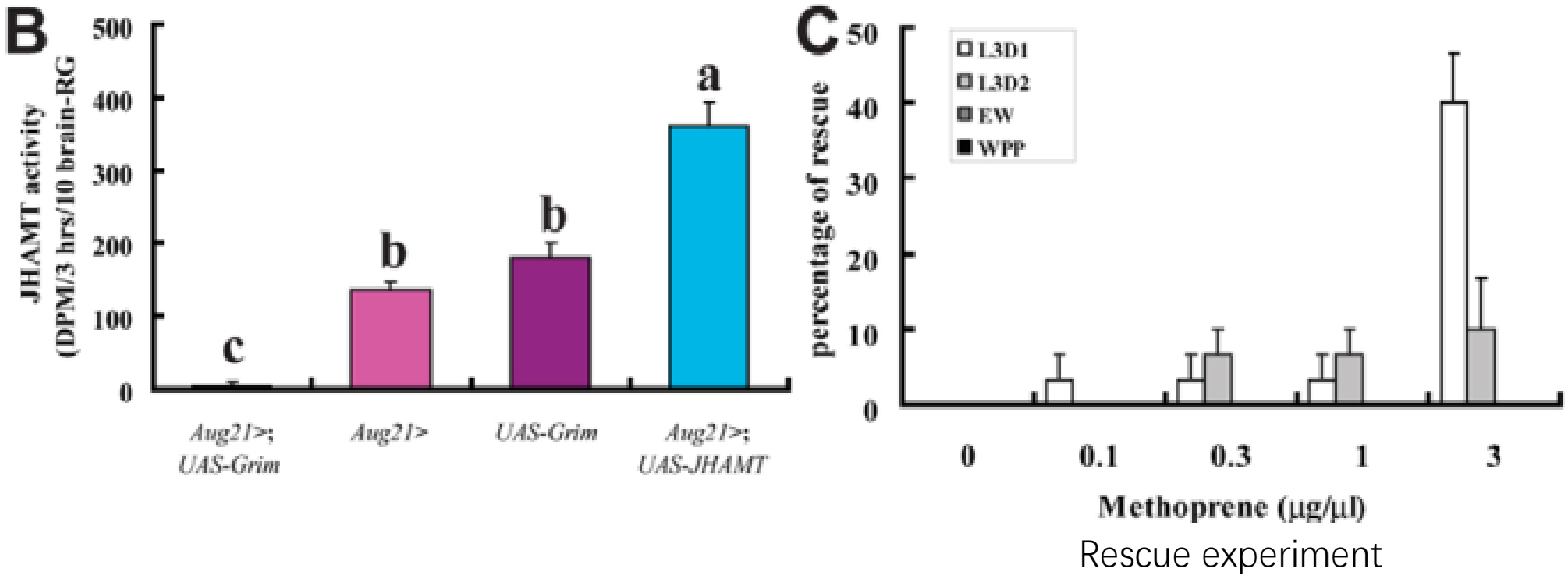






Liu Y et al., 2009, Development

Ablation of the corpus allatum results in JH deficiency leading to pupal lethality



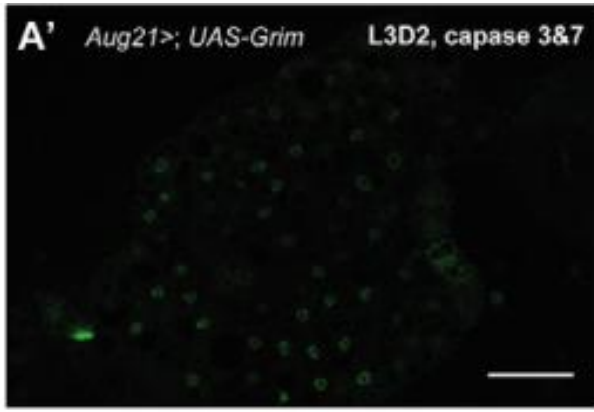
Rescue experiment

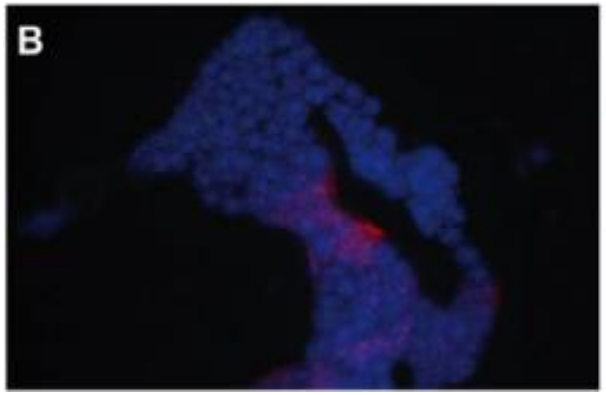
Liu Y et al., 2009, Development

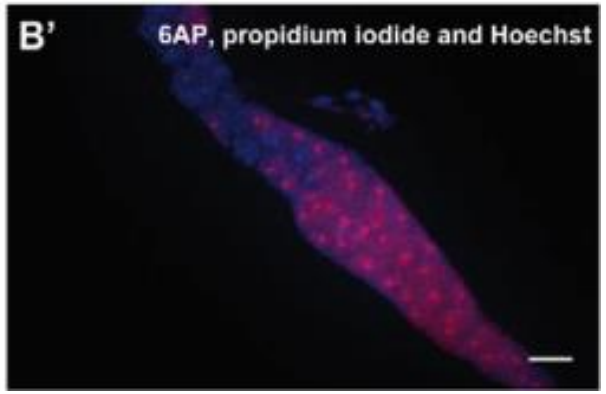
Conclusion

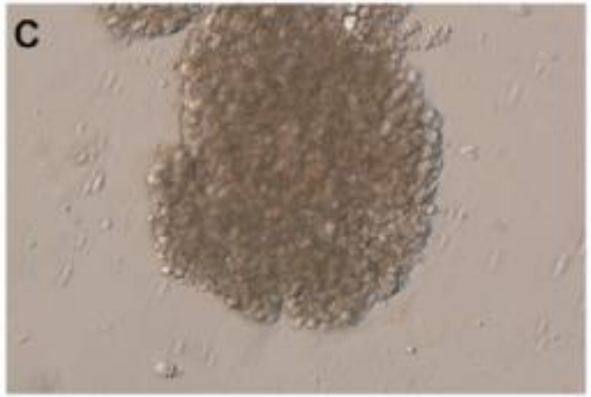
1.CA ablation leads to JH deficiency leading to death in pupae.

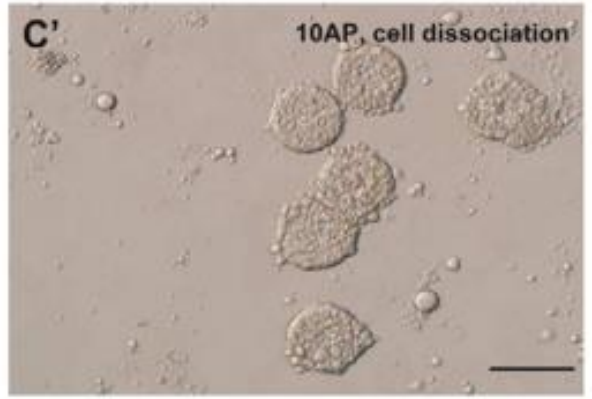
JH prevents PCD during fat body remodeling











Liu Y et al., 2009, Development

Conclusion

1. CA ablation leads to JH deficiency leading to death in pupae.
2. JH plays a crucial role in the control of fat body remodeling in Drosophila by preventing PCD.

Thanks!

PART 3:

Juvenile and Ecdysteroid: the Reproduction Related

Juvenile and Ecdysteroid :

the Reproduction Related

Zhu Huan

4 29 2021

KEY WORDS :

Juvenile/Ecdysteroid + courtship/oviposition/reproduction/mated + drosophila

“Reproduction is energy costly.
Mothers need energy balance to
maximize their reproductive success.”

But how do they realize the function?
What changes occurred during production?

1 Female **Midgut Remodeling**

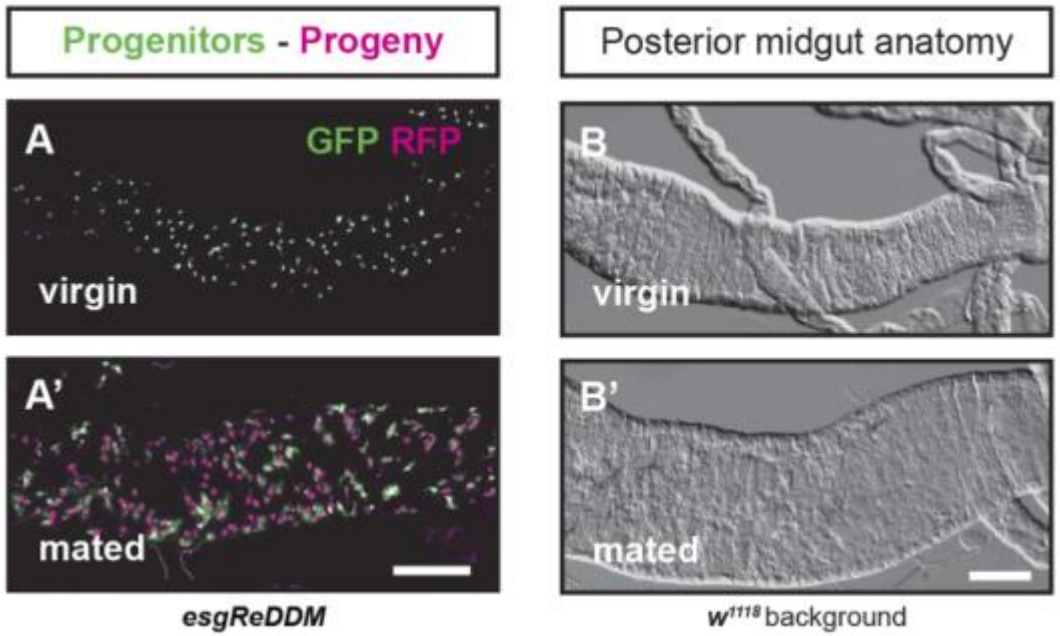
eLIFE
elifesciences.org

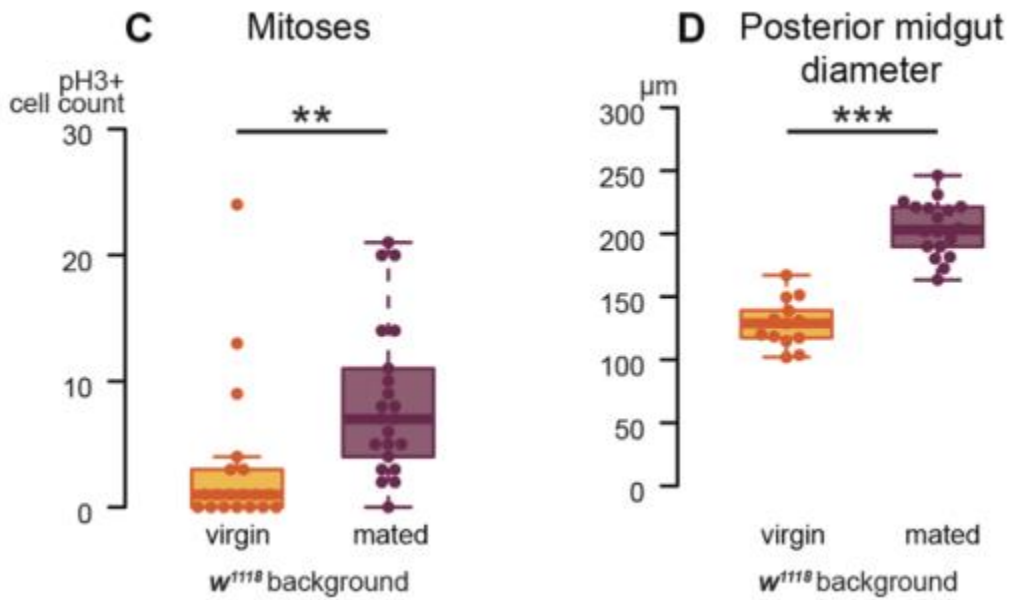
RESEARCH ARTICLE

Endocrine remodelling of the adult intestine sustains reproduction in *Drosophila*

Tobias Reiff[1†], Jake Jacobson[2†], Paola Cognigni[2†‡], Zeus Antonello[1†], Esther Ballesta[1], Kah Junn Tan[3], Joanne Y Yew[3,4§], Maria Dominguez[1*], Irene Miguel-Aliaga[2*]

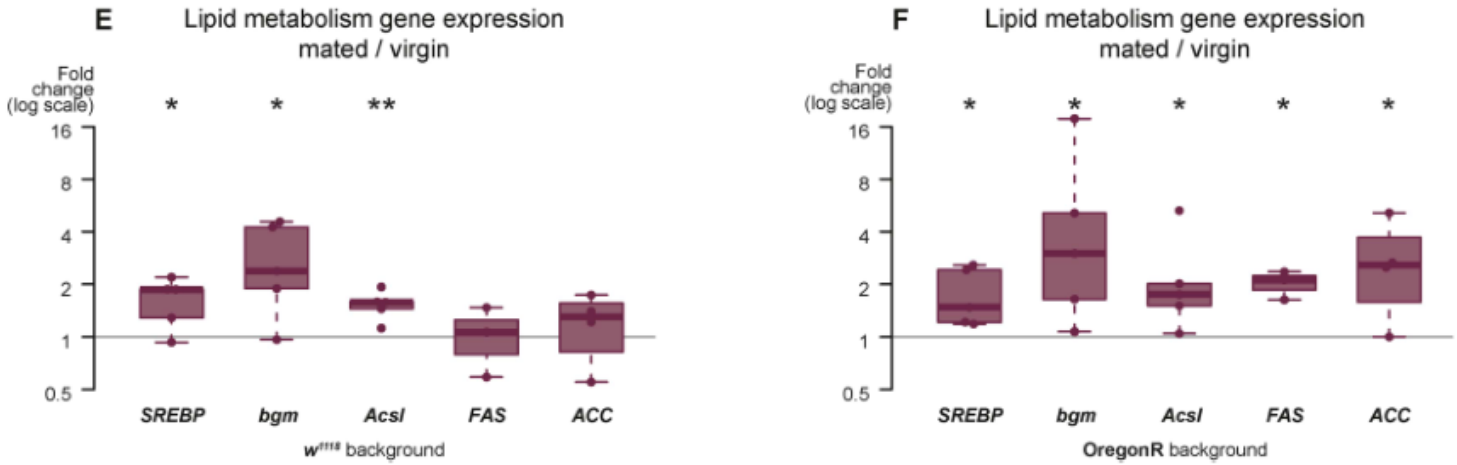
Mated females do have stronger midgut

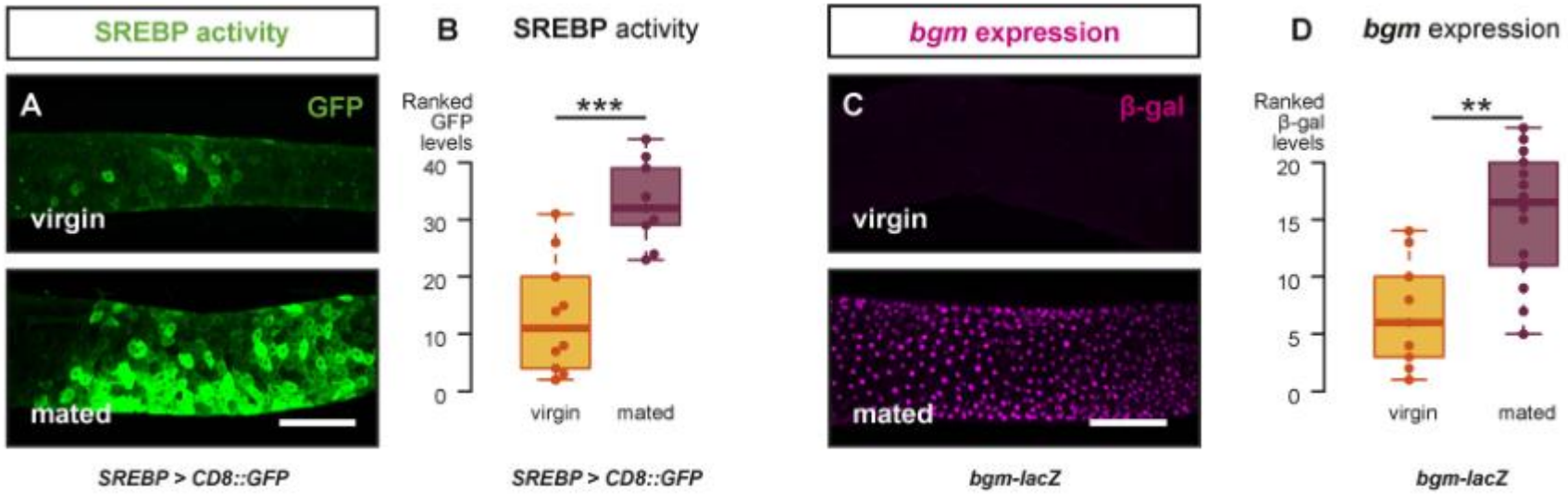




(Tobias Reiff, *et al* , 2015)

Expression of SREBP *bgm Acsl* are upregulated after mating

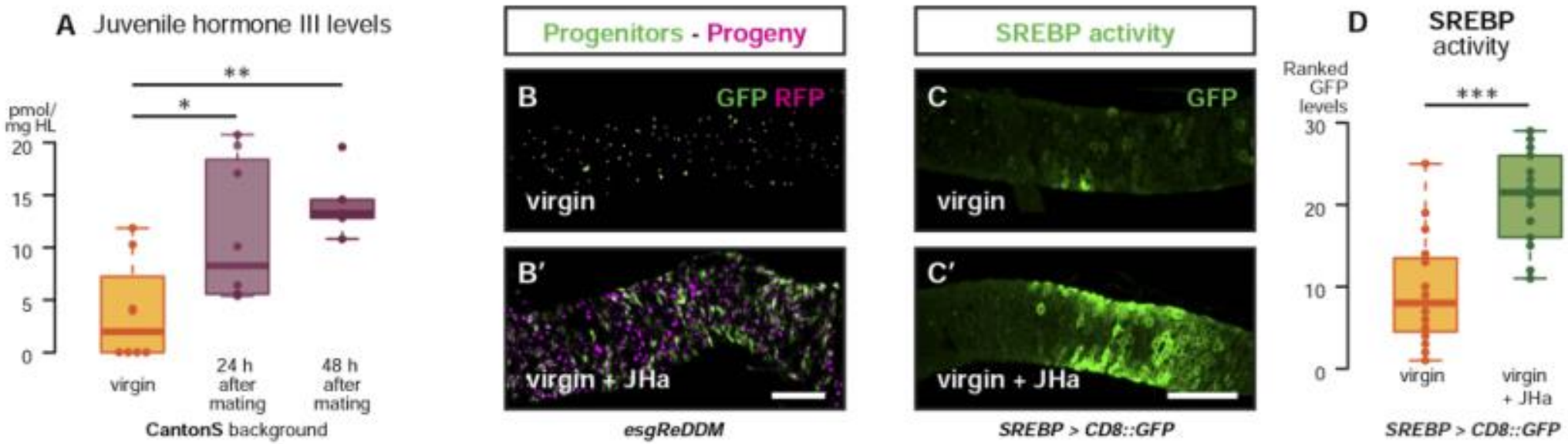




(Tobias Reiff, *et al* , 2015)

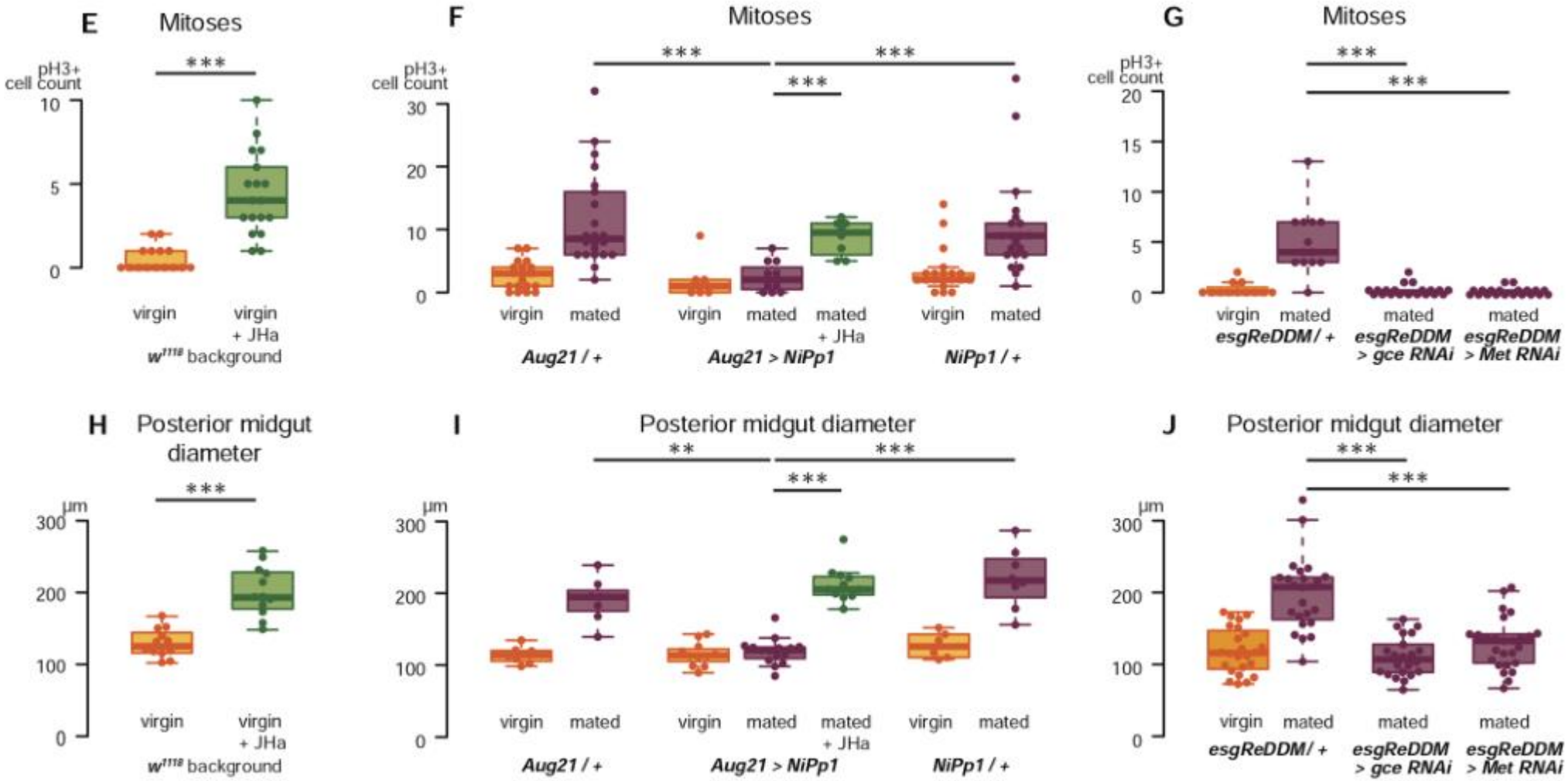
Female **Midgut Remodeling**

By rapid direct analysis in real time (DART) mass spectrometry, haemolymph of both virgin and mated female flies and established that the levels of in vivo circulating are profiled



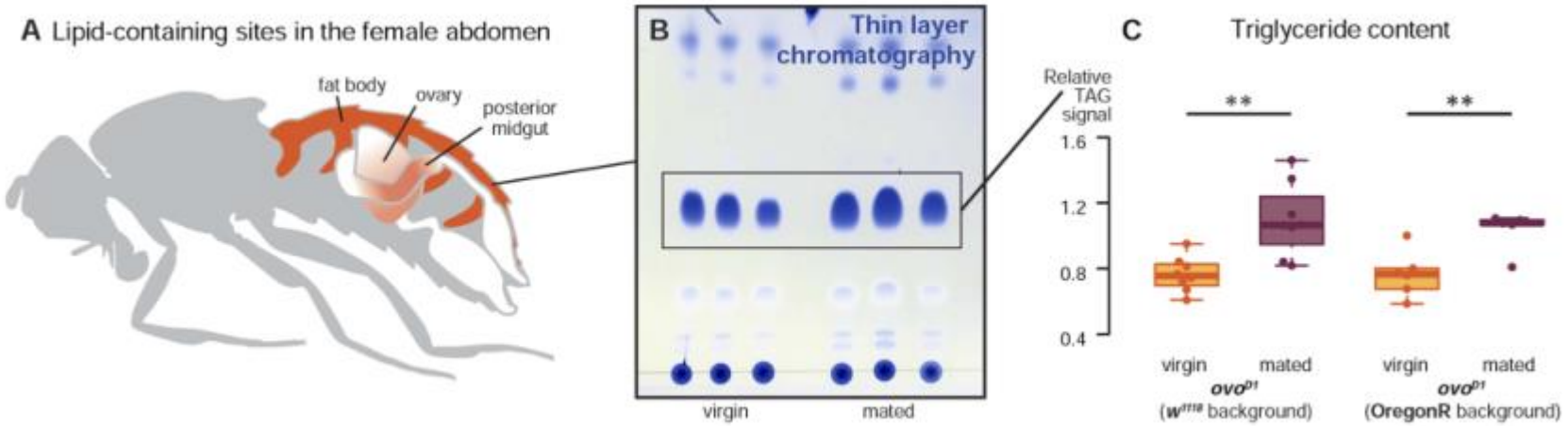
(Tobias Reiff, *et al* , 2015)

After JH blocking, mating-triggered remodeling is prevented



(Tobias Reiff, *et al* , 2015)

Triglyceride content increases after mating



(Tobias Reiff, *et al* , 2015)

“The more fertile individuals always
get a higher degree of mating activity.
Younger males sire less offspring than
older ones, also they are apparently
less inclined to court females
compared to older males.”

HOW DO they ACHIEVE it?

2 **Mating Advantage** of older male

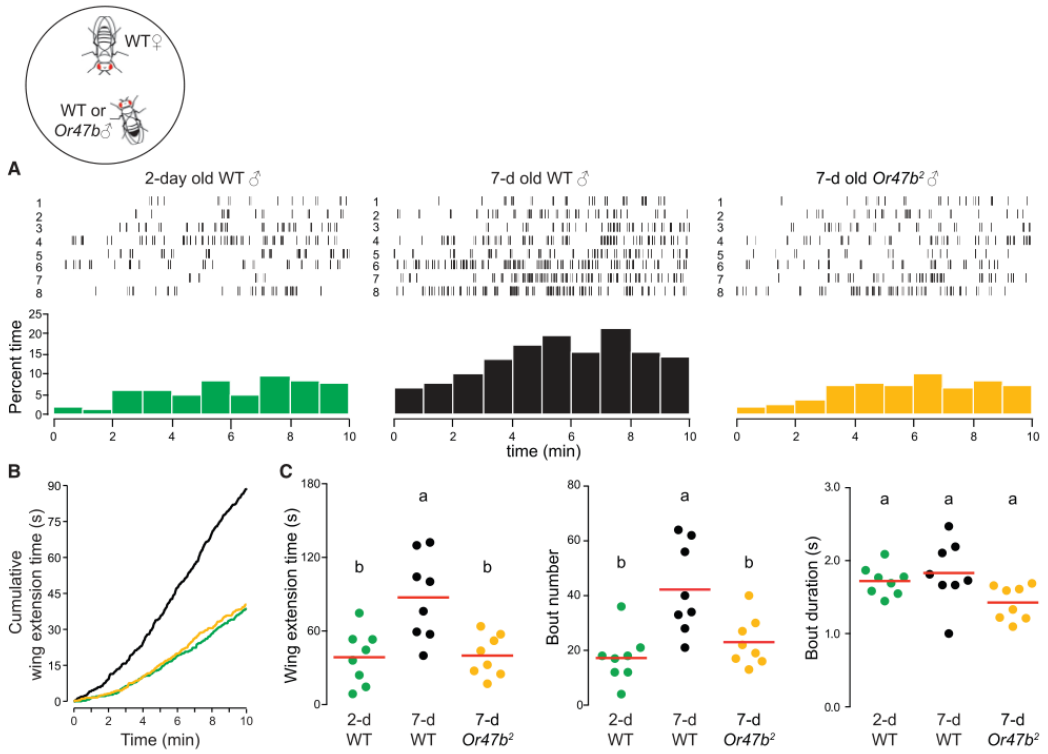
Neuron
Article

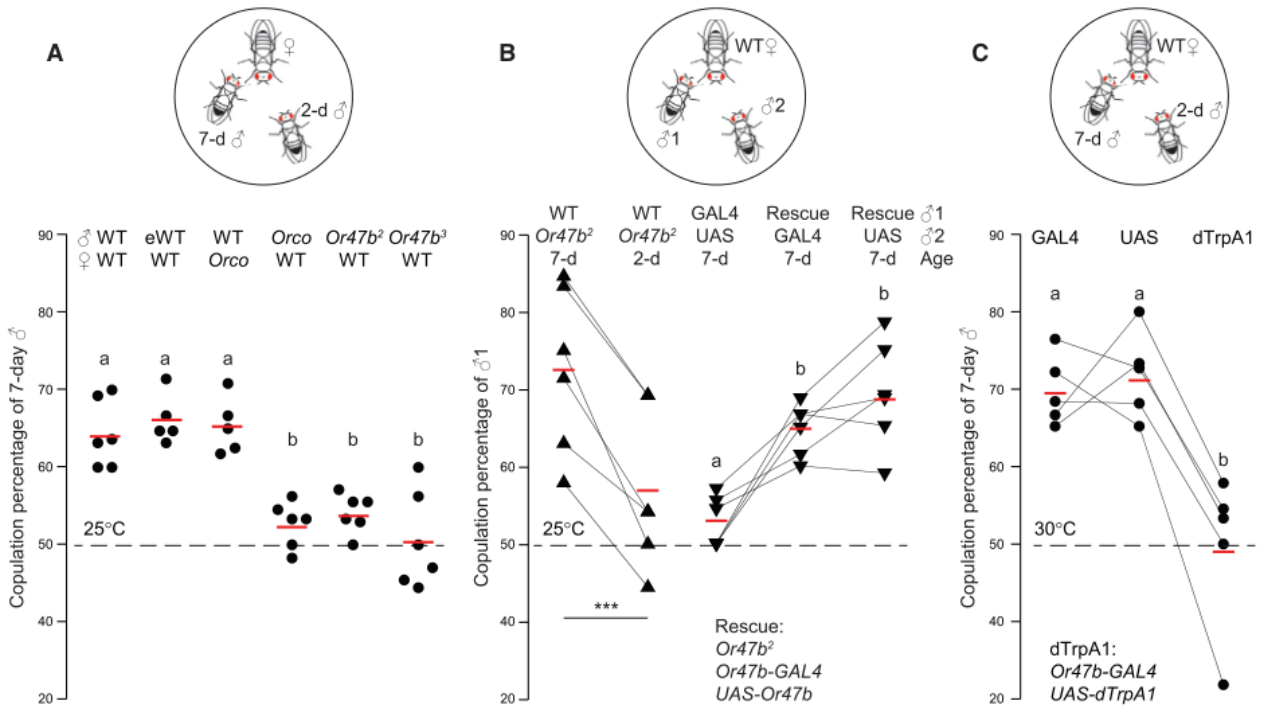
Hormonal Modulation of Pheromone Detection Enhances Male Courtship Success

Hui-Hao Lin,[1,5] De-Shou Cao,[1,5] Sachin Sethi,[1] Zheng Zeng,[1] Jacqueline S.R. Chin,[2,3] Tuhin Subhra Chakraborty,[1] Andrew K. Shepherd,[1] Christine A. Nguyen,[1] Joanne Y. Yew,[4] Chih-Ying Su,[1,*] and Jing W. Wang[1,*]
[1]Neurobiology Section, Division of Biological Sciences, University of California, San Diego, La Jolla, CA 92093, USA
[2]Temasek Life Sciences Laboratory, 1 Research Link, Singapore 117604, Singapore
[3]Department of Biological Sciences, National University of Singapore, 14 Science Drive 4, Singapore 117543, Singapore
[4]Pacific Biosciences Research Center, University of Hawai'i at Mānoa, 1993 East-West Road, Honolulu, HI 96822, USA
[5]Co-first author
*Correspondence: c8su@ucsd.edu (C.-Y.S.), jw800@ucsd.edu (J.W.W.)
http://dx.doi.org/10.1016/j.neuron.2016.05.004

2 **Mating Advantage** of older male

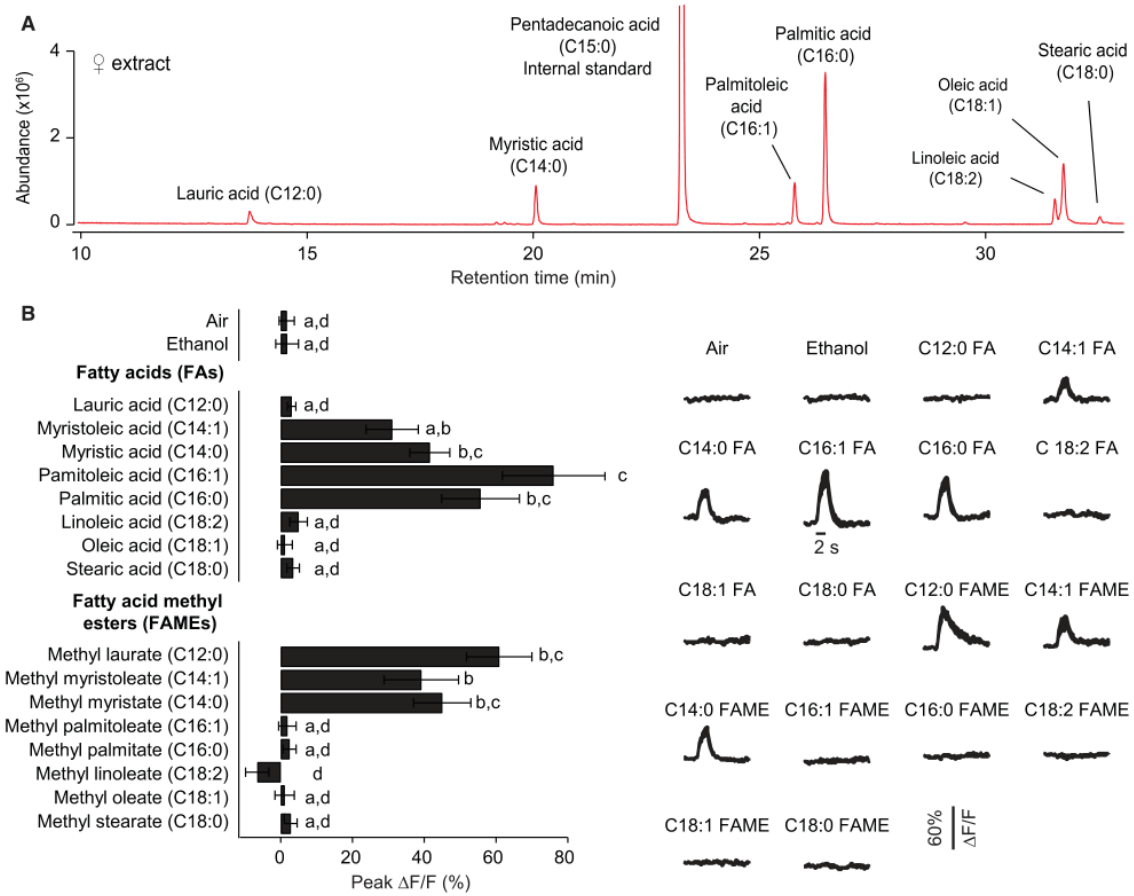
Older males have higher mating intensity,
and Or47b is required for copulation advantage of older males

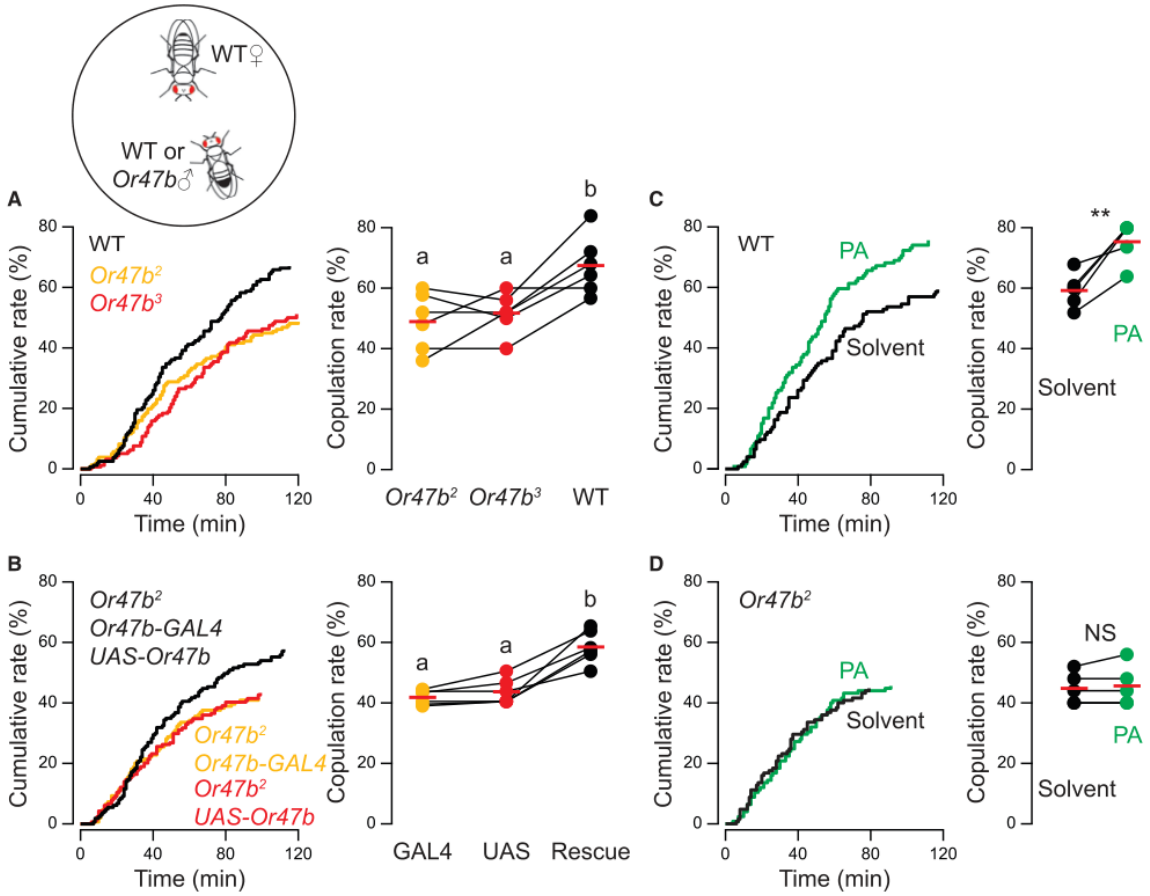




(Lin ,*et al* ,2016)

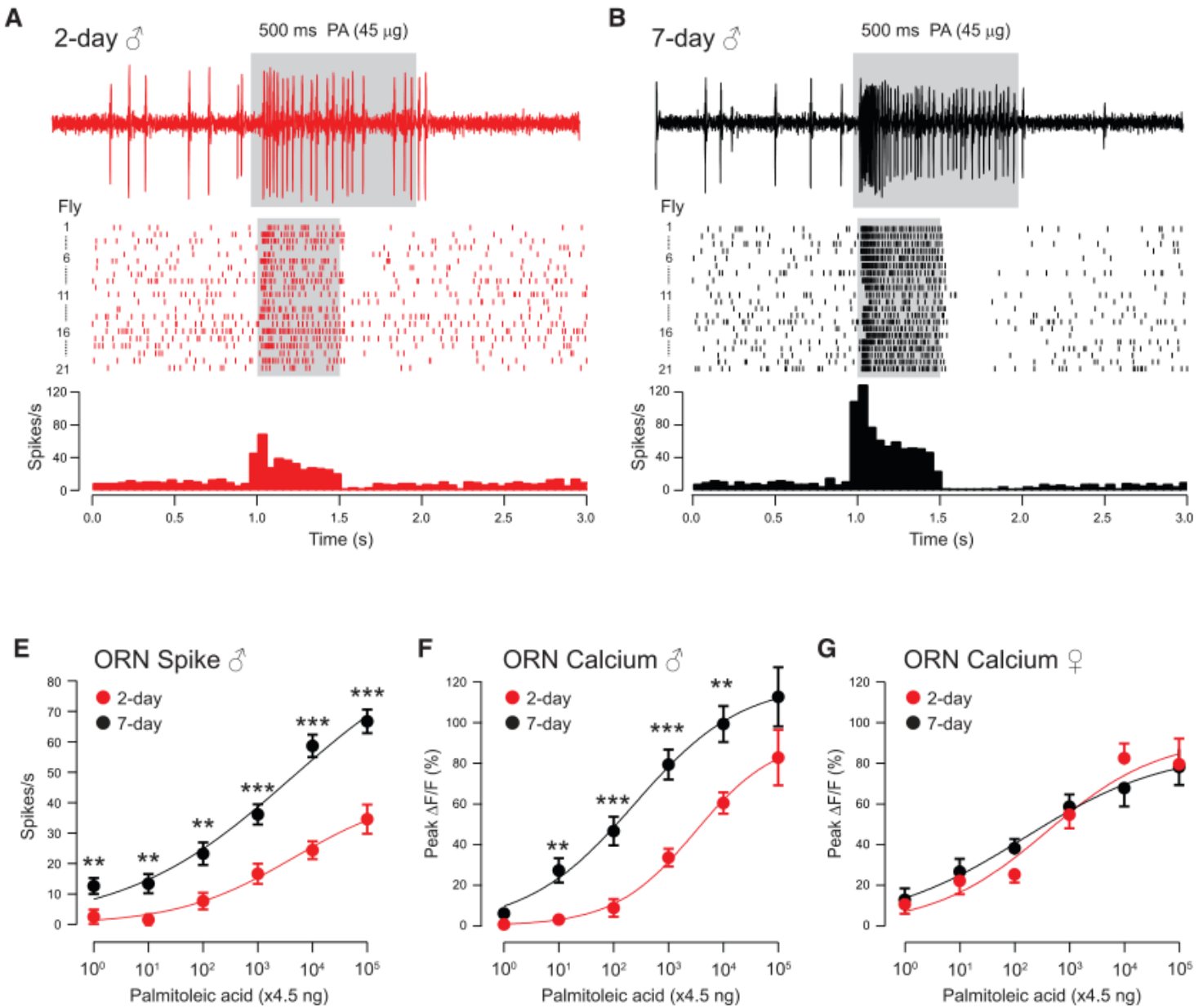
Or47b Neurons Respond to Multiple Cuticular Compounds And palmitoleic acid is the Stimulatory Pheromone that Promotes Male Courtship





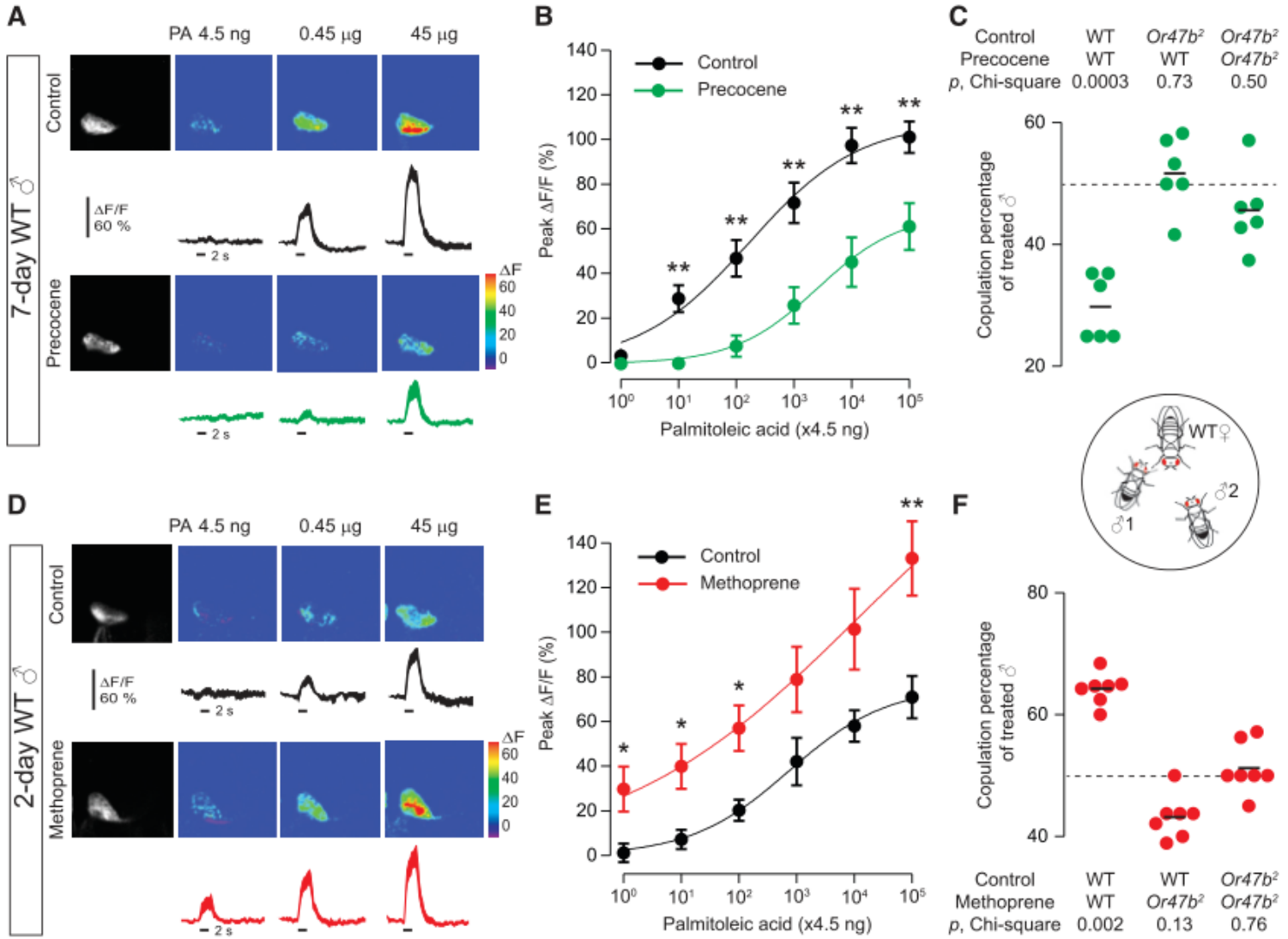
(Lin ,*et al* ,2016)

Sensitivity of Male Or47b ORNs Increases with Age



(Lin ,*et al* ,2016)

The juvenile pathway affecting compounds, Precocene and Methoprene treated males show sensitivity changing to palmitoleic acid



(Lin ,*et al* ,2016)

“FRUM and EcR isoforms are coexpressed in neurons in the CNS during metamorphosis in an isoform-specificmanner.”

3 Deficiency **elevates male-male courtship**

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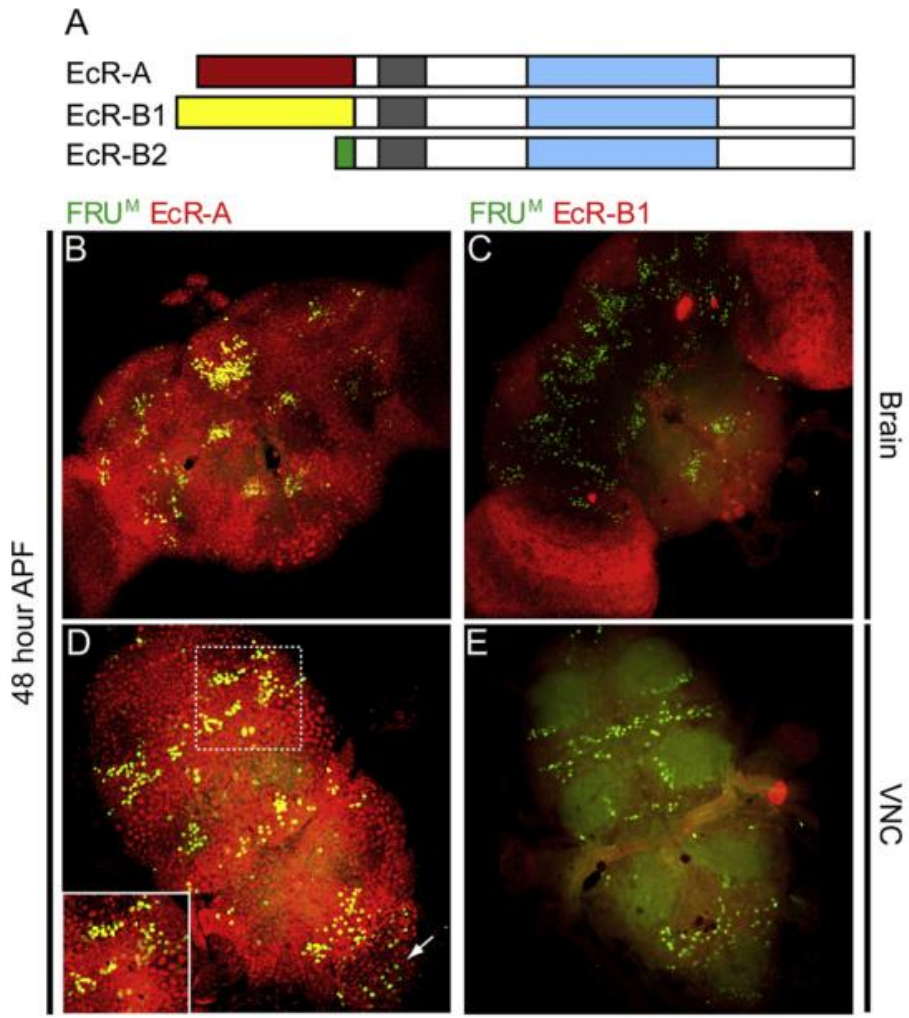
Current Biology *19*, 1447–1452, September 15, 2009 DOI 10.1016/j.cub.2009.06.063

Report

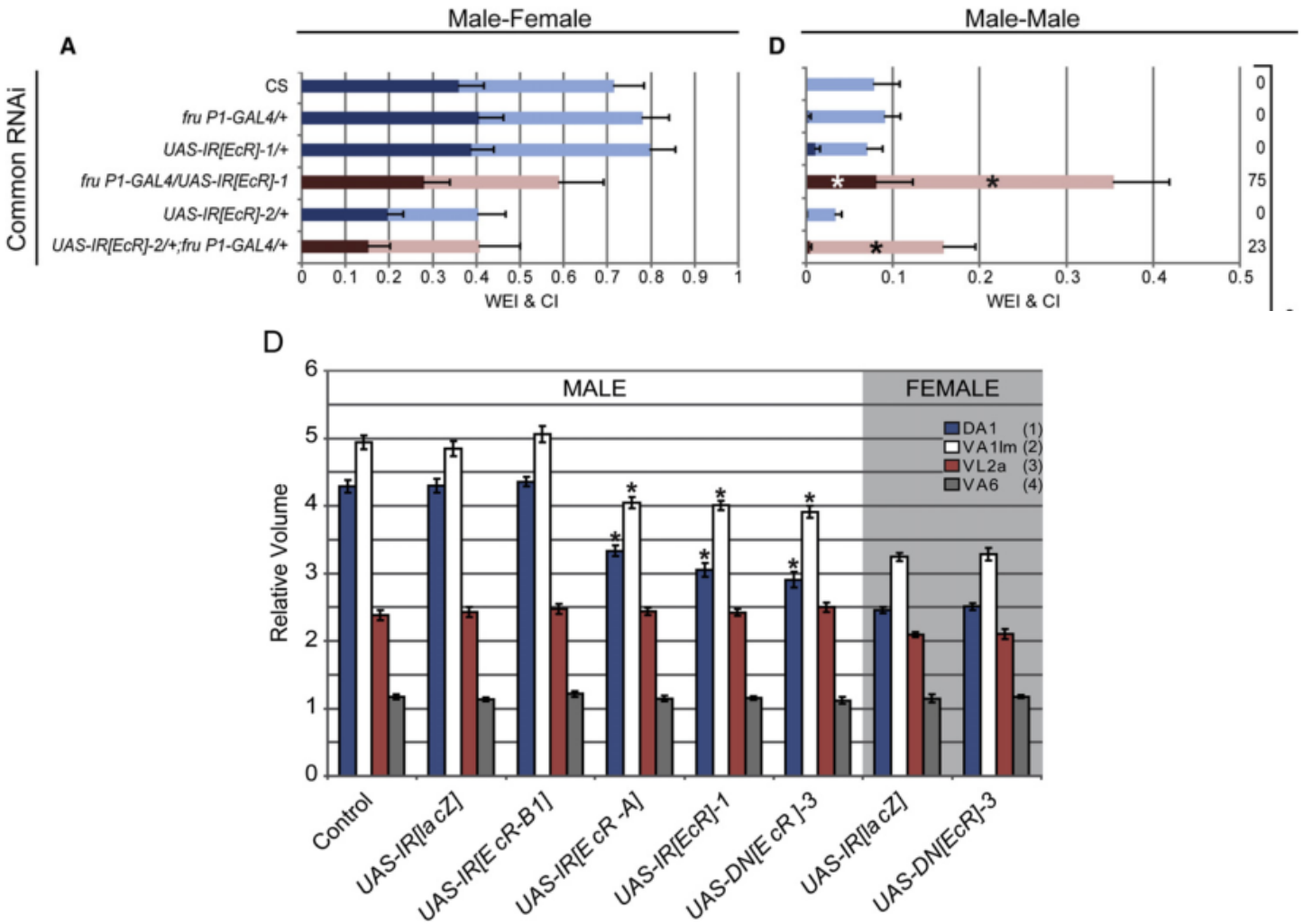
Ecdysone Receptor Acts in *fruitless*-Expressing Neurons to Mediate *Drosophila* Courtship Behaviors

EcR Isoforms Have Different Spatial, Temporal, and FRUM co-expression Patterns



(Justin ,*et al* ,2009)

Male with EcR1 knock down displays high levels of male-male courtship behavior and has lower volume of 2 fru P1-innervated glomeruli



(Justin ,*et al* ,2009)

“Recent work in Drosophila has demonstrated some striking similarities between Drosophila and mammalian ovulation. For example, like mammals, mature oocytes in Drosophila are wrapped in a layer of somatic follicle cells. It’s known that oviposition in mammal is coordinated by steroids.”

Will oviposition in drosophila also mediated by steroids?

4 Important for **follicle maturation**

4 Important for
follicle maturation

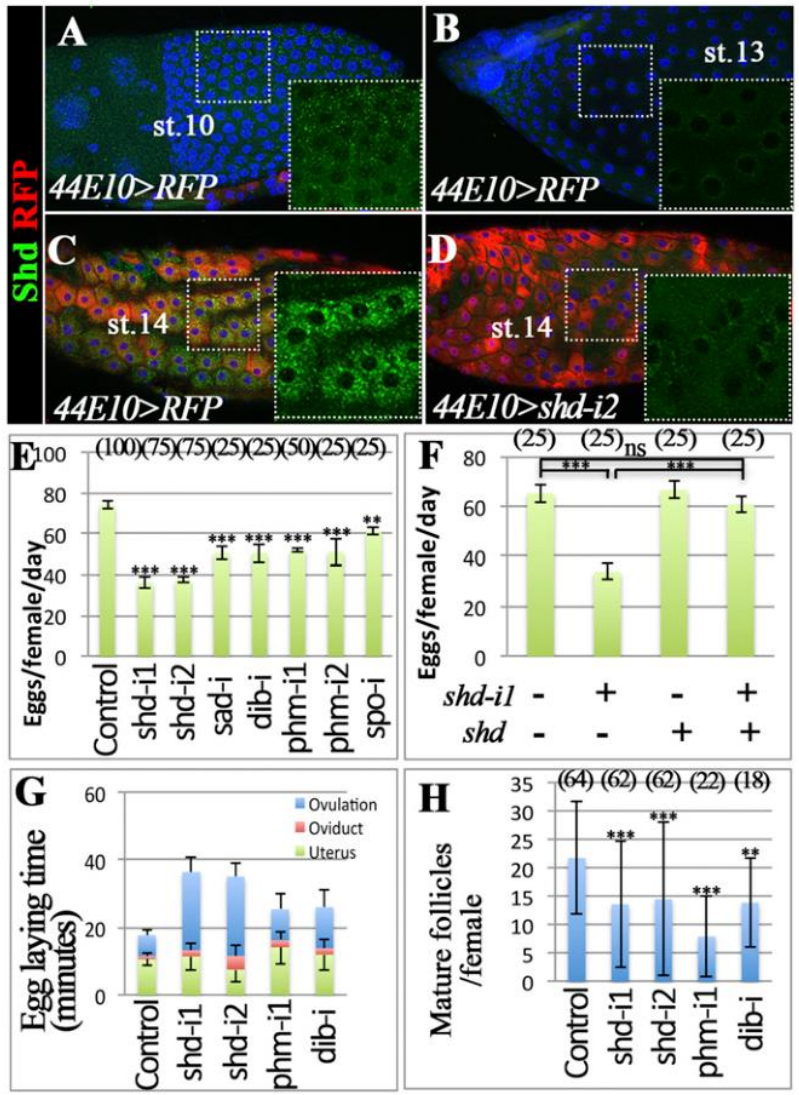
Steroid signaling in mature follicles is important for *Drosophila* ovulation

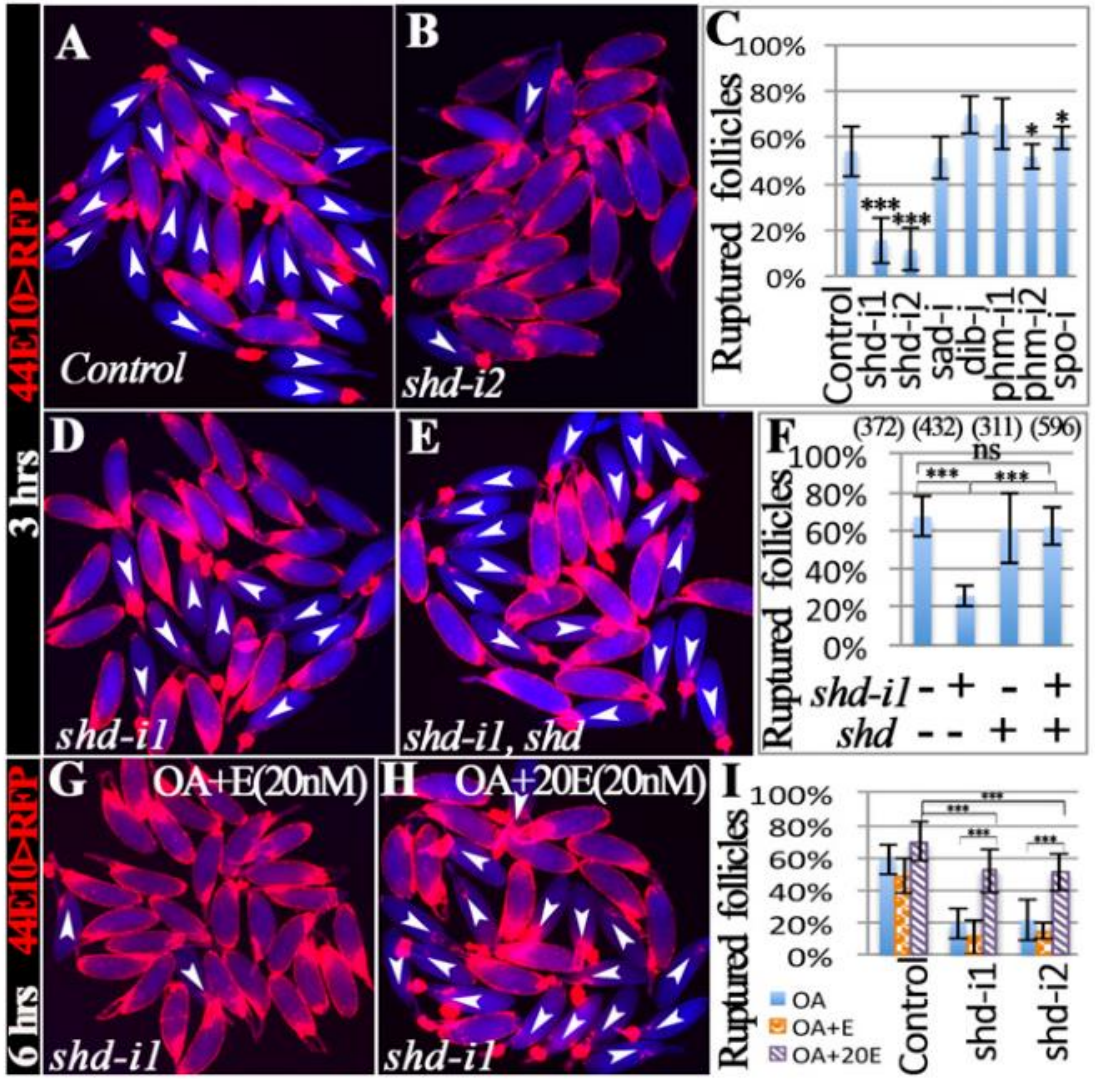
Elizabeth Knapp[a] and Jianjun Sun[a,b,1]

[a]Department of Physiology & Neurobiology, University of Connecticut, Storrs, CT 06269; and [b]Institute for Systems Genomics, University of Connecticut, Storrs, CT 06269

Edited by John J. Eppig, The Jackson Laboratory, Bar Harbor, ME, and approved December 19, 2016 (received for review August 29, 2016)

Shade, a role in steroid signaling, is required in mature follicle cells for ovulation and synthesize 20E for follicle rupture.

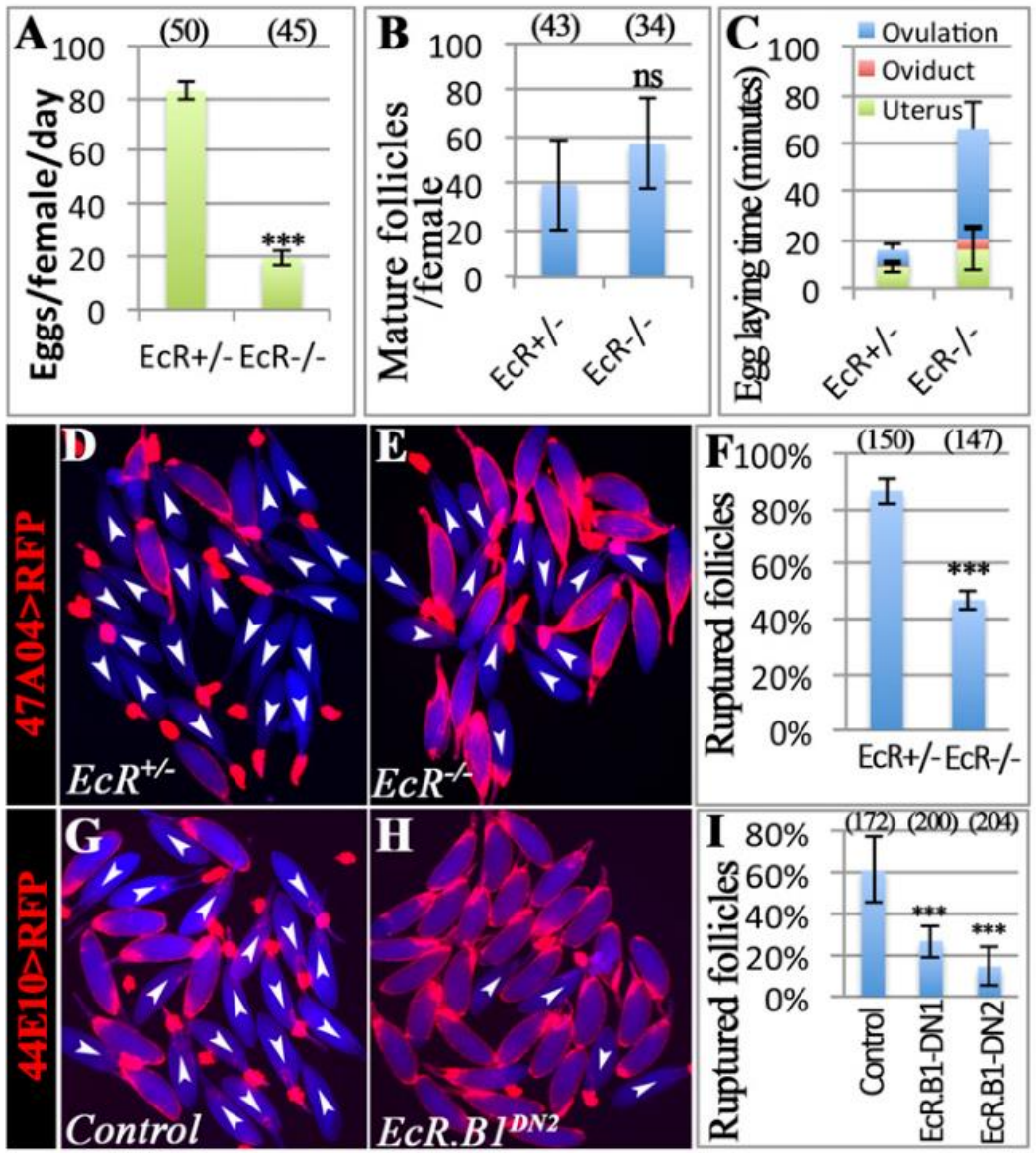


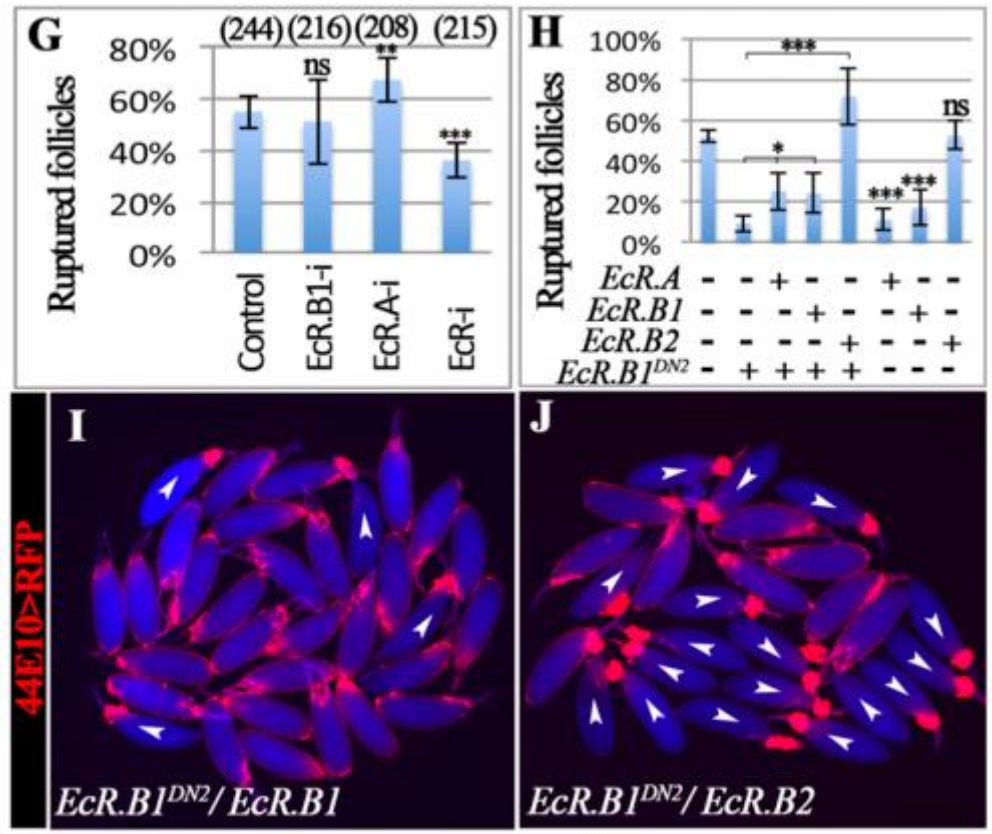


(Elizabeth ,*et al* ,2016)

4 Important for
follicle maturation

EcR and one of its translation product, EcR.B2, are required in mature follicle cells for ovulation.

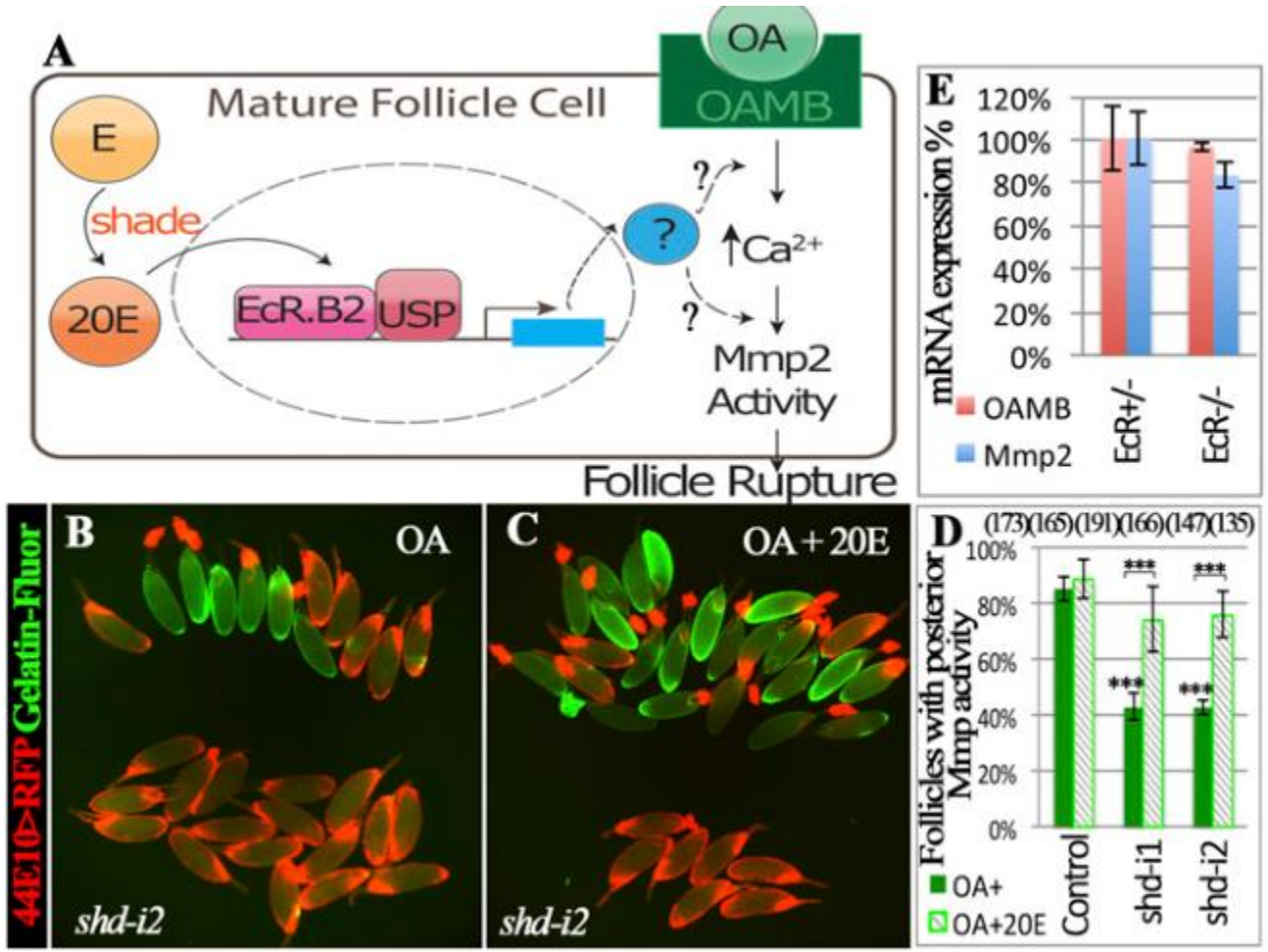




(Elizabeth ,*et al* ,2016)

4 Important for
follicle maturation

Ecdysteroid signaling regulates OA-induced Mmp2 activation



(Elizabeth ,*et al* ,2016)