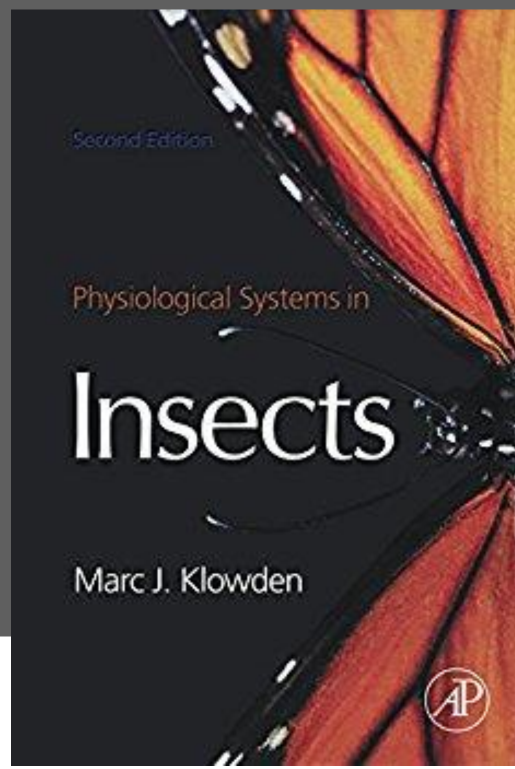
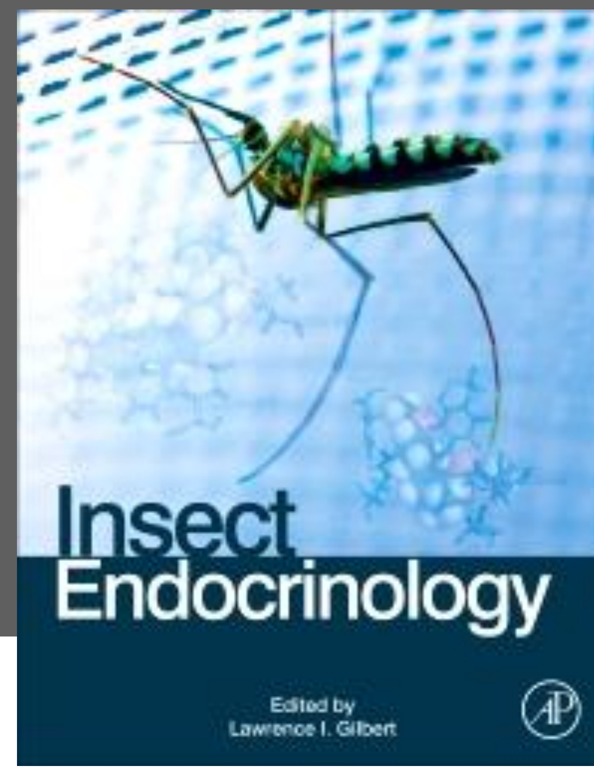
Invertebrate hormones

Physiological systems in insects:Marc J.Klowden.Secondedition, ISBN: 978-0-12-369493-5.
Insect Endocrinology:LawrenceI. Gilbert.First edition2012, ISBN: 978-0-12-384749-2.





Hormones of invertebrates and vertebrates

The most developed endocrine system among invertebrates can be found in **crustaceans and insects**.

Differences:

- unlike vertebrates, invertebrates have many neurohormones
- invertebrates produce few classical hormones

Similarities:

- both groups synthesize many peptide hormones
- the same structural types of hormones
- similar hormones can have similar function (**hormones can also affect individuals in another animal group**)

Groups of invertebrate hormones

Nerves - neurotransmitters
Neurosecretory cells - neurohormones
Endocrine glands - clasical hormones

1) **Steroid hormones** (ecdysteroids - ecdysone, 20-hydroxyecdysone, makisteron A etc.)

2) **Sesquiterpenes / terpenoids** (juvenile hormones)

3) **Peptide hormones** (MIH, RPCH, AKH)

4) **Biogenic amines** (octopamine, tyramine, serotonin)

5) **Eicosanoids** (prostaglandins and others)

Modulation of activity: synthesis, secretion, degradation, number and specificity of receptors

Endocrine system of crustaceans

Endocrine system of crustaceans

1) Neurosecretory complex of the eye:

- **X-organ** (neurosecretory cells) > axonal transport > **sinus gland** (neurohemal) > hemolymph

2) Suboesophageal-postcommissural system:

- **suboesophageal ganglion** > axons > **postcommissural organ** (neurohemal) > hemolymph

3) Pericardial system:

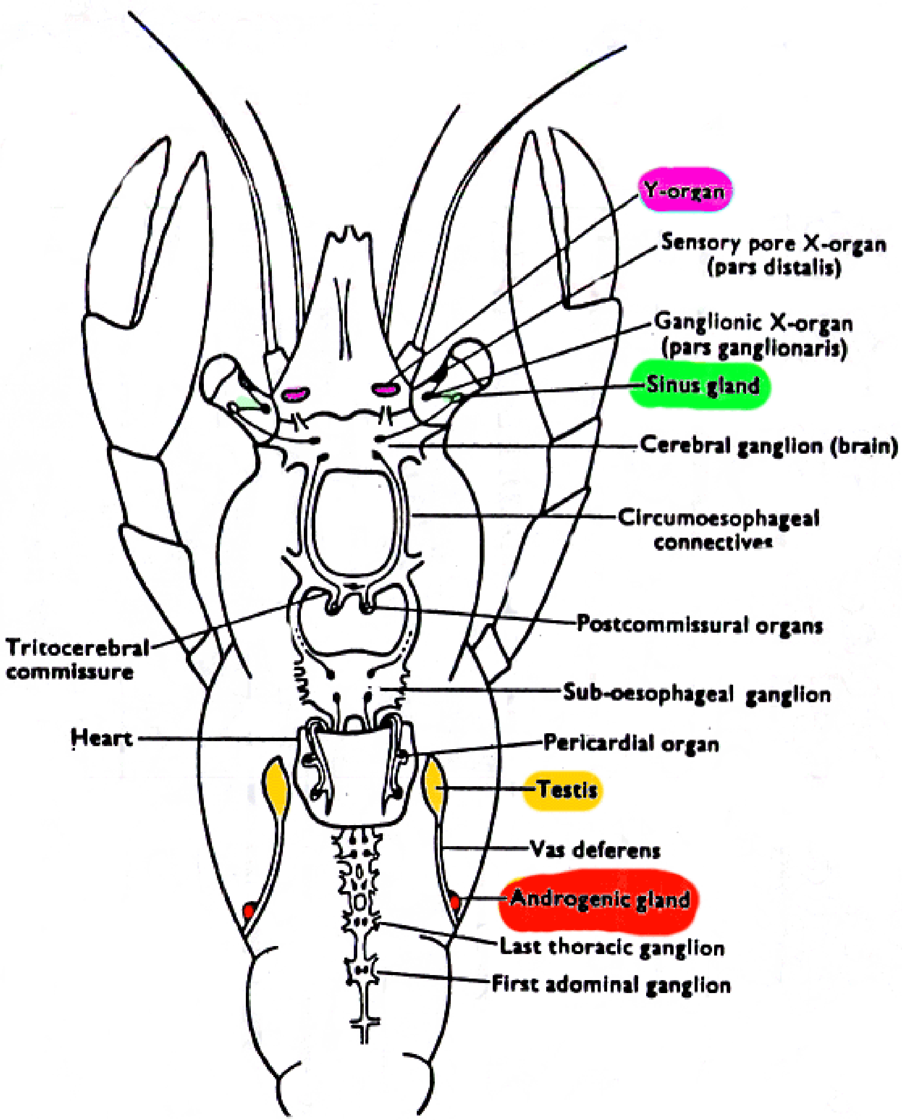
- pericardium > **pericardial organ** (neurohemal)

4) Paired Y-organ

- 20-hydroxyecdysone

5) Androgenic gland

- males



Endocrine system of crustaceans

- Y-organ: **20-hydroxyecdysone** (the same function as in insects)
- X-organ: **moult inhibiting hormone** (MIH) > inhibition of Y-organ
  androgen gland inhibiting hormone > inhibition of
spermatogenesis and development of male characteristics
- X-organ + postcommissural system: **chromatophorotropins** (e.g. red pigment-concentrating hormone belonging to RPCH/AKH family > pigment relocation in omatidia, ovarian maturation, vitellogenesis and other functions)

Endocrine system of insects

Endocrine system of insects

1) <u>Retrocerebral complex</u>

- neurosecretory brain cells, corpora cardiaca, corpora allata
- sometimes connected with prothoracic gland forming the so-called **ring gland** (Weismann‘s ring)
- monopolar neurons produce hormones in their bodies > association with proteins > axonal transport > formation of membrane-bound secretory granules > exocytosis (synaptoids) > release at the site of synthesis or in neurohemal organs

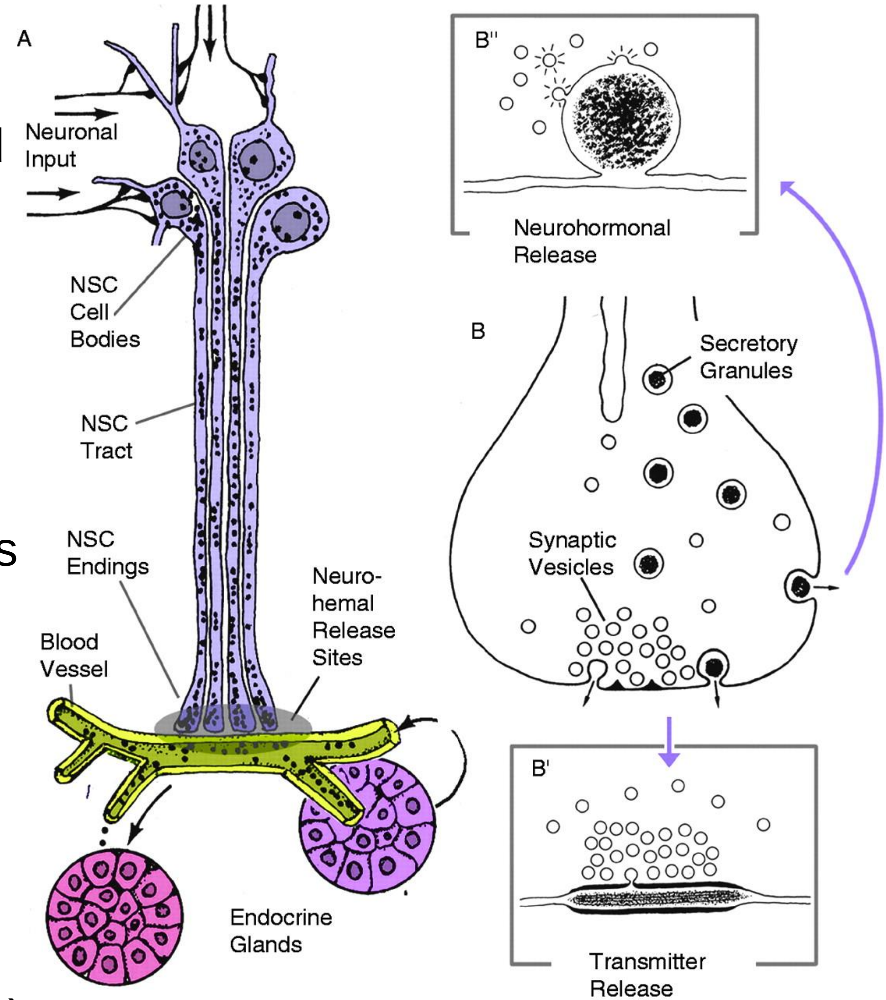
2) <u>Prothoracic gland (PG)</u>

- paired, located in prothorax and head
- **usually not in adult stages**

3) <u>Neurosecretory cells of other ganglia</u>

4) <u>Intestinal endocrine cells</u>

5) <u>Epitracheal cells</u> (ecdysis triggering hormone)



Endocrine system of insects
- brain dissection in *Galleria mellonella*

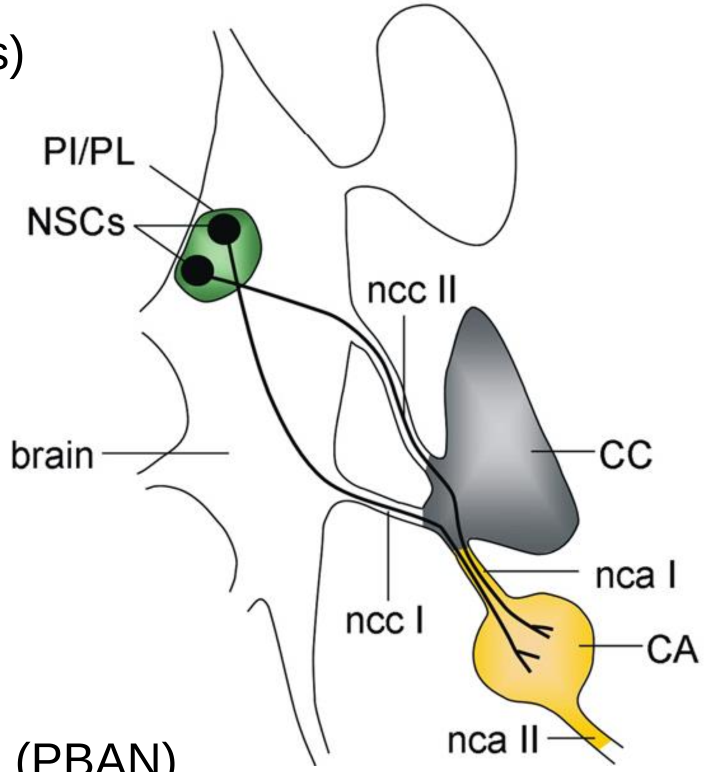
Endocrine system of insects

- brain dissection in *Galleria mellonella*

Insect neurohemal organs

Corpus cardiacum (corpora cardiaca)

- main neurohemal organ derived from ectoderm
- posteriorly from the brain, in the contact with dorsal vein
- axons of central (part intercerebralis) and lateral (variable location) neurosecretory cells in the brain
- storage lobe (storage of neurosecretory products)
- glandular lobe (synthesis of hormones)



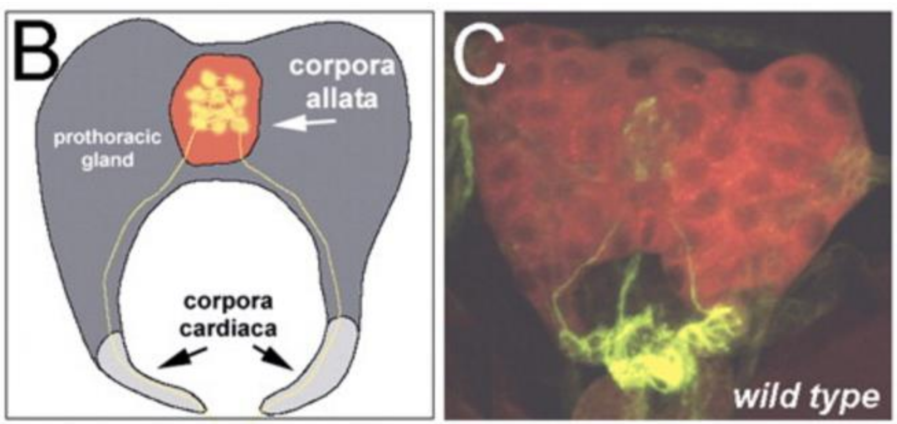
<u>Releases and synthesises:</u>

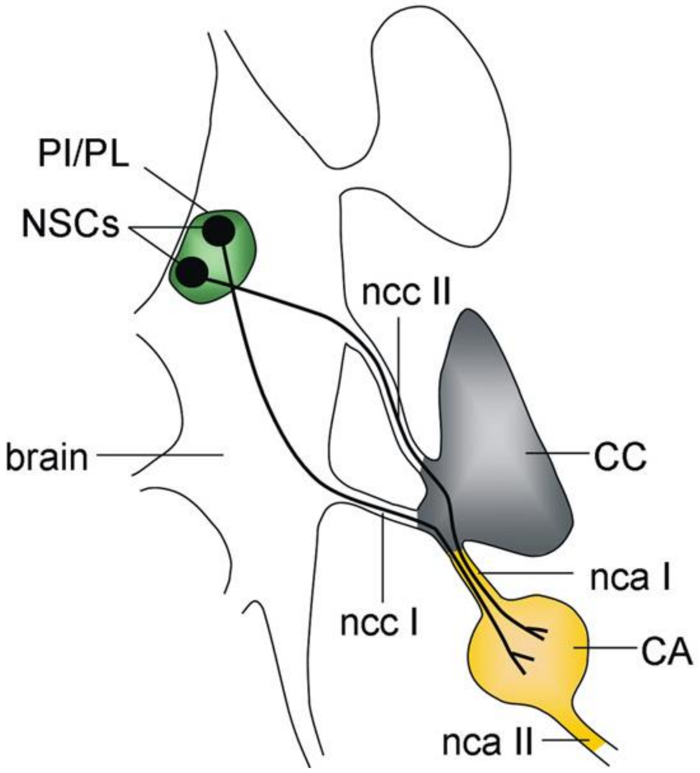
- prothoracicotropic hormone (PTTH)
- adipokinetic hormones (AKH)
- ovarian ecdysteroidogenic hormone
- neuroparsins
- myotropins
- pheromone biosynthesis activating neuropeptide (PBAN)

Insect neurohemal organs

Corpus allatum (corpora allata)

- posterior area of the head near the pharynx
- sometimes merges with prothoracic gland and forms **ring gland** (Diptera, Hemiptera)
- ectodermal origin
- cells with smooth endoplasmic reticulum (cholesterol, terpenoids)





<u>Synthesizes:</u>

- juvenile hormones (JH)

Insect endocrine system:
Summary of the main hormones

Steroids:

- ecdysteroids (prothoracic gland, gonads, epidermis)

Terpenoids:

- juvenile hormones (corpora allata)

Peptides and proteins:

- prothoracicotropic hormone (PTTH; brain)
- eclosion hormone (EH; brain)
- pre-ecdysis triggering hormone (PETH; Inka cells)
- ecdysis triggering hormone (ETH; Inka cells)
- bursikon (brain and ventral nerve cord)
- pheromone biosynthesis activating neurohormone (PBAN)
- adipokinetic hormones (AKH; corpora cardiaca)
- crustacean cardioactive peptide (CCAP)
- and many more (hundreds of them is described)

Insect endocrine system:
General characteristics of neuropeptides

Groups of neuropeptides by genome coding:

1) Preprohormones containing signal peptide and neuropeptide (eclosion hormone, neuroparsins)

2) Preprohormones containing signal peptide, neuropeptide and other structurally unrelated peptides (AKH + bombyxins)

3) Preprohormones containing signal peptide and a number of copies of the same or a similar neuropeptide (isoforms; e.g. allatostatins)

Groups of neurohormones by function:

- adenotropic (glandotropic), gonadotropic, morphogenetic, chromotropic, metabolic and homeostatic, myotropic, etotropic etc.
- usually pleiotropic effect

Insect metamorphosis

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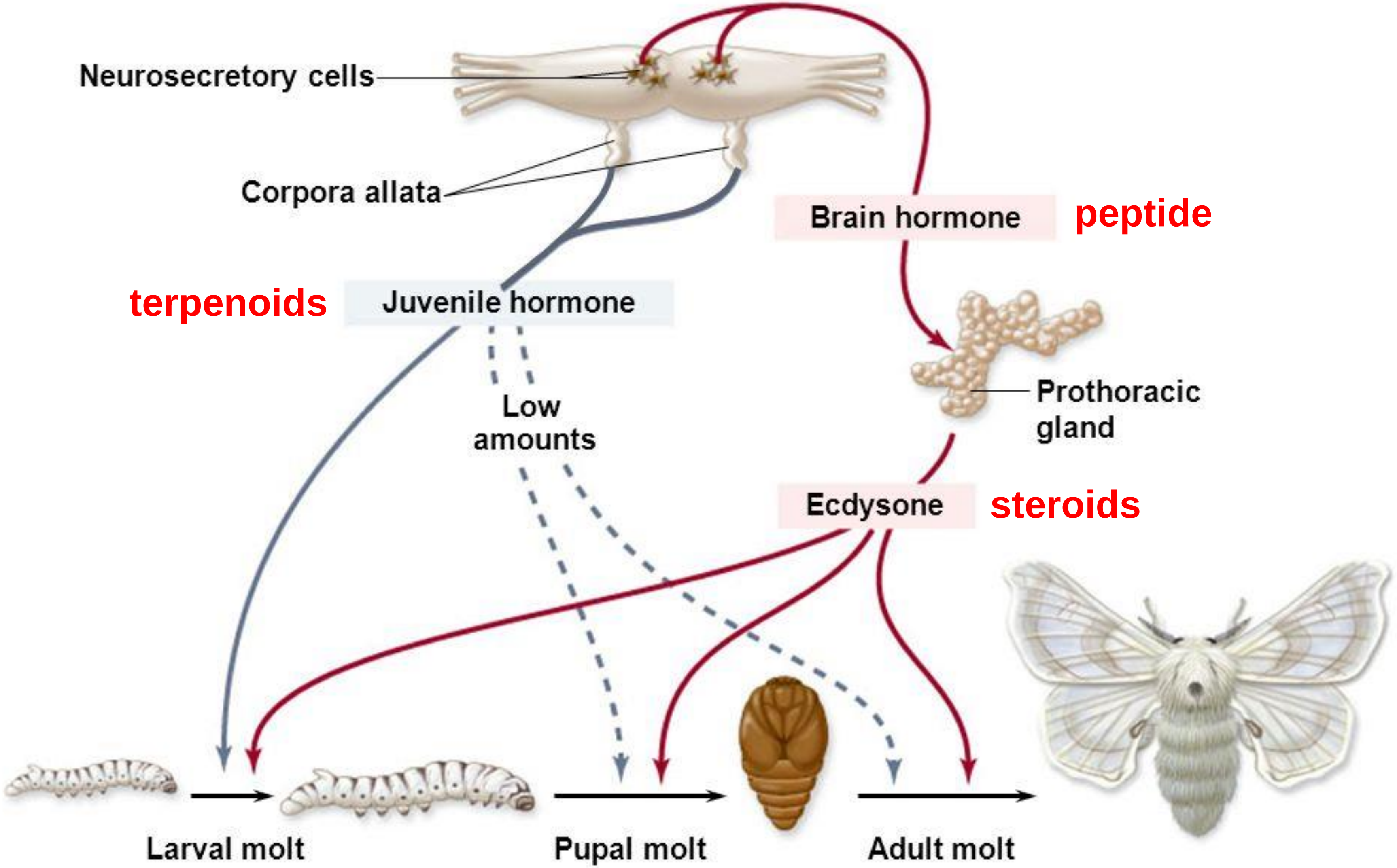


Insect metamorphosis

TABLE 14.6 Major hormones and neurohormones that control insect metamorphosis

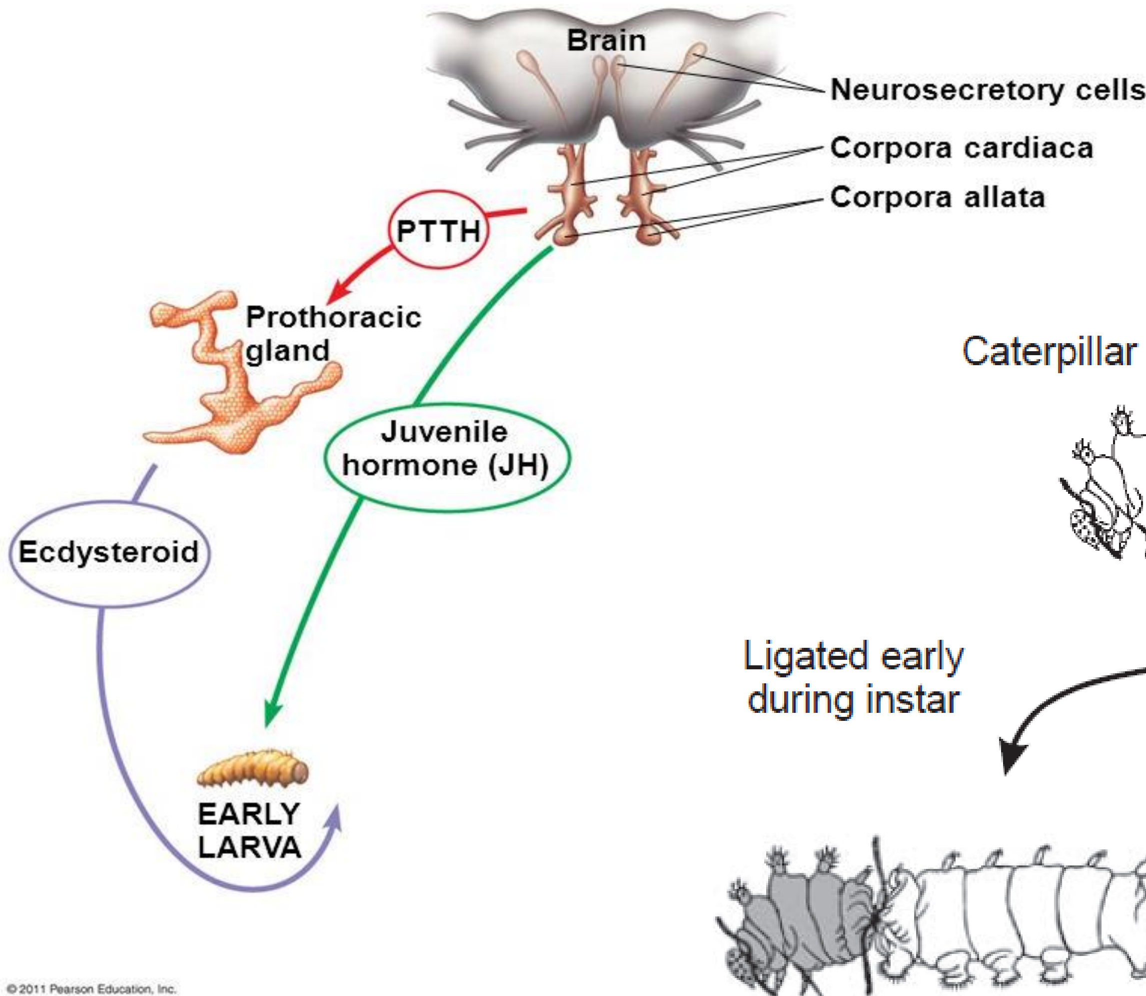
Hormone	Type of molecule	Type of signal	Site of secretion	Major target tissue	Action
Prothoracicotropic hormone (PTTH)	Protein (~5000 molecular weight)	Neuroendocrine	Brain, with axon terminals extending to corpora allata	Prothoracic glands	Initiates molting (ecdysis) by stimulating release of ecdysone from prothoracic glands
Ecdysone (molting hormone)	Steroid	Endocrine	Prothoracic glands in larva/nymph; ovary in adult	Epidermis in larva/nymph; fat body in adult	When activated to 20-hydroxyecdysone, promotes cellular mechanisms to digest old cuticle and synthesize new one; stimulates production of yolk proteins in adult
Juvenile hormone (JH)	Terpene (fatty-acid derivative)	Endocrine	Corpora allata	Epidermis in larva/nymph; ovary in adult	Opposes formation of adult structures and promotes formation of larval/nymphal structures; functions as a gonadotropin in the adult
Eclosion hormone (EH)	Peptide	Neuroendocrine	Brain	Inka cells, possibly others	Promotes PETH and ETH secretion from Inka cells
Pre-ecdysis triggering hormone (PETH)	Peptide	Endocrine	Inka cells of tracheae	Neuronal circuits in brain	Coordinates motor programs to prepare for shedding the cuticle
Ecdysis triggering hormone (ETH)	Peptide	Endocrine	Inka cells of tracheae	Neuronal circuits in brain	Coordinates final motor programs for escaping from old cuticle
Bursicon	Large protein (~35,000 molecular weight)	Neuroendocrine	Brain and nerve cord	Cuticle and epidermis	Tans and hardens new cuticle

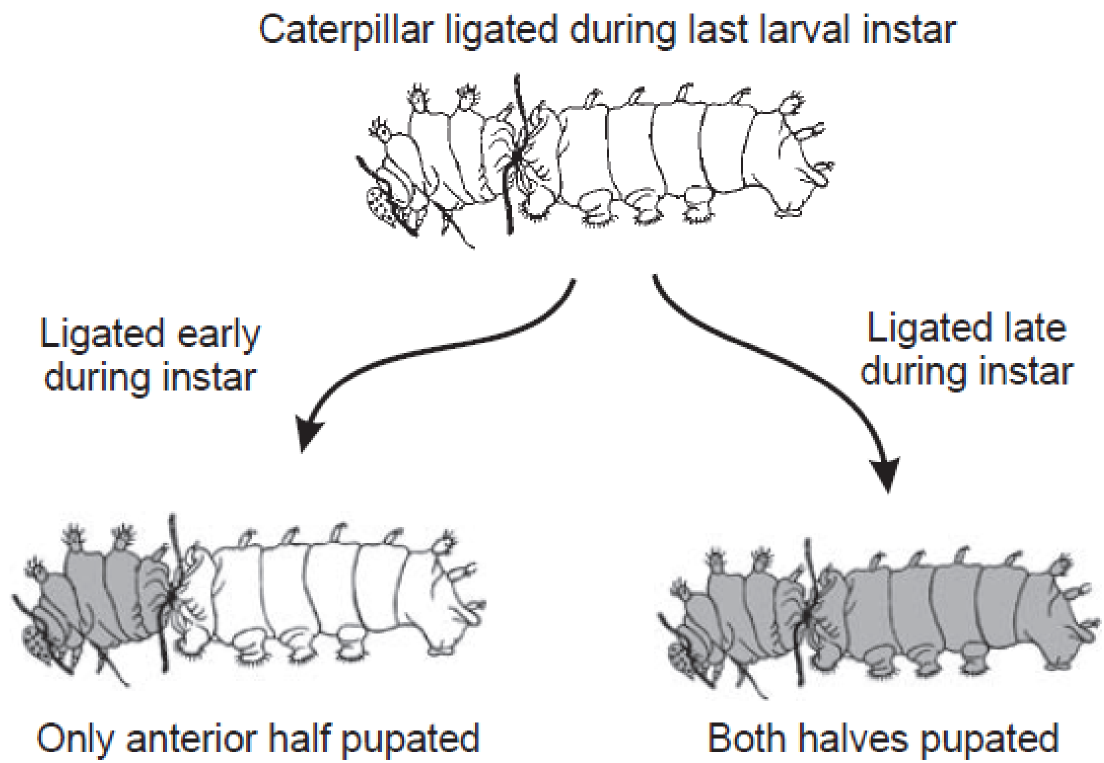
Sources: After Randall, Burggren, and French 2002; and Žitňan et al. 2003.

Insect metamorphosis:
Prothoracicotropic hormone (PTTH)

- the first insect hormone that was discovered
- insulin-like peptide (homodimer consisting of two identical amino acid chains interconnected with disulfide bonds)
- synthetised by **<u>neurosecretory cells in the brain</u>**
- axonal transport and release in neurohemal organs (**<u>corpora cardiaca</u>**/allata)
- development and control of metamorphosis
- photoperiod (*Manduca sexta*), temperature (*Hyalophora cecropia*), nerve stimulus (blood-sucking bug *Rhodnius*: blood volume is the primary stimul > enlarged abdomen > receptor signal > PTTH synthetised in the brain)
- activates prothoracic gland and synthesis of ecdysteroids through cAMP, Ca^{2+}, calmodulin and phosphorylation of specific proteins (exact mechanism still unknown)

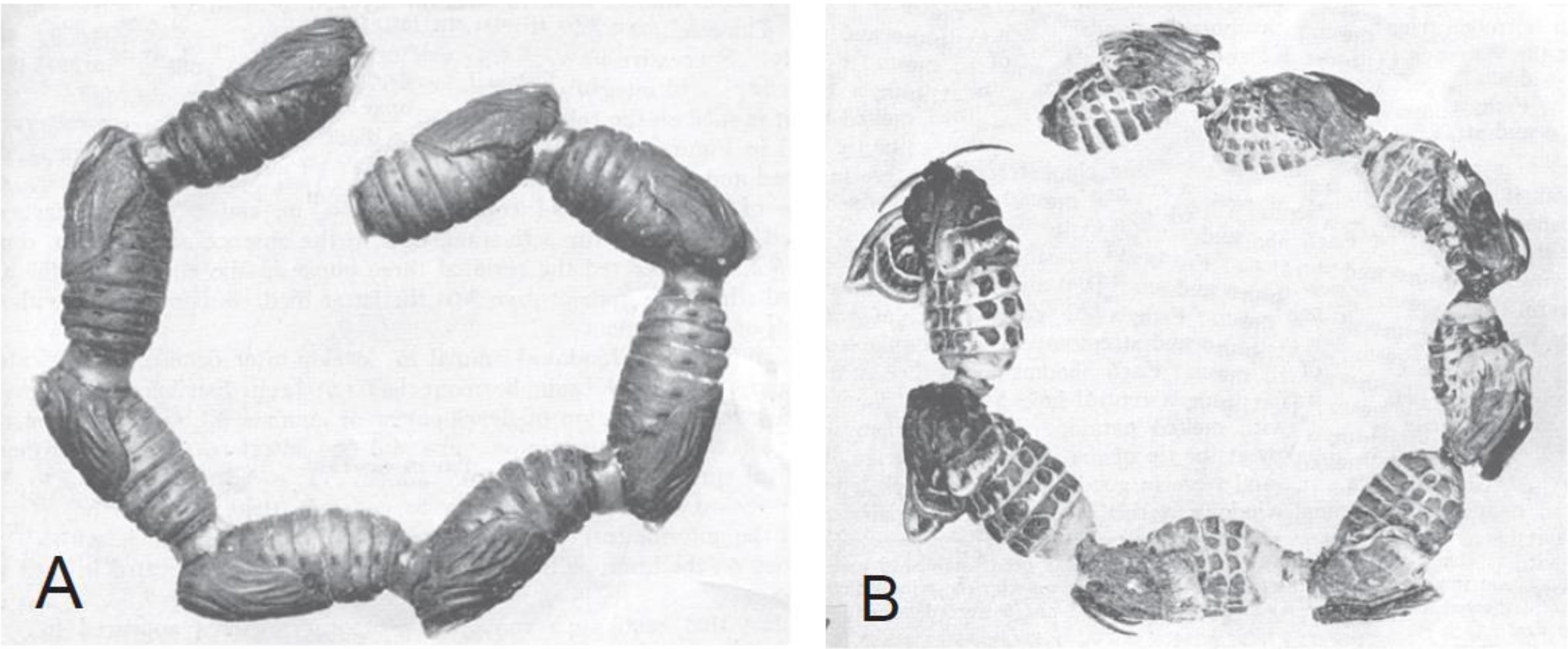
Insect metamorphosis:
Prothoracicotropic hormone (PTTH)





Insect metamorphosis: Prothoracicotropic hormone (PTTH)

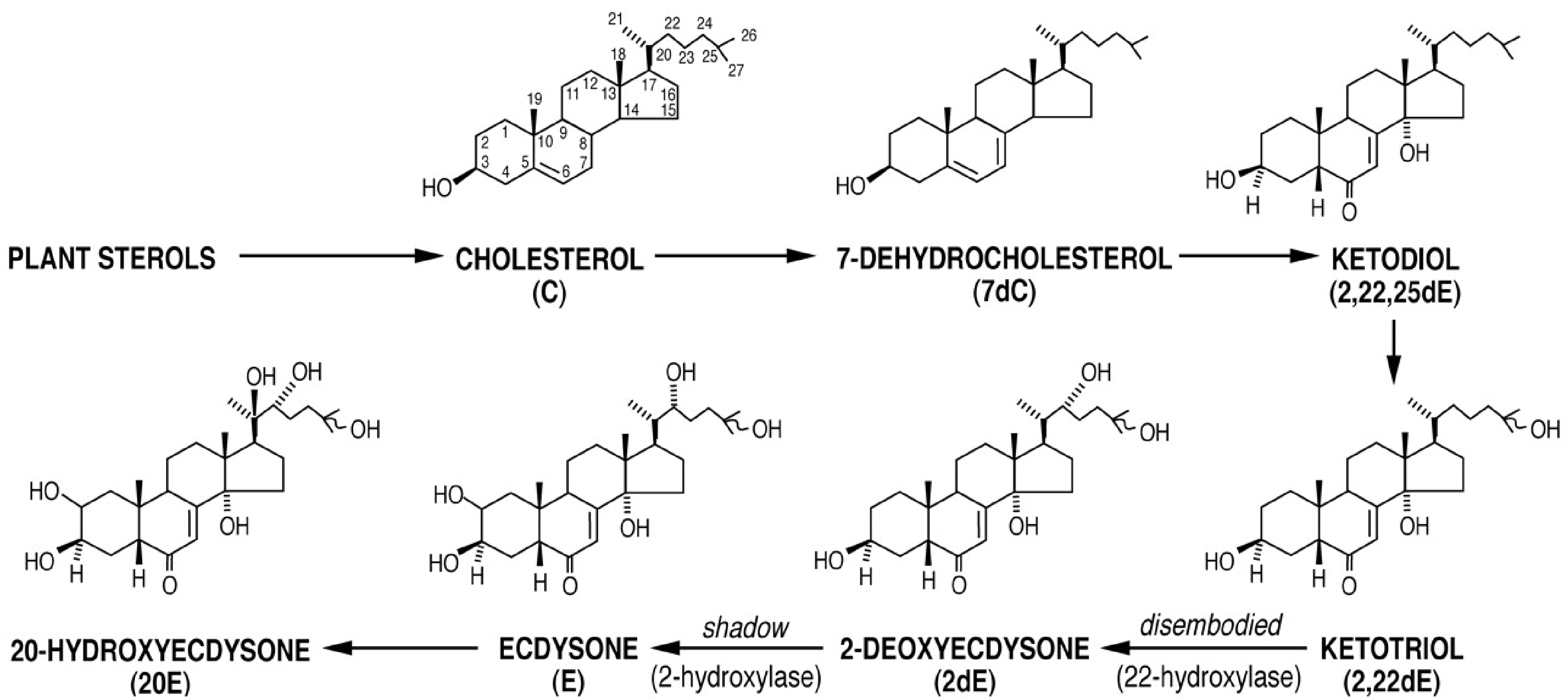
What can one brain do? (Williams1952)



The transformation (B) was induced by the implantation of one brain into the first pupa without the brain (A).

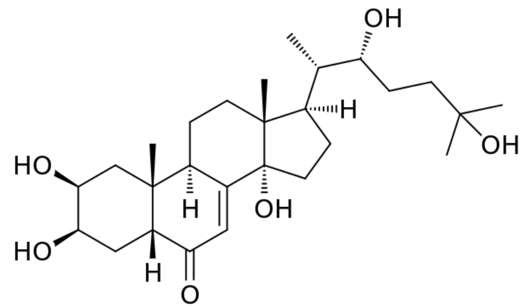
Insect metamorphosis: Ecdysteroids (molting hormones)

- non-polar
- derived from cholesterol or plant sterols (zoophagous x phytophagous: ecdysone, makisteron A, 20-hydroxyecdysone and others)
- controls the metamorphosis, molting of embryos, larvae, nymphs and reproduction of adults

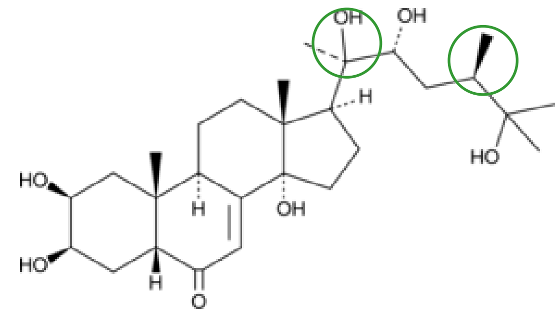


Insect metamorphosis:
Ecdysteroids – synthesis and release

- **ecdysone** (E) keto group on the B ring and five OH groups
- **20-E** (main molting hormone; six OH groups)
- **makisterone A** (24-methyl-20-hydroxyecdysone; e.g. Heteroptera, Hymenoptera, Diptera)



ecdysone



makisteron A

- synthesis in larvae: prothoracic gland vs. adults: accessory glands (main source of ecdysteroids), epithelial cells and ovarian follicles
- regulated by PTTH, ovarian ecdysteroidogenic hormone, prothoracicostatin described in some insect species, excretion by Malpighian tubes
- transported in hemolymph by carriers or freely (↑OH > sufficiently soluble)
- conversion of E to 20-E in target tissues (epidermis, fat body, intestine, ovaries…)
- **nuclear receptors** (ecdysteroid receptor); non-covalent dimers EcR/USP (ultraspiracle protein, RXR homolog)

Insect metamorphosis: Ecdysteroids – function

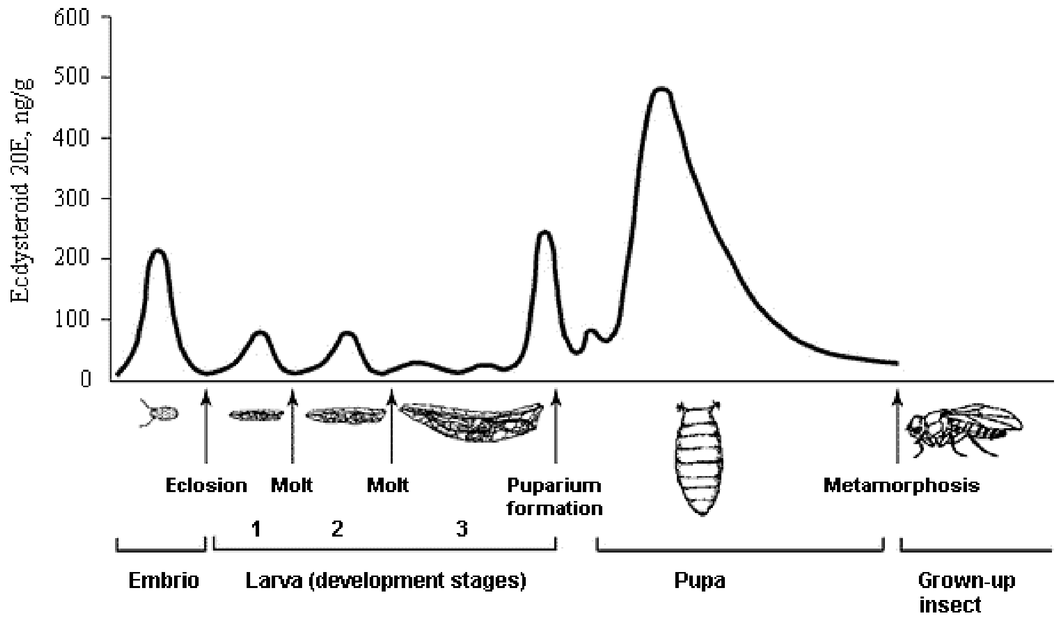
Metamorphosis:

- ecdysteroids control the expression of hundreds of genes (e.g. DOPA decarboxylase), circadian fluctuations of E are related to PTTH level
- in larvae, the titer increases before apolysis of old cuticle
- larva-imago: Hemimetabola - large dose of ecdysteroids neccessary
  Lepidoptera - often two doses of ecdysteroids

E : 20-E = 1 : 1 > reprogaming of larval development and behavior change

E : 20-E = 1 : 5 > triggers larval molting and transformation into pupa

- delayed secretion during the diapause



Insect metamorphosis: Ecdysteroids – function

Reproduction:

- synthetised also in ovaries and stored conjugated in eggs > embryonic molts
- increase vitellogenin synthesis in the fat body and its secretion into the hemolymph (20-E; Diptera)
- stimulation of meiosis, maturation of oocytes and oviposition
- spermatogenesis and formation of spermatophore

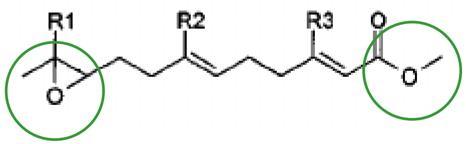
Metabolism and diapause:

- stimulation of proteosynthesis, etc.
- in relation to the above mentioned functions

Insect metamorphosis: Juvenile hormones (JH)

- formerly known as neotenin
- structurally terpenoids (sesquiterpenes, derivatives of farnesol): methyl ester group + epoxy group
- non-polar (enter cells and bind to nuclear receptors)
- JH-I, JH-II, **JH-III**, JH-0, 4-methyl-JH-I, juvenile hormone acid, methyl farnesoate (their use is species specific)

Insect Juvenile Hormones

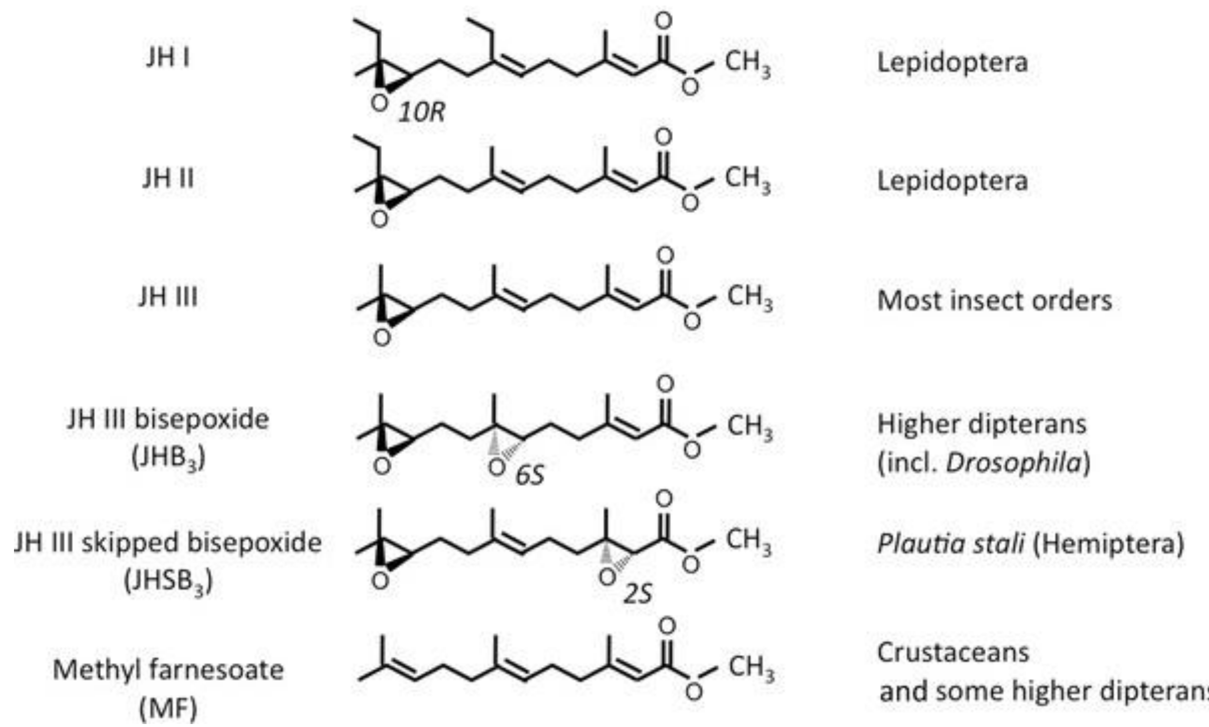


JH O : R1 = Et , R2 = Et , R3 = Et

JH I : R1 = Et , R2 = Et , R3 = Me

JH II : R1 = Et , R2 = Me , R3 = Me

JH III : R1 = Me , R2 = Me , R3 = Me



Insect metamorphosis: Juvenile hormones (JH)

- produced in **corpora allata**
- cholesterol synthesis-like biosynthesis
- not stored, released into the hemolymph immediately after synthesis (the mechanism is not yet known)

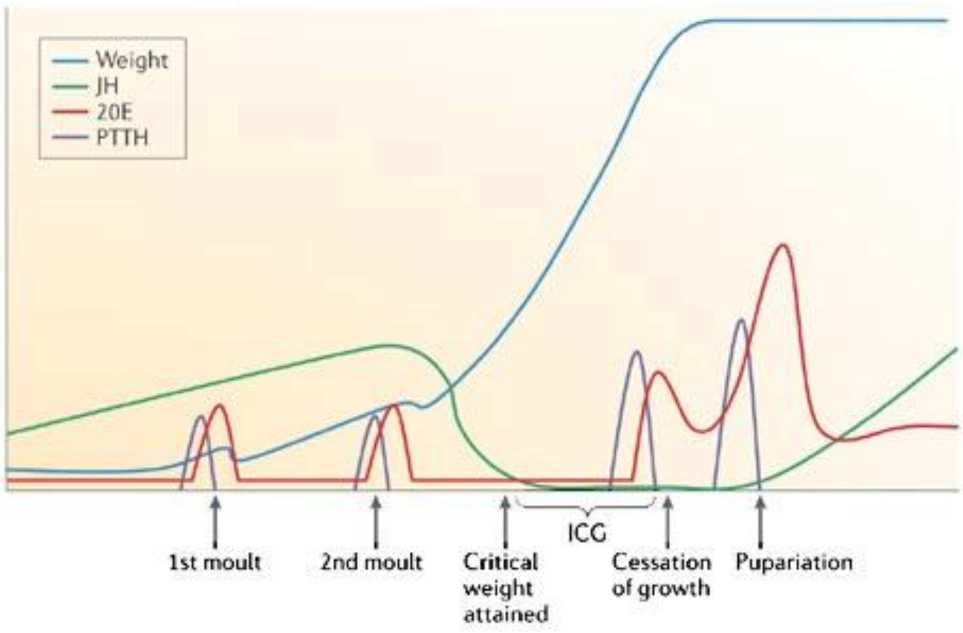
- lipophorine **juvenile hormone binding/carrier protein** (JHBP/JHCP)
- regulated by allatostatin, allatotropin, negative feedback loop
- degradation by specific enzymes (JH esterases and epoxide hydrolases), excretion by Malphigian tubes

- mode of action is assumed similar to steroid hormones
- receptors for JH in target cells have not yet been precisely identified (intracellular proteins methoprene-tolerant / germ cell expressed)

Insect metamorphosis:
Juvenile hormones (JH) – function

Metamorphosis:

- embryogenesis, larval molting, metamorphosis, ending of larval and adult diapause
- JH protects larval brain from reprograming and thus the onset of metamorphosis, keeps the insect in the larval stage
- presence of JH at critical time points in the development or reaching the threshold concentration
- critical body size > JH titer reduction



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Insect metamorphosis:
Juvenile hormones (JH) – function

Reproduction:

- inhibitory during the larval stage, stimulates gene expression in adults
- synthesis of vitellogenins, development of ovaries and oocytes
- stimulation of the accessory glands in adult males to growth and secrete
- pheromone production in males and reproductive behavior of both sexes
- aging (*D. melanogaster*)

Polymorphism:

- social-caste: higher titer drives development of dominant individuals (queen bees)
- phase: solitary vs. gregarious locusts (different color or size of ovaries); development of parthenogenetic female aphids

Insect metamorphosis:
Juvenile hormones (JH) – function

- synthesis of vitellogenins in *Aedes aegypti*

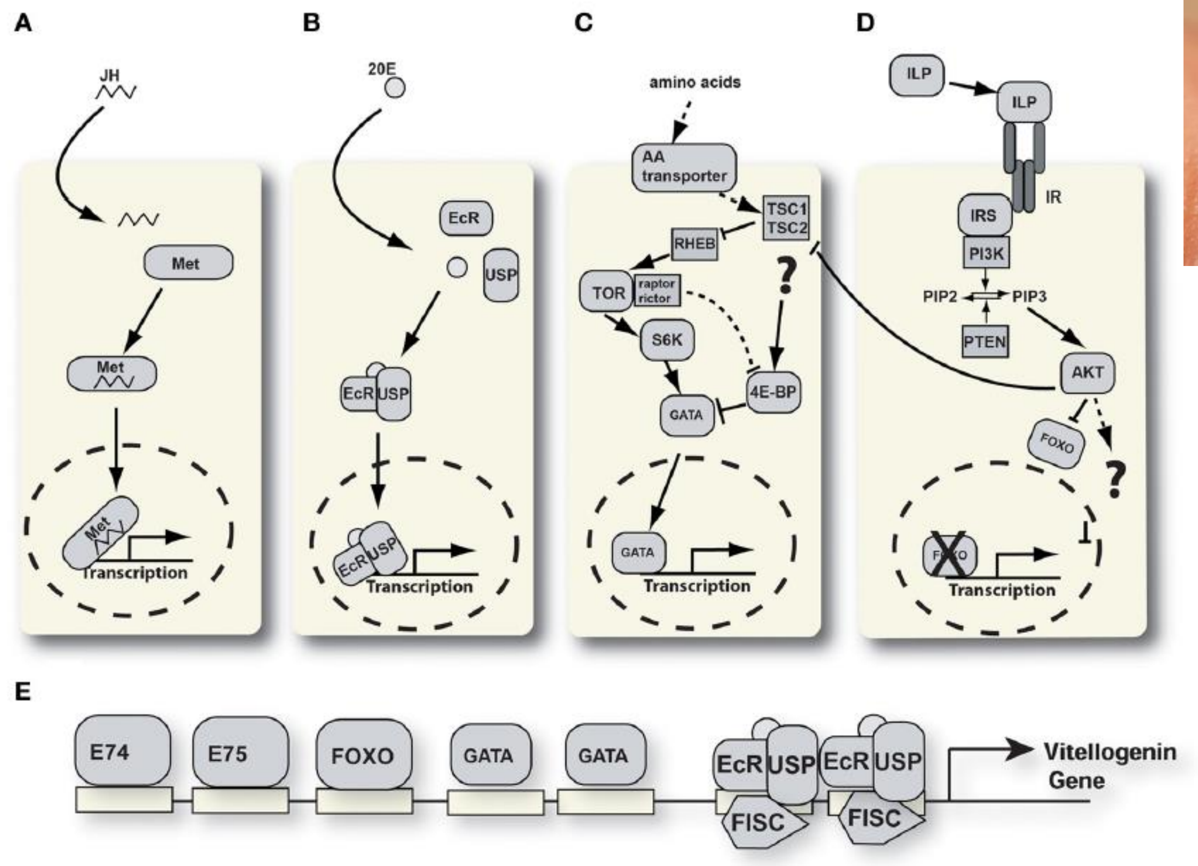
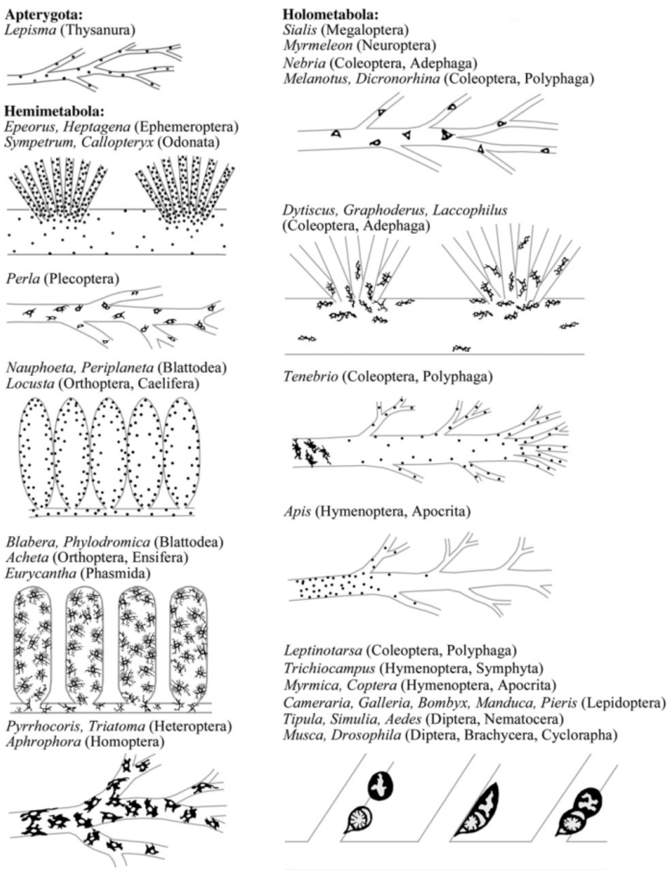
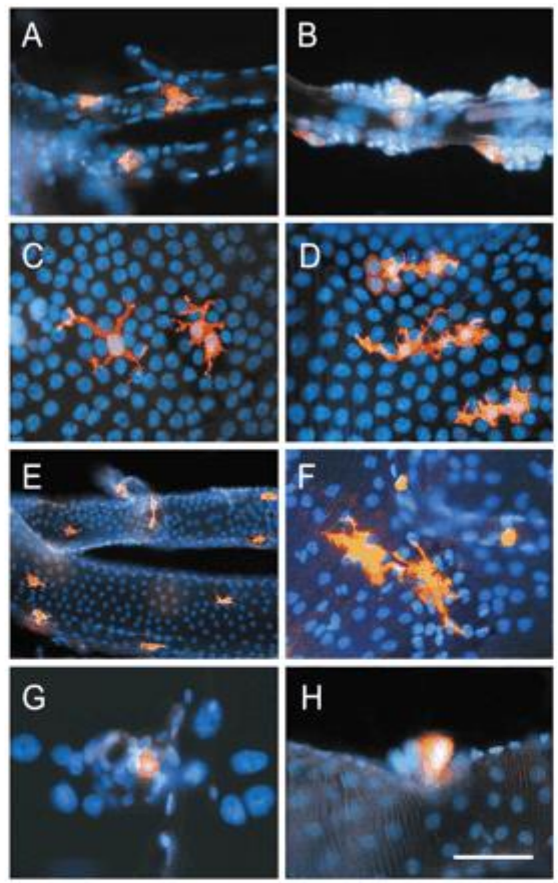


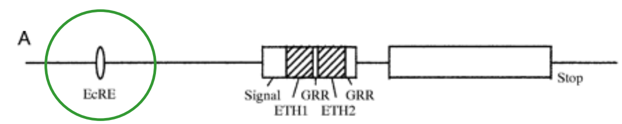
FIGURE 2 | Signaling pathways involved in YPP regulation. (A) Juvenile hormone signaling pathway. JH, juvenile hormone; Met, methoprene tolerant. **(B)** Ecdysone signaling pathway. 20E, 20 hydroxyecdysone; EcR, ecdysone receptor; USP, ultraspiracle. **(C)** Nutrient signaling pathway. 4E-BP, 4E-binding protein; TSC, tuberous sclerosis complex; RHEB, RAS homologue enriched in brain; S6K, S6 kinase; TOR, target of rapamycin. **(D)** Insulin-like peptide signaling pathway. AKT, protein kinase B; FOXO, forkhead box protein O; ILP, insulin-like peptide; IRS, insulin receptor substrate; PI3K, phosphati dylinositide 3-kinase; PIP2, phosphatidylinositol 4,5-bisphosphate; PIP3, phosphatidylinositol (3,4,5)-triphosphate; PTEN, phosphatidylinositol-3,4,5-trisphosphate 3-phosphatase. **(E)** Schematic of the vg-A promoter with transcription factor binding sites.

Ecdysis triggerign hormone (ETH)
Pre-ecdysis triggering hormone (PETH)

- polar peptides, homologues of cardioactive peptides (CAPs)
- synthesis in endocrine **epitracheal glands** close to spiracles (**Inka cells**)
- etotropic effect, acts directly on the CNS
- coordinate the molting and abandoning of the old cuticle







Eclosion hormone (EH)
Bursicon

Eclosion hormone

- polar peptide
- synthesis in the brain and abdominal ganglia; in part secreted in hindgut
- its synthesis is induced by ecdysteroids
- acts in the CNS through cGMP
- supports the secretion of ETH, PETH, bursicon and others
- mediates **positive feedback during ecdysis**
- stimulates molting, hatching (eclosion) and supporting behaviour

Bursicon

- large polar protein (approx. 30 kDa)
- produced by ganglia and stored in corpora cardiaca
- acts on the cuticle and epidermis
- wing formation, coloring and hardening of the new cuticle
- hatching of adult *Glossina morsitans morsitans* (tse-tse)

Hormones regulating metabolism

Adipokinetic hormones (AKH)

- RPCH/AKH family of peptide hormones
- homologs of vertebrate glucagon
- mediate stress reactions, activate metabolism for energy release (inhibit synthesis), stimulate flight, movement and immune response

Synthesis and transport:

- okta- to decapeptides
- glandular lobe of **corpora cardiaca**, in part neurosecretory brain cells
- stored in the storage lobe of corpora cardiaca
- specific mRNA > prepro-AKH (signal peptide + AKH sequence + sequence of another peptide)

$\text{pGlu}^{1}\text{-X}^{2}\text{-X}^{3}\text{-X}^{4}\text{-X}^{5}\text{-X}^{6}\text{-X}^{7}\text{-Trp}^{8}\text{-Gly}^{9}\text{-X}^{10}\text{-NH}_{2}$

-X^{2} - Leu, Val, Ile	-X^{6}- Pro, Ser, Thr, Ala
-X^{3}- Asn, Thr	-X^{7}- Asn, Gly, Ser, Asp, Trp
-X^{4}- Phe, Tyr (arom. AA)	-X^{10}- Thr, Asn, Ser, Tyr
-X^{5}- Thr, Ser	

Adipokinetic hormones (AKH)

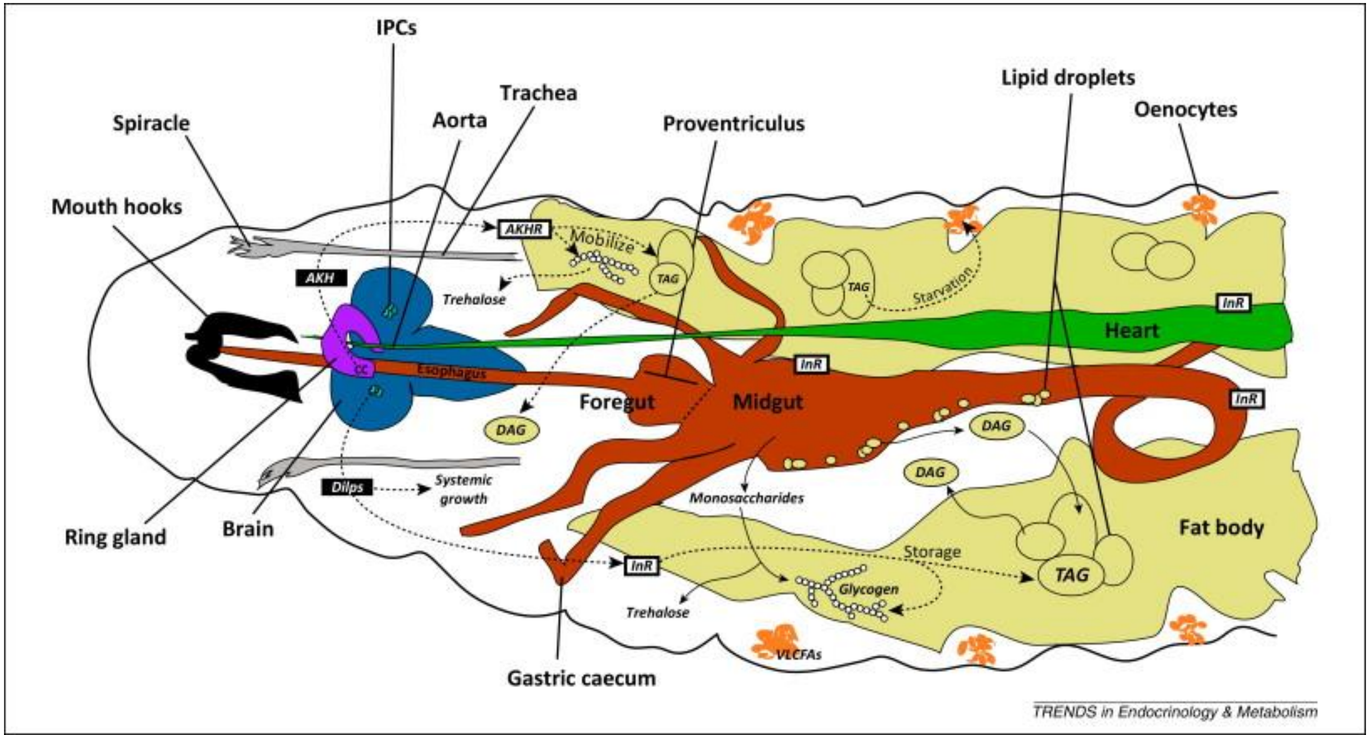
Regulation:

- stimulated by movement and stress conditions (e.g. infection with pathogen)
- level of metabolites and negative feedback (high lipids > ↓ / low trehalose > ↑)
- regulated and degraded by membrane-bound **endopeptidases**

Effect:

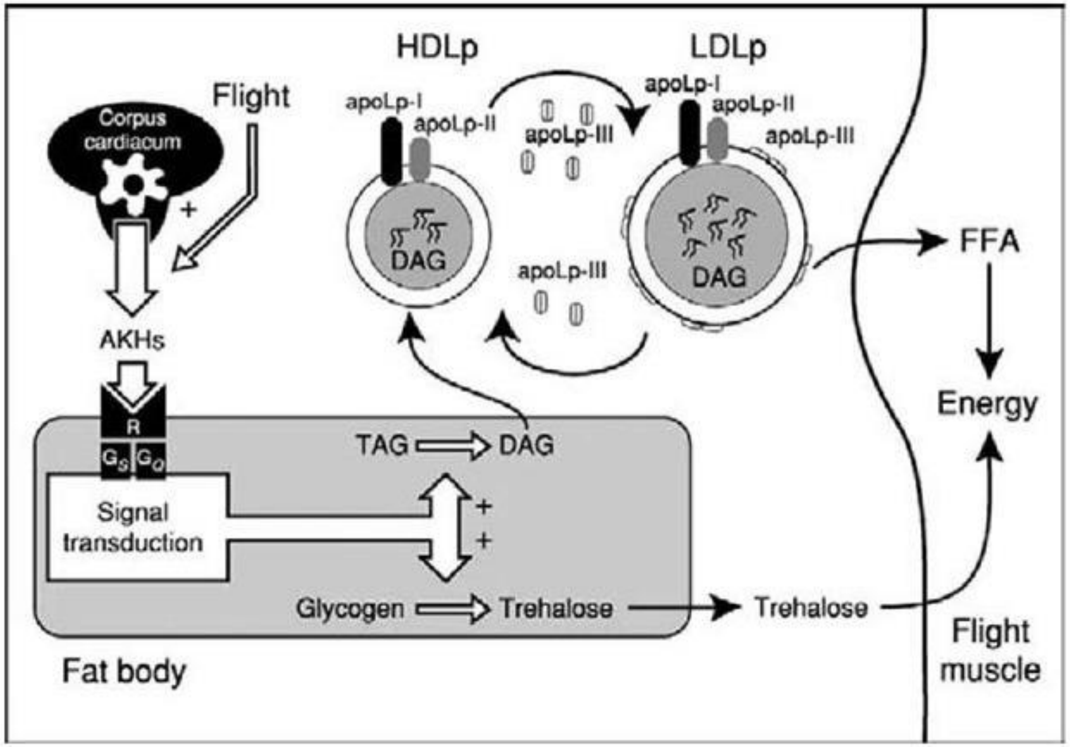
activated lipases

- specific AKHR (e.g. fat body) > cAMP > Ca^{2+} > PKC > TAG > DAG



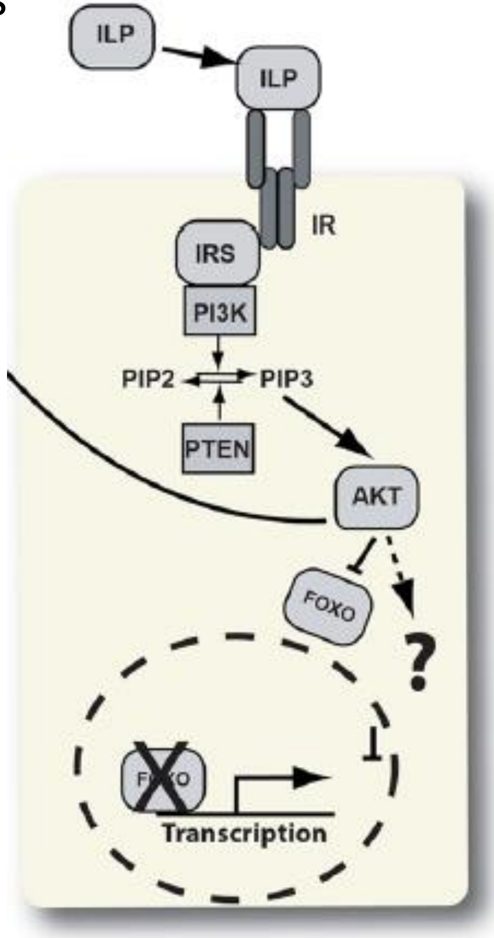
Adipokinetic hormones (AKH)

- activation of glycogen phosphorylase and fat metabolism, stimulation of trehalose release (hypertrehalosemic hormones) from the fat body > switch from carbohydrate metabolism to lipid metabolism
- increased heart activity and muscle contraction
- support immune response, stimulate antioxidant reactions
- inhibition of lipid, protein and RNA synthesis
- inhibition of oocyte maturation

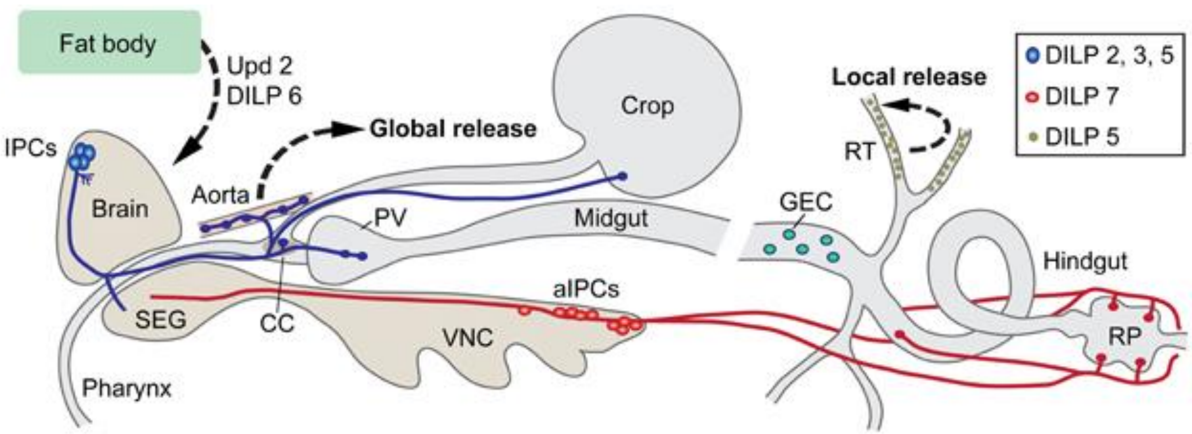


Insulin-like peptides (ILP)

- evolutionarily conserved (structure with disulfide bonds)
- neurosecretory cells in the brain and other ganglia
- linked to **receptor with tyrosine kinase activity** > phosphorylation of receptor substrate > signal via PI3K and other pathways
- metabolism, growth, immunity, reproduction, aging etc.
- glycogen and lipid metabolism (AKH antagonist)



IPCs - DILP-producing cells
DILP - Drosophila insulin-like peptide



Diuretic (DH) and antidiuretic (ADH) hormones

Diuretic hormones:

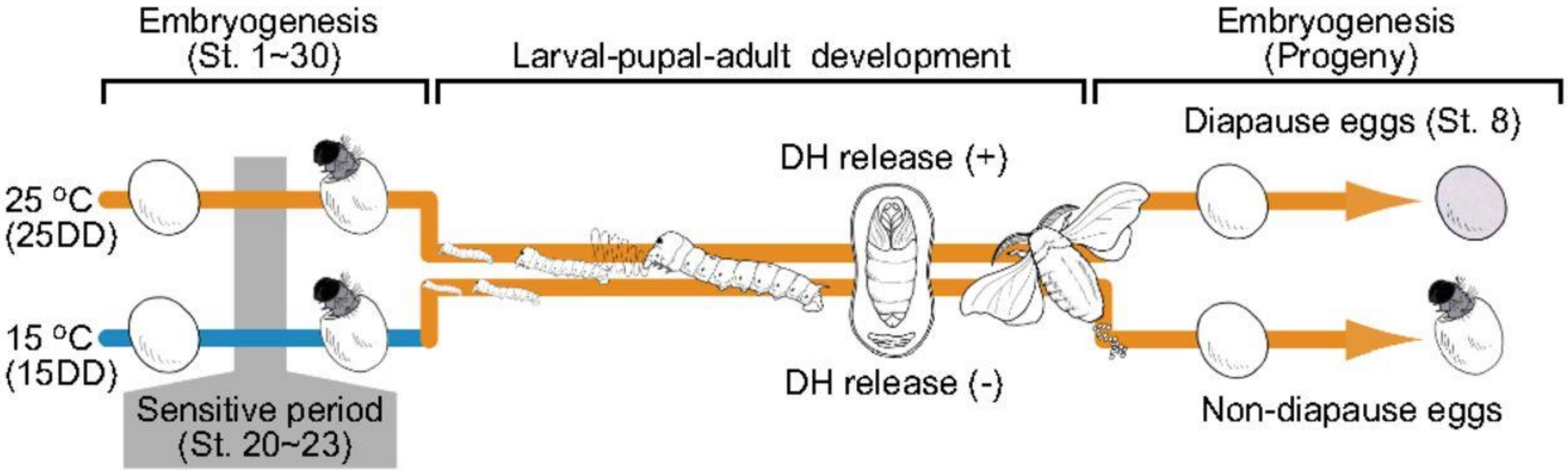
- corpora cardiaca, suboesophageal and thoracic ganglia
- stimulate diuresis in Malpighian tubules:
  1) homologs of corticotropin releasing factor (CRF; vertebrate neuropeptide family) stimulating Na/K transport in Malpighian tubules via cAMP
  2) calcitonin-like (CT-like) peptides
  3) myokinins acting via Ca^{2+} and changing the channel throughput for Cl^- (Na, K)
- they are also involved in meconium excretion after adult hatching

Antidiuretic hormones:

- abdominal nerves
- stimulate the reabsorption of water from the intestine into the hemolymph
- e.g. **neuroparsin** (antigonadotropin, antidiuretic activity, increases the concentration of lipids and trehalose in the hemolymph)

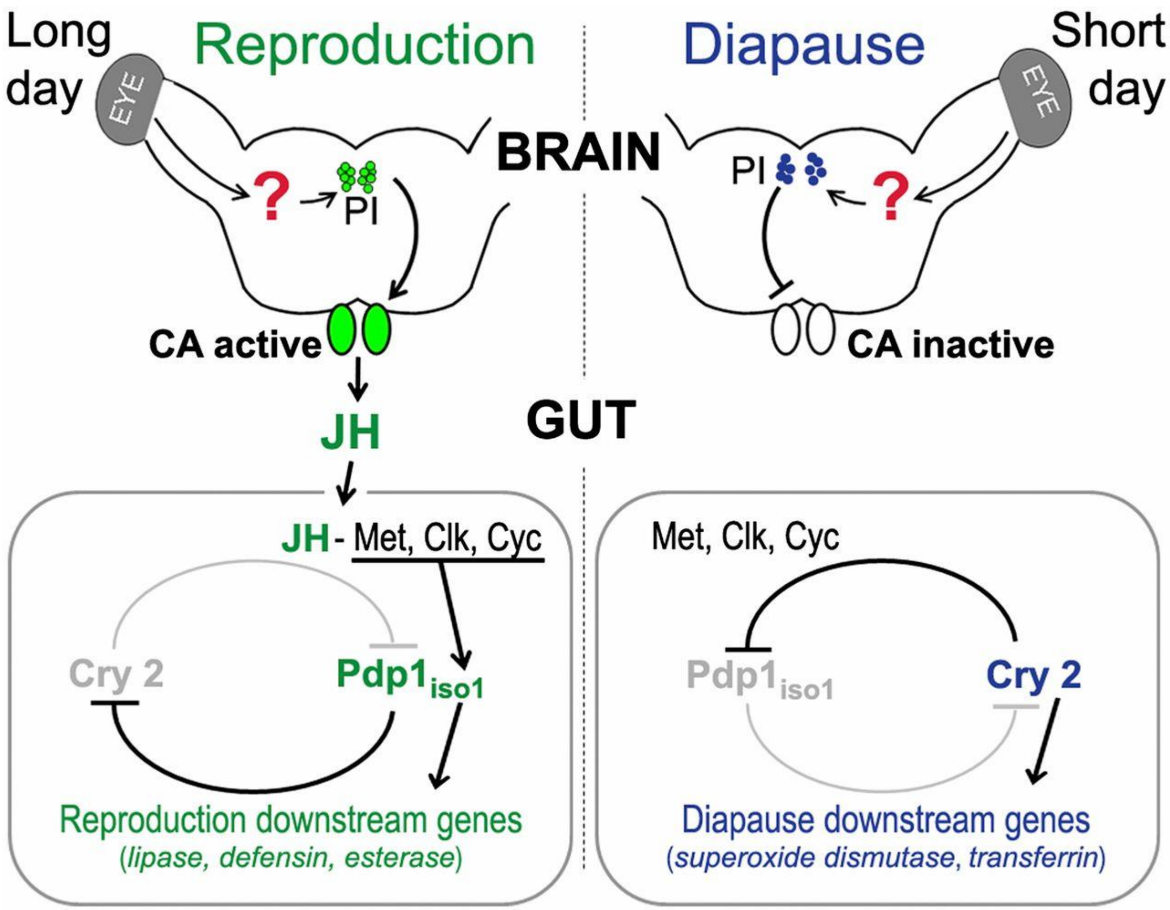
Diapause hormones

- peptide structurally similar to PBAN (pheromone biosynthesis activating neuropeptide) produced in female suboesophageal ganglion and transported to ovaries
- moreover, **pheromonotropic and myotropic** effect
- stimulation of embryonic diapause by supporting glycogen storage in oocytes and activation of trehalase



Diapause hormones

- **diapause is also controlled by PTTH, ecdysteroids and JH**
- diapause mechanisms are connected to molecular clock mechanisms



Gonadotropic hormones

- ovarian and testes development, vitellogenesis, transport of storage molecules from the fat body to the ovaries and others
- key role of **ecdysteroids and juvenile hormones**, involvement of neuropeptides

1) Stimulatory:

- prothoracicotropic hormone (PTTH)
- ovary maturing parsin (OMP) – stimulates synthesis of ecdysteroids and Vg
- folicle cell tropic hormone (FTCH) – synthesis of ecdysteroids in ovaries
- egg development neurohormone / ovarian ecdysteroidogenic hormone (EDNH / OEH) - alternates PTTH in adults, produced in brain and stored in corpora cardiaca

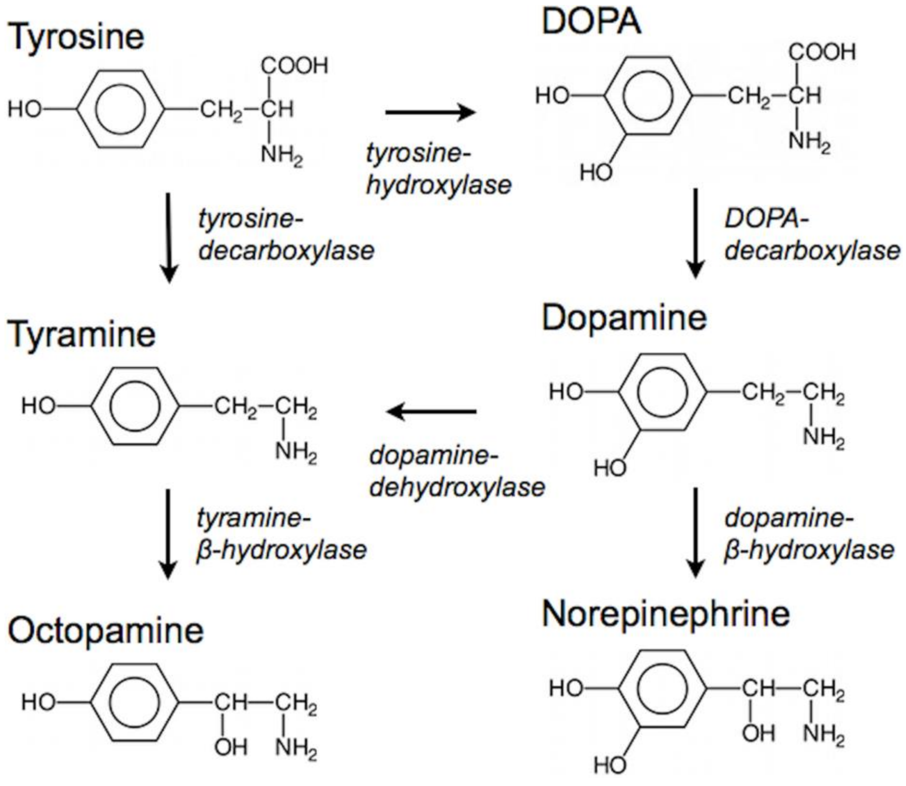
2) Inhibitory:

- neuroparsin – inhibits corpora allata and the production of juvenile hormones
- oostatic hormones and trypsin-modulating oostatic factor (folliclostatins) – inhibits production of ecdysteroids, JH and EDNH

Biogenic amines of insects

Tyramine and octopamine

- equivalents of adrenaline and noradrenalin in vertebrates
- the only non-peptidic hormones found only in invertebrates
- autocrine in prothoracic glands (interacts with PTTH)
- flight-or-fight response, energetic metabolism, muscle contraction, learning and memory in bees, sensory neuron sensitivity (synaptic plasticity)



Biogenic amines of insects

Serotonin (5-hydroxytryptamine)

- mainly neurotransmitter
- present for instance in the CNS and crustacean gonads
- stimulates reproduction (probably via gonads-stimulating hormone, but the exact mechanism is unknown)