INHIBITORS OF RESPIRATORY ENZYMES

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Inhibitors of the Electron Transport System

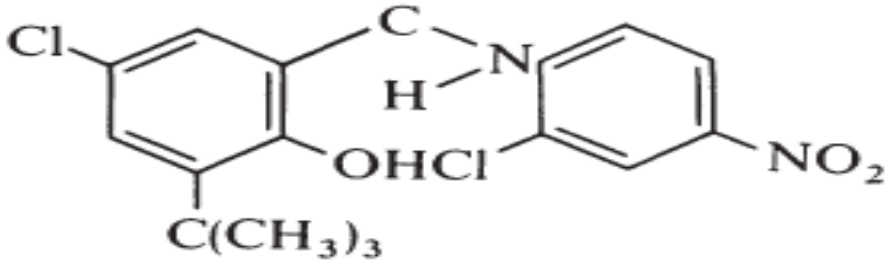
There are a number of insecticidal compounds which affect the respiratory system of animals.

An insecticidal antibiotic, **piericidin A**, for instance, is known to inhibit the process of electron transport between NADH dehydrogenase and Ubiquinone (Tamura and Takahashi, 1971) just as rotenone does (Fukami, 1956, 1961). The mechanisms of inhibition in terms of specific binding of these compounds to electron transport particles have been extensively studied. The site appears to be a protein-lipid complex and a portion of NADH dehydrogenase, which must play an important role in the process of electron transfer. While conformational requirements for the inhibitory property appear to be strict, the binding does not involve a rigid bonding, inasmuch as the inhibitors can be re-extracted in their original forms by the use of organic solvents.

Inhibitors of Oxidative Phosphorylation

Many acaricides and insecticides are known to affect the process of oxidative phosphorylation.

Williamson and Metcalf (1967) studied several salicylanilide derivatives and found that they are excellent uncouplers. Two compounds, 5-CI-3-(p-CI-phenyl)-2'-CI-5'-CF 3-salicylanilide and 5-CI- 3-t-butyl-2' -Cl-4' -N02-salicylanilide (I), had pI50 values (for Pi-A TP exchange) of 9.08 and 9.14 (i.e., in the range of 10-9 M) against a housefly mitochondrial system.



5-Cl-3-*t*-BUTYL-2′-Cl-4′-NO_2-SALICYLANILIDE (I)

In terms of their effects on housefly mitochondrial ATPase activities, these active analogues were 1000-10,000 times more potent (i.e., in their preparation ATPase activity caused stimulation that was increased approximately fourfold by 10 - 4 M dinitrophenol) than dinitrophenol.

Casida (1969) studied the similar effects of substituted 2,4-dinitrophenols, 2-trifluoromethylbenzimidazoles, salicylanilides, carbonyl cyanide phenylhydrazones, and other compounds. They found that, aside from compound I above, carbonylcyanide p-trifluoromethoxyphenylhydrazone and three other compounds are excellent uncouplers, particularly against insect and mouse-brain mitochondrial systems.

Inhibitors Of Mixed-function Oxidases

Inhibitors of mixed-function oxidases have been developed as synergists for pyrethrin insecticides, and generally are methylenedioxyphenyl derivatives.

In some instances, MDP compounds appear to act as alternative substrates (competitive inhibitors), while in other cases the relationship appears to be complex, i.e., interaction with the MFO system through allosteric modification, acylation, or other types of reactions to change the nature of the MFO.

The complicating matter is that such interactions generally involve more than one type of spectral change, and these are also influenced by the conditions of the reaction (e.g., by the presence and absence of oxygen, and by the methods of reduction of P450).

INHIBITORS OF CHITIN SYNTHESIS

Chitin is the essential structure component of the cell wall of Ascomycetes, Basidiomycetes, Fungi Imperfecti, and Oomycetes and the body walls of most invertebrates, including arthropods.

In insects, chitin is found in the cuticle and in the peri trophic membrane of the gut. Within the cuticle chitin forms an interlocking matrix with cuticular proteins, and this matrix assumes a distinct network of fibrinous appearance.

Chitin is a linear polymer of f3-(l,4)-2-acetamino-2-deoxy-o-glucose and the deacetylated polymeric glucosamine (chitosan). Because of the importance of chitin in the structural integrity of the cell walls of fungi and related microorganisms, basic biochemical information on this polysaccharide has been largely obtained from these organisms.

Chitin is synthesized by chitin synthase (UDP-2-acetamido-2-deoxyo- glucose: chitin 4-acetamidodeoxyglucosyl transferase, E.C. 2.4.1.16) by the following scheme:

$$\text{UDP-GlcNAc} + (\text{GlcNAc})_n \xrightarrow{Mg^{2+}} \text{UDP} + (\text{GlcNAc})_{n+1}$$

In the case of insects, the most notable initiation process is the action of 20-hydroxyecdyson, the level of which goes up in vivo after each molting. This is obviously the result of natural evolutionary processes to allow the sclerotization process to synchronize with the molting phenomenon.

Other factors controlling chitin synthesis and deposition are

(I) ATP activation (and UDP and UMP competitive inhibition of it)

(II) Stimulatory action of N-acetylglucosamine

(III) Stimulation by diacetylchitobiose, which is the end product of the chitin-degrading enzyme chitinase

Chitin is also converted to chitosan through the deacetylation process. This process could be viewed as a stabilization step, since the polymers of deacetylated products are more resistant to hydrolysis by lysozyme-type enzymes.

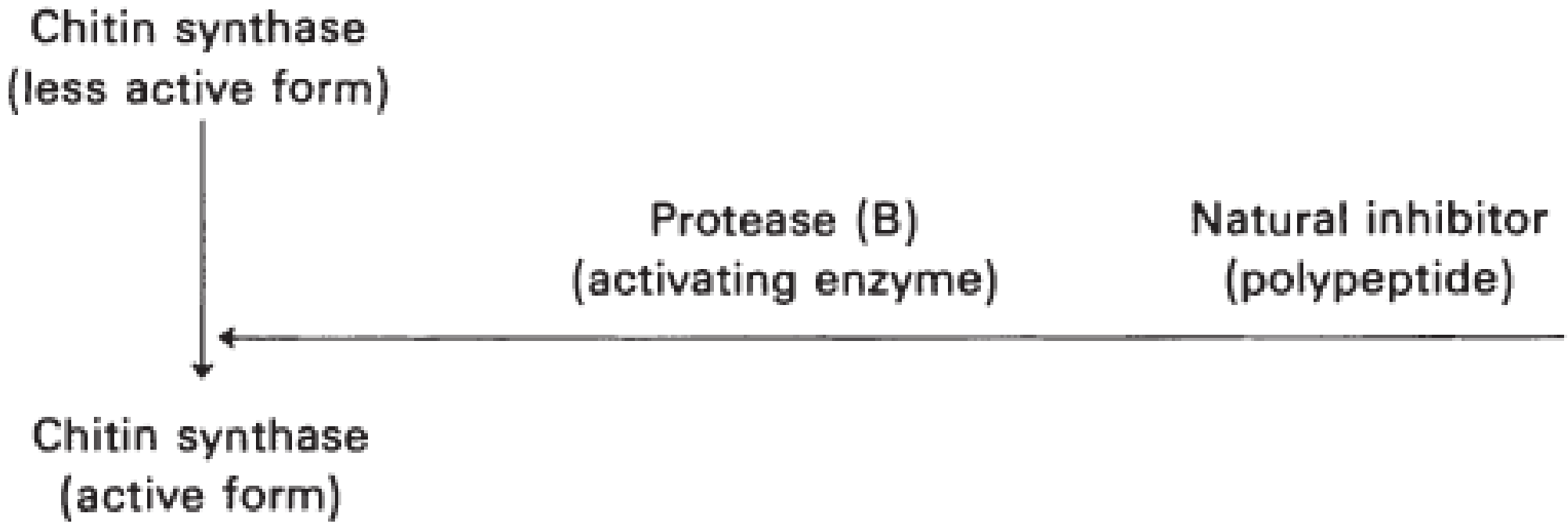


Fig. 4-24. The role of protease in activating chitin synthesis in fungi.

INSECT ENDOCRINOLOGY

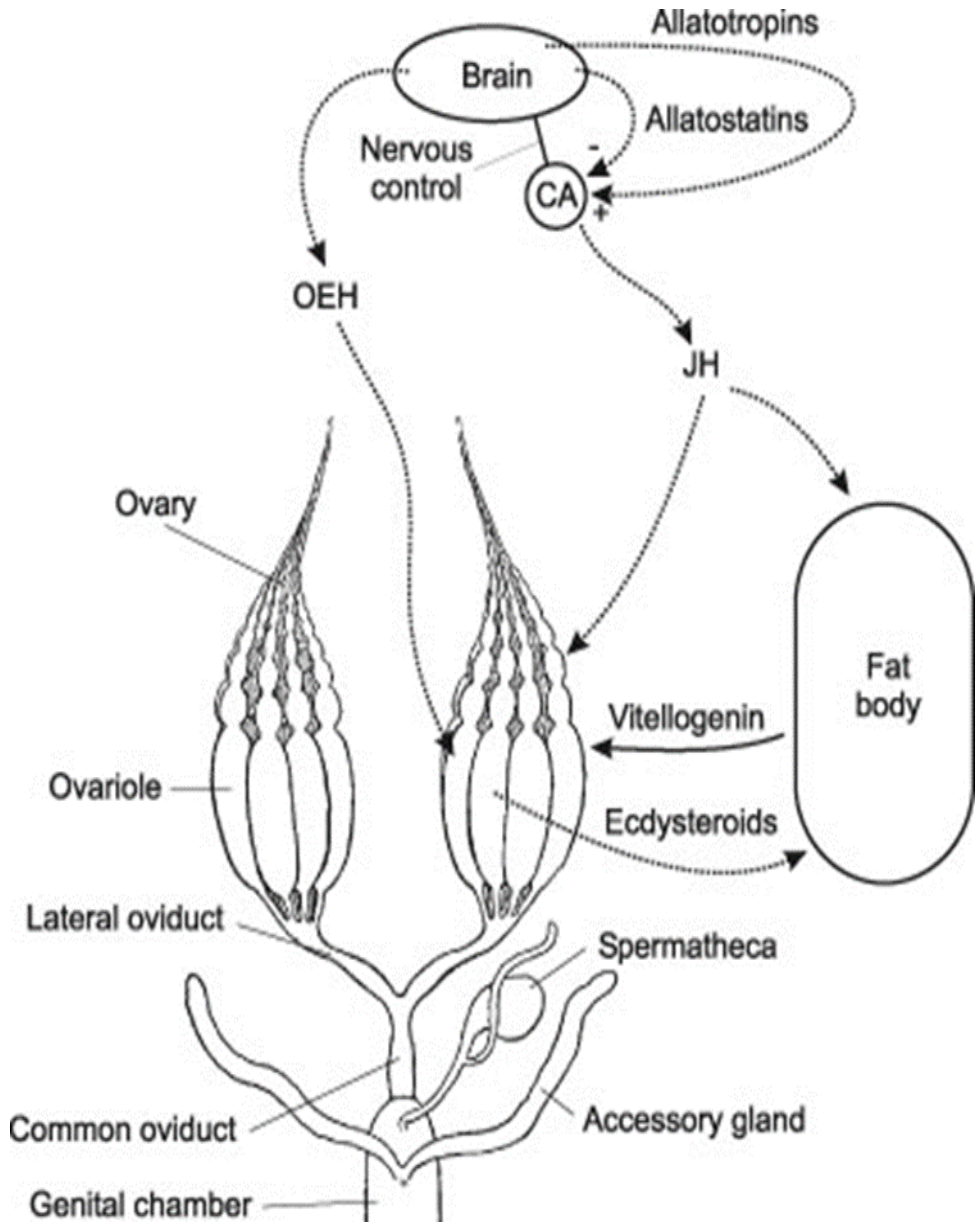
Insect Endocrinology covers the mechanism of action of insect hormones during growth and metamorphosis as well as the role of insect hormones in reproduction, diapause and the regulation of metabolism. There are at least four categories of hormone-producing cells in an insect's body:

Endocrine glands: secretory structures adapted exclusively for producing hormones and releasing them into the circulatory system.

Neurohemal organs: similar to glands, but they store their secretory product in a special chamber until stimulated to release it by a signal from the nervous system (or another hormone).

Neurosecretory cells: specialized nerve cells (neurons) that respond to stimulation by producing and secreting specific chemical messengers. Functionally, they serve as a link between the nervous system and the endocrine system

Internal organs: hormone-producing cells are associated with numerous organs of the body, including the ovaries and testes, the fat body, and parts of the digestive system.


Allatotropins
Brain
Allatostatins
Nervous control
-
CA
+
OEH
JH
Ovary
Fat body
Vitellogenin
Ovariole
Ecdysteroids
Lateral oviduct
Spermatheca
Common oviduct
Accessory gland
Genital chamber

In insects, the largest and most obvious endocrine glands are found in the prothorax, just behind the head.

These prothoracic glands manufacture ecdysteroids, a group of closely-related steroid hormones (including ecdysone) that stimulate synthesis of chitin and protein in epidermal cells and trigger a cascade of physiological events that culminates in molting. For this reason, the ecdysteroids are often called “molting hormones”. Once an insect reaches the adult stage, its prothoracic glands atrophy and it will never molt again.

Prothoracic glands produce and release ecdysteroids only after they have been stimulated by another chemical messenger, **prothoracicotropic hormone** (PTTH for short). This compound is a peptide hormone secreted by the corpora cardiaca, a pair of neurohemal organs located on the walls of the aorta just behind the brain.

The corpora cardiaca release their store of PTTH only after they receive a signal from neurosecretory cells in the brain. In a sense, they act as signal amplifiers, sending out a big pulse of hormone to the body in response to a small message from the brain.

The corpora allata, another pair of neurohemal organs, lie just behind the corpora cardiaca. They manufacture juvenile hormone (JH for short), a compound that inhibits development of adult characteristics during the immature stages and promotes sexual maturity during the adult stage.

Neurosecretory cells in the brain regulate activity of the corpora allata, stimulating them to produce JH during larval or nymphal instars, inhibiting them during the transition to adulthood, and reactivating them once the adult is ready for reproduction.

The neurosecretory cells are found in clusters, both medially and laterally in the insect’s brain.

Axons from these cells can be traced along tiny nerves that run to the corpora cardiaca and corpora allata.

The cells produce and secrete brain hormone, a low-molecular-weight peptide that appears to be the same as (or very similar to) prothoracicotropic hormone (PTTH) manufactured by the corpora cardiaca.

Insect physiologists suspect that brain hormone is bound to a larger carrier protein while it is inside the neurosecretory cell, and some believe that each cluster of cells may produce as many as three different brain hormones.

Many other tissues and organs of the body also produce hormones.

Ovaries and testes, for example, produce gonadal hormones that have been shown to coordinate courtship and mating behaviors.

Ventral ganglia in the nervous system produce one compound (eclosion hormone) that helps an insect shed its old exoskeleton and another compound (bursicon) that causes hardening and tanning of the new one.

There are still other hormones that control the level of sugar dissolved in the blood, adjust salt and water balance, and regulate protein metabolism.

Hormonal Control of Molting & Metamorphosis

When an immature insect has grown sufficiently to require a larger exoskeleton, sensory input from the body activates certain neurosecretory cells in the brain.

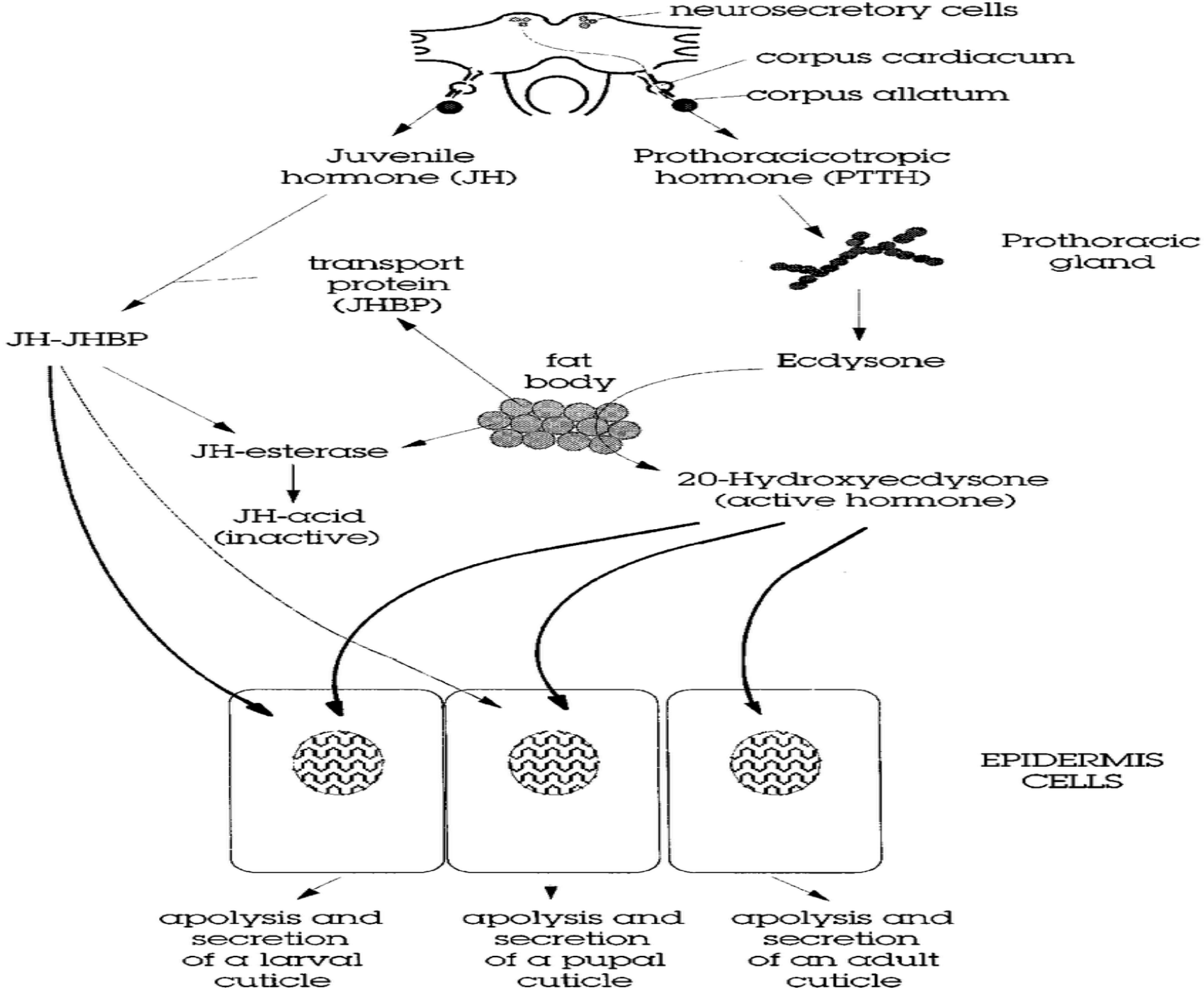
These neurons respond by secreting brain hormone which triggers the corpora cardiaca to release their store of prothoracicotropic hormone (PTTH) into the circulatory system. This sudden “pulse” of PTTH stimulates the prothoracic glands to secrete molting hormone (ecdysteroids).

Molting hormone affects many cells throughout the body, but its principle function is to stimulate a series of physiological events (collectively known as apolysis) that lead to synthesis of a new exoskeleton.

During this process, the new exoskeleton forms as a soft, wrinkled layer underneath the hard parts (exocuticle plus epicuticle) of the old exoskeleton.

The duration of apolysis ranges from days to weeks, depending on the species and its characteristic growth rate.

Once new exoskeleton has formed, the insect is ready to shed what's left of its old exoskeleton. At this stage, the insect is said to be pharate, meaning that the body is covered by two layers of exoskeleton.


neurosecretory cells
corpus cardiacum
corpus allatum
Juvenile hormone (JH)
Prothoracicotropic hormone (PTTH)
Prothoracic gland
transport protein (JHBP)
JH-JHBP
Ecdysone
fat body
JH-esterase
JH-acid (inactive)
20-Hydroxyecdysone (active hormone)
EPIDERMIS CELLS
apolysis and secretion of a larval cuticle
apolysis and secretion of a pupal cuticle
apolysis and secretion of an adult cuticle

As long as ecdysteroid levels remain above a critical threshold in the hemolymph, other endocrine structures remain inactive (inhibited). But toward the end of apolysis, ecdysteroid concentration falls, and neurosecretory cells in the ventral ganglia begin secreting eclosion hormone.

This hormone triggers ecdysis, the physical process of shedding the old exoskeleton. In addition, a rising concentration of eclosion hormone stimulates other neurosecretory cells in the ventral ganglia to secrete bursicon, a hormone that causes hardening and darkening of the integument (tanning) due to the formation of quinone cross-linkages in the exocuticle (sclerotization).

In immature insects, juvenile hormone is secreted by the corpora allata prior to each molt. This hormone inhibits the genes that promote development of adult characteristics (e.g. wings, reproductive organs, and external genitalia), causing the insect to remain “immature” (nymph or larva).

The corpora allata become atrophied (shrink) during the last larval or nymphal instar and stop producing juvenile hormone. This releases inhibition on development of adult structures and causes the insect to molt into an adult (hemimetabolous) or a pupa (holometabolous).

At the approach of sexual maturity in the adult stage, brain neurosecretory cells release a brain hormone that “reactivates” the corpora allata, stimulating renewed production of juvenile hormone.

In adult females, juvenile hormone stimulates production of yolk for the eggs. In adult males, it stimulates the accessory glands to produce proteins needed for seminal fluid and the case of the spermatophore. In the absence of normal juvenile hormone production, the adult remains sexually sterile.

Reference

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