Are Ecdysteroids insect hormones?

The polyhydroxylated derivatives of 7-dehydro, 6-ketocholesterol (Ecdysone, Ecdysteroids, Ecd) were accidentally discovered in the search for an insect moulting hormone in 1965. The first Ecd compound, named ecdysone ("*ecdysis"* = shedding off the cuticle), was isolated from silkworm pupae. It was defined as the insect moulting hormone secreted by the prothoracic glands (PG), in accordance with the currently recognised "brain-PG" hormonal theory. Soon after the elucidation of ecdysone, there emerged numerous literature reports about the presence of these insect hormones (Ecd) in many species of lower and higher plants. Occasionally, as in the fern *Polypodium*, one gram of the plant yielded as much Ecd as did 500 kg of the silkworm pupae.

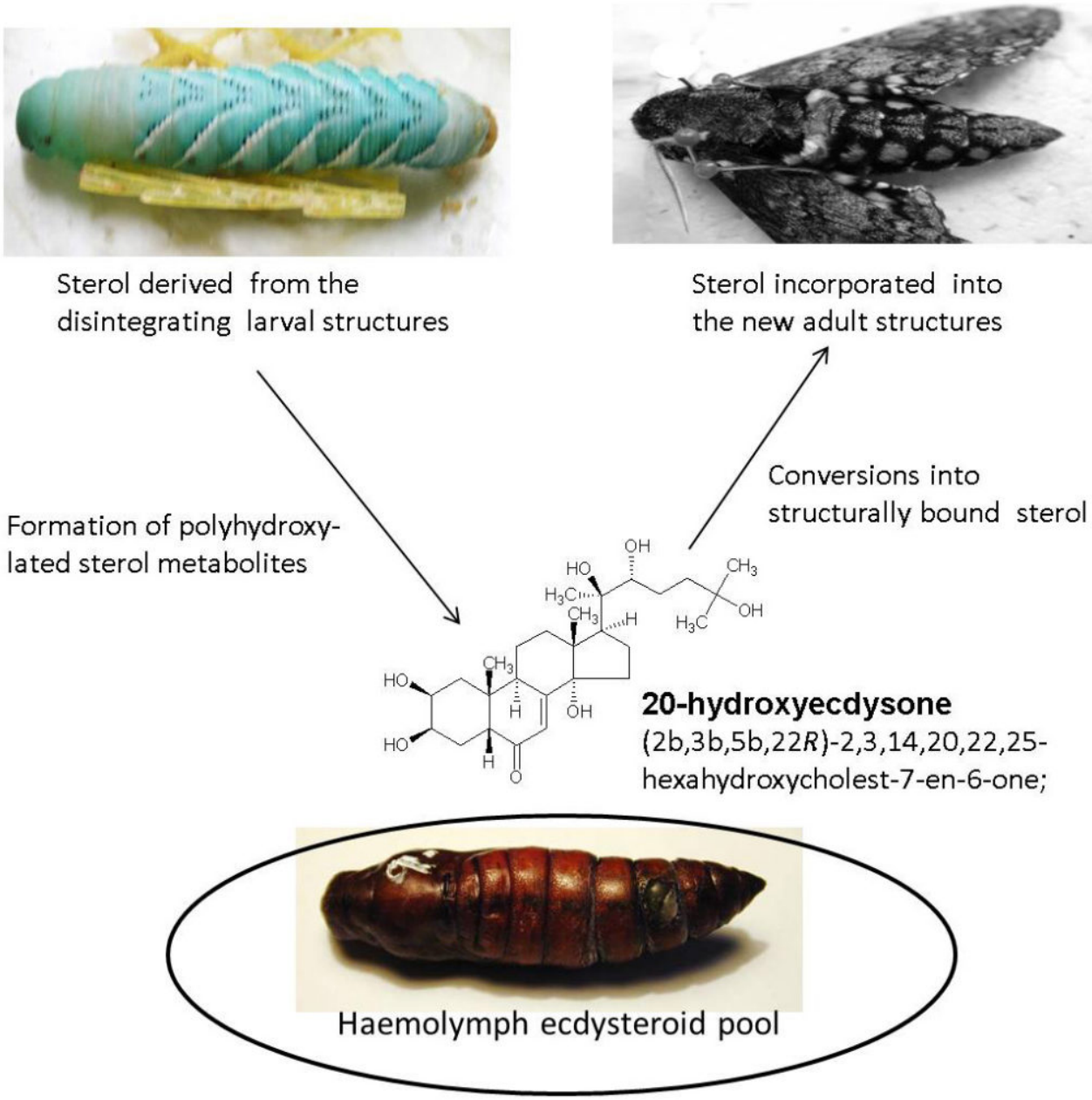
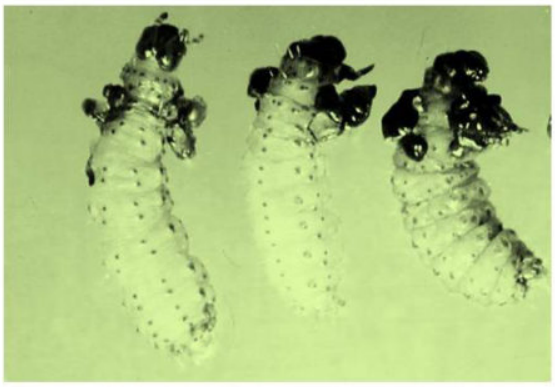


Fig. 1. Insects take sterol from plant and other food sources. During metamorphosis, the structurally bound sterol of the disintegrating larval tissues is reutilised. Hydrogen bonds are converted into hydroxylic groups and the partly water soluble, polyhydroxylated sterol (ecdysteroid) is reutilised for the construction of cell membranes in the proliferating, adult tissues.

During the past 60 years, the brain-PG hormonal theory was abandoned by its creator. The removal of larval PG turned out to have no effect on the timing and succession of insect moults.

The PG evidently served other physiological functions than the release of a moulting hormone. Moreover, it was found that Ecd could not be viewed as insect hormones, because they were produced by multiple disintegrating peripheral organs (see Figure 1). Insects do not synthesize the triterpenoid sterol nucleus. They get it from plants or symbiotic bacteria. Thus, the true biological status of Ecd in insects is not a hormone, but an essential vitamin. In plants, the partly water soluble, "sterolic sugar-like" compounds with 6 or 7 hydroxylic groups (Ecd), become synthesized during the vegetation period of photosynthesis. They get stored in the seeds or roots as the reserve materials for the initiation of future vegetative seasons. It was found, however, that Ecd do not function as phytohormones in plants.

The ontogenetic development of insects is characterised by endogenous peaks in Ecd concentration. The peaks are always correlated with the most intensive histolysis-histogenesis transformations. Artificial injections of Ecd before or after the endogenous Ecd peaks cause dramatic, pathophysiological disturbances of the moulting process. These adverse and mostly lethal effects of Ecd are generally known as the "hyperecdysonic" syndromes (see Figure 2). We tried to avoid these syndromes by administration of relatively low dosages of Ecd, but did not suceed. The partly polar Ecd do not penetrate the lipid-coated integumental layers. We tried to bypass the lack of contact action by preparation of Ecd complexes conjugated to the bulky porphyrin molecule. We did not obtain the contact action, but due to a slow metabolic liberation of the biologically active Ecd from the porphyrin-Ecd complex, we have achieved a more or less normal, larval-pupal transformation, without the adverse hyperecdysonic syndromes.



Acrolepiopsis assectella, precocious metamorphosis induced by addition of 20-E in the larval diet

Galleria mellonella, precocious supernumerary larval creature induced by injection of 20-E into larvae

Manduca sexta, "hyperecdysonic" larval-pupal intermediate creature caused by injection of 20-E into prepupae

Manduca sexta, " hyperecdysonic" pupal-adult creatures induced by injections of 20-E into early pupal stages

In vertebrate animals, Ecd generally exhibit effects that are similar to the vitamin D_3 (calciferol), eventually combined with anabolic growth effects similar to the androgenic steroid hormones. These conclusions can be documented by the pronounced anabolic effects of Ecd in domestic animals (rabbit, swine, cattle, sheep, Japanese quails). In addition, there exists a plethora of beneficial pharmacological effects in the human body (increased growth of bone and muscles, improved physical and mental state, improved muscle strength in athletes, metabolic stimulation, tonic effects, neurogenic, psychogenic, immunogenic, antiallergenic, anti- stressoric, anti-cancerogenic and many other more or less sufficiently supported data). A retrospective look at the history of vitamin D shows that the pioneers working on the elucidation of the rickets bone disease observed long ago (during 1930-ies) that the active compound was somehow related to 7-dehydrocholesterol, which could be converted from other sterols by UV-irradiation. They looked for the antirachitic vitamin D among the purely lipophilic fish oils and animal fat.

I am convinced that Ecd represent a previously overlooked, special group of the amphoteric, both partly lipid and partly water soluble class of the esential vitamin D. Ecd possess the

7-dehydrocholesterol unsaturation, which is stabilised by the conjugated 6-keto group. In contrast to the so far known precursors of calciferol (vitamin D_3), which require activation by ultraviolet radiation and metabolic incorporation of 3 additional hydroxylic groups in the liver, the Ecd type of vitamin D_6 (6 comes from the latin "*Hexapoda*" = insects) contains not only 3, but 6 or 7 prefabricated hydroxylic groups.

There are sufficient data which show that Ecd (Vitamin D_6) can stimulate regeneration and tissue growth or enhance metabolic rates in insects, mammals and also in humans. Unfortunately, due to the limited supply of pure Ecd compounds, there are still limited pharmacological data on avitaminosis due to the lack of the vitamin D_6. It is difficult to cure avitaminosis if you do not know or do not have the responsible vitamin. I have a feeling, however, that the defficiency of vitamin D_6 (Ecd) could be behind the hitherto incurable diseases, especially those related to impaired regeneration, aberrant cell growth or disturbed neuromuscular functions. Investigations along these lines have been persistently hindered by an errant belief in the moulting hormones of insects.

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Publication

Comprehensive physiology and toxicology of ecdysogens - The metabolically activated porphyrin-ecdysteroid complexes in insects.
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