# Role of ecdysone in larval metamorphosis

**Editorial**

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Larvae of almost all insects and nematodes have to undergo a cycle of molting for growing and further development, and with the final molt, adults emerge (complete metamorphosis). In insects, it seems that complete metamorphosis takes place through a dormant stage (pupa), in which all larval cells (muscles, salivary glands, gut, etc.) disintegrate by apoptosis. That is why adult forms appear completely different from their pre-pupa larval stages. In contrast, adult nematodes resemble their final larval stages because dormant pupa stages are absent. In insects, molting with or without pupation requires a pro-thoracicotropic hormone (PTTH) secreted by two pairs of cells in the larval brain. This hormone activates prothoracic glands to secrete a steroid hormone, known as the ecdysone. Also by these glands, sufficient production of the juvenile hormone (JH), promotes larva molting. In case of lower JH production, steroid hormones promote pupation, while complete loss of JH leads to direct formation of the adult from the last final larval molt[1].

Steroid hormones have an essential role on the physiological development and behavior of various organisms. Ecdysone is a major steroid hormone that directs major transitions during developmental stages in the life cycle of some helminth and almost all insects by coordinating larval molting and metamorphosis. Ecdysteroid is produced by the prothoracic gland of all insects as 20-hydroxyecdysone. Increase of ecdysteroid induces the expression of genes controlling protein production for larval development. In adult female insects, ecdysone signaling is critical for reproduction as it mediates egg-chamber maturation during oogenesis, whereas in adult males, ecdysteroids have a role in sperm maturation. It is also present in several plants to protect them from agricultural insects. The ecdysone receptor (EcR) is a nuclear receptor found in the cells of reproduction in all insects, and is activated through binding with ecdysteroid. Once activated, it leads to activation of several genes responsible for physiological changes leading to larval ecdysis (molting). EcR is a non-covalent heterodimer of two proteins; EcR protein and ultraspiracle protein (USP), which are homologous to the mammalian farnesoid X receptor (FXR) and retinoid X receptor (RXR) proteins, respectively. The term USP is usually used for the EcR partner from dipteran and lepidopteran insects, while RXR is applied in other insects. This means that EcR consists of EcR protein and USP for dipteran and lepidopteran insects, whereas it consists of EcR protein and RXR for other insects[2-5].

EcR is mainly applied to control gene expression with two uses; for gene therapy in medical and agricultural fields, and for drug development and vector control in Parasitology researches. The present editorial aims to throw light on the second application.

**Key Words:** 20-hydroxyecdysone, ecdysone, ecdysone receptor (EcR), larva molting, metamorphosis, pro-thoracicotropic hormone, steroid hormone.

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**Historical background:** Ecdysteroids were detected during schistosomula development 10-20 days post infection[6], and as a chemoattractant compound in the extracts of adult female *S. mansoni*[7]. As they were excreted in the biological fluids of infected vertebrates, their use as an efficient chemotherapeutic marker was suggested, based on its marked decrease in urine samples after anti-schistosomal treatment[8]. Ecdysone and 20-hydroxyecdysone were the major identified compounds of ecdysteroids detected in *H. diminuta* adult worms and eggs[9], and in *O. volvulus* and *O. gibsoni* as well as the bovine tissues harboring them[10]. In 1991 was the first study showing that the ecdysteroids have an essential role in larval development of *Brugia pahangi* and *Dirofilaria immitis* similar to that found in insects[11]. For arthropods, ecdysteroids were detected in incubations of salivary glands, coxal glands, testis, midgut and fat bodies of nymphs belonging to an argasid tick (*Ornithodoros parkeri*). It was found that ecdysone was secreted by the epidermal cells and converted to 20-hydroxyecdysone using the fat body cells[12]. In sequencing of *A. gambiae* prophenoloxidase gene, the investigators detected two ecdysteroid regulatory elements and observed the up-regulatory role of 20-hydroxyecdysone on the transcription of this gene *in vitro*[13].

**Drug development:** It was in 1993 when the first report was published, dealing with the use of azadirachtin; a non-steroidal ecdysteroid inhibitor. It was found that it abolished molting of *D. immitis* larvae to the fourth stage *in vitro*[14]. Later, the two components of *B. malayi* EcR (*Bma*EcR and *Bma*RXR) were identified and the

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investigators proposed the opportunity to use these components for further researches to develop potential drug targets[15]. The same American investigators conducted another study to identify presumed ecdysone response elements (EcREs) in *B. malayi* genome. The results revealed the presence of 18 genes which contained presumed EcREs. They were functionally classified to encode proteins involved in metabolism and developmental transcription. One of these genes was cloned and the investigators induced gene mutation which resulted in loss of ecdysone response, indicating the presence of functional EcREs in the *B. malayi* genome[16]. Recently, the idea of using *Bma*EcR as new drug target was validated and the American investigators used Ponasterone A and Muristerone A to treat *B. malayi*-infected gerbils. Both inhibitors proved to be strong ecdysone agonists[17].

**Vector control:** The study conducted in Brazil proposed the use of lignoids as an effective insecticide against winged bugs. The investigators used different phytochemicals compounds added to the diet of different species transmitting Chagas' disease, and fed the winged bugs on blood containing *T. cruzi* epimastigotes. Results revealed that burchellin (a lignoid) significantly decreased their number in the digestive tract[18]. The results of another study conducted in Bolivia to evaluate the effect of azadirachtin on the control of Chagas' disease revealed its efficacy to significantly decrease *T. cruzi* epimastigotes in the digestive tract compared to the control larvae (control and ecdysone-treated groups)[19]. In 2013, Italian investigators demonstrated a close cooperation between 20-hydroxyecdysone and EcR of *A. gambiae* mosquitoes. It was found that eggs development was regulated through interaction between male 20-hydroxyecdysone and a female protein called mating-induced stimulator of oogenesis. The latter was highly expressed after mating and the interaction was produced *via* the female EcR. Therefore, the investigators recommended to benefit from this interaction as a new method for control of malaria transmission[20].

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