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Ecdysone act as a growth regulators hormone

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Abstract
The ecdysone receptor (EcR) belongs to the nuclear-hormone receptor superfamily that functions as a ligand-activated transcription factor. The EcR plays an essential role in arthropod development and reproduction. While the molecular basis for the interaction between the EcR and its ligand has been well investigated in insects, information on the EcR function in crustaceans is limited. EcR bound with ecdysone hormone. The molting hormones, ecdysteroids play important roles in initiating and regulating molting and metamorphosis in arthropods. Besides the function as a molting hormone, ecdysteroids are also involved in the control of reproduction and embryogenesis. Most actions of ecdysteroids are accomplished via the ecdysone receptor (EcR). This receptor is a ligand-dependent transcription factor and forms a heterodimer complex with ultraspiracle protein (USP), which is a homologue of vertebrate retinoid X receptor (RXR).

Keywords: ecdysone receptor, ecdysteroid, molting

Introduction
Insects occupy more than 70% of entire animal kingdom and are the most successful group of organism living on earth. They are usually divided into three groups i.e., harmless, injurious and beneficial. A group of injurious insects referred as pests, annually destroy between 6-30% of agricultural harvest in developing countries. These losses become even more significant for stored cereal products than pre-harvest losses, because post-harvest costs are much higher than the cost of production. Lepidopteran insects are among the major pests of several economically important crops and their control requires a multi-pronged intervention. While insecticides have been used in several IPM (Insect pest management) programmes, pheromone traps have been frequently used to capture and kill insect pests in the field. The capacity of novel chemicals to disturb the mating and molting processes of insects has been capitalized for pest control. Insects on the basis of their ability to undergo metamorphosis are broadly classified into ametabolous (no metamorphosis), hemimetabolous (incomplete metamorphosis) and holometabolous (complete metamorphosis).

Metamorphosis is the characteristic feature of majority of the insects, including holometabola during the postembryonic development i.e., the ontogeny accomplished after hatching. Metamorphosis is marked by abrupt changes in the form and structure during the postembryonic development. The larval forms are the juveniles of holometabola that lack the external rudiments of wings and genitalia but possess imaginal discs. The larvae are voracious feeders and have different habitat and niche from the adult stage. The non-feeding pupal stages are usually hidden or somehow protected stage. The tissue degeneration and rebuilding mainly occurs at the pupal stage, which also possesses the external rudiments of wings and genitalia. The adult stage of holometabolous insect is morphologically very different from the previous stages and they are usually prolific breeders (Sehnal *et al*., 1996; Truman and Riddiford, 1999, 2002; Buszczak and Segraves, 2000; Tissot and Stocker, 2000). Ecdysterone or 20E is responsible for insects development, Molting and metamorphosis. The molting hormone, 20 Hydroxyecdysone (ecdysterone or 20E), is a naturally occurring ecdysteroid hormone that controls the molting of arthropods (Thummel, 1995, 1996) [6]. During insect development, it binds to the ecdysone receptor, a ligand-activated transcription factor found in the nuclei of insect cells (Riddiford, 2000). This in turn leads to the activation of many other genes, as evidenced by chromosomal puffing at over a hundred sites. Ultimately the activation cascade causes physiological changes that result in molting (Henrich, 2005).

Biosynthesis, chemistry and mode of action

PTTH acts on the prothoracic glands (PGL) and stimulates ecdysteroid synthesis (Gilbert *et al*., 1988). Thus 3- [6] hydroxyecdysone is released into the haemolymph where it is reduced by a ketoreductase to ecdysone. The prohormone ecdysone is converted to the principal molting hormone 20-hydroxyecdysone (20E) in the mitochondria and microsomes of peripheral tissues such as haemocytes, fat body, Malpighian tubules and epidermal cells (Riddiford *et al*., 2001) [5]. 20E finally exerts its effect and causes apolysis and secretion of larval, pupal or adult cuticle (Gilbert, 1989). Ecdysteroid is a well-defined term for all compounds structurally related to ecdysone. Further it includes true ecdysteroid and ecdysteroid related compounds. The biologically active ecdysteroid refers to the molting hormone. Chemically ecdysone is the trivial name of a specific compound (22R)-2β, 3β, 14α, 22, 25-pentahydroxy-5β-cholest-7-en-6one, a derivative of cholesterol. 20-Hydroxyecdysone (20E) is the active form, which is a result of ecdysone 20-monoxygenase catalyzed hydroxylation (Grieneisen, 1994; Rees, 1995). The two molting hormones ecdysone and 20E were originally designated as α nd β ecdysone respectively (Horn and Bergamasco, 1985). In arthropods, 20E is one of the most ubiquitously distributed ecdysteroid utilized by the molt cycle and is also associated with various physiological events (Gilbert *et al*., 2002) [1]. The regulation of ecdysteroidogenesis has been studied continuously for the past several decades and recent discoveries using Drosophila molecular genetics have advanced our knowledge further. The availability of genome sequences, the ease of genetic manipulation and the large collection of mutants all make Drosophila an attractive system for understanding the mechanisms regulating steroidogenesis. Regulation of ecdysteroid synthesis is complex, and is under the control of peptide hormones as well as the JH. It has been known for some 85 years that a factor from the insect brain can stimulate the PGLs of both diptera and lepidoptera. PTTH stimulated ecdysteroid production in PGLs occurs via a cascade of events which is yet to be elucidated completely. The isolation and purification of ecdysone and 20E by Butenandt and Karlson (1954) revolutionized the field of insect endocrinology. The pioneering research of Clever and Karlson (1960) revealed puffing patterns of the Chironomous tentans salivary gland polytene chromosome by ecdysteroid. This observation of puff regulation was later confirmed in genetic model organism, the fruit fly Drosophila melanogaster by several other groups (Ashburner *et al*., 1974; Ashburner and Richards, 1976). Based on these observations as well as through a series of detailed and elegant studies, Ashburner and group (1974, 1976) proposed a model for the regulation of gene expression by 20E. Since then this model became the basis of the knowledge of mechanism of steroid hormone action, which suggests that ecdysteroid could initiate a cascade of gene expression by directly acting on the nucleus. According to this model, the ecdysone upon binding to its specific receptor directly regulates two classes of genes, a small class of early regulatory genes and a large class of late genes. The protein products of the early genes in turn repress their own expression and induce the much larger set of late genes that play a more direct role in controlling the biological response of hormone. Extensive studies based on this model have provided insights into the molecular mechanism of 20E action (Henrich and Brown, 1995; Thummel, 1996; Henrich *et al*., 1999; Riddiford *et al*., 2001) [6, 5].

Insects and their nuclear receptor structure function and binding sites

The ecdysone receptor is a noncovalent heterodimer of two proteins the EcR protein and ultraspiracle protein (USP). These nuclear hormone receptor proteins are the insect orthologs of the mammalian farnesoid X receptor (FXR) and retinoid X receptor proteins (RXR) receptively. Indeed, based on sequence homology considerations, some researchers reserve the term USP for the EcR partner from lepidopteran and dipteran insects, and use RXR in all other instances. EcR and USP share multidomain architecture common to all nuclear hormone receptors, namely an Nterminal transcriptional activation domain (A/B domain), a DNA binding domain (C domain, highly conserved between receptors), a linker region (D region), a ligand-binding domain (E domain, moderately conserved) and in some cases a distinct Cterminal extension (F-domain) (Koelle *et al*., 1991) [3] The DNA-binding domains of EcR and USP recognise specific short sequences in DNA, and mediate the binding of the hetero dimer to these ecdysone response elements (EREs) in the promoters of ecdysone responsive genes. The ecdysteroid binding pocket is located in the ligand-binding domain of the EcR subunit, but EcR must be dimerised with a USP (or with an RXR) for high affinity ligand binding to occur. As we found for TR and RAR, comparison of the 3D structure of the hormone-binding domains of EcR and LXR revealed that some hormone-binding residues are conserved (Figure 1). Specifically, Phe-397/Phe-329 (EcR/LXR) and Met- 380/Met-312 have hydrophobic interactions with the center of the hormone, and Arg-387/Arg-319 interacts with the C3-OH group of both ponA and eCH. Trp- 526/Trp-457 has been proposed to be part of a tryptophan/histidine activation switch in LXR (Williams and others 2003). Carmichael and colleagues (2005), however, suggested that this tryptophan does not participate in an activation switch in EcR because this would not explain why ponA, which lacks the 25-hydroxyl group, is an agonist for EcR. Several amino acids of EcR that interact with the hydroxyl groups of ponA are not conserved in LXR, which likely is due to the absence of these hydroxyl groups in the ligands that bind LXR. For example, Tyr-408 in EcR, which forms a strong hydrogen bond to the 20-OH group of ponA, is a phenylalanine in LXR. Other key differences between the hormone binding pockets of EcR and LXR include Arg-383/ Glu-281 and Glu-309/Asn239. Different types of inhibitors or insecticides bind on these binding site where ecdysone bound, some inhibitors act as antagonist and other act as agonists. Agonists act as growth regulators and thus help pre metamorphosis because of that insects died. As compared to it antagonist retard the growth of insects and because of that metamorphosis not occur and adult insect are not formed. So various insecticides binds at these binding sites and help to control pest by retard the insects development, growth, molting, metamorphosis. Insect growth regulators control insect population, by primarily regulating molting, metamorphosis and many other physiological and developmental processes (Williams, 1956). Nonsteroidal dibenzoylhydrazines such as RH5849 and RH5992 exert their insecticidal effect by binding to the 20-hydroxyecdysone binding site and activating the ecdysteroid receptors permanently. Their comprehensive effects and high selectivity as well as lower toxicity to non-target animals and the environment provide new tools for integrated pest management EcR is the target of the environmentally safe bisacylhydrazine insecticides used against pests which cause

severe damage to agriculture. N-tert-butyl-N, N'-dibenzoylhydrazines (DBHs) were discovered as molting hormonal agonists, and causes incomplete molting in insects leading to death. A number of DBH analogs with various substitutes at benzene rings were synthesized and the structure-activity relationship (SAR) studies performed. Recently, four DBH compounds including tebufenozide, methoxyfenozide, chromafenozide and halofenozide have been commercialized. Chromafenozide is found to be significantly potent against various lepidopterous insects, but at the same time almost non-toxic to non-lepidopterous species, including pollinators, predators and parasitoids. Even though 20E is commonly used as molting hormone in most of insects and has similar potency among insects, SARs of non-steroidal ecdysone agonists varied among insect species. The reason for the difference of SARs between ecdysteroids and non-steroidal compounds is disclosed by the three dimensional structure analysis of ligand-bound EcR, showing that ponasterone A (PonA), one of the most potent ecdysteroids, does not necessarily overlap with a chromafenozide analog (BYI06830) in the binding pocket, and therefore, the interaction between EcR and DBHs can be species dependent.

References

1. Gilbert LI, Rybczynski R, Warren JT. Control and biochemical nature of the ecdysteroidogenic pathway. Annu. Rev. Entomol. 2002; 47:883-916.
2. Henrich VC, Siiter TJ, Lubahn DB, Maclntyre A, Gilbert LI. A steroid/thyroid hormone receptor superfamily member in Drosophila melanogaster that shares extensive sequence similarity with a mammalian homologue. Nucl. Acids Res. 1990; 18:4143-4148.
3. Koelle MR *et al.* The Drosophila EcR gene encodes an ecdysone receptor, a new member of the steroid receptor superfamily. Cell. 1991; 67:59-77.
4. Koelle MR, Talbot WS, Segraves WA, Bender MT, Cherbas P, Hogness DS. The Drosophila EcR gene encodes an ecdysone receptor, a new member of the steroid receptor superfamily, Cell, 1991; 67:59-77.
5. Riddiford LM, Cherbas P, Truman JW. Ecdysone receptors and their biological actions. Vitam. Horm. 2001; 60:1-73.
6. Thummel CS. Flies on steroids-Drosophila metamorphosis and the mechanisms of steroid hormone action. Trends Genet. 1996; 12:306-10.