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The pleiotropic allatoregulatory neuropeptides and their receptors: A mini-review

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ABSTRACT

Juvenile hormones (JH) are highly pleiotropic insect hormones essential for post-embryonic development. The circulating JH titer in the hemolymph of insects is influenced by enzymatic degradation, binding to JH carrier proteins, uptake and storage in target organs, but evidently also by rates of production at its site of synthesis, the *corpora allata* (CA). The multiple processes in which JH is involved alongside the critical significance of JH in insect development emphasize the importance for elucidating the control of JH production. Production of JH in CA cells is regulated by different factors: by neurotransmitters, such as dopamine and glutamate, but also by allatoregulatory neuropeptides originating from the brain and axonally transported to the CA where they bind to their G protein-coupled receptors (GPCRs). Different classes of allatoregulatory peptides exist which have other functions aside from acting as influencers of JH production. These pleiotropic neuropeptides regulate different processes in different insect orders. In this mini-review, we will give an overview of allatotropins and allatostatins, and their recently characterized GPCRs with a view to better understand their modes of action and different action sites.

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1. Introduction

Post-embryonic development of insects is highly dependent upon two types of pleiotropic lipophilic hormones, the steroid 20-hydroxyecdysone (20E) and the sesquiterpenoid juvenile hormones (JH). While surges of 20E occur before each insect molt, the presence or absence of JH determines the nature of the insect's developmental transition. Next to its role in metamorphosis, JH has also been shown to be involved in pheromone production, diapause, foraging behavior, caste determination in social insects, locust phase polyphenism and several aspects of insect reproduction such as priming of the fat body, vitellogenesis and patency (Applebaum et al., 1997; Goodman and Cusson, 2012; Goodman and Granger, 2005; Hartfelder, 2000; Verlinden et al., 2009; Verma, 2007). JH is produced and released from the *corpora allata* (CA), a pair of specialized endocrine glands located in the posterior portion of an insect's head. Several JH homologs have been found in different insect orders. These homologs have a methyl ester and an epoxide ring in common, but can differ in the number of methyl and ethyl side chains or in the number of epoxide rings (Richard et al., 1989). Nevertheless, JH III is the most widespread and predominant JH in insects (Darrouzet et al., 1997; Goodman and Cusson, 2012; Kotaki et al., 2009). The complete biosynthetic pathway of JH III comprises 13 discrete enzymatic steps (Bellés et al., 2005; Huang et al., 2015; Nouzova et al., 2011) divided into two parts: early steps following the very conserved mevalonate pathway until farnesyl pyrophosphate is formed and late arthropod-specific steps synthesizing the mature hormone. Studies in moths, cockroaches and mosquitoes have shown that the genes encoding the enzymes involved in the JH pathway are expressed in a highly coordinated manner (Huang et al., 2015; Kinjoh et al., 2007; Nouzova et al., 2011; Ueda et al., 2009), indicating that mechanisms involved in regulating transcription of the JH biosynthetic enzymes will affect the entire synthetic pathway, rather than individual steps, suggesting the existence of common transcription factors influencing the expression of enzymes in the pathway.

JH biosynthesis must be strictly regulated as to respond to environmental cues and developmental needs. Different factors have been shown to regulate JH biosynthesis; these include neural as well as humoral factors. Very recent studies in the yellow fever mosquito, *Aedes aegypti*, and the cockroach, *Blattella germanica*,

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have also indicated that nutritional signals can affect the activity of the CA, placing the very conserved insulin-like peptide (ILP)/TOR pathways upstream of the JH pathway (Maestro et al., 2009; Pérez-Hedo et al., 2013; Süren-Castillo et al., 2012). These reports have underlined the intricate interplay between nutritional signals and JH in the control of vitellogenin synthesis in the fat body of insects.

In this mini-review we will focus on the direct regulation of JH production and/or release mediated by two important classes of neuropeptides, stimulating (allatotropins/ATs) or inhibiting (allatostatins/ASTs) the CA, and their G protein-coupled receptors. These factors are now known to be highly pleiotropic, functioning not only as regulators of JH. With the functional identification of the receptors for these neuropeptides, our understanding of the exact working mechanism of allatoregulatory peptides and their different action sites will greatly improve.

2. Note on GPCRs and methods for their functional characterization

The above mentioned allatoregulatory peptides mediate their actions through G protein-coupled receptors (GPCRs) of the rhodopsin family. In addition to the general structural traits of all GPCRs, such as the presence of seven transmembrane alpha helices (TMs), members of the rhodopsin family also possess an Asn residue in TM1, an Asp residue in TM2, Pro residues in TMs 4–7, Trp residues in TM4 and TM6, three consensus sequences for N-linked glycosylation at the N-terminus, two Cys residues in extracellular loop one and two (forming a conserved disulfide bridge, responsible for receptor stability), phosphorylation and palmitoylation sites located in the C-terminal region (intimately involved in receptor trafficking and signal transduction) and a Asp-Arg-Tyr (DRY) motif at the end of the third TM region, which is suggested to be involved in G protein interaction (Fig. 1). Peptides generally interact with different residues in the extracellular loops and the N-terminal domain (Brody and Cravchik, 2000; Gether, 2000; Vanden Broeck, 1996; Verlinden et al., 2014). Some sequence characteristics of each of the discussed receptors will be treated in the respective paragraphs and can be seen in the alignment of TM1-TM7 of all the pharmacologically characterized A(S)TRs (Fig. 2). Although the consequences of these specific substitutions have not been studied yet for these receptors, one can assume that they will contribute to the specific binding and coupling characteristics of the receptor groups.

Several methods have been used to functionally characterize these GPCRs. We will give a short overview here.

Before a GPCR can be characterized, the complete nucleotide sequence needs to be known. The receptor cDNA is then cloned in an expression vector. Mammalian cell lines (Chinese Hamster Ovary [CHO] cells or Human Embryonic Kidney [HEK] 293 cells) and *Xenopus* oocytes are the most commonly used expression systems. These are used in the bioluminescence-based assay (CHO cells – calcium) (Suppl. Fig. 1), the fluorescence-based assay (HEK293 cells – calcium) (Suppl. Fig. 2), the luciferase-based assay (HEK293 cells – cAMP) (Suppl. Fig. 3) and the electrophysiological assay (*Xenopus* oocytes) (Suppl. Fig. 4).

Since the downstream signaling cascade of orphan receptors is not known, it seems hard to decide which assay to use. This problem was circumvented with the discovery of the promiscuous G protein α subunits $G\alpha_{16}$ (human) and $G\alpha_{15}$ (murine). These Gα proteins possess the ability to interact with most GPCRs and couple to phospholipase C_{β}. They thus redirect the signaling pathways of GPCRs toward the release of calcium (Offermanns and Simon, 1995). The release of intracellular calcium upon receptor activation can be measured by both the bioluminescence and the fluorescence assay. In the bioluminescence assay a bioluminescent protein aequorin, purified from the jellyfish, *Aequoria victoria*, interacts with calcium and causes a light signal (Prasher et al., 1987; Stables et al., 1997) (Suppl. Fig. 1). The fluorescence assay uses a calcium sensitive fluorophore that serves as readout (Bender et al., 2002) (Suppl. Fig. 2). For the luciferase assay a reporter gene plasmid was constructed. The plasmid consists of six cAMP response element (CRE) repeats and will transcribe luciferase relative to the intracellular cAMP levels (Hearn et al., 2002; Johnson et al., 2004) (Suppl. Fig. 3). In the electrophysiological assay, G protein-gated inwardly rectifying potassium channels (GIRKs) are activated upon ligand binding. These channels are expressed in *Xenopus* oocytes together with the receptor of interest. This leads to subsequent inward potassium currents that can be measured (Ho and Murrell-Lagnado, 1999; Kofuji et al., 1995; Ulens et al., 1999) (Suppl. Fig. 4).

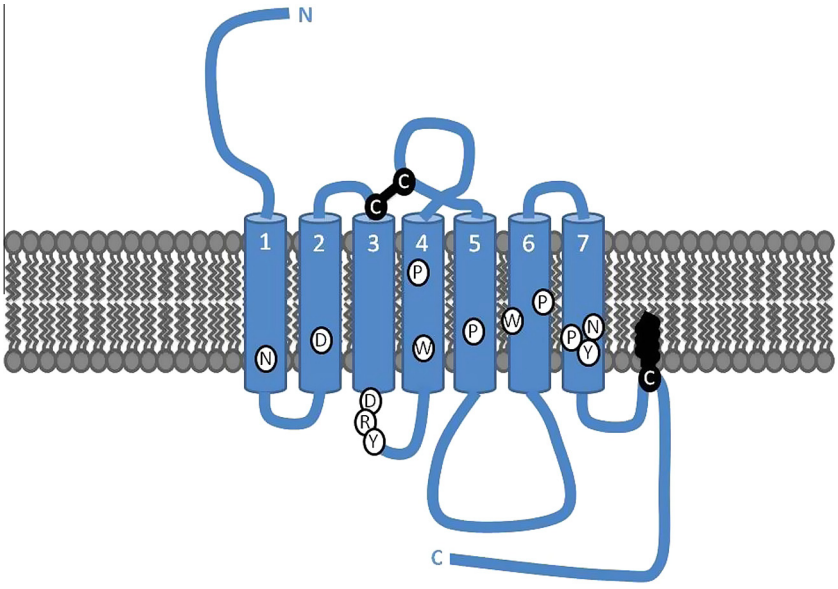

Fig. 1. Snake diagram of the rhodopsin GPCR family. The characteristic features are depicted: highly conserved key residues are indicated by black characters in white circles. A majority of family A members have a palmitoylated cysteine in the C-terminal tail causing formation of a putative fourth intracellular loop.

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