

## Review Article

<https://doi.org/10.20546/ijcmas.2019.802.098>

## Neuropeptides as Novel Insecticidal Agents

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### ABSTRACT

Neuropeptides (protein molecules) are synthesised in the neurons, helps to communicate the impulse from the stimulant to the receptor. Neuropeptides are responsible for regulating a various physiological functions including development, metabolism, water and ion homeostasis, and as neuromodulators in circuits of the central nervous system. Neuropeptides are different from neurotransmitters because, former releases in the haemolymph and the later releases in the neuro-neuro junction or in the neuro-muscular junction. The first neuropeptide isolated from *Periplanata Americana* was proctolin in the year 1975 which helps in muscle contractions in hindgut, reproductive, skeletal and heart muscle. At present a total of 4782 insect neuropeptide records were obtained which perform various related physiological functions. Thus it paves the way for the generation of novel type of putative insect control agents based on backbone cyclic (BBC) peptidomimetic antagonists of insect-neuropeptides. At present four different neuropeptides such as proctolin, kinin, pheromone biosynthesis activating neuropeptide (PBAN) and allatostatin were studied thoroughly and their biologically active sequence were identified. Using this sequence peptidomimetic analogues (either as agonists or antagonists) were synthesized in automated peptide synthesizer and tested for their efficacy as insecticide. Among those four PBAN showed good result as insecticide by reducing pheromone production up to 73% in *Helicoverpa peltigera*. Based on this many neuropeptides were under in vitro test for their antagonist activity. In 2016, a synthetic antagonistic neuropeptide based on pheromone biosynthesis activating neuropeptide was registered for patent by Altstein. This neuropeptide based insecticide is highly insect specific and can be incorporated as apart in integrated pest management though the production of synthetic peptide is critical.

#### Keywords

Insect neuropeptide,  
PBAN, backbone  
cyclic  
peptidomimetic  
antagonists

#### Article Info

Accepted:  
07 January 2019  
Available Online:  
10 February 2019

### Introduction

To meet the requirements of population green revolution has started which results in the use of toxic chemicals and insects too gained resistance to overcome these toxic substances. Continuous use of those toxic substances in turn results in the degradation of environment.

To overcome those difficulties, strategies were approached based on integrated pest management which includes the characteristics of insect specific, non toxic, compatible with other insect control agents, etc. Initially to meet these requirements various compounds such as bio control agents, newer insecticides, transgenic plants

were introduced. Now a days insects are gaining resistance to those compounds and so an innovative approach for pest management such as neuropeptide based pest control were established. Neuropeptides are the neurohormones which are synthesised in the neurons or neuro endocrine cells and are released in the haemolymph. Neuropeptides coordinates complex of physiological functions like mating, oviposition, moulting, water balance, fat mobilization, etc. (Yeoh *et al.*, 2017). Neuropeptides are produced from larger precursor proteins which are known as prepropeptides. Prepropeptide comprise of a signal peptide (which directs the protein to the secretary pathway), progenitors of mature peptides (the biologically active peptides), spacer peptides (peptide fragments with no known biological function and non conserved sequences) and cleavage sites (monobasic and dibasic) (Yeoh *et al.*, 2017). The first neuropeptide isolated was proctolin from cockroach which was found to have myostimulatory activity (Starratt and Brown, 1975). One year later AKH, the adipokinetic hormone of *Locusta migratoria* was found. AKH-related peptides have now been identified in numerous insects, and several other protostomes including arthropods, nematodes, annelids and mollusks (Gade, 1997).

Only with the advent of genomics, protein mass spectrometry and high-field NMR spectroscopy in the late 1980s and 1990s knowledge on insect neuropeptides was increased. Later in the year 1989 PBAN was found to regulate sex pheromone synthesis in female moths (Raina *et al.*, 1989) with this the knowledge on insect neuropeptide has been increased. Neuropeptides were classified into different families based on the homology of amino acid sequence. In order to standardize classification of neuropeptides, DIneR (Database for Insect Neuropeptide Research) adopts the nomenclature for naming insect neuropeptide families proposed

by Coast and Schooley (2011).

### **Families of neuropeptide**

At present, roughly 54 insect neuropeptide families were classified which covers 23 insect orders. Among those 54 neuropeptide families only four neuropeptides (Proctolin, kinin, pheromone biosynthesis activating neuropeptide and allatostatin) were studied thoroughly and tested for their bioassay activity against various insects (Table 1).

### **Steps involved in isolation of neuropeptide:n**

Sequencing of protein is done by isolating the specific gene of interest using AQUA and PROCHECK-NMR (Laskowski *et al.*, 1996). Then artificial synthesis of peptide is done by the condensation reaction of the carboxyl group of one amino acid to the amino group of another using Fmoc (fluorenylmethoxycarbonyl) resin (Shin *et al.*, 1999). After isolation, *in vitro* and *in vivo* protein docking is done using various softwares such as ADAM, AutoDock, DARWIN, DIVALI, DOCK, DockVision, EUDOC, FlexX, FLOG, FTDOCK, GOLD, Hammerhead, ICM, LIGIN, LUDI, MCDOCK, Prodock, Proleads, QXP, SANDOCK, etc. (Sousa *et al.*, 2006). Structural modification of synthesised protein is done to obtain the antagonist activity either by Linear replacement /side chain modification (Fig. 1) or by backbone cyclization (Fig. 2) (Gilon *et al.*, 1997).The final product is produced in the form of dry powder (Alstein, 2003).

### **Proctolin**

Proctolin is produced by motor neurons in locusts and found to regulate corpora cardiac crawling behaviour in *Drosophila* (Clark *et al.*, 2006). The biologically active sequence of proctolin contains arginin, tyrosine, leucine,

threonine (Fig. 3). Replacing an amino group with O<sub>2</sub> between Tyr2 and Leu3 was almost found to inactivate the muscle contraction in *Locusta migratoria* at a concentration of 1 mmol/L. Replacing an amino group with O<sub>2</sub> between Arg1 and Tyr2 was found to retained the activity of muscle O<sub>2</sub> significantly. Cyclization of proctolin (Cycloproctolin) was found to be a potent antagonist of proctolin-induced production of the second messengers InsP3 (insulin P3) and InsP4 (insulin P4) (Scherkenbeck, 2009).

### **Kinins**

The first members of the kinin family was isolated from *Leucophaea maderae* also found to be present in nematodes, annelids and molluscs (Radford *et al.*, 2002) triggers ecdysis behaviour. Kinin shares a common C-terminal pentapeptide sequence of Phe-Phe-Aib- Trp- Gly-NH<sub>2</sub>. When Gly is replaced using any of the following substitute and its aphicidal activity was tested (Zang, 2015).

### **Pyrokinins /pheromone biosynthesis activating neuropeptides (PBANs)**

Pheromone Biosynthesis Activating Neuropeptide (PBAN) regulates pheromone biosynthesis and is a peptide of pyrokinin type. Since no PK precursor gene was yet known these peptides were named after their functions: Pheromone Biosynthesis Activating Neuropeptides (PBAN), Diapause Hormone (DH), Melanization and Reddish Coloration Hormone (MRCH) and so on. PBAN and DH were found primarily in Lepidoptera and drosophila. The pyrokinins/PBANs have been extensively explored to develop biostable analogs to be used in insect pest control (Raina and Menn, 1993). The C-terminal pentapeptide, Phe-Ser-Pro-Arg-Leu-NH<sub>2</sub> is the biologically active sequence of PBAN and found homologous to *Mythimna sapareta* as pheromonotropin and

to *Bombyx mori* as diapause hormone. C-terminal hexapeptide, H-Tyr-Phe-Ser-Pro-Arg-Leu-NH<sub>2</sub>, the active sequence of PBAN was found to dissolve in the solvent and hence chosen for insecticidal activity. The peptide H-Arg-Tyr-Phe-D-Phe-Pro-Arg-Leu-NH<sub>2</sub> exhibited the highest antagonistic activity is because when using dextro (d) phe. It caused jitters action in insect. Injection of 100 pmol of this peptide, inhibited sex pheromone biosynthesis by 63% after 2 h (Gilon *et al.*, 1997). Based on substitution of l-amino acids with d-Phe followed by backbone cyclization (Fig. 4), has led to the discovery of several highly potent linear and conformationally constrained, selective, metabolically stable backbone cyclic (BBC) pure antagonists for PBAN (Harinton, 2010).

### **Allatostatin –A, B, C**

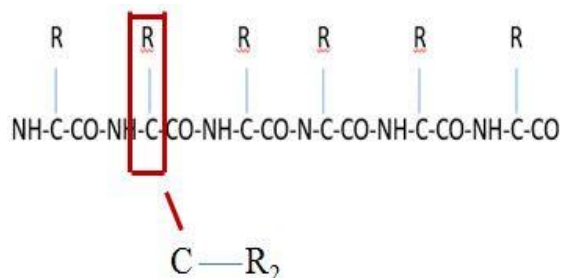
The first member of the insect AST family was isolated in the year 1989 from brain extracts of the cockroach *Diploptera punctata* (Woodhead *et al.*, 1989). AST is found to be three types. AST-A as cockroach type, AST- B as cricket type and AST C as moth type. These peptides were called allatostatins due to their ability to inhibit juvenile hormone (JH) biosynthesis by the corpora allata. AST also regulates various aspects of feeding and metabolism in several species (Yeoh *et al.*, 2017). Allatostatins contains 8-13 amino acids and are amidated. The biologically active peptide sequences of allatostatin are Ala-Pro-Ser-Gly-Ala-Gln-Arg-Leu-Tyr-Gly-Phe Gly-Leu- NH<sub>2</sub>. An in vitro bioassay of the synthesized allatostatins showed >40% inhibition of juvenile hormone synthesis by corpora allata of virgin females with 10<sup>-9</sup>M allatostatin. In addition, allatostatin inhibited juvenile hormone synthesis by corpora allata from mated females and last-instar larvae of *D. Punctata* and corpora allata of adult female *Periplaneta Americana* (Woodhead *et al.*, 1987).

**Table.1** Families of insect neuropeptide

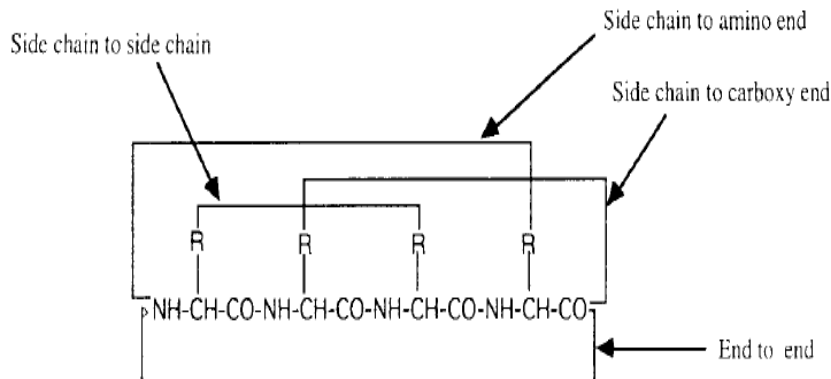
Neuropeptide	Isolated from	Function	References
<b>Adipokinetic hormone</b>	<i>Locusta migratoria</i>	May play a part in development and ecdysis	Siebert, 1999
<b>Anti-diuretic Factor</b>	<i>Tenebrio molitor</i>	Inhibit fluid secretion in Malpighian tubules	Eigenherr <i>et al.</i> , 2002; Schooley <i>et al.</i> , 2012
<b>Allatostatin A,B,C</b>	Cockroach, Cricket, Moth	Inhibits JH synthesis	Woodhead <i>et al.</i> , 1989; Lorenz <i>et al.</i> , 1995; Kramer <i>et al.</i> , 1991
<b>Allatotropin</b>	<i>Manduca sexta</i>	Stimulates JH biosynthesis	Kataoka <i>et al.</i> , 1989
<b>Bursicon</b>	<i>Drosophila melanogaster</i>	Cuticle tanning	Luo <i>et al.</i> , 2005; Mendive <i>et al.</i> , 2005
<b>Capability</b>	<i>Manduca sexta</i>	Impacts desiccation and cold stress tolerance	Huesmann <i>et al.</i> , 1995
<b>Crustacean Cardio-Active Peptide</b>	<i>Locusta migratoria</i>	Initiating the ecdysis	Stangier <i>et al.</i> , 1989
<b>CCHamide</b>	<i>Bombyx mori</i>	Increased the motivation to feed	Roller <i>et al.</i> , 2008
<b>Pigment-dispersing factor</b>	<i>Romalea microptera</i>	Pigment movements in response to light	Rao <i>et al.</i> , 1987
<b>Corazonin</b>	<i>Periplaneta americana</i>	Initiating ecdysis	Veenstra, 1989
<b>Diuretic Hormone 31, 44</b>	<i>Diploptera punctata</i> , <i>Manduca sexta</i>	Fluid secretion in MTs	Furuya <i>et al.</i> , 2000; Kataoka <i>et al.</i> , 1989
<b>Eclosion hormone</b>	<i>Manduca sexta</i> and <i>Bombyx mori</i>	Ecdysis behavior	Kataoka <i>et al.</i> , 1987; Kono <i>et al.</i> , 1987
<b>Ecdysis-triggering hormone</b>	<i>Manduca sexta</i>	Triggers ecdysis	Zitnan <i>et al.</i> , 1996
<b>FMRFamide</b>	<i>Drosophila melanogaster</i>	Ecdysis, myostimulatory in action	Nambu <i>et al.</i> , 1988; Schneider and Taghert, 1988
<b>GP2, 5</b>	<i>Drosophila melanogaster</i>	Anti-diuresis	Hsu <i>et al.</i> , 2002; Sudo <i>et al.</i> , 2005
<b>Insulin-like Peptide</b>	<i>Bombyx mori</i>	Growth, metabolism and reproduction.	Nagasawa <i>et al.</i> , 1986
<b>Ion transport peptide</b>	<i>Apis mellifera</i>	Modulate ion transport	
<b>Kinin</b>	<i>Leucophaea maderae</i>	Myotropic, diuretic activities.	Holman <i>et al.</i> , 1986; Holman <i>et al.</i> , 1987
<b>Limostatin</b>	<i>Drosophila melanogaster</i>	Regulate production and release of DILPs in <i>Drosophila</i>	Alfa <i>et al.</i> , 2015
<b>Myosuppressin</b>	<i>Leucophaea maderae</i>	Inhibit heart and visceral muscle.	Holman <i>et al.</i> , 1986
<b>Neuropeptide F</b>	<i>Drosophila</i>	Helps in foraging and feeding	Brown <i>et al.</i> , 1999
<b>Neuropeptide-like precursor</b>	<i>Drosophila</i>	Role in development	Baggerman <i>et al.</i> , 2002, 2005

<b>Natalisin</b>	<i>Drosophila</i>	Plays role in reproduction	Jiang <i>et al.</i> , 2013
<b>Orcokinin</b>	<i>Bombyx mori</i>	Play roles in gut function.	Yamanaka <i>et al.</i> , 2011
<b>Pheromone Biosynthesis Activating Neuropeptide (PBAN)</b>	<i>Leucophaea maderae</i>	Regulating pheromone biosynthesis	Holman <i>et al.</i> , 1986
<b>Diapause hormone</b>	<i>Leucophaea maderae</i>	Regulation of insect diapause	Holman <i>et al.</i> , 1986
<b>Partner of bursicon</b>	<i>Drosophila melanogaster</i>	Cuticle tanning	Luo <i>et al.</i> , 2005; Mendive <i>et al.</i> , 2005
<b>Pre-ecdysis triggering hormone</b>	<i>Manduca sexta</i>	Tracheal air filling and triggering ecdysis	Zitnan <i>et al.</i> , 1996
<b>Pyrokinin</b>	<i>Leucophaea maderae</i>	Myostimulatory activity and regulates hormone biosynthesis	Holman <i>et al.</i> , 1986
<b>Proctolin</b>	<i>Periplaneta americana</i>	Stimulate muscle contractions	Starratt and Brown, 1975
<b>Prothoracicotropic hormone</b>	<i>Bombyx mori</i>	Regulates molts and metamorphosis	Kataoka <i>et al.</i> , 1991
<b>Sulfakinin</b>	<i>Leucophaea maderae</i>	Induces hyperactivity and aggression	Nachman <i>et al.</i> , 1986
<b>Short neuropeptide F</b>	<i>Drosophila</i>	Roles in feeding, growth.	Nässel and Wegener 2011; Root <i>et al.</i> , 2011
<b>Vasopressin</b>	<i>Locusta migratoria</i>	Triggers diuresis	Proux <i>et al.</i> , 1987
<b>Trissin</b>	<i>Drosophila melanogaster</i>	Regulation of foregut-midgut contractions and food intake	Ida <i>et al.</i> , 2011
<b>SIFamide</b>	<i>Sarcophaga bullata</i>	Involved in control of sexual behaviour	Janssen <i>et al.</i> , 1996
<b>Tachykinin-related peptide</b>	<i>Locusta migratoria</i>	regulation of release of adipokinetic hormone from the corpora cardiac	Schoofs <i>et al.</i> , 1990
<b>Calcitonin</b>	Locust and termite	Not known	Veenstra, 2014
<b>CNMamide</b>	<i>Drosophila melanogaster</i>	Function not available	Jung <i>et al.</i> , 2014
<b>RY amide</b>	<i>Nasonia vitripennis</i>	Not known	Hauser <i>et al.</i> , 2010

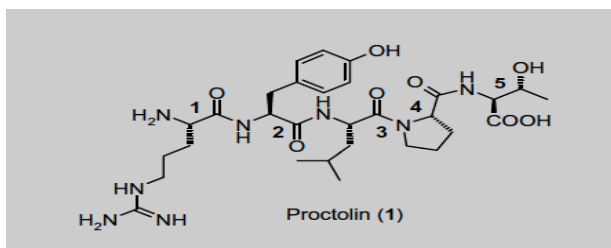
**Figure.1** Linear replacement of a peptide chain



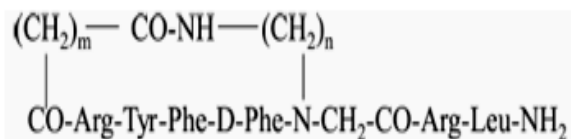
**Figure.2** Backbone cyclization of a peptide chain



**Figure.3** Structure of proctolin



**Figure.4** Backbone cyclization of PBAN



In conclusion, as the neuropeptides play an important role in various physiological activities of insects, modification of these neuropeptides paves the way for the novel pest control strategy. As these neuropeptides are insect specific and environmentally safe it can be used as a component in integrated pest management and this brings an alternative way for using synthetic insecticides (Karuppaiah and Sujithra, 2013). However, the thorough knowledge in the isolation of specific protein sequence in relation to its function is essential to exploit this area. Therefore, by targeting the precursor of neuropeptide and by employing peptidase induced degradation insecticide agent can be produced which would fit well in future pest

management programmes.

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#### **How to cite this article:**

Elakkiya, K., P. Yasodha, C. Gailce Leo Justin and Vijay Akshay Kumar. 2019. Neuropeptides as Novel Insecticidal Agents. *Int.J.Curr.Microbiol.App.Sci.* 8(02): 869-878. doi: <https://doi.org/10.20546/ijemas.2019.802.098>