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The PRXamide Neuropeptide Signalling System: Conserved in Animals

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Abstract
The PRXamide family of neuropeptides is based on the core amino acids at the C-terminal end that are required for activity and on sequence homology of their cell-surface G protein-coupled receptors. The PRXamide family of neuropeptides includes the pyrokinins, pheromone biosynthesis-activating neuropeptides, diapause hormone, CAPA/periviscerokinins (aka cardioacceleratory peptide 2b), and ecdysis-triggering hormone found throughout the Insecta. The vertebrate homologues include neuromedin U because it has a PRNamide C-terminal sequence. The vertebrate G protein-coupled receptors that are homologous to the insect receptors also include receptors for ghrelin, motilin, and thyrotropin-releasing hormone in addition to the neuromedin U receptor. This review will not only summarize the recent literature on this neuropeptide family but also include recent information about the prevalence of the neuropeptides across the Insecta based primarily on genomic and transcriptomic sequence information. Information is also included about the PRXamide ligands and their receptors in other protostome and deuterostome lineages. The conservation of ligands and receptors among all animals will be presented along with ideas on the coevolution of ligands and receptors.

The first four pages of this chapter are available.

Keywords
PBAN, Pheromone, ETH, Ecdysis, CAP2b, CAPA, PVK, Periviscerokinin, Neuromedin U, Ghrelin, Motilin, Thyrotropin-releasing hormone, GPCR, Deuterostomes, Protostomes, Nematoda, Mollusca, Annelida, Echinodermata, Gastropoda

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1. INTRODUCTION

The PRXamide family of neuropeptides is based on the core active amino acids at the C-terminal end and on sequence homology of their cell-surface receptors. The PRXamide neuropeptides have diverse functions that include the pyrokinins (PKs). Within the PK family are several groups that have specific identified functions including the pheromone biosynthesis-activating neuropeptides (PBAN) and diapause hormones (DH). Also within the PRXamide family are the peptides produced by the *capa* gene (CAPA peptides) and the ecdysis-triggering hormones (ETHs). All of these peptides have variable length and N-terminal sequences but have the common C-terminal amide ending, PRXamide (where X indicates a variable amino acid, but most common L, N, V, or I). An indication that these neuropeptide subfamilies have coevolved together is the fact that the G protein-coupled receptors (GPCRs) for these peptides have close sequence homology.

The PRXamide family of peptides and receptors is also found in the deuterostomes. In fact, the receptor for PBAN in the moth *Helicoverpa zea* was identified (Choi et al., 2003) based on the similarity of the vertebrate neuromedin U receptor (NMUr) to the PRXamide receptors from *Drosophila melanogaster* (Park et al., 2002). Cross-reactivity illustrates the closeness of the PRXamide deuterostome and protostome signalling system. The vertebrate NMU peptide has a PRNamide C-terminal ending and will activate the *H. zea* PBAN receptor (Choi et al., 2003). The receptors for NMU are closely related to the insect PRXamide receptors. Coevolution of the PRXamide ligands and their receptors has been experimentally investigated using ligands and receptors from *Tribolium castaneum* (Jiang et al., 2014a). Comparison between deuterostome and protostome peptide ligands and receptors indicates conservation of the PRXamide signalling system (Jékely, 2013; Mirabeau and Joly, 2013). This review will cover background information on both insect and vertebrate, peptides and receptors. In addition, current sequence information indicates that the basal groups of deuterostomes and protostomes have receptors that are closely related to both

vertebrate and insect receptors. These findings indicate that the PRXamide superfamily of peptides and their receptors has been retained as a physiological signalling system throughout the animal kingdom.

2. INSECT PEPTIDE FAMILIES

Insects utilize a plethora of neuropeptides to regulate a variety of physiological functions. The concept of the animal nervous system releasing material into circulation to control growth and development can in fact be dated back to when Kopeć demonstrated that the brain of the gypsy moth, *Lymantria dispar*, releases a factor into circulation that regulates metamorphosis (Kopeć, 1917, 1922). We now know that one of the hormones released by the brain to initiate moulting is the peptide prothoracicotropic hormone, which stimulates the prothoracic gland to produce ecdysone (Bollenbacher et al., 1993). The pioneering work of Ernst and Berta Scharrer in the 1940s initiated the modern concept of neurohormones based initially on morphological studies (Scharrer, 1941; Scharrer and Scharrer, 1945). One of the insects that Scharrer used in her experiments was the oriental cockroach, *Leucophaea maderae*, in which the first PK peptide was later identified. However, the first insect neuropeptide, proctolin, was isolated and identified in 1975 (Brown and Starratt, 1975) followed by adipokinetic hormone in 1976 (Stone et al., 1976). Since then, a large number of insect neuropeptides have been isolated and identified (Gäde, 1997; Gäde and Hoffmann, 2005). With recent genomic, transcriptomic, and proteomic studies of various insects, a large amount of data is available on the neuropeptide signalling system of insects.

Research has indicated neuropeptides belong in families based on primary amino acid sequence and physiological function. Some of the major families of neuropeptides include AKH, FMRFamide, allatotropins, alltostatins, etc. and the PRXamide family (Gäde, 1997). The PRXamide family is based on the active sequence which is a C-terminal motif consisting of PRXamide, where the X is a variable amino acid (Table 1). Within this family are three subfamilies: PK/PBAN/DH peptides, CAPA peptides, and ETH peptides. The PKs were the first to be identified using a cockroach hindgut contraction bioassay during the purification process. It was named leucopyrokinin because it was isolated from the cockroach *Leucophaea maderae* based on stimulating muscle contraction, and a pyroglutamate was found at the N-terminal end (Holman et al., 1986). The PBAN peptide was isolated and sequenced in 1989 based on stimulation of pheromone

Table 1 Selected Amino Acid Sequences of the PRXamide Family of Peptides from Insects Indicating the Conserved Nature of the PRXamide Signal, Shown in Bold

Function and Species	Peptide Sequence	References
Pyrokinins		
Leucophaea maderae	pETSFT**PRLa**	Holman et al. (1986)
Periplaneta americana	HTAGFI**PRLa**	Predel et al. (1997)
	SPPFA**PRLa**	Predel et al. (1997)
	LVPFR**PRLa**	Predel et al. (1999)
	DHLPHDVYS**PRLa**	Predel et al. (1999)
	SESEVPGMWFG**PRLa**	Predel and Eckert (2000)
Drosophila melanogaster	SVPFK**PRLa**	Predel et al. (2004)
PBAN		
Helicoverpa assulta	LSDDMPATPADQEMYRQDP EQIDSRTKYFS**PRLa**	Choi et al. (1998)
Pheromontropic peptides		
Helicoverpa assulta	VIFT**PK**L**a**	Choi et al. (1998)
	SLAYDDKSFENVEFT**PRLa**	Choi et al. (1998)
	TMNFS**PRLa**	Choi et al. (1998)
Diapause hormone		
Helicoverpa assulta	NDVKDGAASGAHSDRLGL WFG**PRLa**	Choi et al. (1998)
CAPA—pyrokinin (DH-1)		
Periplaneta americana	GGGGSGETSGMWFG**PRLa**	Predel et al. (1999)
Drosophila melanogaster	TGPSASSGLWFG**PRLa**	Predel et al. (2004)
CAPA—periviscerokinin		
Drosophila melanogaster	GANMGLYAF**PRVa**	Predel et al. (2004)
	ASGLVAF**PRVa**	Predel et al. (2004)
Periplaneta americana	GSSSGLISM**PRVa**	Neupert et al. (2014)
	GASGLIPVM**RNa**	Neupert et al. (2014)