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REVIEW

NEUROPEPTIDES ARE UBIQUITOUS CHEMICAL MEDIATORS: USING THE STOMATOGASTRIC NERVOUS SYSTEM AS A MODEL SYSTEM

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Summary

The stomatogastric nervous system (STNS) controls the movements of the foregut and the oesophagus of decapod crustaceans and is a good example for demonstrating that peptides are ubiquitously distributed chemical mediators in the nervous system. The stomatogastric ganglion (STG), one of the four ganglia of the STNS, contains the most intensively investigated neuronal circuits. The other ganglia, including the two commissural ganglia (CoGs) and the oesophageal ganglion (OG), are thought to be modulatory control centres. Peptides reach the STNS either as neurohormones or are released as transmitters. Peptide neurohormones can be released either from neurohaemal organs or from local neurohaemal release zones located on the surface of nerves and connectives. There were thought to be no peptidergic neurones with cell bodies in the STG itself. However, some have recently been described in adults of four species, in addition to a transient expression of peptides during development in two species. None of these peptidergic neurones has been investigated physiologically, in contrast to peptidergic neurones that project to the STG and have cell bodies in either the CoGs or the OG. It has been shown that neurones containing the same peptide elicit different motor patterns, that the peptide transmitter and the classical transmitter are not necessarily co-released and that the effect of a peptidergic neurone depends on its firing frequency and on which other modulatory neurones are co-active. The activity of modulatory projection neurones can be elicited by sensory neurones, and their activity can depend on the firing frequency of the sensory neurone. In addition to being found within the neuropile of ganglia, peptides are present in neuropile patches located within the nerves of the STNS, suggesting that these nerves can integrate as well as transfer information. Furthermore, sensory neurones and muscles exhibit peptide-like immunoreactivity and are modulated by peptides. Bath-applied peptides elicit peptide-specific motor patterns within the STG by targeting subsets of neurones. This divergence is contrasted by a convergence at the level of currents: five different peptides modulate a single current. Peptides not only induce motor patterns but can also switch the alliance of neurones from one network to another or are able to fuse different networks. In general, peptides are the most abundant group of modulators within the STNS; they are ubiquitously present, indicating that they play multiple roles in the plasticity of neural networks.

Key words: neuropeptide, neurohormone, modulation, crustacean, neural network, motor pattern generation.

Introduction

Neuropeptides are the most abundant chemical mediators in the nervous system, both in vertebrates (Strand, 1999) and in invertebrates (Nässel, 1993; Schoofs et al., 1997; Keller, 1992). In the 1970s, approximately 20 neuropeptides were known in mammals, and it became clear that peptides produced in the brain have a direct influence on neurones and effect complex behaviours such as learning (De Wied, 1971). The concept of neuropeptides was born, and research on neuropeptides expanded dramatically (Hökfelt, 1991; Nässel, 1993; Strand, 1999). At the same time, the first invertebrate neuropeptides were isolated: in crustaceans, red pigment-concentrating hormone (RPCH) (Fernlund and Josefsson, 1972) and pigment-dispersing hormone (Fernlund, 1971; Fernlund, 1976); in insects, proctolin (Brown and Starrat, 1975; Starrat and Brown, 1975) and adipokinetic hormone (Stone et al., 1976); and in molluscs, FMRFamide (Price and Greenberg, 1977). Since then, the number of neuropeptides isolated has increased greatly. In insects, for example, more than 100 neuropeptides have been isolated, including more than 56 neuropeptides in the two locust species *Locusta migratoria* and *Schistocerca gregaria* alone (Schoofs et al., 1997). Most of the neuropeptides belong to peptide families

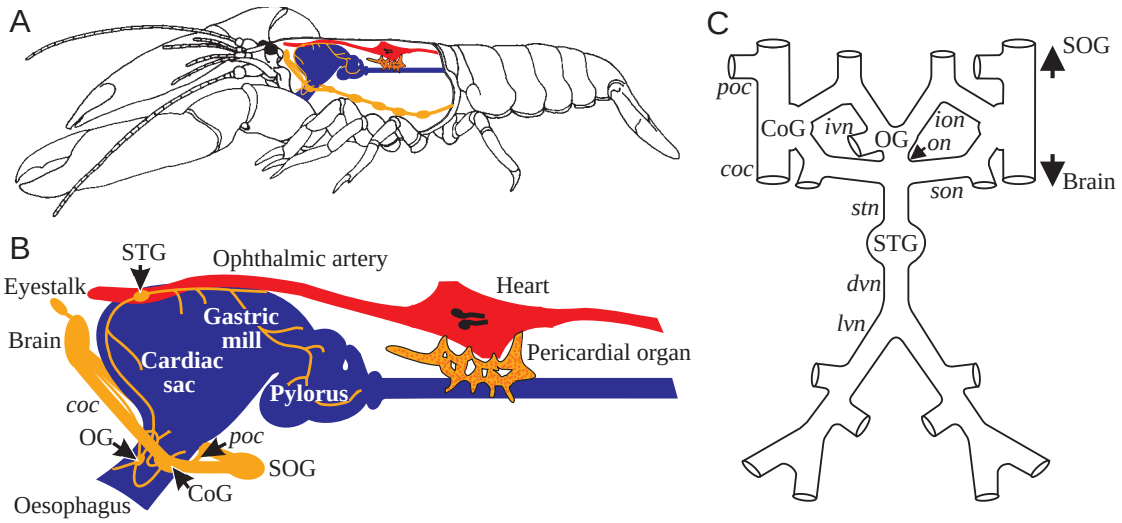


Fig. 1. Schematic drawings showing the stomatogastric nervous system (STNS), stomach, heart and pericardial organs. (A) Location within *Cherax destructor*. (B) Enlarged view: The STNS consists of four ganglia, the paired commissural ganglia (CoGs), the oesophageal ganglion (OG) and the stomatogastric ganglion (STG), together with their connecting and motor nerves. The STNS is located between the brain and the suboesophageal ganglion (SOG), which are connected by the circumoesophageal connective (*coc*) surrounding the oesophagus. The post-oesophageal commissure (*poc*) links both *coc*s close to the SOG. The STG lies within the ophthalmic artery, which carries haemolymph containing hormones released by the pericardial organs to the brain. Another important neurohaemal organ, the X-organ/sinus gland complex, is located in the eystalks. (C) Schematic diagram of an isolated STNS and the location of nerves discussed in the review. *dvn*, dorsal ventricular nerve; *ion*, inferior oesophageal nerve; *ivn*, inferior ventricular nerve; *lvn*, lateral ventricular nerve; *on*, oesophageal nerve; *son*, superior oesophageal nerve; *stn*, stomatogastric nerve. Not drawn to scale (modified from Skiebe, 1999).

while a few, such as proctolin, are orphan peptides that have the same amino acid sequence in all species from which they have been isolated. Most neuropeptides were isolated using bioassays based on physiological effects such as light adaptation, spontaneous contractions of the gut or changes in heartbeat frequency. Immunocytochemistry also flourished in the 1970s and was used to demonstrate that neuropeptides, originally isolated as hormones, are present in the central nervous system (CNS), suggesting additional functions as neurotransmitters (Marder and Hooper, 1985; Nässel, 1993).

To study peptides as neurotransmitters, it was important to study identified neurones containing neuropeptides or the effects of particular peptides on identified neurones embedded in small circuits of known function. Some invertebrate systems fulfilled these needs and have contributed to our understanding of peptide function. The mollusc *Aplysia californica*, for example, has been used to increase our knowledge about peptide co-transmission in studies of the actions of identified motoneurones containing known peptides (Weiss et al., 1993; Brezina and Weiss, 1997). Research on the mollusc *Lymnaea stagnalis* has demonstrated that two alternative mRNA transcripts of the gene coding for FMRFamide-related peptides are expressed in the CNS in a mutually exclusive manner, resulting in the differential distribution of distinct sets of neuropeptides in single neurones (Santama and Benjamin, 2000). In the insect *Manduca sexta*, sequential motor patterns were elicited by neuropetides released in a timed hierarchy (Gammie and Truman, 1997).

This review describes research on neuropeptides performed in another invertebrate system, the stomatogastric nervous system (STNS) of decapod crustaceans. This research has demonstrated that even small neural circuits are modulated by a large number of neuropeptides and has provided insights into mechanisms by which neuropeptides change motor patterns (Harris-Warrick et al., 1992; Marder and Weimann, 1992; Marder et al., 1994; Marder et al., 1997). The STNS is therefore an excellent model system demonstrating that peptides are strongly involved in the plasticity of neural networks. The goal of this review is to summarise our knowledge about the ubiquitous distribution of peptides within the STNS and to reassess the role of peptidergic neurones in the modulation of motor pattern generation in this model system.

The stomatogastric nervous system

The STNS lies between the brain and the suboesophageal ganglion and consists of four ganglia together with connecting and motor nerves (Fig. 1). The ganglia are the paired commissural ganglia (CoGs), the oesophageal ganglion (OG) and the stomatogastric ganglion (STG). The STNS controls the movements of the three regions of the decapod crustacean stomach, the cardiac sac, the gastric mill and the pylorus, in addition to controlling the movement of the oesophagus. The circuits controlling the gastric mill and the pylorus are located in the stomatogastric ganglion (STG). The neurones of the STG can be individually identified and, because of their small number (19–32 neurones depending on the species) and accessibility, the synaptic connections among these neurons have been characterised in the adult STG. The robust firing

patterns under *in vitro* conditions allowed investigation of the effects of peptides ranging from their effects on the general motor pattern to the particular currents the peptide is influencing.

The STG is connected with the rest of the STNS through a single nerve, the stomatogastic nerve (*stn*, Fig. 1C), which therefore carries all the information between the STG and the other ganglia. Within the STNS, a large variety of neuroactive substances have been identified in a number of species. Fig. 2A compares the substances that are present within the STG of five species. These substances include the classical transmitters acetylcholine, glutamate (Marder, 1987) and γ-aminobutryric acid (GABA) (Nusbaum et al., 1989), the biogenic amines (Harris-Warrick et al., 1998a; Harris-Warrick et al., 1998b), the gas nitric oxide (Scholz et al., 1996; Scholz et al., 1998) and a variety of neuropeptides (Marder et al., 1994; Marder et al., 1997). The investigation of peptides within the STNS started in the 1980s (Hooper and Marder, 1984) and since then peptides have become the largest group of chemical mediators found in the STNS or in neurohaemal structures that can influence the STNS.

Peptides in neurohaemal organs and neurohaemal release zones

Peptides as neurohormones can be released by neurohaemal organs and neurohaemal release zones. Neurohaemal organs in decapod crustaceans include the X-organ/sinus gland complex in the eyestalk, the pericardial organs and the postcommissural organ, the latter being a neurohaemal organ associated with the postoesophageal commissure (*poc*, Fig. 1B). The STG lies within the ophthalmic artery, which transports haemolymph, including the neuroactive substances released from the pericardial organs, from the heart to the brain (Fig. 1). It has therefore been assumed that hormones present in the pericardial organs are important for the modulation of the STG motor patterns (Fig. 2B, e.g. *Cancer borealis*, Christie et al., 1995b; *Cherax destructor*, Skiebe, 1999; Skiebe et al., 1999). Putative neurohaemal release zones close to the STNS were found on the *poc* and on the circumoesophageal connectives (*cocs*) of the crayfish *Cherax destructor*, exhibiting allatostatin-like, proctolin-like and crustacean cardioactive peptide (CCAP)-like immunoreactivity (Fig. 3; Skiebe, 1999; Skiebe et al., 1999). In *Cherax destructor*, another putative neurohaemal release zone is located in the sheath of various nerves of the STNS and is marked by an antibody generated against the vesicle protein synaptotagmin (Skiebe, 2000). At the ultrastructural level, profiles packed with dense-core vesicles were found in the perineural sheath of these areas (Fig. 3B; Skiebe and Ganeshina, 2000). Similar profiles have been described in *Panulirus interruptus* and *Homarus americanus* (Friend, 1976; Kilman and Marder, 1997). The content of these vesicles is unknown. It is likely that hormones influence the STG, since peptides not present in the STG, such as CCAP, elicit a strong physiological response (Weimann et al., 1997; Marder and Richards, 1999). Furthermore, muscles not known to receive a peptidergic innervation are modulated by peptides (see below).

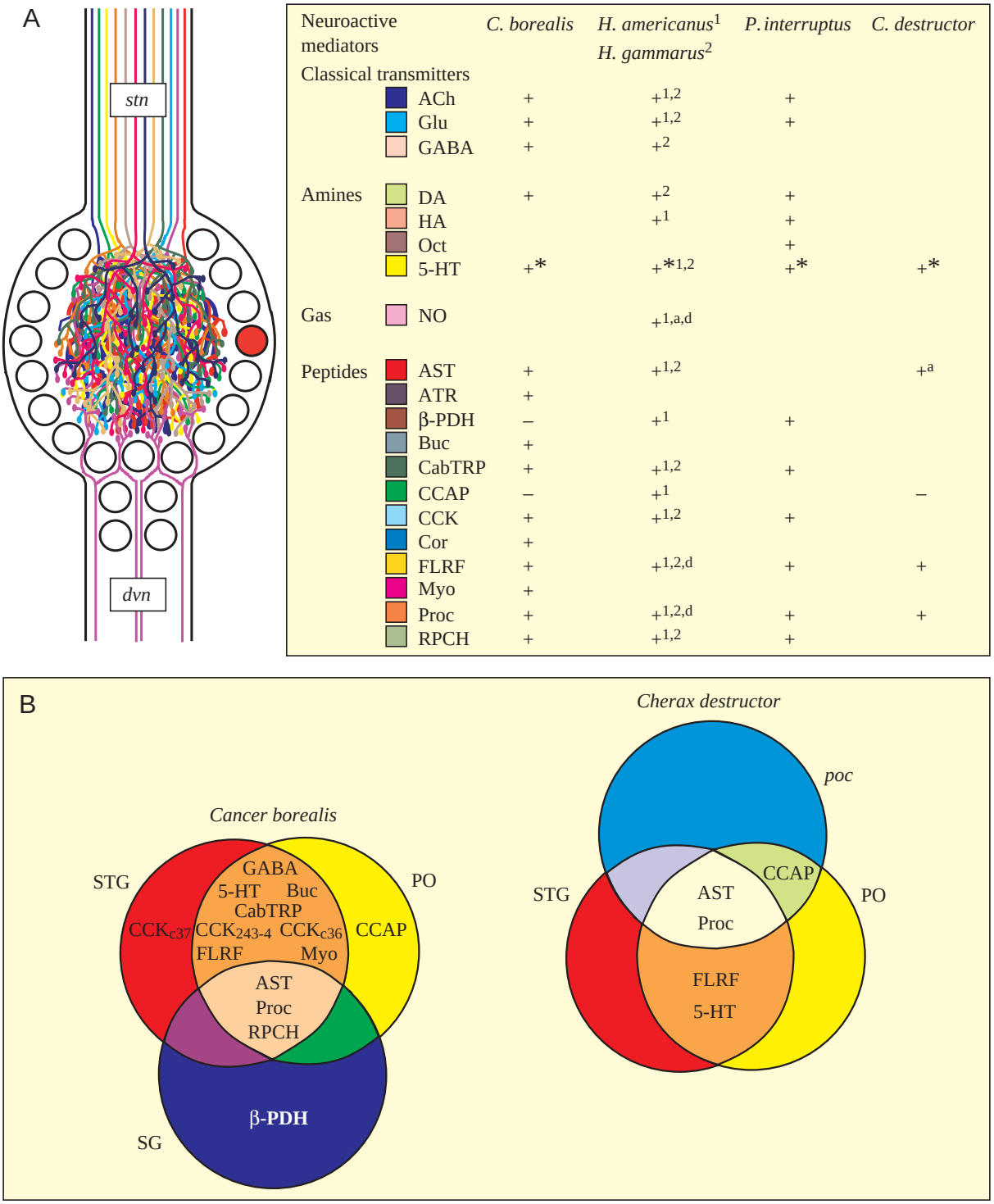
Peptides in the stomatogastric ganglion

Ultrastructural investigation of the neuropile of the stomatogastric ganglion

Most of the synaptic profiles within the STG containing dense-core vesicles (Maynard, 1971; Kilman and Marder, 1996; Skiebe and Ganeshina, 2000) have synaptic specialisations, suggesting that most peptides are released in close proximity to synapses. These presynaptic profiles have been subdivided into five types (types A–E) on the basis of the distribution of clear and dense-core vesicles within them. With the exception of the type E profile, found only in *Cancer borealis*, all species investigated have the same profile types. Other presynaptic profiles that could not be assigned to one of the five types were also present, suggesting the existence of additional types of presynaptic profiles. There are indications that peptides are also released in a paracrine fashion. Possible paracrine release sites have been reported within the STG at the ultrastructural level for both *Panulirus interruptus* (Friend, 1976; King, 1976) and *Cancer borealis* (Kilman and Marder, 1996). In *Homarus americanus* and *Cherax destructor*, similar profiles may be present but are not common (Maynard, 1971; Skiebe and Ganeshina, 2000).

Peptidergic cell bodies in the stomatogastric ganglion

The cell bodies of neurones that release peptides as transmitters within the STG are found either within the STG or projecting to the STG, mostly from the CoGs or the OG (Coleman et al., 1992). Although numerous antibodies against peptides have been used, evidence for peptidergic cell bodies within the adult STG was found only for the FMRFamide and allatostatin families (Fig. 2A: a; Table 1). Since only FLRFamides and no FMRFamides have been isolated from crustaceans (Trimmer et al., 1987; Mercier et al., 1993; Keller, 1992; Weimann et al., 1993), immunoreactivity detected using an antibody against FMRFamide will be referred to as FLRFamide-like immunoreactivity. The first peptidergic neurones noted were three FLRFamide-like immunoreactive cell bodies in the shrimp *Palaemon serratus* (Meyrand and Marder, 1991), and these were thought to be an exception. In *Homarus americanus*, 3–4 FLRFamide-like immunoreactive cell bodies were found in half the animals investigated with one antibody (Table 1; Kilman et al., 1999), which were previously not found using a different antibody (Marder, 1987). Allatostatin-like immunoreactive neurones were found in two crayfish species (*Cherax destructor* and *Procambarus clarkii*; Skiebe, 1999). Over the course of development, peptidergic cell bodies appear in the STG during some stages. In two lobster species (*Homarus americanus* and *Homarus gammarus*), FLRFamide- and proctolin-like immunoreactivity is expressed transiently, although the time window differs even in closely related species (Fig. 2: d; Table 1; Fénelon et al., 1998; Fénelon et al., 1999; Kilman et al., 1999). The identity



Neuroactive mediators		*C. borealis*	*H. americanus*[1] *H. gammarus*[2]	*P. interruptus*	*C. destructor*
Classical transmitters					
	ACh	+	+[1,2]	+	
	Glu	+	+[1,2]	+	
	GABA	+	+[2]		
Amines	DA	+	+[2]	+	
	HA		+[1]	+	
	Oct			+	
	5-HT	+*	+*[1,2]	+*	+*
Gas	NO		+[1,a,d]		
Peptides	AST	+	+[1,2]		+[a]
	ATR	+			
	β-PDH	–	+[1]	+	
	Buc	+			
	CabTRP	+	+[1,2]	+	
	CCAP	–	+[1]		–
	CCK	+	+[1,2]	+	
	Cor	+			
	FLRF	+	+[1,2,d]	+	+
	Myo	+			
	Proc	+	+[1,2,d]	+	+
	RPCH	+	+[1,2]	+	

Fig. 2. Summary of the neuroactive mediators present in the neuropile of the stomatogastric ganglion (STG) and neurohaemal organs identified either biochemically and/or by immunocytochemistry. (A) Neuroactive mediators in the STG of the crab *Cancer borealis*, the lobsters *Homarus americanus* and *Homarus gammarus*, the spiny lobster *Panulirus interruptus* and the crayfish *Cherax destructor*. Large circles in the drawing represent the STG somata. Mediators shown to be present are marked by a plus sign, those not present by a minus sign. The classical transmitters of the STG neurones are acetylcholine and glutamate. Only in a few cell bodies were other mediators found in both adults (a) and during development (d; see also Table 1). The source of the serotonin is the gastropyloric receptor cells (*). ACh, acetylcholine (Marder, 1987); Glu, glutamate (Marder, 1987); GABA, γ-aminobutyric acid (Nusbaum et al., 1989; Cournil et al., 1990; Swensen et al., 2000); DA, dopamine (Barker et al., 1979; Kushner and Barker, 1983; Marder, 1987; Cournil et al., 1994; Cournil et al., 1995); HA, histamine (Claiborne and Selverston, 1984a; Mulloney and Hall, 1991); 5-HT, serotonin (Beltz et al., 1984; Katz et al., 1989; Kilman et al., 1999; P. Skiebe, unpublished data); Oct, octopamine (Barker et al., 1979); NO, nitric oxide (Scholz et al., 1998); AST, allatostatin (Skiebe and Schneider, 1994; Kilman et

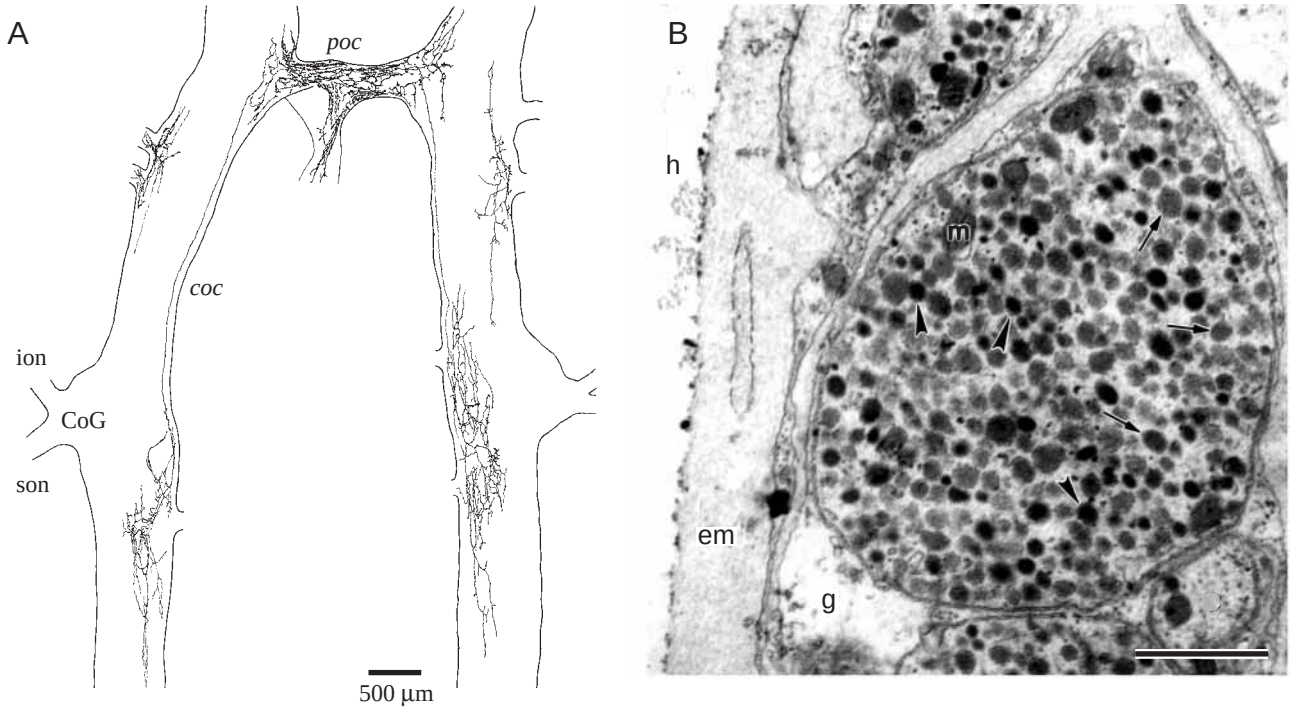


Fig. 3. Putative neurohaemal release zone on the surface of the circumoesophageal connective (*coc*) and the post-oesophageal commissure (*poc*). (A) Drawing of allatostatin-like immunoreactivity on the surface of the *coc*s and the *poc* found only in *Cherax destructor*. Similar staining was found with antibodies generated against crustacean cardioactive peptide and proctolin. Other stained structures, including axons in the *coc* and cell bodies and neuropile in the commissural ganglia (CoGs) were not drawn. *ion*, inferior oesophageal nerve; *son*, superior oesophageal nerve. (B) Transmission electron micrograph of a cross section through the *poc* showing a large profile in the perineural sheath that contains dense-core vesicles (arrowheads) and electron-dense granules (arrows) close to a glial cell (g) process. The profile is separated from the haemolymph space (h) only by a thin extracellular matrix (em) representing a basal lamina. m, mitochondrion. Scale bar, 0.5 µm. A is modified from Skiebe, 1999; B is modified from Skiebe et al., 1999.

of none of these peptidergic neurones is known, either in the adult or in the embryonic or larval STG.

Peptidergic interneurones projecting into the stomatogastric ganglion

Most information about the role of peptidergic neurones in modulating the networks of the STG stems from studies of identified peptidergic neurones that project into the STG. Some of them are sensory neurones, but the majority are interneurones located in the CoGs, the OG, the inferior ventricular nerve (*ivn*) or the junction of the superior oesophageal nerve (*son*) and the *stn* with the oesophageal nerve (*on*, Table 1). That neurones containing the same peptide can elicit a different motor pattern was shown by investigating three pairs of proctolin-like immunoreactive neurones in *Cancer borealis* (Fig. 4; Blitz et al., 1999): the modulatory proctolin neurones (MPNs) with cell bodies located either in the OG or in the *on*, and the modulatory commissural neurones 1 and 7 (MCN1 and MCN7) with cell bodies located in the CoGs. Both MPN (showing proctolin- and GABA-like immunoreactivity, Nusbaum and Marder, 1989a; Blitz et al.,

al., 1999; Skiebe, 1999); ATR, allatotropin (A. E. Christie, unpublished data); β-PDH, β-pigment dispersing hormone (Mortin and Marder, 1991); Buc, buccalin (Christie et al., 1994); CabTRP, *Cancer borealis* tachykinin-related peptide (Goldberg et al., 1988; Blitz et al., 1995; Christie et al., 1997b; Fénelon et al., 1999); CCAP, crustacean cardioactive peptide (Christie et al., 1995b; Kilman, 1998; Skiebe et al., 1999); CCK, cholecystokinin (Turrigiano and Selverston, 1991; Christie et al., 1995a; Meyrand et al., 2000; subscripts indicate different antibodies against CCK); Cor, corazonin (Christie and Nusbaum, 1995); FLRF, FLRFamide-related peptides (only FLRFamides have been isolated from crustaceans; Marder et al., 1987; Weimann et al., 1993; Fénelon et al., 1998; Kilman et al., 1999); Myo, myomodulin (Christie et al., 1994); Proc, proctolin (Marder et al., 1986; Fénelon et al., 1998; Fénelon et al., 1999; Kilman et al., 1999; Skiebe et al., 1999); RPCH, red pigment-concentrating hormone (Nusbaum and Marder, 1988; Dickinson and Marder, 1989; Fénelon et al., 1999). (B) Summary of the neuroactive mediators present in the STG (excluding the classical transmitters ACh and Glu of STG neurones), in the pericardial organs (PO) and in the X-organ/sinus gland complex (SG) of the crab *Cancer borealis* and on the post-oesophageal commissure (*poc*), the STG and the PO of the crayfish *Cherax destructor* (*Cancer borealis*, Christie et al., 1995b; *Cherax destructor*, Skiebe, 1999; Skiebe et al., 1999; P. Skiebe, unpublished data). Fig. 2A, left, is modified from Marder et al., 1994; Fig. 2B, left, is modified from Christie et al., 1995b. *stn*, stomatogastric nerve; *dvn*, dorsal ventricular nerve.

Table 1. *Peptidergic neurones in the stomatogastric nervous system (not including unidentified neurones in the commissural ganglia and oesophageal ganglion)*

Location	Identity	Transmitter	Number	Species	Stage	References
STG	?	FLRFamide-like	3	*Palaemon serratus*	Adult	Meyrand and Marder, 1991
			1–3	*Homarus gammarus*	E50 to LI	Fénelon et al., 1998
			0–3	*Homarus americanus*	E50 to E100	Kilman et al., 1999
			0–3		LI	
			0–4		LII	
			0–5		LIII	
			3–5		LV	
			0–4		Juvenile	
			0–4		Adult	Marder, 1987; Kilman et al., 1999
	?	Allatostatin-like	1	*Cherax destructor*	Adult	Skiebe, 1999
			3–6	*Procambarus clarkii*	Adult	Skiebe, 1999
	?	Proctolin-like	1–2	*Homarus gammarus*	LI to LIII	Fénelon et al., 1998
			0–2	*Homarus americanus*	LII to juvenile	Fénelon et al., 1999
CoG	CG	FLRFamide-like	1 pair	*Homarus gammarus*	Adult	P. Meyrand, unpublished data
	P	GABA-like†	1 pair	*Homarus gammarus*		Nagy et al., 1994
	MCN1	Proctolin-like CabTRP-like GABA-like	1 pair	*Cancer borealis*	Adult	Blitz et al., 1999
	MCN7	Proctolin-like	1 pair	*Cancer borealis*	Adult	Blitz et al., 1999
	LVF	CCK-like FLRFamide-like RPCH-like	1 pair	*Cancer borealis*	Adult	Christie et al., 1997a
OG	CD1 (?)	FLRFamide-like	1	*Cherax destructor*	Adult	Skiebe et al., 1999
on–stn–son junction	MPN	Proctolin-like GABA-like	2	*Cancer borealis*	Adult	Nusbaum and Marder, 1989a; Blitz et al., 1999
	GN1/2	FLRFamide-like CCK-like GABA-like	2	*Homarus americanus*	Adult	Cournil et al., 1990; Meyrand et al., 2000
	?	FLRFamide-like	2	*Procambarus clarkii*	Adult	Tierney et al., 1997
	?	FLRFamide-like Allatostatin-like	2	*Cherax destructor*	Adult	Skiebe et al., 1999; Skiebe, 1999
ivn	*ivn*-TF	Histamine-like FLRFamide-like	2	*Panulirus interruptus*	Adult	Claiborne and Selverston, 1984a; Claiborne and Selverston, 1984b; Kilman, 1998
	PS	Histamine-like FLRFamide-like	2	*Homarus gammarus*	Adult	Le Feuvre et al., 2000
	ivn-TF	Histamine-like*	2	*Homarus americanus* *Pacifastacus leniusculus*		Mulloney and Hall, 1991 Mulloney and Hall, 1991
	?	FLRFamide-like	2	*Procambarus clarkii*	Adult	Tierney et al., 1997
			2	*Cherax destructor*	Adult	Skiebe et al., 1999
	ivn-TF	Histamine-like FLRFamide-like	2	*Cancer borealis*	Adult	Christie et al., 2000
dvn	AGR	Allatostatin-like	1	*Procambarus clarkii*	Adult	Skiebe, 1999
lvn	GPR	Species specific	2–4 pairs	12 species	E50 to adult	For references, see text

†The P neurons were included since they might be homologous with the MCN1 neurone (Nagy et al., 1994; Meyrand et al., 2000).

*The *ivn*-TF neurones were included since they might be homologous with the FLRFamide-like neurones, which also have their cell bodies in the *ivn*.

Abbreviations of locations are explained in Fig. 1; abbreviations of peptides are given in Fig. 2. Abbreviations of identified neurones: AGR, anterior gastric receptor neurone; CD1, cardiac sac dilator neurone 1; CG, commissural gastric neurone; GN1/2, γ-aminobutyric acid-containing neurones 1 and 2; GPR, gastropyloric receptor neurone; *ivn*-TF, inferior ventricular nerve through-fibres; LVF, large varicosity fibre; MCN1, modulatory commissural neurone 1; MCN7, modulatory commissural neurone 7; MPN, modulatory proctolin neurone; P, pyloric modulatory neurone; PS, pyloric suppressor neurone. E50, 50 % of embryonic development; LI to LV: larval stages 1 to 5.

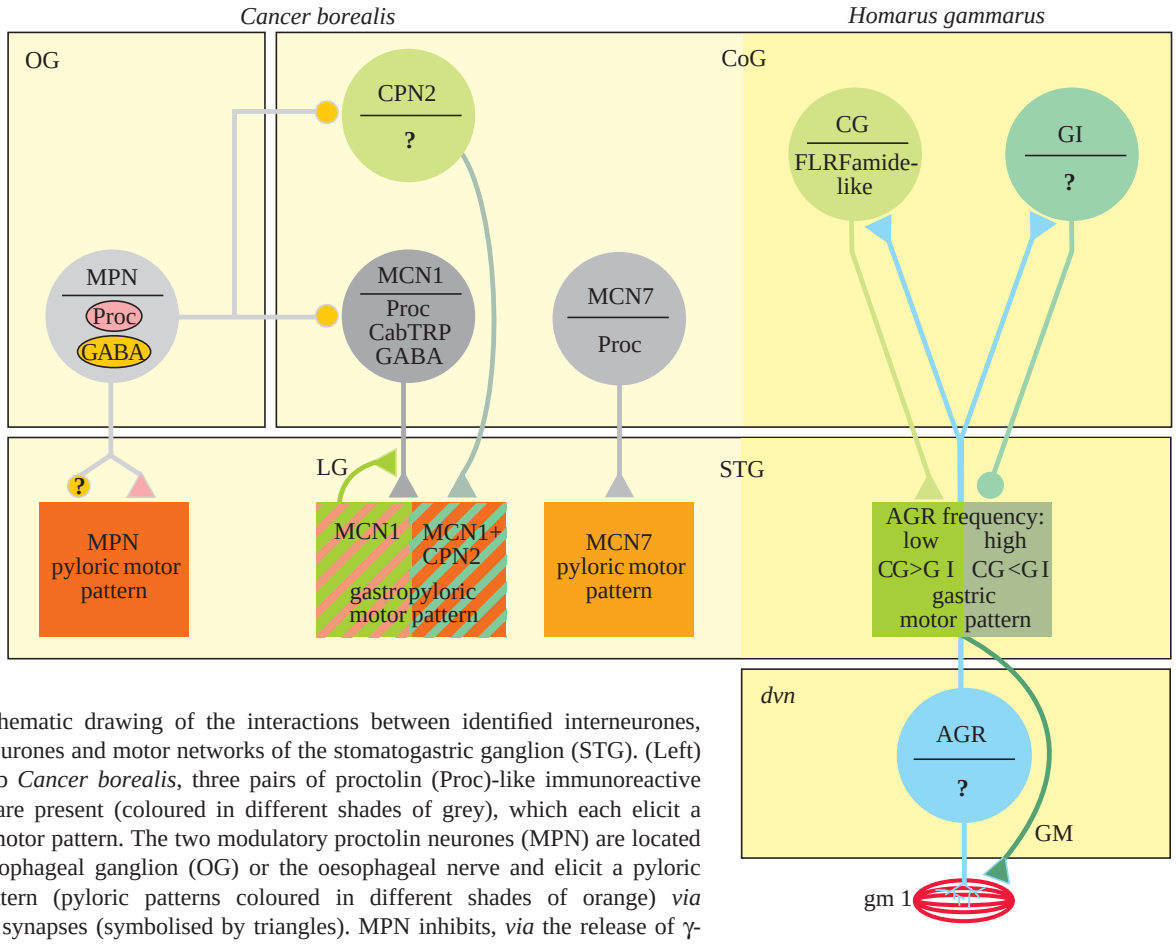


Fig. 4. Schematic drawing of the interactions between identified interneurones, sensory neurones and motor networks of the stomatogastric ganglion (STG). (Left) In the crab *Cancer borealis*, three pairs of proctolin (Proc)-like immunoreactive neurones are present (coloured in different shades of grey), which each elicit a different motor pattern. The two modulatory proctolin neurones (MPN) are located in the oesophageal ganglion (OG) or the oesophageal nerve and elicit a pyloric motor pattern (pyloric patterns coloured in different shades of orange) *via* excitatory synapses (symbolised by triangles). MPN inhibits, *via* the release of γ-aminobutyric acid (GABA; inhibitory synapses symbolised by small circles), two pairs of modulatory neurones located in the commissural ganglia, which are called commissural projection neurones 2 (CPN2) and modulatory commissural neurones 1 (MCN1), thereby preventing a gastric mill rhythm, which the latter neurones normally initiate. Stimulating MCN1 (containing proctolin, *Cancer borealis* tachykinin-related peptide, CabTRP, and GABA) alone elicits a gastropyloric motor pattern (gastric mill motor patterns are coloured in different shades of green, gastropyloric motor patterns are drawn in stripes of orange and green). After blocking the action of CabTRP, MCN1 does not elicit a gastric mill rhythm and the pyloric rhythm it initiates is more similar but still not identical to that elicited by MPN. Co-stimulation of the MCN1 and CPN2 elicits a different type of gastropyloric pattern. MCN1 receives rhythmic inhibition from the lateral gastric neurone (LG) in the STG. This does not influence the MCN1 synapses in the commissural ganglia (CoGs), demonstrating that activity of synapses can vary with the output region. Modulatory commissural neurones 7 (MCN7) also elicit a pyloric motor pattern that differs from that elicited by the MPNs. (Right) In the lobster *Homarus gammarus*, the anterior gastric receptor (AGR) excites two pairs of modulatory interneurones in the CoGs: the commissural gastric (CG) neurones and the gastric inhibitor (GI) neurones. AGR, which is a mechanoreceptor activated by the movements of the gastric mill muscle 1 (gm1), has its soma in the dorsal ventricular nerve (*dvn*) and projects through the STG without any arborization to innervate the CoGs. When AGR fires weakly, one gastric mill pattern is elicited. When AGR fires strongly, a second gastric mill pattern is elicited, demonstrating that the activity of a feedback loop is able to select different motor patterns (modified from Blitz et al., 1999; Blitz and Nusbaum, 1997; Coleman and Nusbaum, 1994; Coleman et al., 1995; Combes et al., 1999a; Combes et al., 1999b).

1999) and MCN7 (showing proctolin-like immunoreactivity) stimulation elicit distinct pyloric rhythms (Fig. 4; Blitz et al., 1999). In contrast, MCN1 (showing proctolin-, GABA- and tachykinin-like immunoreactivity) activates both the pyloric and the gastric mill rhythms (Fig. 4; Coleman and Nusbaum, 1994; Bartos and Nusbaum, 1997). In *Cancer borealis*, two tachykinin-related peptides were isolated, one of which was present in the STG (Christie et al., 1997b). If the action of this peptide is blocked by a tachykinin receptor antagonist, MCN1 stimulation no longer elicits a gastric mill rhythm, suggesting that tachykinin initiates this rhythm (Wood et al., 2000). However, the pyloric rhythm is still elicited, and although it becomes more like the rhythm resulting from MPN stimulation, it remains different. This suggests that either unknown transmitters other than GABA and proctolin, or some other mechanisms, are responsible for these differences in network output. During gastric mill rhythm excitation, the lateral gastric (LG) neurone presynaptically inhibits MCN1, selectively reducing its transmitter-mediated excitation while enabling an increase in its electrically mediated excitation. This is thought to switch the predominantly chemical synapse to a purely electrical one (Coleman et al., 1995). The rhythmic

inhibition in the STG does not influence the activity of MCN1 in the CoG, where MCN1 has aborizations, demonstrating that the activity of synapses can vary according to the output region (Coleman and Nusbaum, 1994).

Investigation of MPN also showed that motor pattern selection occurs not only through direct modulation of the network but also *via* the inhibition of a competing pathway (Fig. 4; Blitz and Nusbaum, 1997). MPN inhibits the gastric mill rhythm not by influencing the circuits of the STG itself but by inhibiting other modulatory projection neurones (MCN1 and commissural projection neurone 2, CPN2) with cell bodies located in the CoGs. For this inhibition, MPN uses only GABA, indicating that proctolin and GABA have distinct functions in mediating motor pattern selection and suggesting that they are not necessarily co-released.

One way to activate modulatory neurones with cell bodies in the CoG is by sensory input. In *Homarus gammarus*, the commissural gastric neurone (CG), which shows FLRFamide-like immunoreactivity (P. Meyrand, unpublished data), and the gastric inhibitor neurone (GI) are excited by the anterior gastric receptor (AGR, Fig. 4; Combes et al., 1999a; Combes et al., 1999b). AGR is a primary mechanoreceptor measuring the tension of a gastric mill muscle. It does not have ramifications in the STG but it projects through the STG to arborize in the CoGs. Depending on the firing frequency of AGR, one of two gastric mill motor patterns is elicited as a result of the different postsynaptic sensitivities of CG and GI to AGR. When AGR fires weakly, one gastric mill pattern is elicited. When AGR fires strongly, the second gastric mill pattern is elicited, demonstrating that feedback from a single mechanoreceptor is able to select different motor patterns (Combes et al., 1999b). This also demonstrates that different modulatory neurones can be co-activated and that pattern selection is dependent on the ensemble of modulatory neurones that are active. A second example of this is MCN1, which elicits a different gastric mill motor pattern when co-activated with CPN2 (Fig. 4; Blitz and Nusbaum, 1997).

In seven species, a pair of neurones with cell bodies in the *ivn* was found that had axons projecting to the STG (Table 1). These neurons are likely to contain histamine and/or FLRFamide-like peptides (Claiborne and Selverston, 1984a; Mulloney and Hall, 1991; Tierney et al., 1997; Kilman, 1998; Skiebe et al., 1999; Le Feuvre et al., 2000; Christie et al., 2000) and are referred to as *ivn*-through fibres (*ivn*-TF; Claiborne and Selverston, 1984a; Claiborne and Selverston, 1984b) or pyloric suppressor (PS) neurones (Cazalets et al., 1987; Cazalets et al., 1990). Both the *ivn*-TF in *Panulirus interruptus* and the PS neurones in *Homarus gammarus* elicit inhibitory effects on the pyloric rhythm of the STG. The inhibitory effect of the *ivn*-TF is frequency-dependent such that, at low frequencies, an excitatory action dominates, but this gives way to an inhibitory action at higher frequencies (Sigvardt and Mulloney, 1982; Claiborne and Selverston, 1984a; Claiborne and Selverston, 1984b), demonstrating that the effects of modulatory projection neurones can be frequency-dependent.

Peptides present within the nerves of the stomatogastric nervous system

In addition to peptidergic varicosities in ganglia, immunocytochemical studies have demonstrated peptidergic varicosities within patches in nerves of the STNS (Marder et al., 1986; Marder et al., 1987; Kilman et al., 1999; Goldberg et al., 1988; Mortin and Marder, 1991; Coleman et al., 1992; Fénelon et al., 1998; Fénelon et al., 1999; Skiebe, 1999; Skiebe and Ganeshina, 2000). In *Cherax destructor*, ultrastructural studies of the *stn–son* junction and the *stn*, where peptidergic varicosities occur, demonstrated the presence of neuropile and all four types of synaptic profiles observed in the STG (Skiebe and Ganeshina, 2000). Similarly, neuropile was found in the *stn* of *Cancer borealis* (Kilman and Marder, 1997). By combining peptide antibodies with an antibody against the vesicle protein synapsin, it was confirmed that proctolin-, allatostatin- and FLRFamide-like immunoreactivity is present in the same patches in *Cherax destructor*. Studies of different species suggest that neurones from all ganglia of the STNS project into the neuropile of the *stn–son* junction (Orlov, 1928; Dickinson et al., 1981; Skiebe and Ganeshina, 2000) and peptides locally applied to the *stn–son* junction produced changes in the pyloric rhythm generated by the networks of the STG (Kilman, 1998; Christie and Nusbaum, 1999; P. Skiebe, unpublished data).

Peptides and sensory neurones

The most investigated sensory neurones in the STNS are the gastropyloric receptor (GPR) neurones. The GPR neurones are peripheral stretch receptors with arborizations within the STG (Table 1; for reviews, see Katz and Harris-Warrick, 1990; Katz and Tazaki, 1992). Recently, the GPR neurones have been described in additional species (Tierney et al., 1999; Skiebe, 1999) and it was shown that the transmitters of GPR neurones in *Homarus americanus* and *Homarus gammarus* (allatostatin-, CCK-, FLRFamide-like peptides and serotonin) are acquired sequentially during development (Kilman et al., 1999). In the crab *Cancer borealis*, the GPR neurones not only contain acetylcholine, serotonin and allatostatin (Katz et al., 1989; Skiebe and Schneider, 1994), but preliminary data suggest that at least one pair of GPR neurones is also influenced by bath application of serotonin and allatostatin (Birmingham et al., 1998). Another peptidergic influence on a mechanoreceptor was demonstrated in *Homarus gammarus*, in which bath application of an FLRFamide-related peptide to the dendritic membrane of AGR, but not to its cell body or axon, switches its firing pattern from a tonic to a bursting one (Fig. 4; Combes et al., 1997).

Peptides and stomach muscles

The stomach of decapod crustaceans has more than 40 striated muscles (Maynard and Dando, 1974). In general, the extrinsic muscles receive cholinergic innervation whereas the intrinsic muscles receive glutamatergic innervation (Marder, 1976; Marder, 1987; Lingle, 1980). With a few exceptions, the

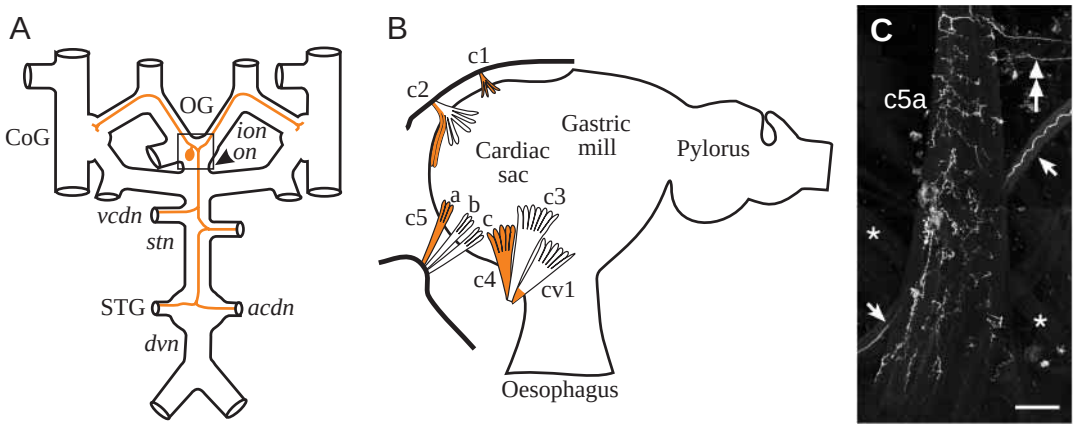


Fig. 5. Example of peptidergic innervation of muscles in *Cherax destructor*. (A) Schematic diagram of the branching pattern of the neurone labelled with an FMRFamide antibody in the oesophageal ganglion (OG), presumably the cardiac dilator neurone 1 (CD1). (B) Schematic diagram of the distribution of FLRFamide-like immunoreactivity on the muscles: regions of the muscles that show FLRFamide-like immunoreactivity are coloured orange; the regions without immunoreactivity are shown in white. (C) An example of the actual FLRFamide-like immunoreactivity on the c5a muscle, which is covered with strongly stained varicosities (montage of two confocal micrographs). Unstained muscles are also present (asterisks). *acdn*, anterior cardiac dilator nerve; c1 to c5, cardiac sac muscles; cv1, cardiac valve muscle; *vcdn*, ventral cardiac dilator nerve (for other abbreviations see Fig. 1). Scale bar, 200 μm (modified from Skiebe et al., 1999). Arrows denote the main axon; the double-headed arrow marks axon collaterals.

muscles do not seem to receive direct peptidergic innervation. In the shrimp *Palaemon serratus*, the dilator muscles of the pylorus exhibited FLRFamide-like immunoreactivity, but the motoneurones innervating the muscles did not (Meyrand and Marder, 1991), and the neuron that is the source of this peptide remained undetermined. In *Cherax destructor*, an FLRFamide-immunoreactive neurone with its cell body in the OG innervates cardiac sac dilator muscles (Fig. 5; Skiebe et al., 1999) and is likely to be the cardiac dilator neurone 1 (CD1). A similar neurone was present in *Procambarus clarkii* (Tierney et al., 1997). At the ultrastructural level, Patel and Govind (Patel and Govind, 1997) described the presence of dense-core vesicles on muscles of the crab *Callinectes sapidus*.

Although most motoneurones do not contain peptides, the interaction between motoneurones and muscles is strongly modulated by peptides (Jorge-Rivera and Marder, 1996; Jorge-Rivera and Marder, 1997; Weimann et al., 1997; Jorge-Rivera et al., 1998). The absence of direct innervation and the threshold of some effects suggest a neurohaemal delivery. Most peptides (CCAP, FLRFamide-related peptides, proctolin, RPCH) increase the amplitude of nerve-evoked contractions, whereas allatostatin reduces this amplitude (Jorge-Rivera and Marder, 1996; Jorge-Rivera and Marder, 1997; Jorge-Rivera et al., 1998). The effects of peptides are frequency-dependent and differ depending on the muscle. A particular muscle can also respond to a variety of modulators. FLRFamide-related peptides can also induce myogenic activity (Meyrand and Marder, 1991; Jorge-Rivera and Marder, 1996).

Peptides and network function

Since 1984, peptides have been applied to the STG to investigate how circuit dynamics relevant for behaviour depend on peptide modulation (Hooper and Marder, 1984). From studies made on a number of different species, it is known that many effects of peptides can be species-dependent, but truly comparative data are lacking (Table 2 therefore lists these effects without regard to species). Peptides initiate rhythms from silent preparations and change the phase relationship between the neurones within a cycle period, and their effects depend on the frequency of the ongoing rhythm. Peptides also induce plateau potentials and increase or decrease the number of spikes per burst produced by particular neurones. Each of the peptides elicits peptide-specific motor patterns in the adult and probably also in the larva (Marder and Weimann, 1992; Marder and Richards, 1999). In the adult, only particular STG neurones respond to a given peptide (Hooper and Marder, 1987; Heinzel and Selverston, 1988; Skiebe et al., 2000; Swenson and Marder, 2000a), and each neurone responds to overlapping subsets of peptides (Swenson and Marder, 2000b). Peptide-specific motor patterns are, therefore, partly a result of the specific distribution and number of receptors for each peptide. Swenson and Marder (Swenson and Marder, 2000a) showed that five different peptides modulate the same ionic current, a current first described as being modulated by proctolin (Golowasch and Marder, 1992). This finding does not exclude modulation of other membrane currents, but it contrasts with the effects of dopamine and serotonin, each of which modulates several currents in STG neurones (Kiehn and Harris-Warrick, 1992a; Kiehn and Harris-Warrick, 1992b; Harris-Warrick et al., 1995a; Harris-Warrick et al., 1995b; Zhang and Harris-Warrick, 1995; Kloppenburg et al., 1999). This convergence of peptides onto one current could contribute to network stability by limiting the number of possible network configurations (Swensen and Marder, 2000a).

Table 2. *Effects of peptides on networks of the stomatogastric nervous system and on muscles of the crustacean stomach obtained from various species**

Peptide	Concentration range (mol l^{-1})	Effects on the rhythms of the STNS	Target neurones	Changes in phase relationship	Dependence on control frequency	Initiation of plateau potentials	Changes in synaptic strength	Activation of a voltage-dependent inward current	Effects on muscle contraction	References
AST-related peptides	10^{-8} to 10^{-6}	Inhibition of the pyloric and gastric mill rhythms	PY	+	+	0	–	0	–	Dircksen et al., 1999; Jorge-Rivera and Marder, 1997; Skiebe and Schneider, 1994; Skiebe et al., 2000
CCAP	10^{-10} to 10^{-4}†	Activation of pyloric rhythms in silent preparation in adults, embryos and larva, reduction in pyloric frequency when rhythm is strongly active only in the adult, activation of gastric rhythm	AB, LP, IC	+	+	0	0	+	+	Jorge-Rivera et al., 1998; Marder and Richards, 1999; Skiebe and Marder, 1994; Richards and Marder, 2000; Swensen, 2000; Swensen and Marder, 2000a; Weimann et al., 1997
CCK	10^{-6} to 10^{-4}	Activation of pyloric neurones, initiation of gastric mill rhythms *in vivo* and *in vitro*, reduction in gastric mill cycle period when rhythm is strongly active	0	+	0	0	0	0	0	Turrigiano and Selverston, 1989; Turrigiano and Selverston, 1990; Turrigiano et al., 1994
FLRFamide-related peptides	10^{-10} to 10^{-4}†	Activation of pyloric and gastric mill rhythms	AB, LP, PY, IC, VD, DG	+	+	+	0	+	+‡	Jorge-Rivera and Marder, 1996; Jorge-Rivera et al., 1998; Marder and Richards, 1999; Tierney et al., 1997; Swensen, 2000; Swensen and Marder, 2000a; Weimann et al., 1993
Proctolin	10^{-10} to 10^{-4}†	Activation of pyloric, gastric mill and cardiac sac rhythms *in vitro* and activation of gastric mill rhythms *in vivo*, effect on cardiac sac rhythm enhanced when RPCH had been applied previously	AB, PD, LP, some PY, IC, VD, LG, DG	+	+	+	+	+	+	Dickinson and Marder, 1989; Dickinson et al., 1997; Golowasch and Marder, 1992; Heinzel, 1988; Heinzel and Selverston, 1988; Hooper and Marder, 1984; Hooper and Marder, 1987; Jorge-Rivera et al., 1998; Marder et al., 1986; Marder and Richards, 1999; Nusbaum and Marder, 1989b; Swensen, 2000; Swensen and Marder, 2000a
RPCH	5×10^{-9} to 10^{-4}†	Activation of pyloric, gastric mill and cardiac sac rhythms, effects dependent on the site of peptide application, changing the network alliance of one neurone, fusing two networks	AB, LP	+	0	+	+	+	+	Dickinson and Marder, 1989; Dickinson et al., 1990; Dickinson et al., 1993; Dickinson et al., 1997; Jorge-Rivera et al., 1998; Marder and Richards, 1999; Nusbaum and Marder, 1988; Swensen, 2000; Swensen and Marder, 2000a
CabTRP	10^{-6} to 10^{-4}†	Activation of pyloric and gastric mill rhythms	AB, PD, LP, LPG, IC, VD	+	+	0	0	+	0	Blitz et al., 1995, Christie et al., 1997b; Marder and Richards, 1999; Swensen, 2000; Swensen and Marder, 2000a

*Some effects are species-dependent, but comparative data are lacking. Effects are therefore listed without regard to species.

†Some of the higher concentrations were pressure-injections of peptides, +, positive effect; –, negative effect; 0, not tested; ‡ induces myogenic activity.

Abbreviations for peptides are given in Fig. 2. AB, anterior burster neurone; LP, lateral pyloric neurone; PD, pyloric dilator neurone; PY, pyloric neurone; LPG, lateral posterior gastric neurone; IC, inferior cardiac neurone; VD, ventricular dilator neurone; DG, dorsal gastric neurone; LG, lateral gastric neurone. Neurones are not in alphabetical order, but are listed according to the network to which they belong. STNS, stomatogastric nervous system.

The embryonic network in the STG of the lobster *Homarus gammarus* generates a single embryonic rhythm, which later splits into different functional adult rhythms (Casasnovas and Meyrand, 1995). This embryonic network is able to generate an adult-like motor pattern if the descending modulatory inputs are all removed and only a single muscarinic agonist is applied, indicating that descending information is responsible for the embryonic pattern (Le Feurve et al., 1999). This suggests that adult networks do not necessarily derive from progressive ontogenetic changes in the networks, a view that is not unchallenged (Richards et al., 1999).

It is not possible to discuss the effects of all peptides on the networks of the STG within the scope of this review (for reviews, see Harris-Warrick et al., 1992; Marder and Weimann, 1992; Marder et al., 2001). I will illustrate this research using studies of red pigment-concentrating hormone (RPCH). The presence of RPCH was demonstrated immunohistochemically in all four ganglia of the STNS (Nusbaum and Marder, 1988; Dickinson and Marder, 1989). Bath application of RPCH either to the CoGs and OG or to the STG activates a previously silent cardiac sac rhythm, but the rhythms differ with the site of application, demonstrating that a pattern-generating network can be modulated at more than one site and that the resultant modulations depend on the site of release of the modulator (Dickinson and Marder, 1989; Dickinson et al., 1993). RPCH is also able to fuse two pattern-generating networks as a result of enhancing the synaptic strength of the synapses between the two networks (Dickinson et al., 1990). That the modulatory 'history' matters was shown by applying the two peptides sequentially. The likelihood that proctolin would initiate a cardiac sac rhythm was greatly enhanced if application of proctolin was preceded by an application of RPCH (Dickinson et al., 1997).

Conclusions and future directions

The studies presented here demonstrate that peptides are ubiquitously present within the STNS of decapod crustaceans and suggest that each peptide or each peptidergic neurone elicits unique motor patterns, but many fundamental questions remain to be answered. Why are so many peptides present? How does the effect of a peptide depend on the presence of other transmitters? Why do neurones change their peptide transmitters during development? Is there is a time window for particular actions of peptides? Why do orphan peptides and peptide families exist and do the members of a peptide family have different roles? Compared with excitatory peptides, far less is known about inhibitory peptides in the STNS, which include at present only the allatostatins and myosuppressin.

To answer questions concerning cotransmission, either pharmacological separation of cotransmitter actions (Wood et al., 2000) or the effect of applying mixtures will have to be studied. For allatostatin and serotonin, the early data show that co-application causes a stronger reduction in the pyloric cycle frequency than either modulator alone (Marder et al., 1994). However, this might be different for co-localised peptides. In the example of proctolin and *Cancer borealis* tachykinin, which are co-localized in MCN1 (Blitz et al., 1999), both peptides competitively activate the same current (Swensen and Marder, 2000a). As this case suggests, to understand how a particular neurone elicits a unique motor pattern, not only will the postsynaptic neurons and currents have to be identified, but also co-application experiments will have to be compared with experiments using various stimulation patterns of the identified neurone.

To understand more about the role of peptides during development, it is necessary to determine the effects of bath-applied peptides, as has been started in *Homarus americanus* (Marder and Richards, 1999), to identify target neurones and individual peptidergic neurones and to study their effects from the cellular to the network level, as has been done in the adult. There is already evidence that embryonic neurones do not possess the same capacity to initiate large regenerative depolarisations as adult neurones (Casasnovas and Meyrand, 1995). It would be beneficial to include additional species (so far only *Homarus americanus* and *Homarus gammarus* have been investigated), since much can be learned by comparing species. The neurones of the crab *Cancer borealis*, for example, are much more flexible with respect to their membership in a particular motor pattern (Weimann et al., 1991) than those of lobsters.

Most of our knowledge concerning the peptide content of neurones is based on immunocytochemistry. In the case peptides such as proctolin and crustacean cardioactive peptide, which have the same amino acid sequence in all arthropod species investigated (Dircksen, 1994), immunocytochemistry provides strong evidence for the presence of the peptide. In the case of peptide families, immunocytochemistry can only be the first step since a given antibody might recognise all or only a subset of the members of a peptide family. Peptides must therefore be identified unambiguously at the level of a single neurone, as has been pioneered in molluscs (for reviews, see Jiménez and Burlingame, 1998; Li et al., 2000).

As a result of the abundant knowledge about the networks of the STG accumulated over the last 40 years and the ability to study identified peptidergic neurones, including sensory neurones, motoneurones and interneurones, both in the adult and during development, research on the STNS of decapod crustaceans will continue to increase our understanding of the role of peptides in the nervous system.

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