
Review

Comparative neuroethology of feeding control in molluscs

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Summary

Over the last 30 years, many laboratories have examined, in parallel, the feeding behaviour of gastropod molluscs and the properties of the nervous system that give rise to this behaviour. Equal attention to both behavioural and neurobiological issues has provided deep insight into the functioning of the nervous system in generating and controlling behaviour. The conclusions derived from studies on gastropod feeding are generally consistent with those from other systems, but often provide more detailed information on the behavioural function of a particular property of the nervous system. A review of the literature on gastropod feeding illustrates a number of important messages. (i) Many of the herbivorous gastropods display similarities in behaviour that are reflected in corresponding similarities in neural anatomy, pharmacology and physiology. By contrast, the same aspects of the behaviour of different carnivorous species are quite variable, possibly because of their specialised prey-capture techniques. Nonetheless, some aspects of the neural control of feeding are preserved. (ii) Feeding in all species is flexible, with the behaviour and the physiology adapting to changes in the current environment and internal state and as a result of past

experience. Flexibility arises *via* processes that may take place at many neural sites, and much of the modulation underlying behavioural flexibility is understood at a systems and at a cellular level. (iii) Neurones seem to have specific functions that are consistent with their endogenous properties and their synaptic connections, suggesting that individual neurones code specific pieces of information (i.e. they are ‘grandmother cells’). However, the properties of a neurone can be extremely complex and can be understood only in the context of the complete neural circuit and the behaviour that it controls. In systems that are orders of magnitude more complex, it would be impossible to understand the functional properties of an individual neurone, even if it also coded specific information. (iv) Systems such as gastropod feeding may provide a model for understanding the functional properties of more complex systems.

Key words: feeding, *Aplysia*, *Lymnaea*, *Limax*, *Helisoma*, *Pleurobranchaea*, gastropod, mollusc, pattern generation, neuromodulation, arousal, learning, feeding choice, grandmother cell.

Introduction

The neural control of feeding has been studied intensively in a number of gastropod molluscs. The most striking feature of gastropod feeding is its flexibility. In most gastropods, feeding consists of a variable sequence of food-finding movements, followed by a series of rhythmic movements in which food is consumed. Both food-finding and consummatory movements are modulated in response to different foods, in response to changes in internal state or as a result of previous learning. Thus, examining gastropod feeding addresses a problem of general interest to all neurobiologists, understanding how the nervous system generates a flexible series of movements. However, the neurones and the neural circuitry that organize and modulate gastropod feeding are amenable to the detailed cellular analysis that has provided seminal insights into the modulation of withdrawal reflexes in

gastropods by serotonin and small peptides (for a review, see Byrne and Kandel, 1996). Studies on neural systems generating feeding have begun to provide rich insights into how complex regulatory phenomena arise from the properties of individual neurones and their interconnections.

Investigations in some genera, notably *Aplysia*, have taken a top-down approach, beginning by characterizing behaviour and then proceeding to the nervous system. In these studies, new information on the cellular and network properties of neurones is systematically interpreted in the light of previous findings on behaviour. By contrast, in other genera (e.g. *Lymnaea* and *Helisoma*), the work initially had the aim of exploring the properties of relatively simple invertebrate nervous systems (Fig. 1). After the features of some of the neurones and networks had been determined, attempts were

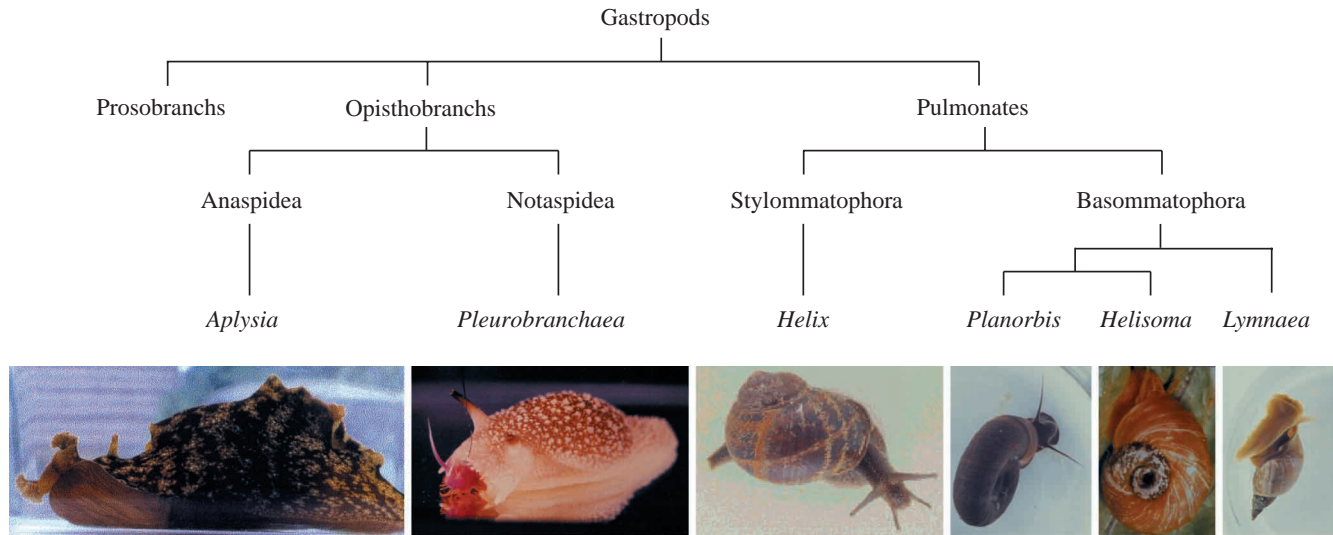


Fig. 1. The herbivorous gastropods studied include the marine opisthobranchs *Aplysia* (10 cm long) and *Pleurobranchaea* (5 cm long, eating a nudibranch, *Flabellina* which is coloured purple and orange) and the pulmonates *Helix* (terrestrial, 2 cm long) and three freshwater genera (*Planorbis*, *Helisoma* and *Lymnaea*, all 1 cm long). The pictures are not to scale. We are grateful to Rhanor Gillette and Andy Bulloch for the pictures of *Pleurobranchaea* and *Helisoma*.

made to relate these findings to behaviour. Initially, this approach minimises functional explanations and stresses system properties and pharmacology. Over the years, work using the two approaches has converged. Our aim is to summarize and compare the results obtained in the different species and, thereby, to point to insights into the functioning of the nervous system that are of general interest.

Feeding has been studied in both carnivorous and herbivorous gastropods. Many aspects of feeding in both herbivores and carnivores will be discussed, although the emphasis will be on herbivores, particularly *Aplysia* and *Lymnaea*. These two genera are currently being studied by many more researchers than are the other gastropods and, consequently, there are many more recent publications on these molluscs.

Structure of the feeding system

Food-finding movements are often effected by muscles of the head and foot that also produce movements unrelated to feeding. After food has been localised, in herbivorous gastropods it is ingested by repeated movements of the radula, a sheet of semi-hardened tissue covered with rows of chitinous teeth. By contrast, many carnivorous molluscs capture prey *via* specialised organs that may be adaptations of structures present in herbivores (e.g. the pharynx in *Pleurobranchaea*) or that may be unrelated to such structures (e.g. buccal cones in *Clione*) (Davis and Mpitsos, 1971; Hermans and Satterlie, 1992). In most gastropods, food is eventually engaged by the radula, which is controlled by the buccal muscles. These muscles cause the radula to protract out of the mouth towards the food and then to pull the food into the buccal cavity, or to rasp the food, with a retraction movement (Fig. 2). In some gastropods (e.g.

Aplysia and *Pleurobranchaea*), a fold in the centre of the radula acts as a hinge that allows the two radula halves to open and close (Kupfermann, 1974; McClellan, 1982a).

The buccal mass is innervated by the paired buccal ganglia, which connect to the cerebral ganglia (or to the fused cerebral-pleural ganglia in *Pleurobranchaea*) by the paired cerebro-buccal connectives. The cerebral ganglia innervate the anterior portion of the animal, including many structures related to feeding, such as the rostral foot, the head, the sensory anterior and posterior tentacles (rhynchophores), the lips and the mouth. The cerebral ganglia also innervate extrinsic buccal muscles, which cause forward and backward movements of the whole buccal mass. These ganglia also communicate with the rest of the central nervous system.

Feeding movements

Food in the environment is sensed by the tentacles (Audesirk, 1975; Bovbjerg, 1968; Bicker et al., 1982). Food initiates appetitive behaviours, which generally include orientation and locomotion towards food. These movements may be similar to those in response to other attractive stimuli, such as potential mates (Leonard and Lukowiak, 1984, 1986; Ziv et al., 1989). Locomotion towards food may also be similar to locomotion away from noxious stimuli. In addition, appetitive movements in *Aplysia* include head-lifting and head-waving (Kupfermann, 1974; Teyke et al., 1990a,b). In *Helix*, the chemosensory posterior tentacles point towards food before the animals locomote towards it (Peschel et al., 1996).

Contact with food is sensed by both mechano- and chemoreceptors (Rosen et al., 1982; Bicker et al., 1982). These initiate the next phase of feeding.

In carnivores, a separate prey-capture phase may occur after

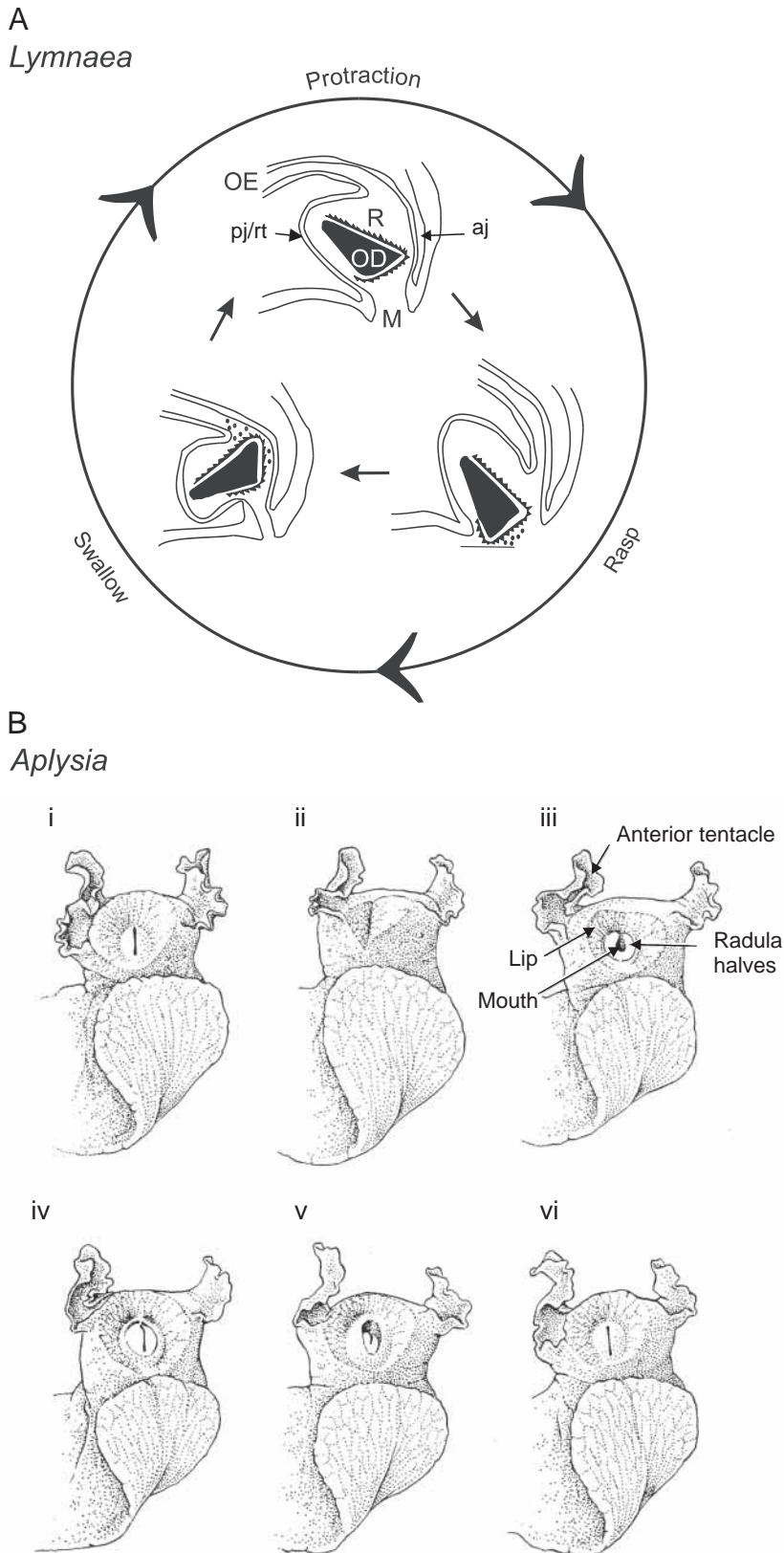


Fig. 2. Feeding movements of (A) *Lymnaea* and (B) *Aplysia*. (A) Schematic diagram of the feeding sequence of *Lymnaea* in which the three phases of movement (protraction, rasp and swallow) are shown diagrammatically. The muscles of the buccal mass – principally the anterior and posterior jugalis (aj, pj) and radular tensor (rt) – contract, squeezing and rotating the odontophore (OD). This is covered by the many-toothed radula (R), which is rasped across the substratum. Food particles are then collected and passed into the oesophagus (OE). M, mouth. After Benjamin and Elliott (1989). (B) A biting sequence in *Aplysia*. The food that elicited the movement is not shown. (i) The animal is in the head-up feeding position. (ii) The animal moves its head and lips to centre the food close to the mouth. (iii) The mouth opens, and the radula protracts forward out of the mouth. Note that the radula halves are open during the protraction. (iv–vi) The radula gradually retracts and the mouth closes. Note that the radula halves close. Closure coupled with the retraction pulls the food into the mouth. After Kupfermann (1974).

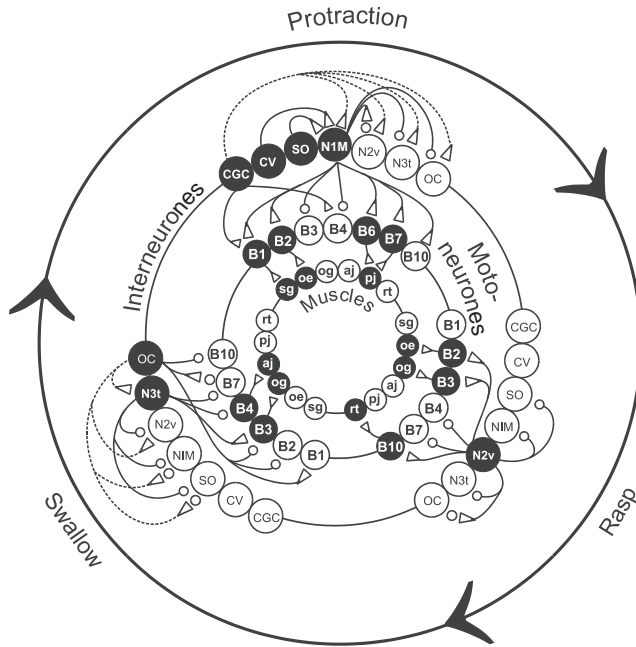
Pleurobranchaea consists of an extension of a unique structure, the proboscis, which precedes a ballistic bite/strike response (Davis and Mpitsos, 1971). *Navanax* pursue their prey (other gastropods) by following their mucus trails (Paine, 1963). They then engulf prey with an unusual expandable pharynx that lacks a radula (Susswein et al., 1984a). *Clione* evert specialised buccal cones surrounding the mouth. The cones bear hooks, which pull at prey before it is consumed (Hermans and Satterlie, 1992; Norekian, 1995).

In *Lymnaea* and other pulmonates, such as *Helisoma*, *Planorbis* and *Helix*, the consummatory phase of feeding consists of a series of repetitions of three sequential movements: (i) protraction, in which the radula extends to contact the food; (ii) retraction, in which the radula rasps the food and brings it into the mouth; and (iii) swallowing or hyper-retraction, in which the food is conveyed to the gut (Fig. 2A) (Kater, 1974; Peters and Altrup, 1984; Rose and Benjamin, 1979). In addition, the radula can rotate over the underlying support tissue, allowing flexibility in the amplitude of a rasp (Smith, 1988). In *Lymnaea*, the feeding pattern can be modified to produce egestion. Furthermore, a motor sequence very similar to that in feeding is used in egg-laying, to clean off the substratum on which animals will lay eggs.

Although the behaviour – seen from outside the snail – appears similar to that in feeding, fine-wire recordings of the neural activity show that the motor pattern for egg-laying is significantly different (Jansen et al., 1997, 1999).

the appetitive movements, but before the food is consumed. Appetitive and prey-capture movements in carnivores are often highly specialised. For example, prey-capture in

A
Lymnaea



B
Aplysia

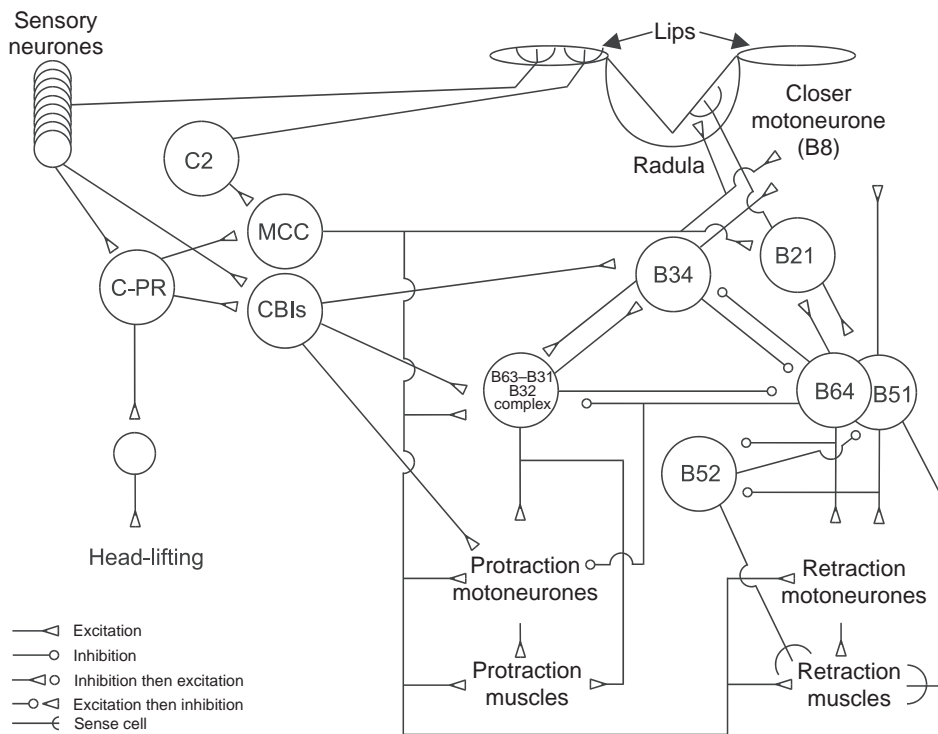


Fig. 3. Neuronal circuits contributing to feeding in (A) *Lymnaea* and (B) *Aplysia*. (A) The main monosynaptic neuronal connections within the feeding system of *Lymnaea* in the three phases of feeding. In each phase, the same set of interneurons, motoneurons and buccal mass muscles are indicated, with active neurons and muscles shown filled. The main chemical outputs of the active neurons are shown, with some connections shown as dotted lines to aid clarity. CGC and CV are cerebral neurons, SO, N1M, N2v, N3t and OC are interneurons in the buccal ganglia. B1–B4, B6, B7 and B10 are motoneurons in the buccal ganglia that innervate the salivary gland (sg) oesophagus (oe), an oesophageal gland (og), the anterior and posterior jugalis muscles (aj, pj) and the radular tensor muscle (rt). Rhythmic cycling of the feeding network arises from the synaptic connections, with a major role for biphasic connections, and the timing of the network is controlled by endogenous properties of the cells, e.g. endogenous bursting or plateau potentials. (B) The main synaptic pathways in the neuronal network for feeding in *Aplysia*. All the connections shown are monosynaptic except for the connection from C-PR to MCC and the CBIs, which go through interneurons in the pleural ganglion. The CBIs and MCC also receive inputs from the central pattern generator, but the synaptic details of this have not been published. The C2, MCC, CBI and C-PR neurons and the lip sensory neurons are in the cerebral ganglia, the other neurons in the buccal ganglia. The B63–B31/B32 interneurons control protraction; B51 and B64 control retraction. The relative activities of B51, B34 and B21 control whether the pattern leads to ingestion or egestion. Note that some neurons, such as B51, have multiple roles. The population of sensory neurons includes both chemosensory and mechanosensory cells.

Consummatory movements in *Aplysia* differ from those in the pulmonates in that there are only two phases, protraction and retraction. Protraction and retraction are synchronized with movements of the lips and jaws, and with radula opening and closing movements, to produce a variety of functionally different consummatory movements. These include biting, which causes

food to enter the mouth (Kupfermann, 1974), swallowing, cutting and related movements triggered by food within the mouth (Hurwitz and Susswein, 1992) and at least two qualitatively different rejection movements, in which food or a non-food object is pushed away (Kupfermann, 1974; Morton and Chiel, 1993a,b; Nagahama et al., 1999). The different movements are

characterised by differences in the relative amplitude of protraction and retraction and by differences in the coupling with radula opening and closing and/or jaw movements. For example, in biting, the radula protracts while open, and then closes on the food during retraction, thereby pulling it in. By contrast, in rejection, protraction is accompanied by radula closing, thereby pushing objects out (Morton and Chiel, 1993a,b). Food is cut by swallowing while holding the food in place with the jaws. Rasp-like grazing movements similar to those in *Lymnaea* may also occur (Kupfermann and Carew, 1974). When *Aplysia* consume their natural food (various species of seaweeds), the frequency and nature of successive movements vary from cycle to cycle, with many cycles representing intermediate states that are difficult to classify.

In *Pleurobranchaea*, the initial bite/strike prey-capture response is followed by two stages of consummatory movements. Repetitive biting movements pull prey into the pharynx, and repetitive swallowing movements transport the prey from the pharynx into the gut. The movements are similar to those in *Aplysia* in that protraction and retraction movements are coordinated with opening and closing of the radula halves (Croll and Davis, 1981; McClellan, 1982a). *Pleurobranchaea* also perform a number of different types of movement that clear objects from the pharynx and gut. These have variously been termed egestion, rejection, regurgitation, writhing or vomiting (Croll and Davis, 1981; McClellan, 1982a,b). These movements may be signalled by the presence of non-food objects in the pharynx or noxious chemical substances in the gut. There have been disagreements as to whether these represent fundamentally different movements or are minor variants of a single movement that are initiated in somewhat different behavioural contexts (Croll et al., 1985a; McClellan, 1982a,b).

Neural circuitry organizing feeding movements

Appetitive movements

In *Aplysia*, head-lifting and head-waving movements that function in orientation towards food are produced by neck muscles innervated by motoneurons in the cerebral, pleural and pedal ganglia (Bablanian et al., 1987). Identified neurone C-PR has a major role in organizing the head-lifting movement (Nagahama et al., 1993). Intracellular stimulation of C-PR produces such movements, and neck motoneurons are excited (mostly polysynaptically, but in some cases monosynaptically) by C-PR firing (Nagahama et al., 1994).

In *Helix*, the tentacles that point towards food are innervated by two peritentacular nerves (PTNs), each projecting to approximately one hemi-section of the tentacle wall. Stimulating the peritentacular nerves causes the tentacles to bend downwards as they do when they orient towards food (Peschel et al., 1996).

Consummatory movements

Consummatory movements are initiated by command-like neurones projecting from the cerebral to the buccal ganglia. These neurones were first characterized in *Pleurobranchaea*,

in which they were termed the paracerebral neurones (Gillette et al., 1978). In *Lymnaea*, *Limax* and *Aplysia*, respectively, these are termed cerebral ventral 1 cells (CV1s), cerebral buccal cells (CBs) or cerebral buccal interneurons (CBIs) (Fig. 3) (Delaney and Gelperin, 1990; McCrohan, 1984; Rosen et al., 1991). The neurones are excited by food stimulating the lips (Davis and Gillette, 1978; Kemenes et al., 2001; Whelan and McCrohan, 1996). At least in *Lymnaea* and *Aplysia*, this activation may be indirect. In *Lymnaea*, sucrose appears to activate the buccal central pattern generator before the CV1 interneurons, whereas in *Aplysia*, some of the CBIs are excited by neurone C-PR, which controls appetitive movements (Hurwitz et al., 1999b; Teyke et al., 1990a). The CBIs directly excite buccal ganglia neurones that generate the repetitive consummatory rhythm (Rosen et al., 1991; Sanchez and Kirk, 2000).

In *Lymnaea*, *Aplysia* and *Pleurobranchaea*, the command-like neurones are a heterogeneous population that are not equally effective in eliciting consummatory movements (Hurwitz et al., 1999b; Kovac et al., 1983; McClellan, 1983a; McCrohan and Croll, 1997; Xin et al., 1999). In *Pleurobranchaea* and *Aplysia*, it has been suggested that different combinations of CBIs may work together at different times and, thereby, differentially give rise to different feeding movements (McClellan 1983a; Xin et al., 1999). In *Pleurobranchaea* and *Aplysia*, the cerebral ganglion command-like neurones may receive input from identified buccal ganglion neurones, which may modify their activity (Davis et al., 1984; Gillette et al., 1978; Chiel et al., 1988) and may influence the choice of the movements used in a feeding sequence. Additional command-like neurones are also found in the buccal ganglia of *Pleurobranchaea* and *Lymnaea* (Gillette and Gillette, 1983; Gillette et al., 1980; McClellan, 1983b; Yeoman et al., 1993), and sucrose application to the lips in *Lymnaea* can recruit these to the feeding pattern (Kemenes et al., 2001).

The rhythmic pattern of consummatory movements is generated primarily by buccal ganglion interneurons. In *Lymnaea*, *Planorbis* and *Helisoma*, three classes of central pattern generator (CPG) interneurone (termed N1, N2 and N3) have been identified. Instantly recognisable (by both anatomy and physiology) homologues are present in all three genera (Arshavsky et al., 1988a,b,c; Brierley et al., 1997b; Elliott and Benjamin, 1985a; Quinlan et al., 1995, 1997; Quinlan and Murphy, 1996; Rose and Benjamin, 1981b; Murphy, 2001). These N-cells fire bursts of action potentials in turn, with the activity in each class confined to the corresponding phase in the feeding pattern. The N-cells are mostly pre-motor interneurons providing a strong chemical synaptic drive to motoneurons that is often supplemented by feedforward electrical connections. In *Lymnaea*, it was initially believed that interneurons acting together in phase are different-sized homologues, but more recent experiments indicate that the interneurons within each group differ in many properties (Brierley et al., 1997b; Elliott and Benjamin, 1985a; Vehovszky and Elliott, 2001). Selective recruitment of

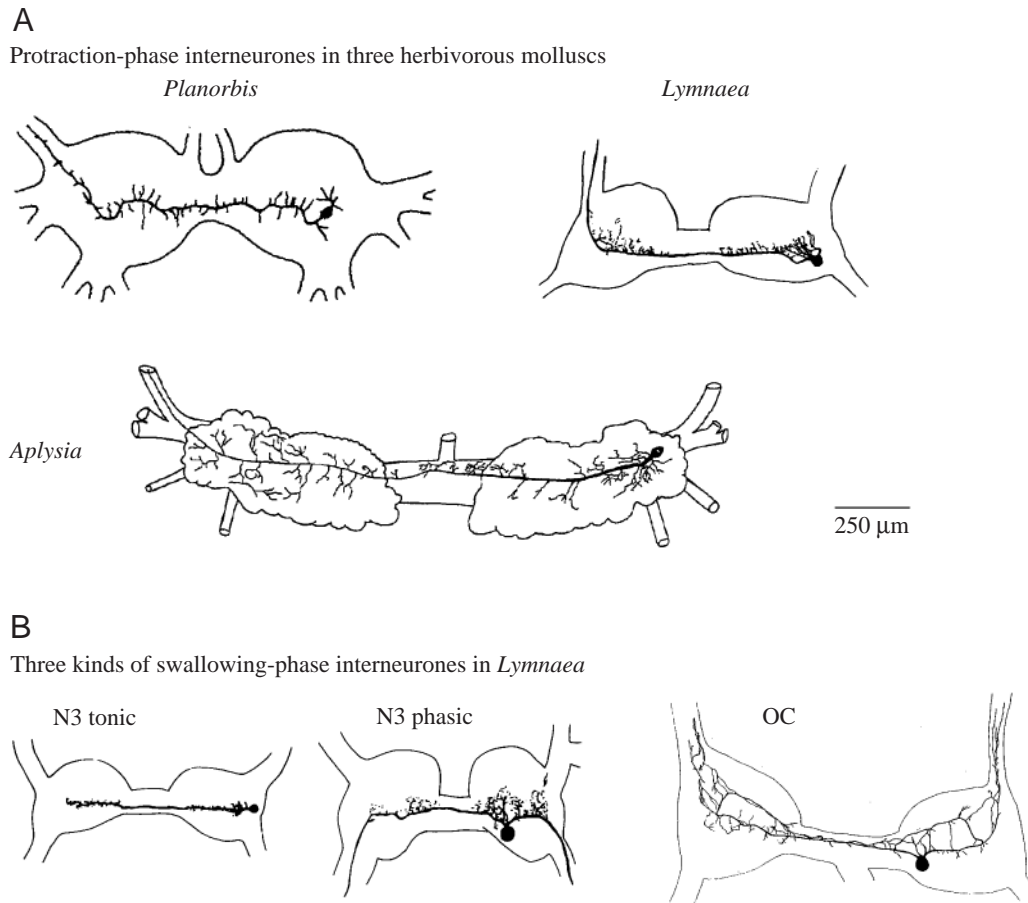


Fig. 4. (A) Consistency among the gastropods in the occurrence of protraction-phase interneurons with axons ascending in the contralateral cerebro-buccal connective. *Planorbis* group 1 interneurone (Arshavsky et al., 1988a); *Lymnaea* N1 interneurone (Elliott and Benjamin, 1985a); *Aplysia* B34 interneurone (Hurwitz et al., 1997). (B) Variation between retraction-phase (N3) neurones in *Lymnaea*. The anatomical variation shown is accompanied by physiological and pharmacological variation: the tonic N3 fires many action potentials, each producing a short excitatory postsynaptic potential on the B3 motoneurone, while the phasic N3 and OC cells fire transiently at the start of this phase. The phasic N3 neurone produces a long-lasting excitation of N3 and the OC an inhibition of the B3 motoneurone. The OC (but not the other interneurons) uses octopamine as its transmitter. Modified from Elliott and Benjamin (1985a) and Vehovszky et al. (1998).

different neurones provides a potential mechanism for modulating the rhythm to produce different motor patterns.

In *Lymnaea*, *Aplysia* and *Helisoma*, rhythmic feeding activity depends both on the endogenous membrane properties of the interneurons and on the synaptic connections between them. As in other CPGs, the membrane properties include bursting, post-inhibitory rebound and plateau potentials, and these properties control much of the timing of a phase. These membrane properties are under modulatory control, and this contributes to the patterning of the feeding rhythm (Straub and Benjamin, 2001).

The synaptic connections determine the sequence of the phases [*Aplysia* (Hurwitz and Susswein, 1996; Hurwitz et al., 1997; Plummer and Kirk, 1990), *Lymnaea* (Brierley et al., 1997a; Elliott and Benjamin, 1985a) and *Planorbis* (Arshavsky et al., 1988b)]. As in many CPGs, interneurons active during the same stage of feeding are often electrically and chemically coupled (Brierley et al., 1997b; Elliott and Benjamin, 1985a; Susswein and Byrne, 1988), whereas neurones active at

different stages often show reciprocal inhibition. However, interneurons active in different phases may also show weak excitatory connections, which provide a mechanism for switching from an earlier to a later phase. For example, in the *Lymnaea* CPG, the N1 (protraction) cells weakly excite the N2 (rasp) interneurons until the N2 interneurons fire, when they inhibit the N1 neurones and terminate protraction (Elliott and Benjamin, 1985a; Brierley et al., 1997b). In *Aplysia*, activity in the protraction-phase interneurons (B63, B34 and B31/B32) is initiated by sensory inputs, in part mediated via the cerebral-buccal interneurons (CBIs) (Rosen et al., 1991). The switch to retraction is initiated by depolarisation of neurones (B64 and B51) that strongly inhibit protraction-phase neurones and strongly excite retraction-phase neurones (Hurwitz et al., 1994; Hurwitz and Susswein, 1996). A cycle is terminated in part via a neurone (B52) that inhibits retraction-phase neurones (Evans et al., 1999a).

Protraction-phase interneurons with remarkably similar properties are found in *Aplysia*, *Lymnaea* and *Planorbis*

(Fig. 4) and in *Helisoma*. These have axons in the contralateral cerebro-buccal connective, display small spikes (presumably because the soma is inexcitable) and gradually depolarise during a burst (Arshavsky et al., 1988b; Elliott and Kemenes, 1992; Hurwitz et al., 1994, 1997). Although neurones with similar small spikes are common in arthropods, in gastropods they have been reported only from the buccal and cerebral (e.g. Perrins and Weiss, 1998) ganglia neurones associated with the control of feeding. The lack of excitability in some portions of a neurone may allow different parts of a neurone to fire at different rates or to use slow potentials in place of spikes in local signalling at specific terminals. These neurones morphologically and physiologically resemble in many ways the corollary discharge (CD) neurones that in *Pleurobranchaea* have been shown to allow communication from the buccal to the cerebral ganglia (see below).

Cyclic feeding movements are expressed in effector organs controlled by both the buccal and cerebral ganglia. It was initially suggested that independently oscillatory circuits are present in the brain (cerebro-pleural ganglion) and buccal ganglia of *Pleurobranchaea* since each is capable of responding with phasic bursts to tonic nerve stimulation. Functionally, the rhythm is set in the buccal ganglia, and coordination between the separate oscillators is effected by a group of 'corollary discharge' or 'efference copy' neurones, which carry information from the buccal to the cerebral ganglion (Davis et al., 1973). However, later studies indicated that phasic bursts in the brain could be generated in the absence of a separate oscillator, because buccal-cerebral interneurones responded phasically to tonic stimulation (Cohan and Mpitsois, 1983). Nonetheless, later studies succeeded in demonstrating convincing phasic bursting in the isolated brain, confirming that a second oscillator is indeed present (Davis et al., 1984; London and Gillette, 1984a,b). Coupled oscillators are also present in the cerebral ganglia of *Aplysia* (Perrins and Weiss, 1996) and *Lymnaea*.

Multifunctional neurones

Many neurones in the feeding circuit seem to have multiple functions. Neurones with proposed multiple functions have been found in several invertebrate circuits. However, the molluscan emphasis on parallel studies on behaviour and on the nervous system has permitted researchers to understand these functions in a detail not available in other systems. For some neurones, the different functions of a neurone enhance one another. For example, in *Aplysia*, neurone B51 acts both as a retraction-phase interneurone (Plummer and Kirk, 1990) and as a proprioceptor (Evans and Cropper, 1998). In addition to exciting many retraction-phase motoneurones, B51 has sensory branches that are activated during retraction. These inputs are enhanced by resistance to retraction and thereby act as a monitor of the success of retraction, which can enhance retraction when the movement is not successful.

A second example of related functions in a single neurone is seen in neurone B52, whose outputs to other CPG neurones suggest that the neurone terminates a cycle of activity (Evans

et al., 1999a). This neurone innervates a flap of connective tissue that is stretched by retraction just before the end of a cycle, allowing the sensory input to enhance the pattern-generating function. Similar peripheral branches have been reported in retraction-phase neurones of *Lymnaea* (Elliott and Benjamin, 1985a). Electrical connections in *Lymnaea* between the motoneurones and interneurones suggest that the motoneurones may also play a secondary part in producing the rhythm (Staras et al., 1998), but the weakness of the connections suggests that this is a minor role.

B21 in *Aplysia* is a striking example of a multi-functional neurone. B21 is a mechano-afferent that responds to food touching the radula (Miller et al., 1994). It has extensive chemical and electrical synapses onto the CPG and motoneurones, and activity in B21 enhances the switch from protraction to retraction (Rosen et al., 2000b). B21 is also depolarised by the CPG during retraction. The central excitation enhances the neurone's sensory function, since depolarising B21 enhances some of its outputs (Rosen et al., 2000a). In addition to acting as an exteroceptor sensing radula touch, B21 also is a proprioceptor. The tissue innervated by B21 consists partially of muscle. B21 senses this muscle's contraction during protraction, causing B21 to fire during the protraction phase of biting. Thus, B21 acts as a proprioceptor during protraction and as an exteroceptor during retraction (Borovikov et al., 2000).

Some protraction-phase neurones in *Aplysia* combine interneurone and motoneurone functions, with the different functions assigned to different parts of the neurone. For example in B31/B32, activity in the soma functions as part of the CPG, whereas activity in the axon drives a major protraction-phase muscle (I2). Spikes in the axon do not actively invade the pattern-generating portion of the neurone (Hurwitz et al., 1994).

Switching between different feeding movements

As in other systems (Marder and Calabrese, 1996), it has been found that a single CPG can give rise to both quantitatively and qualitatively different patterns of activity. However, the parallel studies on behaviour and the nervous system have allowed researchers to examine in detail the relationship between cellular and systems properties of a CPG and the behaviours that are the products of CPG activity.

In *Aplysia*, *Lymnaea*, *Helisoma* and *Pleurobranchaea*, a single CPG in the buccal ganglia generates a number of different patterns of activity (Murphy, 2001). In *Aplysia* and *Pleurobranchaea*, these patterns can be correlated with the expression of different behavioural patterns (Croll and Davis, 1981, 1982; Hurwitz et al., 1996; McClellan, 1982a,b; Morton and Chiel, 1993a,b).

In the isolated central nervous system of *Helisoma*, an alternative pattern can occur in which phase 2 (rasp) and phase 3 (swallow) can alternate without phase 1 (protraction) (Quinlan and Murphy, 1996). In *Aplysia*, a number of different mechanisms contribute to the choice between different behaviours. One mechanism is the recruitment of different

combinations of command-like neurones (Xin et al., 1999). For example, in *Aplysia*, intracellular stimulation of CBI-2 and CBI-12 differentially causes repetitive bursts of bite-like activity (Church and Lloyd, 1994; Hurwitz et al., 1999b), whereas stimulation of CBI-1 induces a rejection-like burst (Rosen et al., 2000a).

Other CBIs produce activity patterns that are difficult to classify. In *Pleurobranchaea*, stimulating the paracerebral cells and the ventral white cell in the buccal ganglia initiates different patterns of activity that are correlates of different movements (Croll et al., 1985b,c; Gillette and Gillette, 1983; McClellan, 1983a,b). A second mechanism contributing to the choice of different behaviours is that different combinations of buccal ganglia CPG neurones are called into play. For example, neurone B34 fires during only some protraction movements. Its activity makes movements more rejection-like, since this neurone amplifies the activity of protraction-phase motoneurones and drives radula closer motoneurones during protraction (Hurwitz et al., 1997). Neurone B51 fires during only some retraction movements and makes movements more ingestion-like (Nargeot et al., 1999b) (or perhaps more swallowing-like) (see Evans and Cropper, 1998) by amplifying firing of retraction-phase neurones and driving radula closer motoneurones during retraction. Sensory neurones such as B21 that respond to food touching the radula may also contribute to biasing a switch between different types of movement. In *Lymnaea*, the pattern produced by stimulating the modulatory SO interneurone (Elliott and Benjamin, 1985b; Rose and Benjamin, 1981a) is different from that seen spontaneously or by stimulating the N1 CPG interneurone (Elliott and Andrew, 1991), suggesting that SO-induced activity represents an alternative behaviour.

A fourth mechanism contributing to the choice between different movements is modulation by different regulatory transmitters (Kabotyanski et al., 2000). The effectiveness of a modulator depends on the state of the network. Stimulation of the cerebral serotonergic cells in *Lymnaea* may activate the feeding pattern only in quiescent preparations. If a fictive feeding pattern is already running, stimulation of the serotonergic cells can either accelerate or reduce the feeding rate depending on the state of the system (McCrohan and Audesirk, 1987; Tuersley and McCrohan, 1988).

The buccal octopaminergic interneurones (OCs) show particularly fascinating modulatory effects. First, their activity will accelerate slow rhythms and slow down fast rhythms. Such mechanisms may promote the stability of particular rhythmic patterns. Second, the OC interneurones also reconfigure the feeding pattern through their network of connections with the other feeding interneurones and motoneurones. Third, they modulate the output of the SO, a cholinergic modulatory interneurone also located in the buccal ganglia. Finally, stimulation of the OC in a quiescent preparation produces fictive feeding, but only well after the end of stimulation (Elliott and Vehovszky, 2000; Vehovszky and Elliott, 2001). Many of their effects are polycyclic, i.e. they last over several repeats of the feeding pattern.

Comparative pharmacology

Many neurotransmitters are utilised in the feeding network. The behavioural role of a transmitter is often known since the functions of the neurones utilising the transmitter have been determined.

In *Aplysia*, most of the motoneurones innervating the buccal muscles are cholinergic (e.g. Cohen et al., 1978) and a small number are glutamatergic (Fox and Lloyd, 1999). Cholinergic and glutamatergic motoneurones may innervate the same muscle (Keating and Lloyd, 1999). At present, it is unclear why different conventional transmitters should be used by motoneurones. CPG neurones also release these two transmitters. Acetylcholine (ACh) is released by the protraction-phase interneurones in *Lymnaea* (Elliott and Kemenes, 1992; Vehovszky and Elliott, 1995; Yeoman et al., 1993), and glutamate is released by the retraction-phase interneurones in *Lymnaea* and *Helisoma* (Brierley et al., 1997c; Quinlan and Murphy, 1991; Quinlan et al., 1995). Each transmitter has excitatory and inhibitory receptors on follower cells, with more than one kind of inhibitory receptor sometimes present on a single cell. In *Aplysia*, some of the command-like neurones, as well as protraction-phase interneurones, are cholinergic (Hurwitz et al., 1999a). Indirect evidence suggests that the chemoreceptors innervating the lips and sensing the presence of food in *Aplysia*, *Limax* and *Pleurobranchaea* are cholinergic, and for this reason the application of cholinergic agonists to the cerebral ganglion induces repetitive feeding bouts (King et al., 1987; Susswein et al., 1996; Morielli et al., 1986).

Serotonin is present in the giant cerebral cell in all species. Serotonin modulates sensory neurones, interneurones and motoneurones as well as the buccal musculature [*Lymnaea* (McCrohan and Benjamin, 1980a,b; Yeoman et al., 1994a,b, 1996); *Aplysia* (for a review, see Kupfermann, 1997), *Achatina* (Yoshida and Kobayashi, 1991), *Helix* (Bernocchi et al., 1998) and *Pleurobranchaea* (Gillette and Davis, 1977; Moroz et al., 1997; Sudlow et al., 1998)]. Other monoamines, including dopamine and octopamine are present in buccal ganglion cells and also modulate the pattern. In *Limax*, *Helisoma*, *Lymnaea* and *Aplysia*, exogenous dopamine application to the buccal ganglia induces fictive feeding (Kabotyanski et al., 2000; Kyriakides and McCrohan, 1989; Quinlan et al., 1997; Wieland and Gelperin, 1983).

In *Aplysia*, one command-like neurone (CBI-1) is dopaminergic. The buccal ganglia of *Helix*, *Lymnaea*, *Helisoma* and *Aplysia* all contain dopaminergic neurones; in the latter two genera, they are protraction-phase neurones that can initiate motor patterns (Elekes et al., 1991; Hernadi et al., 1993; Kabotyanski et al., 1998; Quinlan et al., 1997; Teyke et al., 1993). In addition, many peripheral neurones in the gut of *Helix* and *Aplysia* may be dopaminergic (Hernardi et al., 1998; Susswein et al., 1993). In *Lymnaea*, octopamine antagonists (but not the dopamine antagonists tested) block feeding responses (Vehovszky et al., 1998). Their effect may be explained in part by the presence of three OC (octopamine-containing) neurones in the buccal ganglia (Vehovszky et al.,

1998) which, when stimulated, produce fictive feeding after a significant delay. Similar neurones are present in *Helix* (Hiripi et al., 1998) and *Helisoma* (N3a) (Quinlan and Murphy, 1996). In *Aplysia*, exogenous dopamine and serotonin modulate the rate and form of buccal motor programs (Kabotyanski et al., 2000). The cerebral ganglion also contains an identified histaminergic sensory neurone that excites the giant cerebral neurone (Weiss et al., 1986).

Studies on gastropod feeding were among the first showing that many neurones synthesize and release both conventional neurotransmitters and peptide cotransmitters. Many of the basic insights into the cellular neurobiology of peptide cotransmitters come from work on these systems (for a review, see Kupfermann, 1991). Insight into the function of cotransmitters has been facilitated by the availability of parallel information on behaviour and on network interconnections. Cotransmitters functioning in the feeding system include SCP_A and SCP_B, FMRFamide, FRF_A, FRF_B and FRF_C, APGWamide, buccalin and myomodulin. Cotransmitters are found in motoneurons, interneurons and sensory neurons.

At the neuromuscular junction, the combined release of peptides and conventional transmitters allows the separate regulation of muscle contraction and relaxation (Brezina et al., 2000; Church et al., 1993; Evans et al., 1999b; Fox and Lloyd, 1997; Vilim et al., 1996a,b, 2000), permitting the muscles to be used through a broader frequency range of buccal movements. Co-release of a conventional and of a modulatory transmitter has been demonstrated, with the peptides generally released at higher firing rates. Peptide-releasing interneurons include CBI-12 in *Aplysia*, which contains myomodulin (Hurwitz et al., 1999a,b), and buccal interneurons SO and NIL in *Lymnaea* (Santama et al., 1994; Vehovszky and Elliott, 1995; Yeoman et al., 1993). Mechanoafferents innervating the radula utilise SCP and glutamate (Klein et al., 2000). FMRFamide inhibits feeding in *Helisoma* and *Lymnaea* (Kyriakides and McCrohan, 1989; Murphy et al., 1985) as a result of the action of a pleural ganglion neurone projecting to the buccal ganglia [*Helisoma*: (Murphy, 1990), *Lymnaea* (Alania et al., 2002)]. This connection is conserved in many species, including *Lymnaea* and *Helix*, and even in the carnivorous predator *Clione* (Alania, 1995; Alania et al., 1999).

Nitric oxide (NO) plays a prominent role in a number of sites in the feeding systems of many gastropods. In both *Lymnaea* and *Aplysia*, lip chemosensors with peripheral cell bodies release NO, in addition to ACh, and an increase in NO levels in the cerebral ganglion can induce repetitive bouts of feeding programs (Elphick et al., 1995; Moroz et al., 1993; Moroz, 2000). In *Lymnaea*, gut motoneurone B2 excites other motoneurons via both ACh and NO (Park et al., 1998; Perry et al., 1998). In addition, the serotonergic giant cell in the cerebral ganglia also expresses the gene for nitric oxide synthase (NOS). Expression of this gene may be controlled by a NOS pseudogene with an anti-sense sequence (Korneev et al., 1998, 1999). In *Aplysia*, a primary mechano-afferent neurone produces a slow, conductance-decreasing excitatory postsynaptic potential (EPSP) onto the giant cerebral cell via

the release of both histamine and NO (Koh and Jacklet, 1999). In *Limax*, the procerebral (PC) lobe contains approximately 10⁵ local interneurons that respond to food odours with coherent oscillations. The frequency of the oscillations is affected by both NO and CO. Many neurones in the PC lobe contain NOS (Gelperin et al., 2000). NOS-containing neurones also play a role in the regulation of feeding in the carnivorous gastropods *Pleurobranchaea* (Moroz and Gillette, 1996) and *Clione* (Moroz et al., 2000). In these animals, NOS-containing neurones are found exclusively within the central nervous system, whereas in the herbivorous gastropods many peripheral neurones also contain NOS. It has been suggested that the differences in distribution of NOS-containing neurones may be related to differences in feeding ecology since the carnivores eat large, infrequent meals, whereas the herbivores graze for many hours per day (Moroz et al., 2000).

Other transmitters, including γ -aminobutyric acid (GABA), which is found in buccal and cerebral ganglion neurones in *Lymnaea* (Hatakeyama and Ito, 2000), *Helix* (Hernardi, 1994), *Helisoma* (Richmond et al., 1991, 1994) and *Aplysia* (Diaz-Rios et al., 1999), also play a role in activating the feeding pattern, probably through the actions of the GABAergic cerebro-buccal and buccal-cerebral interneurons. Injection of GABA into the haemocoel of *Clione* also evokes feeding movements (Arshavsky et al., 1993).

Modulation of feeding movements by changes in state

Animals are responsive to food only intermittently, when the external and internal conditions are appropriate for feeding. The effects on the nervous system of stimuli that signal changes in external and internal states have been extensively studied, thereby contributing greatly to our understanding of the neurophysiological basis of changes in motivational state.

Food arousal

Food initiates a state of food arousal, in addition to driving feeding movements (Kupfermann, 1974). Arousal is mediated largely by slow, modulatory connections between neurones (Kupfermann et al., 1991). The neural circuitry underlying food arousal is partially parallel to that generating feeding movements in that some neurones apparently have a purely modulatory function. However, food arousal also partially arises from aspects of neural function that are embedded within the same neurones that effect the feeding movements.

The most prominent purely modulatory neurones are the giant serotonergic cells, which are a constant feature in all the gastropods (although they are known by different abbreviations, MCC, MCG, CGC, in different species). Chronic recordings show that these cells fire during feeding behaviour (Kupfermann and Weiss, 1982) and also (in *Lymnaea*) during egg-laying (Yeoman et al., 1994b). Their axons project to the buccal ganglia and to the buccal muscles, where most of the neurones and muscles are modulated by serotonin (Kupfermann et al., 1991). Both protraction- and retraction-phase muscles and motoneurons are modulated, as

is the sensitivity of mechano-afferents innervating the radula (Alexeeva et al., 1998; McCrohan and Benjamin, 1980a,b; Weiss et al., 1978; Yeoman et al., 1996).

Evidence for the behavioural function of these cells comes from chemical ablation experiments in *Aplysia*, in which radula retraction was delayed and the strength of movements weakened (Rosen et al., 1989). Other aspects of the feeding behaviour, for example the latency to bite, were not affected. In *Lymnaea*, laser ablation of these cells in the isolated central nervous system slowed fictive feeding, with the biggest changes being longer inter-bite intervals (Yeoman et al., 1994a). Injection of the serotonergic neurotoxin 5,6-hydroxytryptamine into the intact *Lymnaea* reduced feeding after 12–18 days, at a time when the levels of serotonin were also reduced (Kemenes et al., 1990). This was mostly due to changes in latency to feed, with shorter bites and longer inter-bite intervals. By contrast to the purely modulatory effects seen in the herbivores, stimulating the MCG in *Pleurobranchaea* accelerates ongoing feeding rhythms or causes short-latency motor output, suggesting that the neurone has a command-like function (Gillette and Davis, 1977).

In *Aplysia*, the MCC is strongly excited by neurone C-PR, which has both mediating and modulatory functions and is activated by food. It elicits head-lifting and also affects a variety of neurones whose activities are changed when *Aplysia* becomes aroused by food. It has been suggested that C-PR may function to elicit food arousal (Teyke et al., 1990a). In addition to driving the MCC, C-PR also drives additional purely modulatory neurones in the pedal ganglion, which modulate body wall postural muscles that are active during food arousal (Nagahama et al., 1994). C-PR also excites some command-like CBIs that initiate repetitive consummatory movements (Hurwitz et al., 1999b). The initiation both of an arousal state and of appetitive behaviours by the firing of a single neurone indicates that the appetitive behaviours may represent a motor read-out of the arousal state (Kupfermann et al., 1991).

Food arousal is also partially mediated *via* the same synaptic connections mediating feeding movements. For example, command-like neurone CBI-2 in *Aplysia* elicits repetitive bite-like activity and also increases the excitability of CPG neurones (Hurwitz et al., 1999a). The mediating and modulating effects of CBI-2 may be partially *via* different transmitters. CBIs release both ACh and peptides (Morgan et al., 1997; Wu-Morgan et al., 1998). In addition, many of the motoneurones driving the buccal muscles release peptides as well as conventional transmitters (e.g. Church et al., 1993; Evans et al., 1999b; Fox and Lloyd, 1997, 1999).

A major insight into the neural basis of arousal arises from the finding that modulatory cells affect several successive levels of processing: sensory neurones, other modulatory interneurones, CPG interneurones and motoneurones. Modulatory effects benefit from the feedforward organization, leading to a cumulative modulation. Examples of this are provided by the cerebral giant serotonergic cells, by the buccal ganglia SO and OC of *Lymnaea* and by the C-PR and CBI neurones in *Aplysia*.

Satiation

In *Aplysia*, *Limax* and *Lymnaea*, feeding is inhibited by mechanical stimuli that result from filling the gut with food (Elliott and Benjamin, 1989; Kuslansky et al., 1987; Reingold and Gelperin, 1980; Susswein and Kupfermann, 1975a,b). The inhibition is a graded function of the degree to which the gut is filled (Susswein et al., 1976). In *Lymnaea*, gut dilation activates the mechanosensory OM cells, which inhibit modulatory and pattern-generating neurones and also activate radular retractor motoneurones (Elliott and Benjamin, 1989). In *Pleurobranchaea*, satiation causes food stimuli to initiate withdrawal movements, in part because food stimuli inhibit cerebral ganglion command-like neurones, instead of exciting them (Davis and Gillette, 1978).

Other stimuli associated with feeding contribute to the patterning of feeding into meals. In *Aplysia*, gut stimuli arising from the consumption of small quantities of food facilitate feeding (Susswein et al., 1984b), before the inhibition begins as a result of filling the gut with larger quantities of food. Feeding in *Aplysia* and *Limax* is also patterned into meals by the build-up and decay of sensory adaptation, which occur when the lips are stimulated with food (Horn et al., 1999; Reingold and Gelperin, 1980; Schwarz et al., 1988). In addition, satiation affects the ability to arouse an animal, and this effect can contribute to the patterning of feeding into discrete meals (Susswein et al., 1978). Changes in haemolymph glucose concentration do not affect feeding in *Aplysia* (Horn et al., 1998).

Behavioural hierarchy

Classic studies in *Pleurobranchaea* examined the choice made by an animal in response to simultaneously presented stimuli that elicit different behaviours. Initially, these studies showed that behaviours are hierarchically organized, with feeding dominant over other behaviours, such as mating, withdrawal and righting (Davis et al., 1974a). The inhibition of withdrawal by feeding is attributed to the action of 'corollary discharge' neurones, which convey information from the buccal ganglia to the brain (Kovac and Davis, 1977, 1980a,b). However, it was later shown that feeding and withdrawal both modulate one another and are mutually inhibitory (Kovac and Davis, 1980a,b). Interestingly, food stimuli continue to inhibit withdrawal even after the animals are satiated, indicating that the stimuli causing satiation specifically modulate feeding behaviour by modulating the reciprocal inhibition between feeding and withdrawal (Davis et al., 1977). The relatively dominant position of feeding in the hierarchy can also be modified by hormonal control. For example, the release of hormones inducing egg-laying inhibits feeding (Davis et al., 1974b).

Aplysia, like *Pleurobranchaea*, displays mutual inhibition between feeding and defensive behaviours. However, the mechanisms underlying mutual inhibition differ. In *Aplysia*, mutual inhibition arises because stimuli that elicit one class of behaviour inhibit the other. Thus, noxious stimuli elicit withdrawal responses and also inhibit feeding (Kupfermann

and Pinsker, 1968). A blood-borne factor found in satiated animals also inhibits withdrawal responses (Lukowiak, 1987). In addition, food stimuli inhibit withdrawal responses even in the absence of ingestion of food or of feeding movements (Advokat, 1980). By contrast, in *Pleurobranchaea*, both food and noxious stimuli can elicit either feeding or withdrawal responses. The specific response elicited depends on the previous feeding history and on the strength of the stimulus (Gillette et al., 2000). The choice between feeding and withdrawal arises *via* inhibition of withdrawal responses by specific motor elements in the feeding system (Jing and Gillette, 1995, 2000) as well as *via* inhibition of command-like neurones that initiate feeding by neurones that initiate escape responses (Kovac and Davis, 1977, 1980a,b).

In *Clione*, *Helisoma* and *Lymnaea*, a pleural interneurone that has been suggested to be activated by stimuli that cause withdrawal projects to the cerebral and buccal ganglia and inhibits the feeding system. This may provide a partial explanation for the coordination of the feeding and withdrawal behaviours (Murphy, 1990; Alania, 1995; Alania et al., 1999, 2002).

Interaction with sexual behaviour

Feeding in *Aplysia fasciata* is strongly modulated by the animal's sexual state. As in most grazing animals, a major proportion (up to 25%) of the animal's time is budgeted to feeding (Susswein et al., 1983). *A. fasciata* spend an additional 25–50% of their time mating (Susswein, 1984), leaving little time for other activities. The large blocks of time spent mating and feeding suggest that these behaviours may compete for the animals' time and are mutually inhibitory. Removing food should then cause an increase in mating, and removing mates should facilitate feeding. Removal of food indeed causes increased mating (Nedvetzki et al., 1998; Susswein, 1984). By contrast, isolation from potential mates inhibits feeding, indicating that sexual stimuli facilitate feeding rather than inhibiting it (Botzer et al., 1991; Ziv et al., 1989).

In *Aplysia*, conspecifics signal their presence *via* peptide pheromones (Painter et al., 1998; Susswein and Benny, 1985) that are sensed by the chemosensory rhinophores (Levy et al., 1997), and the presence of putative pheromones in the water at concentrations of 10^{-9} mol l⁻¹ facilitates both the appetitive and consummatory components of feeding (Blumberg and Susswein, 1998; Blumberg et al., 1998). Facilitation of appetitive behaviours occurs in part by exciting the neurone C-PR (Teyke and Susswein, 1998). Thus, C-PR is a site of convergence in the control of feeding by food and by pheromones. The seemingly paradoxical facilitation of feeding by pheromones may be a mechanism for helping to synchronize mating (Nedvetzki et al., 1998), which occurs in large groups in which animals are constantly exchanging sexual roles (animals can mate as males, as females or as both simultaneously) and partners (Ziv et al., 1989). If animals eat at times that should be devoted to mating, their mating patterns would be severely disrupted. The facilitation of feeding by pheromones in conditions of sexual arousal causes animals to

eat vigorously and effectively and, consequently, to become thoroughly satiated. Feeding will then be relatively inhibited, allowing animals to devote the rest of the day to effective mating, which is not impeded by feeding.

Feedback as a result of feeding movements

The nature of feeding movements changes as a result of feedback. In *Aplysia*, radula mechanoafferents can switch movements from being bite-like to being more similar to swallowing. In addition, increasing the resistance against which animals must pull induces animals to cut the food instead of swallowing it (Hurwitz and Susswein, 1992). In *Limax*, the load on the radula is monitored by the medial tooth. An increase in load causes a decrease in bite rate (Reingold and Gelperin, 1980).

Modulation of feeding by learning and memory

The neural basis of associative learning has been intensively studied in gastropod feeding systems. One of the first such studies demonstrated that *Limax* learn to stop responding to a food if they become sick after ingesting it (Gelperin, 1975). A later study demonstrated inhibition of locomotion towards a food odour if ingestion of the food had been paired with a bitter taste (Sahley et al., 1981a). Using this learning paradigm, it was possible to show that a variety of phenomena affecting learning in vertebrates (second-order conditioning, blocking and the effect of pre-exposure to the unconditioned stimulus, UCS) also affect odour-learning in *Limax* (Sahley et al., 1981b). Later studies developed an appetitive conditioning paradigm in which the responses to an initially aversive odour were increased by pairing the odour with an attractive taste (Sahley et al., 1990). Neural correlates of learned inhibition of feeding are retained in a reduced preparation (Gelperin and Culligan, 1984). In addition, a reduced preparation can be trained (Culligan and Gelperin, 1983). Since the primary mechanism of learning seems to be a change in processing of an odour stimulus, subsequent studies have focused on the effects of training on odour processing (e.g. Teyke et al., 2000).

An important study has shown that separable memory processes follow learned inhibition of feeding in *Limax* (Yamada et al., 1992). Long-term memory can be disrupted by cooling before the memory is consolidated. For approximately 1 week after memory consolidation, the ability to disrupt the memory by cooling can be reactivated by exposure to the food conditioned stimulus (CS). A similar ability to disrupt memory only when it is re-activated has been reported in mammals (Nader et al., 2000). In a later stage of memory, cooling can no longer disrupt memory even after it has been reactivated (Yamada et al., 1992).

Another early study showed that pairing food with intense, prolonged shock in *Pleurobranchaea* causes the animals subsequently to withdraw from the food instead of eating it (Mpitsos et al., 1978). Studies examining the effects of differential training showed that the training is moderately

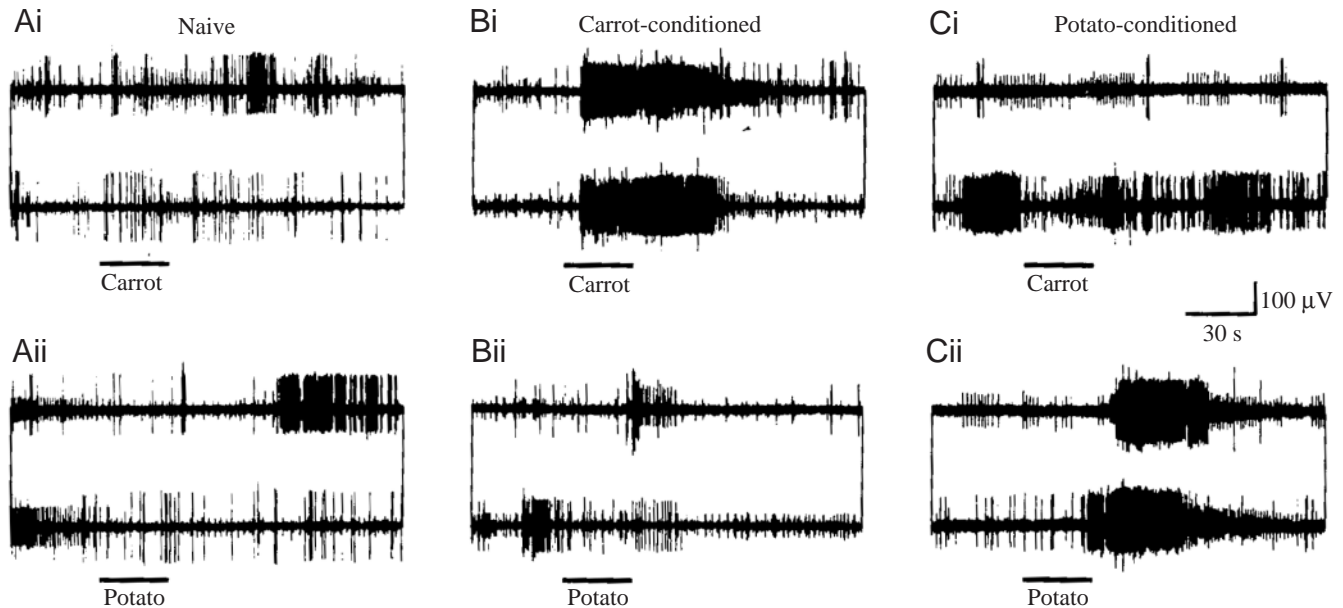


Fig. 5. Conditioning *Helix* to carrot or potato changes the responses recorded in the peritentacular nerves in an isolated tentacle/ganglion preparation. Snails were presented with either carrot (i) or potato (ii) and allowed to feed. (A) Naïve snails; (B) carrot-conditioned snails; (C) potato-conditioned snails. The extracellular recordings of nerve activity show increased activity when the odour of their food was blown across the tentacle. Reproduced from Peschel et al. (1996) with permission.

specific to the taste of the food stimulus paired with the shock (Davis et al., 1980; Mpitsos and Cohan 1986a,b).

Many studies have been aimed at finding the neural correlates of learning. One striking correlate is that after training, in a whole-animal preparation, the command-like phasic paracerebral neurones are inhibited by food, whereas food excites them in untrained animals. A similar change in the effect of food is seen following a second procedure that inhibits feeding, satiation (Davis and Gillette, 1978; Davis et al., 1983). The inhibitory effects of learning and satiation can be separated by examining the response to food in a severely reduced preparation, in which the gut is removed, thereby eliminating the stimuli underlying satiation (Kovac et al., 1985).

Subsequent studies were directed at finding the possible neuronal sites at which the excitatory response to food is decreased and is replaced by an inhibitory response. Three such sites have been found. One study identified a positive feedback loop that increases the excitability of the phasic paracerebral neurones. In trained animals, the efficacy of this positive feedback loop is diminished as a result of a decrement in the amplitude of EPSPs at a specific synapse (from a subpopulation of the paracerebral neurones and buccal ganglion corollary discharge neurones, which in turn excite paracerebral neurones) (Kovac et al., 1986). A second site at which the excitatory response to food is reduced is at the paracerebral neurones themselves. These neurones apparently contain muscarinic receptors, which respond to the ACh that is thought to be released from chemoreceptors responding to food. Following training, the response of the paracerebral neurones to applied ACh is reduced (Morielli et al., 1986).

Finally, additional studies focused on finding sources of inhibitory input to the phasic paracerebral neurones whose change in activity could account for the inhibition of the paracerebral neurones in response to food after training. A variety of inhibitory interneurons were identified (London and Gillette, 1984a,b; Kovac et al., 1983). One group of such neurones (Int-2s) is excited by food. Their excitability is enhanced following training, causing an enhanced response to food and an enhanced inhibition of the phasic paracerebral command-like neurones (London and Gillette, 1986). It is important to note that all the neural correlates identified are in the motor system and they cannot, therefore, explain the behavioural results showing differential conditioning in pathways that can differentiate between different foods. Thus, it is likely that additional neural sites are also affected by learning. An important message arising from these studies is that learning is likely to occur as a result of plasticity at a number of discrete neural sites, which together cause changes in behaviour.

Appetitive conditioning has been demonstrated in *Helix* (Teyke, 1995). A food triggers appetitive responses such as tentacle-pointing only if the animal has previously experienced successful consumption of the food. This learning is acquired by pairing a food odour with a bulk stimulus in the gut that arises from ingesting the food. Even a single pairing is sufficient to induce subsequent appetitive responses (Friedrich and Teyke, 1998; Peschel et al., 1996). Neural correlates of learning are retained in a reduced preparation in which nerve activity that is a correlate of the tentacle-pointing response is used as a monitor of learning (Fig. 5). NO is involved in the conditioning process: no memory is seen if NO synthase is

blocked during training, but not subsequent to the training (Teyke, 1996).

In *Lymnaea*, a number of learning paradigms affect feeding. In the most intensively studied paradigm, touch to the lips is repeatedly paired with sucrose. After the pairing, touch alone becomes more likely to induce feeding responses. Appetitive learning has also been demonstrated using stimuli of two additional modalities. One study showed that a neutral chemical stimulus can induce feeding after pairing it with sucrose (Audesirk et al., 1982). A second study showed that a patterned visual stimulus elicits feeding after pairing with sucrose (Andrew and Savage, 2000). Finally, a food-aversion task has been shown to cause learned inhibition of feeding (Kojima et al., 1997).

The effects of appetitive conditioning to touch have been examined in a reduced preparation consisting of central ganglia remaining attached to the lips. The reduced preparation can be trained by pairing lip touch with intracellular stimulation of a neurone (the SO) that drives feeding bursts (Staras et al., 1999b). In addition, examining the response to lip touch in a reduced preparation after training in the intact animal shows that touch elicits significantly more fictive feeding bursts (Kemenes et al., 1997). After training, there is an enhanced response in the CPG cell N1M in response to lip touch, with little change in the response of two modulatory neurones (CGC and SO). In comparison, in a taste-avoidance paradigm, input to the CGC was unaffected and the N1M cell was more strongly inhibited by the CGCs, thereby weakening its rhythmic activity (Kojima et al., 1997). Additional changes in the response to lip touch are also seen after training. One such change is an increase in the excitatory drive to motoneurons that precedes the excitation during a feeding program. A second change is an enhancement of touch-evoked responses recorded in the cerebro-buccal connectives. These findings suggest that the primary mechanism of the learning may be an enhancement of touch-induced activity, and this enhancement can be monitored at many sites within the feeding circuit (Staras et al., 1999a).

A number of learning tasks affect feeding in *Aplysia*. In one (Colwill et al., 1997), consumption of food is paired with one of two tastes or with one of two textures of a tactile stimulus to the lips. Biting is increased in response to the paired stimulus.

A second study (Lechner et al., 2000a) showed a pairing-specific increase in biting when a tactile stimulus to the lips was paired with food touching the lips and then being consumed. Preventing the animals from consuming the food blocked their ability to learn. Denervating the anterior portion of the foregut also prevented learning, indicating that the reinforcement necessary for learning arises here. A correlate of the learning was found in a reduced preparation (Lechner et al., 2000b). In animals that had been trained, electrical stimulation of a nerve innervating the lips elicited more buccal motor programs than in untrained animals. This was related to a greater level of excitation in protraction-phase pattern-generating neurones.

Additional experiments showed that *Aplysia* modify their response to a specific food after their success or failure to swallow it (Susswein et al., 1986). Success causes increases in ingestion, and failure causes increases in rejection and an eventual cessation of responses. Differential training and testing showed that learning is specific to a particular combination of taste and texture (Schwarz et al., 1988; Susswein et al., 1986). Stimuli from the gut are needed for learning since denervating the gut before training blocks learning (Schwarz and Susswein, 1986). However, denervation after training does not affect memory (Schwarz et al., 1991).

Training with inedible food also initiates a number of memory processes. Training until animals stop responding induces short-term memory that decays within 1 h and long-term memory that appears only after a delay of 12–24 h (Botzer et al., 1998). The long-term memory is maintained for over 3 weeks (Schwarz et al., 1991). Cooling immediately after training attenuates long-term, but not short-term, memory. Short- and long-term memories are independent, parallel processes, as shown by the finding that a brief (5 min) training causes only long-term memory. A separable intermediate-term memory is obtained after short-term memory has declined, but before long-term memory has appeared, if animals receive three separate 5 min trainings (Botzer et al., 1998).

Aplysia fasciata learn that food is inedible only in the presence of other *Aplysia* (Schwarz and Susswein, 1992). In addition, isolation from conspecifics after training blocks long-term memory (Schwarz et al., 1998). In mammals, emotionally charged events, or physiological analogues of stress, modulate learning and memory (McGaugh, 1989). Isolation in *A. fasciata* induces behavioural changes reminiscent of stress in mammals, suggesting that *Aplysia* may display an analogue of stress-induced modulation learning and memory (Schwarz et al., 1998).

An analogue of learning that food is edible has been demonstrated in an isolated buccal ganglion (Nargeot et al., 1997). Electrical stimulation of a buccal nerve elicits a mixture of ingestion- and rejection-like buccal motor programs. Ingestion-like programs are reinforced by electrical stimulation of the oesophageal nerve. This leads to an increase in ingestion-like programs in response to stimulation of the buccal nerve alone. The reinforcement caused by stimulating the oesophageal nerve is partially due to dopaminergic inputs from the oesophageal nerve (Nargeot et al., 1999c). Intracellular stimulation of a neurone (B51) specifically active during ingestion or swallowing-like movements also successfully reinforces ingestion-like patterns, and this neurone is excited by stimulating the oesophageal nerve (Nargeot et al., 1999a,b).

Concluding remarks: why are we still doing this?

Intensive studies on the neural basis of gastropod feeding began approximately 30 years ago. The strategy has been to study a variety of species that share many common features of behaviour, anatomy, pharmacology and physiology. The

similarities and differences between species are a striking example of the conservation across evolutionary time of a fundamentally successful neural circuit and of the adaptation of the circuit to specific physiological needs. These studies have been spectacularly successful in examining phenomena in parallel at the level of the intact, behaving animal as well as in neurones and in circuits in a variety of dissected preparations. The data have shown that feeding is organised to suit the current circumstances of food availability as well as the recent and not so recent experiences of the animal. Studies on gastropod feeding were among the first to demonstrate phenomena such as cotransmission and coordinated modulation of multiple targets and to explain the behavioural significance of such phenomena. These preparations are now producing real insights into the neural basis of learning and memory in a complex neural network.

A comprehensive review of a field not only impels us to assess how far we have come, but also to determine where we are going. At the time that these studies began, it was generally thought that the best way to gain insight into the neural basis of behaviour was to study the properties of individual nerve cells. Neurones were thought to be the functional units of the nervous system, and understanding the entire system was thought to entail understanding it one neurone at a time. The prototypical parody of the common thinking about the nervous system in this period was the idea of the 'grandmother cell'. In this era, relatively simple nervous systems with large neurones were particularly attractive, since the cellular biophysical properties of individual nerve cells could be easily examined and these properties could be related to behaviour. Grandmother cells could be more easily identified and their properties understood in simpler, more accessible, systems than in complex systems.

Over the last 10 years, this view of the nervous system has been under attack. Information and representations are generally thought to be stored in distributed ensembles of interconnected neurones rather than in individual cells. This approach derives from connectionist models of neural function, in which neurones are modelled as signalling *via* standard all-or-none spikes that influence other neurones *via* synaptic functions of variable strength. In part as a result of this view, invertebrates have become much less popular experimental models since access to the detailed cellular processes of individual neurones seems much less important in understanding the functioning of neural systems.

Our review of gastropod feeding allows us to gain some perspective on the utility of invertebrate systems in understanding the fundamental principles of neural organization. A striking finding is that the properties of a cell are usually consistent with its being designed 'for' a specific function that is easily described in a few words. In spite of their complex properties, cells are easily understood, and easily summarised, as being protractors, phase-switchers or amplifiers of a movement. Their complex biophysical properties, and their complex pharmacologies, become understandable in terms of their function. This finding suggests

that the circuits operate *via* local coding, in which the activity of a specific neurone codes a particular piece of information (i.e. they *are* Grandmother cells). It is possible that all nervous systems are composed of Grandmother cells, but the function of a Grandmother cell is more readily identified in systems such as gastropod feeding because the investigators have paid attention to behaviour, which in these preparations can be studied in tandem with investigations of cellular properties.

If more recent ideas on distributed coding (Churchland and Sejnowski, 1994) are correct, it is possible that the fundamental mechanisms of information processing differ in vertebrates and invertebrates. An alternative possibility is that the seeming ability to understand the function of a neurone represents self-deception arising from the biases of the investigators, who actively search for neurones with properties that conform to preconceived notions derived from behavioural experiments. In this view, nervous systems utilize distributed coding in both vertebrates and invertebrates, but it is easier to misinterpret a neurone's function in a relatively simple invertebrate system than in a more complex mammalian system. In the buccal motor systems, the propensity to misinterpretation may be compounded since the systems are reprogrammed as a result of changes in state and experience, but they are examined only in a highly artificial experimental situation.

The findings summarized above suggest an intermediate position. Our understanding has grown from both a behavioural and a circuit approach, with much common ground now well developed. This may reduce the likelihood of false interpretation. Furthermore, even when the function of a neurone appears to be understood, it often has complex properties that would not easily have been predicted. For example, even motoneurones, which might be predicted to be prototypical single-function local coding units, release peptide cotransmitters that complicate their functioning and also connect with CPG and modulatory interneurones so that they become modulators of their own actions. As neurones become more complex, and embed within their properties more features, their function becomes more difficult to understand. In systems such as those controlling gastropod feeding, we are probably close to the limit of our ability to understand the behavioural function of an individual neurone. In systems that are orders of magnitude more complex, it would be a hopeless task to name the function of a complex neurone or to relate its biophysical properties with its function. Although a neurone may still have a specific function, and its complex properties match that function, it may be easier to study it as part of a distributed processing network, at least until experimental and analytical tools have been developed to study and understand the cellular properties of massive numbers of interconnected neurones.

Studies on systems such as those controlling gastropod feeding, in which the cellular and system properties can be connected with function, may therefore indeed be good models of the functioning of more complex systems and may provide key ideas in understanding how the cellular properties of neurones match their function. Such ideas will be relevant to

investigations of larger and more complex systems. If these ideas are correct, it will be worth investing additional effort to understand the control of gastropod feeding in greater detail, by identifying and characterizing additional neurones, and expanding our understanding of the animals' behaviour. To help us test our ideas on the functioning of individual neurones, and how behaviours are built from them, future studies must also utilise techniques such as network modelling, recording from multiple identified neurones in behaving animals and the removal of identified neurones with 'known' functions from the system.

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