SEROTONERGIC MODULATION OF BEHAVIOUR: A PHYLOGENETIC OVERVIEW

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(Received 23 June 1995; revised 10 April 1996; accepted 11 April 1996)

ABSTRACT

Serotonergic neurons are present in all phyla that possess nervous systems. In most of these phyla, serotonin modulates important behaviours, including feeding, sexual and aggressive behaviour. Serotonin exerts its effects by acting in three basic modes: as a classical neurotransmitter, as a neuromodulator, or as a neurohormone. In a number of invertebrate species, the neural circuitry underlying the effects of serotonin has been well characterized, whereas in vertebrates, the mechanisms by which serotonin affects behaviour are currently less fully understood. The following review examines the role played by serotonin in the generation and modulation of behaviour in successively more complex species, ranging from coelenterates to humans.

Key words: Serotonin, behaviour, neurotransmitter, neuromodulator, neurohormone, biogenic amine.

I. INTRODUCTION

The orchestration of complex behaviour by the nervous system relies on a surprisingly small number of neurotransmitters. Each transmitter, however, may act in multiple ways: it may bind to a variety of receptors to open or close ion channels or to activate any of several different second messenger systems. Furthermore, a single transmitter may, in different systems, function in any of three basic modes: as a classical neurotransmitter, as a neuromodulator, or as a neurohormone. A classical neurotransmitter exerts its effects directly on a postsynaptic cell. A neuromodulator does not directly alter the activity of a postsynaptic cell, but rather alters either presynaptic
release of, or postsynaptic response to, another compound which acts as the primary neurotransmitter at a synapse. Neuromodulators may be released in a diffuse manner into a region of the nervous system rather than onto discrete postsynaptic sites. A neurohormone is released into the general circulation rather than onto a specific postsynaptic cell and can therefore exert modulatory effects throughout an entire organism.

Serotonin (5-hydroxytryptamine, 5-HT) functions as a neurotransmitter in even the most primitive nervous systems. The following review assesses the role that serotonin plays as a classical neurotransmitter, as a neuromodulator, and as a neurohormone in the various phyla of the animal kingdom. By examining the role of serotonin in successively more complex nervous systems, an understanding will emerge of the ways in which a single neurotransmitter can contribute to the generation and modulation of complex behaviours, including feeding, sexual and aggressive behaviour.

II. SEROTONERGIC MODULATION OF BEHAVIOUR IN ANIMAL PHYLAE

(1) Coelenterates

Coelenterates are the most primitive organisms that possess a nervous system. Serotonin appears to be present in the neurons of some members of this phylum (Wood & Lentz, 1964; Umbriaco, Anctil & Descarries, 1990). In the sea pansy (Renilla koellikeri), the morphology of serotonin-immunoreactive neurons suggests that they are sensory (Anctil, 1989; Umbriaco et al., 1990). In this animal, serotonin enhances the amplitude of endogenous rhythmic contractions, and it may be the transmitter that mediates an increase in the amplitude of such contractions in response to slow water movement. Water flow may activate mechanosensory serotonergic neurons directly, causing a release of serotonin that modifies motor activity in the animal in accordance with changing environmental conditions (Anctil, 1989).

Serotonin is also found in the stinging nematocysts of some coelenterates (Wood & Lentz, 1964; Castano & Rossi, 1978; Umbriaco et al., 1990). As a component of the toxin released by these organelles, serotonin may exert effects on the neuromuscular system of predators or prey (Welsh, 1957).

(2) Platyhelminths (flatworms)

Welsh (1970) reported that planarians have serotonergic neurons in the brain, ventral nerve cord and peripheral nervous system. Serotonergic sensory neurons also appear to be present.

Serotonin-immunoreactive neurons are observed in the central and peripheral nervous systems of the monogenean parasite, Diclidophora merlangi, and possible serotonergic sensory fibres are also found (Halton et al., 1987). Exogenous serotonin enhances spontaneous muscular contractions (Maule et al., 1989). Serotonergic innervation of the reproductive system is found in male D. merlangi only, suggesting a role for serotonin in the control of gender-specific reproductive behaviour (Maule et al., 1990).

(3) Nematodes

Horvitz et al. (1982) identified two serotonergic neurons in Caenorhabditis elegans. These are known as the pharyngeal neurosecretory motor neurons; they innervate
pharyngeal muscles and appear to have neurohumoral outputs to the pseudocoelom. Exposure of intact animals to exogenous serotonin increases the rate of pharyngeal pumping, stimulates egg release and depresses locomotion. These results suggest that serotonin plays the role of a classical neurotransmitter or neuromodulator in feeding and a neurohormonal role in reproduction and locomotion.

Octopamine application decreases both the rate of pharyngeal pumping and that of egg laying. Although individual octopaminergic neurons were not identified in this study, octopamine was found in crude extracts of *C. elegans*. Phentolamine, an octopamine antagonist, stimulates egg laying, which suggests that octopamine tonically inhibits egg laying *in vivo*. Octopamine suppresses the serotonergic stimulation of egg laying (although it does not suppress serotonergic stimulation of the pharynx), indicating that serotonin and octopamine may act antagonistically *in vivo* to control the rate of egg laying in the animal. Opposition between the effects of serotonin and octopamine (or norepinephrine, the vertebrate analogue of octopamine) is also found in the mollusc *Tritonia diomedea*, in crustaceans and in gymnotid fish, and will be described below.

(4) Molluscs

The best-understood molluscan nervous system is that of *Aplysia californica*. A number of studies have implicated a pair of large serotonergic neurons in the cerebral ganglion in the modulation of feeding behaviour in this organism. Axonal branches of these metacerebral cells (MCCs) project to the buccal ganglion, to the muscles of the buccal mass (which mediate biting and swallowing) and to the lips (Kupfermann & Weiss, 1981).

In the buccal ganglion, the MCC terminals play a neuromodulatory role. Firing of the MCCs may produce excitatory potentials in buccal motor neurons, although these inputs are usually insufficient to elicit spikes. However, if these neurons have been brought close to firing threshold by some other excitatory input, then MCC activity may facilitate the primary excitation and result in buccal motor neuron activity. In a preparation in which the buccal neurons are firing rhythmically, MCC activity can increase the bursting frequency; this effect may result from input to premotor pattern-generating interneurons (Kupfermann & Weiss, 1981).

Serotonin from the MCCs also plays a modulatory role at the buccal motor neuron-buccal muscle junction. First, serotonin enhances excitatory junctional potentials (EJPs). This effect may be pre- or postsynaptic. Secondly, serotonin enhances muscle contraction even when EJP size is not increased. This postsynaptic effect on the muscle fibre is mediated through the stimulation of muscle adenylate cyclase and the subsequent phosphorylation of five muscle proteins, possibly including the contractile protein paramyosin (Kupfermann & Weiss, 1981).

The MCC cells thus potentiate biting at two levels: the buccal ganglion and the buccal musculature. Kupfermann & Weiss (1981, 1982) demonstrated the behavioural relevance of this potentiation to the state they termed ‘food-induced arousal’. Food arousal is initiated by exposure of the animal to food and results in an increased efficiency of feeding. Strength and frequency of biting increases, as does bite speed (defined as the inverse of the length of time from presentation of food on the lip to maximal radula protration). Food arousal is decreased by satiation or by noxious
stimuli. Extracellular recordings from freely moving animals showed that food stimuli can activate the MCCs, and that at all levels of arousal the corresponding bite speed correlates directly with the firing rate of the MCCs.

Experiments in which the MCCs were inhibited or lesioned support their role in the potentiation of biting. When a food stimulus was presented to a single semi-intact preparation during depolarization and hyperpolarization of both MCCs, the movements of the buccal muscles were slower and weaker when the MCCs were hyperpolarized (Weiss et al., 1986a). Furthermore, Rosen et al. (1983, 1989) found that selective lesioning of the MCC cells in otherwise intact animals produces abnormal biting behaviour, characterized by reduction of bite speed, prolongation of mouth opening, an increase in interbite interval, and an exaggerated reduction in bite magnitude over the course of a meal. However, several other measures of feeding behaviour are unaffected by MCC lesions. These include the time interval between exposure to food and assumption of the feeding posture, rate of swallowing and meal size. The MCCs are not necessary for the manifestation of any component of feeding behaviour, and their modulatory effects appear to be restricted to biting.

Teyke, Weiss & Kupfermann (1990) clarified the position of the MCCs in the neural hierarchy controlling feeding behaviour. Sensory input (a food stimulus to the tentacles, rhinopores, or lips) activates a pair of high-level neurons known as the cerebral-pedal regulators (CPRs). These neurons act through connections in the pedal-pleural ganglia to coordinate all aspects of feeding behaviour (Fig. 1). Neck motor neurons are activated to produce the characteristic feeding posture; head and gill withdrawal neurons and defensive secretion neurons are inhibited; and heart rate is increased through activation of neurons that control the cardiovascular system. Finally, the paired CBI-2 neurons, putative biting command elements, are activated; the MCCs are also excited and enhance the speed and frequency of biting. CPR activation of the MCCs may be mediated through the CBI-2 cells; intracellular stimulation of CBI-2 can excite the ipsilateral MCC (Rosen et al., 1991). Extracellular recordings from free-moving animals suggest that the CPRs are activated by presentation of a food stimulus, and that increased CPR firing correlates with lifting of the head to assume the feeding posture. Secondary MCC activation should accompany this enhanced CPR activity (Teyke, Weiss & Kupfermann, 1991).

The MCCs receive direct sensory inputs in addition to those mediated through the CPRs. One such input arises from the interganglionic cerebral-buccal mechaanertents (ICBMs). These mechaanertent cells in the cerebral ganglion respond to tactile stimulation of specific receptive fields in the perioral zone or on the inner wall of the buccal mass. Intracellular stimulation of an ICBM can evoke a compound excitatory postsynaptic potential (EPSP) in the ipsilateral MCC. The first component of this EPSP appears to be monosynaptic, while the later components appear polysynaptic. The ICBMs also monosynaptically excite neurons in the buccal ganglion and can evoke coordinated output from this ganglion (Rosen et al., 1982). Both the CPRs and the ICBMs, therefore, respond to sensory stimuli relevant to feeding by co-activating the modulatory MCCs along with other neurons that participate in the generation of feeding behaviour.

Another direct sensory input to the MCCs comes from C2, a paired histaminergic neuron that innervates the perioral region. C2 is excited by mechanical stimulation of
the perioral zone, and also appears to be activated by deformation of the perioral tissue during movements of the buccal muscles. Rapid train stimulation of \( C_2 \) evokes a slow, prolonged depolarization of an impaled MCC that appears to result from a monosynaptic connection. This effect is at least in part due to a postsynaptic decrease in \( K^+ \) conductance. Although slower stimulation of \( C_2 \) may fail to produce any obvious synaptic potential, MCC excitability is nonetheless increased and the response to exogenous inputs is enhanced. Conversely, hyperpolarization of \( C_2 \) during presentation of a food stimulus decreases MCC activation. \( C_2 \) also affects the activity of a number
of other cerebral neurons. Some of these are motor neurons that innervate the extrinsic buccal muscles and the muscles of the body wall. Although the extrinsic buccal muscles are not necessary for biting or swallowing, they appear to increase the amount of food that can be ingested on a single swallow, thereby enhancing feeding efficiency. C2, therefore, appears to serve as a modulator of the feeding motor apparatus rather than as a command element. However, C2 provides the potential for a positive feedback loop. An initial food stimulus may excite the MCCs through activation of the CPRs, the ICBMs, and the C2 neurons. MCC activity potentiates biting, and the resulting movements of the buccal mass will again activate the C2 cells, which will then further excite the MCCs. This loop may promote continuity of the feeding behaviour (Chiel, Weiss & Kupfermann, 1986; Weiss et al., 1986a; Weiss, Chiel & Kupfermann, 1986b; Weiss, Shapiro & Kupfermann, 1986c).

Another behaviour in *Aplysia californica* in which serotonin has been implicated is the gill- and siphon-withdrawal reflex. When the siphon is mechanically stimulated, the siphon and gill withdraw into the mantle cavity. After the animal receives a noxious stimulus, it enters a state of ‘defense arousal’ in which the gill- and siphon-withdrawal reflex is sensitized and biting is inhibited. This defensive state is in sharp contrast to the food-induced arousal state previously discussed in which gill and siphon withdrawal are depressed and biting is enhanced. Serotonin appears to play a modulatory role in defense arousal as well as in food arousal. A simplified diagram of the neural circuitry underlying the sensitization of the gill- and siphon-withdrawal reflex is illustrated in Fig. 2. A siphon sensory neuron stimulates a gill or siphon motor neuron, either directly or through an excitatory interneuron. Facilitating interneurons, activated by noxious stimuli to the head or tail, enhance transmission at the sensory neuron terminals (Kandel et al., 1981; Glanzman et al., 1989; Hawkins & Schacher, 1989; for review see Kandel & Schwartz, 1982).

The primary mechanism underlying short-term facilitation of the monosynaptic sensory-motor neuron connection appears to be an increase in cyclic AMP in the sensory terminal, which results in a decreased probability of opening of a subset of K+ channels. The resulting suppression of K+ efflux prolongs the action potential, leading to an increase in Ca2+ influx and therefore in transmitter release. The end result is an
enhanced EPSP in the postsynaptic motor neuron which contributes to sensitization of the gill- and siphon-withdrawal reflex. Exogenous application of serotonin mimics these effects of stimulation of the facilitating interneurons in dissected preparations and induces facilitation of sensory-motor synapses in culture (Kandel et al., 1981; Montarolo et al., 1986; Glanzman et al., 1989; Mackey, Kandel & Hawkins, 1989; for review of early work see Kandel & Schwartz, 1982). At sensory-motor synapses that have become depressed as a result of repeated sensory neuron stimulation, there appears to be a second mechanism that contributes to presynaptic facilitation (Hochner et al., 1986). Studies of depressed synapses in culture suggest that exogenous serotonin can also activate this second mechanism, which may be mediated by protein kinase C (Ghirardi et al., 1992).

A single noxious stimulus produces short-term sensitization of the gill- and siphon-withdrawal reflex; in sensory-motor co-culture, a single pulse of serotonin produces short-term facilitation of the sensory-motor synapse. Repeated noxious stimuli or multiple pulses of higher concentrations of serotonin result in long-term enhancement lasting 24 h or more (Castellucci et al., 1989; Ghirardi, Montarolo & Kandel, 1995; for review of early work see Kandel & Schwartz, 1982). The transition from short- to long-term facilitation requires both protein and RNA synthesis. Inhibition of protein synthesis blocks long-term sensitization in semi-intact preparations subjected to tail shocks, and inhibitors of protein or RNA synthesis block long-term facilitation in sensory-motor co-cultures treated with serotonin (Montarolo et al., 1986; Castellucci et al., 1989).

Potential mechanisms for induction of transcription by serotonin have been explored in sensory neurons from pleural ganglia. Application of serotonin increases the cytosolic concentration of cyclic AMP. Although this effect is most pronounced in distal processes, smaller increases are noted in the perinuclear cytoplasm. Prolonged application or multiple pulses of serotonin can lead to translocation of the free catalytic subunit of the cyclic-AMP-dependent protein kinase into the nucleus (Bacskai et al., 1993). The next step is phosphorylation of cyclic AMP response element binding proteins (CREBs). These proteins then induce the transcription of genes regulated by the cyclic AMP response element (CRE) (Kaang, Kandel & Grant, 1993).

Long-term sensitization appears to rely in part on the same mechanisms that contribute to the short-term process. In animals showing long-term behavioural sensitization, there is a drop in the ratio of the regulatory to catalytic subunit of the Aplysia cyclic-AMP-dependent protein kinase in tissue containing the siphon sensory neurons. This reduction in the regulatory subunit would make the catalytic subunit of this kinase less dependent on cyclic AMP, so that the same substrate proteins phosphorylated during short-term sensitization would remain phosphorylated in the long term when cyclic AMP is no longer elevated (Greenberg et al., 1987). In vitro, exogenous serotonin lowers the ratio of regulatory to catalytic subunits in Aplysia californica pleural sensory neurons, suggesting that similar changes in siphon sensory neurons might be mediated by serotonin in vivo (Bergold et al., 1990).

Another important change that accompanies long-term sensitization is an increase in the number of presynaptic varicosities of abdominal sensory neurons. This growth is observed in long-term behaviourally sensitized animals as well as in sensory-motor co-cultures treated with serotonin (Bailey & Chen, 1989; Glanzman, Kandel & Schacher,
One factor that may contribute to this growth is a decrease in cell surface proteins that mediate adhesion. These proteins, known as *Aplysia* cell adhesion molecules (apCAMs), appear to belong to the immunoglobulin class of cell adhesion molecules and are similar to another member of this class, the neural cell adhesion molecule (NCAM), which is found in vertebrates. Exposure to serotonin alters both synthesis and distribution of apCAM in *Aplysia californica* sensory neurons. It decreases synthesis of new apCAM and increases endocytosis of apCAM that is already present at the cell surface (Bailey *et al.*, 1992; Mayford *et al.*, 1992).

An increase in the number of sensory presynaptic varicosities may be accompanied by corresponding changes in postsynaptic motor neurons. In the intact abdominal ganglion, a prolonged application of serotonin that produces long-term sensory-motor facilitation also results in long-term enhancement of the response of an identified gill motor neuron to an applied agonist (Trudeau & Castellucci, 1995).

The evidence presented above indicates that exogenous serotonin can produce both short- and long-term changes that mimic the effects of sensitizing sensory stimuli. However, identified facilitating interneurons in the abdominal ganglion are not serotonergic (Ono & McCaman, 1984; Kistler *et al.*, 1985; Longley & Longley, 1986; Hawkins, 1989). A pair of serotonergic facilitating interneurons (CB1s) has been found in the cerebral ganglion. These neurons, LCB1 and RCB1, show a prolonged activation following tail shock (application of an electrical current to the tail, a stimulus known to produce sensitization). CB1 stimulation enhances the monosynaptic EPSP produced in gill or siphon motor neurons by stimulation of siphon sensory neurons through a mechanism that appears to be at least partly presynaptic (Mackey *et al.*, 1989).

In addition to its well-characterized effects on sensory-motor synapses, serotonin may act at other sites in the circuitry mediating the gill- and siphon-withdrawal reflex. Both connective stimulation (which can be used to simulate head or tail shock) and exogenous serotonin enhance the central excitability of sensory neurons; this effect is demonstrated by an increase in the number of spikes elicited in abdominal sensory neurons by current injection into the cell body. In addition, both connective stimulation and application of serotonin to the siphon can produce a small enhancement of the response of siphon sensory neurons to tactile stimulation of the siphon (Klein, Hochner & Kandel, 1986). At the level of the motor neurons, both tail shock and exogenous serotonin cause an increase in the tonic firing rate of a subset of siphon motor neurons. This tonic increase in activity can amplify phasic siphon contractions produced by brief high-frequency activation of these neurons (Frost, Clark & Kandel, 1988).

As noted above, serotonin is not the only transmitter that modulates the gill- and siphon-withdrawal reflex. However, serotonin depletion by injection of 5,7-dihydroxytryptamine (5,7-DHT) significantly reduces the enhancement of gill withdrawal by tail shock. Serotonin thus appears to be an important mediator of the sensitization of the withdrawal reflex in *Aplysia californica* (Glanzman *et al.*, 1989).

In another mollusc, the sea slug *Tritonia diomedea*, serotonin appears to act both as a classical neurotransmitter and as a neuromodulator in the central pattern generator (CPG) network that controls escape swimming. In *Tritonia diomedea*, contact with the tube feet of predatory starfish causes a series of 2–20 alternating ventral and dorsal flexions that move the animal away from the predator (McClellan, Brown & Getting,
Serotonergic modulation of behaviour: a phylogenetic overview

Numerous observations support the importance of serotonin in the generation of escape swimming behaviour. In whole animals, injection of serotonin can initiate swimming in the absence of epithelial stimulation, whereas methysergide, a serotonin antagonist, inhibits swimming in response to stimuli. In isolated brain preparations, peripheral nerve stimulation elicits the swim motor programme; shortly after bath application of serotonin, a similar pattern of neural activity is observed. Methysergide inhibits production of the swim motor programme both by nerve stimulation and by bath-applied serotonin (McClellan et al., 1994). A number of other compounds, including octopamine, inhibit the production of swimming activity by nerve stimulation; some of these compounds may oppose the effects of serotonin in vivo.

The neurons that form the CPG circuit for escape swimming in Tritonia diomedea have been well characterized (Katz, Getting & Frost, 1994; McClellan et al., 1994). On each side of the brain, there are one cerebral cell 2 interneuron (C2), three dorsal swim interneurons (DSIs), and two ventral swim interneurons (VSIs). The CPG neurons on a given side of the brain form a complex set of monosynaptic interconnections. They also project to two classes of flexion neurons: the ventral flexion neurons (VFNs) and the dorsal flexion neurons (DFNs), which are further subdivided into two groups (DFN-A and DFN-B).

The DSIs are serotonin-immunoreactive (Katz et al., 1994; McClellan et al., 1994). They make monosynaptic excitatory connections with C2 and DFN-A, and monosynaptic inhibitory connections with the VSIs, DFN-B and VFN. However, the DSIs play an additional neuromodulatory role. DSI stimulation enhances the synaptic potentials produced by C2 in the VSIs, DFN-A, DFN-B and VFN, as well as the potentials evoked by C2 in other DSIs (Katz et al., 1994; Katz & Frost, 1995a). DSI activation increases the amplitude of both excitatory and inhibitory potentials evoked by C2. This enhancement of the effects of C2 occurs regardless of whether the direct synaptic action of DSI on a given neuron is excitatory or inhibitory. The mechanism underlying the enhancement appears to be an increase in presynaptic release of transmitter from C2 terminals.

The effects of DSI activation on DFN-A show an additional level of complexity (Katz & Frost, 1995a). As noted above, stimulation of a DSI monosynaptically excites DFN-A; it also increases the amplitude of the EPSP produced in DFN-A by C2. However, there is at least one other effect: stimulation of one DSI decreases the amplitude of EPSPs evoked by subsequent stimulation of other DSIs. Future studies may reveal further complexity in the modulation of the Tritonia diomedea swim network.

As already stated, the DSIs are serotonin-immunoreactive. Specific evidence indicates that both the synaptic and modulatory effects of these neurons are mediated by serotonin (Katz et al., 1994; Katz & Frost, 1995b). Exogenous puffs of serotonin mimic both the fast and slow monosynaptic EPSPs evoked in DFN-A by DSI stimulation, and bath application of high concentrations of serotonin during DSI activation occludes both EPSPs. The fast EPSP is blocked by the serotonergic antagonist gramine, whereas the slow EPSP is reduced by methysergide. The modulatory effects of DSI stimulation also appear to be mediated by serotonin. Bath-applied serotonin increases the amplitude of the EPSP evoked in DFN-A by C2 stimulation, and no further enhancement follows DSI activation. Methysergide blocks
both the modulatory effects of DSI activation and those of exogenous serotonin. Imipramine, a serotonin reuptake inhibitor, enhances both the synaptic effects evoked by DSIs in DFN-A and the modulatory effects of DSI activation on the C2/DFN-A synapse.

In the *Tritonia diomedea* swim network, the serotonergic DSIs synaptically excite or inhibit CPG and efferent neurons and enhance transmission between C2 and its targets within the network. Afferent pathways that initiate swimming strongly activate the DSIs. These neurons may play an important role in the reconfiguration of the swim network from the resting state to the oscillatory state that produces the rhythmic swim motor output (Katz *et al*., 1994; McClellan *et al*., 1994; Katz & Frost, 1995a).

The DSIs may also play a role in sensitization of the escape swimming response. Following exposure to a stimulus that causes an animal to swim, the animal displays a decreased onset latency for swimming in response to further stimulation (Abraham & Willows, 1971). After a swim episode ends, the firing frequency of the DSIs remains elevated for several minutes. This increase in spontaneous DSI activity may continue to enhance transmission between C2 and its targets and predispose the animal to initiate swimming in response to sensory stimuli (Katz *et al*., 1994; McClellan *et al*., 1994). In this regard, the DSIs in *Tritonia diomedea* may play a role analogous to that served by *Aplysia californica* serotonergic neurons in sensitization of the gill- and siphon-withdrawal reflex.

### (5) Annelids

The most thoroughly analysed annelid nervous system is that of the leech (*Hirudo medicinalis*, *Macrobdella decora*, *Haementeria ghilianii*). The leech ventral nervous system consists of 32 ganglia: the rostral four are fused into the compound suboesophageal ganglion, 21 lie in individual segments, and the caudal seven are fused into another compound ganglion. 5–11 serotonin-containing neurons are found in every ganglion. Each ganglion contains a pair of large Retzius (RZ) neurons, which project peripherally and appear to play a neurohormonal role. The first ganglion has an additional pair of peripherally projecting cells, the large lateral (LL) neurons. Each ganglion also contains serotonergic interneurons which project only within the central nervous system (CNS) (Willard, 1981; Glover & Kramer, 1982; Lent & Dickinson, 1984; Nusbaum & Kristan, 1986; for review see Lent, 1985). All serotonergic neurons within a ganglion are electrically coupled to varying degrees; some interganglionic coupling also exists (Nusbaum & Kristan, 1986).

A number of studies indicate that the central serotonergic neurons play an important role in initiating and modulating leech feeding behaviour. Fig. 3 presents a summary of the known serotonergic effects on feeding which will be discussed below.

The first component of leech feeding behaviour requires swimming towards the source of a vibrational stimulus. Willard (1981) found that bath-applied serotonin can initiate swim motor output in isolated nerve cords. Additional findings confirmed that serotonin normally plays a role in the promotion of swimming in the intact leech. In whole leeches, bath-applied serotonin decreases the latency to initiate swimming towards a vibrating point source (Lent & Dickinson, 1984). In adult leeches, treatment with 5,7-DHT reduces serotonin levels in RZ and LL cells, while serotonergic interneurons remain largely unaffected. Such treatment increases swim onset latency
Serotonergic modulation of feeding behaviour in the leech. Serotonergic neurons are listed in bold type. All connections are excitatory unless marked by (–). (Summarized from Willard, 1981; Kristan & Nusbaum, 1983; Lent & Dickinson, 1984, 1987; Lent, 1985; Nusbaum, 1986; Nusbaum & Kristan, 1986; Lent, Dickinson & Marshall, 1989; Szczupak & Kristan, 1995.)

(Groome, Clark & Lent, 1993; for review see Lent, 1985). Willard (1981) discovered that blood serotonin levels of untreated leeches are higher in frequent swimmers than in infrequent swimmers, and that injection of serotonin increases the percentage of time spent swimming. Mechanical stimuli which increase swimming also increase blood serotonin levels. 5,7-DHT injections in embryonic leeches, which ablate all serotonergic neurons (both neurohormonal cells and interneurons), prevent the development of normal swimming movements (Glover & Kramer, 1982). These movements can be reinstated in lesioned leeches by the injection of serotonin or by immersion in a serotonin bath.

Further studies have shown that the neurohormonal RZ and LL cells and the serotonergic interneurons are part of a complex network controlling swimming. Mechnosensory stimuli (which would include vibrational stimuli) activate serotonergic interneurons, which, in turn, synaptically excite swim pattern generators (Nusbaum, 1986; Nusbaum & Kristan, 1986). Although there are also non-serotonergic swim-initiating interneurons, stimulation of a single serotonergic interneuron is sufficient to cause swim motor output in some preparations. The swim pattern generators then...
exert positive feedback on the serotonergic interneurons. RZ neurons are also activated by mechanosensory stimuli and by swim pattern generators (Lent & Dickinson, 1984; Nusbaum & Kristan, 1986; Szczupak & Kristan, 1995; for review see Kristan & Nusbaum, 1983). Direct stimulation of RZ neurons, which releases serotonin into extraganglionic fluid, initiates swim motor output in isolated nerve cords when the volume of saline in the surrounding bath is similar to the blood volume in the intact animal (Willard, 1981). The RZ neurons do not appear to make synaptic connections with any swim-related neurons (Willard, 1981; for review see Kristan & Nusbaum, 1983). RZ cells, therefore, appear to promote swimming through neurohormonal release of serotonin rather than through synaptic contacts with the swim circuitry.

Serotonin superfusion affects various central neurons involved in swimming. Serotonin decreases the threshold current injection required for an identified non-serotonergic swim-initiating interneuron, cell 204, to elicit swim episodes in isolated nerve cords (Angstadt & Friesen, 1993). Serotonin also decreases inhibitory synaptic interactions between swim motor neurons (Mangan, Cometa & Friesen, 1994). However, the concentrations of serotonin used in these studies (50 µM) were higher than those necessary to initiate swim motor output in isolated nerve cords (Willard, 1981).

The swimming phase of feeding behaviour is followed by the consummatory phase, which begins once a vibrational target has been located and recognized as suitable by virtue of its warm temperature. Stimulation of RZ and LL neurons induces five components of consummatory feeding behaviour: bite-like jaw movements, salivary secretion, pharyngeal peristalsis, mucus secretion and a relaxation of the body wall in preparation for meal ingestion (Lent & Dickinson, 1984; for reviews see Lent, 1985; Lent, Dickinson & Marshall, 1989). Exogenous application of serotonin produces the same effects. Jaw movement, salivation and peristalsis are evoked by serotonin superfusion even when the effector organs are isolated from the leech, indicating that serotonin acts directly on peripheral targets to produce these behaviours. Depletion of serotonin in the RZ and LL cells of starved leeches causes a failure of biting, while bathing lesioned leeches in serotonin reinstates biting.

The activity of RZ and LL cells is affected by sensory input relevant to biting behaviour. Thermal stimulation of the lip, a major sensory determinant for bite initiation, synaptically excites RZ and LL cells; chemical stimulation of the lip can excite RZ neurons (Lent & Dickinson, 1984; Groome & Lent, 1991; for review see Lent, 1985). Body wall distension, which suppresses biting, hyperpolarizes RZ and LL cells. Bathing leeches in serotonin before a meal increases the volume of blood they ingest; bathing well-fed, distended leeches in serotonin restores biting. These observations suggest that the effects of distension on behaviour may be primarily mediated through this inhibition of serotonergic neurons (Lent & Dickinson, 1984, 1987; for review see Lent, 1985).

After feeding, leeches have lower ganglionic and intracellular levels of serotonin than are found in hungry leeches (Lent et al., 1991; for review see Lent, 1985). This reduction of serotonin may account for the primary behavioural alterations that follow feeding: increased latency to initiate swimming when exposed to a vibrational stimulus and decreased frequency of biting (Groome et al., 1993).

In summary, the data indicate that the serotonergic interneurons, acting through
classical synaptic connections, and the RZ and LL neurons, acting as neurohormonal cells, promote swimming, while the RZ and LL cells also control the consummatory phase of feeding behaviour. The serotonergic neurons are activated and inhibited by appropriate environmental and internal stimuli.

(6) Arthropods: crustaceans

Crustaceans comprise an arthropod class in which serotonergic modulation of behaviour has been extensively studied. In the east coast lobster *Homarus americanus*, serotonin may play a role in aggressive behaviour. When two lobsters are placed together, they engage in agonistic encounters; eventually, one emerges as dominant and the other as subordinate (Scrivener, 1971; Huber & Kravitz, 1995; for review see Kravitz, 1988). In larger groups, aggressive interactions still occur, although the resulting hierarchies may take a variety of forms and dominance status may change over time. Dominant animals, when approaching subordinates, assume a characteristic posture in which the animal stands high on its walking legs with its tail flexed beneath it and its claws raised. This posture is characterized by contraction of the postural flexor muscles. Subordinate animals assume a posture characterized by contraction of postural extensors, in which the animal crouches low to the substrate, with its tail extended and its claws stretched out in front at substrate level. Livingstone, Harris-Warrick & Kravitz (1980) discovered that a dominant-type posture can be produced by the injection of serotonin into the haemolymph, while a subordinate-type posture results from octopamine injection.

Among the first steps in understanding the mechanism of this monoaminergic modulation of posture were attempts to identify the serotonergic and octopaminergic neurons. Beltz & Kravitz (1983) used immunocytochemical techniques to identify approximately 120 serotonergic neurons in the lobster ventral nerve cord. The nerve cord consists of a chain of 14 ganglia: the supra-, circum-, and suboesophageal ganglia, five thoracic and six abdominal ganglia. Each ganglion contains at least one serotonin-immunoreactive neuronal cell body. Among the largest serotonergic neurons are two bilaterally symmetrical neurosecretory pairs, one each in the fifth thoracic (T5) and first abdominal (A1) ganglia. Each of these neurons has extensive central projections within the neuropil of the ganglion of origin. These cells also send axonal projections out via the thoracic second roots of at least four anterior ganglia; terminals are found in neurosecretory regions near the base of each root and in the pericardial organs at the distal ends of the roots (Beltz & Kravitz, 1987). These neurons also contain the peptide proctolin (Siwicki, Beltz & Kravitz, 1987).

Schneider et al. (1993) identified approximately 86 octopamine-immunoreactive neurons in the lobster ventral nerve cord. Twenty-eight neurons (two pairs in each thoracic ganglion and four pairs in the suboesophageal ganglion) appear to be neurosecretory. These neurons have extensive projections within the neuropil and project out of the CNS via suboesophageal and second thoracic roots, where they form varicosities in the neurosecretory regions near the base of each root.

The proximal neurosecretory plexuses of the thoracic ganglia were studied in detail by Evans, Kravitz & Talamo (1976) and by Livingstone, Schaeffer & Kravitz (1981). The serotonergic and octopaminergic terminals are distinct. The terminals take up radioactive precursors of these transmitters, synthesize the transmitters and release...
them in a Ca$^{2+}$-dependent manner when depolarized. These terminals are therefore a site of release of serotonin and octopamine into the haemolymph. Actual concentrations of serotonin and octopamine in the haemolymph typically fall between $10^{-9}$ and $10^{-8}$ M (Livingstone et al., 1980).

Monoaminergic modulation of posture is mediated at both the central and peripheral levels. In the periphery, both serotonin and octopamine facilitate transmission at the neuromuscular junction (Battelle & Kravitz, 1978; Florey & Rathmayer, 1978; for review see Kravitz, 1988). Serotonin acts at the presynaptic excitatory terminal to enhance transmitter release. This effect appears to be mediated both by the phosphatidylinositol system (inositol triphosphate and protein kinase C) and by cyclic AMP (Glusman & Kravitz, 1982; Dixon & Atwood, 1989a, b; Goy & Kravitz, 1989; for review see Kravitz et al., 1980). Serotonin also increases transmitter release from inhibitory nerve terminals (for reviews see Kravitz et al., 1980; Kravitz, 1988). Octopamine enhances the release of excitatory transmitter, but its effects are less than those of serotonin (Breen & Atwood, 1983; for review see Kravitz, 1988). Serotonin and octopamine also facilitate muscle contraction at the postsynaptic level. There are four effects produced by both amines in exoskeletal muscles: an increase in resting tension, a small (1–2 mV) depolarization, a small (10–15%) increase in input resistance, and a decreased threshold for the generation of Ca$^{2+}$ spikes (Battelle & Kravitz, 1978; Florey & Rathmayer, 1978; for reviews see Kravitz et al., 1980, 1981). Although these amines increase cyclic AMP levels within the muscle, this increase is not the primary mediator of aminergic effects; agents which only raise cyclic AMP levels do not fully mimic the effects of the amines (Battelle & Kravitz, 1978; Goy & Kravitz, 1989).

Thus, the peripheral effects of both serotonin and octopamine are to prime all muscles, whether extensors or flexors, to respond to excitatory input. The antagonism between the effects of the two amines is generated in the central nervous system. The motor output of the dissected ventral nerve cord can be monitored in the presence of serotonin and octopamine (Livingstone et al., 1980; Harris-Warrick & Kravitz, 1984). Octopamine increases the firing rate of extensor excitor motor neurons and flexor inhibitor motor neurons; it decreases the firing rate of extensor inhibitors and flexor excitors. Overall, these effects combine to enhance postural extension. Conversely, serotonin alters central motor output so as to enhance postural flexion. It increases the firing rate of flexor excitors and extensor inhibitors, and decreases the firing rate of flexor inhibitors and extensor excitors.

Harris-Warrick & Kravitz (1984) investigated the cellular basis of the antagonistic effects of serotonin and octopamine on central motor neurons by recording from M$_{15}$, an identified extensor excitor, and F$_{5}$, an identified flexor inhibitor. They found that octopamine reduces the necessary depolarization for spike initiation while serotonin increases it; these effects are dependent upon synaptic inputs and are blocked by low Ca$^{2+}$ levels. Octopamine increases the frequency of EPSPs in these cells and causes the appearance of a new, larger size-class of EPSPs in F$_{5}$; serotonin decreases the EPSP frequency. Harris-Warrick (1985) also looked at the effects of serotonin and octopamine on extension-command-evoked excitation of M$_{15}$ and F$_{5}$. Octopamine enhances extension-command excitation of M$_{15}$ and F$_{5}$ while serotonin decreases F$_{5}$ excitation. Octopamine enhances the amplitude of the command-evoked EPSPs in both neurons while serotonin reduces EPSP amplitude in F$_{5}$. In cases where the extension command
inhibits flexor excitors, octopamine also enhances this inhibition while serotonin reduces it. The high experimental concentrations of amines ($10^{-6}$–$10^{-5}$ M) required to exert these effects suggests that they are mediated in vivo by direct release from central synapses. Levels of amines in the haemolymph are in the nanomolar range and well below the threshold for these central effects.

Ma, Beltz & Kravitz (1992) analysed the role played by individual serotonergic neurons in postural command circuits. They recorded intracellularly from the large A1 serotonin neurons, and found that stimulation of flexion command fibres tends to excite these serotonergic neurons, while stimulation of extension command fibres tends to inhibit them. Furthermore, stimulation of the A1 serotonin cells together with flexion command fibres enhances the effects of the commands on A1 flexion motor output. The A1 serotonin cell thus appears to act as a 'gain setter' in the flexion command circuit. Activation of the A1 serotonin cell increases the flexion motor output for a given level of flexion command excitation. A circuit that would account for these effects is proposed in Fig. 4. If forced to fire by intracellular stimulation during activation of an extension command, the A1 serotonin cell may either enhance or suppress extension motor output.

In summary, serotonin and octopamine both prime the postural musculature to
respond to excitatory impulses from the CNS. In the CNS, however, the two amines act antagonistically: serotonin biases the CNS towards the readout of the flexion motor programme, while octopamine biases the CNS towards extension motor output.

Serotonin has a number of effects in the lobster other than those exerted on the postural musculature and postural command circuitry. Aminergic modulation of lobster sensory input has been observed (Pasztor & Bush, 1987). The lobster oval organ contains three mechanoreceptors which project to the CNS; in the intact animal, a sinusoidally oscillating force is applied to these receptors as the ventilatory appendage moves water over the gills. Rhythmic stimulation produces a stable pattern of depolarizing receptor potentials, a certain percentage of which give rise to spikes. Application of nanomolar concentrations of serotonin or octopamine decreases the percentage of receptor potentials which give rise to spikes. In the case of a single rather than a sinusoidal stimulus, both amines decrease the amplitude of the resulting receptor potentials, although the effects of octopamine are somewhat inconsistent. These effects have concentration thresholds that can be surpassed by neurohormonal release into the haemolymph, suggesting that serotonin and octopamine modulate sensory input \textit{in vivo}.

Serotonin also affects the circulatory system and digestive tract of the lobster. Serotonin and octopamine both increase the intensity and frequency of the heartbeat (Battelle & Kravitz, 1978; Florey & Rathmayer, 1978). Serotonergic fibres are observed in the cardiac ganglion, although no serotonergic cell bodies are present (Beltz & Kravitz, 1983). Serotonin may modulate the endogenous rhythm of the cardiac ganglion through synaptic release (Hartline, 1979). In the gut, serotonin alters the pyloric motor output of the lobster stomatogastric ganglion by affecting the activity of a number of neurons. As in the heart, no serotonin-immunoreactive cell bodies are seen in the stomatogastric ganglion; however, fibres in the stomatogastric nerve and ganglion and the ganglionic neuropil stain for serotonin (Beltz \textit{et al.}, 1984).

Serotonergic innervation of the crustacean stomatogastric ganglion has been more extensively studied in crabs (\textit{Cancer borealis} and \textit{Cancer irroratus}) than in \textit{Homarus americanus}. The sole serotonergic innervation of the ganglion is provided by two bilateral pairs of muscle receptor cells known as the gastropyloric receptor (GPR) cells (Katz, Eigg & Harris-Warrick, 1989). These cells employ both serotonin and acetylcholine as transmitters. The dendritic processes of these cells cover muscles of the gastric mill (which macerates food before it travels to the pylorus) as well as the pylorus (Katz \textit{et al.}, 1989; Katz & Harris-Warrick, 1990a). The two receptor cells on each side of the foregut are designated as GPR\textsubscript{1} and GPR\textsubscript{2}, and each innervates different muscles. GPR\textsubscript{2} is excited when the muscles it innervates are stretched by movements of the gastric mill; it can also produce endogenous rhythmic activity in the absence of gastric mill movement.

In the stomatogastric ganglion, there are two semi-autonomous central pattern generators that control foregut movement: the gastric mill CPG and the pyloric CPG. GPR activity affects neurons in both of these CPGs (Katz & Harris-Warrick, 1989; Katz & Harris-Warrick, 1990b). With regard to the gastric mill CPG, the interactions of GPR\textsubscript{2} with the dorsal gastric (DG) motor neuron are of particular interest. First, GPR activation evokes a nicotinic cholinergic EPSP in the DG. Secondly, train stimulation of a GPR often causes changes in the DG that allow a plateau potential to
be elicited by brief depolarizing input. A plateau potential is a prolonged depolarization that leads to high-frequency firing; it is followed by an after-hyperpolarization. The effects of GPR stimulation on plateau induction in the DG are not blocked by cholinergic antagonists and are mimicked by serotonin (Katz & Harris-Warrick, 1989; Kiehn & Harris-Warrick, 1992a). Train stimulation of a GPR can produce a series of summating EPSPs that provide adequate depolarization to elicit a plateau potential in the absence of further excitatory input. A plateau potential in DG causes contraction of gastric mill muscles that stretch a muscle innervated by GPR2. Therefore, a positive feedback loop may exist: GPR2 excites DG, which in turn leads to further activation of GPR2. GPR2 exhibits endogenous activity and could initiate this cycle; alternatively, DG could begin firing as a result of gastric mill CPG activity and cause secondary excitation of GPR2 (Katz & Harris-Warrick, 1989).

The ionic mechanisms underlying the production of plateau potentials by DG neurons have been explored. Serotonin modulates four different ionic currents in these cells. First, serotonin enhances a hyperpolarization-activated net inward current carried by Na\(^+\) and K\(^+\) ions. Secondly, serotonin reduces a Ca\(^{2+}\)-dependent outward current carried by K\(^+\) ions (Kiehn & Harris-Warrick, 1992b). Thirdly, serotonin enhances a voltage-dependent Ca\(^{2+}\) current that is activated by depolarization (Zhang & Harris-Warrick, 1995). The resulting increase in Ca\(^{2+}\) influx secondarily enhances a fourth current, a Ca\(^{2+}\)-activated slow inward cation current (Zhang, Wootton & Harris-Warrick, 1995). This serotonergic enhancement of inward currents and suppression of outward current promotes the generation and maintenance of plateau potentials in DG neurons.

As noted above, the GPR neurons also modulate activity in the pyloric CPG. All neurons in this CPG appear to receive GPR input. The effects of GPR stimulation include rapid nicotinic synaptic potentials and slower neuromodulatory input that appears to be mediated by serotonin. GPR stimulation can initiate rhythmic activity in the pyloric CPG or increase pyloric cycle frequency in an active preparation. This effect largely results from a direct enhancement of bursting in the pyloric dilator/anterior burster (PD/AB) pacemaker cell group that is mediated by serotonin (Katz & Harris-Warrick, 1989, 1990b; Zhang & Harris-Warrick, 1994). GPR stimulation can also recruit gastric mill CPG neurons to fire in phase with the pyloric motor pattern. This effect may also be mediated by serotonin (Katz & Harris-Warrick, 1991).

Although the GPR cells have been most extensively studied in the crab, homologous cells are found in the lobster Homarus americanus. In the lobster, these neurons are immunoreactive for the peptides cholecystokinin (CCK) and FMRFamide as well as serotonin (Katz & Harris-Warrick, 1990a, b). Future work may identify similarities and differences between the lobster cells and their counterparts in the crab.

Another crustacean whose nervous system has been extensively studied is the crayfish Procambarus clarkii. Injection of serotonin or octopamine into the haemolymph produces flexed or extended postures similar to those seen in the lobster (Livingstone et al., 1980). Presumably, then, serotonin and octopamine have similar effects on the tonic postural motor system in the crayfish and lobster.

The most carefully analysed behaviour in the crayfish Procambarus clarkii is the lateral giant escape reaction, which is a phasic rather than a tonic motor response. The lateral giant fibres (LGs) consist of a series of large-diameter, bilaterally paired
segmental interneurons connected through electrical junctions (Remler, Selverston & Kennedy, 1968). Mechanosensory stimuli to the tail activate the LGs, resulting in a rapid upward movement that propels the animal away from the source of the stimulus (Wine, 1984). In the intact animal, this reflex is facilitated by painful stimuli, and inhibited by restraint or by feeding (Glanzman & Krasne, 1986). Electrical stimulation of sensory roots produces a compound biphasic EPSP. The first peak of the EPSP corresponds to monosynaptic excitation of the LG by sensory axons through nicotinic cholinergic and rectifying electrical synapses. The second peak corresponds to excitation of the LG through a disynaptic pathway; a sensory axon excites an interneuron that forms a rectifying electrical synapse on the LG (Edwards et al., 1991; Yeh, Opdyke & Edwards, 1993).

Initial experiments on adult crayfish indicated that serotonin and octopamine produce opposing effects on the amplitude of this biphasic EPSP (Glanzman & Krasne, 1983). In semi-intact preparations, octopamine increases the amplitude of both components of the EPSP, while serotonin decreases it. The second component of the EPSP shows greater change in amplitude than the first. The activation of the LG by sensory root shocks is correspondingly affected.

Further studies explored the mechanisms underlying these effects. Octopamine was shown to cause the appearance of a new class of EPSP in an identified sensory interneuron. Octopamine lowers the minimum stimulus required for interneuronal activation, probably as a result of this modulation of exogenous inputs (Glanzman & Krasne, 1983; Bustamante & Krasne, 1989). The net result would be the observed enhancement of the second, or disynaptic, peak of the LG EPSP following sensory root stimulation. Serotonin has no consistent effect on the activation threshold of the interneuron affected by octopamine, suggesting that serotonergic inhibition of LG activation is mediated at some other point in the circuit (Glanzman & Krasne, 1983). Serotonin appears to induce a conductance increase in distal dendrites of the LG. This increase in conductance, as well as serotonergic reduction of the first, or monosynaptic, component of the biphasic EPSP persist in the absence of chemical synaptic transmission, indicating that serotonin acts directly on the LG itself (Vu & Krasne, 1993).

Initial experiments suggested that serotonin might mediate the restraint-induced inhibition of the escape response. A descending tonic inhibition of the LG neuron in the crayfish suppresses LG activation during restraint. Like serotonin, this tonic inhibition decreases the amplitude of both peaks of the biphasic LG EPSP. Furthermore, animals whose serotonergic neurons are depleted of transmitter (by injection of 5,7-DHT) fail to show normal suppression of the LG escape response when restrained (Glanzman & Krasne, 1986). However, the tonic inhibition is blocked by picrotoxin application, suggesting that it is GABAergic rather than serotonergic in nature. Serotonin continues to reduce EPSP amplitude in the presence of picrotoxin and therefore cannot mediate the effects of tonic inhibition on the LG (Vu & Krasne, 1993). It is possible, however, that serotonin plays a facilitatory role in the rostral centres that generate tonic inhibition in vivo, and that the absence of this facilitation blocks tonic inhibition in animals treated with 5,7-DHT.

Recent studies indicate that the effects of serotonin on sensory activation of the LG may be more complex than previously suspected. Crayfish living in pairs in which one
animal is dominant and the other subordinate show differing effects of serotonin on LG inputs. In dominant animals, serotonin enhances both components of the biphasic EPSP and reduces the stimulus threshold for an LG spike. In subordinate animals, serotonin decreases the amplitude of both EPSP components and increases the stimulus threshold. A vertebrate 5-HT₁ receptor agonist reduces the LG EPSP and raises the stimulus threshold regardless of dominance status, whereas a vertebrate 5-HT₂ agonist enhances the EPSP and lowers the stimulus threshold in all animals. The ratio of 5-HT₁-like to 5-HT₂-like receptors may be lower in dominant animals and higher in subordinates (Yeh, Fricke & Edwards, 1996).

Why serotonin enhances escape responses in dominant animals is not clear; subordinates might be expected to employ escape behaviour more often. However, in juvenile Homarus americanus, the LG tail flip may be used in an offensive manner; animals grip the appendages of opponents with their claws and use tail flips to attempt to tear the appendages off (Huber & Kravitz, 1995). Future work should elucidate the mechanisms underlying these status-related changes in the response to serotonin. Of particular interest is the identity of the compound or compounds that communicate the dominance status of the animal to its nervous system. One of these compounds may be serotonin itself.

A third crustacean in which serotonin appears to play a role in the modulation of posture and the behavioural response to sensory stimuli is Gammarus lacustris (Helluy & Holmes, 1990). In normal gammarids, a mechanical disturbance results in movement away from a light source and burrowing behaviour. However, in gammarids infected with the parasite Polymorphus paradoxus, a marked alteration in escape behaviour is seen: the gammarid moves towards a light source and clings to the first object it encounters in a flexed posture reminiscent of the serotonin-induced posture in lobsters and crayfish. This altered behaviour makes the infected gammarids more susceptible to predation by the definitive host of the parasite. Helluy & Holmes (1990) found that serotonin injected into normal gammarids causes them to adopt the photopositivity and clinging behaviour exhibited by infected gammarids. Octopamine injected into infected gammarids suppresses the clinging behaviour but not the photopositivity. The high (millimolar) experimental concentrations required for serotonergic effects suggest that serotonin acts in the CNS, where high concentrations of transmitter may routinely be found in synaptic clefts. It appears that an endogenous postural control system in which serotonin and octopamine act antagonistically may be manipulated by the parasite. Serotonin is implicated not only in the control of posture, but in the modulation of the motor response to light stimuli. Gammarus lacustris illustrates the dangerous effects of pathological changes in behavioural modulatory systems.

(7) Echinoderms

In sea urchins, serotonin appears to serve as a neurotransmitter. Serotonin-immunoreactive neurons have been found in larval Strongylocentrotus purpuratus (Bisgrove & Burke, 1986). In larvae of other species, endogenous serotonin as well as receptors that bind [³H]serotonin are present (Toneby, 1977; Brown & Shaver, 1989). In larval Psammechinus miliaris, serotonin and its precursors stimulate muscular activity (Gustafson, Lundgren & Treufeldt, 1972).

Serotonin has also been found in larvae of the starfish Pisaster ochraceus (Toneby,
The nervous system of the starfish *Pycnopodia helianthoides* has little serotonin but shows high levels of tryptamine, which is closely related to serotonin (5-hydroxytryptamine). In this organism, tryptamine may perform the functions served by serotonin in other animals (Robertson & Juorio, 1976).

(8) **Chordates**

Serotonin is present in several cell types in vertebrates, including mast cells and platelets (Cooper, Bloom & Roth, 1982). Serotonin derives its name from the fact that it exerts potent vasoconstrictive effects in mammals (Rapport, Green & Page, 1948). Serotonin is also found in the chromaffin cells of the intestinal mucosa and causes constriction of the smooth muscle of the gut (Cooper *et al.*, 1982). Wood & Mayer (1979) found evidence that, in the guinea pig gut, stimulation of interganglionic fibre tracts causes the release of serotonin, which produces EPSPs in myenteric neurons through the closing of hyperpolarizing ion channels.

All vertebrates have central serotonergic neurons. The anatomical organization is similar in all vertebrate classes: most cell bodies cluster in the brainstem raphe, and their axons project widely throughout the forebrain. In at least some species, including primates, some serotonergic cell bodies are found elsewhere in the brainstem, in regions including the reticular formation and locus coeruleus (Thor & Helke, 1987; for reviews see Parent, 1981; Törk & Hornung, 1990). In mammals, the serotonergic raphe neurons extend dendrites to ventricular tanycytes, the midline blood vessels, and the dendrites of other raphe neurons, suggesting that they receive information from the blood and cerebrospinal fluid (CSF) as well as from neighbouring neurons. Axons from these neurons descend to the spinal cord and ascend to the hypothalamus, basal ganglia, olfactory bulb, hippocampus and neocortex; serotonergic axons also project to the walls of the ventricles. A single raphe neuron may send axon collaterals to more than one forebrain region (for review see Parent, 1981). In the rat brainstem, serotonin-immunoreactive neurons project to the nucleus tractus solitarii, where serotonin release may regulate autonomic function (Thor & Helke, 1987).

According to early reports, the axonal varicosities of the serotonergic neurons seldom displayed the membrane differentiation typically seen at synaptic terminals, suggesting that these terminals released serotonin in a diffuse manner rather than onto discrete postsynaptic neurons (for reviews see Parent, 1981; Papadopoulos & Parnavelas, 1991). More recent evidence indicates that a larger number of serotonergic terminals than were previously suspected form conventional synaptic junctions (for review see Papadopoulos & Parnavelas, 1991).

Although serotonergic neurons project widely throughout the cerebral cortex, their projections show some specificity. In a given region, the density of serotonergic innervation may vary from layer to layer. Furthermore, the density of serotonergic innervation appears to be greater in primary sensory cortex than in secondary sensory or association cortex (for review see Papadopoulos & Parnavelas, 1991).

Stimulation of raphe neurons in the rat or iontophoresis of serotonin onto different areas of the brain causes a variety of effects, some excitatory, some inhibitory (Aghajanian, 1981). Serotonin may facilitate or inhibit the response in a certain region to a particular neurotransmitter, which may itself be either excitatory or inhibitory. One especially well-characterized example is the facial nucleus of the rat (McCall &
Serotonergic modulation of behaviour: a phylogenetic overview

Aghajanian, 1979). Iontophoresis of serotonin onto the facial motor neurons does not excite them; however, it facilitates the excitatory response produced by glutamate. Serotonin application reduces the amount of glutamate required to produce a given level of depolarization and also facilitates the excitation of facial motor neurons produced by stimulation of the red nucleus or motor cortex. The relevance of this effect in vivo is supported by the fact that p-chloroamphetamine (PCA), which causes the release of endogenous serotonin from terminals, also produces this facilitation. The effect of PCA is blocked by pre-treatment with p-chlorophenylalanine (PCPA), which blocks serotonin synthesis by inhibiting the enzyme tryptophan hydroxylase.

Another example of serotonergic modulation of synaptic transmission is provided by the glycinergic inhibitory inputs to the Mauthner neurons in the teleost fish Carassius auratus (Mintz et al., 1989; Mintz & Korn, 1991). Serotonergic terminals are present at the inhibitory synapses and serve to enhance presynaptic release of the inhibitory neurotransmitter. Serotonin may cause a decrease in presynaptic K⁺ conductance as it does in sensory terminals in Aplysia californica (for review see Kandel & Schwartz, 1982). Serotonin also acts postsynaptically to induce a transient inward-rectifying K⁺ current in the Mauthner cell (Mintz et al., 1989). Since the Mauthner neuron coordinates the motor escape response to visual or auditory stimuli, serotonergic potentiation of its inhibition will have significant behavioural effects (Eaton & Bombardieri, 1978; Rock, Hackett & Brown, 1981; Hackett & Faber, 1983).

In vertebrates, serotonin may exert widespread effects on the state of the central nervous system that secondarily alter all behavioural interactions between the animal and its environment. An example is provided by the proposed role of serotonin in arousal in mammals. Slow-wave sleep, in which an animal is relatively unresponsive to external sensory input, is characterized by slow, synchronous, rhythmic activity of thalamocortical circuits and synchronization of the electroencephalogram (EEG). Increased release of serotonin and other modulatory transmitters (including noradrenaline, acetylcholine and histamine) may diminish the ability of thalamocortical circuits to generate these synchronous oscillations and promote desynchronous neural activity and arousal, with a concomitant increase in responsiveness to environmental stimuli (for reviews see McCormick, 1992a, b).

There are a large number of studies in vertebrates that suggest that serotonin also modulates specific behaviours, including feeding, sexual and aggressive behaviour. Injection of PCPA into the ventricles of rats causes an increase in food intake and a corresponding increase in body mass relative to saline-injected controls (Breisch, Zemlan & Hoebel, 1976). In juvenile rats, intraventricular injection of 5,7-DHT, which depletes serotonin, results in increased food intake and growth (Saller & Stricker, 1976). These results suggest that the net effect of serotonin is a tonic inhibition of feeding behaviour in the normal rat. This hypothesis is further supported by the fact that drugs that enhance serotonin release and block serotonin reuptake (such as fenfluramine) or simply block reuptake (such as sertraline) cause anorexia in rats. Some direct serotonergic agonists are also anorectics. However, 8-OH-DPAT [8-hydroxy-2-(di-n-propylamino)tetrinal], a selective 5-HT₁A agonist, can actually increase food intake in free-feeding rats (for review see Garattini, Mennini & Samanin, 1989). This effect is difficult to interpret because 5-HT₁A receptors mediate autoinhibition of serotonergic raphe neurons (for review see Hen, 1992). Therefore, a 5-HT₁A agonist
may simultaneously reduce the release of endogenous serotonin and stimulate postsynaptic serotonin receptors.

The role of serotonin in the modulation of sexual behaviour has been examined in rats of both sexes. In male rats, the post-ejaculatory refractory period is defined as the time from ejaculation to the next mount or intromission. McIntosh & Barfield (1984) depleted serotonin in male rats using three different methods: systemic administration of PCPA, intraventricular or intraraphe injection of 5,7-DHT, and electrolytic lesion of the dorsal raphe. Each of these interventions produces a significant decrease in refractory period, implicating serotonin as a tonic enhancer of the refractory period in vivo. Serotonin also appears to play a role in inhibition of female mating behaviour. In female rats, removal of the ovaries decreases the frequency of the normal lordotic response to male mounting. In ovariectomized females, several methods have been used to reduce the effects of endogenous serotonin: application of systemic PCPA, systemic methysergide, intrahypothalamic methysergide or cinanserin (serotonin receptor blockers) and intrahypothalamic 5,7-DHT. All of these treatments increase the frequency of the lordotic response (Zemlan et al., 1973; Luine et al. 1983). Serotonin, therefore, appears to inhibit certain aspects of sexual behaviour in both males and females: it prolongs the refractory period in males and inhibits the lordotic response in females.

Finally, several studies have implicated serotonin in the control of aggressive behaviour in a number of vertebrates. Male gymnotid fish (Apteronotus leptorhynchus) use transient increases in electric organ discharge (EOD) frequency, known as chirps, as aggressive signals to other males. Maler & Ellis (1987) elicited such chirps by stimulating fish with a simulated EOD. They found that intraventricular injection of serotonin results in a decrease in the chirping response. Application of norepinephrine enhances chirping, while dopamine has inconsistent effects. These opposing effects of serotonin and norepinephrine (the vertebrate analogue of octopamine) on aggressive displays in fish are reminiscent of the opposing actions of serotonin and octopamine on dominance-related postures in the lobster Homarus americanus.

Golebiewski & Romanuk (1985) found that carbachol (a cholinergic agonist) elicits growling when injected into the anteromedial hypothalamus of the cat. Injection of serotonin or methysergide alone has no effect; however, serotonin inhibits and methysergide potentiates carbachol-evoked growling. 5,7-DHT injection also potentiates carbachol induction of growling. In this case, serotonin appears to act as an inhibitory neuromodulator of cholinergic function.

Other studies have examined the role played by serotonin in conspecific and interspecific aggression in rats. With regard to conspecific aggression, Vergnes et al. (1988) reported that injection of 5,7-DHT into the lateral hypothalamus of rats results in an increased frequency and duration of offensive behaviours when an intruder rat is placed in the cage. Effects of more global lesions vary. Vergnes, Depaulis & Boehrler (1986) found that a systemic PCPA injection enhances offensive behaviour when a rat is confronted with an intruder. Sijbesma et al. (1991) reported that 5,7-DHT lesions of the dorsal and median raphe cause a modest reduction of offensive behaviour against an intruder. File, Hyde & MacLeod (1979) found that lesion of the median raphe alone causes an increase in jumping and standing on an intruder, whereas lesion of the dorsal raphe alone causes a non-specific decrease in social interaction with an intruder.
Some of the variation in experimental results may be due to differences in the strain of rat used, the rats’ environment, or the parameters used to quantify aggressive behaviour. However, it appears that serotonin exerts a mixed effect on conspecific aggressive behaviour. Certain populations of serotonergic neurons and serotonergic projections to certain areas apparently facilitate such behaviour, while other neurons and their projections exert an inhibitory effect (Sijbesma et al., 1991).

Differing effects of serotonin on conspecific aggression may be mediated through different receptor subtypes. Genetic knockout mice lacking the 5-HT$_{1B}$ receptor attack intruder mice more quickly and more intensely than wild-type controls (Saudou et al., 1994). Further evidence for the role of the 5-HT$_{1B}$ receptor in the control of aggressive behaviour is provided by serotonergic agonists that are specific for certain receptor subtypes. Eltoprazine, widely used as a 5-HT$_{1A/1B}$ agonist, reduces conspecific aggressive behaviour in rats and mice in a variety of behavioural tests (for review see Miczek et al., 1994). Both 5-HT$_{1A}$ and 5-HT$_{1B}$ receptors mediate autoinhibition of serotonergic raphe neurons (for review see Hen, 1992). However, eltoprazine exerts anti-aggressive effects in rats even after lesioning of the raphe nuclei with 5,7-DHT, thereby ruling out an autoinhibitory mechanism of action (Sijbesma et al., 1991). Injection of eltoprazine into the lateral ventricles of rats suppresses aggression, whereas injection of 8-OH-DPAT, a specific 5-HT$_{1A}$ agonist, does not (Mos et al., 1992). These results suggest that the anti-aggressive effects of eltoprazine may be mediated primarily through 5-HT$_{1B}$ receptors on non-serotonergic neurons. 5-HT$_{1B}$ receptors appear to be present on the terminals of various types of neurons; in the hippocampus, 5-HT$_{1B}$ receptors present on cholinergic terminals inhibit acetylcholine release (for review see Hen, 1992).

The evidence to date is consistent with the following hypothesis: serotonin, acting through 5-HT$_{1B}$ receptors to modulate the release of other transmitters, suppresses at least some types of conspecific aggressive behaviour in rats and mice. The absence of these receptors in the genetic knockout mice may prevent this inhibition and increase aggression. However, more data must be gathered on the effects of eltoprazine and the 5-HT$_{1B}$ receptors on both aggressive and non-aggressive behaviours and on various transmitter systems before firm conclusions can be reached. It should be noted that eltoprazine has some affinity for 5-HT$_{1C}$ receptors. Furthermore, it acts only as a weak agonist at 5-HT$_{1A}$ receptors on rat hippocampal pyramidal neurons and can actually reduce the effects of applied serotonin (Joëls et al., 1990). Therefore, caution must be used in interpreting studies in which eltoprazine is assumed to act as a 5-HT$_{1A/1B}$ agonist.

Molecular biological techniques may further clarify the role of serotonin in conspecific aggression. Chen et al. (1994) found that intruder mice missing one copy of the gene encoding α-calcium-calmodulin-dependent kinase II show increased aggression in response to attacks by resident mice. This enhancement of defensive aggression may result from decreased fear. Serotonin release from dorsal raphe neurons appears to be reduced in these mutants, and altered serotonergic function may contribute to the observed behavioural effects of the mutation. However, many non-serotonergic neurons are undoubtedly affected by this mutation, and transmitters other than serotonin may play a role in the noted behavioural changes.

With regard to interspecific, or predatory, aggression, Vergnes & Kempf (1982)
found that when naive rats receive 5,7-DHT injections into the lateral hypothalamus, a significantly higher percentage will kill mice on their first exposure to them. Injection of 5,7-DHT into the medial hypothalamus, septum, hippocampus, amygdala, or cingulate cortex fails to affect muricidal behaviour. Molina et al. (1987) found that 40–50% of rats who do not spontaneously kill mice develop killing behaviour following systemic PCPA injection or electrolytic raphe lesions. Both of these lesioned groups of rats, as well as rats who spontaneously kill mice, show a reversible and dose-dependent inhibition of muricidal behaviour when systemically treated with serotonergic agonists (5-methoxy-N,N-dimethyltryptamine or 8-OH-DPAT) or serotonin reuptake blockers (fluoxetine, also known as Prozac, or citalopram). These studies suggest that serotonin is an inhibitory modulator of predatory aggression in the rat, and that its locus of action may be the lateral hypothalamus.

Earlier studies supported the importance of the lateral hypothalamus in predatory aggression. Carbachol, acetylcholine plus phystostigmine or neostigmine (cholinesterase inhibitors), and neostigmine alone all facilitate muricidal behaviour when injected into the lateral hypothalamus of the rat, while lateral hypothalamic injection of atropine (a muscarinic agonist) inhibits such behaviour (Smith, King & Hoebel, 1970; Bandler, 1970). In rats who do not spontaneously kill mice, lateral hypothalamic injection of carbachol or neostigmine may induce such behaviour (Smith et al., 1970). Thus, it appears that lateral hypothalamic acetylcholine is a trigger of interspecific aggression in rats. The control of offensive or killing behaviour by the lateral hypothalamus may be similar to the control of growling by the anteromedial hypothalamus in the cat. Acetylcholine may elicit aggressive behaviour, while serotonin inhibits it.

Serotonin also appears to modulate complex social behaviour in primates. Raleigh et al. (1991) explored the role of serotonin on dominance status in vervet monkeys (Cercopithecus aethiops sabaueus). In these animals, male dominance appears to depend more on the formation of alliances with female group members than on individual fighting ability. At the beginning of the study, stable mixed-sex groups were established; each group contained one dominant and two subordinate males. The dominant male was removed and one of the two remaining males received a drug that affected the serotonergic system. Fenfluramine, which acts as an indirect agonist in the short term but causes serotonin depletion in the long term, or cyproheptadine, a serotonergic receptor antagonist, were used to suppress serotonergic function. Tryptophan, a serotonin precursor, or fluoxetine, a reuptake inhibitor, were used to enhance serotonergic function. Fenfluramine and cyproheptadine decreased affiliative behaviours (approaching, grooming and proximity), while aggressive behaviour increased; animals receiving these treatments invariably remained subordinate. Tryptophan and fluoxetine increased affiliative behaviours and decreased aggression; animals receiving these treatments invariably became dominant.

In this example, it appears that serotonergic suppression of aggressive behaviour promotes dominance. However, the long-term effects of drugs intended to diminish or enhance serotonergic function are not fully understood. For example, fluoxetine is a serotonin reuptake blocker, and in the short term it should increase the amount of serotonin in synaptic clefts or extracellular fluid. However, this increase in serotonin will enhance activation of autoinhibitory receptors and may cause down regulation of postsynaptic receptors. In the long term, it is difficult to determine whether
Serotonergic modulation of behaviour: a phylogenetic overview

Serotonergic function will remain elevated. Similar arguments could be applied to the other drugs used in this study. Raleigh & McGuire (1991) noted that the effects of tryptophan on aggressive behaviour vary for animals in different social circumstances. Dominant animals in a social group, subordinate animals in a group, and animals living in isolation differ in the degree and even the direction of their response to tryptophan. Nonetheless, it is clear that drugs that affect serotonergic function also affect affiliative and aggressive behaviour and can lead to changes in dominance status.

Yodyingyuad et al. (1985) examined the relationship of serotonergic function to dominance status in talapoin monkeys (Miopithecus talapoin). They measured levels of 5-HIAA (5-hydroxyindoleacetic acid, a serotonin metabolite) in the CSF of monkeys before and after the formation of social dominance hierarchies as well as in established hierarchies. They found that when a group of monkeys is placed together, 5-HIAA levels fall as a monkey becomes dominant and rise as a monkey becomes subordinate. Monkeys who assume intermediate positions show no consistent changes in CSF 5-HIAA. In established groups, the top-ranking monkeys have significantly lower 5-HIAA levels than intermediate or low-ranking monkeys, who do not differ significantly from each other. No correlation was found between levels of homovanillic acid (a dopamine metabolite) and position in the dominance hierarchy.

As with the work on vervet monkeys, this study clearly supports a link between the central serotonergic system and dominance status. At first glance, reduced CSF 5-HIAA levels might suggest lowered central serotonin levels and diminished serotonergic function. However, many factors could potentially affect 5-HIAA levels as well as the ratio of serotonin to 5-HIAA in the brain. Decreased release of serotonin, which would diminish serotonergic function, would lower 5-HIAA; reduced serotonin degradation, which would enhance serotonergic function, would also lower 5-HIAA. For example, juvenile mice lacking functional monoamine oxidase type A (MAOA), which degrades serotonin as well as other amines, have increased levels of brain serotonin and reduced levels of 5-HIAA (Cases et al., 1995). Agonistic encounters can raise the ratio of 5-HIAA to serotonin in the amygdalas of inexperienced mice; this observation suggests that situations that result in serotonin release may alter this ratio in the short term (for review see Miczek et al., 1994). Chronically raised or lowered levels of 5-HIAA indicate alterations in the serotonergic system, but it is difficult to say whether overall serotonergic function is enhanced or diminished.

Serotonin clearly serves as a behavioural modulator in humans. Several drugs that specifically affect serotonergic transmission are used to treat psychiatric illnesses. The serotonin reuptake blockers fluoxetine and fluvoxamine effectively treat depression, bulimia, panic attacks and obsessive-compulsive disorder (Schatzberg & Cole, 1991). The 5-HT\textsubscript{1A/1B} agonist eltoprazine may suppress pathological aggression and self-injurious behaviour in some patients (Verhoeven et al., 1992; Kohen, 1993; Tiihonen et al., 1993). Many other drugs that affect the serotonergic system along with noradrenergic or dopaminergic function are used to treat a wide variety of mental illnesses (Schatzberg & Cole, 1991).

Although the behavioural effects of these drugs are obvious, the mechanisms underlying their effects are difficult to unravel. As noted above with regard to non-human primate studies, long-term administration of a drug may cause changes both up- and downstream of its initial site of action. Some of these poorly understood long-term
changes are clearly important for clinical efficacy. For example, fluoxetine may take weeks to relieve depression even though maximum blood levels of the drug and effective inhibition of serotonin reuptake are achieved much sooner.

A number of studies have sought a relationship between indices of serotonergic function and self-directed aggression (suicide or suicide attempts) or outwardly directed aggressive behaviour. A few studies have reported decreased levels of serotonin in the brainstems of suicide victims, while other studies found no change. Some studies of suicide victims found decreased levels of 5-HIAA in various regions of the brain, although other studies did not confirm these findings (for review see Mann et al., 1989). Several studies have found lowered levels of CSF 5-HIAA in subjects who have attempted suicide as compared to various controls (for reviews see van Praag, Plutchik & Conte, 1986; Coccaro, 1989). A number of studies indicate that lower levels of CSF 5-HIAA correlate with aggressive, violent or criminal behaviour and with ratings of hostility. In particular, some studies suggest that lower CSF 5-HIAA levels correlate with impulsive aggression (for reviews see van Praag et al., 1986; Coccaro, 1989; Golden et al., 1991). The potential pitfalls in using 5-HIAA as a measure of serotonergic function have already been discussed. Furthermore, many of the subjects in these studies took drugs that may have altered 5-HIAA levels (for reviews see Mann et al., 1989; Golden et al., 1991). Other available indices of serotonergic function (post-mortem analyses of agonist binding to serotonergic receptors or, in living patients, hormonal responses to serotonin mimetics) are similarly difficult to interpret (for reviews see Coccaro, 1989; Mann et al., 1989; Golden et al., 1991).

Molecular techniques may uncover a genetic basis for some of the differences noted between suicidal or aggressive patients and controls. One recent study revealed a correlation between a particular allele of tryptophan hydroxylase and a history of suicide attempts in a group of alcoholic violent offenders (Nielsen et al., 1994).

Another study focused on a family that displayed an X-chromosome-linked behavioural disturbance characterized by a tendency towards impulsivity and aggression (Brunner et al., 1993a, b). Affected males were found to have a mutation in the gene for MAOA. An inappropriate termination codon resulted in a complete loss of activity of this enzyme. Altered serotonergic function was indicated by increased urinary levels of serotonin and decreased levels of 5-HIAA. However, excretion of the metabolites of other amines, including norepinephrine and dopamine, was also lowered; alterations in these other aminergic systems may contribute to the behavioural effects of this mutation in humans.

A subsequent study has shown that transgenic adult male mice lacking functional MAOA also show increased aggression (Cases et al., 1995). These mice attack intruders more quickly than non-transgenic controls. Transgenic juvenile mice lacking MAOA have increased brain levels of serotonin and norepinephrine and decreased brain levels of 5-HIAA. As these mice age, however, their levels of serotonin, norepinephrine and 5-HIAA eventually return to normal, perhaps as a result of an increase in activity of monoamine oxidase type B (MAOB). There are two possible explanations for persistent behavioural alterations. First, despite the evident compensation for the missing enzyme, it is possible that short-term imbalances in amine metabolism could still occur. For instance, transient increases in transmitter release triggered by environmental stimuli might temporarily overload compensatory mechanisms. Secondly, exposure to
high levels of amines during development could result in permanent structural abnormalities in the brain. Cytoarchitectural changes have been discovered in the somatosensory cortex of the transgenic mice and may be present in other brain regions as well. Further study of these mice should yield more detailed information about the mechanisms underlying the effects of a mutation that appears to alter human behaviour.

### III. CONCLUSIONS

Serotonergic neurons are present in all phyla that possess nervous systems, and in most of these phyla, serotonin modulates important behaviours, including feeding, sexual and aggressive behaviour. In invertebrates, the mechanisms underlying these effects have been well characterized. In the nematode *Caenorhabditis elegans*, serotonin enhances feeding and egg release. In the mollusc *Aplysia californica*, serotonergic neurons potentiate biting and enhance a defensive reflex. In the mollusc *Tritonia diomedea*, serotonin acts as both a classical neurotransmitter and as a neuromodulator in a neural network that generates escape swimming. In the leech (*Hirudo medicinalis*, *Macrobdella decora*, *Haementeria ghilianii*), serotonin plays an important role in the initiation and modulation of both appetitive and consummatory components of feeding behaviour. In the lobster *Homarus americanus*, serotonin promotes the adoption of a flexed or dominant-type posture. In the crayfish *Procambarus clarkii*, serotonin affects sensory activation of the circuitry controlling tail flips, which may be used defensively or offensively in aggressive encounters; the direction of the effect depends on the dominance status of the animal.

Three basic mechanisms underlie the effects of serotonin on invertebrate nervous systems. In the central nervous system, serotonin may act as a classical neurotransmitter to initiate a behaviour; an example is provided by the serotonergic swim-initiating interneurons in the leech (*Hirudo medicinalis*, *Macrobdella decora*). More commonly, serotonin acts as a neuromodulator to enhance transmission at a synapse which employs some other compound as the primary transmitter; an example is serotonergic facilitation of presynaptic release from sensory terminals in *Aplysia californica*. In *Tritonia diomedea*, these two roles of serotonin are combined: serotonin released by the dorsal swim interneurons acts both as a classical neurotransmitter and as a neuromodulator. A third role for serotonin is that of a neurohormone: through release into the circulation, it can affect sensory neurons or alter transmission at neuromuscular junctions. Such effects are observed in the lobster *Homarus americanus* as well as in other invertebrates.

Serotonin also modulates behaviour in vertebrates. It appears to inhibit feeding and sexual behaviour in rats and many studies support an important role for serotonin in the control of aggression. Serotonin inhibits aggressive vocalizations in gymnotid fish (*Apteronotus leptorhynchos*) and cats and may inhibit predatory aggression in rats. With regard to rat conspecific aggression, serotonin may act on different receptor subtypes or in different brain regions to facilitate or inhibit such behaviour. In non-human primates, alterations in serotonergic function clearly correlate with changes in aggressive behaviour and dominance status. In humans, drugs that affect serotonergic function produce a variety of behavioural effects; in particular, studies of 5-HIAA levels and of genes for enzymes that synthesize or degrade serotonin indicate that serotonin modulates aggressive behaviour.
The mechanisms by which serotonin affects behaviour are not as well understood in vertebrates as in invertebrates. In vertebrates, only a few serotonergic neurons are present in the nervous system. These neurons can be reliably identified in each animal and their interactions with other identified neurons in well-defined circuits can be determined. In vertebrates, no individual neurons can be identified from preparation to preparation. It is difficult to predict the long-term effects of drugs that alter serotonergic function and is often impossible even to tell whether overall serotonergic function is enhanced or diminished. While it is possible to examine various indices of ongoing serotonergic activity, such as the levels of serotonin metabolites in the nervous system or urine, these results are likewise difficult to interpret. More thorough analysis of simpler organisms may suggest future directions for the study of serotonergic actions in more complex systems.

IV. ACKNOWLEDGEMENTS

The author would like to thank Dr Edward A. Kravitz for his critical reading of the original version of this manuscript and his many helpful suggestions, and would also like to thank Dr Doreen Valentine for her valuable recommendations. This work was supported by Public Health Service National Research Service Award 2 T32 GM07753, a Ryan Fellowship, and a Sackler Scholarship in Psychobiology to W. A. Weiger, and National Institute of Neurological Disorders and Stroke Grant NS-25915 to E. A. Kravitz.

V. REFERENCES


Serotonergic modulation of behaviour: a phylogenetic overview


Serotonergic modulation of behaviour: a phylogenetic overview


Serotonergic modulation of behaviour: a phylogenetic overview


Serotonergic modulation of behaviour: a phylogenetic overview


