Chemical codes for the control of behaviour in arthropods

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Neuromodulators and hormones elicit and modify well-defined behaviours. Their mode of action can be studied to advantage in arthropods, where the natural releasing cells and neuronal target circuits are concisely identified. The coordinated actions of biogenic amines and peptides on both central and peripheral neural activity and metabolic processes bias the whole organism to perform a coherent behavioural routine.

The Greek physician Galen believed that the brain, with its fluid-filled cavities, was mainly a secretory organ that regulated all aspects of health, mood and nervous function. The modern view of the brain stresses that its computational tasks are based on the connections between its constituent nerve cells. But chemistry plays a vital role in expressing this connectivity, the extent of which is only just being appreciated. Although the importance of chemical transmitters for mediating information transfer at the synaptic connections between neurons is well established, in the past few years it has become apparent that this transmission can be altered or modulated by other chemicals, also produced by neurons, known as neuromodulators.

The actions of neuromodulators at the cellular level and their effects on behaviour are known in some detail but it has been difficult to bridge the gap between these two levels. Here we review recent work on crustaceans and insects which is demonstrating how modulators affect the connectivity in neural circuits, tuning and orchestrating their outputs to fit the immediate needs of the animal.

The production of behavioural sequences requires the temporal and spatial coordination of many neural circuits. In addition, there has to be flexibility in the ways in which circuits can be combined because sensory, central and motor neurons can participate in various combinations in many different behaviour patterns. The work in crustaceans and insects is showing that neuromodulators promote this plasticity by concordantly altering the responsiveness of neurons and muscles, together with changes in metabolism. Through the interplay of several modulators, basic circuitry can be allocated in a variety of ways at different times.

Transmitters, modulators and hormones

The 'classical' transmitters such as acetylcholine, glutamate and GABA directly affect the operation of ion channels and thus rapidly either excite or inhibit the postsynaptic cell. In contrast, the neuromodulators, which include biogenic amines and peptides, act indirectly on the ion channels, modifying their responses to the classical transmitters on a longer time scale. The neurohormones, a third class of chemical messengers, work in a similar way to the modulators, but usually over yet longer times and on targets at a distance from their release sites.

In mammals, neuromodulators and neurohormones are involved in generating specific behavioural states; experimental alteration of neuromodulator levels can evoke specific body movements, postures and motivational states, and alter sensory processing. For example, depletion of the biogenic amine 5-hydroxytryptamine (5-HT, or serotonin) in the brain leads to an increase in arousal and motor activity, evidence that 5-HT normally has a depressing or braking effect on behaviour. On the other hand, stimulation of pathways that release another biogenic amine, noradrenaline, increases activity and may

Neurons in the insect nervous system can be identified by a combination of immunohistochemistry and intracellular injection of a fluorescent dye marker. a. Serially homologous neurons in the suboesophageal ganglion of the bee that react with antibodies to 5-HT (peroxidase-antiperoxidase reaction). b. One of these neurons after intracellular injection with Lucifer yellow. Subsequent processing of this preparation with antibodies to 5-HT confirms that this is one of the neurons shown in a. These neurons may be involved in modulating the proboscis-extension reflex, discussed on page 37. Scale bar, 50 μm. Small arrows: cell bodies; broad arrows: commissural fibres. Photos: Martin Hammer.
facilitate learning by acting on selective attention or alternatively on stimulus reinforcement. The circuitry in the mammalian brain that regulates these behaviours is, however, so complex that it is difficult to investigate the facilitatory or depressing effects of a neuromodulator in terms of its influence on specific synaptic connections.

**Arthropod preparations**

In animals such as the crayfish, the lobster and various insects, the circuitry is much more accessible and the cellular mechanisms by which neuromodulators induce behavioural changes can be investigated directly. These animals display sophisticated behaviours, the generation of which is reasonably well understood at the neuronal level.

The arthropod central nervous system (Fig. 1) is built on a clearly segmented plan and contains many neurons that can reliably be identified from one preparation to another. These are amenable to intracellular microelectrode recording and network analysis, and the interactions between modulatory substances and their target neurons and muscles can be studied on a cell-by-cell basis. In vertebrates the only comparable studies are of very simple behaviours, such as swimming in the lamprey.

**Modulation of rapid-response circuits**

In several invertebrate species the experimental activation of single interneurons can initiate complete behavioural acts. One of the best studied examples is the escape behaviour of the crayfish, which begins with a tail flip that propels the animal away from strong tactile stimulation of the tail fan at the end of the abdomen. The inputs from the sensory receptors on the tail fan connect either directly or through a group of sensory interneurons with the lateral giant fibres that mediate the tail-flip response (Fig. 2a). When the tail fan is touched, the inputs evoke action potentials in the lateral giant fibres that in turn excite the motor neurons that drive the flexor muscles of the abdomen. The resulting tail flip pitches the animal away from the source of stimulation.

The threshold for triggering the response varies with the behavioural context: it becomes more difficult to evoke a tail flip when a crayfish is restrained or when it is feeding, and the threshold for triggering action potentials in the lateral giant neurons goes up under these conditions. In the sensory pathways, sensitivity can be altered by repeated tactile stimulation which leads to a gradual decrease in the probability that the reflex will occur. This so-called habituation results from depression of the synaptic transmission between the tactile input neurons and sensory interneurons. Conversely, the probability of eliciting a tail flip can be enhanced or sensitized, if the animal is subjected to strong electric shocks, because the firing threshold in the largest sensory interneuron decreases.

Both habituation and sensitization can be mimicked by applying biogenic amines to the nervous system. 5-HT, the serotonin, has the depressive effects of habituation, whereas octopamine mimics the sensitization produced by a traumatic stimulus. Neither amine elicits or affects the performance of the escape behaviours but, rather, they modulate synaptic transmission in the sensory circuits. The excitatory postsynaptic potentials in the lateral giants produced by stimulating sensory neurons are reduced when 5-HT is perfused through the arterial system and enhanced by octopamine perfusion (Fig. 2a); destroying cells that are immunoreactive for 5-HT with specific neurotoxins also removes the inhibitory effect of 5-HT on transmission at the synapses. From such results, it can be assumed that 5-HT and octopamine have modulatory roles in the escape response.

Once it is initiated by the firing of the giant fibres, the escape response goes automatically to completion, so it seems reasonable that only the synapses in the input circuits should be modifiable. In other behaviours, such as aggressive and submissive postures in the lobster, several levels both centrally and peripherally are modulated simultaneously. The injection of
5-HT into freely moving lobsters evokes a sustained flexion of limbs and abdomen resulting in an aggressive-looking stance, whereas injection of octopamine leads to sustained extension producing a submissive-looking posture. The posture evoked by 5-HT results from the contraction of the postural flexor muscles, whereas octopamine produces contraction of the antagonistic extensors. Application of both amines at the peripheral synapses between motor neurons and muscles, however, induces a more vigorous response in both flexors and extensors, so the antagonistic actions of the two amines must result from modulation of circuits in the CNS (Fig. 2b). Electrophysiological recordings show that the spike frequency in flexor motor neurons is increased by 5-HT and decreased by octopamine, and vice versa in the extensor motor neurons. A corresponding antagonism is also found in the excitatory and inhibitory motor neurons that innervate each muscle (unlike vertebrates, arthropods have direct inhibitory innervation of their muscles).

Immunohistochemistry shows over 100 cells reacting with antibodies raised against 5-HT, widely distributed throughout the nervous system; experimental attention has focussed on two pairs of these neurons that have cell bodies in the first abdominal ganglion and fifth thoracic ganglion (Fig. 2c). Their morphology provides some insight into how the opposing motor patterns could be coordinated by actions at both central and peripheral sites: each has two separate sets of endings, one in the peripheral neurometabolic tissue, where chemicals released can enter the blood, and the other in the neurometabolic tissue, where integration of information for the activation of the flexor motor programme takes place. The specificity for the action of the amine must be in the CNS, whereas the periphery is simply primed to be more responsive to the central command.

Modulation of transmission at the neuromuscular junction may be quite widespread. Cockroaches, locusts and crayfish all have some motor neurons that release the pentapeptide proctolin, as well as a classical excitatory transmitter, which is probably glutamate. Proctolin does not depolarize the muscle membrane if applied alone, even though its detailed action is different in each animal, its general affects are to enhance contractions evoked by application of glutamate, or to cause sustained tension instead of a rapid twitch.

**Selection of activity patterns**

Many rhythmic behaviours result from patterns of activity in central pattern generators (CPGs) which consist of neural circuits capable of producing motor output patterns in the absence of sensory feedback. Sensory inputs are nevertheless essential for the activation and shaping of a precisely coordinated motor output. In the lobster, food is ground by three teeth in the anterior part of the stomach, known as the gastric mill, and is then pumped and filtered by the rhythmic contractions and dilations of the posterior or pyloric end of the stomach. The muscles involved in the movements of the stomach are controlled by a CPG of about 30 neurons located in a small nerve centre termed the stomatogastric ganglion, together with some neurons in the commissural ganglia. The rhythm-generating circuits in the stomatogastric ganglion are capable of producing many different output patterns in response to different transmitters in the input fibres, allowing a cellular analysis of the interactions between neuromodulators and their target neurons. Using an endoscope and video recordings, rhythmic patterns in the outputs of the isolated stomatogastric ganglion have been related to the movements of the gastric teeth in the intact animals. Injections of proctolin into the blood of an intact animal alters the integration in the CPG circuit in such a way that several modes of chewing and grinding movements are produced in a dose-dependent manner. Neuromodulators such as proctolin may not only influence which output is produced but also modulate the strength of the interaction between the gastric and pyloric burst-generating circuits in the stomatogastric ganglion, thus promoting the integrated activity of the stomach when dealing with foods of different qualities.

**Orchestration of behavioural units**

Fully coordinated sequences of behaviour in several insects can be released by the injection of transmitters or their analogues either into the haemolymph or directly into the nervous system. In general, octopamine has a releasing or enhancing effect that is opposed by 5-HT.

Octopamine not only promotes the expression of a behaviour in insects but also helps to integrate performance at several levels of organization. In restrained locusts, for example, flight motor activity can be initiated by the iontophoretic application of octopamine into the neuropile of the metathoracic ganglion. Octopamine also influences the kinetics of contraction in flight muscles, resulting in an energy saving increase in power output. During long flight sequences, octopamine induces the release of the adipokinetic hormones from stores in the corpora cardiaca, resulting in mobilization of lipid (see Fig. 1). Thus, this biogenic amine not only induces flight motor activity in the CNS but also mobilizes the metabolic fuel required for flight.

The main candidates for neurotransmitters that release octopamine in the ventral nerve cord of locusts are a group of approximately 90 dorsal unpaired median (DUM) neurons (Fig. 1). Most of these are local interneurons but a few of the larger cells have axons that bifurcate to innervate the musculature on both sides of the body. Sombati and Hoyle proposed that the release of octopamine from DUM neurons is causally related to the initiation and modulation of behaviour, because iontophoretical...
administration in the appropriate ganglia elicits flight or rhythmic stepping movements of the legs, or suppresses the abdominal digging rhythm used by females during egg laying. As electrical stimulation of single DUM cells does not elicit any behaviour,22 the probability that a behaviour will occur may depend on the pattern of activity over the whole population of DUM cells. The resulting pattern of release in the neuropile could thus determine "which parts of which circuits are most likely to be thrown into (or out of) action" — the so-called orchestration hypothesis.22

Indeed, application of octopamine and its receptor agonists, such as the formamidines, have strong behavioural effects; nocturnal moths become hyperactive during daytime,22 the male cabbage looper moth becomes hypersensitive to the olfactory signal that induces sex-pheromone mediated flight, and engorged ticks detach from their hosts. In the fly and the bee, octopamine or its agonists enhances the reflex response to stimulation of sugar receptors on the feet or antennae with sucrose and causes the animals to feed twice as much as the controls (refs 35, 36 and R.M.A., unpublished results). Thus, formamidines disturb behavioural coordination,7,8 they may prove to be potent insecticides.

The antagonistic effects of octopamine and 5-HT have been demonstrated by injecting the amines into the haemolymph in several preparations. Octopamine and 5-HT induce opposite postures in males of the cabbage looper moth when they attempt to take off to fly in response to a sex pheromone. In honeybees the two biogenic amines may act antagonistically in the visual system. In response to moved striped patterns, bees make direction-specific adjustments of antennal position, a reflex which is enhanced by application of octopamine and reduced by 5-HT in a dose-dependent fashion.9 In flight behaviour, different amines may regulate different aspects of the control system: in the hawkmoth Manduca, octopamine evokes flight sequences, presumably by enhancing the efficacy of sensory transmission, whereas dopamine seems to have a direct excitatory effect on the interneurons of the flight motor and 5-HT suppresses flight motor output.86

Hormonal orchestration of development

The natural release of hormones during the life cycle of an animal provides the most striking examples of the orchestration of behaviour by circulating chemicals over a time span of hours to days. In insects, hormone levels are known to affect reproductive behaviours, such as courtship in crickets or the division of labour in the honeybee hive. A cellular approach to hormone-mediated behavioural changes during development has been possible in the moth Manduca, which undergoes a complete metamorphosis from the larval or caterpillar stage, through the pupa to the adult.32

The transition through the various stages is regulated by the relative levels of ecdysone hormones and juvenile hormones in the haemolymph. A third hormone, ellosion hormone, regulates the final shedding of the pupal cuticle and emergence of the adult, a process termed ellosion. This consists of two phases, the splitting of the cuticle over the thorax by rhythmic movements of the wing bases; and peristaltic waves of the abdomen, which propel the shed cuticle posteriorly. Both phases are centrally programmed, because the appropriate motor patterns can be triggered when the isolated nerve cord is exposed to ellosion hormone.

The nervous system is sensitive to ellosion hormone only shortly before the normal time of hatching. A circadian clock in the brain gates the release of ellosion hormone from neurosecretory centres located in the brain. Ellosion hormone is released as a pulse 2.5 hours before the adult emerges and during this period neurons in the nerve cord become sensitive to the hormone as they start to express two proteins that may be required for the transduction of its signal. The control of the expression of these proteins requires the presence of ecdysone hormone, but also its subsequent removal. Timing is also essential for the sequential activation of the two phases of ellosion behaviour, brought about by a different latency of the action of ellosion hormone on the motor circuits controlling the two phases.

If the pupal cuticle is peeled off before the animal enters the ellosion period, adult behaviours such as walking and the resting reflexes are absent. These appear with a delay of several hours if the ellosion hormone is injected, transforming the prematurely born, uncoordinated animal into an adult with a normal behavioural repertoire. The changing levels of hormones thus orchestrate profound cellular changes during postembryonic development that are manifested in stage-specific behaviours. And not only do they affect the responses of neurons
Fig. 4 The experimental procedures used to study the effect of drugs injected into the brain of the honeybee learning, memory and retrieval from memory. The basic learning procedure is to test a group of bees for their spontaneous responses to an odour and then to condition the non-responding animals once to this odour by pairing the odour with sucrose solution (the learning trial, LT). After conditioning, about 70% of the animals extend the proboscis to the presentation of the odour alone. a, Storage test: to see whether a drug interferes with the formation of memory, it is injected before the learning trial. After the drug or a saline control is injected, the animals are conditioned by one trial (LT) at the time when the action of the drug is optimal, as determined in the recall test (see below); dotted curved line indicates that this is a background effect not particularly tested in this experiment). The repeated presentations of odour alone follow when the immediate effect of the drug has vanished. The example given is for an injection of 5-HT (10^{-8} M, 5 nl) into each of the mushroom bodies (see Fig. 5): the experimental animal shows a persistent reduction in the conditioned response. This proves that 5-HT injected into or in the lobe interferes disruptively with the formation of a memory trace. Other drugs like octopamine or noradrenaline may persistently improve the memory when injected before the conditioning trial (see Fig. 5, unpublished results reproduced by kind permission of M. Sugawa). b, Retrieval test: the drug is injected into the brain after the learning trial and the animals are tested by repeatedly presenting the odour stimulus alone. The control group (same amount of saline injected) shows a small decline in response, the extinction effect, which is due to repeated testing. The experimental group transiently responds less but the effect of the drug disappears at longer intervals. The example given here is for dopamine (10^{-6} M, 100 nl injected into the protocerebrum), which inhibits conditioned responding maximally at 20-30 min after injection. The animals can be successfully conditioned at a time when the action of dopamine is optimal, showing that the dopamine injection does not interfere with the sensory or motor components or those underlying memory formation.

to hormones: they also influence remodelling of neuronal circuits by incorporation of new neurones, reorganization of neuronal arborizations and cell death.

**Behavioural plasticity and learning**

As neuromodulators confer flexibility on neuronal circuits and trigger intracellular biochemical events that outlast the signal, they have been implicated in learning, memory and the performance of learned tasks in vertebrates, molluscs, and fruit flies. There is some debate, however, about the site of modulatory action in associative learning.

Classical conditioning is a type of associative learning in which the animal establishes a connection between a neutral conditioned stimulus (CS), for example, a sound or coloured light and a reinforcing unconditioned stimulus (US) such as food. The repeated temporal pairing of the two stimuli during training elicits a response to presentation of the initially neutral stimulus that is normally caused only by the US. The association of events during classical conditioning requires a locus in the nervous system where the US and CS can converge. An analysis of classical conditioning at the cellular level in the mollusc *Aplysia* has pinpointed an allosteric regulation of an enzyme, membrane-bound adenyl cyclase, as the most likely point of convergence. It is stimulated by the release of a neuromodulator, 5-HT, in the US pathway and its activity is amplified by activity in the CS pathway, which increases intracellular calcium levels.

Some studies in the vertebrate literature, however, consider the US and CS pathways separately from the modulatory functions of biogenic amines, which are assumed to regulate affective states and thus are seen as a third and independent component in the neural substrate of learning. Amines are thought to cause an arousal state in the memory-forming part of the nervous system, so directing ‘attention’ to the conjunction of stimuli. The honeybee provides an excellent preparation for addressing this question. Under restrained conditions in the laboratory a memory lasting for days is produced after a single trial in which the CS is an odour, paired with a sucrose reward as the US. The animal extends its tongue (proboscis), its normal response to sucrose, as a conditioned response (CR) when an initially neutral odour stimulus is presented. This learning process can be manipulated by global or local injections of small quantities of drugs (around 5 nl) directly into the brain. As learning occurs in a single trial that lasts only a few seconds, drugs can be used to separate memory formation from memory retrieval, particularly to examine the unresolved question of whether these are conceptually separate processes. By injecting drugs before the learning trial, storage can be disrupted; injection after the trial disrupts retrieval (Fig. 4).

As an example, consider the action of a global injection of dopamine (10^{-6} M). If it is injected before the learning trial and the animals are tested at a time when the action of dopamine should be optimal (storage test), learning is not impaired but injections after the learning trial (retrieval test, Fig. 4), induces a transient reduction in the conditioned response to the presentation of the CS alone. Thus, dopamine interferes selectively with the retrieval process. Because performance in the storage test is unchanged, dopamine has no effect on olfactory coding, motor response or memory storage. In contrast, injections of amines such as 5-HT interfere with the storage process (Fig. 4a) leading to irreversible effects in the conditioned response.

As the motor performance during the period when the action of 5-HT is optimal is unaltered, 5-HT must interfere with the storage processes, not with the sensory or motor components of the task.

Local injections of biogenic amines into particular regions of the brain reveal a different pattern of action for each modulator that depends on the area injected and the behavioural components tested (Fig. 5). For example, in the chemosensory processing area, the antennal lobes, octopamine seems to be involved in stimulus reinforcement. In the higher association areas, the mushroom bodies, octopamine enhances both memory storage and retrieval, whereas noradrenaline enhances only storage and only when injected into the output areas of the mushroom bodies. The facilitatory effects of both octopamine and noradrenaline are antagonized by 5-HT (see Fig. 5 legend for more details).

The most important outcome of these experiments is that learning and retrieval can be improved or depressed by different amines acting at different locations and at different stages in the learning process. The experiments also support earlier conclusions that the memory system in the bee brain involves...
The effect of local drug injections on the proboscis-extension reflex and on storage and recall of the conditioned response during olfactory learning in honeybees is summarized on a schematic side view of the main pathways in the brain and the subesophageal ganglion (Sog) mediating the proboscis-extension reflex. Chemosensory afferents from the antenna terminate in the protocerebrum of the antennal lobe. Referral neurons transmit olfactory information through the antenna-glomerular tract (AGT) into the calyx of the mushroom body. The mushroom body (stippled) contains approximately 170,000 intrinsic Kenyon cells (K cell), which project from the calyx to the two output regions, the α- and β-lobe. Monoaminergic interneurons (FN) connect the subesophageal ganglion with neuropil around the α- and β-lobe. The subesophageal ganglion contains the motor circuits and motor neurons responsible for the extension of the proboscis. The table summarizes the action of locally injected amines on the three components of behaviour—proboscis extension reflex, storage and recall. In the table, the arrows pointing upwards indicate facilitation of the reflex or conditioned response, those pointing downwards indicate an inhibition. Bold arrows indicate the injection sites. Octopamine (OA) mimics the sensitizing action of the US (sacrose stimulus) and stimulates feeding behaviour when injected into the antennal lobe, suggesting octopamine has a role in reinforcement. If OA is injected into the pedunculus of the mushroom bodies close to the input synapses of the chemosensory relay neurons in the calyx, no changes are found in the reflex performance but both components of learning, memory formation and recall are enhanced. OA has no effect when injected into the output regions of the mushroom body, the α-lobe, whereas noradrenaline (NA) injections into this region enhance memory formation, particularly in animals with lower learning rates. 5-HT on the other hand antagonizes the facilitatory actions of OA and NA in the mushroom body but does not affect the non-associative modulation of the reflex. The substances (2.5 nL, 10^-10 M) were injected into either both antennal lobes, or both α-lobe or both pedunculi (PD) of the mushroom bodies (the volume of the brains is ~1 μL). The drug effects were compared with control animals which were injected at the same sites with the same volumes of saline. Several hundred animals were tested. Data for DA* from 60 Dors, Dorsal; Ant, anterior (orientations refer to the position of the brain in the head in life).

There is evidence for several regions, with non-associative modulation of the feeding reflex taking place in the antennal lobes, whereas the mushroom bodies, an area thought to be involved in other insect species to be involved in the coordination of behaviour patterns, are necessary for the long-term formation and read out of associative memory. Identified neurons innervate the 5-HT that link these areas have been impaled with dye-filled electrodes, so it should be possible to analyse the learning capabilities of an insect brain at the cellular level.

The distinction between storage and retrieval mechanisms implies that the location of the memory trace is not the direct sensory pathway between the chemosensory afferents of the antennae and the motor circuit for the proboscis response in the subesophageal ganglion (Fig. 5). Because this pathway remains functional when the conditioned response is blocked pharmacologically. Anatomical studies reveal prominent fibre tracts that leave the direct sensory pathway and enter the mushroom bodies (Fig. 5). Storage of the memory trace in a pathway parallel to the main sensory-motor pathway contrasts the memory system of the bee with the model developed for associative and non-associative plasticity in molluscs, where activity-dependent modulation has been found at the synapses between sensory and motor neurons.

Chemical codes and behaviour

Both vertebrate and invertebrate nervous systems contain neurons with widespread branching patterns that seem suitable for coordinating neural activity in a large population of follower cells by a rather diffuse release of neuromodulatory substances. The investigation of some of these identified cells and their targets in arthropod nervous systems suggests that neuromodulators orchestrate behaviour by acting simultaneously at many synaptic levels in the nervous system to integrate neuronal activity, and also by widespread regulation of metabolism. Sensory circuits may be sensitized or depressed, motor circuits can be biased towards favourable states, muscle tone is adjusted to the correct endpoint and the metabolism fueling the muscle power is activated. This coordination of neuronal activity in different parts of the organism has also been observed in molluscs and leeches, where identified amine-containing neurons integrate several appetitive and consummatory components of feeding behaviour, such as food arousal, swimming toward food sources, bite frequency and meal size.

Experimental manipulation using neuromodulators or their analogues to mimic the natural release of neuromodulators can evoke coherent behaviour. The chemical code for regulating behaviour arises from the patterns of release of the various modulatory substances. These in turn are decoded by the distribution in the target tissue of receptors specific for each type of modulator. As the receptors are linked to the intracellular biochemical signalling pathways, the neuromodulators can modify the excitability of nerve cells on a longer time scale than that of conventional rapid synaptic transmission, leading to longer lasting functional changes in neural circuitry that serve processes such as arousal, selective attention, reinforcement and retention of memory.

Although the behavioural responses to neuromodulators are becoming increasingly better understood, the sensory pathways for activating neuromodulatory neurons are an enigma. A great deal of circuit chasing remains to be done to establish the connectivity between these neurons and external sense organs. Electrophysiological recordings from neuromodulatory neurons of motor circuits has been done, but has so far provided little evidence for a direct link to the mainstream of rapid sensory information processing. But it is conceivable that some neuromodulatory neurons may form, remote from sensory input, a central system for integrating the activity states of many neural circuits. Thus, a release of neuromodulators may mediate the translation of the activity pattern of many neurons into the activity in biochemical pathways in single target cells.

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