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Cellular, synaptic and network effects of neuromodulation

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Abstract

All network dynamics emerge from the complex interaction between the intrinsic membrane properties of network neurons and their synaptic connections. Nervous systems contain numerous amines and neuropeptides that function to both modulate the strength of synaptic connections and the intrinsic properties of network neurons. Consequently network dynamics can be tuned and configured in different ways, as a function of the actions of neuromodulators. General principles of the organization of modulatory systems in nervous systems include: (a) many neurons and networks are multiply modulated, (b) there is extensive convergence and divergence in modulator action, and (c) some modulators may be released extrinsically to the modulated circuit, while others may be released by some of the circuit neurons themselves, and act intrinsically. Some of the computational consequences of these features of modulator action are discussed.

Keywords: Stomatogastric ganglion; Dynamic clamp; Cotransmission; Neuromodulator

1. Introduction

One of the most striking features of biological brains is that neurons contain and release a very large number of neurotransmitters and neuromodulators (Hökfelt et al., 2000; Kupfermann, 1991). These include biogenic amines, amino acids, neuropeptides, and gases. In early formal models of neural function, the nature of the neurotransmitter(s) mediating the modeled synaptic connections was ignored. Nonetheless, a wealth of biological data now indicates that synapses mediated by different neurotransmitters can differ enormously in their time course and voltage-dependence, and that neuromodulators can alter both the properties of synaptic conductances and the intrinsic membrane properties of individual neurons (Harris-Warrick & Marder, 1991; Marder, 1998). Consequently, computational models of many neurons and circuits should now include provisions for modeling their neuromodulatory control (Baxter, Canavier, Clark, & Byrne, 1999; Butera, Clark, Canavier, Baxter, & Byrne, 1995; Fellous & Linster, 1998) and there are a growing number of models of the signal transduction pathways underlying neuromodulation (Baxter et al., 1999). In this review, we will describe many of the ways in which neuromodulators modify the properties of neurons, synapses, and networks, and outline some of the computational consequences of these alterations. We start with the examination of the effects of single neuromodulators, and conclude this review with the computational issues raised by neuromodulatory substances that are found together as cotransmitters in the same modulatory projection neurons (Nusbaum, Blitz, Swensen, Wood, & Marder, 2001).

2. Neuromodulators alter the intrinsic properties of neurons

2.1. Intrinsic membrane properties

Neurons can display a wide variety of different intrinsic membrane properties that depend on the number, kind, and distribution of voltage-gated ion channels in their membranes. Some neurons are silent when isolated, others fire single action potentials tonically, and still others fire bursts of action potentials. Fig. 1 shows these kinds of behaviors in a neuronal model (Liu, Golowasch, Marder, & Abbott, 1998), with the values of the maximal conductance of each current in the model also shown. This figure shows that alterations in the balance of conductances in a neuron can be

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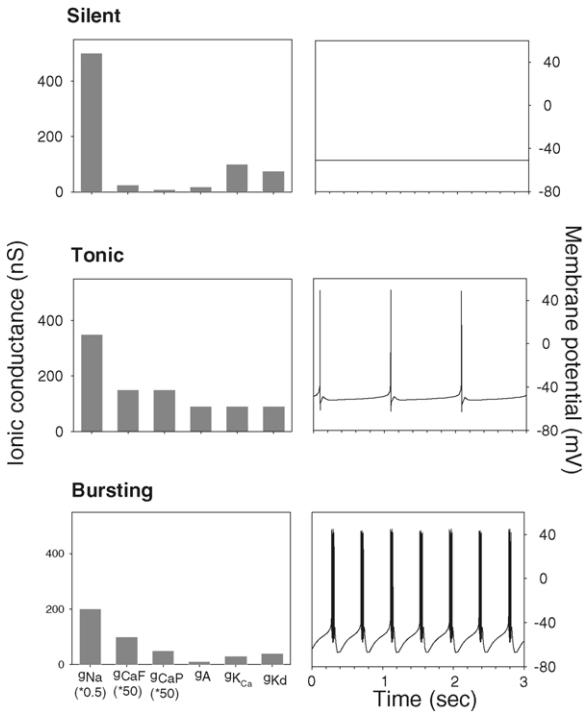

Fig. 1. Intrinsic properties of a model neuron with different balance of conductances. This model neuron has six voltage dependent conductances—Na^+ (gNa), fast Ca^{2+} (gCaF), persistent Ca^{2+} (gCaP), transient K^+ (gA), Ca^{2+}-dependent K^+ (gKCa) and a delayed rectifier K^+ (gKd). When the maximal values of these conductances are varied, the model neuron changes its activity patterns. The panels on the left show the maximal conductances in nS and the panels on the right show the activity that resulted from those combinations of conductances (unpublished data, Zheng Liu).

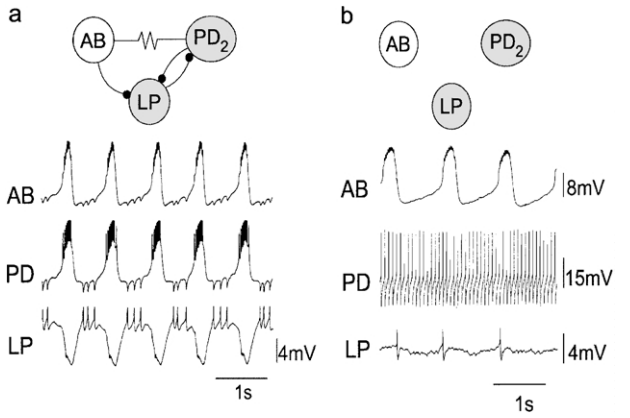

Fig. 2. Activity patterns of pyloric neurons in the intact circuit and when isolated. (a) The AB, PD and LP neurons of the pyloric circuit burst when they are synaptically coupled. In the intact circuit, the AB and PD neurons are electrically coupled (shown by the resistor symbol) and they both inhibit the LP neuron (shown by connections ending in filled black circles). The LP neuron inhibits the PD neuron. (b) When these neurons were isolated from their synaptic partners, only the AB neuron continued to burst, while the PD and LP neurons fired tonically. Modified from Hooper and Marder (1987) and Eisen and Marder (1982).

sufficient to modify qualitatively the firing properties of that neuron. The same five voltage-dependent currents are found in all three cases, and the only changes are in the maximal conductances of these currents, but the top neuron was silent, the middle neuron was tonically firing single action potentials, and the bottom neuron was firing in bursts of action potentials separated by long interburst intervals. When we consider that biological neurons may display eight, ten, or more different voltage-dependent currents, and that the subunit composition of each channel type can regulate its kinetics and voltage-dependence (Hille, 2001), it is clear that there are biological mechanisms for producing neurons with widely different intrinsic properties that in turn shape their responses to synaptic inputs.

Small invertebrate rhythmic systems have been extremely useful for understanding the role of intrinsic properties in determining network dynamics. Therefore, we use specific examples from these preparations to illustrate many general principles common to neuromodulation in all nervous systems. That said, we could have equally well chosen examples from the vertebrate central nervous system to make many of the same points. Neurons in the pyloric rhythm of the crustacean stomatogastric ganglion (STG) routinely fire in rhythmic bursts of action potentials in the intact network (Fig. 2(a)). However, when isolated by photoablating (Miller & Selverston, 1979) presynaptic neurons or by pharmacologically blocking the synaptic potentials evoked by presynaptic neuron activity (Marder & Eisen, 1984b), individual neurons show a variety of different intrinsic properties (Fig. 2(b)). Fig. 2(a) shows intracellular recordings from three neurons during ongoing pyloric rhythm activity, the anterior burster (AB), pyloric dilator (PD) and lateral pyloric (LP) neurons. Although all of them fire in bursts while synaptically coupled, when these neurons are isolated from their presynaptic inputs from other pyloric network neurons, only the AB is intrinsically bursting, but the PD and LP neurons fire tonically (Fig. 2(b)). This figure makes the obvious, but often overlooked, point that it is necessary to isolate neurons from their synaptic inputs to determine the nature of their intrinsic membrane properties (Miller & Selverston, 1982).

2.2. Neuromodulators alter intrinsic properties

Neuromodulators alter the excitability and intrinsic properties of neurons in all nervous systems (Harris-Warrick & Marder, 1991). Fig. 3 compares the action of several neuromodulatory substances on the isolated PD and AB neurons of the lobster STG (Ayali & Harris-Warrick, 1999; Flamm & Harris-Warrick, 1986b; Marder & Eisen, 1984a). Dopamine inhibits and silences the PD neuron, serotonin has no effect while the muscarinic agonist pilocarpine activates slow bursts. In contrast, all three substances increase the frequency and amplitude of the AB neuron burst. This figure shows the following general principles: (a) the same neuron can be the target of multiple modulatory substances, (b) some modulators can produce qualitative changes in the intrinsic properties of neurons, e.g. transform

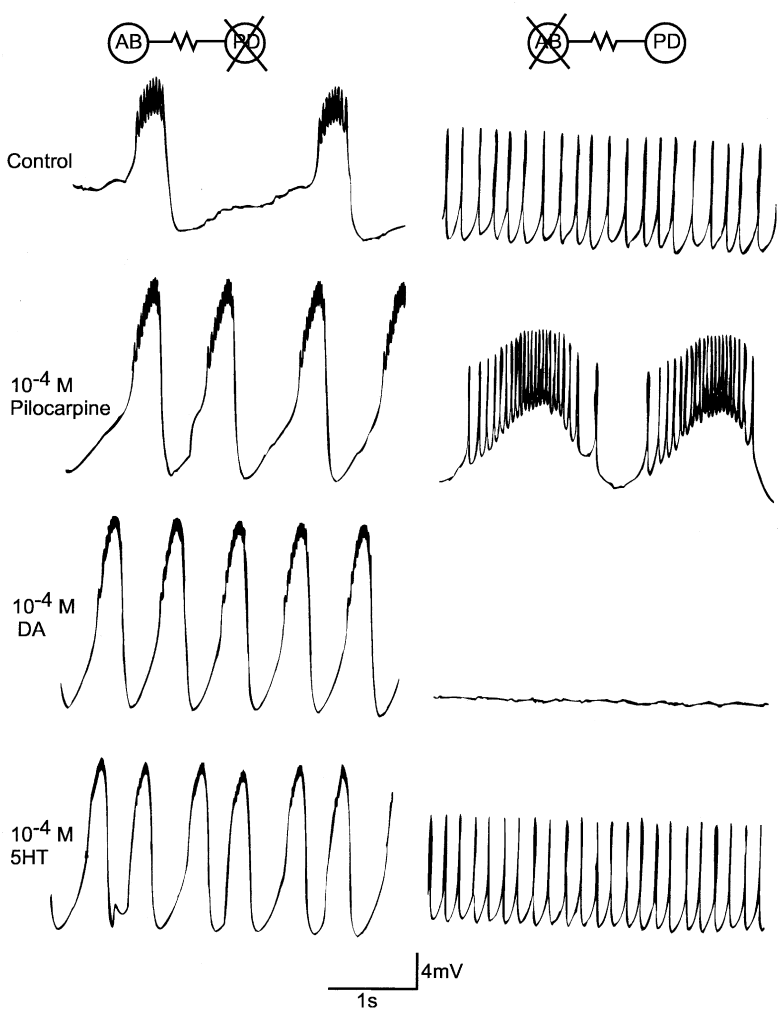

Fig. 3. Alteration of intrinsic properties by neuromodulators. Left, the AB neuron was isolated by photoinactivation of the PD neurons and by pharmacological blockade of all other chemical synaptic interactions. Right, the PD neurons were isolated by photoinactivation of the AB neuron and pharmacological blockade of all other synaptic interactions. From top to bottom, the traces show the activity of isolated AB and PD neurons in control, in 10^{-4} M pilocarpine (a muscarinic agonist), 10^{-4} M dopamine and 10^{-4} M serotonin, respectively. Modified from Marder and Eisen (1984a).

a tonically firing neuron into a bursting neuron, (c) modulators can influence the frequency of either tonic activity or bursting, and (d) different cell types within a network can be influenced differentially by the same neuromodulatory substances.

2.3. Neuromodulators influence one or more membrane currents

Most neuromodulators act on membrane currents via second messenger pathways (molecular cascades that transduce information from the binding of ligand to the receptor to intracellular protein targets) intervening between the receptor for the modulator and the current which is activated, inhibited, or otherwise altered (Hille, 2001). There is a vast literature describing the intracellular second messenger pathways involved in the modulation of membrane currents. Most often, these studies are done focusing on a single current at a time. This approach is ideal for detailed studies of mechanism, but can lead to the mistaken impression that second messenger modulation of a single current occurs in isolation. Instead, modulation of membrane currents by second messengers has several important computational consequences (Hille, 2001): (A) Second messenger activation is often associated with *amplification*. That is, binding of relatively few ligands by a receptor can result in a large concentration change in an intracellular second messenger. (B) Receptors activated by different substances can *converge* on the same second messenger signal and consequently on the same target protein. (C) The same intracellular second messenger molecule might have *divergent* effects by being part of multiple pathways or by influencing several cellular targets. In fact, it is important to remember that all the signaling networks in the cell are interlinked, so that modulation of one current by a given neurotransmitter is likely to change the state of a number of pathways in the cell and possibly alter responses to other substances.

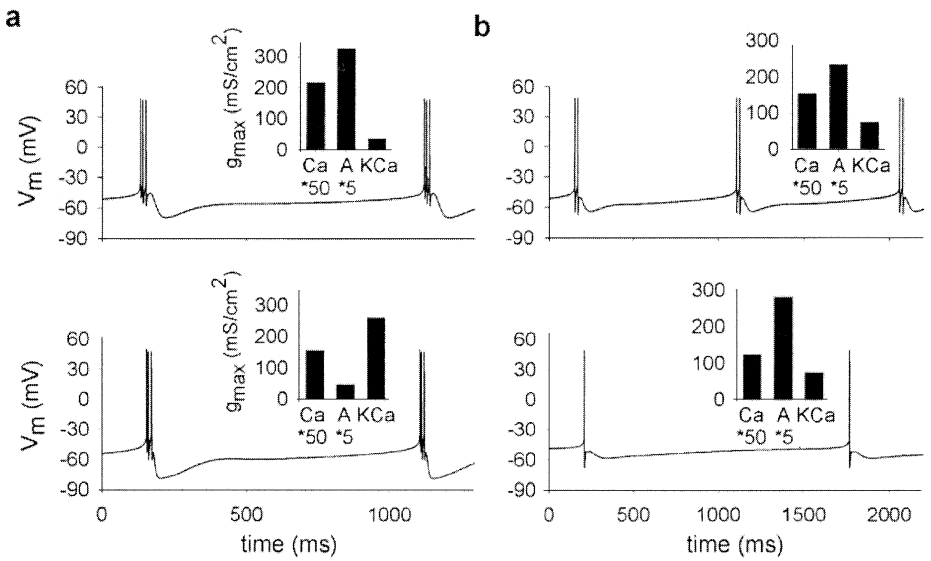

Fig. 4. Activity patterns and maximal conductances in a model neuron. (a) Different values of maximal conductances result in similar activity patterns. The model neurons in the top and bottom panels show similar firing properties although their maximal conductances are very different (shown in the insets). (b) Conversely, two model neurons whose maximum conductance values are similar give rise to different activity patterns. Modified from Goldman et al. (2001).

Although many neuromodulators act simultaneously on two or more membrane currents in the same neuron (Baxter & Byrne, 1989; Kiehn & Harris-Warrick, 1992; Levitan & Levitan, 1988), it is often assumed that modulation of one ionic current is responsible for alterations in the intrinsic properties of a neuron. Nonetheless, even when only a single current is modulated by a neurotransmitter, there can be a non-straightforward relationship between modulation of that current and the neuron's firing properties. This can occur because there is a non-trivial relationship between the maximal conductances found in a neuron and its intrinsic properties. This is illustrated in a recent modeling study (Goldman, Golowasch, Marder, & Abbott, 2001) in which the maximal conductances of each of five currents were systematically varied in model neurons and their intrinsic properties mapped. This model has three different K^+ currents, as well as Ca^{2+} and Na^+ currents. Fig. 4(a) shows that similar intrinsic properties can result from quite different values of the maximal conductances of these currents, while Fig. 4(b) shows that similar values of the maximal conductances of these currents can produce quite different firing properties. In fact, the intuition that one takes from the simple case shown in Fig. 1 needs to be modified: careful analyses of the relationships between conductance densities and intrinsic properties show that no single current determines in this model whether a neuron is silent, tonically firing, or a burster (Goldman et al., 2001). Rather, the correlated values of three of the five currents (I_A, the Na^+ current, and the Ca^{2+} current) are needed to produce a map of conductance density that partitions into clear regions that predict intrinsic firing properties (Goldman et al., 2001).

All measurements of conductance densities in biological neurons show some variance (Golowasch, Abbott, & Marder, 1999; Golowasch, Goldman, Abbott, & Marder, 2002; Liu et al., 1998), although this variance was commonly assumed to be due to experimental measurement errors. Because we have learned from modeling studies that very similar intrinsic properties can be produced by different conductance densities (Goldman et al., 2001; Golowasch et al., 2002), this suggests that individual biological neurons of the same class may also be considerably more variable in conductance density than usually thought, especially since the measured conductance densities can be altered by only several hours of stimulation (Golowasch et al., 1999).

How then do neuromodulators alter the intrinsic properties of neurons? If a neuromodulator acts on a single membrane current, it may or may not bring the neuron across the boundaries between different behaviors, depending on the initial values of the membrane conductances (Goldman et al., 2001; Guckenheimer, Gueron, & Harris-Warrick, 1993). By using the dynamic clamp Goldman et al. (2001) and Sharp, O'Neil, Abbott, & Marder (1993a,b) were able to construct parameter maps of the intrinsic properties of biological neurons by varying the amounts of one or two added membrane currents. These maps indicate that modulation of a membrane current could have either relatively little influence on the intrinsic activity of the neuron, or could produce a state change. This places 'state-dependent modulation' on a firm biophysical basis: depending on the underlying conductance densities of the neuron, a given modification of a current, or addition of a novel current may have a large effect, or virtually no effect.

Guckenheimer et al. (1993) studied the bifurcations produced by parameter alterations in a model bursting neuron. These authors argued that it might be advantageous for a neuron to live close to bifurcations, thus making it highly sensitive to neuromodulatory inputs (Guckenheimer

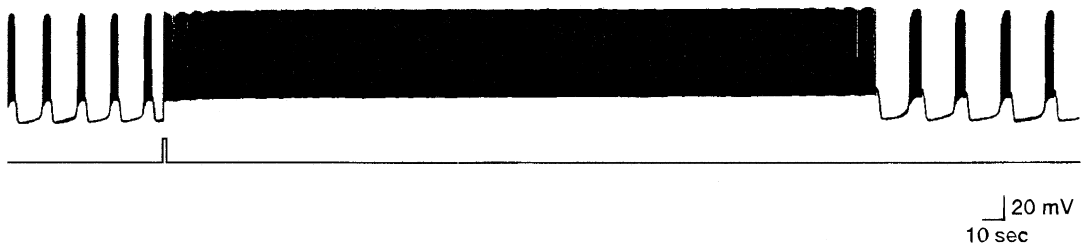

Fig. 5. The R15 neuron in *Aplysia* can be stably switched from bursting to tonic firing by brief inputs. A short pulse of current injected into R15, switches it from bursting to tonic firing which lasts for several minutes before returning to the bursting mode. Modified from Lechner et al. (1996).

et al., 1993). However, this could also make individual neurons overly sensitive to modest fluctuations in conductance density associated with normal processes of channel turnover, and therefore there is an obvious trade-off between sensitivity to modulatory activity for plasticity and the requirement for stability in function.

R15 is a bursting neuron found in the abdominal ganglion of *Aplysia californica*. R15 is involved in the control of a variety of physiological functions, including respiratory pumping and reproduction (Alevizos, Weiss, & Koester, 1991a,b,c). R15 is subject to modulation by a number of different neurotransmitters, including serotonin, dopamine, and neuropeptides that can convert it to tonic firing or silence (Benson & Levitan, 1983; Drummond, Benson, & Levitan, 1980; Kramer, Levitan, Carrow, & Levitan, 1988; Lechner, Baxter, Clark, & Byrne, 1996; Levitan, 1988; Levitan & Levitan, 1988; Levitan, Harmar, & Adams, 1979). Physiological studies had indicated that the same synaptic input would evoke different physiological actions when R15 neurons were silenced by different neuromodulatory treatments, each of which produces different alterations in membrane conductances. These results have stimulated a number of modeling studies (Baxter et al., 1999; Bertram, 1994; Butera, Clark, & Byrne, 1996; Butera et al., 1995; Canavier, Baxter, Clark, & Byrne, 1993, 1994; Canavier, Clark, & Byrne, 1991).

2.4. Neuromodulation and bistability

There are some parameter regimes in neuronal models that support multistability. This has been carefully studied in a model of the *Aplysia* R15 bursting neuron (Canavier et al., 1993). This model can fire tonically or burst, depending on initial values of the state variables, but at the same parameter values. Simulated synaptic inputs can produce long-lasting switches among a number of different limit cycles in the model. Moreover, electrophysiological studies show that R15 can be stably switched by brief synaptic inputs from bursting to tonic firing (Fig. 5) and that serotonin applications influence the duration of the two states (Lechner et al., 1996).

Bistability is most commonly found in neurons with 'plateau' properties (Marder, 1991; Russell & Hartline, 1978). In neurons with plateau properties brief depolarizing or hyperpolarizing pulses can switch the neuron between two different voltages and firing states. Many vertebrate motor neurons display plateau properties that extend the duration of a motor neuron discharge beyond the time of its excitatory synaptic drive (Kiehn & Eken, 1997, 1998; Kiehn, Johnson, & Raastad, 1996). Neuromodulators often influence the extent to which plateau properties are seen (Weimann, Marder, Evans, & Calabrese, 1993).

2.5. Neuromodulation and behavioral state

Neuromodulators that alter the intrinsic firing properties of neurons can be associated with significant changes in behavioral state. One of the most dramatic examples is seen in the mammalian thalamus (Fig. 6), where modulatory substances control a transition between tonic firing and bursting, thought to be associated with the transition between awake and sleep states (McCormick, 1992a,b; McCormick & Pape, 1990a,b; Steriade, McCormick, & Sejnowski, 1993). Work using in vitro thalamic slices shows that when thalamic neurons are depolarized they fire tonically, but when hyperpolarized they can fire in a bursting mode. This switch in intrinsic properties occurs because these neurons have a low threshold Ca^{2+} current that rapidly inactivates with depolarization that is necessary for the slow wave underlying bursting. If the neuron remains depolarized, this current remains inactivated, and the neuron fires tonically. Hyperpolarization deinactivates this current, thus allowing bursting to occur (McCormick & Pape, 1990a, b). These neurons are modulated by acetylcholine, norepinephrine, and serotonin (McCormick, 1989; McCormick & Pape, 1990a,b), and the premise is that the behaviorally relevant release of these substances governs the arousal status of the animal.

2.6. Modulation of intrinsic properties alters a neuron's response to synaptic drive

Although much has been learned from network models in which the individual neurons are simple, and have no variable intrinsic properties, it is important to stress that the *functional efficacy* of a synapse depends critically on the intrinsic properties of the neuron receiving that synapse. There are numerous examples of potential computational significance: (1) the impact of synaptic inputs to neurons

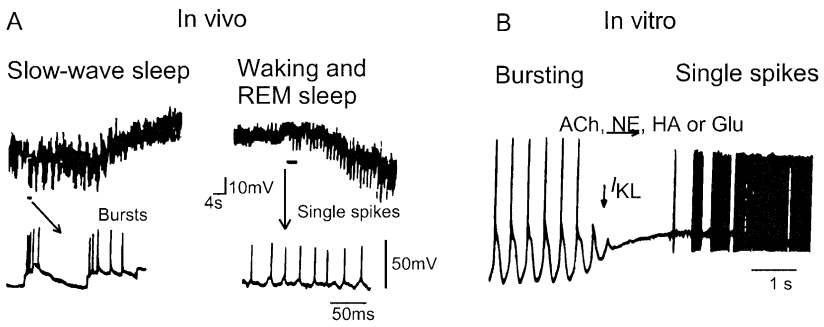

Fig. 6. Modulation of firing properties correlates with change in behavioral state. (A): In vivo, thalamocortical neurons change their firing properties from bursting to tonic firing when transitioning from slow wave sleep to awake or REM sleep states. (B) A similar change from bursting to tonic firing can be produced by applying acetylcholine (ACh), serotonin (5-HT), norepinephrine (NE), histamine (HA) or glutamate (Glu) in vitro. Modified from Steriade et al. (1993).

with plateau properties is temporally extended by the bistability properties of the neuron (Kiehn & Eken, 1998). (2) Postinhibitory rebound in a follower neuron transforms inhibition into delayed excitation, as the follower neuron is depolarized and excited following inhibition (Marder & Bucher, 2001). (3) Synaptic inputs to neurons with robust oscillatory properties will have different effects depending on the phase of the oscillator at which they occur (Ayali & Harris-Warrick, 1999; Ayers & Selverston, 1979; Marder, Abbott, Turrigiano, Liu, & Golowasch, 1996). Consequently, modulators that transform the intrinsic properties of a neuron, for example, transforming a tonic firing neuron to an oscillatory or plateau neuron, completely transform the computational consequences of a given synaptic input to that neuron.

3. Modulation of synaptic strength

The strength of many synapses is modulated by amines and neuropeptides. In fact, it is possible that the number of synapses that are not subject to modulation may turn out to be smaller than those that are subject to modulation by one or another mechanism. In some cases, this modulation is effected by direct synaptic contacts with the presynaptic terminal, in presynaptic inhibition (Fig. 7(a)) or heterosynaptic facilitation (Fig. 7(b)). In other cases, the modulation may be effected by diffusely acting neuromodulatory substances, acting either to alter transmitter release (Fig. 7(c)) or on some property of the postsynaptic neuron (Fig. 7(d)).

3.1. Presynaptic modulation of synaptic efficacy

In the 1960's Dudel and his colleagues studied the modulation of synaptic transmission using the crayfish neuromuscular junction (Dudel, 1965; Dudel & Kuffler, 1961). In their classic study, Dudel and Kuffler (1961) provided the first clear demonstration of presynaptic inhibition using the excitatory synaptic input to the crayfish opener muscle. To do so, they pioneered the use of quantal analysis to distinguish between presynaptic and postsynaptic mechanisms of action. Not much later, Dudel (1965) demonstrated that serotonin enhanced transmission at this junction as well.

Subsequently, the biophysical and biochemical mechanisms underlying facilitation by serotonin have been studied intensively in crustacean neuromuscular junctions

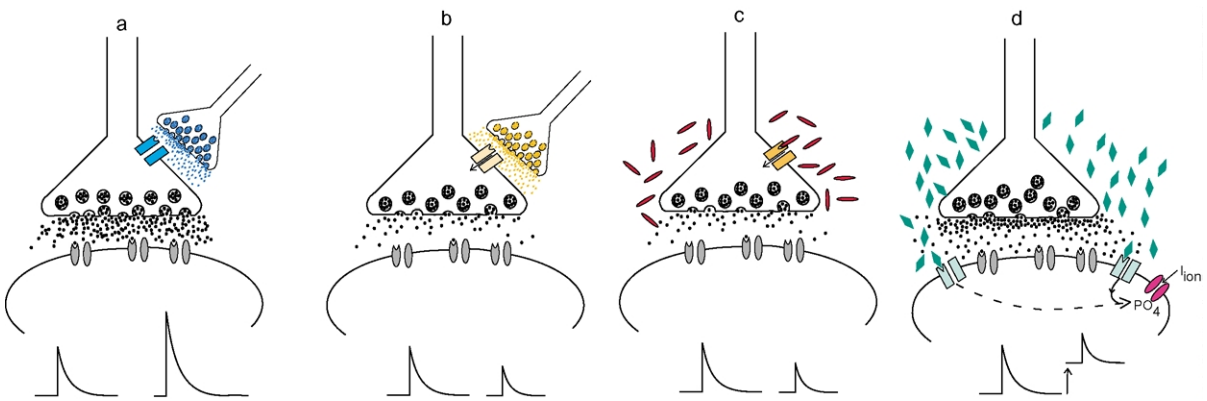

Fig. 7. Modulation of synaptic properties. (a) Heterosynaptic facilitation, (b) presynaptic inhibition, (c) diffusely delivered modulator can act on presynaptic release mechanism or (d) postsynaptic receptors. Such diffuse actions of modulators on the presynaptic terminal are known to change the probability of transmitter release (P_r). Alternatively, modulators could bind to receptors on the postsynaptic membrane and activate or inhibit intrinsic conductances. These might affect the effectiveness of a synapse in contributing to neural computation.

(Beaumont, Zhong, Fletcher, Froemke, & Zucker, 2001; Beaumont & Zucker, 2000; Delaney, Tank, & Zucker, 1991; Dixon & Atwood, 1985, 1989; Glusman & Kravitz, 1982; Goy & Kravitz, 1989; Vyshedskiy, Delaney, & Lin, 1998). A fascinating new study by Beaumont and Zucker (2000) shows that hyperpolarization of the presynaptic terminal activates I_H, which results in an after depolarization of the terminal, and a long-lasting increase in transmitter release. Serotonin applications are associated with increases in the second messenger, cAMP, which modulates I_H (Luthi & McCormick, 1999), so this study illustrates the complex interaction between the dynamics of the signal transduction networks in the presynaptic terminal, the voltage-gated channels in the terminal, and the resulting dynamics of transmitter release.

Modulation of transmitter release has been extensively studied at *Aplysia* sensory motor synapses (Kandel, 2001) in the context of understanding the cellular basis of both short-term and long-term plasticity. Kandel and his group established that serotonin activated presynaptic adenylyl cyclase, leading to increases in cAMP (Bernier, Castellucci, Kandel, & Schwartz, 1982). They eventually established that serotonin facilitates transmitter release by changes in K^+ conductances (Camardo, Shuster, Siegelbaum, & Kandel, 1983; Hochner & Kandel, 1992; Shuster, Camardo, Siegelbaum, & Kandel, 1986; Siegelbaum, Camardo, & Kandel, 1982), Ca^{2+} channels (Braha et al., 1990; Braha, Edmonds, Sacktor, Kandel, & Klein, 1993; Edmonds, Klein, Dale, & Kandel, 1990) and the release machinery of the terminal via activation of several different signal transduction pathways (Kandel, 2001). Again, an important generalization from these studies is that neuromodulators appear to act via a complex network of second messenger pathways to alter many different processes that regulate transmitter release.

Interesting new studies suggest that endogenous cannabinoids may function as a retrograde signal that is released by postsynaptic cerebellar Purkinje neurons to modulate presynaptic release (Kreitzer & Regehr, 2001a,b). This makes the important point (Marty & Llano, 1995) that postsynaptic activity can control the strength of the presynaptic drive to that neuron.

3.2. Multiple substances may modulate the same presynaptic terminals

Release of neurotransmitter from the *Aplysia* sensory neuron terminals is modulated not only by serotonin, but by neuropeptides as well (Belardetti, Kandel, & Siegelbaum, 1987; Castellucci et al., 1986; Sweatt, Volterra, Siegelbaum, & Kandel, 1988). There are numerous other instances in which several, or many, substances also modulate transmitter release (Jorge-Rivera, Sen, Birmingham, Abbott, & Marder, 1998; Pieroni & Byrne, 1992; Svensson, Grillner, & Parker, 2001). If these substances differentially activate signal transduction pathways, there can be quite complex changes in synaptic efficacy that depend crucially on the history of presynaptic firing and of the extent to which modulators alter the dynamics of transmitter release when acting singly or in concert.

3.3. The interaction between synaptic dynamics and modulator action

Most synapses show some time-dependent changes in synaptic strength such as facilitation and depression (Abbott, Sen, Varela, & Nelson, 1997; Manor, Nadim, Abbott, & Marder, 1997; Marder, 1998; Nadim & Manor, 2000; Nadim, Manor, Kopell, & Marder, 1999; Vyshedskiy and Lin, 1997a,b; Zucker, 1989) which are thought, at least in part, to reflect intracellular Ca^{++} dynamics (Delaney et al., 1991; Kreitzer & Regehr, 2000; Sabatini & Regehr, 1997, 1999; Zucker, 1989). Therefore, it is not surprising that modulators can themselves have actions that are dependent on the frequency of presynaptic firing (Jorge-Rivera et al., 1998) and that neuromodulators can alter the extent to which synapses show short-term plasticity.

4. Modulation of sensory encoding

All kinds of neurons, including sensory neurons, motor neurons, and interneurons are subject to neuromodulation. In many systems the encoding of sensory information in primary neuron spike trains is subject to modulation. For example, crustacean muscle stretch receptors are sensitive to a number of amines and neuropeptides that alter both the spike rate and adaptation properties of the neuron (Birmingham, 2001; Pasztor & Bush, 1989). Moreover, some of these neurons can operate in both spiking and bursting modes and neuromodulators may influence the switch between these states (Birmingham, Szuts, Abbott, & Marder, 1999; Combes, Simmers, & Moulins, 1997). Thus, there is not a unique relationship between the sensory stimulus and the resulting spike train. It remains unclear how the central nervous system decodes these variable spike trains found under different modulatory conditions. It will also be interesting to see how the information carried in these spike trains varies with modulatory processes that change the number and dynamics of the elicited spikes.

Modulation of sensory encoding is not specific to encoding of stretch. Rather, it is likely to be the rule rather than the exception. For example, the terminals of vertebrate touch and nocioceptive neurons are sensitive to a large number of hormones and neuromodulatory substances that influence their excitability, and modulation of synaptic release from the spinal cord terminals of dorsal root ganglion cells is thought to be important in pain regulation (Dunlap & Fischbach, 1978, 1981; Holz, Kream, Spiegel, & Dunlap, 1989; Levine, Fields, & Basbaum, 1993; Mudge,

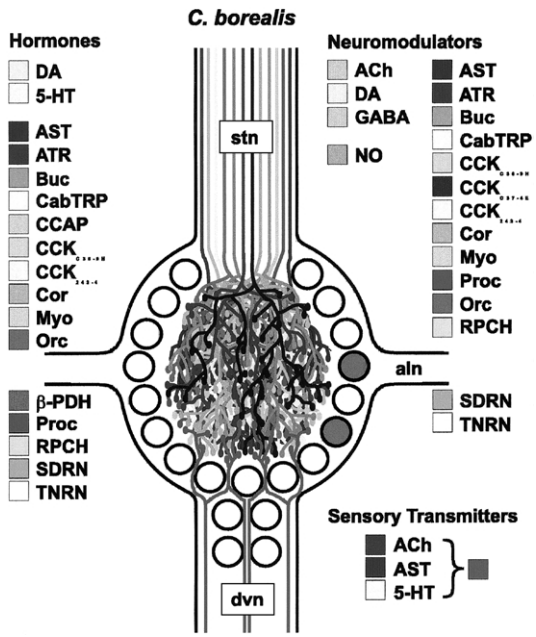

Fig. 8. Modulators present in the STG of the crab, *C. borealis*. Modified from Marder and Buchner (2001) which also has all the abbreviations and original references.

Leeman, & Fischbach, 1979; Riley, Trafton, Chi, & Basbaum, 2001; Skinner, Basbaum, & Fields, 1997).

5. Modulation of central pattern generating circuits

Many of the other articles in this issue will deal with the effects of neuromodulators on processing in higher brain regions. Therefore below we chose to use the modulation of rhythmic central pattern generating circuits found in the vertebrate spinal cord and brainstem and in invertebrate ganglia to illustrate features of modulation of brain circuits that are likely to be quite general. Central pattern generating circuits are groups of neurons that are capable of producing rhythmic motor discharges that result in rhythmic movements in vertebrates and invertebrates (Marder & Bucher, 2001; Marder & Calabrese, 1996). There is a great deal known about the organization of these circuits and their modulation precisely because their outputs are so well defined. Many preparations have contributed considerably to the conceptual frameworks presented below (Calabrese, 1998; Marder, 2000; Marder & Bucher, 2001; Pearson, 1993; Stein, Grillner, Selverston, & Stuart, 1997), and space limitations make it impossible to do justice to any of them. Many of the same organizational principles are found in most of these preparations, some of which can be illustrated in the crustacean stomatogastric nervous system.

The STG contains 26–30 neurons that generate two different rhythmic motor patterns, the fast pyloric rhythm and the slower gastric mill rhythm (Harris-Warrick, Marder, Selverston, & Moulins, 1992; Selverston & Moulins, 1987). Although the essential central pattern generating circuitry is present in the STG, the pyloric and gastric mill rhythms are highly dependent on descending inputs from anterior ganglia and peripheral sensory neurons. Fundamental understandings of the mechanisms of pattern generation and modulation in the STG have come because each of the neurons is individually identifiable (recognizable from animal to animal on the basis of physiological, biochemical, and anatomical properties), and because the central pattern generating circuitry is found at the level of the motor neurons. Moreover, it is routinely possible to record all of the relevant neurons simultaneously, in mixtures of intracellular and extracellular recordings. This has facilitated the establishment of connectivity wiring diagrams, as well as the determination of the intrinsic properties of the neurons.

There are several immediate conclusions from this work that hold to a greater or lesser degree in other central pattern generating networks: (a) All the chemical synaptic connections in the STG are inhibitory, and functional antagonists are often connected with reciprocal inhibition (Harris-Warrick et al., 1992; Selverston & Moulins, 1987). The importance of reciprocal inhibition in the generation of rhythmic movements and in central pattern generating circuits has been long recognized, and many rhythmic motor systems operate largely on rebound from inhibition, rather than by excitation (Brown, 1911; Calabrese, 1998; Dale, 1985; Friesen, 1994; Perkel & Mulloney, 1974; Satterlie, 1985). (b) Each class of identified neuron in the STG has characteristic intrinsic properties (Hartline, Russell, Raper, & Graubard, 1988) (Fig. 2). In recent years, these differences in intrinsic properties have been attributed to cell specific differences in channel expression (Baro et al., 2000; Baro, Cole, & Harris-Warrick, 1996; Baro, Cole, Zarrin, Hughes, & Harris-Warrick, 1994; Baro & Harris-Warrick, 1998; Baro et al., 1997). (c) Network dynamics are constant interplay between synaptic and intrinsic properties. (d) Frequency and phasing of neurons within the motor pattern are controlled by multiple cellular mechanisms.

5.1. Networks are multiply modulated

Fig. 8 shows the results of a large number of studies determining the neuromodulators found in the inputs to the crab STG (Marder & Bucher, 2001). When applied individually to the isolated STG each of these substances produces characteristic and different effects on the pyloric rhythm (Marder & Hooper, 1985; Marder & Weimann, 1992), as illustrated for the pyloric rhythm in Fig. 9.

Data such as those seen in Figs. 8 and 9 led to the notion that different modulators reconfigure an anatomically defined network into different functional circuits, by altering the synaptic strength and intrinsic properties of neurons within the network (Harris-Warrick & Marder, 1991; Marder & Hooper, 1985; Marder & Weimann, 1992). By doing so, the network is biased into different functional

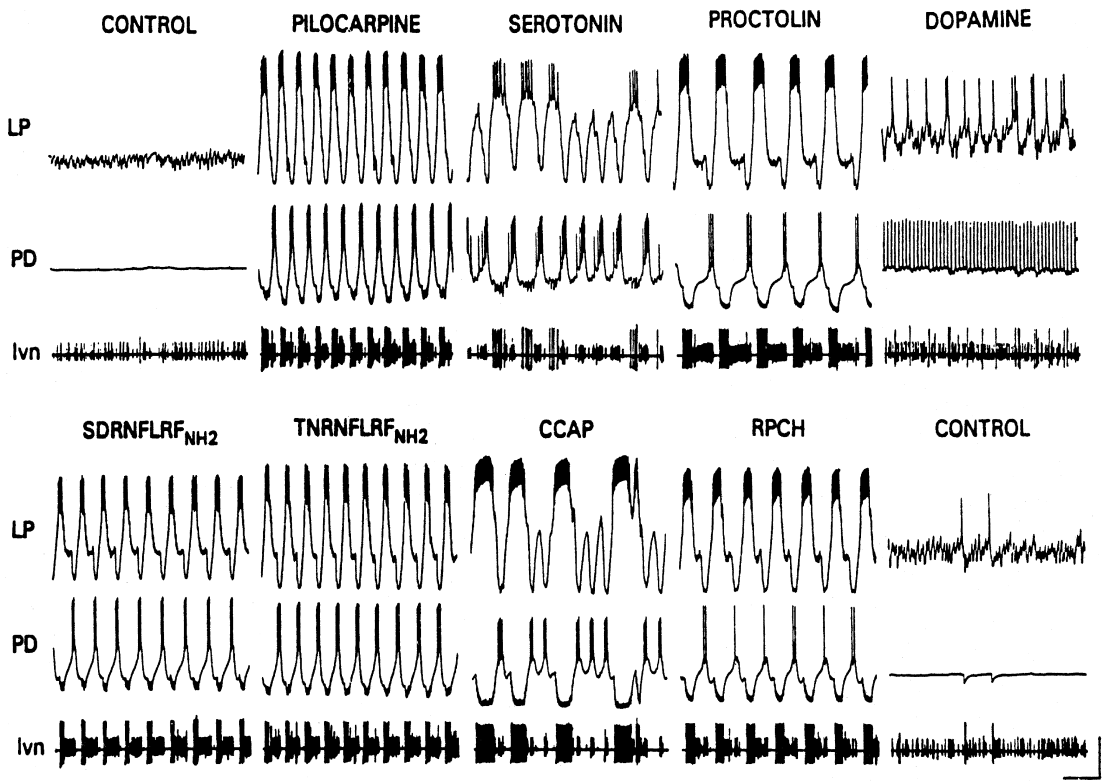

Fig. 9. Modulators reconfigure the pyloric network. When the STG is isolated from all modulatory inputs, the pyloric neurons LP, PY and PD become silent (control). In all panels, the top two traces are intracellular records from the LP and PD neurons. The bottom trace is an extracellular nerve recording from the lateral ventricular nerve that shows the spiking patterns of the LP, PY and PD neurons. When one of many modulators (pilocarpine, serotonin, dopamine, proctolin, SDRNFLRFamide, TNRNFLRFamide, crustacean cardioactive peptide -CCAP, red pigment concentrating hormone) is bath-applied, the pyloric network once again produces characteristic modulator-induced motor patterns (taken from Marder & Weimann, 1992).

outputs, in much the same way as changing parameters in a network model should bias or modify the output of the network. Extensive studies on the pyloric rhythm have worked out many of the actual mechanisms by which amines and peptides reconfigure the pyloric network into different output patterns (Eisen & Marder, 1984; Flamm & Harris-Warrick, 1986a,b; Hooper & Marder, 1987). In the STG of the lobster, *Panulirus interruptus*, the effects of dopamine on the inhibitory synapses within the pyloric rhythm have been studied (Johnson & Harris-Warrick, 1990; Johnson, Peck, & Harris-Warrick, 1993, 1994, 1995), and the effects of dopamine on many of the voltage-dependent currents that control the bursting and postinhibitory rebound properties of the neurons have also been measured (Harris-Warrick, Coniglio, Barazangi, Guckenheimer, & Gueron, 1995; Harris-Warrick, Coniglio, Levini, Gueron, & Guckenheimer, 1995; Harris-Warrick et al., 1992; Kloppenburg, Levini, & Harris-Warrick, 1999). Together, these data show that dopamine acts both on many neurons within the pyloric network, and on a number of different synaptic and voltage-dependent currents, and therefore the network alterations evoked by dopamine are an emergent feature of many distributed actions of the amine.

This is then an example of modulator *divergence* at the circuit level: the same modulator has many targets on multiple circuit neurons and synapses, mediated by multiple voltage-dependent currents. In contrast, a number of the peptide modulators converge onto the same voltage-dependent inward current (Swensen & Marder, 2000, 2001). These substances include several neuropeptides that are found colocalized in the same input neurons (Blitz et al., 1999; Nusbaum et al., 2001). In this case, differential action at the network level appears to be produced because each of the neuropeptides acts on a different subset of network neurons, albeit on the same current in each of them (Swensen & Marder, 2000, 2001). Interestingly, the different cotransmitters released by a projection neuron can act on a different subset of neurons, as each neuron displays a characteristic mixture of receptor types (Swensen & Marder, 2000; Thirumalai & Marder, 2002).

Fig. 3 shows that the same neuron can be modulated by many different substances, but does not reveal the full extent of how rich the neurotransmitter and modulator inputs to a neuron can be! The LP neuron of the pyloric rhythm responds to ACh, glutamate, serotonin, dopamine, proctolin, crustacean cardioactive peptide, red pigment concentrating hormone, *Cancer borealis* tachykinin related peptide, octopamine, histamine, GABA, TNRNFLRFamide, SDRNFLRFamide, allatostatin, and likely others as well (Flamm & Harris-Warrick, 1986b; Golowasch & Marder, 1992; Hooper & Marder, 1987; Marder & Eisen, 1984b; Skiebe & Schneider, 1994; Swensen et al., 2000; Swensen

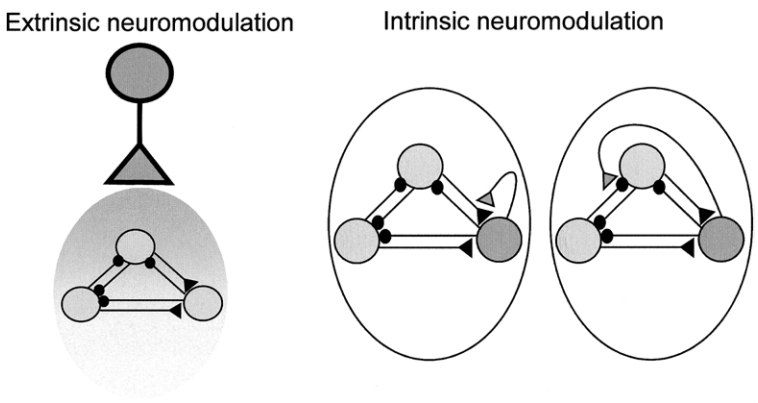

Fig. 10. Extrinsic vs intrinsic neuromodulation. Extrinsic neuromodulation is seen when neural circuits are modulated by neurons that are not integral members of the circuit being modulated. Intrinsic neuromodulation is seen when neurons within a circuit release modulators that change synaptic strength and excitability within the network. Modified from Katz and Frost (Katz & Frost, 1996).

& Marder, 2000; Weimann et al., 1993, 1997). A number of these substances converge onto the same current and can saturate and occlude each others' actions (Swensen & Marder, 2000) while others mediate rapid synaptic potentials or modulate other currents. That said, it could be seen that this neuron is constantly integrating synaptic and modulatory inputs with widely different time scales and second messenger consequences, but is not simply summing a large number of seemingly identical synaptic inputs.

Although considerably less is known about the central pattern generating circuits in the vertebrate spinal cord, it is clear that they are also multiply modulated by amines and neuropeptides found in descending projections and local interneurons (Cazalets, Sqalli-Houssaini, & Clarac, 1992; Sqalli-Houssaini & Cazalets, 2000).

5.2. Intrinsic and extrinsic modulation

Some neuromodulatory substances have been termed 'extrinsic' as they are released by neural projections that are clearly outside of, or not part of, the circuits that they modulate (Katz, 1995; Katz & Frost, 1996). Others are termed 'intrinsic' because they are released by some of the self-same neurons that are part of the circuit that they modulate (Cropper et al., 1987; Katz, 1995; Katz & Frost, 1996). In this case, when the circuit is operational or active, some of its neurons may release neuromodulators that alter synaptic strengths and intrinsic membrane properties of other circuit components (Fig. 10).

An elegant study of intrinsic modulation was carried out in the *Tritonia* swim system (Katz, 1995; Katz & Frost, 1995a,b, 1996; Katz, Getting, & Frost, 1994). In this system the dorsal swim interneurons (DSIs) are serotoninergic. The DSIs both make conventional inhibitory synapses and modulate the strength of the synapses and excitability of the C2 neuron. Thus, excitatory drive to the DSIs initiates the episode of the swim, but the intensity and duration of the swim is modulated by serotonin released by one of the circuit neurons themselves.

What are the computational differences between intrinsic and extrinsic modulation (Katz & Frost, 1996)? Extrinsic modulation can be used not only to regulate one neural circuit, but can be used to organize ensembles of circuits found in myriad regions of the nervous system. Intrinsic modulation may be more restricted, both spatially and temporally, as it may primarily be used to maintain ongoing activity. For example, in a circuit with significant intrinsic modulation that produces an enhanced level of excitability, a short synaptic input can 'jump start' a circuit, causing the release of an intrinsic modulator that would maintain the activity significantly after the initiating signal. There are a significant number of instances in which intrinsic modulation is known to occur (Katz & Frost, 1996). Because it is now clear that many neurons may have both ionotropic and metabotropic receptors to the same neurotransmitters, it is possible that some amount of metabotropic-mediated intrinsic modulation commonly accompanies strong circuit activation that liberates significant transmitter. For example, many of the inhibitory synapses in the STG are mediated by glutamate (Marder & Eisen, 1984b), and recent work has demonstrated that there are glutamate metabotropic receptors in the STG (Krenz, Nguyen, Perez-Acevedo, & Selverston, 2000), some of which have excitatory actions. Therefore, strong drive to an inhibitory neuron could be balanced by an intrinsic excitatory modulatory action resulting from increased glutamate release.

6. The role of neuromodulators in development

Modulators can have important functions during the development of neural circuits. Because the activity of a network may itself play important roles in tuning networks (Shatz, 1994; Wong, 1999; Wong, Chernjavsky, Smith, & Shatz, 1995), early acting modulators can influence developing networks indirectly by altering activity patterns. That said, there is growing evidence that neurotransmitters and modulators themselves can influence process outgrowth

and synapse formation (Benton & Beltz, 2001; Haydon & Kater, 1988; Haydon, McCobb, & Kater, 1984; Sullivan, Benton, & Beltz, 2000). Additionally, the neuromodulatory environment itself also changes over development, as there is a sequential acquisition of cotransmitters in modulatory projection neurons, with some modulators appearing early and others quite late (Fénelon, Kilman, Meyrand, & Marder, 1999; Kilman et al., 1999; Le Feuvre, Fénelon, & Meyrand, 2001). Receptors to many neuromodulators are present early in neural circuit development, and therefore can play roles in altering circuits at different developmental stages (Le Feuvre, Fénelon, & Meyrand, 1999; Richards & Marder, 2000).

7. Conclusions

The extensive use of neuromodulation by all nervous systems has several important computational consequences. If most synapses are subject to modulation by one or more substances, then synaptic strength and its plasticity are not fixed, but are ever changing. If the intrinsic properties of neurons within a circuit are also ever changing, then the responses of these neurons to given synaptic inputs are also not fixed. The potential advantage of extensive modulation is flexibility. The complication is that such extensive potential for modulation must be accompanied by circuit designs that preclude and prevent these circuits from over-modulation or loss of function. Much computational work will be needed to understand how it is possible for biological circuits to be so richly modulated while retaining stable function.

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