Neuromodulation of Neurons and Synapses

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Abstract

Neuromodulation underlies the flexibility of neural circuit operation and behavior. Individual neuromodulators can have divergent actions in a neuron by targeting multiple physiological mechanisms. Conversely, multiple neuromodulators may have convergent actions through overlapping targets. Additionally, the divergent and convergent neuromodulator actions can be unambiguously synergistic or antagonistic. Neuromodulation often entails balanced adjustment of nonlinear membrane and synaptic properties by targeting ion channel and synaptic dynamics rather than just excitability or synaptic strength. In addition, neuromodulators can exert effects at multiple timescales, from short-term adjustments of neuron and synapse function to persistent long-term regulation. This short review summarizes some highlights of the diverse actions of neuromodulators on ion channel and synaptic properties.

Introduction

The current understanding of nervous system function holds a prominent place for the role of neuromodulators in shaping electrophysiological activity. All nervous system function, from simple reflexes to sleep, memory and higher cognitive tasks, ultimately result from the activity of neural circuits. A wide variety of substances, including small molecule transmitters, biogenic amines, neuropeptides and others can be released in modes other than classical fast synaptic transmission, and modify neural circuit output to produce extensive adaptability in behaviors [1]. They do so by changing the properties of a circuit's constituent neurons, their synaptic connections or the inputs to the circuit. Such functional reconfiguration of hard-wired circuits is essential for the adaptability of the nervous system.

Neuromodulators are often thought to convey global control of brain states that underlie different behaviors, such as sleep and arousal. Implicit in this view is that one or a few modulators can dominate the operation of a large number of neurons and interconnected circuits, and that the global presence or absence of a neuromodulator is equivalent to a specific behavioral state. However, this view appears to contradict studies at the cellular level which show that multiple neuromodulators can act simultaneously on any single

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neuron, that intrinsic excitability and synaptic efficacy are always under neuromodulatory influence and, therefore, reconfiguration of neural circuits by neuromodulators is an intricately balanced process that involves multiple synergistic or antagonistic pathways. These conflicting views do not arise from contradictory experimental results, but rather from the challenge to bridge multiple levels of analysis from cellular to circuit to behavior. A comprehensive description of the variety of neuromodulator actions at these different levels is beyond the scope of a single review. Here we summarize findings that highlight the diversity of neuromodulatory effects on cellular and synaptic properties and discuss them in the context of local circuit activity.

Neuromodulation of synapses

Neuromodulators modify synaptic communication through a number of mechanisms which can be broadly divided into effects that target synapses directly and those that indirectly modify synaptic interactions by changing the excitability of neurons. Indirect effects include presynaptic modulation that can lead to changes in action potential shape [2–4••], and postsynaptic modulation that for example increases voltage-gated inward currents to enhance EPSPs [5–7•]. We will discuss these effects in detail in the next section.

Direct effects on synaptic interactions can also be divided into pre- and postsynaptic mechanisms. Presynaptically, neuromodulators often target the probability of vesicular release by modifying presynaptic Ca^{2+} influx, the size of the reserve pool, or proteins in the active zone [8–11]. On the postsynaptic side, the expression and properties of transmitter receptors can be modified to change postsynaptic responses independent of neurotransmitter release [12,13]. Modulation of neurotransmitter release can also occur through local feedback that alters the level of release through retrograde messengers [14] or autoreceptors [15–17]. Finally, neuromodulator release itself can be subject to modulation. For example, nitric oxide (NO) can modify modulatory actions of glutamate or serotonin (5-HT) [18,19], an example of a broader category of neuromodulatory actions referred to as meta-modulation [20–22].

Neuromodulation of synaptic strength

The simplest functional consequence of synapse modulation is the modification of synaptic strength. Multiple modulators can act on the same synapse to modify its strength, presumably depending on the behavioral need [24,25]. Such effects can be drastic: 5-HT can functionally silence synapses in the crustacean stomatogastric ganglion (STG), whereas dopamine can unmask synapses that are normally silent [26]. The combined action of multiple neuromodulators on synapses can be more than simply additive [27], and the same neuromodulator can have opposing actions on synaptic strength, depending on the network state [28–30].

An important lesson from small invertebrate networks is that neuromodulation of synaptic strength does not always have obvious consequences at the network level. In the STG, the inhibitory synaptic connection from one follower neuron to another is strengthened by dopamine without changing its influence on the postsynaptic activity [31]. In the same system, the inhibitory feedback connection from a follower neuron to pacemaker neurons is

greatly strengthened by two neuropeptides [32,33•] with no apparent consequence for network frequency. However, the increase in synaptic efficacy acts to stabilize network oscillations [33•].

Neuromodulation of gap-junctions is less explored [34]. However, early work in the retina showed that electrical synapses are also subject to neuromodulation [35,36] and more recent work has shown that electrical synapses in other vertebrate and invertebrate systems are modulated by monoamines and NO [37–42], although the main influence of a modulator on the functional strength of the electrical synapse may be due to changes in neuronal input conductance [38,43].

Neuromodulation of synaptic dynamics

In many systems, neuromodulators also act on synaptic dynamics (short-term synaptic plasticity, STP) [30,44–46]. The effect of modulators can be drastic and in some cases can switch the sign of synaptic dynamics from depression to facilitation [33•,47–49]. If the presynaptic neuron is active repetitively, STP can act as a gain-control mechanism, modifying synaptic strength as a function of the frequency of presynaptic activity [50,51]. The modulation of STP can therefore be as important as the modulation of synaptic strength in determining the efficacy of the synapse during network activity (Fig. 1a).

The effects of neuromodulators on synaptic strength and dynamics are best understood in the *Aplysia* gill and siphon withdrawal reflex [52]. This reflex is mediated by a sensory to motor neuron connection which normally habituates but becomes sensitized by serotonergic modulation activated by pairing touch with a noxious tail shock [53]. 5-HT facilitates synaptic strength through activation of protein kinase A (PKA), resulting in a reduction of presynaptic potassium currents. This leads to an increase in the width of the presynaptic action potential and increased transmitter release [54]. A longer training paradigm, equivalent to prolonged exposure to 5-HT, results in an intermediate-term facilitation that involves presynaptic protein kinase C (PKC) and postsynaptic Ca^{2+}-dependent pathways and leads to the insertion of AMPA-like receptors [55,56]. Long-term facilitation of the synapse, associated with long-term sensitization of the behavior, involves a PKA-dependent modification of transcription through CREB phosphorylation, which results in new protein expression and structural changes at the synapse [57].

The *Aplysia* example demonstrates that neuromodulators can act at different time scales and can also affect more persistent changes in synaptic function in the context of learning and memory. In insects, aminergic modulation is an important mechanism in the formation of associative memory [58]. A number of studies over the last two decades have also shown that neuromodulators play an important role in long-term potentiation (LTP) and depression (LTD) of mammalian central synapses [59–63]. Recently, a unifying narrative has emerged that describes how different neuromodulators change the balance of LTP and LTD. The exploration of neuromodulator effects on spike-timing-dependent plasticity (STDP) unmasked a simple rule: the activation of the PKA pathway, e.g. by β-adrenergic receptors, promotes and gates LTP, whereas the activation of the phospholipase C (PLC) pathway, e.g. by M1 muscarinic receptors, promotes LTD [23,64,65]. These modulatory actions require

pairing with the induction protocols that enable NMD-Adependent synaptic plasticity and the simultaneous activation of both modulatory pathways enables the bidirectional long-term changes in STDP [65] (Fig. 1b). Interestingly, activation of each pathway also suppresses the other, suggesting a push-pull rule for the neuromodulation of long-term synaptic plasticity [66] that seems to be independent of the underlying mechanisms of LTP and LTD [67•].

Neuromodulation of neuronal excitability

Responses to synaptic input, as well as spontaneous activity, critically depend on input conductance and the complement of voltage-gated currents. Differences in these properties across and within cell types can be due to differences in the types and spatial distribution of ion channels [68], in their relative expression levels [69], or in the gating properties of similar channels [70]. Accordingly, neuromodulators can change activity and excitability by adding or subtracting ionic currents, changing the relative magnitudes across the complement of currents, or changing voltage- and time dependence of channel gating. It has long been known that neuromodulators affect the availability of voltage-gated ion channels and the gating properties underlying activation and inactivation [71] and, in some cases, also the magnitude of unitary conductances [72]. Over the last two decades, work on a large number of neuron types in different model systems has shown that ion channel modulation is ubiquitous and that each channel is likely to be under modulatory control at all times. Any given neuromodulator can affect multiple types of ion channels, and any given ion channel type can be affected by multiple neuromodulators [1].

The canonical mechanism of ion channel modulation involves binding of a neuromodulator to G protein coupled receptors, subsequent activation of second messengers, and activation of kinases and phosphatases that phosphorylate or dephosphorylate target channel proteins. However, ion channel modulation can occur through other mechanisms, such as direct gating by cyclic nucleotides [73,74] or G proteins [75], or direct and indirect effects of tyrosine kinases [76,77]. All these mechanisms share the common theme that different phosphorylation sites control different aspects of channel gating. Even voltage-gated sodium channels, long thought not to be modulated, are now known to respond to a wide variety of modulators [78] which target multiple phosphorylation sites at the α-subunits [79–81]. The sensitivity to multiple signaling pathways suggests a balanced modulation by many neuromodulators.

Even though neuromodulators are often released diffusely or reach target neurons through the circulatory system, they can have specific effects across different cell types and different compartments within one cell. Neuromodulators can target multiple ion channel types in the same cell, either through shared signaling pathways or different receptors. Similarly, the same signaling pathway can have different effects on different channels (Fig. 2a). Gq-coupled receptors, for example, can have opposite effects on different types of Na^+-dependent K^+ channels, both mediated by PKC [82]. The same modulator can also act through different signaling pathways. Dopamine, for instance, acts through different second messenger systems that synergistically modulate Ca^{2+} currents in teleost retinal horizontal

cells [83], and the same is true for μ-opioid receptor mediated modulation of Na^+ channels in the prefrontal cortex, which depends on both PKA and PKC [84].

Different neuromodulators often affect different subsets of ion channels in a neuron, but there can be convergence of modulatory effects onto the same channel. If these effects have the same sign, they can either be occluding, i.e. simply additive [85], or synergistic [86••].

The pattern of differential modulation of ion channels across different cell types is difficult to unravel in large circuits with ambiguous cell types, but has been relatively straightforward in invertebrate circuits with identified cells. In the STG, at least two principles have emerged. Biogenic amines, such as dopamine, affect multiple currents in each cell, but the subset of target currents is cell-type specific and so is the sign of the effect on a given current [87]. In contrast, different neuropeptides converge onto the same voltage-dependent channel type, but each peptide affects different subsets of cells in the circuit [85,88]. Therefore, in order to understand neuromodulator effects on neuron and circuit activity, one has to identify the pattern of convergence and divergence seen both at the single neuron level and across different neurons [1].

A major contributing factor to the specificity of neuromodulator actions is that intracellular signaling, despite global effects of second messenger pathways, is often restricted to local intracellular domains [89,90]. Consequently, neuromodulation can be restricted to subsets of ion channels in specific cell compartments, even if channels of the same type in different compartments, or channels of a different type in the same compartment could potentially respond to the same pathways [91•,92]. This specificity may arise from the organization of both ion channels and enzymes into local signaling complexes, associated with specific anchoring proteins [93–95] and may give rise to local differences in gating properties within the same cell [96].

While modulation of voltage-gated channels is particularly important because it directly affects the nonlinear dynamics underlying membrane excitability, neuromodulators can have equally significant effects on other types of ion channels. Neuronal input resistance and resting potential are important determinants of excitability and are changed when modulators activate ligand-gated channels or modify "leak" channels. Modulation of leak conductance is best understood for the family of two-pore domain K^+ channels. These channels are responsible for a substantial portion of leak conductance in a variety of neurons, are modulated by a number of intracellular signaling pathways [97], and can be the target of convergent actions of neuromodulators [98]. Inhibition of these channels can be important in the control of excitability [99], whereas their activation, which leads to membrane hyperpolarization, is a molecular target for anesthetics [100].

Ionotropic receptors are best known for mediating postsynaptic responses during fast synaptic transmission. However, ionotropic receptors for small-molecule transmitters can also function in an unambiguously modulatory context. Acetylcholine, the classic fast transmitter at the vertebrate neuromuscular junction, predominantly acts as a neuromodulator in the vertebrate CNS, even when activating ionotropic receptors [101–103]. GABA$_A$ receptors, which mediate fast postsynaptic inhibitory responses and fast

presynaptic inhibition [104], are often found in non-synaptic membrane, where they respond to low-concentration tonic GABA signals [104–106][107]. Even AMPA receptors, the ubiquitous mediators of fast glutamatergic transmission in the brain, have recently been shown to have presynaptic neuromodulatory actions [4••]. Apart from presynaptic effects, modulation of axonal excitability through ionotropic receptors can also have a substantial influence on action potential generation and propagation [108,109••].

Although the neuromodulation of ion channel properties has been best described in terms of acute effects, there is evidence that neuromodulators are also involved in long-term modifications of ion channels [110]. The removal of endogenous modulators from STG neurons is known to affect both the expression and the co-regulation of ion channels [111,112]. These modifications depend on both translation [113•] and transcription [114•]. Similarly, disruption of aminergic modulation in spinalized animals drastically increases the sensitivity of spinal interneurons to modulators [115] and enables motor neurons to recover persistent Ca^{2+} currents as amine receptors become constitutively active [6,7•].

From cellular and synaptic properties to circuit function

The modulation of neural circuits depends on the type, location and temporal dynamics of neuromodulator release [116]. The examples discussed above show that even a single neuromodulator can have complex effects on ion channels in each cell and on the strength and dynamics of synapses and, therefore, its effect on circuit output is not straightforward.

Changes in excitability are not always unequivocal. In the simplest case, a neuron's firing response to presynaptic activity increases or decreases. Consequently, the divergent effects of a neuromodulator on multiple ion channels or synaptic parameters become intuitive if the changes are additive or synergistic; for example, enhanced excitability due to decreased outward currents and increased inward currents, as seen for 5-HT modulation of many motor neurons [117]. However, electrical activity in most neurons is nonlinear, giving rise to a repertoire of membrane behaviors, including post-inhibitory rebound, plateau potentials, bistability, resonance and endogenous bursting. For such neurons, translating changes in synaptic strength and excitability to a firing rate is too simplistic. In this context, neuromodulation fine tunes specific nonlinear response properties and activity patterns [118] (Fig. 2b). For example, some neurons in the rhythmically-active STG respond to dopamine with an increase in a subset of both inward and outward currents and a decrease in others, and effects on pre-and postsynaptic parameters can be functionally opposing. Additionally, dopamine changes the synaptic strength and dynamics in these circuits [87].

Such fine-tuning clearly implies that neuromodulatory effects can only really be understood in the context of how neurons are activated and how they function within a circuit, which is a nontrivial task. Although some computational studies have examined the role of neuromodulation on synaptic or neuronal properties [119,120], there are few modeling studies that explore the integrative role of neuromodulators on network output [121–123]. A full description of neuromodulatory actions requires a new generation of theoretical and computational models [124] that take into consideration the dynamic short- and long-term actions of neuromodulators on their multiple targets.

Summary and conclusions

Neuromodulators target ion channels and synaptic interactions to modify circuit dynamics, which allows for adaptability of circuit operation in different behavioral contexts. Synaptic modulation is not limited to changes in the strength of connections, but involves modifications of short- and long-term synaptic plasticity. Similarly, neuromodulation of intrinsic excitability is not limited to simple amplification or reduction of responsiveness to input, but can shape the nonlinear interactions between different currents to give rise to qualitatively different membrane behaviors. A single modulator can control multiple aspects of synaptic and intrinsic dynamics in a single neuron, and multiple modulators can affect these properties through converging and diverging intracellular pathways. The complexity of cell-type specific effects, their highly nonlinear dynamics, as well as the fact that multiple neuromodulators may act at the same time, presents a challenge in trying to understand consequences for circuit output. Even if much of the modulatory effects are described quantitatively in a given circuit, their functional synthesis will require new theoretical approaches and computational modeling.

Acknowledgments

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Highlights

- Modulation of synaptic strength can be through changes in short-term plasticity.

- Modulators can shape or induce long-term synaptic plasticity.

- Modulators can have spatially specific and divergent targets in single neurons.

- Modulators can change neuronal excitability qualitatively and nonlinearly.

- Classical ionotropic receptors can exert unambiguously modulatory effects.
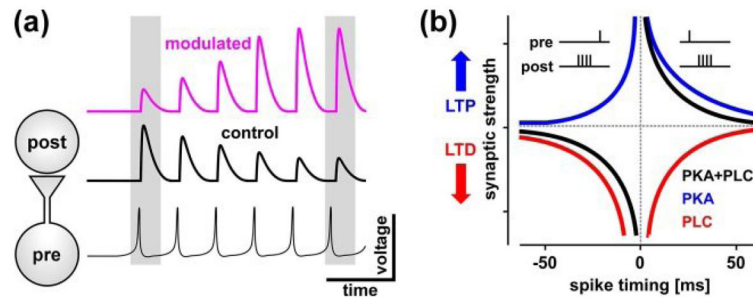
Figure 1.

Neuromodulation of short- and long-term synaptic plasticity. **(a)** Neuromodulators can target synaptic strength, which modifies the response to a single presynaptic input (left gray box), as well as short-term synaptic plasticity, which modifies the synaptic efficacy in response to sustained input (right gray box). These two effects can be functionally opposite. **(b)** The LTP and LTD components of STDP are controlled by modulators. Normally, the relative timing of pre- and postsynaptic spikes determines the direction of the modification in synaptic strength. However, activation of the PKA pathway promotes LTP and activation of the PLC pathway promotes LTD, independent of the relative spike timing. Each suppresses the other, producing a push-pull rule for the control of STDP. Panel modified from [23].
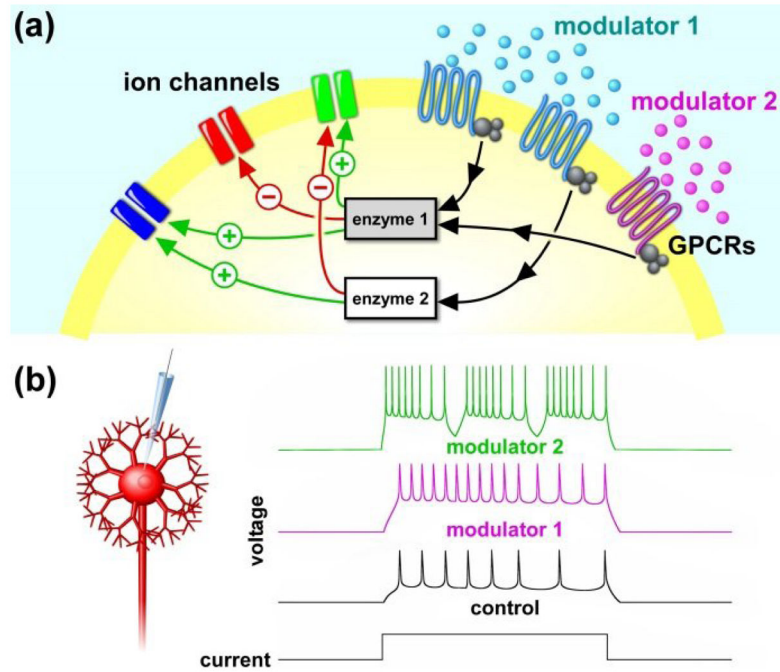
Figure 2.
Neuromodulation of ion channels and membrane excitability. **(a)** Even in a single cell, neuromodulators can have convergent or divergent actions. Different modulators can converge on the same intracellular pathway to target the same or different ion channel types. Conversely, one modulator may activate different intracellular pathways depending on receptor type. **(b)** The modulatory effect on excitability may be straightforward (modulator 1) or change the membrane properties qualitatively in a nonlinear fashion (modulator 2).