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Microcircuits Special Feature

Tuning the network: modulation of neuronal microcircuits in the spinal cord and hippocampus

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Adaptation of an organism to its changing environment ultimately depends on the modification of neuronal activity. The dynamic interaction between cellular components within neuronal networks relies on fast synaptic interaction via ionotropic receptors. However, neuronal networks are also subject to modulation mediated by various metabotropic G-protein-coupled receptors that modify synaptic and neuronal function. Modulation increases the functional complexity of a network, because the same cellular components can produce different outputs depending on the behavioural state of the animal. This review, which is part of the *TINS Microcircuits Special Feature*, provides an overview of neuromodulation in two neuronal circuits that both produce oscillatory activity but differ fundamentally in function. Hippocampal circuits are compared with the spinal networks generating locomotion, with a view to exploring common principles of neuromodulatory activity.

Introduction

For their dynamic action neuronal networks rely on chemical synaptic transmission and, in some cases, electrical signalling via gap junctions. Fast synaptic transmission occurs via ionotropic glutamate, glycine and GABA receptors, which are ligand-gated ion channels. In addition, two of the fast transmitters (GABA and glutamate) act on G-protein-coupled metabotropic receptors and exert actions that can last between minutes and hours. Whereas fast synaptic transmission controls whether a cell will discharge action potentials or be inhibited, the slower modulator actions are mediated by a great variety of metabotropic receptors that activate complex intracellular signalling pathways. Activation of these receptors ultimately affects different molecular targets such as ion channels, other receptors or long-term and short-term synaptic plasticity [1–5]. If a network that utilizes GABA and glutamate is turned on, these metabotropic receptor systems can be activated, provided that the appropriate presynaptic or postsynaptic receptors are available. In addition, metabotropic receptors can also be activated by ACh, 5-hydroxytryptamine (5-HT or serotonin), dopamine, noradrenaline and different neuropeptides.

The focus of this review is to explore the effects of neuromodulator systems on two different microcircuits*, both of which generate oscillatory activity, in a partially overlapping frequency range. We will compare the spinal networks generating locomotion (0.3–25.0 Hz) with the hippocampal networks generating theta (4–12 Hz) and gamma (30–80 Hz) frequency oscillations because these two networks have been studied in some detail and are reasonably well understood (Grillner et al., in this issue). We will show that despite having fundamentally different functions, these two networks are subject to similar modulation at the cellular level, often by the same neuromodulators.

Modulation and network activity

Spinal cord

Fast synaptic interactions via excitatory interneurons (releasing glutamate to activate AMPA and NMDA receptors) and inhibitory interneurons (releasing glycine) are responsible for the basic motor pattern in the spinal microcircuits generating vertebrate locomotor activity [1]. GABAergic interneurons in the spinal cord are not required for generating the locomotor activity because rhythmic activity persists when both $GABA_A$ and $GABA_B$ receptors are blocked. Networks in the spinal cord can generate locomotor activity in a frequency range that varies markedly with the species concerned. Such networks are referred to as central pattern generators (CPGs), and here we will focus on the lamprey CPG because it is the best understood among adult vertebrate CPGs. The frequency range of the lamprey CPG is 0.3–10.0 Hz. Modulation of neuronal properties in the spinal cord not only enables the system to adapt its output to relatively brief changes in the environment, but also provides the means for long-lasting changes in behaviour.

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* In this *TINS* special feature, the term 'microcircuit' is used to denote a minimal number of interacting neurons that can collectively produce a functional output, such as locomotor central pattern generators, hippocampal circuits producing gamma and theta rhythms, and circuits in the neocortex and cerebellum.

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Hippocampus

The hippocampus consists of ~90% glutamatergic pyramidal neurons and only ~10% GABAergic interneurons [6,7]. Pyramidal neurons provide chemical synaptic excitation to each other and to the interneurons, and can also be electrically coupled via axo-axonic gap junctions [8]. Interneurons form diverse groups, each with specific axonal projections, interconnections and neuropeptide content [6,7]. Different interneurons target distinct somatodendritic domains of pyramidal cells, and are thus positioned to control both the inputs to the pyramidal cell and its output in terms of action potential firing. One feature of hippocampal activity is the generation of different types of rhythmic synchronized activity, at a range of frequencies including theta (4–12 Hz), beta (15–30 Hz), gamma (30–80 Hz) and ultrafast (>80 Hz) [8,9]. Rhythmic network activity underlies several cognitive functions, including sensory processing and memory [8,9]. In contrast to the spinal cord, where GABA interneurons are not important in generating rhythmic activity, theta and gamma oscillations in the hippocampus depend on interactions between pyramidal cells [8,9] and specific subtypes of interneuron [10–13] (Grillner et al., in this issue). We will focus on theta and gamma oscillations in this review because we now have a reasonably good understanding of which interneuron subtypes contribute to these types of activity (Grillner et al., in this issue). Distinct groups of inhibitory cells express receptors for different neuromodulators [14–17], although each interneuron is controlled by multiple modulator systems [17]. Thus in the hippocampus, changing the activity of subsets of interneurons enables highly specific regulation of network function.

Modulation by glutamate

Metabotropic glutamate receptors, kainate receptors and endocannabinoids

The modulatory effects of glutamate are mediated by metabotropic glutamate receptors (mGluRs) in the spinal cord, and by mGluRs and metabotropic actions of kainate receptors in the hippocampus. Activation of mGluRs alters neuronal activity in both regions via several different mechanisms [18,4] (Tables 1 and 2). mGluR sequences are highly conserved across species, and most of the eight mGluR subtypes cloned in mammals are also found in non-mammalian vertebrates, including lampreys [18]. The eight subtypes can be classified into three groups: group I (mGluR1 and mGluR5 subtypes), group II (mGluR2 and mGluR3) and group III (mGluR4, mGluR6, mGluR7 and mGluR8). In both the hippocampus and the spinal cord, group I mGluRs are located on postsynaptic somatodendritic domains, whereas group II and group III mGluRs are predominantly located in the presynaptic membrane. Five kainate receptor subtypes are present in the hippocampus (Table 2). In both the spinal cord and hippocampus, endocannabinoid effects are mediated by the CB_1 receptor.

Spinal cord

Modulation of the lamprey spinal locomotor network by mGluRs involves activation of both presynaptic and postsynaptic receptors. Paired intracellular recordings have demonstrated the colocalization presynaptically of two pharmacologically distinct types of mGluR, corresponding to Group II and III, on the same reticulospinal axons [18,19]. These receptors mediate presynaptic inhibition of glutamate release through mechanisms that are independent of an effect on Ca^{2+} entry. These receptors also inhibit synaptic transmission between sensory neurons and network interneurons; thus, presynaptic inhibition by mGluRs serves as a form of autoinhibition. mGluRs can be activated by spillover of glutamate from neighbouring synapses, so a high level of activity at the same synapse or adjacent synapses could lead to depression of transmission at reticulospinal synapses.

The two subtypes of group I mGluRs (mGluR1 and mGluR5) are located postsynaptically. They are activated by endogenously released glutamate and produce opposite effects on the frequency of the locomotor rhythm, with mGluR1 activation increasing the burst frequency and mGluR5 activation decreasing it. At the cellular level, mGluR5 activation induces release of Ca^{2+} from internal stores, resulting in oscillations of intracellular Ca^{2+} levels [20]. The increase in the frequency of the locomotor

Table 1. Neuromodulation in the lamprey spinal cord[a]

Neuromodulator or receptor	Presynaptic gating	Ca_V3 (LVA)	$Ca_V2.1$, $Ca_V2.2$ (HVA)	IP_3	SK1-K_{Ca}	K_{NA}	K^+	NMDA receptor	Network frequency
$GABA_B$ receptor	Inhibition	↓	↓	NR	↓*	0	NR	NR	↓
mGluR1	0	0	0	NR	NR	0	↓	↑	↑
mGluR5	0	0	0	Ca^{2+} osc.	NR	0	NR	NR	↓
mGluR groups II and III	Inhibition	NR	0	↑	NR	0	NR	NR	↓
$5HT_{1A}$ receptor	Inhibition	NR	↓	NR	↓*	0	NR	NR	↓
D2 dopamine receptor	Inhibition	↓	↓	NR	↓*	0	NR	NR	↓
Tachykinin	Facilitation	NR	NR	NR	↓*	NR	↓	↑	↑
Neuropeptide Y	Inhibition	NR	NR	NR	NR	NR	NR	NR	0
Somatostatin	NR	0	0	NR	0	NR	↑	NR	↓
Neurotensin	NR	0	0	NR	0	NR	NR	NR	↑

[a]A summary of results from several studies (see also main text). The effects of different transmitters and receptors on different targets are listed. The presynaptic actions can be targeted to sensory afferents, excitatory or inhibitory interneurons and descending reticulospinal axons [44,54], and different transmitters have selective actions on different presynaptic cellular targets. The locomotor network modulates phasically, in each cycle, the synaptic transmission from sensory afferents and interneurons. For modulation of low-voltage-activated (LVA) Ca^{2+} channels (Ca_V3), high-voltage-activated (HVA) Ca^{2+} channels [$Ca_V2.1$ (N-type) and $Ca_V2.2$ (P/Q type)], actions mediated by inositol 1,4,5-trisphosphate (IP_3), the Ca^{2+}-sensitive K^+ channel K_{Ca} (SK1), other K^+ channels and NMDA receptors, a downward arrow indicates depression and an upward arrow indicates facilitation [75–82]. For the effects on K_{Ca} channels, the asterisk indicates that the decrease caused by the different agonists is indirect and due to reduced Ca^{2+} entry. Again, the effects can be specific to particular cell types. Finally, effects on the network level have been studied on the background of locomotor activity (arrows relate to locomotion burst frequency) and in related modelling experiments [83–85]. 0 indicates no effect. Additional abbreviations: NR, not reported; osc., oscillations.

Table 2. Neuromodulation in the hippocampus[a]

Receptor	Pyramidal cells	Interneurons
$GABA_B$ receptor [5]	↑ K^+ conductance (postsynaptic); slow IPSP ↓ Ca^{2+} conductance (presynaptic); ↓ glutamate release	Same effects as on pyramidal cells
Kainate receptors (GluR5–7, KA1–2)	↑ Presynaptic Ca^{2+}; ↑ glutamate release ↓ sAHP	↓ GABA release; axon depolarization
mGluRs [4,15,27]	Mainly ↓ I_M, I_{AHP}, N-type Ca^{2+} Net ↑ excitability	↓ I_{APH}
CB_1 endocannabinoid receptor [38,39,41]	No effect	CB_1 ↓ GABA release
mAChRs [56]	M1 and M3 subtypes ↑ I_h, I_{CAT}; ↓ I_M, I_{AHP}, I_{Kleak}	M2 and M4 subtypes; mostly depolarizing M2 ↓ GABA release
α1, α2, β1 and β2 adrenoceptors [16,17]	β ↓ sAHP; ↓ spike frequency adaptation ↑ Excitability	α ↓ K conductance; β ↑ I_h Net ↑excitability
$5HT_1$, $5HT_2$, $5HT_4$, $5HT_6$, and $5HT_7$ [70]	$5HT_{1A}$ hyperpolarizes – ↓ I_h $5HT_4$ ↑ I_h ↓ I_{AHP} $5HT_7$ ↑ I_h	$5HT_2$ is excitatory ↑ GABA release $5HT_1$ is inhibitory
D1-like dopamine receptor (D1, D5)	D1 ↓ I_{AHP}	? ↓ GABA release
D2-like dopamine receptor (D2, D3, D4) [69]	D1 ↓ Na^+ current	? Depolarize

[a]Some of the main neuromodulators and the receptor subtypes mediating metabotropic effects are listed, along with the main effects on pyramidal cells and interneurons. Upward arrows indicate increases and downward arrows indicate decreases in channel or neuronal activity. Key references are indicated. Abbreviations: I_{AHP}, afterhyperpolarization current; I_{CAT}, cation current; I_h, hyperpolarization-activated current; I_M, M current.

rhythm was initially thought to be mediated solely by two postsynaptic actions of mGluR: (i) by an interaction with NMDA receptors that increased their inward current and the associated Ca^{2+} influx [21], and (ii) by blocking a leak conductance resulting in depolarization of spinal cord neurons [22]. However, recently it has been shown that mGluR1 activation also induces release of endocannabinoids (Figure 1) from neurons of the locomotor network. These endocannabinoids act as a retrograde messenger to depress inhibitory synaptic transmission that controls left–right alternation during locomotion [23], further contributing to the increase in the locomotor frequency induced by mGluR1 activation. The glutamate released in each cycle will activate ionotropic receptors, and the concomitant mGluR1 activation will further boost the depolarization of neurons by enhancing the NMDA current and blocking leak channels. At the same time, it will reduce the efficacy of the inhibitory synaptic inputs by inducing a retrograde release of endocannabinoids. The net effect will be depression of inhibitory inputs to network neurons via retrograde signalling, to ensure that the excitatory effect of mGluR1 prevails at the cellular and network levels.

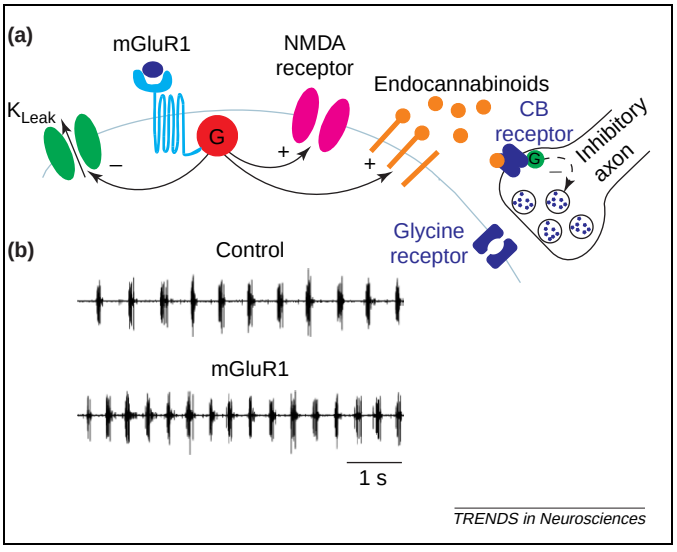

Figure 1. Mechanisms of mGlurR1-mediated modulation of the spinal locomotor circuitry. **(a)** mGluR1 activation inhibits K^+ leak channels and potentiates NMDA-receptor-mediated currents. In addition, it induces release of endocannabinoids, which act as retrograde messengers, activating presynaptic cannabinoid (CB) receptors to depress glycine-mediated inhibition of synaptic transmission, which is responsible for the left–right alternation during locomotion. These cellular effects lead to an increase in the locomotion burst frequency **(b)**.

Hippocampus

Activation of mGluRs in the hippocampus by glutamate diffusion from the synaptic cleft has a range of effects [4] on neuronal excitability (Table 2), and it is implicated in plasticity and the generation and modulation of synchronized network activity. As in the spinal cord, expression of mGluR subtypes is highly delineated in the hippocampus [24,25] and the effect of mGluR activation varies across cell types. Interneurons in stratum oriens and the alveus that project to stratum lacunosum moleculare, the oriens lacunosum moleculare (O–LM) cells (Figure 2a), have large group I mGluR responses (Figure 2b) and express both mGluR1 and mGluR5. By contrast, other interneurons in stratum oriens that innervate the soma and proximal dendrites of pyramidal cells, including basket cells, have smaller responses and express only mGluR5 [26]. This differential expression of mGluRs could alter the excitatory input these interneuron subtypes receive, and modulate their activity during different patterns of rhythmic activity. A further delineation is seen with expression of mGluR7 receptors in presynaptic glutamatergic terminals – these receptors are preferentially located at synapses onto hippocampal interneurons rather at synapses onto pyramidal cells [25], and thus provide target-specific plasticity and bidirectional control of feed-forward inhibition [27]. More mGluRs have been found at pyramidal-to-O–LM cell connections than at pyramidal-to-basket cell connections, and this might contribute to the short-term plasticity seen in O–LM cells (Silberberg et al. in this issue). Recently, a Hebbian form of long-term potentiation has been observed in oriens–alveus interneurons [28] that depends on mGluR1a activation, and could alter the flow of information into the hippocampus from the entorhinal cortex. In addition, mGluR activation

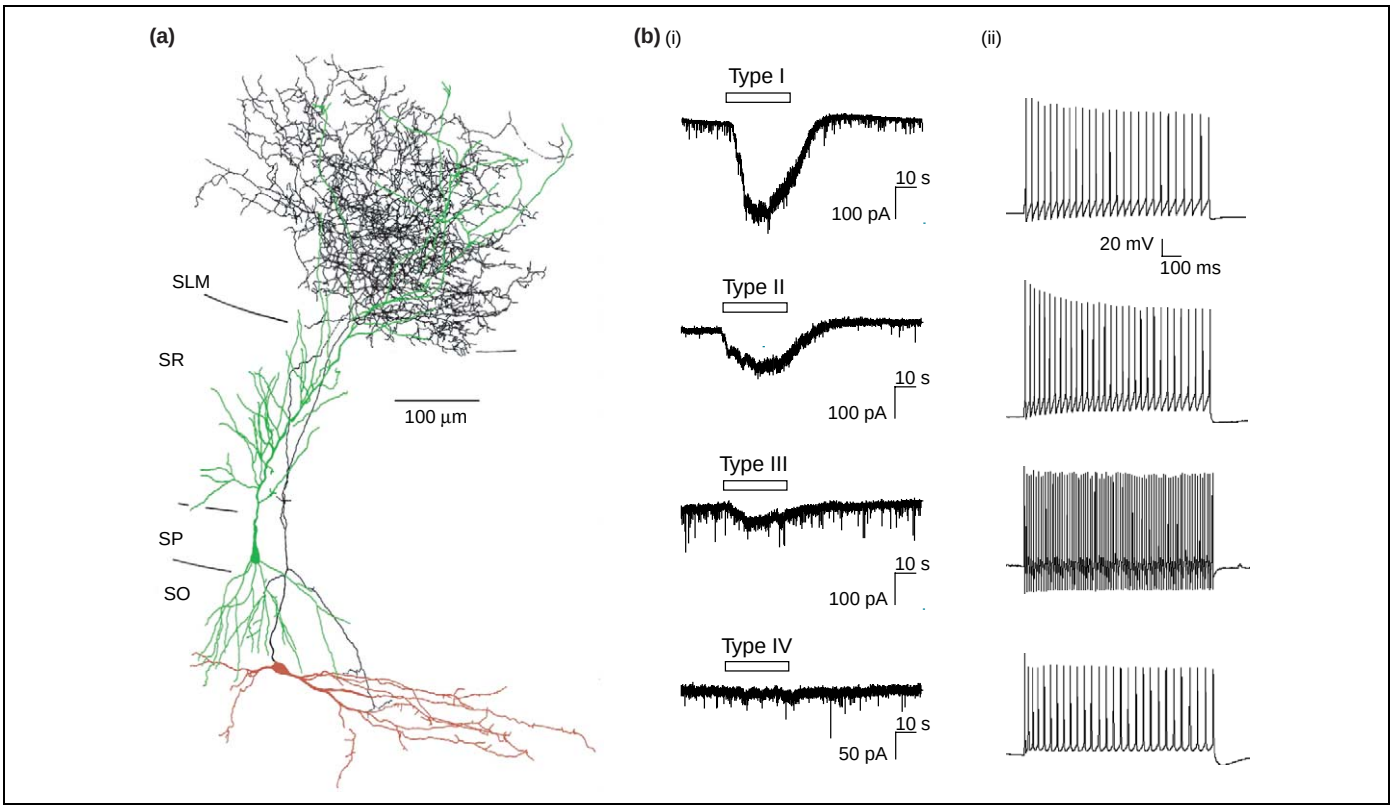

Figure 2. Effects of metabotropic receptor activation on hippocampal interneurons. **(a)** Reconstruction of a pyramidal cell and an O–LM interneuron in the CA1 subfield of the hippocampus. The cell body and horizontal dendrites (red) are located in stratum oriens (SO). The axons (black) of the O–LM cell traverse stratum pyramidale (SP) and stratum radiatum (SR) to arborize extensively in stratum lacunosum moleculare (SLM). The pyramidal cell (green) soma lies in the stratum pyramidale, its basal dendrites project to the stratum oriens and its apical dendrites project into stratum radiatum and stratum lacunosum moleculare, where they overlap with the axonal terminal zone of the O–LM cell. **(b)** Hippocampal interneurons exhibited different responses to local application (white bar) of the non-selective mGluR agonist *trans*-(1S,3R)-1-aminocyclopentane-1,3-dicarboxylic acid (ACPD; 100 μM). ACPD evoked inward currents (i) and action potential firing induced by 150 pA current injection for 1 s in the four different types of interneurons (ii). The magnitude of the inward current varied in different interneurons that are classified as types I–IV. All ACPD-induced currents were recorded in the presence of 1 μM tetrodotoxin. Panel (a) modified and reproduced, with permission, from [86]; (b) modified and reproduced, with permission, from [26].

of interneurons leads to the generation of synchronized network activity that might contribute to plastic changes in the network. Both gamma-frequency and theta-frequency (Figure 3a) activity have been seen following mGluR activation *in vitro* [29,30] and *in vivo* [31].

Glutamate can also activate metabotropic responses from kainate receptors, resulting in suppression of the post-spike afterhyperpolarization (sAHP) [32]. Low concentrations of kainate (<300 nM) are sufficient to trigger gamma-frequency activity in the hippocampus *in vitro* [8,33]. However, we will not consider kainate receptors further, and their role is discussed elsewhere [33,34]

As in the spinal cord, activation of group I mGluRs causes release of endocannabinoids in the hippocampus [35] (Figure 3b) that has been implicated in synaptic plasticity [36]. Endocannabinoids, released following depolarization of pyramidal cells, act retrogradely to suppress GABA release [37,38]. This depolarization-induced suppression of inhibition (DSI) is mediated via CB_1 receptors [38], which are expressed only at a specific subset of interneurons that express the neuropeptide cholecystokinin (CCK) [39]. Generally, large increases in intracellular Ca^{2+} are required for endocannabinoid release, limiting the circumstances in which this modulation can occur [40]. However, persistently active cannabinoid receptors can effectively silence a subset of hippocampal interneurons in the CA3 region [41].

Modulation by GABA

The transient and specific release of GABA following a presynaptic action potential gives rise to phasic inhibition via ionotropic $GABA_A$ receptors. However, GABA also exerts a neuromodulatory effect via metabotropic $GABA_B$ receptors in both the spinal cord and the hippocampus (Tables 1 and 2).

Spinal cord

Although, as already discussed, GABA interneurons are not essential for locomotor rhythm generation *per se*, they are active and have a powerful effect because they markedly reduce the burst frequency of locomotor activity. Blockade of either $GABA_A$ or $GABA_B$ receptors increases the rate of locomotor activity, and the effects are additive in that blockade of both receptor subtypes enhances the effect further [42]. The GABA effects are exerted at several levels. First, the terminals of presynaptic inhibitory and excitatory interneurons are subject to phasic presynaptic inhibition due to action of both $GABA_A$ and $GABA_B$ receptors in phase with the ipsilateral burst activity [43]. This action reduces both the excitatory and inhibitory drive to motoneurons, so the synaptic interaction within the pool of excitatory interneurons will be less efficient. Second, there are GABA-mediated effects at the somato-dendritic level, where $GABA_B$ receptors reduce Ca^{2+} entry via both high-voltage-activated Ca^{2+} channels

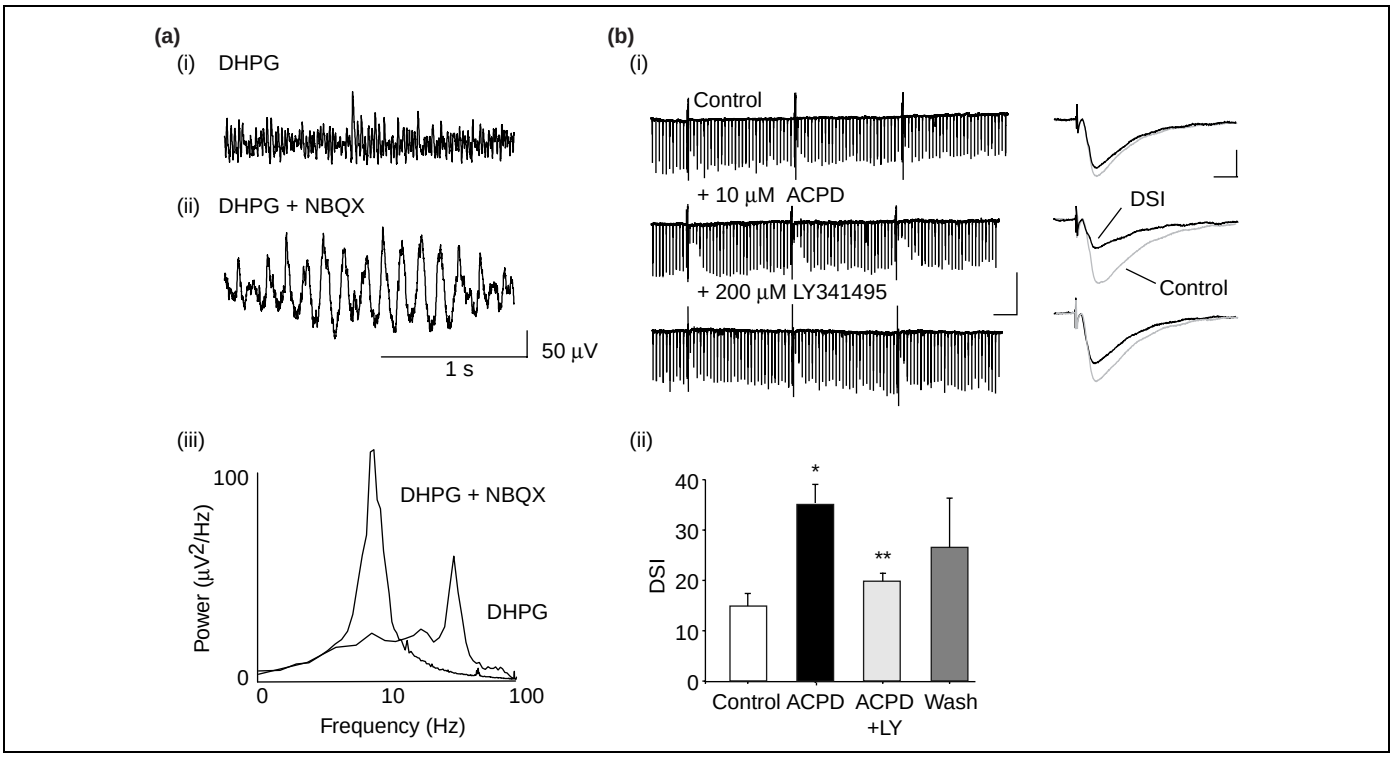

Figure 3. Effects of metabotropic receptor activation on hippocampal network oscillations and depolarization-induced suppression of inhibition (DSI). **(a)** Extracellular field recordings from stratum pyramidale in the CA1 region of a hippocampal slice. (i) Bath application of the group 1 mGluR agonist (S)-3,5-dihydroxyphenylglycine (DHPG, 20–200 μM) induces a gamma-frequency (~40 Hz) oscillation in area CA1. (ii) Subsequent blockade of AMPA and kainate receptors using 1,2,3,4-tetrahydro-6-nitro-2,3-dioxo-benzo[f]quinoxaline-7-sulfonamide (NBQX) abolished the gamma activity and reveals a theta-frequency (~7Hz) oscillation. (iii) Power spectra show that blockade of AMPA and kainate receptors abolished the gamma-frequency oscillation and unmasked a theta-frequency oscillation. **(b)** (i) Sample traces show evoked inhibitory postsynaptic currents (IPSCs) recorded in voltage-clamp mode from CA1 pyramidal cells in the presence of blockers of fast glutamate-mediated neurotransmission. Three 1–3 s voltage steps to 0 mV (longer upward bar) induced a small suppression of the IPSC a few seconds after the step in control conditions – the DSI. Following bath application of the broad group I mGluR agonist ACPD (10 μM), DSI is enhanced with a larger, longer-lasting suppression of the IPSC following each depolarizing step. The enhanced DSI is blocked by the group I mGluR antagonist LY341495. Scale bar, 500 pA and 20 s. Mean traces show evoked IPSCs for the corresponding conditions: the thin line shows the average IPSC before the depolarizing step and the thick line shows the average IPSC afterwards. Scale bar, 300 pA and 30 ms. (ii) Group data show percentage reduction in IPSC amplitude (DSI). There is significant enhancement of DSI by ACPD, and this is blocked by LY341495 (LY). Single asterisk denotes significant difference from control values; double asterisks denotes significant difference compared with values in the previous treatment. Panel (a) modified and reproduced, with permission, from [29]; (b) modified and reproduced with permission from [35].

($Ca_v2.1$ and $Ca_v2.2$), and low-voltage-activated Ca^{2+} channels (Ca_v3). This will reduce the slow afterhyperpolarization following the action potential due to K_{Ca} channels (SK 1) and result in less spike-frequency adaptation, leading to longer bursts. Thus, the presynaptic and postsynaptic actions of the GABA system produce complementary effects. GABAergic bipolar interneurons in the dorsal horn act on the terminals of sensory neurons mediating touch and pressure [44]. They provide phasic presynaptic inhibition of these terminals, and co-stored neuropeptide Y (NPY) provides an additive and more long-lasting effect than that of $GABA_B$ activation alone [45]. NPY is presumably released when the interneurons are strongly activated.

Hippocampus

As in the spinal cord, $GABA_B$ receptors are present both presynaptically and postsynaptically at synapses between pyramidal cells and interneurons in the hippocampus, and activation of $GABA_B$ receptors modulates synaptic neurotransmission and plasticity [5] (Table 2). Differential localization of $GABA_B$ labelling between interneuron classes has demonstrated a high level of expression in interneurons expressing CCK and somatostatin, but not in parvalbumin-positive basket cells [46]. The highest level of $GABA_B$ receptor expression is in the stratum lacunosum moleculare, in the distal dendritic region of pyramidal cells where the perforant path and thalamic inputs terminate [46]. Recently this high level of expression was found to be predominantly postsynaptic [47] and to correspond to electrophysiological data suggesting that the $GABA_B$ receptor contributes significantly to the perforant path sAHP but not the Schaffer collateral sAHP [48]. Despite the high level of expression of $GABA_B$ receptors, functional activation is rarely detected following GABA release from a single interneuron [49]; rather, activation requires simultaneous excitation of many interneurons, as occurs during theta activity [9]. *In vitro* $GABA_B$-receptor blockade increased the frequency of the theta oscillation recorded [50] and prolonged transient gamma-frequency activity [30].

Modulation by neuropeptides

Several different neuropeptides are present in the spinal cord and hippocampus including substance P, CCK, NPY, vasoactive intestinal polypeptide (VIP), somatostatin and neurotensin. In the spinal cord, substance P has been studied in some detail and has been shown to have a long-lasting action, enhancing burst frequency through several different actions. The effects of substance P include

depression of contralateral inhibition and potentiation of the NMDA component of glutamate-mediated fast synaptic transmission [51]. Tonic substance P release contributes to an increase in burst frequency during locomotion. CCK and NPY provide presynaptic depression of glutamatergic synaptic transmission [52]. In the hippocampus, little is known about the detailed effects of these neuropeptides, or the conditions under which they are released. As in the spinal cord, NPY inhibits glutamate release [53], whereas most of the other neuropeptides increase the excitability of different subsets of interneurons [54]. The co-release of a neuropeptide modulator, often at higher levels of activity, can thus provide a long-lasting action on synaptic signalling in both the spinal cord and the hippocampus.

Modulation by ACh, 5-HT and catecholamines

Network activity in both the spinal cord and the hippocampus is modulated by systems arising from several subcortical nuclei, such as the 5-HT, noradrenaline, dopamine and ACh systems. Although there are differences between the two microcircuits, all of the neuromodulators in both networks act at multiple receptor subtypes and have a wide range of cellular effects (Tables 1 and 2). Importantly, individual cellular components in both the spinal cord and the hippocampus can be influenced by multiple modulator systems (Figure 4a). Because each of these extrinsic inputs is activated during specific behavioural states, the activity within any network can be modulated in a behaviourally relevant manner both transiently and in the long term.

ACh in the spinal cord

In the lamprey, activation of nicotinic ACh receptors (nAChR) and muscarinic ACh receptors (mAChR) both contribute to the level of burst frequency [55]. In the *Xenopus* tadpole, ionotropic nAChRs also contribute to the overall excitation, responding preferentially to release of ACh from motoneuron collaterals [56].

ACh in the hippocampus

Activation of cholinergic inputs to the hippocampus generates a range of rhythmic activities, including theta and gamma oscillations, and is important in synaptic plasticity [57]. mAChRs (of M1–M4 subtypes) show a specific distribution, with M1 and M3 receptors mainly expressed in pyramidal cells, whereas M2 and M4 receptors are expressed in interneurons [58]. One type of hippocampal theta activity recorded *in vivo* is abolished by the mAChR antagonist atropine [9], and mAChR activation *in vitro* evokes intrinsic theta-frequency oscillations in O–LM interneurons [59] that can synchronize pyramidal cell activity [57]. Activation of mAChRs triggers gamma-frequency oscillations in the hippocampus *in vitro* [60] that require the activation of postsynaptic M1 receptors [61], resulting in membrane depolarization of pyramidal cells. The depolarization was proposed to occur through increases in the hyperpolarization-activated current (I_h) and a Ca^{2+}-dependent non-specific cation current (I_{CAN}) [61], although in a separate study using mGluR activation to evoke gamma oscillations [29], I_h did not contribute to the activity. In mice lacking the M1 receptor, the non-selective mAChR agonist muscarine failed to induce a gamma-frequency oscillation [61] although, importantly,

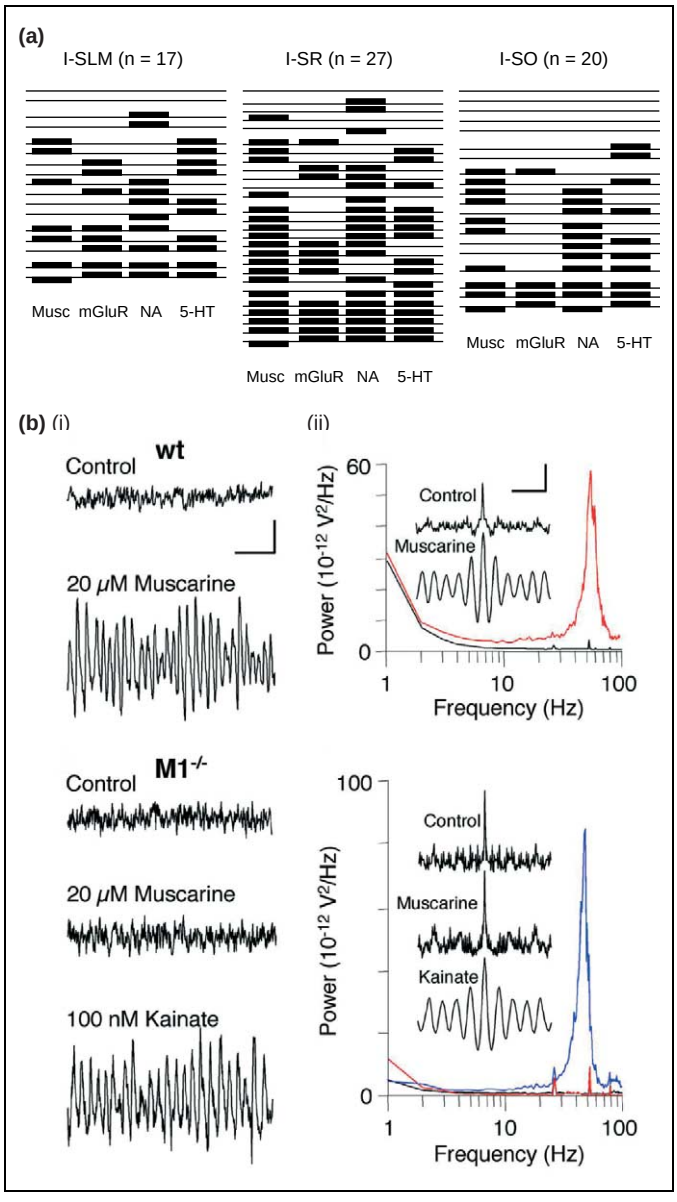

Figure 4. Cellular and network effects of extrinsic neuromodulators in the hippocampus. **(a)** Inhibitory cell responses to neurotransmitter agonists are represented as a bar code with each horizontal line corresponding to a different cell. A bar above the line represents excitation, one below inhibition and no bar indicates no effect. Interneurons are separated according to their location: in the stratum lacunosum moleculare (I-SLM), in the stratum radiatum (I-SR), or in the stratum oriens (I-SO). Drugs tested were the mAChR agonist muscarine (Musc), the group 1 mGluR receptor agonist ACPD (mGluR), noradrenaline (NA) and 5-HT. Each interneuron was tested with all four neuromodulators. The majority of interneurons in all strata were excited by the neuromodulators, but some diversity of responses was observed. Many interneurons responded to all four neuromodulators tested but with variable effects. **(b)** (i) Examples traces of extracellular field recordings in stratum pyramidale of the CA3 region in the hippocampal slice from a wild-type (wt) mouse and a knockout mouse lacking the M1 mAChR receptor subtype ($M1^{-/-}$). Scale bars, 50 μV and 100 ms. In slices from both wild-type and $M1^{-/-}$ mice, no oscillatory activity is seen in control (drug free) conditions. Application of the mAChR agonist muscarine (20 μM) to slices from wild-type mice evoked gamma-frequency activity. No gamma-frequency activity was seen in recordings from slices from $M1^{-/-}$ mice, although oscillations in the same slices could be evoked with bath application of kainate (100 nM). (ii) Corresponding power spectra and autocorrelations (insets) for control conditions (black), and after muscarine (red) and kainate (blue) application. Scale bar for inset, 0.5 and 50 ms. Panel (a) modified and reproduced, with permission, from [17]; (b) modified and reproduced, with permission, from [61].

gamma activity in hippocampal slices from these mice could still be evoked using kainate (Figure 4b). Thus, it is possible to generate the same (gamma-frequency) output from the network by the action of different modulators, which is consistent with recent findings that gamma activity evoked *in vitro* by mAChR and mGluR agonists can be differently modulated by exogenously applied agonists [62]. Several interneuron subtypes have now been identified that can contribute to the generation of gamma activity evoked by mAChR activation [12].

5-HT, dopamine and noradrenaline in the spinal cord

In the lamprey, as in most vertebrates, a set of 5-HT-releasing midline neurons form a dense plexus in which network interneurons extend their medial dendrites (Figure 5a). In fact, these neurons co-store 5-HT and dopamine, and a proportion of them also contain a substance-P-like neuropeptide. 5-HT-releasing neurons are turned on during fictive locomotion and are phasically active [1]. Because they activate metabotropic receptors (primarily 5-HT_{1A} in the lamprey), which have a long delay in exerting their action and a long-lasting action on their molecular targets, it is likely that the net effect is exerted tonically over several cycles. The 5-HT released during locomotion slows the burst rate, and makes the activity more regular and stable (Figure 5b). This action of 5-HT appears to apply to all vertebrate models tested, and is sometimes a precondition for regular fictive locomotion. Dopamine has a similar effect on locomotor activity.

5-HT and dopamine have complementary, but not identical, effects at the cellular level in that both act at Ca^{2+} channels (Figure 5d). 5-HT acts on N and P/Q Ca^{2+} channels ($Ca_v2.1$ and $Ca_v2.2$) and, in addition, dopamine modulates L-type (Ca_v1) channels. This action is exerted both presynaptically on glutamatergic terminals, leading to presynaptic inhibition, and postsynaptically, resulting in a reduced activation of K_{Ca} channels (i.e. an sAHP; Figure 5c), leading to reduced spike-frequency adaptation [63,64]. In addition, the inhibitory synaptic transmission from the contralateral side is potentiated in that the decline of inhibitory postsynaptic potential (IPSP) amplitude occurring during a spike train is reduced. These effects combine to reduce the burst frequency. In addition to the intraspinal 5-HT-releasing neurons present in many species, there is also a prominent descending contribution from the raphe nuclei. In adult rats the raphespinal projection is dominant, so that during locomotion these neurons are turned on and provide a tonic descending 5-HT drive to the spinal cord. 5-HT_2 receptors appear to contribute to these effects [65]. In turtles and mammals (rats and cats), prominent plateau potentials have been demonstrated in which 5-HT has an important role, through a facilitation of low-threshold L-channels (Ca_v1). This effect of 5-HT probably contributes to locomotor and postural stability.

In the lamprey there is no or little noradrenaline in the spinal cord, but in mammals there is a noradrenergic coeruleospinal projection that is activated from the locomotor command centres in the spinal cord and

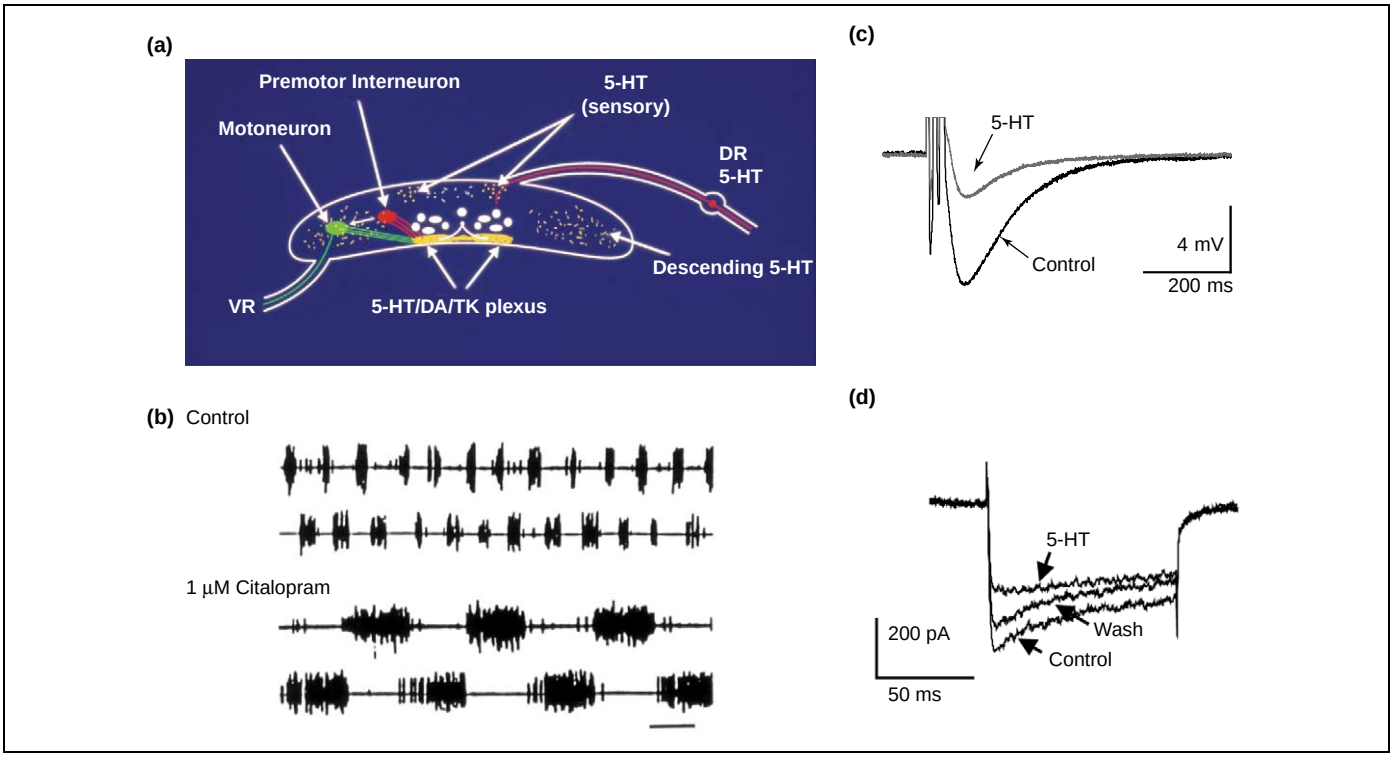

Figure 5. Modulation by 5-HT at the cellular and network levels. **(a)** Organization of the 5-HT innervation in the spinal cord of the lamprey with a focus on the intraspinal network that forms a dense plexus, in which all network interneurons distribute their medial dendrites. These network interneurons also store and release dopamine (DA), and some also express tachykinins (TK; substance-P-like peptides). **(b)** Rhythmic locomotor burst activity recorded in two opposing ventral roots in the isolated lamprey spinal cord. The lower record shows the effect of enhancing the extracellular level of endogenously released 5-HT, by administering the 5-HT uptake blocker citalopram. Scale bar, 1 s. **(c)** Effect of 5-HT on the afterhyperpolarization (due to K_{Ca}) following the action potential. It is reduced because of 5-HT-induced depression of the Ca^{2+} current **(d)**. Abbreviations: DR, dorsal root; VR, ventral root.

enhances the excitability of the locomotor CPG. Noradrenaline precursors or agonists such as clonidine can induce activity in spinal-cord-transected mammals on a treadmill.

Noradrenaline, 5-HT and dopamine in the hippocampus

The noradrenaline system is important in attention, arousal and novelty detection [66]. Stimulation of the locus coeruleus to activate noradrenergic inputs *in vivo* produces a predominantly inhibitory effect on pyramidal cell activity [66]. Noradrenaline acts at both α and β adrenoceptors with different effects (Table 2). β-Adrenoceptor activation is predominantly associated with enhanced memory and synaptic plasticity, whereas α-adrenoceptors can induce long-term depression of synaptic transmission [67]. Noradrenaline predominantly excites interneurons (Figure 4a) in all hippocampal strata [17], and this effect is due to α-adrenoceptor-mediated depolarization of interneurons [16]. Activation of the locus coeruleus *in vivo* evokes theta activity in the hippocampus [66] and, recently, was shown to reduce the activity of feedforward interneurons in the dentate gyrus [68]; this reduction was accompanied by an increase in hippocampal theta activity but a decrease in beta and gamma frequencies. It was proposed that this decreased inhibition would increase the signal detection of novel events because concomitant excitatory inputs would be enhanced, and the increased theta activity could be associated with synaptic plasticity. These data suggest that noradrenaline can differentially modulate different network oscillations, perhaps reflecting activation of distinct subtypes of interneurons with specific receptor expression profiles.

Dopamine and 5-HT are also important neuromodulators of hippocampal activity [69,70], and functionally exert excitatory or inhibitory effects on hippocampal neurons depending on which receptor subtypes are activated (Table 2). However, their effects on rhythmic network activity are not well understood. At the network level, inhibition of 5-HT-releasing neurons that project from the raphe nucleus to the hippocampus leads to an increase in theta activity in the hippocampus [71]. In the hippocampus there is a high level of the dopamine D4 receptor in interneurons in the stratum oriens [72], and in other cortical areas D4 receptor activation has been shown to be a powerful modulator of GABA transmission [73]. This raises the possibility that dopamine could affect rhythmic activity, and one study *in vitro* has reported that dopamine reduced gamma-frequency activity, although that effect was mediated via D1 receptors [74].

Concluding remarks

Despite the marked difference in function between hippocampal microcircuits generating theta and gamma rhythms and the spinal CPGs of the lamprey, both networks are subject to similar neuromodulation. The presynaptic and postsynaptic actions of the different classes of mGluRs are organized in a similar fashion. For example, the postsynaptic action of mGluR activation is depolarizing in both networks. In the locomotor CPG, mGluR1 produces three complementary effects: enhancement of the NMDA current, reduction of a leak current, and reduction of the inhibitory input through a retrograde endocannabinoid action on the presynaptic inhibitory terminals. In the hippocampus, the mGluR1-mediated depolarization also enhances endocannabinoid release. $GABA_B$ receptor activity reduces the Ca^{2+} current both presynaptically and postsynaptically, and can also potentiate a K^+ current in both the spinal cord and the hippocampus. Also common to the locomotor CPG and hippocampal microcircuit is modulation of neuronal activity by several extrinsic systems (those of 5-HT, dopamine, noradrenaline and ACh). In both the spinal cord and hippocampus all of these neuromodulators reduce Ca^{2+} current in the somatodendritic membrane and thereby reduce the sAHP due to K_{Ca}. Because this sAHP component is a major factor controlling neuronal action potential frequency in the spinal cord and hippocampus, its reduction would be expected to have a profound effect on discharge rate, burst intensity and/or burst frequency.

We now have a fairly detailed knowledge of the cellular effects of many of these different modulators, and how they modify activity at the microcircuit level. It thus appears that the different subtypes of modulator and receptor systems discussed here can be considered as building blocks that are used to exert similar cellular effects in microcircuits with widely varying function. However, the actual effect of each neuromodulator on the output of the network can be markedly different, and depends on the distributions of receptors across the cellular components of the network. We now need to learn under which behavioural contexts the different modulator systems are turned on. This will probably require chronic recordings of modulator neurons in animals during different patterns of behaviour. The different modulator systems targeting different structures such as the hippocampus and the spinal cord are, however, evolutionarily well conserved, suggesting that their roles in adapting behaviour might also be conserved.

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