Neuromodulation of Hippocampal Cells and Circuits

J. Josh Lawrence and Stuart Cobb

Abstract The hippocampus is a major brain centre for information processing, where subcortical neuromodulatory circuits interface with intrinsic learning circuits to assign salience to sensory information relevant to behavioural state. Glutamatergic principal cells (PCs) of the dentate gyrus (DG), CA3 and CA1 regions comprise the classic trisynaptic circuit, which compare patterns of incoming sensory stimuli with internal representations, enabling the detection of novelty. Within the trisynaptic circuitry, distinct feedforward and feedback inhibitory circuits spatiotemporally constrain the timing of PC excitability, which, together with disinhibitory circuits, synchronize PC ensembles to generate network rhythms. Neuromodulation alters network rhythms and synaptic plasticity by releasing neurotransmitters and neuropeptides onto diverse receptor subtypes, often expressed in a cell type- and circuit-specific manner. Moreover, extrinsic neuromodulation can induce the secondary release of intrinsic neuromodulators. For each neurotransmitter system, we review the structural organization and target specificity of afferent innervation, receptor subtype distribution and, where known, their functional effects on hippocampal cells and circuits. Despite the complexity involved and evident gaps in scientific knowledge, general principles of neuromodulation are emerging. With the development of next-generation technologies, the vision of understanding how neuromodulatory mechanisms engage circuit elements to regulate hippocampal memory encoding and recall is coming into sharper focus.

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Overview

Neuromodulation is the processes by which the properties of neurons and synapses are altered by neuroactive substances termed neuromodulators. The distinction between neuromodulation and classical neurotransmission can be fuzzy, but, in general, neuromodulation is more diffuse and less targeted and acts over a longer time course than classical fast neurotransmission. Often the same neurochemical may have rapid neurotransmitter-like effects followed by more sustained modulator-like actions. What makes neuromodulation an important consideration is that it appears to be a fundamental process in modifying all aspects of neural network functioning and information processing. Neural networks are not hard-wired, but plastic, and the neuromodulation of its components yields distinct activity patterns that are associated with behavioural state, allowing the same neural circuit to have added computational power. These components include the modification of neuronal excitability, integrative properties of neurons, synaptic transmission and synaptic plasticity. Neuromodulators often have more than one cellular or synaptic consequence. Moreover, not all cellular or synaptic targets of neuromodulation produce the same effects. Due the omnipotent control of the user over parameter space, computational modelling is a powerful tool for gaining insight into how cellular and synaptic targets of neuromodulation alter the functional output of neuronal populations and the processing of synaptic signals within networks. Beyond the acute effects of neuromodulation on cellular and synaptic excitability are longer-term changes in gene expression and neuronal architecture that are essential in regulating developmental processes and structural plasticity. This chapter circumscribes the acute cellular and synaptic effects of neuromodulation on cellular targets within the hippocampal formation. Whilst necessary to constrain the scope of this chapter, the multi-faceted parameter space involved in neuromodulation is so complex that it invites, if not demands, computational modelling to validate specific neuromodulatory mechanisms at work.

The Data

Introduction

The hippocampus receives input from a multitude of neuromodulatory substances, the release of which is often associated with external factors or dependent upon particular behavioural states. This chapter summarizes some of the primary neuromodulators including those that arise from sources extrinsic to the hippocampus (mainly subcortical nuclei) as well as those originating from cells intrinsic to the hippocampal formation. There may be important functional distinctions between intrinsic and extrinsic forms of neuromodulation (Katz and Frost 1996; Marder 2012) with the most obvious being that extrinsic neuromodulation is usually inde-

pendent of ongoing activity within the circuits being modulated, whereas cells or synapses undergoing intrinsic modulation often do so as a result of ongoing activity within those same circuits. However, the extensive reciprocal interconnectivity from the hippocampus to cortex (Melzer et al. 2012), hypothalamus (Jimenez et al. 2018) and subcortical neuromodulatory nuclei (Mattis et al. 2014; Yuan et al. 2017) makes this distinction somewhat superficial (Caputi et al. 2013). As discussed in earlier chapters, glutamate and GABA have multiple modes of action, which still provide important foundational principles upon which to understand other neurotransmitter systems. In addition to ligand-gated ion channels for rapid transmission, slower, often intrinsic neuromodulatory actions are also produced through metabotropic signalling. Many of the 'classical' neuromodulators presented here act in a similar manner and generally provide extrinsic neuromodulation as their sources of input are derived predominantly from subcortical nuclei. Although some modulators, such as acetylcholine and serotonin, appear to possess machinery for fast, point-to-point transmission, 'volume transmission', in which neurotransmitters are released at non-synaptic varicosities, diffuses to high-affinity metabotropic receptors and appears to be a major mode of transmission. It is possible, due to differences in the proximity of neuromodulatory release sites and postsynaptic composition of receptors, that specific cellular targets may employ point-to-point, volume or both modes of transmission. Along the lines of how views of GABAergic transmission have evolved (Farrant and Nusser 2005), one may view these modes of synaptic transmission along a continuum, in that any given hippocampal postsynaptic neuronal cell type may possess a different ratio of point-to-point and volume transmission. Furthermore, this ratio may change dynamically depending on firing frequency of the presynaptic neuromodulatory neurons, magnitude of the neurotransmitter concentration transient, short-term plasticity dynamics of neurotransmitter release, state of occupancy of postsynaptic receptors and neurotransmitter transporters and pooling in the extracellular space. Optogenetic strategies that allow for stimulation of specific neurochemically restricted synapse types are leading to a better understanding of the spatiotemporal dynamics of synaptic neurotransmission (Lorincz and Adamantidis 2017). As with $GABA_A$ receptors, it may soon be possible to categorize neuromodulatory receptors as synaptic ('phasic'), perisynaptic ('spillover' or 'augmented transmission') and tonically active, high-affinity receptors (Farrant and Nusser 2005). Therefore, it is important to recognize that classic pharmacological manipulations, such as bath application of a fixed agonist concentration, may not necessarily mimic volume transmission. Indeed, it is increasingly likely that populations of 'extrasynaptic' receptors can be stimulated by bath application of exogenous agonists but are simply too far away from release sites to be activated by the spatiotemporal concentration transient of endogenous neurotransmitter release. Artificial, pathological or therapeutic interventions may dynamically alter spatiotemporal concentration transients, effectively redefining which neurotransmitter receptors can be classified as synaptic receptors. Whilst extrasynaptic receptors that are not normally activated under physiological circumstances may be considered irrelevant, or even confounding, in understanding synaptic transmission from a 'purist' biophysical perspective, their existence becomes important in understanding

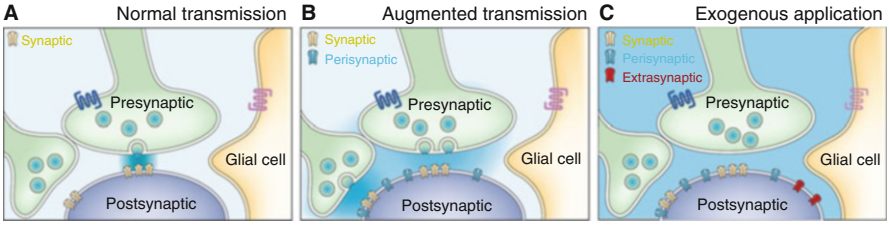

Fig. 1 Different types of neuromodulatory receptors. (**a**) Synaptic receptors (yellow) localized in the immediate vicinity of neurotransmitter release sites are activated. (**b**) Both perisynaptic (blue) and synaptic receptors are activated when multiple simultaneously active synaptic terminals induce 'spillover' from delayed neurotransmitter clearance or when neurotransmitter transport is compromised. (**c**) Exogenous application of neurotransmitter or a non-specific receptor agonist will activate synaptic, perisynaptic and extrasynaptic (red) receptors. In addition, if extrasynaptic receptors are tonically active, application of an antagonist will block these receptors. (Modified from Farrant et al. 2005, with permission)

roles that some neurotransmitters play in setting the 'tone' of transmission. Moreover, pharmacological and therapeutic interventions, such as the use of specific neurotransmitter receptor agonists, allosteric modulators and antagonists, may ultimately change cellular excitability by altering these extrasynaptic receptors. It is therefore important not only to understand how specific neuromodulatory afferents interact with their associated postsynaptic receptors but also to understand the receptor distribution on postsynaptic neurons independent of its relationship to the endogenous neurotransmitter (Fig. 1).

In addition to classical neuromodulatory transmitters, many neuropeptides exert effects in the hippocampus that originate from extrinsic sources, but also from local hippocampal circuits, to provide additional layers of intrinsic modulation. Other modulators including endocannabinoids and nitric oxide have an even more localized autocrine/paracrine modulatory action and are thought to mediate exclusively intrinsic modulation. In some cases, extrinsic neuromodulation by classical neurotransmitters induces secondary effects mediated by intrinsic modulation, as demonstrated by the capacity of metabotropic receptor activation or elevated intracellular calcium to induce release of endocannabinoids. However, whether the modulation is driven by extrinsic or intrinsic sources, the loci of action is an essential factor and can include modification of (1) the properties of presynaptic neurotransmitter release, (2) the modification of postsynaptic responsiveness/receptor signalling and/or (3) the modulation of the postsynaptic intrinsic electrical and biochemical properties or gene regulation. Understanding the overall actions of a neuromodulator that occur on multiple timescales is thus especially challenging. The challenge is even greater if one considers that receptors, intracellular signalling pathways and effectors all could be independently expressed in a cell type-specific manner. The most significant obstacle is that neuromodulators do not simply excite or inhibit neurons in the classical sense. Rather, they usually signal through intracellular messenger cascades to modulate not one but a range of effectors.

This may include the gating of ion channels that orchestrate the response to classical neurotransmitters. That is, they change the way neurons respond to signals arising from other neurons whether that be due to altered intrinsic properties of the receptive neuron or to altered postsynaptic responsiveness or as a result of altered properties of the presynaptic neuron such as action potential patterns and/or neurotransmitter release probability. As a consequence, what an experimenter sees following manipulation of neurotransmitter/modulator mechanisms depends upon how the cell or system is investigated. As pointed out by Surmeier (Surmeier 2007), different questions produce different answers!

Modulation of Intrinsic Properties

Neuromodulators can regulate a diverse range of ion channels and other effectors that modify the active and passive properties of hippocampal neurons. The excitability of cells can be altered in three different ways. (1) Neuromodulation can alter the resting membrane potential, in the form of depolarization or hyperpolarization. This action has several consequences. First, it will bring the cell closer or farther away from the threshold for action potential initiation. This makes a given excitatory synaptic input more or less effective. Secondly, alteration in the resting membrane potential may be associated with a different set of cellular conductances, which themselves could influence the intrinsic membrane properties of the neuron. (2) Neuromodulation also can directly alter the passive properties of the cell, including the cell input resistance and membrane time constant. This is done through neuromodulation of the conductances involved at a given resting potential, such as leak conductances or steady-state conductance. This effect changes the computational properties of the neuron. For example, an increase in the membrane time constant will broaden the excitatory postsynaptic potential (EPSP) so that fewer EPSPs are required to summate to action potential threshold. Another consequence of increasing the input resistance and membrane time constant is to alter the RC filtering characteristics of the cell, thereby impacting the ability of the cell to follow frequency-specific input. (3) Active conductances may also undergo neuromodulation. Depending on the kinetics of activation of the conductances modulated, the action potential waveform, various afterhyperpolarizing potentials and/or action potential discharge patterns are altered by neuromodulation. Some of these effects are summarized in Table 1 and described under the individual neuromodulator headings.

Different neuromodulatory substances often converge onto common effectors to produce similar actions. For example, activation of metabotropic $GABA_B$ receptors, adenosine A1 receptors and serotonin 5-HT_{1A} receptors in CA1 pyramidal cells all increase a common potassium conductance (Nicoll et al. 1990; Sodickson and Bean 1998), thereby providing several redundant and/or synergistic cellular mechanisms for reducing cellular excitability. However, whilst some generalizations may be made, the situation often is far more complex. As seen in the earlier chapters, different hippocampal neurons are endowed with different channels and

Table 1 Summary of key neuromodulator actions

Modulator	Pyramidal cells	postsynaptic	Interneurons	postsynaptic
		presynaptic		presynaptic
Acetylcholine	Depolarization, ↓adaptation, phasic inhibition ↑ I_h, I_{CAT}; ↓ I_M, I_{AHP}, I_{Kleak} (m), ↑$_{IK(Ca)}$		Depolarization, ↓adaptation or hyperpolarization (m / n) I_{CAT}; ↓ I_M, I_{AHP}, ↑ I_{Kir}	
	↓ glutamate release (m), ↑(n)		↓ GABA release (m), ↑ (n)	
Norepinephrine	↓ sAHP; ↓ adaptation (β)		↓K conductance (α); ↑ *I*h (β)	
Dopamine	Hyperpolarization, ↓adaptation, ↓AHP, ↓ Ca^{++} activated *I*k		ND	
	↓ glutamate release (most pathways), ↑ transmitter release (mossy fibers)		↓ GABA release (D_3)	
Serotonin	Hyperpolarization, ↓adaptation ↓I_h (5HT1A); ↑I_h, ↓I_{AHP} ($5HT_7$, $5HT_4$)		$5HT_2$ is excitatory	
	↓ glutamate release, ↓ induction of LTP		↑ GABA release ($5HT_{2+3}$)	
Histamine	Depolarization (dominant, H_2) or hyperpolarization (H_1)		Depolarization (H_2) ↓*I*Kv3.2	
	↓ glutamate release, direction action on NMDA receptors		ND	
Adenosine	Hyperpolarization (A_1, A_{2A}), ↑gK		ND	
	↓ glutamate release, ↓ induction of LTP		Little effect	
ATP	Fast inward current (P2X), ↑gK		ND	
	Contribute to fast EPSP/C (P2X), regulate LTP/LTD		ND	
Endocannabinoids	Modest depolarization, ↓I_M		Little effect	
	↓ glutamate release, DSE		↓ GABA release, DSI	
Nitric oxide	None		None	
	↑LTP		May contribute to DSI	
Neuropeptides	See table 7			

Arrows indicate direction of change. White and grey boxes represent postsynaptic and presynaptic actions, respectively (for more detail and other actions, see text below). Parentheses show receptor subtypes where known

Abbreviations: *ND* not determined, I_{AHP} afterhyperpolarization current, I_{CAT} cation current, I_h hyperpolarization-activated current, I_M M current

neurotransmitter receptor subtypes. For any given modulatory substance in any given cell, the exact channels modulated will depend upon the presence and spatial localization of particular subtype(s) of receptors, together with the presence and spatial localization of coupled ion channels and other effectors. Intracellular signalling is another major determinant of the response, and despite its ubiquity, studies suggest that signalling can be very specific and targeted to specific loci or subcellular compartments within a cell (Kulik et al. 2006; Shigemoto et al. 1996). Moreover, if release of calcium from internal stores is involved, the response will also depend on the history of action potential activity, since intracellular calcium stores can be depleted unless replenished through activation of voltage-gated calcium channels (Gulledge and Kawaguchi 2007; Gulledge et al. 2009). It is through calcium imaging (Grienberger and Konnerth 2012), voltage-sensitive dye imaging (Acker et al. 2011) and the introduction of molecular biosensors and other transduction processes (Sanford and Palmer 2017) that we are beginning to learn how modulation can be restricted to localized microdomains or compartments yet have profound effects on output.

Modulation of Excitatory Synaptic Transmission

The laminar structure of the hippocampal formation lends itself to the study of excitatory pathways. It has long been observed that a wide range of neuromodulatory substances can affect glutamatergic neurotransmission. Whilst many modulators have general actions across very many synapses, such as the suppressant actions of adenosine, others appear to have very precise synapse-specific actions. One of the best examples of synapse-specific effects is the suppression of transmission by activation of group II mGluRs at the mossy fibre (MF)-to-CA3 pyramidal cell synapse but not at Schaeffer collateral (SC) synapses onto the same neuron (Toth and McBain 1998, 2000) (see Chapter 3). Conversely, the same glutamatergic axon can generate different responses depending on the postsynaptic neuron subtype (Maccaferri et al. 1998; Toth and McBain 2000). These examples, amongst others, have made the concept of a generic glutamatergic synapse essentially obsolete. Several other examples of synapse-specific neuromodulation at different hippocampal glutamatergic synapses are illustrated in this chapter. Finally, neuromodulators are known to modulate synaptic plasticity, including activity-dependent changes in the efficacy of glutamatergic transmission, called long-term potentiation (LTP) and long-term depression (LTD).

Modulation of Inhibitory Synaptic Transmission

As described in earlier chapters, GABAergic cells and circuits show great diversity in terms of their neurochemistry, morphology, connectivity and expression of neurotransmitter receptors. Similarly, the neuromodulation of GABAergic circuits appears to be complex, yet general principles are emerging even as the number

of interneuron subtypes is growing. This stems in part from issues that arise from attempting to classify GABAergic interneurons into defined subtypes (Maccaferri and Lacaille 2003; Klausberger and Somogyi 2008; Petilla Interneuron Nomenclature Group et al. 2008). However, it is also complicated by the findings that application of the same neuromodulator to what are considered anatomically discrete cell types can often give rise to variable and unpredictable responses even when considering a simple question such as whether a modulator is excitatory or inhibitory (Parra et al. 1998; Widmer et al. 2006). From this muddle, some patterns are starting to emerge, and we are beginning to understand principles by which neurochemically and functionally distinct interneuron subtypes are differentially recruited, suppressed or modified in a coordinated manner to orchestrate the flow of information in hippocampal circuits (Lawrence 2008; Madison and McQuiston 2006). As has been shown in the neocortex (Bacci et al. 2005; Kawaguchi 1997; Porter et al. 1999; Xiang et al. 1998), one important factor is the neurochemical identity of the hippocampal interneuron subtype (Cea-del Rio et al. 2010; Freund and Katona 2007; Glickfeld et al. 2008; Glickfeld and Scanziani 2006; Lawrence 2008; Lawrence et al. 2006c; McQuiston 2014a). Synaptic plasticity, including LTP and LTD, can also occur in inhibitory circuits, which is dependent on neurochemical identity (Monday and Castillo 2017; Monday et al. 2018). Important clues to interneuron diversity have been revealed by investigating the lineage of interneuron subtypes (Kepecs and Fishell 2014; Rudy et al. 2011). Understanding exactly how the neuromodulatory specializations of each neurochemically distinct interneuron subtype contribute to the modulation of the frequency and magnitude of network oscillations continues to remain a major challenge.

'Classical' Modulators

Many of the classical modulators have an established role in mediating synaptic transmission/neuromodulation, and indeed their discovery as such significantly predates the discovery of glutamate and GABA as neurotransmitter substances. Despite this however, our knowledge of the precise action of classical modulators on hippocampal cells and circuits remains rather disjointed and incomplete. It is with acetylcholine that most progress towards a systematic understanding of its multitude of actions has been achieved and we therefore start with a detailed account of the current state of knowledge with this system. Thereafter, we provide an overview of other classical neuromodulators, highlighting their key features as well as the significant gaps in our current knowledge.

Acetylcholine

Acetylcholine (ACh) is a key neuromodulator that plays a key role in arousal (Jones 2004; Lee et al. 2005), attention (Sarter et al. 2005), assigning salience (Hangya et al. 2015; Raza et al. 2017), spatial navigation (Dannenberg et al. 2016) and learning (Dannenberg et al. 2017; Haam and Yakel 2017; Hasselmo 2006). Cholinergically induced oscillatory activity in the hippocampus (Dannenberg et al. 2015; Vandecasteele et al. 2014) correlates with these behavioural states (Lee et al. 1994). Despite major advances in understanding the cell type-specific (Cobb and Davies 2005; Lawrence 2008; McQuiston 2014a) and subcellular (Lawrence et al. 2015; Szabo et al. 2010) targets of cholinergic modulation, large knowledge gaps remain at cellular and synaptic levels. Although some insights have been gained through computational modelling (Hummos and Nair 2017), knowledge gaps still exist in understanding how cholinergic neuromodulation coordinates the activation of diverse hippocampal circuit elements to give rise to large-scale cholinergically induced population-level oscillatory dynamics (Vijayaraghavan and Sharma 2015). However, the recent discovery of the role of astrocytes in the cholinergic modulation of hippocampal dentate granule cells (Pabst et al. 2016) suggests that the inventory of circuit elements capable of undergoing cholinergic modulation is not even complete.

Origin and Structural Organization of Cholinergic Afferents

The medial septum/diagonal band of Broca (MS-DBB) provides the major source of cholinergic innervation to the hippocampus (Dutar et al. 1995; Gielow and Zaborszky 2017; Lucas-Meunier et al. 2003; Swanson et al. 1987; Woolf 1991) and presents a direct synaptic input to both principal neurones and interneurons (Deller et al. 1999; Frotscher and Leranth 1985; Leranth and Frotscher 1987). The MS-DBB also contains septohippocampal GABAergic (Freund 1989; Freund and Antal 1988; Toth et al. 1997) and glutamatergic (Huh et al. 2010) projection neurons, which serve distinct but complementary roles in cognition (Dannenberg et al. 2015; Muller and Remy 2017). MS-DBB cholinergic neurons are rhythmically active during waking and quiescent during sleep (Lee et al. 2005). Cholinergic axons ramify extensively throughout all regions of the hippocampal formation and in all layers (Aznavour et al. 2002; Aznavour et al. 2005; Leranth and Frotscher 1987). At the ultrastructural level, a significant proportion of cholinergic boutons are not associated with distinct postsynaptic specializations (Vizi and Kiss 1998; Vizi et al. 2004). These observations support two forms of cholinergic transmission: precise synaptic transmission, involving highly localized ACh transients onto low-affinity nAChRs, and volume-mediated cholinergic transmission, where ACh is released into the extracellular space, diffusing to high-affinity receptors at some distance from the synaptic terminal (Vizi and Kiss 1998; Vizi et al. 2004).

A recent study has shown that GABA is co-released with ACh (Takacs et al. 2018), as has been shown at cortical neurons receiving input (Granger et al. 2016; Saunders et al. 2015). Whilst co-transmission of acetylcholine with other classical neurotransmitters, such as glutamate (Allen et al. 2006), also has not been shown directly, MS-DBB cholinergic neurons appear to possess the appropriate cellular machinery for co-release of glutamate or GABA with acetylcholine (Sotty et al. 2003; Takacs et al. 2018).

Laminar and Target Specificity of Cholinergic Afferents

The effects of ACh on hippocampal function first commence with where ACh is released, which relates to the specific pattern of cholinergic afferent innervation in the hippocampus. There are differences in the pattern of innervation across DG, CA3 and CA1, as well as within specific layers (termed lamina). Stratum oriens and stratum pyramidale receive a higher density of cholinergic terminals than in other layers (Aznavour et al. 2002). In addition to this laminar specificity, there are several lines of evidence that suggest that cholinergic septohippocampal fibres preferentially target specific hippocampal cell types. Given that nAChRs cluster under cholinergic terminals (Zago et al. 2006), it is possible that a high expression level of postsynaptic nAChRs may indicate a higher level of cholinergic terminal contacts relative to interneuron subtypes associated with lower nAChR expression. Consistent with this idea, we recently used a statistical approach to demonstrate that the density of cholinergic terminals onto hippocampal GAD65-GFP inhibitory neurons is non-random, implying synaptic targeting mechanisms at work (Smith et al. 2015). In the dentate gyrus, cholinergic afferents appear to exhibit some target selectivity, preferentially innervating NPY- over PV-containing neurons (Dougherty and Milner 1999). Moreover, using vesicular acetylcholine transporter (vAChT) labelling in combination with anterograde labelling of basal forebrain afferents, Jones and colleagues found that cholinergic terminals more closely appose calbindin-positive than PV-positive interneurons (Henny and Jones 2008). These observations are consistent with the demonstration of fast α7 nAChR-mediated synaptic responses in stratum radiatum (SR) interneurons (Alkondon et al. 1998; Chang and Fischbach 2006; Frazier et al. 1998a, b), which likely correspond to CCK-/CB-positive interneurons. Several studies have confirmed that electrical stimulation can evoke α7 nAChR-mediated synaptic responses (Alkondon et al. 1998; Chang and Fischbach 2006; Frazier et al. 1998a, b). Recent optogenetic experiments also have shown that α7 nAChR-mediated synaptic responses can be evoked, but it is more rarely observed than through electrical stimulation (McQuiston 2014b), raising the question as to whether α7 nAChRs are truly synaptically localized (Bell et al. 2011; Bell et al. 2015a; McQuiston 2014a). Finally, cholinergic afferents may target precise spatial locations relative to other afferents. The overlap of cholinergic and GABAergic terminal specializations (Henny and Jones 2008; Zago et al. 2006), combined with the demonstrated crosstalk between nAChRs and $GABA_A$ receptors

(Wanaverbecq et al. 2007; Zhang and Berg 2007), suggests that cholinergic afferents target GABAergic synapses.

Intrinsic Cholinergic Interneurons of the Hippocampus

In addition to the extrinsic cholinergic input, the hippocampus possesses a numerically sparse population of cholinergic interneurons (Frotscher et al. 1986, 2000). Recent studies have used transgenic mouse technology to visualize cholinergic circuit elements by driving expression of fluorescent proteins under the control of the choline acetyltransferase (ChAT) promoter, encountering populations of fluorescently labelled hippocampal neurons (Blusztajn and Rinnofner 2016; Grybko et al. 2011; von Engelhardt et al. 2007; Yi et al. 2015). Monyer and colleagues recorded from ChAT-GFP cells in the neocortex (von Engelhardt et al. 2007). Although evoked nicotinic EPSPs onto postsynaptic targets were not observed, a modest enhancement in spontaneous glutamatergic transmission was detected, suggesting that ACh release from these neurons may spill over to presynaptic nAChRs located on glutamatergic terminals (von Engelhardt et al. 2007). In the cortex, ChAT-GFP cells co-express VIP (von Engelhardt et al. 2007) and possess a high density of nAChRs (Porter et al. 1999), raising the possibility that ACh itself may promote cortical ACh release through a feedforward excitatory cholinergic circuit (Tricoire and Cea-Del Rio 2007). In a recent study in the hippocampus, only a minority of ChAT-GFP or ChAT-CRE/YFP cells expressed VIP but were excited by ACh (Yi et al. 2015). Optogenetic stimulation of ChAT-CRE cells in the hippocampus surprisingly evoked a glutamatergic synaptic current, which may be attributable to a special class of CA3 pyramidal cells that either ectopically or developmentally express ChAT (Yi et al. 2015). ChAT-GFP and ChAT-CRE/YFP cells also were encountered in CA1 (Yi et al. 2015), consistent with earlier studies (Frotscher et al. 2000). However, the unambiguous determination of the neurotransmitter phenotype of ChAT-GFP cells in CA1 awaits future studies.

Acetylcholine Receptors

To complement their rich cholinergic input, hippocampal neurons express a broad range of acetylcholine receptors (Buckley et al. 1988; Lebois et al. 2017; Levey 1996; Levey et al. 1995; Rouse et al. 1999). Cholinergic neuromodulation has complex effects on both glutamatergic and GABAergic neurons in the hippocampus, which occur by the binding of ACh to ionotropic nicotinic receptors (nAChR) and metabotropic muscarinic receptors (mAChRs) at pre- and postsynaptic locations (Cobb and Davies 2005; Dannenberg et al. 2017; Giocomo and Hasselmo 2007). Many of the effects are mediated through metabotropic muscarinic acetylcholine receptors (mAChRs, M1-5). Early studies suggested M1 and M3 receptor proteins being mainly expressed in principal neurones and M2 and M4 receptors predominantly expressed on interneurons (Levey et al. 1995). Within glutamatergic circuits

of the hippocampal formation, there is extreme variability in mAChR immunoreactivity between subfields and laminae (Rouse et al. 1999). The termination zones of the perforant path differentially express presynaptic M2, M3 and M4 receptors.

The septohippocampal pathway is also thought to activate nicotinic acetylcholine receptors (nAChRs). The exact expression of nAChR subunits with respect to the afferent cholinergic input is not fully established, but binding studies suggest that populations of interneurons that are suspected to receive direct septohippocampal innervation bind the nAChR ligand α-bungarotoxin (Freedman et al. 1993), implying the expression of α7 nAChRs. Immunocytochemical studies have demonstrated the α7 AChR subunit to be highly expressed across multiple cell types and multiple cellular and synaptic compartments, including somata, dendrites, spines, axon fibres, glutamatergic axon terminals and GABAergic axon terminals (Fabian-Fine et al. 2001).

Action of Acetylcholine on Intrinsic Properties of Hippocampal Neurones

Pyramidal Cells

ACh has been known for many years to excite hippocampal pyramidal cells (Cobb and Davies 2005; Cole and Nicoll 1983, 1984a, b; Dodd et al. 1981), and the ionic basis of such effects has now been elucidated in some detail. Through mAChRs, ACh is known to modulate a large number of conductances and second messenger cascades in pyramidal neurones. These include I_M, the Kv7/KCNQ-mediated K^+ current; I_{AHP}, the slow Ca^{2+}-activated K^+ current responsible for the slowing of action potential discharges; I_{leak}, the ohmic leak current responsible in large part for the resting membrane potential (Halliwell and Adams 1982; Madison et al. 1987; Halliwell 1990); and I_{Kir}, an inwardly rectifying potassium conductance (Seeger and Alzheimer 2001). mAChR activation also potentiates two mixed cation currents (I_h, the hyperpolarization-activated non-specific cation current; I_{cat}, Ca^{2+}-dependent non-specific cation current) (Brown and Adams 1980; Colino and Halliwell 1993; Fisahn et al. 2002; Halliwell and Adams 1982) as well as modulates a voltage-dependent Ca^{2+} current (Toselli et al. 1989). The action of exogenously applied ACh on hippocampal pyramidal cells is that of a pronounced membrane potential depolarization and increase in cell membrane resistance (Cole and Nicoll 1984a, b; Fraser and MacVicar 1996). Through mAChR knockout mice (Dasari and Gulledge 2011; Fisahn et al. 2002) and pharmacological manipulation (Thorn et al. 2017), M1 mAChRs are largely responsible for ACh effects on the intrinsic excitability of hippocampal pyramidal cells (Dennis et al. 2016). Puff application of mAChR agonists to soma/proximal dendritic regions of principal cells induces a transient hyperpolarization caused by mAChR-induced release of calcium from internal stores, which then activates Ca^{2+}-dependent SK channels (a component of I_{AHP}) (Dasari and Gulledge 2011; Dasari et al. 2017; Gulledge and Kawaguchi 2007). Using electrical stimulation of cholinergic afferents, Power and Sah demonstrated

that synaptic activation of mAChRs leads to propagating calcium signals within the somatodendritic axis of pyramidal cells (Power and Sah 2002).

Despite difficulties in interpreting nAChR pharmacology from early studies using cultured hippocampal neurones, in acute native tissues, pharmacological activation of nAChRs is generally reported to produce either no a or barely detectable response in principal cells (Frazier et al. 1998a, b; McQuiston and Madison 1999c; Reece and Schwartzkroin 1991). There are some reports that nAChRs are detected postsynaptically in principal cells (Hefft et al. 1999) where they facilitate the induction of LTP (Ge and Dani 2005; Gu and Yakel 2011) through enhanced cellular excitability (Szabo et al. 2008). However, with the hippocampal circuit intact, the effect may be minor, since bath application of nicotine reduces the excitability of pyramidal cells through activation of non-desensitizing α2-containing nAChR-containing O-LM interneurons (Jia et al. 2009).

Inhibitory Neurons

In the majority of GABAergic interneurons, pharmacological activation of mAChRs results in a similar membrane depolarization to that seen in pyramidal cells but with a less prominent change in cell input resistance (Lawrence et al. 2006c; McQuiston and Madison 1999a, b; Parra et al. 1998), confirming earlier studies (Benardo and Prince 1982a; Benardo and Prince 1982b, e; Reece and Schwartzkroin 1991). GABAergic interneurons represent a highly heterogeneous population of neurone with respect to their connectivity and neurochemistry (Freund and Buzsaki 1996; Klausberger and Somogyi 2008), and there is wide variation in their response to activation of mAChRs compared to that seen in the relatively homogeneous population of principal neurones (McQuiston and Madison 1999a; Parra et al. 1998; Widmer et al. 2006). In contrast to the slow sustained mAChR-mediated modulation of both pyramidal cells and interneurons, activation of nAChRs produces a more transient response. Similar to neocortical interneurons (Couey et al. 2007; Gulledge and Kawaguchi 2007; Porter et al. 1999; Xiang et al. 1998), there is evidence for cell type specificity in postsynaptic expression of nAChRs in hippocampal interneurons (Bell et al. 2015a).

Oriens-Lacunosum Moleculare (O-LM) Cells

O-LM cells exhibit a highly reproducible response to bath application of acetylcholine, mAChR agonist or nAChR agonist activation (Jia et al. 2009; Lawrence et al. 2006c), similar to neocortical Martinotti cells, another somatostatin-positive interneuron subtype (Fanselow et al. 2008; Kawaguchi 1997). When induced to fire in the presence of mAChR agonists, O-LM cells exhibit an acceleration in firing frequency that is accompanied by a prominent suprathreshold afterdepolarization (ADP) (Lawrence et al. 2006c; McQuiston and Madison 1999b). The ADP, mediated by M1/M3 mAChR activation, is associated with the activation of a non-selective cationic current (I_{CAT}) and the inhibition of both M- (I_M) and

slow afterhyperpolarization K+ currents (I_{AHP}) (Lawrence et al. 2006c). mAChR modulation of O-LM cells enhances their intrinsic oscillatory properties to theta-specific input (Lawrence et al. 2006a), which is mimicked by inhibition of I_M (Lawrence et al. 2006b) and a shift in the voltage dependence of HCN channels in O-LM multicompartmental models (Lawrence 2008; Lawrence et al. 2006b; Sekulic and Skinner 2017). In vivo, pirenzepine-sensitive activation of calcium signalling in O-LM cells by MS-DBB cholinergic afferents occurs during fear learning (Lovett-Barron et al. 2014) via a mechanism consistent with M1/M3 mAChR activation (Lawrence et al. 2006c).

In stratum oriens (SO), a mixed fast α7-mediated and slow non-α7 nAChR-mediated response is consistently observed in oriens-lacunosum moleculare (O-LM) cells (Alkondon et al. 1998; Buhler and Dunwiddie 2001; McQuiston and Madison 1999c). O-LM cells exist as two distinct subpopulations, a PV-positive, 5-HT_3 receptor-lacking population derived from the medial ganglionic eminence (MGE) and a PV-lacking, 5-HT_3R-expressing population derived from the caudal ganglionic eminence (CGE) (Chittajallu et al. 2013). Both populations express α7 nAChRs. O-LM cells that express α2 nAChRs (Jia et al. 2009; Leao et al. 2012; Mikulovic et al. 2015) lack PV and are therefore most likely derived from CGE. Cholinergic inputs onto α2 nAChR-expressing O-LM cells have been shown to evoke a nicotinic EPSC, which is blocked by α7-and non-α7 nAChR antagonists (Leao et al. 2012). Due to their non-desensitizing response upon activation with nicotine, α2 nAChRs may play a role in the activation of O-LM cells by exogenous nicotine (Jia et al. 2009).

M2 mAChR-Positive Trilaminar Cells

There are populations of GABAergic interneuron in stratum oriens that are hyperpolarized in response to mAChR activation (Lawrence et al. 2006c; McQuiston and Madison 1999a; Parra et al. 1998). The neurochemical identity of ADP-lacking SO interneurons is less clear, but likely comprises M2 mAChR-expressing trilaminar cells (Ferraguti et al. 2005; Hajos et al. 1998; Klausberger 2009) and horizontally oriented PV+ BCs (Lawrence et al. 2006c; Maccaferri 2005; Widmer et al. 2006). Immunocytochemical studies showing that mGluR1a-positive and M2-positive SO interneurons are distinct cell types (Ferraguti et al. 2005), which likely correspond to O-LM and trilaminar cells (Gloveli et al. 2005), strengthen the evidence that SO interneuron subtypes possess a different complement of postsynaptic mAChRs. Trilaminar cells are CGE-derived (Craig and McBain 2015) and therefore are likely to possess both nAChR and 5-HT_3 receptors (Chittajallu et al. 2013). The most likely consequence of cholinergic activation in these cells is an initial hyperpolarization and reduction in cellular excitability (Lawrence et al. 2006c), possibly mediated through $G_{i/o}$-coupled M2 and/or M4 mAChRs (McQuiston and Madison 1999a; Seeger and Alzheimer 2001). It is also possible that a biphasic response could be generated, but it is not clear whether trilaminar cells possess G_q-coupled M1/M3 receptors that could mediate a late depolarizing response.

Parvalbumin-Positive (PV) Basket Cells

Fast-spiking basket cells, corresponding to PV BCs, do not express high levels of nAChRs in the neocortex (Gulledge and Kawaguchi 2007; Kawaguchi 1997; Xiang et al. 1998) or hippocampus (McQuiston and Madison 1999c; Buhler and Dunwiddie 2001) but do express mAChRs (van der Zee et al. 1991). With the use of transgenic mice that allows the visualization of PV interneuron circuits (Hippenmeyer et al. 2005; Kaiser et al. 2016), CA1 PV BCs can be specifically targeted (Cea-del Rio et al. 2010; Lawrence et al. 2015; Yi et al. 2014). In response to bath application of 10 μM muscarine, PV BCs strongly depolarize, increase in firing frequency and exhibit a loss of an afterhyperpolarization, all of which do not occur in PV BCs lacking the M1 mAChR subtype (Cea-del Rio et al. 2010; Yi et al. 2014). This depolarizing response profile is consistent with that observed previously in a subset of morphologically defined BCs (McQuiston and Madison 1999a; Widmer et al. 2006). Fast-spiking interneurons in the dentate gyrus, corresponding to PV BCs, also depolarize strongly to bath application of ACh or muscarine and are most likely mediated by M1 mAChRs (Chiang et al. 2010). Interneurons that are insensitive to nAChR activation are encountered predominantly in stratum pyramidale (SP) (McQuiston and Madison 1999a) and tend to be fast spiking, a hallmark of PV BCs (Buhler and Dunwiddie 2001).

Consistent with earlier experiments using electrical stimulation to evoke ACh release (Widmer et al. 2006), recent experiments using optogenetic stimulation of ACh release induce a range of atropine-sensitive response profiles in PV BCs, including depolarizing only, hyperpolarizing only and biphasic hyperpolarizing-depolarizing responses (Bell et al. 2013, 2015b; McQuiston 2014a). The hyperpolarizing response is likely mediated by activation of inward-rectifying potassium channels (McQuiston and Madison 1999a; Seeger and Alzheimer 2001) through $G_{i/o}$-coupled M2 (Hajos et al. 1998) and/or M4 mAChRs (Bell et al. 2013), whereas depolarization most likely occurs through G_q-coupled M1 mAChRs (Cea-del Rio et al. 2010; Yi et al. 2014). The capability of synaptically released ACh to activate different mAChR subtypes on PV BCs likely reflects differences in spatiotemporal dynamics of ACh release from cell to cell or possibly differences in synaptic localization of mAChR subtypes. PV BCs in CA1 (Lawrence et al. 2015) and CA3 (Szabo et al. 2010) also undergo presynaptic cholinergic modulation, which reduces synaptic depression. In a mathematical model of short-term synaptic depression, presynaptic cholinergic modulation can be explained by inhibition of presynaptic calcium channels (Lawrence et al. 2015; Stone et al. 2014) through presynaptic M2 and/or M4 mAChRs (Bell et al. 2013; Cea-del Rio et al. 2010; Hajos et al. 1998).

CCK-Positive Basket Cells

Cholinergic neuromodulation of CCK BCs was investigated with the use of a GAD65 GFP transgenic mouse line in which GFP is expressed in non-PV-positive cells (Cea-del Rio et al. 2010; Cea-del Rio et al. 2012; Daw et al. 2009; Lopez-Bendito et al. 2004). CCK BCs show characteristics of cholinergic neuromodulation

differently than PV BCs (Cea-del Rio et al. 2010; Cea-del Rio et al. 2012). First, a prominent mAChR-induced ADP is observed in these cells, with a time course slower than seen in O-LM cells, and is sometimes briefly interrupted by a mAChR-insensitive fast afterhyperpolarization (AHP) that occurs after the offset of a suprathreshold current step (Cea-del Rio et al. 2010). Hyperpolarization followed by depolarization is often observed, consistent with biphasic response profiles of a subset of basket cells reported previously (McQuiston and Madison 1999a; Widmer et al. 2006). This biphasic response is also seen upon optogenetic stimulation (Bell et al. 2013; McQuiston 2014a). One interesting feature of CCK BCs is that M3 mAChRs appear to control mAChR-induced changes in firing but both M1 and M3 mAChRs control the emergence of the mAChR-induced ADP (Cea-del Rio et al. 2010, 2012). Therefore, the expression of M3 mAChRs and its differential coupling to mAChR-sensitive conductances distinguishes CCK BCs from PV BCs (Cea-del Rio et al. 2010, 2012).

There are two types of CCK BCs, identified based on their expression of vasoactive intestinal peptide (VIP) or vesicular glutamate transporter 3 (vGluT3) (Klausberger and Somogyi 2008). VIP-containing CCK BCs are consistently depolarized upon optogenetic stimulation of ACh release (Bell et al. 2015b), consistent with the relative absence of M2/M4 mAChRs on CCK BCs (Freund and Katona 2007). This observation reinforces the existence of principles governing cell type-specific cholinergic neuromodulation in the hippocampus (Lawrence 2008; Madison and McQuiston 2006; McQuiston 2014a). Consistent with a higher sensitivity of CCK BCs than PV BCs to mAChR stimulation (Cea-del Rio et al. 2010, 2012), inhibitory postsynaptic currents evoked by optogenetic ACh release are sensitive to depolarization-induced suppression of inhibition (DSI), a mechanism mediated by endocannabinoids acting at presynaptic CB1 receptors on CCK interneurons (Nagode et al. 2011; Alger et al. 2014).

CCK is highly co-localized with α7 nAChR mRNA transcripts (Morales et al. 2008) and protein (Freedman et al. 1993). In this context, SR interneurons, which likely comprise CCK interneuron subtypes, exhibit only fast, presumably α7-mediated responses upon puff application of ACh (McQuiston and Madison 1999c), suggesting cell type specificity of nAChR receptor subtypes compared relatively to additional nAChR subtypes found in O-LM interneurons. However, optogenetically evoked ACh responses mediated solely by α7 nAChRs are rare (McQuiston 2014b).

CCK-Positive Schaeffer Collateral-Associated (SCA) Interneurons

CCK SCA interneurons are similar to CCK BCs in that they exhibit a similar mAChR-induced ADP (Cea-del Rio et al. 2010; Cea-del Rio et al. 2011; Cea-del Rio et al. 2012). The presence of M4 mAChR mRNA transcripts in a subset of CCK SCA and CCK BCs (Cea-del Rio et al. 2010, 2011, 2012) may explain the often biphasic hyperpolarizing-depolarizing phenotype of the mAChR-mediated response in CCK SCA cells, observed with bath application of mAChR agonists (Parra et al. 1998; Cea-del Rio et al. 2011, 2012), electrical stimulation (Widmer et al. 2006) and optogenetic stimulation (Bell et al. 2013). The M4-positive allosteric modulator

potentiates the hyperpolarizing component of the biphasic response, consistent with expression of M4 mAChRs on these cells (Bell et al. 2013), in contrast to the absence of a hyperpolarizing component onto VIP CCK BC subtypes (Bell et al. 2015b). mAChR activation boosted its response to oscillatory input in CCK SCAs (Cea-del Rio et al. 2011, 2012). Like CCK BCs, this cell type is likely to be modulated by endocannabinoids through presynaptic CB1 receptors (Nagode et al. 2011; Alger et al. 2014) and therefore unlikely to possess presynaptic M2/M4 receptors, as presynaptic CB1 and M2/M4 receptors are thought to be from mutually exclusive presynaptic terminal populations (Freund and Katona 2007; Armstrong and Soltesz 2012).

CCK-Positive Perforant Path-Associated (PPA) Interneurons

Although likely comprising more than one neurochemically distinct interneuron population (Freund and Buzsaki 1996; Bowser and Khakh 2004; Klausberger 2009), interneurons located at the stratum radiatum/stratum lacunosum moleculare (SR/SLM) border are depolarized by mAChR activation and exhibit intrinsic subthreshold membrane potential oscillations (Chapman and Lacaille 1999a, b). Approximately half of these interneurons exhibit a mAChR-induced transient hyperpolarization that precedes mAChR-induced depolarization (Chapman and Lacaille 1999a), similar to responses observed in CCK BCs and CCK SCAs (Cea-del Rio et al. 2010, 2011, 2012). There are likely common cellular mechanisms across CCK interneuron subtypes; M2/M4 mAChRs mediate the transient hyperpolarizing response, whilst M1/M3 mAChRs mediate the late depolarizing response (Cea-del Rio et al. 2010, 2011, 2012; Bell et al. 2013, 2015b).

SR/SLM interneuron populations also express functional nAChRs (Reece and Schwartzkroin 1991; Jones and Yakel 1997; McQuiston and Madison 1999c). Activation typically induces brief depolarization or inward current which tends to desensitize rapidly. The kinetics and pharmacology of the response vary, but fast depolarization by α7 subunit-containing nAChRs is the predominant response seen in interneurons. The nAChRs expressed on SR/SLM interneurons can also be synaptically activated (Frazier et al. 1998a). Unlike agonist-activated responses, optogenetically activated nAChRs are rarely mediated by α7 subunit-containing nAChRs (Bell et al. 2011; McQuiston 2014b). The reason for this discrepancy is unclear.

VIP/Calretinin-Expressing Interneuron-Selective Interneurons

VIP- and calretinin-expressing neurons form local 'disinhibition circuits', interneuron subtypes that are specialized to inhibit other inhibitory neurons (Acsady et al. 1996a; Francavilla et al. 2015; Tyan et al. 2014). These cells are negative for M2 mAChRs (Tyan et al. 2014). A recent study by McQuiston and colleagues found that VIP-positive interneurons are synaptically activated by α4/β2-containing nAChRs (Bell et al. 2015a), consistent with the enrichment of nAChRs on VIP interneuron

subtypes in cortex (Porter et al. 1999). A subset of these VIP/calretinin interneurons co-express ChAT, which are excited by bath application of ACh (Yi et al. 2015).

Other Hippocampal Interneuron Subtypes

Since publication of the previous edition of this chapter, much knowledge has been gained, greatly increasing our understanding of cholinergic modulation of specific circuit elements and demonstrating general principles in cell type-specific cholinergic neuromodulation in the hippocampus (Lawrence 2008; Madison and McQuiston 2006; McQuiston 2014a). Despite these advances, of the 21 specific interneuron subtypes in the hippocampus (Klausberger and Somogyi 2008), cholinergic modulation has been systematically explored in only a third (8/21). Of the remaining subtypes to be explored, long-range GABAergic projection neurons, such as the hippocamposeptal (HS) neurons (Caputi et al. 2013; Mattis et al. 2014; Melzer et al. 2012) are a major class. Finally, the neurochemical identity of inhibitory interneurons that are totally nonresponsive to cholinergic neuromodulation, which apparently lack both mAChRs and nAChRs, is not clear (McQuiston and Madison 1999a; Parra et al. 1998).

Clearly, the activity of the cholinergic septohippocampal afferents excites the hippocampal network generally and differentially gates inhibitory circuits through both nAChR- and mAChR-mediated mechanisms. This has been proposed to result in switches in inhibition between perisomatic and pathway-specific dendritic domains (Gulyas et al. 1999). A major challenge for the future is to understand how different patterns of cholinergic afferent input can differentially recruit different receptor populations and cell types. McQuiston and colleagues have shown that a single stimulation of cholinergic fibres can be effective at evoking nAChR-mediated postsynaptic potentials in interneurons and that additional stimuli will evoke both mAChR-mediated hyperpolarizing and depolarizing responses. In contrast, trains of stimuli delivered at 10–20 Hz, within the range at which most putative septal cholinergic cells discharge (Brazhnik and Fox 1999; Lee et al. 2005), result in a robust mAChR-mediated synaptic response whilst at the same time depressing nAChR-mediated responses (Morton and Davies 1997). During more sustained ACh release, it is also possible that mAChR activation induces postsynaptic depression of nAChR responses (Shen et al. 2009).

Action of Acetylcholine on Defined Excitatory Synapses

Presynaptic Muscarinic Receptors Located on Defined Excitatory Synapses

ACh depresses Schaffer collateral (SC) afferents onto CA1 pyramidal cells through a presynaptic mechanism involving mAChR activation (Valentino and Dingledine 1981) and presynaptic N-type calcium channels (Qian and Saggau 1997). The nAChR antagonist hexamethonium does not block the action of ACh, suggesting that nAChRs are absent from presynaptic SC afferents (Valentino and Dingledine

1981). mAChR activation also inhibits glutamatergic transmission of CA3 collateral glutamatergic transmission (Vogt and Regehr 2001; Kremin and Hasselmo 2007). The mAChRs involved in presynaptic inhibition of SCs are most likely M2 mAChRs (Seeger and Alzheimer 2001) but possibly include M4 mAChRs (Sanchez et al. 2009). Whilst ACh generally suppresses glutamatergic neurotransmission at most excitatory synapses tested (Valentino and Dingledine 1981), mAChR modulation has a greater effect at SC synapses than on perforant path (PP) synapses in both CA1 (Hasselmo and Schnell 1994) and CA3 (Kremin and Hasselmo 2007). Similarly, in the dentate gyrus, cholinergic suppression of transmitter release differs between medial and lateral pathway (Kahle and Cotman 1989). mAChRs are not present at MF glutamatergic synapses, but bath application of muscarine enhances GABA release from local interneurons, which then inhibits MF transmission indirectly through activation of $GABA_B$ receptors (Vogt and Regehr 2001). This same indirect effect on presynaptic $GABA_B$ receptors, however, is not present at SC synapses (Kremin et al. 2006). This differential effect of cholinergic neuromodulation on specific glutamatergic circuits has been suggested to amplify the impact of sensory input arriving to hippocampus, whereby mAChR activation shifts the weight of glutamatergic input in favour of external (entorhinal cortical) influences over internal (intrahippocampal pathways) activity such as recall from internal CA3 recurrent collaterals upon cholinergic modulation (Giocomo and Hasselmo 2007). This synaptic 'heightening' of sensory awareness has interesting implications for the behavioural manifestation of attention (Giocomo and Hasselmo 2007; Sarter et al. 2005).

Concomitant with acute mAChR-induced presynaptic inhibition of glutamate release discussed above, the action of ACh can induce synaptic plasticity at SC synapses, including long-term potentiation (Auerbach and Segal 1994, 1996; Dennis et al. 2016; Fernandez de Sevilla et al. 2008; Shinoe et al. 2005) and, usually at higher concentrations of cholinergic agonist, long-term depression (Auerbach and Segal 1996; Scheiderer et al. 2006, 2008). Release of ACh by stimulation of the medial septum reproduces this effect on synaptic plasticity (Fernandez de Sevilla et al. 2008; Habib and Dringenberg 2009). The underlying mechanisms appear to be an enhancement in the NMDA receptor component of the excitatory postsynaptic event (Markram and Segal 1990a, b). More recently, Fernandez de Sevilla and colleagues have discovered a postsynaptic mechanism that involves enhanced surface trafficking of AMPA receptors (Fernandez de Sevilla et al. 2008). Presumably through a convergence underlying synaptic, intrinsic and network mechanisms, LTP is preferentially induced at synapses firing on the positive phase of the θ rhythm during cholinergically induced theta oscillations in the hippocampus in vitro and in vivo (Pavlides et al. 1988; Huerta and Lisman 1993; Holscher et al. 1997; Hyman et al. 2003).

Presynaptic Nicotinic Receptors Located on Hippocampal Glutamatergic Terminals

Nicotine application increases the frequency of miniature glutamatergic EPSCs in tissue culture from hippocampus (Radcliffe and Dani 1998), strongly suggesting that presynaptic nAChRs exist. Several lines of evidence support the presence of nAChRs on CA3 MF terminals, where calcium influx through α7 nAChRs induces concerted release of multiple quanta (Gray et al. 1996; Sharma and Vijayaraghavan 2003; Sharma et al. 2008). Nicotine selectively depresses PP but not SC glutamatergic transmission in CA3 (Giocomo and Hasselmo 2005), but this effect is accounted for by an indirect effect on inhibitory interneurons (Giocomo and Hasselmo 2005), possibly related to tonic activation of O-LM interneurons by nicotine (Jia et al. 2009). Similar indirect effects of ACh at MF synapses are also likely (Vogt and Regehr 2001).

Action of Acetylcholine on Defined Inhibitory Synapses

As demonstrated by the early work of Pitler and Alger (Pitler and Alger 1992a), as well as other laboratories (Behrends and ten Bruggencate 1993), the actions of ACh on GABAergic interneurons not only include direct excitation but also presynaptic inhibition. Pharmacological activation of mAChRs directly increases the frequency and amplitude of spontaneous IPSCs whilst at the same time depressing monosynaptically evoked IPSCs and reducing the frequency of miniature IPSCs (Pitler and Alger 1992a; Behrends and ten Bruggencate 1993). In a landmark study demonstrating the differential expression of mAChRs on hippocampal interneurons, Hajos and colleagues found that M2 receptors (M2Rs) were expressed on the presynaptic axon terminals of PV+ basket cells (Hajos et al. 1998). Consistent with M2-mediated inhibition of GABAergic transmission evoked in the pyramidal cell layer (Seeger et al. 2004), mAChR activation reduces GABA release from PV-positive BC terminals (Lawrence et al. 2015). Whether presynaptic mAChRs are present on other hippocampal interneuron subtypes still remains an open question. Interestingly, Soltesz and colleagues demonstrated that mAChR activation inhibits GABA release from identified CCK BCs (Neu et al. 2007). Here, mAChR modulation was indirect (Fukudome et al. 2004), occurring via postsynaptic release of endocannabinoids from pyramidal cells and subsequent activation of presynaptic CB1 receptors (Lawrence 2007; Neu et al. 2007) (Fig. 2). Therefore, mAChR-induced modulation of GABA transmission from PV BCs likely involves direct activation of presynaptic M2 receptors, whilst mAChR-induced modulation of GABA transmission from CCK BCs is indirect, involving endocannabinoid signalling (Freund and Katona 2007). Finally, in addition to mAChR-mediated presynaptic inhibition of GABA release, calcium-permeable nAChRs also regulate GABAergic inhibition through postsynaptic intracellular signalling pathways (Wanaverbecq et al. 2007; Zhang and Berg 2007). Therefore, cholinergic neuromodulation can alter the efficacy of GABAergic transmission through both pre- and postsynaptic mechanisms (Fig. 3).

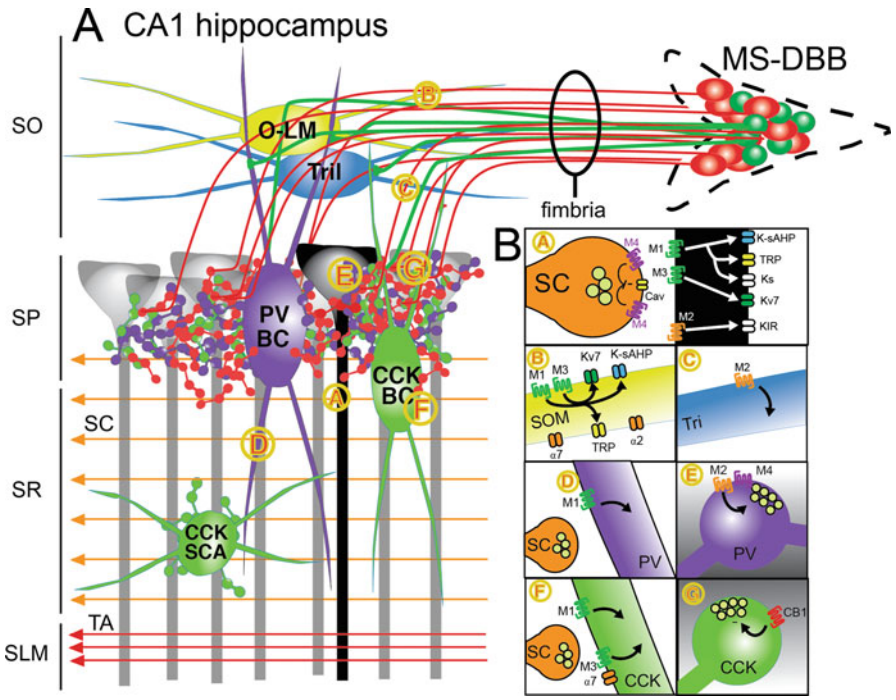

Fig. 2 The medial septal-diagonal band of Broca (MS-DBB) projection to defined cellular and synaptic targets of the CA1 hippocampus. (**a**) The MS-DBB is composed of cholinergic (red) and GABAergic (green) neurons that project via the fimbria to hippocampal regions. Cholinergic projection fibres (red) pass through stratum oriens (SO), where the somatostatin (SOM)-positive oriens-lacunosum moleculare (O-LM) neurons (yellow) and trilaminar (blue) interneurons are located, and arborize in a dense network within stratum pyramidale (SP) with CA1 pyramidal cells (black), CCK BCs and PV BCs (cholinergic terminals in stratum oriens and stratum radiatum (SR) omitted for clarity). MS-DBB GABAergic neurons (*A*, green cells) are thought to innervate exclusively hippocampal interneurons. Areas of interest, denoted by circled numbers in *A*, are expanded in *B*. Known cellular and synaptic targets, denoted by circled numbers, are shown. These are (*A*) the dendrites of pyramidal cells, acting at M1, M2 and M3 mAChRs and presynaptic terminals of Schaffer collaterals (orange) acting at M2 mAChRs (*B*) somatodendritic regions of O-LM cells acting at M1 and M3 mAChRs, α7 nAChRs and non-α7 nAChRs, (*C*) somatodendritic regions of trilaminar interneurons acting at M2 mAChRs, (*D*) somatodendritic regions of PV BCs acting at M1 mAChRs, (*E*) presynaptic terminals of PV BCs acting on M2 mAChRs, (*F*) somatodendritic regions of CCK BCs acting on M1 and M3 mAChRs and α7 nAChRs and (*G*) presynaptic terminals of CCK BCs acting indirectly through presynaptic CB1 mAChRs

Presynaptic Modulation of ACh Release

M2 mAChRs additionally occur at septohippocampal cholinergic terminals where they are thought to have an autoregulatory role (Rouse et al. 1999). Other studies have shown more directly that whilst ACh auto-feedback can regulate, the activation of a range of other transmitters can suppress evoked cholinergic responses including

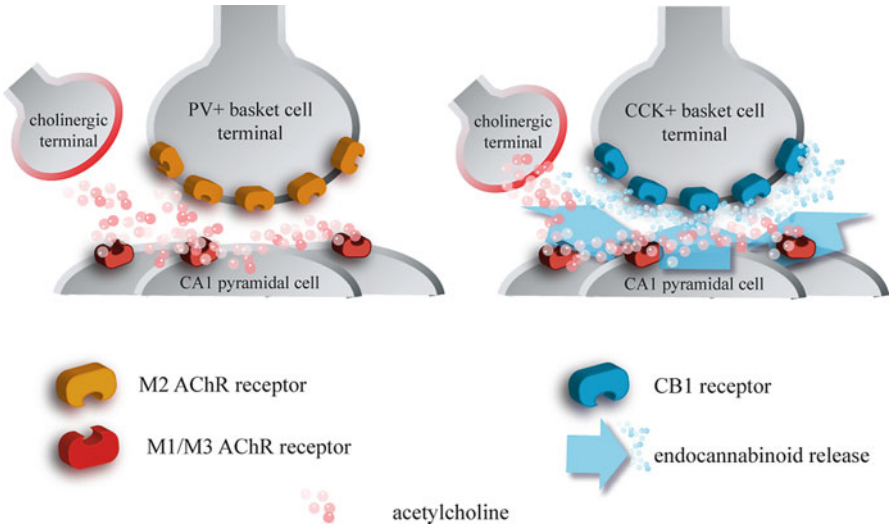

Fig. 3 Cholinergic modulation of GABA release from PV and CCK BC terminals through direct and indirect mechanisms. There is evidence that mAChRs can regulate GABA release through both direct and indirect mechanisms (Freund and Katona 2007). The direct mechanism involves binding of ACh to presynaptic M2 mAChRs (Lawrence et al. 2015; Szabo et al. 2010). The indirect mechanism involves postsynaptic M1/M3 mAChR activation and release of endocannabinoids onto CB1 R-expressing terminals of CCK+ BCs (Neu et al. 2007). (Reproduced from Lawrence 2007, with permission)

A1 adenosine receptors (Morton and Davies 1997), opiate receptors (Kearns et al. 2001) and $GABA_B$ receptors (Morton et al. 2001). The inhibition of ACh release occurs through a common mechanism, where presynaptic $G_{i/o}$ receptor activation converges to reduce calcium influx through presynaptic calcium channels. This mechanism has recently been supported by the observation that optogenetically induced nAChR-mediated EPSCs are potentiated by atropine, consistent with block of presynaptic $G_{i/o}$-coupled mAChRs on cholinergic terminals (Bell et al. 2011).

Dopamine

Dopamine (DA) is considered to play an important role in hippocampal-dependent learning by enhancing the saliency of relevant stimuli and is released into the hippocampus when animals are exposed to a novel environment (Ihalainen et al. 1999; Lisman and Grace 2005; Muzzio et al. 2009). Lesions of the dopaminergic system impair learning and memory (El-Ghundi et al. 1999; Gasbarri et al. 1996) and dysfunction of the DA system have been implicated in neurological disease (Seeman and Van Tol 1994). At the cellular and network levels, the action of DA is complex, involving neuromodulation of intrinsic membrane properties, synaptic

receptors and feedforward inhibition, which collectively act to lower the threshold for spike timing-dependent plasticity, thereby facilitating synaptic plasticity and memory storage.

Origin and Structural Organization of Dopaminergic Afferents

Early histological microdialysis studies have reported that the hippocampal formation receives dopaminergic projections from A9 (substantia nigra) and A10 (ventral tegmental area or VTA) cell groups (Scatton et al. 1980; Swanson et al. 1987). The VTA projects heavily to the subiculum and CA1 and to a lesser extent to the CA3 and dentate gyrus (Gasbarri et al. 1994, 1997). However, through retrograde tracing study, only a small percentage (10–18%) of these fibres are positive for tyrosine hydroxylase (TH) (Gasbarri et al. 1994). Interestingly, there has been a growing appreciation that the VTA is not the only source of DA to the hippocampus (McNamara and Dupret 2017; Smith and Greene 2012). Recent tract tracing in transgenic mice has confirmed that the VTA projection to dorsal hippocampus is sparse, whereas there is a high density of TH-positive fibres originating from locus coeruleus (LC) (Takeuchi et al. 2016). A sophisticated set of optogenetic experiments revealed that novelty-induced memory enhancement is primarily due to the activation of D1/D5 receptors from LC, which is largely independent of VTA (Kempadoo et al. 2016; Takeuchi et al. 2016). Moreover, DA transporter (DAT) expression, an indicator of DA terminals, is relatively absent from the hippocampus (Ermine et al. 2016; Smith and Greene 2012). Finally, retrograde labelling of fibres innervating the dentate gyrus revealed that the origin of TH-positive fibres is in LC, not midbrain DA neurons in SN or VTA (Ermine et al. 2016). Despite the very strong evidence that LC, not VTA, is the primary source of DA, loss of VTA neurons in Alzheimer's disease mice is associated with reduced DA outflow to hippocampus, whereas norepinephrine levels stay the same (Nobili et al. 2017).

Dopamine Receptors

All five DA receptors (DARs) are expressed in the hippocampus with G_s-coupled D1/5 and G_i-coupled D2-4 receptors being positively and negatively coupled to adenylyl cyclase, respectively. The expression pattern of DARs at the level of single cells remains relatively poorly defined, but DARs have been shown to display both presynaptic and postsynaptic localization (Bergson et al. 1995) and to be expressed both in principal cells and interneuronal populations (Mrzljak et al. 1996). There is often a mismatch between the expression patterns of particular DARs and the innervation pattern (Goldsmith and Joyce 1994). This has led some authors to hypothesize that it is the distribution of the DARs and not of dopaminergic fibres that determines the neuronal systems influencing dopaminergic afferent activation.

Through immunocytochemical analysis in D1-GFP mice, D1 receptors have recently been shown to be exclusively expressed on inhibitory interneurons and are

particularly enriched on SR interneurons (Puighermanal et al. 2017). The Drd1a-EGFP-positive neurons were not positive for PV and enriched in stratum oriens and radiatum, suggesting that D1 Rs are present on 5-HT_3 R- and SST-containing interneurons (Gangarossa et al. 2012). With the development of improved transgenic mouse technology, D2 R expression has similarly evolved from initially what was thought to be widespread hippocampal expression to, recently, very limited expression primarily in inhibitory interneurons and hilar neurons (Puighermanal et al. 2015, 2017). D_3 R level is lower than any other dopamine receptor subtype in the hippocampus (Andersson et al. 2012a) but has been detected immunocytochemically in the neuropil of stratum oriens and radiatum (Khan et al. 1998). D_4 Rs are expressed in GABAergic neurons (Mrzljak et al. 1996), specifically PV interneurons (Andersson et al. 2012a). D_4 R activation reduces an outward potassium current in fast-spiking hippocampal interneurons (Andersson et al. 2012b). This observation is counterintuitive given that the D_4 R is a $G_{i/o}$-coupled receptor and expected to increase potassium conductance.

Because DA, serotonin and norepinephrine all have similar structures (are monoamines), DA can activate some receptors that are not the classic D_1-D_5 receptors. DA has low affinity for 5-HT_3 Rs (Solt et al. 2007) and α_1 adrenergic receptors (Cilz et al. 2014).

Action of Dopamine on Intrinsic Properties

Principal Cells

DA has been reported to produce a range of actions, which are largely attributed to the activation of D1-like (D1/5) and D2-like (D2-4) Rs, respectively (Table 2). The effects of DA on intrinsic properties have historically been examined through bath application of DA and/or DAR agonists. In CA1 pyramidal neurons, bath application of DA produces a pronounced hyperpolarization and elevation of action potential threshold (Benardo and Prince 1982c) coupled with a suppression of the I_{AHP} and inhibition of spike frequency adaptation (Malenka and Nicoll 1986; Pedarzani and Storm 1995). This is mainly attributed to suppression of the activation of Ca^{2+}-sensitive potassium channels (Benardo and Prince 1982c, d; Bernardi et al. 1984; Stanzione et al. 1984). Activation of the selective D2 R agonist quinpirole was shown to increase the cellular excitability of hilar mossy cells (Etter and Krezel 2014). However, it is important to keep in mind that bath application of DAR agonists may not be comparable to the actions of synaptically released DA. Indeed, optogenetically stimulated synaptic release of DA fails to substantially alter passive membrane properties (Rosen et al. 2015).

Table 2 Summary of D1-like and D2-like receptors and their actions

Receptor family	D1-like receptors		D2-like receptors		
Subtype	D1	D5	D2	D3	D4
Expression in the hippocampus	Mainly SR interneurons	Pyramidal cell dendrites	Interneurons and hilar cells	Low expression (SO and SR neuropil)	Mainly PV interneurons
Signalling	G_s		G_i		
Gross effect of dopamine on: intrinsic properties	Hyperpolarization, ↑AP threshold, ↓AHP, ↓accommodation (but see text above)				
Synaptic transmission	↓ perforant path signalling, ↑mossy fibre signalling		↓ perforant path signalling		
Network	Modulation of gamma oscillations				

Inhibitory Neurons

Much of what is known about the effects of DA on inhibitory neurons has been studied in cortex (Gorelova et al. 2002; Towers and Hestrin 2008; Zhou and Hablitz 1999) (see (Tritsch and Sabatini 2012) for review). In cortical GABAergic interneurons, D_1 R activation induces a depolarization, accompanied by an increase in input resistance (Zhou and Hablitz 1999; Towers and Hestrin 2008), consistent with the expected actions of G_s-coupled receptors (Nicoll 1988). In the hippocampus, PV-positive interneurons possess D_4 Rs (Andersson et al. 2012a; Mrzljak et al. 1996), which control feedforward excitation of Shaffer collateral inputs onto CA1 pyramidal cells (Rosen et al. 2015). However, effects of DA on intrinsic membrane properties of other neurochemically defined hippocampal interneuron subtypes have not been systematically investigated.

Action of Dopamine on Defined Excitatory Synapses

The actions of DA on excitatory synaptic transmission are generally suppressant in nature (Hsu 1996). However, in parallel with other modulators, certain excitatory pathways are more profoundly affected than others. For instance, DA together with noradrenaline and serotonin produces a strong (30–50%) acute suppression of the PP input to CA1 pyramidal cells in comparison to no or very minimal change in SC input to the same cells (Otmakhova and Lisman 2000). This is consistent with the SLM having an especially high concentration of DARs. The action of DA is thought to involve both D_1 (Noriyama et al. 2006)- and possibly D_2 (Otmakhova and Lisman 1999)-type Rs and induce presynaptic suppression of glutamate release. A similar acute suppressant action is reported in the subiculum (Behr et al. 2000). Conversely, in area CA3, DA produces a pronounced synaptic potentiation of the MF inputs but no effect on associational/commissural synapses onto CA3 pyramidal cells (Kobayashi and Suzuki 2007).

Another important aspect is the temporal aspect of dopaminergic modulation. Many reports describe a biphasic action whereby an initial acute action (e.g. suppression) of synaptic transmission is followed by a long-lasting enhancement of the evoked synaptic response (Gribkoff and Ashe 1984). In this context, DA is considered an important modulator of synaptic plasticity whereby it enhances long-term potentiation (LTP) (Frey et al. 1993; Huang and Kandel 1995; Otmakhova and Lisman 1996; Thompson et al. 2005) and inhibits depotentiation (Otmakhova and Lisman 1998). During exposure to a novel environment, the threshold for LTP is reduced transiently (absent in animals exploring a familiar environment), and this facilitation is suggested to be dependent upon DA acting via D1/5 receptors (Li et al. 2003). In agreement with this observation, D_1 R knockout mice display deficits in hippocampal-dependent spatial learning (El-Ghundi et al. 1999). Moreover, amphetamine, which induces release of endogenous DA, enhances hippocampal-dependent memory tasks (Packard et al. 1994).

There appear to be several mechanisms by which DA may induce synaptic plasticity. These include increased surface expression of AMPA receptors through both direct phosphorylation of AMPA receptors and through the stimulation of local dendritic protein synthesis (Gao and Goldman-Rakic 2003; Smith et al. 2005; Wolf et al. 2003; Yang 2000). Also, DA may enhance NMDA receptor expression (Yang 2000). Interestingly, depending on the GluN2A/GluN2B subunit composition, synaptic NMDA receptor-mediated currents are differentially modulated by D_1/D_5 R agonists (Varela et al. 2009). SC synapses, which contain abundant GluN2B NMDA receptor subunits, are potentiated by D_1/D_5 R activation, whereas GluN2A-rich PP synapses are depressed (Varela et al. 2009). DA may gate synaptic transmission and plasticity in a frequency and synapse-specific manner, which includes modulation of excitatory synapses onto hippocampal interneurons (Ito and Schuman 2007).

Recently, optogenetic release of dopamine has been shown to enhance feed-forward inhibition by increasing the magnitude of the SC EPSP onto PV-positive neurons (Rosen et al. 2015). D_4 Rs have been demonstrated on PV interneurons in the CA1 hippocampus (Rosen et al. 2015; Andersson et al. 2012a, b). In response to SC stimulation, activation of D_4 Rs on PV interneurons increases the AMPA receptor-mediated EPSP, likely due to increased expression and stabilization of AMPA receptors (Rosen et al. 2015). The enhancement of gamma oscillations by D_4 R stimulation is consistent with this mechanism (Andersson et al. 2012a). This mechanism at least partly accounts for DA-induced suppression of SC EPSPs in CA1 pyramidal cells (Rosen et al. 2015). The action of haloperidol, a D_2 R antagonist, on inhibitory transmission, reinforces the idea that DA modulates GABAergic inhibition in the hippocampus (Brady et al. 2016).

Action of Dopamine on Inhibitory Synapses

As optogenetically released DA does not change the amplitude of directly stimulated IPSCs across all hippocampal layers (Rosen et al. 2015), it is unlikely that presynaptic DA heteroreceptors, if present, are modulated by synaptically released DA on any of the major classes of inhibitory neurons in the hippocampus. A detailed understanding of DA effects on hippocampal interneurons and modulation of GABAergic synaptic transmission is extremely sparse, though some analogous systematic studies have been conducted in cortex (Gao and Goldman-Rakic 2003; Gao et al. 2003; Gonzalez-Burgos et al. 2005; Gorelova et al. 2002; Kroner et al. 2007; Towers and Hestrin 2008). In the hippocampus, activation of D_3 Rs can modulate GABAergic transmission in area CA1, suppressing evoked IPSCs in SR but not in SO (Hammad and Wagner 2006). This laminar-specific action has been reported to be due to dopamine (via D_3 Rs) modulating postsynaptic $GABA_A$ receptor endocytosis in apical dendrites of CA1 pyramidal cells and has been postulated to be a significant postsynaptic means of modulating inhibitory synaptic transmission (Swant et al. 2008). Because D_3 R agonists did not alter paired-pulse ratio of GABAergic IPSCs, presynaptic D_3 Rs on GABAergic neurons are unlikely

(Swant et al. 2008). Such a mechanism of D_3 R-mediated inhibition of IPSCs may contribute to a reduction in gamma oscillations by D_3 R agonists (Lemercier et al. 2015).

Additional indirect evidence suggests that DA may also modulate feedforward inhibition of the PP input to the DG and hippocampal area CA1 through D_4 R signalling (Romo-Parra et al. 2005).

Further indirect evidence for DA regulation of hippocampal inhibitory networks comes from the finding that DA depresses cholinergically generated gamma band oscillatory activity in the hippocampus (Weiss et al. 2003; Wojtowicz et al. 2009). Gamma oscillations are increasingly appreciated to involve fast-spiking PV-positive interneurons (Bartos et al. 2007; Sohal et al. 2009). However, DA enhances stimulus-evoked gamma oscillations (Wojtowicz et al. 2009), which may be consistent with the notion that DA increases neuronal synchrony (Muzzio et al. 2009) mediated by its depolarizing action on fast-spiking, PV-positive basket cells (Bartos et al. 2007; Sohal et al. 2009; Towers and Hestrin 2008). Finally, the connectivity and GABAergic levels of PV interneurons, termed PV plasticity, are regulated by D_1/D_5 Rs and are important for memory consolidation (Karunakaran et al. 2016).

Norepinephrine

Norepinephrine (NE) is a major monoamine neuromodulator, and its actions in the hippocampus appear complex and sometimes paradoxical. Through multiple actions on intrinsic excitability and synaptic transmission, NE is considered to be important in learning and memory processes (Gibbs and Summers 2002; Murchison et al. 2004). More recent studies have found a role of astrocytes in mediating effects of NE (Bazargani and Attwell 2017; Paukert et al. 2014).

Origin and Laminar Specificity of Central Adrenergic Afferents

The hippocampus receives dense input from the locus coeruleus (LC), terminating heavily in the polymorph layer of the DG, stratum lucidum (SL) of area CA3 and SLM in area CA1 (Loy et al. 1980; Oleskevich et al. 1989; Swanson et al. 1987). The total NE bouton density varies across hippocampal regions but is estimated to be about twice as high as in cortex (Oleskevich et al. 1989). In the DG, it has been estimated that two-thirds of NA boutons form synaptic specializations with the remainder forming no specialized synaptic profiles and presumably mediating volume transmission (Milner and Bacon 1989a). GABAergic interneurons are often the targets of NA boutons forming synaptic specializations (Milner and Bacon 1989b). More recently, several studies have shown that the LC is a major source of DA to the hippocampus, particularly in dorsal hippocampus (Kempadoo et al. 2016; McNamara and Dupret 2017; Smith and Greene 2012).

Cell Type-Specific Expression of Adrenoceptors

NE acts on a range of adrenoceptors with both alpha and beta classes being widely expressed on both dendritic and axonal elements (Harley 2007; Nicholas et al. 1996). The α1d receptor appears to be the predominant α-receptor in all areas, with the exception of the hilus where α1a R appears to be the dominant subtype (Day et al. 1997). The α2a R appears to be located mainly presynaptically (Milner et al. 1998) but, like many other adrenoceptor subtypes, show dramatic changes in expression level during development. β-Adrenoceptors show laminar-specific differences and are mainly expressed postsynaptically on both principal cells and interneurons (Cox et al. 2008; Milner et al. 2000). Studies that utilize neurochemically defined interneuron subtypes indicate that the expression of both α (Hillman et al. 2005)- and β (Cox et al. 2008)-adrenoceptor subunits is cell type-specific. However, they can also be found on presynaptic profiles. In terms of signalling, all adrenoceptors are G-protein-coupled receptors with α1 being coupled to G_q, β2 being coupled to $G_{i/o}$ and the β-family receptors being coupled to G_s (Harley 2007; Nicholas et al. 1996).

Action of Norepinephrine on Intrinsic Properties

Principal Cells

NE is reported to produce a wide and sometimes contradictory range of effects in principal cells. These include hyperpolarization and reduced excitability in some cells to a depolarization, increased input resistance (Lacaille and Schwartzkroin 1988; Madison and Nicoll 1986; Ul Haq et al. 2012), reduction of afterhyperpolarizing potentials and loss of action potential accommodation (Madison and Nicoll 1982) in cells of the same class (see Table 3). Pharmacological studies suggest that these inhibitory versus excitatory actions may, in part, be due to a differential recruitment of α- versus β-subclasses of adrenoceptors (Bijak 1989; Harley 2007; Lacaille and Schwartzkroin 1988). Activation of β-adrenoceptors reduces resting K^+ conductances (Lacaille and Schwartzkroin 1988), whereas α2 receptor activation strongly suppresses cellular excitability in CA1 pyramidal cells (Otmakhova et al. 2005), most likely through postsynaptic activation of K_{ir} potassium channels (Luscher et al. 1997; Sodickson and Bean 1998). Studies investigating hilar neurons suggest that the dominant response in putative GABAergic cells is depolarization and loss of a slow AHP. In contrast, the dominant response in putative mossy cells was a loss of spike frequency adaptation (Bijak and Misgeld 1995).

The underlying ion mechanisms for the change in intrinsic properties are thought to be a reduction in a Ca^{2+}-activated K conductance leading to an inhibition of the slow AHP and a reduction in spike frequency adaptation (Haas and Rose 1987; Lacaille and Schwartzkroin 1988; Madison and Nicoll 1982; Pedarzani and Storm 1996). In DG granule cells, β1 receptors are also reported to enhance the voltage-dependent Ca^{2+} currents (Gray and Johnston 1987).

Table 3 Primary actions of norepinephrine on hippocampal neurons

Cell Type	Cellular effects	Ion channels effects
Pyramidal	Hyperpolarization,	↓ A-type current (α receptors)
	↑ increased input resistance	
	or	
	Depolarization,	↓ Ca^{++} activated K^+/I_{AHP} (β1 receptors)
	↓ input resistance,	
	↓ AHP,	
	↓ spike frequency adaptation	
	or	
	Hyperpolarization followed by depolarization	Both above (α and β1)
Granule	As above	As above
		Activation of L type current (via β receptor) leading to ↓gK^+

Inhibitory Neurons

In addition to its action on principal neurons, NE is also known to depolarize specific subsets of hippocampal interneurons (Bergles et al. 1996; Hillman et al. 2009; Papay et al. 2006). The effect is primarily due to an α1 receptor-mediated decrease in potassium conductance, though a modest β-receptor component is also sometimes apparent, especially in interneurons displaying a pronounced time-dependent inward rectification (see chapter 'Physiological Properties of Hippocampal Neurons'). Though not tested systematically, NE appears to produce these potent depolarizing actions across multiple classes of interneurons including BCs located outside of the pyramidal cell layer (Bergles et al. 1996) and interneurons located in SO (Bergles et al. 1996; Papay et al. 2006). Depolarizing actions of NE are blocked by the α1AR antagonist (Bergles et al. 1996) and resemble responses to other G_q-mediated GPCRs (Parra et al. 1998). The β AR agonist isoprenaline increases spontaneous firing in O-LM cells through a mechanism consistent with a shift in the activation curve for the hyperpolarization-activated cationic current I_h (Maccaferri and McBain 1996). Consistent with these observations, SO interneurons that contain somatostatin (SOM) mRNA transcripts also possess mRNA transcripts for both α1a and α1b receptors, in striking contrast to the complete absence of α1a and α1b receptors in SR interneurons that contain CCK mRNA transcript (Hillman et al. 2005). A smaller subpopulation of hippocampal interneurons located in SR or SLM exhibit hyperpolarization or reduced excitability to NE application (Bergles et al. 1996; Parra et al. 1998), although the neurochemical identity of these cells is not clear.

Action of Norepinephrine on Excitatory Synapses

NE has a general suppressant action on hippocampal excitatory pathways. The PP input to CA1 is profoundly suppressed by NE (~55%) (Otmakhova et al. 2005), whereas the SC pathway is more weakly (10–15%) suppressed (Otmakhova and Lisman 2000). Studies in acute brain slices provide evidence for α2 receptor-mediated postsynaptic mechanisms (Otmakhova et al. 2005). However, detailed studies in culture systems provide evidence for a presynaptic mode of inhibition of excitatory transmission via α1 (Scanziani et al. 1993) and α2 receptors (Boehm 1999).

In terms of synaptic plasticity, β adrenoceptors enhance both early and late phases of LTP in area CA1 as well as the DG (Hopkins and Johnston 1984, 1988; Huang and Kandel 1996; Gelinas and Nguyen 2005). NE has been shown to regulate AMPA-receptor trafficking (Hu et al. 2007), whilst early studies show that NE modulated glutamate release in the DG (Lynch and Bliss 1986). PKA activation following β-adrenoceptor activation is essential for both MF-mediated and SC-mediated LTP (Huang and Kandel 1996; Gelinas and Nguyen 2005; Gelinas et al. 2008). It is possible that these processes involve the phosphorylation of vesicular proteins including synapsin 1 and 2 (Parfitt et al. 1991, 1992). More recent studies suggest that NE may also trigger long-lasting synaptic potentiation through transcriptional regulation (Maity et al. 2015, 2016).

Action of Norepinephrine on Inhibitory Synapses

Information on the regulation of inhibitory synaptic transmission by NE is relatively sparse. Intracellular studies have shown NE to produce a marked (~50%) suppression of evoked inhibitory synaptic potentials recorded in CA1 pyramidal cells (Madison and Nicoll 1988b). Subsequent studies have suggested this effect to be independent of a direct action of NE on interneuron soma or axon terminals and instead be due to decreased excitatory input to the interneurons (Doze et al. 1991). However, more recent whole-cell recording has demonstrated a subpopulation of CA1 interneurons that are excited by α1a R activation (Hillman et al. 2009). NE, like other transmitters, is also reported to facilitate depolarization-induced suppression of inhibition (DSI) (Martin et al. 2001) (see cannabinoids below). Finally, NE may also influence hippocampal network behaviour through the modulation of electrical coupling of GABAergic circuits in SLM (Zsiros and Maccaferri 2008). Overall, there remains a paucity of data on the selective modulation of discrete inhibitory hippocampal cells and circuits by this modulator.

Serotonin

Serotonin (5-hydroxytryptamine or 5-HT) is an important modulator of hippocampal-dependent behaviours and cognitive performance (Richter-Levin and

Segal 1996). In general terms, 5-HT plays a role in the regulation of mood, anger and aggression. By its association with other limbic structures, more recent studies implicate roles of 5-HT and the hippocampus in fear learning (Balazsfi et al. 2017; Bauer 2015), assigning emotional salience (Mlinar and Corradetti 2017), encoding of reward signals (Li et al. 2016) and memory consolidation (Wang et al. 2015). Transgenic mice have revealed important insights into the function of 5-HT and its receptors in behaviour (Gardier 2009). Cells providing serotonergic input show an interesting dichotomy with one population of cells displaying state-dependent fluctuations in activity across the sleep-wake cycle whilst another population is tightly regulated to the hippocampal theta rhythm (Kocsis et al. 2006). These findings suggest that ascending serotonergic projections regulate both fast, dynamical information processing and slow, state-dependent transitions.

Origin and Structural Organization of Serotonergic Afferents

The serotonergic projection of the hippocampus originates in the dorsal raphe nucleus (DRN) and ramifies extensively throughout the hippocampal formation (Miettinen and Freund 1992; Varga et al. 2009; Vertes et al. 1999). A subset of DRN neurons project only to the medial septum, implying that serotonin transmission can impact hippocampal function both directly and indirectly through the medial septum (Acsady et al. 1996b). The DRN is neurochemically heterogeneous, containing neurons that express 5-HT, glutamate, 5-HT/glutamate and GABA (Domonkos et al. 2016; Gras et al. 2002; Hioki et al. 2010; Sos et al. 2017). DRN fibres innervating the hippocampus co-localize with the vesicular monoamine transporter VMAT2 and the vesicular glutamate transporter vGluT3 (Amilhon et al. 2010; Varga et al. 2009). Consistent with the co-release of both 5-HT and glutamate from DRN fibres, optogenetic activation of DRN afferents evokes synaptic currents onto hippocampal neurons that are mediated by both glutamate receptors and 5-HT_3 receptors (Varga et al. 2009). Similar co-transmission has been observed in the amygdala (Sengupta et al. 2017).

Within the rodent hippocampus, serotonergic afferents exhibit exquisite laminar specificity, with dense innervation at the SR/SLM border in areas CA3 and CA1, and a secondary, lower density in SO (Ihara et al. 1988; Lidov et al. 1980; Miettinen and Freund 1992; Varga et al. 2009; Vertes et al. 1999). This laminar specificity has been confirmed with quantitative autoradiography (Moore and Halaris 1975; Oleskevich and Descarries 1990). The majority of DRN axon varicosities do not make direct synaptic contacts with target neurons, implying that volume transmission is a primary mode of serotonergic transmission (Oleskevich et al. 1991). As a result of the differential laminar localization of 5-HT afferents, interneurons located in SR/SLM, such as calbindin-positive and NPY-positive interneurons, are major cellular targets (Freund et al. 1990; Gulyas et al. 1999; Miettinen and Freund 1992; Varga et al. 2009). The exact anatomical identity of these interneurons is not explicitly known but likely includes dendritically projecting neurons such as CCK/5HT_3-positive SCA and PP-associated interneurons (Klausberger 2009; Varga

et al. 2009) and neurogliaform cells (Overstreet-Wadiche and McBain 2015). The density of 5-HT innervation in principal cell layers is much lower; therefore, PV-positive interneurons embedded in the principal cell layers receive less innervation.

Cell Type-Specific Expression of 5-HT Receptors

There are many different 5-HT R subtypes expressed in the hippocampus, and these have been linked to an array of neurophysiological responses (reviewed by Andrade (1998); Barnes and Sharp (1999); Dale et al. (2016); Fig. 4). There are diverse expression patterns across the dorsoventral axis (Mlinar and Corradetti 2017; Tanaka et al. 2012), between hippocampal cell types (Dale et al. 2016) and even between subcellular neuronal compartments (Fink and Gothert 2007) (Table 4). For instance, in CA1 pyramidal cells, 5-HT_{1A} and 5-HT_4 receptors mediate the

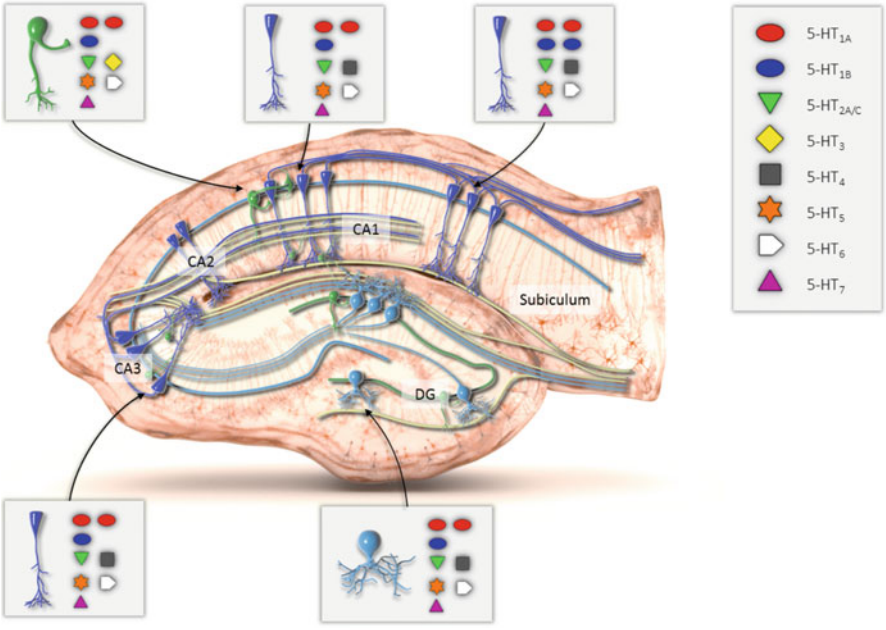

Fig. 4 Schematic illustration of the hippocampal circuit with 5-HT receptor localization. The main areas of the hippocampus together with primary synaptic connections are indicated. Principal (granule and pyramidal) cells are shown in blue, and interneurons are shown in green. Expression of 5-HT receptor subtypes on hippocampal CA1 and CA3 pyramidal cells, granule cells and interneurons is shown. Note that the 5-HT_{1A} heteroreceptor is expressed at high levels throughout the hippocampus. The 5-HT_{1B} receptor is found at highest levels in the subiculum. Based on histology data, the 5-HT_3 receptor is only expressed on the interneurons, and the 5-HT_4 receptor is only expressed on pyramidal cells. Other 5-HT receptor subtypes are found on both principal cells and interneurons (Reproduced from Dale et al. 2016, with permission)

Table 4 Summary of serotonin receptors in the hippocampus

Receptor family	5HT1a	5HT2A	5HT3	5HT4	5HT5	5HT6	5HT7
Expression in the hippocampus	5HT1a,b,f widespread $5HT1_c$ strong in CA3	CA1 SR/SLM interneurons	Strong in SLM and interneurons	Widespread, dendritic and axonal (mf)	5HT5a widespread, 5HT5B restricted to CA1	Widespread	Strongest in CA3
Signalling	$G_{i/o}$	$G_{q/11}$	Cation channel	G_s	G_i	G_s	G_s
Gross effect	Hyperpolarization, secondary depolarization, ↓accommodation, ↓EPSPs	depolarization	Fast depolarization of SR interneurons and DG basket cells; strong negative slope conductance, effect very depended upon MP	↓AHP	?	?	Increased Ih
References	Pompeiano et al. (1992) and Wright et al. (1995)	Weber and Andrade (2010) and Wyskiel and Andrade (2016)	Tecott et al. (1993)	Vilaro et al. (2005), Compan et al. (2004) and Waeber et al. (1996)	Matthes et al. (1993)	Ruat et al. (1993) and Ward et al. (1995)	Gustafson et al. (1996) and Bonaventure et al. (2002)

main postsynaptic actions, whereas $5HT_{1B}$ receptors, considered to be expressed at presynaptic terminals, regulate neurotransmitter release (Dale et al. 2016).

In CA1 hippocampus and DG principal cells, 5-HT_{1A} receptor mRNA is highly expressed, correlating with dense autoradiographic binding of 5-HT_{1A} in these areas (Chalmers and Watson 1991; Pompeiano et al. 1992). The CA3 region exhibits less 5-HT_{1A} mRNA and binding (Pompeiano et al. 1992). The mismatch between mRNA localization and autoradiographic binding in the CA1 region led to the conclusion that 5-HT_{1B} Rs are mainly presynaptic (Boschert et al. 1994). However, functional studies support that 5-HT_{1B} receptors are dendritically localized (Cai et al. 2013). The localization of 5-HT Rs has improved with the generation of GFP mice driven by 5-HT R-specific promoters. Although dense immunocytochemical staining of 5-HT_{2A} receptors in principal cells of CA1, CA3 and DG has been previously reported (i.e. Cornea-Hebert et al. (1999); Li et al. (2004)), the recent use of a 5-HT_{2A}-GFP mouse, combined with a 5-HT_{2A} antibody validated against a 5-HT_{2A} knockout mouse, has demonstrated a total absence of 5-HT_{2A} expression in CA1 pyramidal cells (Weber and Andrade 2010). A recent in situ hybridization study corroborates that 5-HT_{2A} R mRNA expression is not detectable in CA1 pyramidal cells (Tanaka et al. 2012). However, 5-HT_{2A} R mRNA is present in CA3 (Tanaka et al. 2012). $5HT_3$ Rs are preferentially expressed on a specific subclass of hippocampal interneurons (Chameau and van Hooft 2006; Morales et al. 1996; Morales and Bloom 1997; Tecott et al. 1993). 5-HT_4 R mRNA and binding is present in the principal neurons of the hippocampus (Vilaro et al. 2005; Waeber et al. 1996), which has been validated in a 5-HT4 R knockout mouse (Compan et al. 2004).

Action of Serotonin on Intrinsic Properties

Principal Cells

The release of serotonin can activate several different types of receptors on hippocampal neurons. In hippocampal CA1 principal cells, activation of somatodendritic $5HT_{1A}$ Rs leads to the activation of $K_{ir3.2}$ inward-rectifying potassium channels through a membrane-delimited $G_{i/o}$-coupled pathway (Andrade 1998; Luscher et al. 1997). The consequence is membrane hyperpolarization and a decrease in cellular input resistance (Andrade et al. 1986; Andrade and Nicoll 1987; Andrade and Chaput 1991; Jahnsen 1980; Segal 1980; Behr et al. 1997; Luscher et al. 1997). The same $K_{ir3.2}$ channel conductance mediates both $GABA_B$ and 5-HT_{1A} receptor activation (Andrade et al. 1986; Andrade and Nicoll 1987; Booker et al. 2018; Colino and Halliwell 1987; Degro et al. 2015). A similar 5-HT_{1A}-mediated mechanism exists in CA3 pyramidal cells (Beck and Choi 1991; Beck et al. 1992; Corradetti et al. 1998; Johnston et al. 2014; Okuhara and Beck 1994; Sodickson and Bean 1998) and DG granule cells (Baskys et al. 1989; Ghadimi et al. 1994; Nozaki et al. 2016; Piguet and Galvan 1994). Although this mechanism has not yet been demonstrated to occur in response to DRN afferent stimulation, the

abundant expression of 5-HT_{1A} Rs in DG cells (Samuels et al. 2015; Tanaka et al. 2012) and K_{ir} responses to synaptic $GABA_B$ R activation (Otis et al. 1993) suggests that 5-HT_{1A} R-mediated $K_{ir3.2}$ responses can be evoked in DG cells. Interestingly, deletion of 5-HT_{1A} Rs from adult DG cells eliminates the antidepressant effect of the selective serotonin reuptake inhibitor fluoxetine, implying a critical role of 5-HT_{1A} receptors on mature DG cells in the regulation of mood and anxiety (Samuels et al. 2015).

Consistent with the virtual absence of mRNA transcripts and protein expression for G_q-coupled 5-HT_{2A}, 5-HT_{2B} and 5-HT_{2C} Rs (Tanaka et al. 2012), there are no published studies that attribute activation of these receptors to alterations in CA1 pyramidal cell excitability. However, in subicular neurons, 5-HT_{2C} R activation inhibits T-type calcium channels, which reduces burst firing (Petersen et al. 2017).

Expression and activation of 5-HT_3 Rs are thought to occur exclusively in hippocampal interneurons (Kepecs and Fishell 2014; Rudy et al. 2011; Tremblay et al. 2016). However, the absence of 5-HT_3 R expression has not been confirmed functionally in all hippocampal principal cell types (Kawa 1994).

Activation of G_s-coupled 5-HT_4 Rs increases cellular excitability by modulating at least three different channel conductances in CA1 pyramidal cells. First, 5-HT_4 R activation reduces afterhyperpolarization (AHP) potentials by increasing cAMP, leading to the activation of PKA, inhibition of Ca^{2+}-induced Ca^{2+} release and reduction in a Ca^{2+}-activated potassium channel current ($I_{K(Ca)}$) (Andrade and Chaput 1991; Torres et al. 1995; Torres et al. 1996). The likely underlying molecular mechanism is the inhibition of $K_{Ca3.1}$, a Ca^{2+}-activated potassium channel modulated by G_s-coupled receptors (Andrade et al. 2012) and expressed in hippocampal CA1 pyramidal cells (King et al. 2015). Secondly, activation of 5-HT_4 Rs induces a long-lasting inhibition of a barium-sensitive K_{ir} current (I_{Kir}), which is likely the same $K_{ir3.2}$ that is activated by $G_{i/o}$-coupled 5-HT_{1A} Rs (Mlinar et al. 2006). Activation of 5-HT_4 Rs increases hyperpolarization-activated cyclic nucleotide-gated channel-mediated currents (I_h), whereas activation of 5-HT_{1A} Rs decreases them (Bickmeyer et al. 2002). These findings are consistent with opposing roles of $G_{i/o}$-coupled 5-HT_{1A} Rs and G_s-coupled 5-HT_4 Rs in modulating $I_{K(Ca)}$, I_{Kir} and I_h.

CA3 pyramidal cells also express 5-HT4 Rs (Tanaka et al. 2012). AHP potentials are reduced by G_s-coupled 5-HT_7 Rs, probably via similar mechanisms (Bacon and Beck 2000).

Inhibitory Neurons

Early studies found that bath application of 5-HT increases the frequency of spontaneous GABAergic potentials in the hippocampus in the presence of glutamate receptor blockers (Ropert and Guy 1991). This depolarizing action was blocked by a 5-HT_3 R antagonist, largely accounting for the 5-HT-induced increase in depolarizing drive onto GABAergic interneurons (Ropert and Guy 1991).

Cortical interneurons expressing 5-HT_3Rs are now recognized as a major class of interneurons, which have led to a reorganization in the way that interneurons are classified (Kepecs and Fishell 2014; Rudy et al. 2011; Tremblay et al. 2016). Interneurons expressing 5-HT_3Rs are derived from the caudal ganglionic eminence (CGE) that co-express calretinin, VIP, CCK, NPY and reelin. In contrast, the 5-HT_3R-expressing interneurons exhibit minimal overlap with PV- and SST-containing populations that are derived from the medial ganglionic eminence (MGE). Consistent with this governing principle, cortical VIP interneurons, which are a subtype of CCK interneurons, exhibit enriched expression of 5-HT_3 Rs in cortex (Ferezou et al. 2002). On the basis of this reasoning, this governing principle likely applies to the hippocampus as well (Chittajallu et al. 2013). These observations align reasonably well with previous studies of 5-HT_3 R-positive responses in SR/SLM interneurons (McMahon and Kauer 1997; Sudweeks et al. 2002), in DG BCs (Kawa 1994) and in CA1 BCs, which are most likely to comprise CCK+ interneuron subtypes co-expressing presynaptic CB1 receptors (Ferezou et al. 2002; Freund and Katona 2007; Kepecs and Fishell 2014; Morales and Backman 2002; Rudy et al. 2011; Tremblay et al. 2016).

Synaptic activation mediated by 5-HT_3 Rs has been demonstrated in amygdala (Sugita et al. 1992) and cortex (Ferezou et al. 2002; Roerig et al. 1997). Optogenetic activation of DRN elicits a strong fast excitation of hippocampal interneurons mediated by co-release of 5-HT and glutamate onto 5-HT_3 and glutamatergic receptors, respectively (Varga et al. 2009).

In addition to 5-HT_3 R expression in hippocampal interneurons derived from the CGE, there is evidence that several other types of 5-HT Rs are expressed in distinct hippocampal interneuron subpopulations. In the presence of a 5-HT_3R antagonist, 5-HT_2 R agonists enhance the frequency and amplitude of spontaneous inhibitory postsynaptic currents in CA1 pyramidal cells, indicating that 5-HT_2 receptors are expressed on a population of inhibitory neuron populations (Shen and Andrade 1998). Consistent with this mechanism, 5-HT-mediated enhancement of GABAergic signalling requires 5-HT_{2A} receptors and involves the inhibition of TASK-3 type potassium channels (Deng and Lei 2008).

5-HT responses that resemble 5-HT_2 responses have been anecdotally reported previously in hippocampal interneurons (McMahon and Kauer 1997; Parra et al. 1998). More recently, the use of 5-$HT2_A$-GFP mice have revealed that this interneuron population is located at the SR/SLM border (Wyskiel and Andrade 2016), overlapping strongly with the 5-HT_{3A}-GFP population (Chittajallu et al. 2013). SR/SLM interneurons expressing 5-HT_{2A} Rs strongly depolarize in response to bath application of 5-HT, which is almost completely blocked by the specific 5-HT_{2A} R antagonist MDL 100,907 (Wyskiel and Andrade 2016). In a subset of SR interneurons, the 5-HT response includes a hyperpolarization that precedes the depolarization, suggesting co-expression of 5-HT_{1a} Rs, 5-HT_3 Rs and 5-HT_{2A} Rs (Aznar et al. 2003; Dale et al. 2017). The anatomical and physiological characteristics of 5-HT_{2A}-expressing interneurons are consistent with CCK/5-HT_3 R-containing SCA and PPA interneuron subtypes (Wyskiel and Andrade 2016).

Within the CA1 SO layer, several subpopulations of SOM-positive interneurons are present that express 5-HT Rs. These include 5-HT_3 R-expressing O-LM cells derived from CGE (Chittajallu et al. 2013). In addition, a subset of SO interneurons express 5-HT_{2A} Rs (Wyskiel and Andrade 2016), though it is currently not clear whether this is the same O-LM cell population that co-expresses 5-HT_3 Rs. The majority of SO interneurons are depolarized by 5-HT_2 agonists (Lee et al. 1999b). A subset of SO interneurons hyperpolarize in response to 5-HT, which have axon arborizations that suggest O-LM or basket cells (Parra et al. 1998), and may therefore represent 5-HT_3 R-lacking cells derived from MGE (Chittajallu et al. 2013). The activation of $GABA_B$ Rs was shown to induce substantial $K_{ir3.2}$ channel-mediated currents in CA1 PV interneurons (Booker et al. 2013) but not O-LM cells (Booker et al. 2018). Because 5-HT_{1a} and $GABA_B$ receptors share common $G_{i/o}$ signalling mechanisms (Andrade et al. 1986; Andrade and Nicoll 1987; Colino and Halliwell 1987; Degro et al. 2015), it is possible that $5HT_{1A}$ R activation is more likely to induce a K_{ir3}-mediated hyperpolarization in perisomatically targeted interneurons than dendritically targeted interneurons. However, visually identified PV interneurons in CA3 do not consistently hyperpolarize, on average, in response to bath application of 5-HT (Johnston et al. 2014). In the basolateral amygdala, 5-HT_{1A} Rs are expressed in fast-spiking, presumably PV, interneurons and activated in response to optogenetic stimulation of DRN afferents (Sengupta et al. 2017). Although theoretically plausible, the question of whether 5-HT afferents are localized close enough to hippocampal PV interneurons to sufficiently activate synaptic 5-HT_{1A} Rs remains to be determined.

Action of Serotonin on Excitatory Synapses

Serotonin is known to regulate neurotransmission at a wide range of synapses in the brain (Fink and Gothert 2007). Because diverse 5-HT R subtypes in the hippocampus are expressed in a cell type- and pathway-specific manner, synaptic release of 5-HT has complex pre- and postsynaptic actions that occur on multiple time scales. The diverse ways that 5-HT can modulate glutamatergic transmission could lead to plausible treatment strategies for disorders involving dysfunction of glutamatergic transmission, such as depression (Dale et al. 2016; Pehrson and Sanchez 2014).

Some of the effects of 5-HT at excitatory synapses can be explained by a purely postsynaptic action via alteration of intrinsic membrane properties. For example, the 5-HT_{1A} R-mediated reduction of EPSP amplitude by SC input onto CA1 pyramidal cells can be explained by the postsynaptic dendritic activation of $K_{ir3.2}$ channels, leading to reduced input resistance, effectively shunting glutamatergic EPSPs (Pugliese et al. 1998). A similar mechanism is likely present in DG granule cells (Nozaki et al. 2016). Conversely, dendritic 5-HT_4 R activation increases cellular input resistance by inhibiting $K_{ir3.2}$ channels, which increases cellular excitability, enhancing the ability of EPSPs to generate action potentials (Mlinar et al. 2006). Consistent with this postsynaptic mechanism, SC-stimulated population spikes are

enhanced in vivo by 5-HT_4 R agonists (Matsumoto et al. 2002). Conversely, with 5-HT_{1A} Rs inhibited, fluvoxamine-induced enhancement of SC-stimulated population spikes is blocked by a 5-HT_4 R antagonist (Matsumoto et al. 2002).

In addition to modulating postsynaptic EPSPs by altering the intrinsic membrane properties of postsynaptic neurons, there is strong evidence that 5-HT R activation can alter presynaptic release and postsynaptic neurotransmitter receptor function within the CA1 hippocampus. At SC synapses, 5-HT_{1A} R activation reduces EPSC amplitude, increases paired-pulse ratio and reduces mEPSC frequency, consistent with the presynaptic expression of 5-HT_{1A} and/or 5-HT_{1B} Rs on glutamatergic SC terminals (Costa et al. 2012). Postsynaptically, activation of 5-HT_{1A} Rs reduces the amplitude of AMPA R-mediated EPSCs, whereas activation of 5-HT_7 Rs potentiates AMPA R-mediated EPSCs (Costa et al. 2012). Thus, postsynaptic $G_{i/o}$ and G_s signalling bidirectionally modulates cAMP levels, enabling bidirectional modulation of the phosphorylation state of synaptic AMPA receptors (Andreetta et al. 2016; Costa et al. 2012). Endogenous 5-HT release, induced by administration of the selective 5-HT reuptake inhibitor fluvoxamine, depresses SC evoked CA1 population spikes in vivo through a 5-HT_{1A}-dependent mechanism (Matsumoto et al. 2002).

The CA1 region is proposed to compute novelty signals by comparing PP input encoding ongoing sensory input with SC input encoding stored predictive information (Lisman and Grace 2005). DRN neurons are active during novelty and reward (Kobayashi et al. 2008; Li et al. 2016), and their axons densely innervate the CA1 SLM layer where PP synapses are localized (Ihara et al. 1988; Lidov et al. 1980; Miettinen and Freund 1992; Varga et al. 2009; Vertes et al. 1999). Early studies found that 5-HT more effectively suppressed field EPSPs arising from PP than SC synapses (Otmakhova and Lisman 2000; Otmakhova et al. 2005; Schmitz et al. 1995; Segal 1980). In these studies, paired-pulse ratio was unaffected by 5-HT R activation at PP synapses, implying a postsynaptic mechanism of 5-HT R action (Otmakhova et al. 2005). The underlying mechanism involves the differential postsynaptic expression of 5-HT_{1B} Rs at PP but not SC synapses (Cai et al. 2013; Peddie et al. 2008). In these studies, activation of 5-HT_{1B} Rs potentiates AMPA R-mediated EPSCs at CA1 PP synapses but not at SC synapses (Cai et al. 2013). In this case, postsynaptic 5-HT_{1B} R activation causes the activation of Ca^{2+}/calmodulin-dependent protein kinase (CaMK), which then phosphorylates AMPA Rs, thereby accounting for the pathway-specific potentiation of AMPA R-mediated EPSCs (Cai et al. 2013).

Serotonin also appears to have synapse-specific effects at SC synapses innervating different hippocampal interneuron subtypes. Activation of presynaptic 5-HT_{1B} Rs on SC terminals inhibits feedback excitation onto CCK-expressing interneurons but not PV-expressing interneurons (Winterer et al. 2011). The underlying presynaptic mechanism of presynaptic 5-HT_{1B} R modulation presumably occurs through $G_{i/o}$-induced inhibition of presynaptic Ca^{2+} channels (Winterer et al. 2011). A similar presynaptic mechanism occurs at glutamatergic synapses onto O-LM cells, but in this case 5-HT_{1A} receptors mediate the presynaptic effect (Bohm et al. 2015).

Dense binding sites for 5-HT_4 are found in the CA3 SL layer within MF termination zones (Vilaro et al. 2005). Bath application of serotonin potentiates MF transmission, reduces paired-pulse facilitation and is partially occluded by the adenylate cyclase activator forskolin, consistent with the presynaptic localization of 5-HT_4 receptors on MF terminals (Kobayashi et al. 2008). In DG, 5-HT has differential effects between EPSPs arising from medial and lateral PP synapses in DG granule cells, which may be due to differences in the shunting of these EPSPs by 5-HT_{1A} Rs (Nozaki et al. 2016). However, in anesthetized animals, the 5-HT uptake inhibitor fenfluramine causes enhanced population spikes in the DG, implying the existence of additional indirect mechanisms (Levkovitz and Segal 1997).

Serotonin is also an important modulator of synaptic plasticity at glutamatergic synapses. Postsynaptic activation of 5-HT_{1A} Rs inhibits induction of LTP (Corradetti et al. 1992; Kojima et al. 2003; Shakesby et al. 2002), which could occur by either hyperpolarization and/or shunting of EPSPs (Pugliese et al. 1998) and/or cAMP-dependent dephosphorylation of AMPA receptors (Andreetta et al. 2016; Costa et al. 2012). Serotonin also inhibits LTP at SC synapses in CA3 probably via a similar mechanism (Villani and Johnston 1993). However, $5HT_2$ antagonism enhances NMDA receptor-mediated currents, facilitating LTP induction (Wang and Arvanov 1998).

As revealed by a $5HT_3$ R antagonist, activation of 5-HT_3 Rs suppresses LTP (Staubli and Xu 1995), presumably through an indirection action involving activation of inhibitory interneurons. Similarly, the $5HT_3$ receptor-mediated suppression of MF-CA3 LTP by 5-HT may be due to indirect actions through enhanced activation of 5-HT_3 R-containing GABAergic interneurons (Maeda et al. 1994). Unlike other receptors, $5HT_4$ R activation is reported to enhance glutamatergic transmission (Matsumoto et al. 2002).

Action of Serotonin on Inhibitory Synapses

In addition to the capability of 5-HT to alter cellular excitability through somatodendritic 5-HT R activation and effects on glutamatergic drive onto GABAergic neurons, there is also evidence that 5-HT R activation can alter GABAergic transmission by the activation of presynaptic 5-HT Rs. Consistent with a presynaptic 5-HT_3 Rs, an increase in the frequency of miniature IPSCs is observed upon application of 5-HT or a 5-HT_3 agonist (Choi et al. 2007; Dorostkar and Boehm 2007; Turner et al. 2004). Additional evidence for the activation of presynaptic 5-HT Rs has been shown in a preparation that allows a single GABAergic presynaptic terminal to be stimulated (Katsurabayashi et al. 2003). Two separate populations of GABAergic terminals were discovered. One population expressed only presynaptic 5-HT_{1A} Rs, which reduced release probability, most likely through inhibition of presynaptic calcium channels (Katsurabayashi et al. 2003). A second population co-expressed presynaptic 5-HT_3 and 5-HT_{1A} Rs. Presynaptic 5-HT_3 Rs increases release probability by causing calcium influx directly through the presynaptic 5-HT_3 channels and does not appear to require the activation of presynaptic voltage-

gated calcium channels (Turner et al. 2004). These distinct presynaptic GABAergic populations of 5-HT_3 R-containing and 5-HT_3 R-lacking GABAergic terminals likely arise from two different populations of inhibitory interneuron subtypes. However, presynaptic 5-HT R activation was not detected at CCK basket cell to pyramidal cell synapses (Neu et al. 2007). Therefore, it remains to be determined which hippocampal interneuron subtypes possess presynaptic 5-HT_3 Rs.

Histamine

Histaminergic neurons comprise a small cluster of cells in the tuberomammillary nucleus (TMN) that project to most brain areas, including the hippocampus. As with other neuromodulatory systems associated with the reticular activating system, the activity of histaminergic neurons innervating the hippocampus is strongly modulated across the sleep-wake cycle (Haas et al. 2008). The histamine (HA) system is considered to be important in a number of central nervous system functions, including wakefulness and sleep, cognition, learning, feeding and stress-related behaviours (Alvarez 2009; Brown et al. 2001; Panula and Nuutinen 2013). The histaminergic system operates synergistically with the cholinergic system to modulate hippocampal function (Blandina et al. 2004; Mochizuki et al. 1994; Passani et al. 2007). Histamine receptor (HAR) activation can excite septohippocampal cholinergic and GABAergic neurons (Xu et al. 2004), increasing ACh release in the hippocampus (Bacciottini et al. 2002). In basal forebrain cholinergic neurons (Zant et al. 2012), the mechanism occurs through H1R-mediated inhibition of a leak potassium channel (Vu et al. 2015). However, because TMN afferents also project to the hippocampus, HA can play a direct role in hippocampal learning and retrieval (Fabbri et al. 2016).

Origin and Structural Organization of Histaminergic Afferents

All histaminergic neurons originate in the TMN of the hypothalamus (Haas and Panula 2003; Haas et al. 2008; Panula et al. 1984). TMN neurons send projections to most parts of the brain, including the hippocampus (Watanabe et al. 1984). Within the hippocampus, TMN inputs terminate in all areas but are particularly pronounced in the subiculum and DG, with sparser innervation of hippocampal areas CA1 and CA3 (Barbin et al. 1976; Brown et al. 2001; Inagaki et al. 1988; Panula et al. 1989). Principal neurons of the hippocampus are the major postsynaptic targets of TMN afferents and do not exhibit preference for postsynaptic inhibitory neurons (Magloczky et al. 1994). Like other aminergic modulators, histaminergic axons form varicosities with very few synaptic specializations consistent with a volume transmission mode of action (Takagi et al. 1986). Recently, TMN neurons were shown to optogenetically co-release GABA in cortex and striatum (Yu et al. 2015). Therefore, TMN neurons innervating the hippocampus likely also co-release both

HA and GABA. Whether histaminergic afferents exhibit laminar and/or cell type specificity has not been systematically examined in the hippocampus.

Histamine Receptors

The HAR family is comprised of G-protein-coupled H1-H4 Rs (H1-H4Rs) (Panula et al. 2015). H1Rs have been detected throughout the hippocampus in both in situ hybridization (Andersson et al. 2017) and autoradiographic binding (Bouthenet et al. 1988; Martinez-Mir et al. 1990; Palacios et al. 1981) studies (Haas and Panula 2003; Panula et al. 2015). H1R mRNA is expressed at the highest densities in the CA3 pyramidal cell layer (Andersson et al. 2017). H2R mRNA and autoradiographic ligand binding has also been detected in the hippocampus (Vizuete et al. 1997). H3Rs are most prominent in the subiculum and DG (Pillot et al. 2002; Pollard et al. 1993) and are thought to be autoreceptors at presynaptic terminals (Arrang et al. 1983; Nieto-Alamilla et al. 2016). H4Rs do not appear to be expressed in the hippocampus (Andersson et al. 2017; Schneider and Seifert 2016).

In terms of signalling mechanisms leading to cellular changes in excitability, HA can cause myriad cellular effects due to divergent G-protein-mediated signalling pathways involved (reviewed by (Brown et al. 2001; Haas and Panula 2003)). H1Rs are G_q-coupled receptors, which can reduce a K_{leak} conductance. Recently, in cholinergic neurons, the HA-sensitive leak conductance has been determined to be mediated by the TWIK-like acid-sensitive K+ channel (Vu et al. 2015). G_q signalling activates phospholipase C, generating IP_3 and DAG, PKC activation, Ca^{2+} release from intracellular stores and downstream modulation of numerous conductances, such as a cationic conductance (Haas and Panula 2003). TRP channels remain the leading molecular candidates in underlying H1R-activated cationic conductances, yet no study has yet definitively linked H1Rs to TRP channel activation. Through PKC signalling, H1R activation can lead to phosphorylation of ligand-gated ion channels, including NMDA receptors. However, HA is also reported to directly potentiate NMDA receptor-mediated currents in a process distinct from classical HA receptors (Bekkers 1993; Vorobjev et al. 1993). This action is due to binding of HA to a site distinct from the polyamine site of the NMDA receptor (Burban et al. 2010). Other downstream signalling cascades likely activated by H1Rs include generation of nitric oxide and the modulation of expression of various proteins including gap junctions (Brown et al. 2001). Given the effectiveness of multiple types of G_q-coupled receptors in causing endocannabinoid release (Alger et al. 2014), it is possible that H1Rs also can cause endocannabinoid release. In contrast, H2Rs are G_s-coupled, causing increasing cAMP production and PKA activation. Like other G_s-coupled receptors, H2R activation is associated with the reduction a Ca^{2+}-activated potassium conductance (Greene and Haas 1990; Haas and Konnerth 1983) and shifting the activation threshold of HCN-mediated conductances (McCormick and Williamson 1991; Zhang et al. 2016). H3Rs are $G_{i/o}$-coupled, and their presynaptic activation leads to inhibition of high-threshold voltage-gated Ca^{2+} channels (Takeshita et al. 1998), a mechanism most likely to

underlie histaminergic suppression of neurotransmitter release (Nieto-Alamilla et al. 2016).

H1 and H2 knockout mice exhibit cognitive and/or learning impairment (Ambree et al. 2014; Dai et al. 2007), implicating hippocampal localization of H1Rs and H2Rs. As expected by their function as autoreceptors in regulating histaminergic release, H3 knockout mice exhibit increased histaminergic transmission and increased wakefulness (Gondard et al. 2013). H4 knockout mice appear normal in hippocampal-dependent tasks (Sanna et al. 2017), consistent with a relative absence of H4Rs from the hippocampus (Andersson et al. 2017).

Action of Histamine on Intrinsic Properties

Pyramidal Cells

HA is a powerful modulator of cellular excitability in the hippocampus. In principal cells (Haas and Konnerth 1983; Haas and Greene 1986; Pedarzani and Storm 1993; Selbach et al. 1997; Yanovsky and Haas 1998) and DG granule cells (Greene and Haas 1990), HA decreases a Ca^{2+}-activated potassium conductance, through G_s-coupled H2Rs. Selective activation of H1Rs can however result in a reduction in firing frequency (Selbach et al. 1997). The dominant depolarizing action is caused by enhancing HCN conductance and reducing the Ca^{2+}-activated potassium conductance responsible for the slow AHP and action potential accommodation (Brown et al. 2001; Haas and Konnerth 1983; Pedarzani and Storm 1993, 1995). Intracellular studies show HA to promote burst discharge patterns in CA3 pyramidal cells (Yanovsky and Haas 1998).

Interneurons

HA is reported to regulate interneuronal excitability, as indicated by an increase in spontaneous inhibitory synaptic potentials in the DG (Greene and Haas 1990), CA1 hippocampus (Haas and Greene 1986) and entorhinal cortex (Cilz and Lei 2017). Although effects of HA on neurochemically identified interneuron types have not been systematically investigated, several interneuron populations have been examined in various hippocampal regions. In CA3, bath application of HA enhances the cellular excitability of fast-spiking interneurons (most likely PV interneurons) primarily through H1R-mediated inhibition of Kv7 potassium channels (Andersson et al. 2017). Such a mechanism implies a convergence with postsynaptic M1/M3 mAChR-mediated signalling mechanisms (Lawrence et al. 2006b; Lawrence et al. 2006c). In the layer 3 medial entorhinal cortex (MEC), HA depolarizes Type I and Type II inhibitory neurons through both H1R- and H2R-mediated mechanisms (Cilz and Lei 2017). The conductances modulated involve the activation of a TRP-like cationic conductance and reduction in a K_{ir} conductance (Cilz and Lei 2017). Histaminergic modulation of interneurons in the DG molecular layer occurs

via H2R-mediated inhibition of Kv3.2 channels involved in rapid action potential repolarization (Atzori et al. 2000). HARs are in putative O-LM interneurons confirm an enhanced firing activity in response to HA (Brown et al. 2001).

Action of Histamine on Excitatory Synapses

HA depresses EPSPs from PP stimulation of the DG through H3R-mediated reduction in glutamate release in vitro (Brown and Haas 1999) and in vivo (Chang et al. 1998). The action of HA on evoked synaptic responses at the SC to CA1 pyramidal cell synapse is an enhanced population spike (Segal 1981; Yanovsky and Haas 1998) but modest reduction (~10%) in the excitatory synaptic potential (Brown et al. 1995). These data are consistent with HA suppressing transmitter release but with the enhanced postsynaptic excitability dominating the response. HA is also known to potentiate NMDA-mediated synaptic transmission and enhance LTP through a direct action on the NMDA receptor (Bekkers 1993; Brown et al. 1995) (Fig. 5).

Action of Histamine on Inhibitory Synapses

Early studies using paired-pulse stimulation provided early evidence that HA may modulate inhibitory synaptic transmission in the hippocampus (Springfield and

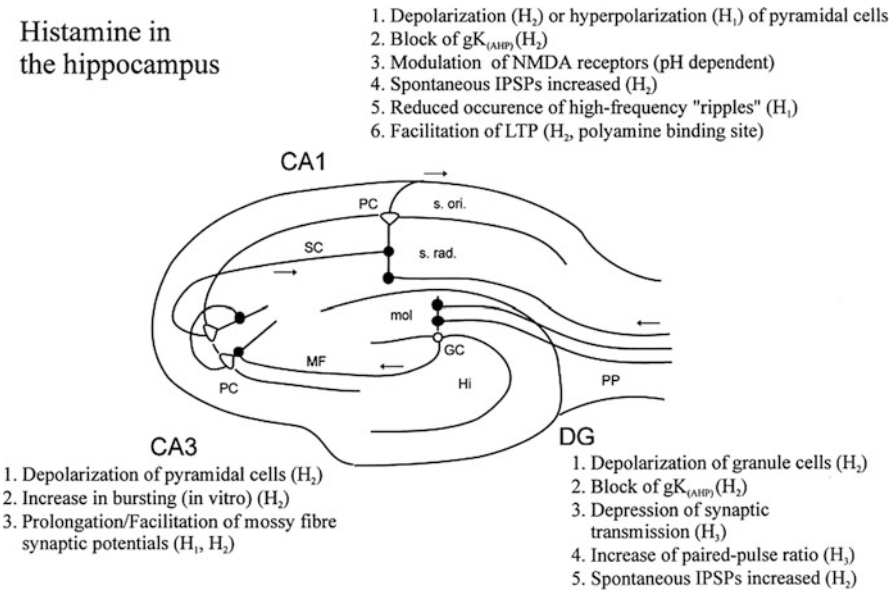

Fig. 5 Primary actions of histamine in the hippocampal formation. (From Brown et al. 2001, with permission)

Geller 1988). HA may modulate inhibitory synaptic transmission indirectly by modulating the action potential frequency and short-term plasticity of GABAergic transmission (Atzori et al. 2000). However, a detailed understanding of how HA modulates GABAergic transmission and the specific interneuron subtypes that express HARs remains to be systematically investigated.

Purines

Production and Release of Purine Transmitters

Adenosine, adenosine triphosphase (ATP) and other purine nucleotides (UTP, UDP etc.) are important cellular metabolites but also are released as modulatory substances in the central nervous system where they display a range of actions. ATP is often stored with other transmitters including GABA and glutamate but can also be released independently. It has been suggested that in the hippocampus, ATP is stored and released from distinct pools of vesicles independent of GABA and glutamate (Pankratov et al. 2006). ATP may be transmitted through gap junctions and other channels. It may also be the source of adenosine, especially when released from astrocytes (Pascual et al. 2005). A component of adenosine release in the hippocampus arises from the extracellular metabolism of ATP released from astrocytes (Wall and Dale 2013). In contrast to ATP, the release of adenosine is more enigmatic. It is not stored in vesicles, and in general the level of adenosine rises with increasing neuronal activity as well as in disease conditions such as epileptic seizures and hypoxia. Recent evidence suggests that adenosine release can be stimulated by glutamate receptor activation via equilibrative nucleoside transporters (Wall and Dale 2013). Despite not being released by exocytosis, adenosine is nevertheless a powerful homeostatic modulator of neuronal excitability and synaptic transmission (Dunwiddie and Masino 2001; Fredholm and Dunwiddie 1988; Rombo et al. 2016b).

Purine Receptors

Separate receptors exist for adenosine (P1 receptors) and ATP (P2 receptors). The latter is broadly divided into ion channel receptors (P2X) and metabotropic receptors (P2Y). Overall, the purine receptors are widely expressed and mediate a number of actions as summarized in Table 5.

Action on Intrinsic Properties

Adenosine causes a hyperpolarization of all hippocampal neurons (Thompson et al. 1992) that has been attributed to the activation of inwardly rectifying K^+

Table 5 Summary of purine receptors, signalling and primary actions

Receptor	Adenosine ($A_{1,\ 2A,\ 2B,\ 3}$)	P2X	P2Y
Family		($P2X_{1\text{-}7}$)	($P2Y_{1,2,4\text{-}6,\ 8\text{-}14}$)
Expression in the hippocampus	A1, widespread	Widespread	Widespread
	A2A, A2B, widespread		
	A3, presynaptic		
Signalling	A_1, $G_{i/o}$; $A_{2A/B,}$ G_s; A_3, $G_{i/o}$	Cation channels (subunits confer biophysics, some have very high Ca^{++} permeability)	$P2Y_{1,2,4,6,14}$ $G_{q/11}$
			$P2Y_{4,\ 12,\ 13}$ G_i
			$P2Y_{11}$ $G_{Q/11}$ and G_s
Gross effect	A_1 (high-affinity) hyperpolarization (↑GIRK), suppression of synaptic transmission (↓VDCCs)	Depolarization, can contribute to evoked EPSPs	Poorly defined
	A2A Depolarization, ↑ synaptic transmission/plasticity		
	A2B		
	A3		
References	Dunwiddie and Masino (2001) and Rombo et al. (2016b)	Pankratov et al. (1998) and Abbracchio et al. (2009)	Abbracchio et al. (2009)

(GIRK) channels (Dunwiddie and Masino 2001). The postsynaptic actions of ATP are mediated through both P2X and P2Y receptors as well as indirectly via P1 receptors when metabolized to adenosine. P2X receptors mediate a fast inward current that is reported to contribute to the EPSC recorded upon afferent fibre (e.g. SC) stimulation (Pankratov et al. 1998). It is proposed that ATP is co-released with glutamate at associational fibres but not MF synapses (Mori et al. 2001). The cationic current associated with P2X-mediated signalling is generally modest (typically 50–100 pA). However, it has often a significant Ca^{2+} component which can in turn give rise to activation of Ca^{2+}-dependent potassium conductances (Illes et al. 1996). Little is known about the action of P2Y receptors in regulating hippocampal primary neurons. Studies in cultured hippocampal neurons report the activation of an outwardly rectifying K^+ current (Ikeuchi et al. 1996) or inhibition of the I_M (Filippov et al. 2006). In contrast to principal cells, hippocampal interneurons in stratum radiatum, identified as calbindin- and calretinin-positive interneurons, are excited by ATP (Bowser and Khakh 2004). This depolarization is associated with a reduction of potassium conductances and activation of non-selective cationic conductances mediated by P2Y1 receptor activation (Bowser and Khakh 2004; Kawamura et al. 2004).

Action of Purines on Excitatory Synapses

The primary action of adenosine is to profoundly (up to ~75–100%) suppress glutamatergic transmission at all hippocampal synapses tested (Dunwiddie and Hoffer 1980; Thompson et al. 1992). This may be mediated by multiple mechanisms, but principal amongst these is a profound suppression of terminal calcium currents by A1 Rs (Fredholm and Dunwiddie 1988; Wu and Saggau 1994, 1997). The exact role of A2A receptors in regulating transmission is complex, but it may counteract the suppression of glutamatergic transmission by A1 Rs (Lopes et al. 2002) and involve the enhancement of glutamate receptor expression and AMPA R-mediated currents (Dias et al. 2012). A2A receptors also facilitate the release of other transmitters in the hippocampus, notably ACh (Cunha et al. 1994). In line with this modulatory action, adenosine is also reported to depress the induction of LTP at a range of synapses (Alzheimer et al. 1991). However, the situation is complex in that low-frequency plasticity induction paradigms are more sensitive to adenosine than higher-frequency patterns which appear to overcome the effect of adenosine (Mitchell et al. 1993). A number of more recent studies point to the fact that adenosine may serve a pivotal role in modulating plasticity (reviewed by (Dias et al. 2013).

As mentioned above, ATP appears to act as a classical neurotransmitter by mediating fast excitatory synaptic reposes through P2X receptors. However, it may also modulate excitatory synaptic transmission and plasticity although the precise mechanistic detail remains unclear (Inoue et al. 1999; Pankratov et al. 2009). Despite this, it has been shown that ATP can induce LTP and LTD in its own right depending on the level of Ca^{++} influx associated with the ATP

current (Yamazaki et al. 2003). ATP can also regulate plasticity induced by classical induction methods (Pankratov et al. 2002). P2X channel-mediated modulation may show some selectivity between different synapses in the hippocampus. For instance, presynaptic P2X2 channels are reported to facilitate excitatory synapses onto SR interneurons in area CA1 but not CA1 pyramidal neurons (Khakh et al. 2003; Khakh 2009). Relatively little is known concerning the possible role of P2Y receptors in regulating synaptic transmission and plasticity in the hippocampus (Guzman and Gerevich 2016). However, a recent report suggests a requirement of P2Y receptor activation in a form of heterosynaptic LTD (Chen et al. 2013).

Action of Purines on Inhibitory Synapses

The actions of adenosine on GABAergic signalling are poorly defined. Early studies suggested that adenosine could suppress GABA release in cortical tissues (Hollins and Stone 1980). However, similar experiments in hippocampal slices failed to find an effect of adenosine on GABA release (Burke and Nadler 1988). Electrophysiological studies using cultured neurons (Yoon and Rothman 1991) and in slices have failed to show a direct suppressant action of adenosine A1 Rs on action potential-dependent GABA release (Rombo et al. 2016b). However, adenosine A1 Rs appear to modulate tonic GABA current (resulting from extrasynaptic $GABA_A$ receptors) (Rombo et al. 2016a) and are known to strongly modulate disynaptic inhibition in the hippocampus through actions on glutamatergic transmission (Lambert and Teyler 1991). A detailed overview of the actions on adenosine A1 and A2A Rs on select GABAergic circuits has recently been described (Rombo et al. 2016b). The actions of ATP via P2X and P2Y classes of receptor on GABAergic signalling remain to be defined.

Paracrine/Autocrine Modulators

Endocannabinoids

Production and Release of Endocannabinoids

Cannabinoids are a group of related lipid-derived modulators that regulate hippocampal circuits through activation of specific cannabinoid receptors (Kano et al. 2009; Castillo et al. 2012). Some endocannabinoids (eCBs) such as anandamide can also signal through TRPV1 receptors and thus also mediate endovanilloid actions (Castillo et al. 2012). Anandamide and other major cannabinoids including 2-AG (2-arachidonyl glycerol) are not stored but synthesized and released tonically on demand in response to neuronal and synaptic activity (Stella et al. 1997; Castillo et al. 2012). The primary action of eCBs is to mediate retrograde signalling and in particular induce various forms of presynaptic inhibition. Common forms of

eCB-mediated STD are driven by postsynaptic depolarization, Ca^{2+} influx through NMDA receptors or via mAChR-mediated activation (Kano et al. 2009). However, the most significant trigger for eCB release and subsequent suppression of synaptic transmission is activation of metabotropic glutamate receptors (Varma et al. 2001).

Endocannabinoid Receptors

The two major forms of cannabinoid receptors (CB1 and CB2 Rs) are both metabotropic receptors with the CB1 being the archetypal 'brain' form. CB2 Rs, once thought to be mainly restricted to immune cells including microglia, recently have been shown to be expressed in the hippocampus (Stempel et al. 2016). The orphan receptor GPR55 is activated by anandamide (Ryberg et al. 2007) and L-α-lyso-phosphatidylinositol (LPI) (Oka et al. 2007) and widely expressed in the hippocampus (Henstridge et al. 2009; Hurst et al. 2017). CB1 Rs are highly abundant but most strongly expressed in CCK interneurons (Freund and Katona 2007). Hippocampal pyramidal cells and DG granule cells are lightly immunopositive for CB1 receptors but are surrounded by a dense plexus of CB1 R-positive GABAergic terminals (Tsou et al. 1998). However, low but significant levels of CB1 mRNA are expressed in principal cells suggesting low levels of CB1 R-mediated signalling in these cells (Marsicano and Lutz 1999). Within the GABAergic cell population, it appears that CB1 receptors are preferentially expressed in the terminals of perisomatically terminating BCs. The two main classes of BCs are PV- and CCK-expressing cells, and it is striking that over 95% of CCK-positive cells express CB1 Rs, which contrasts with PV cells for which only ∼5% of cells are CB1 immunoreactive (Katona et al. 1999). However, CB1 Rs are also expressed at glutamatergic terminals (Katona et al. 2006) (Table 6).

Action of Endocannabinoids on Intrinsic Properties

Most of the actions of eCBs are attributed to their influence on synaptic transmission. Studies addressing the actions of eCBs on hippocampal neuronal excitability are very limited (Kirby et al. 2000), but the primary postsynaptic action of eCB appears to be a modest increased excitability that is mediated through a reduction (∼45%) in I_M (Schweitzer 2000). More detailed studies in somatosensory cortex suggest that low-threshold spiking-type interneurons can exhibit a long-lasting form of action potential suppression whereby activity-dependent release of endocannabinoids causes an autocrine-like enhancement of potassium conductances, consistent with $G_{i/o}$-mediated activation of a K_{ir} conductance (Bacci et al. 2004). Whilst a similar postsynaptic mechanism is yet to be described in the hippocampus, an activity-dependent, autocrine-like, endocannabinoid-mediated hyperpolarization was recently described in CA3 pyramidal cells (Stempel et al. 2016). This hyperpolarization is mediated by endogenous release of 2-AG and postsynaptic activation

Table 6 Summary of cannabinoid signalling in the hippocampus

Receptor	CB1	CB2	GPR55
Expression in the hippocampus	Strongly expressed in interneurons (esp. CCK basket cells)	Highly expressed in non-neuronal cell types (e.g. microglia), weak neuronal expression	Widely expressed
Signalling	Gi and others, ↑A-type K^+, ↓N & P/Q Ca^{2+}, ↓M and D type K^+; ↑ Ih	Gi and others	Gq, Gα13 and others
Gross effect	Decrease GABA release (main effect) and other transmitters, decrease in dendritic excitability	Hyperpolarization of CA3 pyramidal cells	Increases release probability at glutamatergic synapses, enhances LTP
References	Kano et al. (2009), Pagotto et al. (2006) and Maroso et al. (2016)	Onaivi et al. (2006) and Stempel et al. (2016)	Henstridge et al. (2009), Lauckner et al. (2008), Ryberg et al. (2007) and Hurst et al. (2017)

of CB2 Rs (Stempel et al. 2016). Surprisingly, the effect was not mediated by K_{ir}, but by a sodium-dependent bicarbonate transporter (Stempel et al. 2016). GPR55 activation, through G_q-mediated release of calcium from internal stores, has been shown to inhibit I_M in expression systems (Lauckner et al. 2008), but it is not clear whether this is a common postsynaptic mechanism shared with CB1 Rs (Schweitzer 2000). Finally, CB1 receptors have recently been shown to enhance tonic I_h in a subset of CA1 pyramidal cells, which impairs dendritic integration of EPSCs and reduces LTP (Maroso et al. 2016; Vargish and McBain 2016).

Action of Endocannabinoids on Excitatory Synapses

Pharmacological activation of CB1 receptors has been shown to cause a profound (~86%) suppression of EPSCs in cultured neurons (Shen et al. 1996), and this effect is consistent with a presynaptic reduction in glutamate release. In terms of functional control of synaptic transmission, endocannabinoids have been shown to act as a retrograde messenger at glutamatergic synapses to produce a suppression glutamate release (Ohno-Shosaku et al. 2002). This is an activity-dependent depolarization-induced suppression of excitatory transmission (DSE) and is analogous to the more rigorously characterized suppression seen at inhibitory synapses (below). However, the CB1-mediated suppression of excitatory and inhibitory transmission differs in certain respects. Firstly, a more pronounced depolarization (~10 sec) is necessary to induce DSE than to cause suppression at inhibitory synapses (Ohno-Shosaku

et al. 2002). Secondly, the excitatory terminals themselves are less sensitive to cannabinoid receptor activation (Ohno-Shosaku et al. 2002). Activation of GPR55 has recently been shown to increase release probability at SC synapses through the mobilization of internal presynaptic calcium stores (Sylantyev et al. 2013) and enhance LTP (Hurst et al. 2017).

Action of Endocannabinoids on Inhibitory Synapses

Early reports by Pitler and Alger first described a phenomenon known as depolarization-induced suppression of inhibition (DSI) in CA1 pyramidal cells (Pitler and Alger 1992b). This phenomenon has subsequently been demonstrated in CA3 pyramidal cells, DG cells, mossy cells, CCK-positive interneurons (Kano et al. 2009) as well as other brain areas, notably the cerebellum. DSI is a transient but profound suppression of inhibition (spontaneous or evoked inhibitory postsynaptic events) that follows activity (e.g. depolarization and action potentials) in the postsynaptic cell. Studies in brain slices and cultured hippocampal neurons later confirmed that postsynaptic depolarization and resultant increase in intracellular free Ca^{2+} to cause a transient suppression of IPSCs and that this suppression was due to retrograde cannabinoid signalling-mediated reduction of GABA release (Ohno-Shosaku et al. 2002; Wilson and Nicoll 2001). It is now widely accepted that retrograde signalling by CB1 receptors is an important process in the dynamic regulation of GABAergic transmission (Castillo et al. 2012) (Fig. 6a). However, there is considerable evidence that cannabinoid signalling is not ubiquitous but preferentially regulates specific interneuronal connections (Younts and Castillo 2014). For instance, the output of major classes of basket cell is proposed to be differentially sensitive to cannabinoid regulation with the PV-containing basket cells being insensitive to CB1R activation, whereas GABA released from CCK-containing population are exquisitely sensitive (Freund and Katona 2007; Glickfeld and Scanziani 2006). However, the nature of the suppression of release is complex with evidence for both presynaptic and postsynaptic loci of action (Foldy et al. 2006; Neu et al. 2007).

The actions of eCBs at inhibitory synapses highlight the need to view neuromodulation as complex network phenomena. In addition to classical DSI, cannabinoids are known to mediate activity-dependent long-lasting heterosynaptic LTD at GABAergic synapses (Castillo et al. 2012) (Fig. 6b). This mechanism is initially triggered by the synaptic release of glutamate and activation of group 1 mGluRs on CA1 pyramidal cells. In turn, release of endocannabinoids is triggered which then initiates LTD of GABA release (Chevaleyre and Castillo 2003; Castillo et al. 2012) with the ultimate effect being a long-lasting increase in pyramidal cell excitability.

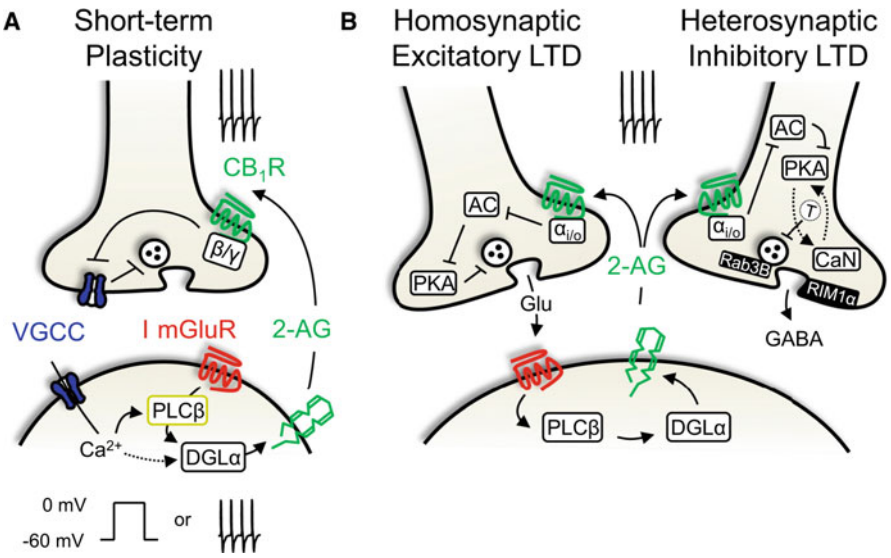

Fig. 6 Molecular mechanisms underlying endocannabinoid-mediated short- and long-term synaptic plasticity. (**a**) In endocannabinoid-mediated short-term plasticity, voltage-gated calcium channels (VGCC) or G_q-coupled receptors (i.e. Type 1 mGluRs) increase postsynaptic intracellular activities of diacylglycerol lipase (DGLα), causing the retrograde diffusion of eCBs to presynaptic CB1Rs. Activation of presynaptic CB1Rs inhibits VGCCs, which reduces neurotransmitter release. (**b**) Presynaptic activity activates postsynaptic mGluRs, inducing release of eCBs and presynaptic activation of CB1Rs at glutamatergic or GABAergic presynaptic terminals. At glutamatergic synapses, CB1-mediated $G_{i/o}$ signalling reduces cAMP levels and PKA activity, causing a LTD of glutamate release. At inhibitory synapses, a similar presynaptic mechanism activates calcineurin (CaN), which induces LTD of GABA release. (From Castillo et al. 2012, with permission)

Nitric Oxide

Production and Release of Nitric Oxide

Nitric oxide (NO) is synthesized de novo by a series of enzymes known as NO synthases (NOS) (Zhou and Zhu 2009). All three forms of NO synthase are expressed in the hippocampus. Original studies suggested pyramidal cells to express high levels of the endothelial form of NOS, whereas the neuronal form of the protein was restricted to diffuse populations of interneurons (Dinerman et al. 1994). However, more recent evidence has shown principal cells and selected interneurons to express the neuronal form with the endothelial form being restricted to vascular endothelium (Blackshaw et al. 2003). As NO is not stored and is a highly membrane-permeable molecule, the wide distribution of the enzymes in dendrites, soma and axon is likely to reflect the nature of its dispersal and suggested primary role as a retrograde transmitter. The prototypical activator of NOS is postsynaptic Ca^{2+} entry via the NMDA receptor leading Ca^{2+}/calmodulin interaction and NO production (Garthwaite 2008). NO may be released from presynaptic nerves by action potential-dependent activation of voltage-gated Ca^{2+} channels. Reports also suggest that

calcium-permeable AMPA receptors are an important regulator of NO production (Frade et al. 2008). Once produced, NO gas is itself is highly soluble, rapidly diffusible, highly membrane permeant but also highly labile (Garthwaite 2016).

Nitric Oxide Effectors

Nitric oxide acts through the regulation of soluble guanylyl cyclase. Within the context of neurons, guanylyl cyclase (the nitric oxide 'receptor') occurs in various isoforms and is often associated with the postsynaptic density in both principal cells and interneurons (Szabadits et al. 2007, 2011). However, other forms of the receptor may be transported to the membrane by signals including cannabinoids (Jones et al. 2008). The resultant production of cGMP regulates a range of cyclic nucleotide-gated channels as well as regulating multiple effectors (Maroso et al. 2016; Garthwaite 2016).

Action of Nitric Oxide on Intrinsic Properties

Despite abundant literature on the role of nitric oxide in regulating synaptic transmission, the action of NO on intrinsic postsynaptic properties of hippocampal neurons is sparse. However, a recent study provided evidence that CB1 R activation generated NO, which increased tonic dendritic I_h in CA1 pyramidal cells (Maroso et al. 2016; Vargish and McBain 2016).

Action of Nitric Oxide on Excitatory Synapses

There exists a significant body of evidence suggesting that certain forms of hippocampal LTP are dependent upon the action of NO as a diffusible retrograde messenger (Feil and Kleppisch 2008; Garthwaite and Boulton 1995; Schuman and Madison 1991, 1994). Blockade of NO signalling prevents LTP, whereas application of NO donors promotes the development of LTP (Schuman and Madison 1991; Arancio et al. 1996). However, the significance of NO in regulating synaptic plasticity seems to vary between species and between synapses. For instance, in areas CA1, NO-mediated/NO-regulated LTP is more prominent at apical dendrites than at synapses targeting basal dendrites (Haley et al. 1996; Son et al. 1996). In terms of the action of NO on basal synaptic transmission, there is evidence to suggest that NO may also produce an enhancement of glutamatergic transmission distinct from the enduring forms of potentiation such as LTP (Bon and Garthwaite 2001). However, studies have shown that NO may also transiently suppress glutamatergic transmission (Boulton et al. 1994). This may in part be mediated through triggering the release of adenosine (Arrigoni and Rosenberg 2006). A recently described mechanism is that CB1 activation on CA1 pyramidal cell dendrites generates NO, which activates I_h, reduces dendritic integration and impairs LTP (Maroso et al. 2016; Vargish and McBain 2016).

Action of Nitric Oxide on Inhibitory Synapses

Whilst morphological studies suggest that hippocampal GABAergic synapses are endowed with the molecular machinery for NO signalling, functional studies to assess the significance of nitric oxide in regulating inhibitory transmission are rather limited (Szabadits et al. 2007; Szabadits et al. 2011). However, recent evidence suggests that NO signalling may be an important mediator in depolarization-induced suppression of inhibition (Makara et al. 2007). The CCK BCs in CA1 and CA3, but not in DG, appear to be the major interneuron subtypes that increase cGMP signalling in response to NO donors (Szabadits et al. 2011). Hippocampal neurogliaform and ivy cells express NOS, but the function of NO within these interneuron circuits is not yet clear (Armstrong et al. 2012; Overstreet-Wadiche and McBain 2015).

Neuropeptides

Production and Release of Neuropeptides

The hippocampal formation is modulated by a diverse array of neuroactive peptides. Some of these are released from neurons intrinsic to the hippocampus (mainly interneurons but also principal cells), whereas others are supplied by inputs from diverse brain regions (Baraban and Tallent 2004). In general, neuropeptides are synthesized and stored for action potential-dependent release. The levels of neuropeptides and their receptors are often dynamically regulated, especially in association with plasticity processes and disease states. The neuropeptides represent a major category of modulator, and a detailed description of their expression, signalling and actions at different hippocampal cells and circuits is beyond the scope of this chapter. Whilst some actions of peptide modulators are rather ubiquitous, other effects can be highly cell type- or synapse-specific. Although much knowledge has been gained on neuropeptide expression and function in the hippocampus, for brevity, the table below summarizes some of the major peptide systems and their primary mechanisms of modulation in the hippocampus.

Action of Neuropeptides on Intrinsic Properties (Table 7)

Miscellaneous Neuromodulators

This chapter has aimed to provide a primer to the concept of neuromodulation by reviewing some of the major neuromodulator systems. However, it should be noted that there are likely to be very many other systems that may be significant regulators of hippocampal cells and circuits. Most of these are activators of metabotropic receptors. Examples here would include sphingolipids (Kajimoto et al. 2007),

Table 7 Summary of neuropeptide transmitter actions in the hippocampus

Neuropeptide	Expression	Receptors	Signalling	Modulation of intrinsic properties	Modulation of synaptic transmission	References
NPY	Neurogliaform cells. Various interneurons (bistratified cells), small amounts in principal cells. Strongest in dentate gyrus. NB. Important species differences in expression between human and rodent brain	$Y_{1\text{-}5}$	Y1	↓ N-type Ca^{++} currents (Y1 and Y2) but little overt postsynaptic action	↓glutamatergic transmission (Y2), ↓ LTP induction and short-term facilitation; ↓IPSC frequency	Haas et al. (1987), Klapstein and Colmers (1993), Ledri et al. (2011), Li et al. (2017), McQuiston et al. (1996), Overstreet-Wadiche and McBain (2015), Sperk et al. (2007) and Whittaker et al. (1999)
		Y1 mainly postsynaptic on principal cell dendrites in areas CA1 and CA3; Y2 postsynaptic on principal cells (DG) and on presynaptic mossy terminals	Y2			
Substance P	Various interneurons and granule cells as well as extrinsic projections (e.g. supramammillary)	$NK_{1\text{-}3}$	Most actions mediated by NK1	Depolarization on pyramidal cells and interneurons	↓EPSP (∼30%) and IPSP amplitude in pyramidal cells, ↑IPSPs between interneurons; ↑ excitability of interneurons	Borhegyi and Leranth (1997), Davies and Kohler (1985), Dreifuss and Raggenbass (1986), Kouznetsova and Nistri (1998), Ogier and Raggenbass (2003), Ogier et al. (2008) and Zaninetti and Raggenbass (2000)

(continued)

Table 7 (continued)

Neuropeptide	Expression	Receptors	Signalling	Modulation of intrinsic properties	Modulation of synaptic transmission	References
CCK	Various interneurons (basket, Schaffer-associated, PP-associated), released mainly as CCK8	Mainly CCK_2 (CCK_B)	CCK_2	Depolarization, $\downarrow K_{leak}$, $\downarrow Ca^{++}$ activated K^+ currents; signalling through endo-cannabinoid pathway; increase tonic inhibition through depolarization of interneurons – non-selective cationic conductance in PV+ basket cells	↓glutamatergic transmission (Schaffer collateral), ↑or↓ GABAergic transmission depending on interneuronal class	Boden and Hill (1988), Bohme et al. (1988), Dodd and Kelly (1979), Foldy et al. (2007), Lee et al. (2011), Karson et al. (2008), MacVicar et al. (1987), Miller et al. (1997) and Shinohara and Kawasaki (1997)

Opioids	Widely distributed	μ, δ, κ	Various	Hyperpolarization of interneurons – PV+ve basket cells, ivy and neurogliaform cells, mixed action on principal cells	↓glutamatergic transmission, ↓LTP, ↓GABAergic transmission	Glickfeld et al. (2008), Krook-Magnuson et al. (2011), Madison and Nicoll (1988a), McDermott and Schrader (2011), Moore et al. (1994), Rezai et al. (2013), Wagner et al. (1993), Weisskopf et al. (1993) and Zieglgansberger et al. (1979)
CGRP	Widely distributed but important species differences, some (CA2) pyramidal cells and strongly expressed in specific interneurons; hilar mossy cells and CA3c pyramidal cells	$CGPR_1$	cAMP	↓Ca^{++} activated K^+ current I(sAHP)	↓LTP	Freund et al. (1997) and Sakurai and Kosaka (2007)
Leptin	Synthesized in adipocytes and transported into brain, local biosynthesis	Ob-$R_{a\text{-}f}$	Cytokine receptor, JAK2	Hyperpolarization, ↑BK channel activity	Modulation of LTP and LTD;↑ GABAergic transmission	Durakoglugil et al. (2005), Guimond et al. (2014), Harvey (2007), Irving and Harvey (2014), Luo et al. (2015), Mercer et al. (1996), and Shanley et al. (2001)

(continued)

Table 7 (continued)

Neuropeptide	Expression	Receptors	Signalling	Modulation of intrinsic properties	Modulation of synaptic transmission	References
Somatostatin	Various interneurons (e.g. bistratified, O-LM cells)	$SST_{1\text{-}5}$	↓N-type Ca++ currents, ↑M current, ↑K_{leak}	Hyperpolarization of pyramidal cells, modulation of various K^+ channels	↓glutamatergic transmission, suppress PP-GC LTP	Baratta et al. (2002), Moore et al. (1988), Pittman and Siggins (1981), Qiu et al. (2008), Schweitzer et al. (1990), Tallent and Siggins (1997) and Tallent and Qiu (2008)
VIP	Various interneurons (basket cells, interneuron targeting cells)	$VPAC_1$ and $VPAC_2$	Various inc. I_{SAHP}	Depolarization of pyramidal cells, ↑ NMDA currents	Enhance GABAergic and glutamatergic transmission (may be indirect)	Cunha-Reis et al. (2004), Cunha-Reis et al. (2005), Haas and Gahwiler (1992), Haug and Storm (2000) and Yang et al. (2009)
Oxytocin	Produced in hypothalamo-neurohypophyseal cells as well as neurons terminating throughout CA1, CA3 and DG	OXTR	Multiple	No direct effect on pyramidal cells. Depolarize subset of interneurons (important species differences)	Suppress PP-DG LTP; ↑ SC-CA1 LTP; alter chloride transporter expression to regulate polarity of inhibition, use-dependent ↓IPSC	Dubrovsky et al. (2002), Lin et al. (2012), Owen et al. (2013), Raggenbass (2001), Tyzio et al. (2006) and Zaninetti and Raggenbass (2000)

Vasopressin	As above	AVPR1A, AVPR1B are major brain forms		Depolarize subset of interneurons	Conflicting reports showing ↑and ↓ LTP	Chafai et al. (2012), Chen et al. (1993), Dubrovsky et al. (2002), Hallbeck et al. (1999), Muhlethaler et al. (1984) and Ramanathan et al. (2012)
Cortistatin	Hippocampal interneurons, partially co-localized with somatostatin-positive cells	SST_{1-5}		↑Ih	↓ LTP	de Lecea and Sutcliffe (1996), de Lecea et al. (1997), Schweitzer et al. (2003) and Tallent et al. (2005)
Bombesin (neurmedin B and gastrin-releasing peptide)	Widely expressed	BB1 and BB2		Depolarize subset of interneurons (BB2)	↑EPSC amplitude (GRP)	Battey and Wada (1991), Dreifuss and Raggenbass (1986), Lee et al. (1999a) and Yang et al. (2017)
TRH	Widespread expression of hormone mRNA and receptors	TRHR	IP3 and PKC pathways	Hyperpolarization, regulation of various K^+ channels in CA1 pyramidal cells	↓PP-GC LTP, ↑Mossy fibre-CA3 LTP, ↓IPSPs	Deng et al. (2006), Ebihara and Akaike (1993), Ishihara et al. (1992), Manaker et al. (1985) and Stocca and Nistri (1996)
Melanocortin	ACTH and other related peptides released systemically	MC1R-MC5R			↑LTP (MC4R)	Shen et al. (2013)

Abbreviation: *ND* not determined

neurosteroids (Belelli and Lambert 2005), and various orphan and recently deorphanized receptors. Moreover, it is possible that other forms of neuromodulation may be brought about by less orthodox forms of signalling such as the proteolytic cleavage of protease activated receptors (Bushell et al. 2006; Gingrich et al. 2000). In addition to metabotropic receptor signalling, there are many additional modulators that act through direct orthosteric modulation of channels and receptors. One of the best characterized forms of such modulation is neurosteroids which are widely distributed and which produce an orthosteric modulation of the $GABA_A$ receptor. Whilst they do not overtly affect postsynaptic excitability, they exert a powerful potentiation of GABAergic transmission within hippocampal circuits (Belelli and Lambert 2005; Fester and Rune 2015).

Experimental Techniques

Most of the functional data concerning the action of neuromodulators on cellular and synaptic properties is obtained from electrophysiological experiments conducted in vitro either in brain slices experiments or using hippocampal neuronal cultures as described in earlier chapters. Classically this has been extracellular, intracellular (sharp) and more recently patch-clamp recordings. Clearly in vitro hippocampal preparations enable detailed scrutiny of the action of neuromodulators on active and passive intrinsic properties as well as synaptic transmission. They also permit detailed pharmacological investigation as drugs can be applied directly to the cells at a precise concentration. However, as mentioned earlier, optogenetic strategies are filling a niche as a more physiological means of activating specific synaptic neuromodulatory receptors with spatiotemporal precision (Lorincz and Adamantidis 2017; Spangler and Bruchas 2017), though this strategy still has some caveats and limitations, particularly at the synaptic level (Jackman et al. 2014). In contrast, the majority of in vivo recordings (multiunit recording or evoked field potentials) provide less mechanistic cellular/synaptic information, and pharmacological studies are limited by the difficulty in directing drugs to the site of action at a known concentration. Studies in vivo are typically limited to detecting changes in action potential discharge rate to when specific drugs/modulators are applied. However, in vivo studies are often valuable in determining the endogenous action of neuromodulators within the context of behavioural states. Moreover, in vivo recording can be used to relate the activity of neuromodulator sources (e.g. specific subcortical nuclei) with activity within hippocampal circuits. The introduction of the juxtacellular recording technique (Pinault 1996) has permitted the labelling of recorded neurons so that it is possible to relate the activity and modulation of recorded cells with their morphological characteristics and connectivity (Klausberger et al. 2003; Klausberger and Somogyi 2008). Moreover, patch-clamp recording from neurons in vivo (Ferster and Jagadeesh 1992; Jagadeesh et al. 1992) has undergone recent technical advances so that it is now not only possible to record from fine structures such as presynaptic boutons (Rancz et al. 2007; Geiger and Jonas 2000) but also to visualize and target

individual neurons in vivo (Kitamura et al. 2008; Pernia-Andrade and Jonas 2014). Finally, the introduction of optical (Deisseroth et al. 2006; Zhang et al. 2007) and genetic (Gong et al. 2007; Miyoshi and Fishell 2006) techniques to selectively excite or silence specific cells and circuits has already begun to address precise roles of specific cell types in behaviourally relevant network activity (Sohal et al. 2009; Lorincz and Adamantidis 2017). Finally, voltage-sensitive dyes are coming of age, which provide greater access to fine neuronal structures (Rowan and Christie 2017), and their use in conjunction with calcium indicators would prove particularly powerful. Aided by computational modelling, such correlated physiological, pharmacological, transgenic and morphological studies will be essential for the future understanding of how hippocampal cells and circuits are modulated at the whole organism level.

The Future

As has been apparent from the content this chapter, compared with previous chapters, the field of hippocampal neuromodulation is still at a nascent stage, with many unresolved questions remaining for the years ahead. Even for the most well-characterized classical modulators, there are still many unresolved questions, particularly in the context of how neuromodulators couple to specific channels across discrete neuronal subtypes. Questions also remain regarding the magnitude and time course of concentration transients reached by neuromodulatory receptors. The development of low-affinity antagonists for neuromodulatory receptors, in combination with optogenetic stimulation, would be particularly useful in this regard. The cellular and synaptic specificity of many neuromodulators demands molecular tools for systematic targeting of discrete afferents and cell types. Whilst one could argue that the increasing availability of these resources as one of the major technological developments over the last decade, research at the frontier in neuronal classification has shown that next-generation molecular tools are needed to differentiate between an increasing number of distinct cell types. Combining electrophysiological, genetic, molecular, pharmacological and anatomical techniques have revealed striking differences in cell type specificity of cholinergic neuromodulation (Cea-del Rio et al. 2010), which is likely to reveal cell type-specific differences with additional neuromodulators. The availability for genetic manipulation in transgenic animals is already proving very useful, especially in defining the importance of receptor subtypes in specific circuits where specific pharmacological tools may not be useful or available. The increasing use of Cre-loxP systems whereby specific modulator systems can be modified in a cell type-specific manner shows great potential over conventional pharmacological or global knockout strategies in resolving the precise functions of neuromodulators in specific cell types (i.e. Yi et al. 2014). At the level of neurochemically and anatomically defined hippocampal cell types, we are still far from gaining detailed knowledge of the repertoire of neuromodulator receptors expressed and localized.

Some progress is being made in this direction using techniques such as single-cell RT-PCR (Monyer and Markram 2004; Toledo-Rodriguez and Markram 2007) in which it is possible to fully characterize the expression profile of specific receptor classes in neurochemically defined cell types (Hillman et al. 2005; Cea-del Rio et al. 2010). With the availability of large-scale single-cell RNA sequencing, however, the goal of knowing all possible neuromodulatory receptor subtypes within a single-cell type may soon be achievable (Cadwell et al. 2017; Foldy et al. 2016; Zeisel et al. 2015). However, a single-cell transcriptomics approach does not allow the visualization and precise spatial localization of neuromodulatory receptors and their effectors with respect to cellular and synaptic domains (Triller and Choquet 2008). The widespread use of genetically encoded epitope-tagged receptors and channels would facilitate subcellular localization studies even if classic immunocytochemical approaches are not practical or possible.

Whilst the current chapter has focused on individual neuromodulator systems and receptors essentially in isolation, it is important to be mindful that a single neuromodulator can often induce secondary effects that are mediated through different neuromodulators. For example, mAChR activation can induce endocannabinoid release, resulting in CB1-dependent presynaptic depression of GABAergic transmission (Fukudome et al. 2004; Kim et al. 2002; Neu et al. 2007; Alger et al. 2014; Nagode et al. 2011). An additional complication is that multiple neuromodulators may be present in the in vivo milieu in any given point in time; substantial crosstalk across multiple neuromodulatory systems is probably a common occurrence, with both synergistic and antagonistic interactions possible. Behavioural states, rather than discrete neuromodulatory systems turning on and off, are probably comprised of alterations of many different neuromodulatory systems that occur across a broad range of activity levels. At the level of the postsynaptic cell, the dimerization and oligomerization of different G-protein-coupled receptors (Milligan 2007) and neuromodulatory channels (van Hooft et al. 1998) might create novel interactions between different neuromodulators. These interactions and their modulation in hippocampal cells and circuits remain to be fully explored.

Finally, the synaptic and cellular architecture places important spatial constraints on the physiological functions of neuromodulators. Experiments in which receptors are activated exogenously will yield very different results from studies in which endogenous transmitter is released in a naturalistic fashion from endogenous sources within spatially restricted microdomains. The physiological significance of neuromodulation will be greatly assisted by understanding the in vivo activity of neuromodulatory neurons during learning behaviours, short-term plasticity of neurotransmitter release, neurotransmitter receptor kinetics, brain slice preparations that preserve neuromodulatory pathways (Manseau et al. 2008; Widmer et al. 2006) and new molecular or transgenic strategies to optically target neuromodulatory centres or afferents (Deisseroth et al. 2006; Zhang et al. 2007; Lorincz and Adamantidis 2017). It is only by adopting a range of these approaches that it will be possible to fully understand the action of neuromodulators on hippocampal circuitry.

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