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Neuromodulation by Glutamate and Acetylcholine can Change Circuit Dynamics by Regulating the Relative Influence of Afferent Input and Excitatory Feedback

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Abstract Substances such as acetylcholine and glutamate act as both neurotransmitters and neuromodulators. As neuromodulators, they change neural information processing by regulating synaptic transmitter release, altering baseline membrane potential and spiking activity, and modifying long-term synaptic plasticity. Slice physiology research has demonstrated that many neuromodulators differentially modulate afferent, incoming information compared to intrinsic and recurrent processing in cortical structures such as piriform cortex, neocortex, and the hippocampus. The enhancement of afferent (external) pathways versus the suppression at recurrent (internal) pathways could cause cortical dynamics to switch between a predominant influence of external stimulation to a predominant influence of internal recall. Modulation of afferent versus intrinsic processing could contribute to the role of neuromodulators in regulating attention, learning, and memory effects in behavior.

Keywords Memory function · Neuromodulation · Learning · Acetylcholine · Metabotropic glutamate receptors · Presynaptic inhibition

Introduction

Extensive physiological research has demonstrated the importance of neuromodulators in memory, attention, and cortical function. Understanding the functional role of neuromodulation in cortical structures requires the synthesis of physiological research utilizing in vitro and in vivo techniques to bridge between the observed effect at the cellular and molecular level, and the behavioral function of these effects. This review provides an overview of the physiological effects of neuromodulators and interprets behavioral data in the context of these effects. In particular, it focuses on how neuromodulators can regulate the relative influence of external stimulation and intrinsic processing, changing the dynamics from those appropriate for the encoding of new information to those appropriate for the recall of previously encoded information.

The same chemical, such as glutamate, can act as either a neurotransmitter or a neuromodulator, depending on the receptors the chemical binds to and the effects the chemical has on synaptic transmission and cell signaling. In general, the term neurotransmission refers to fast ionotropic effects, whereas the term neuromodulation refers to slower effects at metabotropic receptors. Compared to neurotransmitters, neuromodulators have slower, longer-lasting, and more diffuse effects on neuronal physiology, often due to effects at metabotropic receptors rather than ionotropic receptors. Neuromodulators do not directly participate in the transfer of information, via excitatory and inhibitory pathways, through a cortical structure. Instead, they modulate the transfer into or through a region by physiologically altering cellular properties, such as release probability and pyramidal cell adaptation, which affects the overall transmission of information. Neuromodulators are not just "excitatory" or "inhibitory", their effect on synaptic transmission or cellular excitability depends on the type of pre- or postsynaptic receptor the modulator binds to. For example, the effect of acetylcholine varies greatly depending on whether or not it binds to nicotinic compared to muscarinic acetylcholine receptors.

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Neuromodulators affect cellular activity and synaptic transmission in multiple ways (Fig. 1). Cortical structures, such as the hippocampus, receive sensory information about the environment from afferent fiber pathways. The rapid transmission of sensory information along afferent pathways into the cortical region occurs via excitatory glutamatergic synaptic transmission. Once glutamate is released from the presynaptic terminal, it evokes excitatory postsynaptic currents by activating alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) and *N*-methyl-D-aspartic acid (NMDA) receptors. Neuromodulators, such as acetylcholine, can modulate afferent fiber input by enhancing or reducing the release of glutamate from the presynaptic afferent fiber terminals, often by changing presynaptic calcium dynamics and release probability. Once arriving into a cortical region, sensory information then continues through the region by transmission along association and intrinsic fiber pathways, by excitatory glutamatergic synaptic transmission mediated by pyramidal cells. In addition to presynaptically regulating glutamate release from associational and intrinsic terminals, neuromodulators can also modulate network function by influencing the adaptation or persistence of spiking activity in pyramidal cells and resting membrane potential.

Feedforward and feedback inhibition, mediated by GABAergic interneurons, also influences the transmission of information through a cortical region. In contrast to pyramidal cells, principal cells whose projections provide output to other brain regions, interneurons can modulate activity locally, due to their shorter axons. Incoming afferent input from outside cortical regions can activate inhibitory interneurons, causing feedforward inhibition and influencing

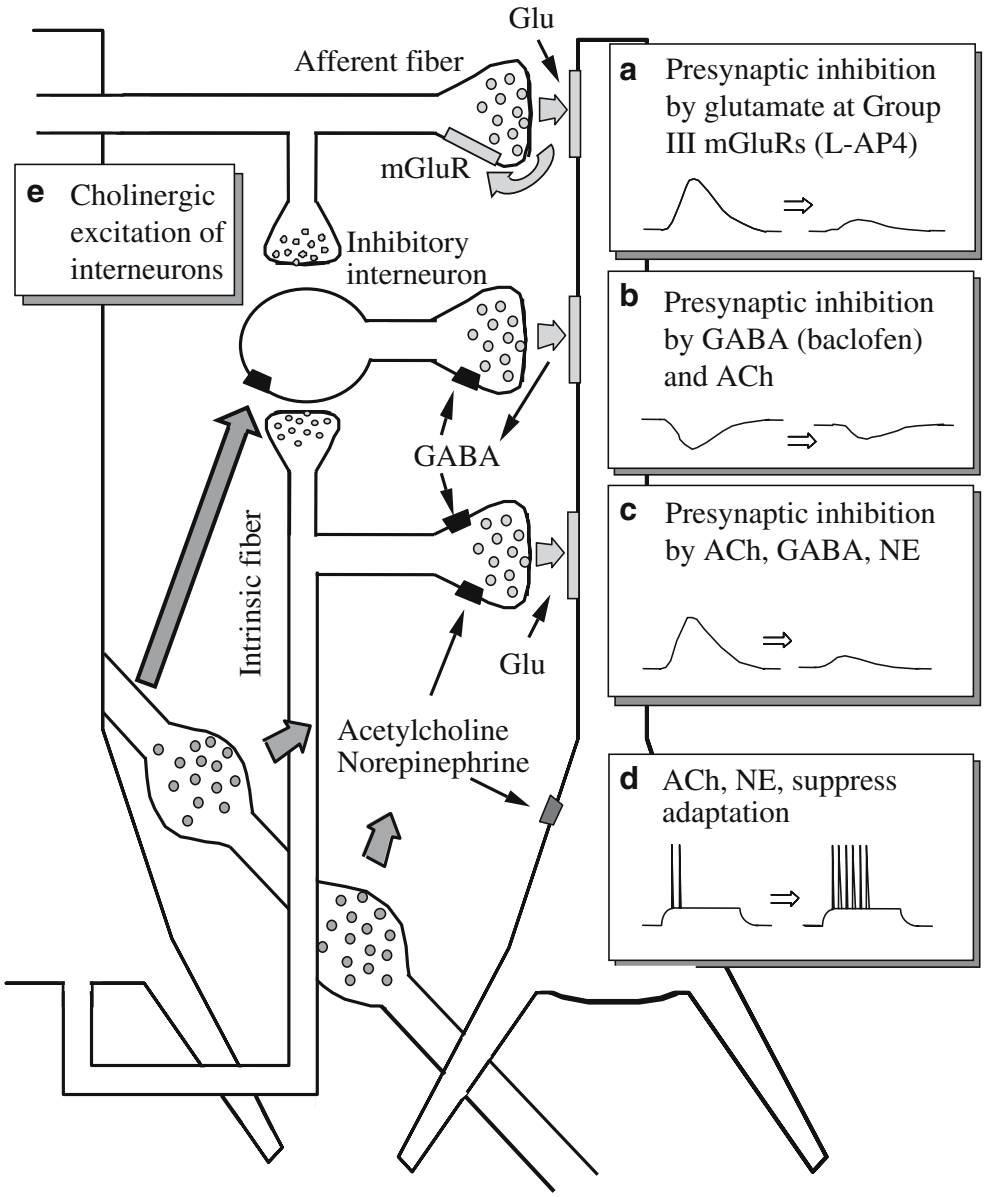

Fig. 1 Complementary effect of neuromodulation on synaptic transmission and pyramidal cell activity. Afferent and intrinsic fibers release glutamate, which has fast neurotransmitter effects and metabotropic glutamate receptors and GABA, which has neuromodulatory effects at $GABA_B$ receptors. Volume transmission of other neuromodulators, such as acetylcholine and norepinephrine, can influence synaptic transmission and cortical function as well. **a** Activation of presynaptic group III metabotropic glutamate receptors causes reduction of glutamate release and reduction of synaptic potentials. Experimentally induced by DL-AP4, this effect is stronger at afferent synapses compared to intrinsic synapses. **b** Presynaptic suppression of inhibitory synaptic transmission by activation of presynaptic $GABA_B$ or cholinergic receptors located on inhibitory interneurons. **c** Activation of presynaptic muscarinic cholinergic receptors causes presynaptic inhibition of glutamate release. A similar effect is caused by norepinephrine (NE) and $GABA_B$ receptors. **d** Postsynaptic acetylcholine and NE receptors reduce pyramidal cell adaptation by suppressing potassium currents underlying adaptation, causing an increased spiking response to current injection. **e** Cholinergic activation of interneurons results in depolarization [54] and excitation of interneurons [62]

pyramidal cell activity. Examples of feedforward inhibition mediated by interneurons has been observed in layer Ia of piriform cortex [1] and in stratum-lacunosum moleculare of CA1 in the hippocampus [2]. Recurrent and associational excitatory transmission can also excite inhibitory interneurons and cause feedback inhibition. The activation of inhibitory interneurons, either by feedback or feedforward inhibition, causes the release of GABA. Once GABA is released, it can evoke two inhibitory postsynaptic currents with different time courses [1, 3]. $GABA_A$ receptor activation results in very rapid and brief chloride currents, while $GABA_B$ receptor activation results in slower and longer-lasting potassium currents.

Based on in vitro slice physiology, many neuromodulators appear to differentially modulate intrinsic and association pathways compared to afferent pathways. The lamina selective modulation of synaptic transmission by some neuromodulators can act in a complementary manner, as in the effects of acetylcholine in the hippocampus [4]. Behavioral work in vivo has suggested that the lamina selective effects of neuromodulators could serve an important role in circuit dynamics, and ultimately, in memory and attentional processing.

Anatomical Constraints on Neuromodulatory Effects

The dynamic influences of neuromodulators on afferent input versus intrinsic input depend on the broad and diffuse transmission of neuromodulators. While some neuromodulators are only synthesized in neuronal pathways arising from specific subcortical nuclei, glutamate can, under some circumstances, act as a neuromodulator by activating presynaptic metabotropic glutamate receptors. Although the rapid removal of glutamate from the synapse and the low affinities of postsynaptic ionotropic glutamate receptors appears to suggest that glutamate release only activates postsynaptic receptors, extrasynaptic glutamate has been shown to activate presynaptic metabotropic glutamate receptors. For example, the spillover of glutamate released from excitatory mossy fibers in the cerebellar glomerulus activates presynaptic metabotropic glutamate receptors and inhibits GABA release from Golgi cells [5]. In addition, high frequency activity has been shown to increase the concentration of glutamate and delay the clearance from the synapse at hippocampal mossy fibers, causing the activation of presynaptic metabotropic glutamate receptors [6].

While neurons throughout the brain synthesize and release glutamate, the majority of neuromodulators, such as acetylcholine, are synthesized only in a subset of neurons located in specific nuclei. Volume transmission of neuromodulators has been hypothesized to underlie the broad and diffuse transmission of these modulators in cortical regions. Volume transmission could provide a general activation of cholinergic receptors at a number of receptor sites, rather than focused effects localized at individual synaptic contacts [7]. Anatomical evidence supports this concept of volume transmission for acetylcholine. Postsynaptic densities rarely accompany the axonal varicosities on cholinergic fibers [8, 9], suggesting that the release sites of acetylcholine do not associate with specific clusters of cholinergic receptors. For example, in the hippocampus, only 7% of varicosities on cholinergic fibers have associated synaptic structures, contrasting with GABAergic varicosities, which all show synaptic specializations [8]. In the parietal cortex, less than 15% of the cholinergic varicosities were associated with postsynaptic junctions [9]. Volume transmission could allow almost constant presence of acetylcholine in the extracellular fluid, and fluctuations in these levels could have effects on neuronal activity both at the presynaptic and postsynaptic level.

Modulation of Excitatory Synaptic Transmission

The vesicular release of neurotransmitter is caused by an increase in the intracellular concentration of calcium, dependent on the action potential activating voltage sensitive calcium channels. Modulation of presynaptic vesicular release can either suppress or enhance excitatory transmission, often by decreasing or increasing release probability. Presynaptic modulation of excitatory transmission has been extensively researched in cortical structures with a laminar organization of fiber pathways and excitatory synapses, such as the hippocampus and piriform cortex. Laminar segregation of the fiber pathways and excitatory synapses facilitates the selective investigation of modulatory effects on afferent versus intrinsic synapses.

Presynaptic Effects: Acetylcholine

Activation of presynaptic muscarinic or nicotinic acetylcholine receptors results in significantly different effects on excitatory synaptic transmission. Muscarinic cholinergic agonists suppress synaptic transmission in piriform cortex [10, 11], the hippocampus [12–14], layer II/III of prefrontal cortex [15], and visual cortex [16]. A lamina selective cholinergic modulation of intrinsic versus afferent fibers was described in piriform cortex, where the cholinergic agonist carbachol selectively suppresses synaptic transmission at intrinsic synapses of layer Ib but not at the afferent fiber synapses of layer Ia [10]. In the hippocampus, early research found that cholinergic agonists suppressed synaptic potentials in the afferent, perforant path to the middle molecular layer of the dentate gyrus [18, 19], and in the Schaffer collaterals in SR of CA1 [14, 20, 21]. Recent research demonstrates a clear laminar difference in the relative amount of suppression by acetylcholine in these two layers [12, 22–24]. In region CA1 of the hippocampus, the

cholinergic agonist carbachol causes significantly greater suppression of transmission in the intrinsic pathways terminating in SR compared to transmission by afferent pathways terminating in SLM [12] and depends partly on activation of M1 muscarinic acetylcholine receptors, although other receptors are also involved [25]. In the dentate gyrus, acetylcholine suppresses synaptic transmission more in the middle molecular layer compared to the outer molecular layer [19]. The two layers receive inputs from different regions of entorhinal cortex, with the middle molecular layer receiving inputs from the medial entorhinal and the outer molecular layer receiving inputs from lateral entorhinal cortex. Carbachol also selectively suppresses intracortical connections in neocortex while having little effect on afferent thalamocortical inputs to neurons in layer IV of the same region [26, 27]. The selective presynaptic suppression of intrinsic connections by muscarinic receptors could prevent old, previously stored cortical information from interfering with new incoming information, arriving via afferent connections [28].

While muscarinic agonists selectively suppress intrinsic activity compared to external input, nicotinic agonists can enhance excitatory synaptic transmission at afferent synapses compared to intrinsic synapses. Enhancement of afferent input may occur as the result of direct, selective nicotinic enhancement of glutamatergic synaptic transmission [15, 29]. Direct glutamatergic enhancement, modulated by nicotinic acetylcholine receptors (nAChRs), has been observed for thalamocortical input into the prefrontal cortex [30]. Nicotine has also been shown to enhance evoked glutamatergic currents elicited by olfactory bulb explant fibers onto dispersed amygdala neurons [31]. Data from thalamocortical slices demonstrates that nicotinic receptors selectively enhance afferent thalamocortical input versus intrinsic neocortical connections by activating presynaptic $\alpha 7$ receptors [27]. Nicotine has also been shown to enhance fast, excitatory transmission in the hippocampus [32, 33], perhaps by activating presynaptic $\alpha 7$ receptors [34], which cause extracellular Ca^{2+} to flow into the presynaptic terminal and increase the release of glutamate [32, 34]. The increase in intracellular calcium caused by $\alpha 7$ activation could explain how nicotine application converts low probability synapses to high probability synapses, causing an increase in the probability of glutamate release [35]. At synapses between the medial habenula and interpeduncular neurons, nicotine enhances the number of tetrodotoxin resistant spontaneous postsynaptic currents, suggesting that nicotine presynaptically enhances transmitter release [36]. The selective nicotinic enhancement of afferent glutamatergic synaptic transmission could enhance the relative influence of afferent incoming information and complement the effects of muscarinic suppression of intrinsic synaptic transmission.

Presynaptic Effects: Metabotropic Glutamate Receptors

Groups II and III metabotropic glutamate receptors presynaptically suppress excitatory synaptic transmission in piriform cortex [37, 38], the hippocampus [39, 40], and in the neocortex [41]. In the hippocampus, the group III metabotropic glutamate receptor agonist L-AP4 has been shown to presynaptically reduce synaptic transmission in stratum lacunosum moleculare of CA1 [39], the Schaffer collaterals of CA1 [42, 43], the mossy fiber input to CA3 pyramidal cells [44], and perforant path input to dentate gyrus granule cells [45]. In the dentate gyrus, group III mGluR activation suppresses perforant path inputs from medial entorhinal cortex to the mid-molecular layer less than perforant path inputs from lateral entorhinal cortex to the outer molecular layer [17]. Lamina selective mGluR suppression in the inner and outer molecular layer of the dentate gyrus could help regulate theta discharge of entorhinal projection neurons that influence synaptic transmission in the perforant path [17]. In region CA1, activation of group III mGluRs with DL-AP4 causes a lamina selective suppression of synaptic transmission, resulting in more suppression of synaptic transmission in the afferent fiber synapses of SLM compared to the Schaffer collateral inputs to SR [40]. Similar to the lamina selective effect of DL-AP4 in the hippocampus, group III mGluR activation in the piriform cortex causes more suppression at afferent fiber synapses in layer Ia, while having little effect on the proximal fiber synapses in layer Ib [46]. This selective suppression of synaptic transmission of layer Ia synapses compared to proximal layer Ib synapses in piriform cortex mimics the selective suppression of afferent SLM synapses compared to intrinsic SR synapses in the hippocampus. In addition, in both piriform cortex and the hippocampus, an increase in paired pulse facilitation accompanies the suppression of synaptic transmission at distal or afferent synapses but does not accompany the suppression of synaptic transmission at proximal or intrinsic synapses [40, 46]. While the increase in paired pulse facilitation in the afferent synapses of piriform cortex and the hippocampus indicate a presynaptic effect, the nearly negligible change in paired pulse facilitation in the intrinsic synapses of the same regions indicates a more complex, possibly postsynaptic effect. The same laminar selectivity of group III mGluR activation is observed in region CA3 of the hippocampus (Giocomo and Hasselmo, unpublished data), with greater suppression of synaptic transmission observed in the perforant path inputs through SLM compared to the recurrent connections of SR (Fig. 2). The activation of mGluRs with high frequency stimulation [6] suggests that the selective suppression of afferent pathways by group III may serve to act as a low-pass filter for information coming into the hippocampus.

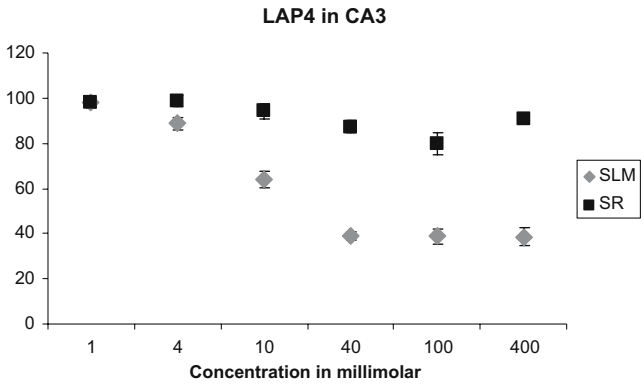

Fig. 2 Dose–response curve for presynaptic inhibition of evoked synaptic field potentials by the group III mGluR agonist DL-AP4 in stratum radiatum and stratum lacunosum moleculare of CA3. For the dose–response curve experiments, the potential was allowed to stabilize, and recording began with a 10-min baseline, followed by a 10-min perfusion of either 1, 4, 10, 40, 100, or 400 μM DL-AP4 (Sigma-Aldrich, St. Louis, MO) and ended with a 30- to 40-min washout period to ensure fEPSPs returned to more than 90% of baseline. For data analysis, the baseline amplitude was calculated by averaging the amplitude of ten excitatory synaptic field potentials before perfusion of the agonist. As illustrated by the dose–response curve, activation of group III mGluRs causes more presynaptic inhibition of synaptic transmission in the afferent, perforant path inputs in stratum lacunosum moleculare compared to the intrinsic connections in stratum radiatum of region CA3 in the hippocampus

Group II mGluRs presynaptically suppress synaptic transmission in layers Ia and Ib of piriform cortex [38] and in the perforant path inputs to the hippocampus and dentate gyrus [47]. In piriform cortex, group II mGluR agonists suppress Ia distal and Ib proximal synapses equally, but at synapses in hippocampal region CA1 and the dentate gyrus, activation of group II mGluRs results in a lamina selective suppression of synaptic transmission which is stronger in SLM [38, 47]. In the dentate gyrus, group II mGluR activation suppresses perforant path inputs from medial entorhinal cortex to the mid-molecular layer of the dentate gyrus and stratum-lacunosum moleculare of the hippocampus [47]. Group II mGluR activation causes a lamina-specific suppression of synaptic transmission within SLM and SR of region CA1 of the hippocampus [40]. Group II mGluRs are not localized to region SR of CA1, which accounts for the extreme lamina selectivity of group II mGluR activation in region CA1 of the hippocampus [48]. Recent time course experiments have demonstrated that in SLM of CA1, application of group II mGluR agonists results in a rapid onset of suppression of synaptic transmission, while in SR and SLM, application of group III mGluR agonists results in a slower onset of suppression of synaptic transmission. The more selective and faster suppression of synaptic transmission due to mGluR activation in the afferent pathways synapses could filter out high frequency, strong stimuli, and allow the mGluR activation to act as a low pass filter for information coming into the hippocampus [40]. Behavioral data demonstrating a role for presynaptic mGluRs in neuroprotection and sensory habituation support this hypothesis [49, 50]. In addition, the presynaptic filtering of afferent noise by mGluRs could complement the effects of cholinergic activation in reducing interference, allowing the system to better encode new information (Fig. 3). In contrast to modulation by acetylcholine which allows afferent information to dominate, while intrinsic feedback is reduced, the neuromodulatory effects of metabotropic glutamate receptor activation reduces the influence of afferent information, while allowing intrinsic feedback to dominate. The opposite effects of acetylcholine and metabotropic glutamate receptor activation on excitatory synaptic transmission could set up cortical dynamics in which cholinergic modulation prevents interference from previously stored memories during encoding of new memories and metabotropic glutamate receptor modulation prevents new information from interfering with the retrieval of previously stored information.

Modulation of Interneurons and GABA

In addition to modulating excitatory synaptic transmission, neuromodulators can also modulate inhibitory synaptic transmission. Experimental research indicates that neuromodulators cause a wide variety of changes in interneuron excitability and postsynaptic inhibitory currents. Neuromodulatory effects of acetylcholine and mGluR receptors influence inhibition in a somewhat complicated manner, often simultaneously exciting interneurons while causing presynaptic inhibition of GABA release. This can result in inhibition of background activity, but enhancement of response to afferent input [51]. The neuromodulation of GABAergic synaptic transmission also demonstrates some lamina selectivity. The interplay between enhancement of interneuron activity and presynaptic inhibition of GABA release could allow a transition from more distributed cortical activity to more focused activity in response to sensory input.

Modulation of Interneurons and GABA Release: Acetylcholine

Muscarinic agonists influence synaptic transmission by modulating interneuron activity in the cingulate cortex [52] and the hippocampus [53]. Activation of mAChRs in these brain regions causes a direct depolarization of inhibitory interneurons [54], resulting in an increase in the spiking activity of interneurons [53]. In the hippocampus, muscarinic receptor activation of interneurons simultaneously increases postsynaptic spiking, while also decreasing inhibitory synaptic transmission through presynaptic inhibition [55], mimicking the changes observed with mAChR activation of hippocampal pyramidal cells [56]. In most

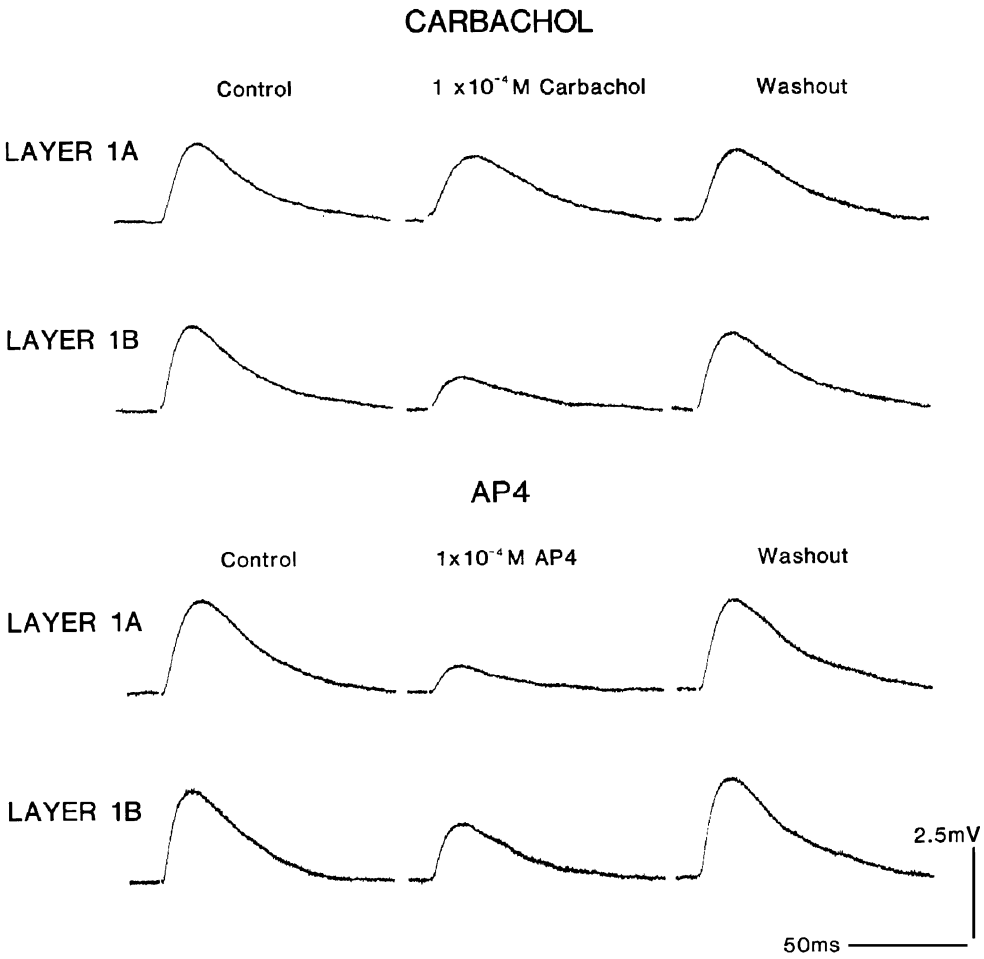

Fig. 3 Opposite effects on excitatory synaptic transmission recorded in a single neuron in piriform cortex due to activation of either group III metabotropic glutamate receptors or muscarinic receptors. From *left to right*, postsynaptic excitatory potentials recorded during control conditions, after perfusion of an agonist, and after washout of the agonist. *Top*: Application of carbachol causes presynaptic inhibition of synaptic transmission at the afferent synapses of layer 1B but does not significantly affect synaptic transmission at afferent synapses in layer 1A. *Bottom*: Application of L-AP4, a group III mGluR agonist, results in more presynaptic inhibition of synaptic transmission in the afferent fiber synapses in layer IA compared to the intrinsic synapses of layer IB

cases, stimulation of the cholinergic afferent fiber causes a slow depolarization in CA1 hippocampal interneurons [57]. In stratum oriens, cholinergic modulation of interneurons differs between stratum-oriens lacunosum moleculare (O-LM) interneurons, a specific subtype of interneuron which projects to SLM, and other interneurons located in stratum oriens (SO) [58]. Muscarinic activation of O-LM interneurons causes an increase in firing frequency and the size of the after-depolarization current due to the suppression of the M-current, the suppression of a calcium sensitive potassium current, and the activation of a nonspecific cation current [58]. In the presence of acetylcholine, O-LM cells increase their firing reliability in response to a subthreshold, oscillatory current injection. Activation of muscarinic receptors improves phase-locked firing and spike timing precision of O-LM interneurons when the oscillatory input is in the theta-band frequency (5–12 Hz) [59]. O-LM interneurons have been shown to play a role in theta modulation in the hippocampus in vivo [60], and this recent in vitro research suggests that in the presence of acetylcholine, hippocampal interneurons could contribute to the generation of theta rhythm and the synchronization of incoming input to theta frequencies [59].

Nicotinic acetylcholine receptors also modulate interneuron activity. Anatomical data indicates that in the hippocampus, a high number of nicotinic receptors are localized on interneurons [61]. In region CA1, nicotine excites interneurons and increases GABA currents [62, 63] by activating either $\alpha 7$ or $\alpha 3\beta 4$ nAChRs located on the interneurons [63–65]. Due to anatomical localizations of nicotinic receptors, nicotinic acetylcholine activation results in a lamina selective modulation of interneuron activity in region CA1 of the hippocampus. While interneurons in stratum radiatum do not show any nicotinic response, interneurons in SLM express $\alpha 7$ receptors, which cause rapid depolarization, and O-LM interneurons express more slowly activating non-$\alpha 7$ receptors [66]. The cholinergic depolarization of interneurons could reduce the background-firing rate of pyramidal cells during weak afferent input. In contrast, the cholinergic suppression of GABAergic transmission has the effect of enhancing the response to strong afferent input. Thus, these cholinergic effects reduce background activity, but heighten the response to suprathreshold stimuli [51].

In region CA3, nicotinic receptor activation modulates synaptic transmission in the perforant path through SLM but does not affect synaptic transmission in the recurrent, intrinsic connections of SR [4]. The lamina selective effect of nicotine application appears to act mostly on interneurons, as the modulation of synaptic transmission is not observed in the presence of the $GABA_A$ antagonist, picrotoxin. Suppression of interneuron activity by nicotine in SLM of region CA3 could result in the disinhibition of glutamatergic synaptic transmission, causing the selective enhancement of afferent input. Nicotine has been shown to inhibit interneurons in region SLM of CA1, causing the disinhibition of pyramidal cells [63, 67, 68]. More specifically, nicotine application results in greater inhibition of interneurons in SLM, compared to other cell layers of the hippocampus, suggesting that nicotine may more selectively disinhibit feedforward zones of the hippocampus [63]. Nicotinic inhibition of GABAergic interneurons, resulting in a disinhibition of excitatory activity, appears more selective for the feedforward connections of the perforant path and could allow for nicotinic receptor activation to selectively enhance incoming information.

Modulation of Interneurons and GABA Release: Metabotropic Glutamate Receptors

Presynaptic groups II and III metabotropic glutamate receptors modulate the release of GABA from inhibitory interneurons in the hippocampus [5, 69, 70]. Excess synaptic glutamate, or "spillover" glutamate, activates presynaptic metabotropic glutamate receptors and can cause a direct inhibition of GABA release from interneurons [5]. In the hippocampus, group III mGluR activation has been shown to depress inhibitory postsynaptic currents in the perforant path [69, 70] perhaps by depressing glutamate release onto GABAergic interneurons [70]. Group II metabotropic glutamate receptors depress excitatory synaptic transmission from mossy fiber inputs to interneurons in young rats [71]. In region SLM of CA1, group II mGluR activation results in a reduction of EPSC's and mEPSC's recorded from interneurons, suggesting that a decrease in excitatory transmission could contribute to reduced interneuron activity [69]. Interneuron modulation by metabotropic glutamate receptors could contribute to some of the lamina selective effects of presynaptic mGluR activation.

Postsynaptic Effects on Pyramidal Cell Adaptation and Resting Membrane Potential

Transmission of information through a cortical structure relies heavily on pyramidal cell activation. Sustained excitatory synaptic input will initially evoke high frequency generation of action potentials in the pyramidal cell. Over time, the rate of action potential firing decreases, as the pyramidal cell shows adaptation to the depolarizing event, due to the activation of voltage sensitive and calcium dependent potassium channels [3, 72]. Calcium-dependent potassium channels also contribute to the after-hyperpolarizing current (AHP), a long-lasting hyperpolarizing current that follows a string of action potentials.

Postsynaptic Effects on Pyramidal Cells: Acetylcholine

Muscarinic agonists influence pyramidal cells by postsynaptically suppressing the adaptation of pyramidal cells in brain slice preparations of region CA1 of the hippocampus [73]. Muscarinic agonists reduce the two currents that contribute to pyramidal cell adaptation after a series of action potentials, a calcium-activated potassium current and the M-current, blocking the adaptation of pyramidal cells [73]. Simultaneously, activation of postsynaptic cholinergic receptors depolarizes hippocampal pyramidal cells, enhancing the spiking response to excitatory synaptic input [56]. Cholinergic agonists also suppress adaptation of pyramidal cells in piriform cortex [74] and cingulate cortex, by blocking the slow after-hyperpolarization that follows a train of action potentials and blocking the M-current [75].

A slow depolarization of the resting membrane potential accompanies cholinergic activation, after iontophoretic and bath application in brain slice preparations [3, 76]. Cholinergic activation causes a slow depolarization by suppressing the tonically active potassium "leak" current, causing movement away from the reversal potential of potassium, which typically lies well below the resting potential of the cell [73]. In contrast to the effects of muscarinic agonist application, nicotine application does not affect the resting membrane potential of pyramidal cells [15]; however, it does depolarize the resting membrane potential of interneurons [66].

Long-Term Potentiation

Long-term potentiation appears to serve as a cellular mechanism contributing to learning and memory processes. Neuromodulators such as acetylcholine can modulate synaptic modification by contributing to or preventing long-term potentiation or long-term depression.

Long-Term Potentiation: Acetylcholine

Although muscarinic activation causes acute suppression of synaptic transmission, it also appears to enhance long-term potentiation, resulting in longer-term enhancement of synaptic strength. Application of muscarinic agonists causes an increase in the amplitude of long-term potentiation in the dentate gyrus [77], region CA1 of the hippocampus [78], the piriform cortex [79], and in neocortical structures [80].

The enhancement of LTP after cholinergic application may be due to the enhancement of NMDA currents or the suppression of pyramidal cell adaptation [81, 82], which would allow cells to be more readily excitable. Recently, administration of nicotinic agonists has also been shown to enhance short and long term synaptic plasticity at CA3–CA1 synapses in mice [83]. Nicotine also facilitates long-term potentiation in region CA1 of the hippocampus, perhaps by reducing inhibition on NMDA receptors by modulating interneuron activity [84]. While the selective suppression of intrinsic synaptic transmission could serve to prevent interference between new information and previously encoded information, enhanced LTP could facilitate encoding by allowing input to more easily form associations.

Long-Term Potentiation: Metabotropic Glutamate Receptors

Research on the role of mGluRs and long-term potentiation has had mixed and conflicting results. In vivo, ACPD has been shown to block the induction of LTP but this absence of LTP did not result in any learning impairments on spatial and nonspatial tasks in both a water maze and radial arm maze [85]. In vitro, the mGluR agonist ACPD has been shown to facilitate, prolong, or induce a slowly developing form of LTP [86]. The conflicting results of ACPD on LTP may be due to the fact that ACPD is a broad-spectrum agonist, and each group of mGluRs may differentially affect LTP. Group II agonists can inhibit LTP at CA1 synapses and the dentate gyrus, while application of group I agonists induce LTP in the hippocampus [87]. Group II mGluR3 has been shown to play a vital role in the modulation of long-term depression in the dentate gyrus [89]. The group III agonist, L-AP4, causes significant short-term depression in the perforant path, and this depression is more pronounced in the medial perforant path than the lateral perforant path [88].

Complementary Effect of Muscarinic and Nicotinic Receptors During Encoding Processes

Based on in vitro slice work, it is hypothesized that cholinergic modulation of afferent versus intrinsic connections facilitates encoding, while lower levels of acetylcholine allow consolidation and retrieval of memories. Behavioral research using humans and animals supports the hypothesis for the role of cholinergic modulation in memory processing, and specifically, the vital role of cholinergic modulation during the encoding process. A variety of experiments have utilized scopolamine, a muscarinic antagonist, to demonstrate that blocking muscarinic modulation prevents the encoding of new memories, as observed in free recall tasks or other memory tasks, but does not prevent recall of previously stored memories [90, 91]. Complementary to the effect of scopolamine, behavioral work in humans and animals has shown that administration of nicotine enhances attention and performance on memory-related tasks. In addition, similar to muscarinic blockade, nicotinic antagonists such as mecamylamine often cause impairments on memory-related tasks. The suppression of intrinsic connections by muscarinic activation and the enhancements of afferent synaptic transmission by nicotine, as demonstrated in slice work, may act as complementary mechanisms during the encoding of new information. Cholinergic modulation during encoding serves not only to prevent the interference of old information with new information, by muscarinic suppression of intrinsic connections, but also to enhance the input of new information, by nicotinic enhancement of afferent connections, and to enhance synaptic storage of associations by muscarinic enhancement of the mechanisms for long-term potentiation. The cholinergic suppression of feedback excitation and enhancement of afferent input during encoding gives afferent input a stronger influence than feedback during encoding. However, during retrieval, the afferent input is still present; it is just weaker relative to excitatory feedback. Thus, retrieval can still be triggered by afferent input to the hippocampal formation when cholinergic modulation is reduced. Disruption of either one of these two systems could cause behavioral impairments on memory-related tasks, particularly those that were dependent on the encoding of new or overlapping information.

Behavioral Work: Muscarinic Cholinergic Receptors

Behavioral research (Table 1) has consistently demonstrated that administration of scopolamine, the muscarinic antagonist, impairs the encoding of new verbal information, while having little effect on retrieval of previously stored information [91–93]. The effect of scopolamine on encoding appears to be due to the disruption of cholinergic innervation of parahippocampal cortices. Local infusions of scopolamine into the perirhinal and entorhinal cortices cause recognition impairments, while local infusions into the dentate gyrus or inferotemporal cortex do not have the same effect on recognition [94]. In addition, human lesions or surgery that causes damage to the fornix, destroying cholinergic innervation of the hippocampus by the medial septum, results in memory impairments. Patients with fornix damage often suffer from confabulations, a tendency to confuse their own memories with stories heard from or about other people [95–97]. In addition, patients with fornix lesions have difficulty on memory tasks in a manner similar to subjects who have been given scopolamine before the task. Fornix lesion patients are impaired on free recall tasks involving words or paragraphs [98–100]. The lack of cholinergic neuromodulation may cause chronic interference between encoding and retrieval, contributing to confabula-

tion, while also preventing the encoding of new stimuli. In animals, infusion of scopolamine directly into region CA1 or CA3 of the hippocampus impairs the encoding of spatial information on a maze task, while delivery of physostigmine, a cholinesterase inhibitor, impairs retrieval of spatial information on the same maze task [101]. Infusion of scopolamine into perirhinal cortex also impairs encoding, as measured by the performance on an object recognition task by rats given scopolamine before the sampling phase [102]. The selective impairment of encoding by scopolamine, and impairment of retrieval by physostigmine, supports the hypothesis that high levels of acetylcholine in the hippocampus facilitate encoding processes, while lower levels of acetylcholine in the hippocampus are necessary for correct retrieval processes. The importance of high acetylcholine levels in the hippocampus during encoding processes has also been supported by microdialysis studies, which have demonstrated an increase in levels of acetylcholine in the hippocampus specifically while learning a new task such as the T-maze [103] and food-rewarded mazes [104].

In normal human subjects, scopolamine administration just before learning a list of words impairs later recall on verbal free recall tasks, after a delay, for the words learned after scopolamine injection [91, 105, 106], but not for stimuli learned before scopolamine administration [91, 105]. Scopolamine also impairs performance on a variety of other memory-related tasks such as the detection of novel objects from a growing list of objects [107], memorizing the position of a chess piece [108], or memorizing pictures or objects [109]. The mnemonic impairment of scopolamine appears specific to short- or long-term memory and not to immediate recall, as digit span is not impaired [107, 110]. The same selective impairment has been demonstrated in nonhuman primates. In monkeys, recognition of a series of visual objects was disrupted only for new objects encoded after the systemic injection of scopolamine. Objects encoded in the absence of scopolamine were recognized normally [111, 112]. Administration of scopolamine also reduced the ability of rats to detect novel objects, indicating detrimental mnemonic effects from muscarinic blockade [113]. The selective impairment of scopolamine on recall for stimuli encoded subsequent to muscarinic blockade indicates that muscarinic modulation is a vital part of the encoding process. In combination with in vitro work, it suggests that blockade of muscarinic activation during the encoding process allows interference between previously encoding information and new incoming information, resulting in inadequate encoding of the new information.

The hypothesis that muscarinic modulation prevents interference between previously stored information and information being encoded is further supported by research using a paired-associate learning task. In a study by Atri et al. [114], scopolamine was administered to subjects who were then asked to learn work pairs (A–B), and after a delay, overlapping word pairs (A–C) and nonoverlapping word pairs (D–E). Subjects who were given scopolamine showed significantly greater impairment during recall for overlapping pairs compared to nonoverlapping word pairs [114]. The same impairment for overlapping stimuli has been demonstrated in rats. Administration of scopolamine in rats caused impaired learning for overlapping odor pairs compared to nonoverlapping odor pairs [115]. These behavioral experiments support the in vitro work and the hypothesis that muscarinic acetylcholine modulation may prevent interference of previously stored information during the encoding of new information. This interference problem is particularly notable when the task stimuli directly overlap with a previously encoded stimulus.

Activation of muscarinic receptors by acetylcholine also facilitates long-term potentiation in some intrinsic networks, such as in the hippocampus, and suppresses pyramidal cell adaptation thereby increasing spiking contributing to synaptic modification. These two cellular properties could allow connections between stimuli to form more easily during the encoding process and result in better retrieval. This hypothesis is supported by behavioral data that has demonstrated that scopolamine impairs episodic memory, memories that encode the relationship between a specific time and place, more than semantic or procedural memory [116, 117]. Episodic memory can be tested in animals by use of a water maze task in which a hidden platform is moved at the start of each testing day, requiring the animal to remember where the platform is on a given day. In rats, scopolamine impairs performance on this task, most likely by impairing the encoding of platform location [118, 119]. Similarly, performance in the eight-arm radial maze is significantly impaired with scopolamine administration or fornix lesions [120], due to the disruption of encoding for previously visited arms. When a delay is imposed between sample and test phases of the task, the impairment in performance increases [121]. Similar to human and nonhuman–primate work with scopolamine, this impairment on maze tasks is only observed when scopolamine is given before the encoding period and not if given during the delay between sample and test phases [119]. Memory tasks requiring the association of a time (sample versus test) and a specific place (arms visited or platform location) appear to be impaired with the blockade of muscarinic receptors. This supports the hypothesis that muscarinic modulation is also needed to enhance long-term potentiation in recurrent networks to create the appropriate connections needed for proper memory formation. In addition, some of the effects described above may be due to the interference during initial encoding, causing the difficulty in accurate retrieval of memories.

Research using scopolamine in a classical conditioning paradigm has also demonstrated that muscarinic blockade

results in a weakened inability to form connections between stimuli. Medial septal lesions, which destroy cholinergic innervation of the parahippocampal cortices, impairs rat learning in eye blink conditioning tasks [122], and scopolamine administration impairs learning of classical conditioning eye blink in rabbits [123] and humans [124]. Scopolamine administration also impairs appetitive jaw movement conditioning [125] and classical fear conditioning [126]. Scopolamine infused directly into region CA3 of the hippocampus caused impairment during the encoding of tone/shock induced fear conditioning and during the context test for the pairing, as determined by freezing behavior [127]. Physostigmine administration resulted in no impairment during encoding but did cause less freezing behavior during the context test for pairing.

Administration of scopolamine not only affects memory but also affects attention. Administration of scopolamine does appear to decrease the attention of subjects in a variety of attentional tasks, including the Stroop test and visual vigilance tasks [128–130]. The behavioral role of acetylcholine in attention versus memory may result from the same modulatory influences affecting different cortical regions. This is particularly evident in behavioral research involving nicotine effects.

Behavioral Work: Nicotinic Acetylcholine Receptors

Administration of nicotine or nicotinic antagonists has profound affects on attention and memory processing (Table 1). Similar to scopolamine, the injection of the nicotinic antagonist mecamylamine also results in impaired performance on tasks such as the radial arm maze [131]. Administration of nicotine or nicotinic agonist enhances attention and performance of humans and animals, such as rodents and monkeys, on a variety of memory-related tasks. While acetylcholine may suppress intrinsic connections to prevent interference between new information and previously encoded information, nicotinic receptors could complement this effect by enhancing the transmission of new information entering via afferent synapses. Physiological evidence suggests that at least in some cortical structures, nicotinic receptors are selectively distributed in a way that selectively enhances afferent input. For example, the selective enhancement of afferent input has been shown in stratum lacunosum moleculare of the hippocampus and in thalamo-cortical slice preparations of somatosensory cortex [4, 27].

Behavioral work in humans supports the hypothesis that nicotinic enhancement of synaptic transmission would result in enhanced memory and attention performance. In human participants, chronic transdermal administration of nicotine increases the performance of both nonsmokers and smokers on various attention tasks [132–134]. In addition to increasing attention, nicotine also increases performance of normal participants on several memory tasks. Oral administration of nicotine increases the number of words recalled during free recall tasks in nonsmoker subjects [135] and smoker subjects [136]. Smoking nicotine-containing cigarettes increased the number of words retrieved in free recall after they had been paired with a semantic fact compared to smokers who smoked a non-nicotine-containing cigarette [137]. Some evidence specifically suggests that nicotine may enhance consolidation of memories. Smokers of nicotine cigarettes performed better than nonsmokers and smokers of nicotine-free cigarettes on a paired associate task when tested 1 week after learning the word pairs [138]. Nonsmoker subjects given nicotine recall more information from prose material after nicotine administration [139].

The effect of nicotine on attention versus memory may depend on what cortical structure nicotine affects. Research suggests that nicotine can enhance both attention and memory processing. One study, in particular, showed that nicotine improved the performance of human subjects on both an immediate and delayed-free recall task. Subjects recalled more words for the later portion of the word list on the immediate recall task, a result indicating increased attention during the task. However, on the delayed recall task, subjects remembered more words from the beginning portion of the list, suggestive of a memory effect [140]. A second study also supports the role of nicotine specifically in memory processes. Smokers, who continued to smoke throughout the task, and nonsmokers, who continued to refrain from smoking, were tested on memorized material 1/2 hour after studying, and then again, 1 month later. Nonsmokers out-performed the smokers in the early recall test, but smokers significantly out-performed nonsmokers in the later recall test, suggesting that nicotine enhanced consolidation [141]. Although some of the effects of nicotine on memory tasks could be attributed to subjects' increased attention to the task, these two studies appear to also validate the role of nicotine in the enhancement of memory processing outside of attentional effects.

Animal behavioral work has also demonstrated the memory enhancing effects of nicotine administration. On delayed-non-match-to-sample tasks, nonhuman primates perform better after nicotine administration [142]. In both young and old rats, nicotine and nicotinic agonists improve acquisition and retention of platform location in a Morris Water Maze task [143]. Nicotine also enhances object recognition memory, as rats administered nicotine spend more time investigating novel over familiar objects compared to control rats [144]. In aged rats, nicotine improves learning and reference memory in the radial arm maze task and improves their acquisition of an active avoidance task [145]. The memory-enhancing effects of nicotine depend on

the hippocampus as direct infusion of nicotine into the hippocampus, in rats, enhances learning of the one-trial step-down inhibitory avoidance task [146]. Some of the memory enhancing effects of nicotine may be due to the enhancement of the synaptic transmission of sensory information along afferent pathways into cortical regions associated with memory [4].

Destroying or blocking cholinergic activation of nicotinic receptors impairs memory, perhaps due to inefficient transmission of new information. Nicotinic antagonists, such as mecamylamine, cause impaired performance on memory tasks such as the 16-arm radial maze [147, 148], supporting the vital role of nicotinic receptors in memory processing. The effect of mecamylamine on radial arm maze performance is due to the central nervous system effects of the antagonist and not a locomotive effect on the peripheral nervous system [149]. While administration of nicotine in mice enhances contextual fear conditioning, this effect is abolished with the administration of mecamylamine, perhaps by reducing the sensory transmission of information relevant to the task [150 ,151]. Nicotinic receptor selective antagonists also impair memory performance in rats. Administration of either a selective $\alpha 7$ receptor antagonist or selective $\alpha 4\beta 2$ receptor antagonist results in an increased number of errors on the 16-arm radial maze task [152], supporting the role of both of these specific receptors in nicotinic modulation in cortical structures. Lesions of the nucleus basalis magnocellularis, which provides the hippocampus with acetylcholine, impaired the performance of rats on a five-choice serial reaction time task. Nicotine reversed the impairment caused by the lesion in a dose-dependent manner [153]. While muscarinic blockade allows interference between new and old information, nicotinic blockade may result in information failing to reach the target cortical structure due to inefficient afferent synaptic transmission.

Clinical behavioral data also indicates a role of nicotinic acetylcholine receptors in memory and cognition. Patients with Alzheimer's disease show a significant loss of high affinity nicotinic receptors, an effect correlated with a loss of memory processing [154], and the application of nicotine patches can initially improve the rate of learning and attention in Alzheimer's patients [154, 155], supporting the hypothesis that nicotinic acetylcholine receptors enhance afferent sensory information in cortical structures vital for memory processes.

Acetylcholine and Sleep—Regulation of Consolidation

Microdialysis studies have demonstrated that the level of acetylcholine dramatically changes during stages of waking and sleeping. This change in the level of acetylcholine also correlates with changes in the EEG recordings of oscillations. During active waking behavior, the level of acetylcholine is high, as demonstrated in rats and cats [156, 157]. During this high level of acetylcholine and active exploration, the EEG in the hippocampus shows large amplitude oscillations in the theta frequency range [158]. The level of acetylcholine rises even more dramatically during tasks which require sustained attention for the detection of a stimulus [159, 160]. When animals participate in quiet waking behavior, sitting and grooming, levels of acetylcholine drop [157]. This is accompanied by a change in the EEG activity in the hippocampus with the appearance of large amplitude events termed sharp waves [161]. Levels of acetylcholine drop even further during deep sleep [157], and this drop is accompanied by a change in the EEG to slow waves in neocortex [162].

Administration of the cholinesterase inhibitor physostigmine during slow wave sleep impaired the consolidation of word pairs subjects had memorized before sleeping [163]. Physostigmine did not impair performance when given during waking periods. This supports the hypothesis that low levels of acetylcholine during sleep are critical for consolidation of declarative memory [163]. Administration of the nicotinic antagonist mecamylamine and the muscarinic antagonist scopolamine after learning in awake subjects enhanced consolidation of learned material when tested 10 h after administration. At the same time, it prevented the learning of new, similar material [164]. This supports the hypothesis that acetylcholine shifts networks

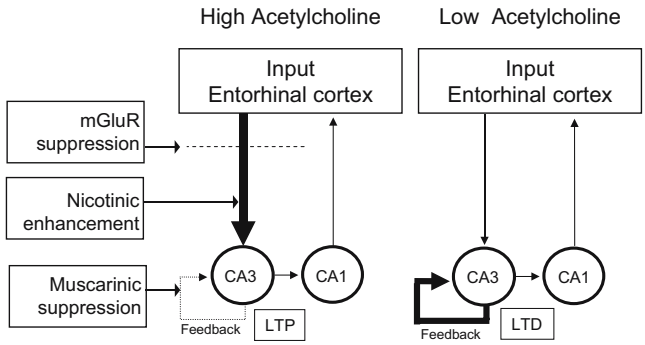

Fig. 4 Summary of the modulatory effects of acetylcholine and glutamate on synaptic transmission within the hippocampus during high levels of acetylcholine (*left*) and lower levels of acetylcholine (*right*). *Thick arrows* represent strong glutamatergic synaptic transmission (affecting postsynaptic ionotropic glutamate receptors). *Thin arrows* represent weaker glutamatergic synaptic transmission. *Dashed line* (mGluR suppression) represents activity-dependent presynaptic inhibition by presynaptic metabotropic receptors, which filter input from entorhinal cortex into the hippocampus. *On the left*, the *thick arrow* indicates nicotinic enhancement of entorhinal input during high acetylcholine. This complements the muscarinic presynaptic inhibition of intrinsic connections in CA3 and CA1 (*dotted lines on left*). High levels of acetylcholine also contribute to long-term potentiation in the intrinsic inputs of CA1 and CA3. In contrast, on the right, low levels of acetylcholine result in less enhancement of entorhinal input and much stronger recurrent excitation due to lack of muscarinic presynaptic inhibition (*thick arrow on right*)

between the dynamics of encoding and consolidation, with high levels important for encoding and lower levels important for consolidation.

Behavioral Work: Metabotropic Glutamate Receptors

Behaviorally, the anxiolytic effects of presynaptic mGluR agonists ([165], *for review see* [166]) support the hypothesis that these presynaptic receptors act as a filter for environmental stimuli, reducing the information that reaches cortical structures like the hippocampus. Injections of ACPT-1, a group III mGluR agonist, into area CA1 of the hippocampus has been shown to decrease anxiety and have an antidepressant-like effect on rats, as determined by behavioral measures [167]. Knockout mice deficient in mGlu8, a group III mGluR, show an increased amount of anxiety-related behavior in the elevated plus maze in low illumination [168]. In addition, the deletion of the mGlu8 receptor results in a reduced threshold of neuronal activation in stress-related brain regions. This reduction in the threshold leads to increased anxiety-related behavior in the elevated plus maze and is associated with a significantly higher number of c-Fos positive cells in the centromedial nucleus of the thalamus [169]. The increase in c-Fos positive cells in the centromedial nucleus of the thalamus indicates that mGlu8 receptors may be important for appropriate behavioral responses to a novel and fearful environment. The reduction of low pass network filtering properties when

Table 1 Table summarizing the behavioral effects of manipulating acetylcholine receptors and metabotropic glutamate receptors

Receptor	Experimental technique	Population	Effect
Muscarinic (mAChR)	Scopolamine	Humans	↓ Encoding for later free recall [92, 95] ↓ Detection of novel object [97] ↓ Memorize position of chess piece [98] ↓ Paired associates [104] ↓ Encoding for later recall of overlapping paired associates [104] ↓ Eyeblink conditioning [114] ↓ Stroop test, visual vigilance task [125–127]
Muscarinic (mAChR)	Fornix lesion patients	Humans	↓ Free recall tasks [112]
Muscarinic (mAChR)	Scopolamine	Nonhuman primates	↓ Encoding for later recognition of novel object [101, 102]
Muscarinic (mAChR)	Scopolamine	Rats	↓ Novel object detection [103] ↓ Encoding of spatial information on a maze task [102] ↓ Learning overlapping odor pairs [105] ↓ Location of hidden water maze platform [108] ↓ 8-arm radial maze performance [110] ↓ Classical fear conditioning [117] ↓ Eyeblink conditioning, in rabbits [113]
Muscarinic (mAChR)	Physostigmine	Rats	↓ Retrieval of spatial information on a maze task [102]
Muscarinic (mAChR)	Fornix lesions	Rats	↓ 8-arm radial maze performance [117]
Nicotinic (nAChR)	Nicotine	Human	↑ Attentional tasks [129–131] ↑ Free recall tasks [132, 133] ↑ Paired associate and prose recall [135, 136] ↑ Immediate and delayed recall [137]
Nicotinic (nAChR)	Nicotine	Nonhuman primates	↑ Delayed non-match to sample task [139]
Nicotinic (nAChR)	Nicotine	Rats	↑ Location of hidden water maze platform [140] ↑ Object recognition [142] ↑ Learning of one-trial step-down inhibitory avoidance task [143]
Nicotinic (nAChR)	Mecamylamine	Rats	↓ Radial arm maze [128] ↓ Contextual fear conditioning [147, 148]
Group II mGluR	mGluR II agonists	Rats	↓ Epileptic seizures [168] ↓ Conditioning to context [175]
Group II mGluR	mGluR III antagonists	Rats	↓ Familiarity discrimination [176]
Group III mGluR	mGluR III agonists	Rats	↓ Anxiety and depression [165] ↓ Epileptic seizures [168]
Group III mGluR	Knockouts	Mice	↑ Anxiety in the elevated plus maze [167] ↓ 4-arm and 7-arm radial maze short-term memory task [173]

↓ Impairs, ↑ improves

group II or III mGluRs are inactivated could explain why groups II and III agonists prevent epileptic seizures [170]. Application of a group II agonist significantly reduces cell death, often an associated side effect of epilepsy, after mechanical neuronal injury in rat neuron cultures [171].

Metabotropic glutamate receptor agonists and antagonists have also been shown to have some memory-disrupting effects [172–174]. Intracerebroventricular injections of the mGluR antagonist MCPG during the pretraining stage of a shock-reinforced spatial alternation task blocks the consolidation of memory in rats and results in significantly poorer performance when rats are tested on the maze 24 h later [172]. Knockout mice deficient in mGluR7, a group III metabotropic glutamate receptor, were impaired in a 4-arm and 7-arm radial maze working memory task but not in a long-term memory task. This suggests that group III metabotropic glutamate receptors are important for short-term working memory but may not play as significant a role in long-term memory [175]. Injections of ACPD, an mGluR agonist, weakens spatial learning in the Morris water maze but actually facilitates the formation of olfactory learning in a mate discrimination task [174]. Facilitation of olfactory learning by mGluR agonists may be due to the role of mGluRs in the habituation of odors. Blockade of mGluRs in the olfactory cortex of awake, behaving rats diminishes habituation of a simple odor, supporting the hypothesis that mGluRs play a key role in odor habituation [50]. The crucial role of mGluRs in the habituation of odor responses suggests that mGluRs might play a role in cortical adaptation [176]. It has been suggested that cortical adaptation and habituation serve as mechanisms aiding the analysis of complicated or overlapping patterns of activity. Cortical adaptation could allow the cortex to act as a filter that responds selectively to a change in the quality or intensity of a stimulus while suppressing background information [50]. Supporting this hypothesis is conditioning data that has shown that application of the group II agonist, (2R,4R)-APDC, disrupts conditioning to context (the CS). Increasing the salience of the context (CS) or the shock (UCS) abolishes the effect of the drug [177]. Metabotropic glutamate receptors may help determine the signal to noise ratio in neural networks. Systemic administration of the group II antagonist, LY341495, impairs familiarity discrimination 24 h after the exposure phase. A group III antagonist did not have the same effect on long-term recognition memory suggesting that group II over group III is more important for this type of memory processing [178]. In one experiment, amnesia was induced in rats by subjecting them to hypoxia. Administration of the group II agonist, (2R,4R)-APDC, impaired acquisition and consolidation, but enhanced retrieval, in a passive avoidance task for the normal rats. In the hypoxic rats, the group II agonist improved acquisition, consolidation, and retrieval in the passive avoidance task [179].

Concluding Remarks

Here it is proposed that neuromodulators can cause cortical dynamics to switch between a dominant influence of extrinsic afferent input (encoding) and a dominant influence of intrinsic feedback (recall). For example, the modulatory effects of acetylcholine at both nicotinic and muscarinic receptors allow afferent information to dominate, while intrinsic feedback is reduced, preventing interference from previously stored memories during encoding of new memories. In contrast, neuromodulatory effects such as those at metabotropic glutamate receptors can serve to reduce the influence of afferent information while allowing intrinsic feedback to dominate, preventing new information from interfering with the retrieval of previously stored information (Fig. 4). Neuromodulators can attain these effects through numerous changes that include presynaptic suppression of glutamatergic and GABAergic synaptic transmission, modulation of pyramidal cell spiking activity and modulation of long-term potentiation (Fig. 1).

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