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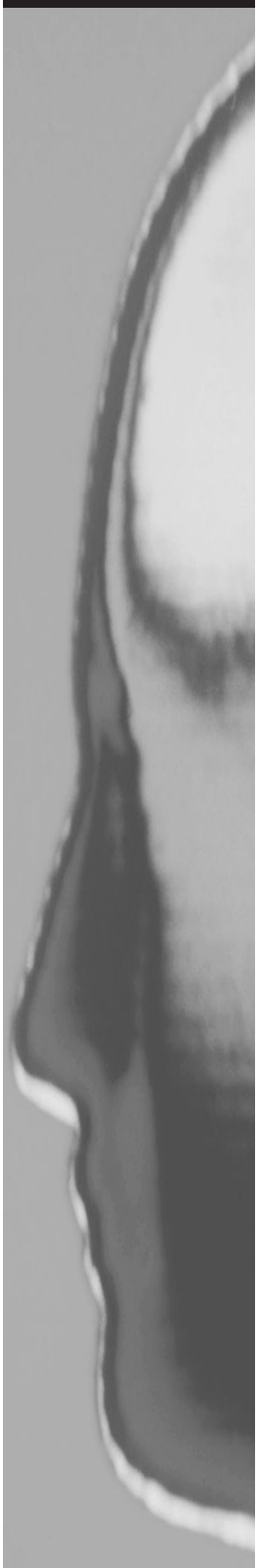
Neuromodulation: acetylcholine and memory consolidation

Michael E. Hasselmo

Clinical and experimental evidence suggests that hippocampal damage causes more severe disruption of episodic memories if those memories were encoded in the recent rather than the more distant past. This decrease in sensitivity to damage over time might reflect the formation of multiple traces within the hippocampus itself, or the formation of additional associative links in entorhinal and association cortices. Physiological evidence also supports a two-stage model of the encoding process in which the initial encoding occurs during active waking and deeper consolidation occurs via the formation of additional memory traces during quiet waking or slow-wave sleep. In this article I will describe the changes in cholinergic tone within the hippocampus in different stages of the sleep–wake cycle and will propose that these changes modulate different stages of memory formation. In particular, I will suggest that the high levels of acetylcholine that are present during active waking might set the appropriate dynamics for encoding new information in the hippocampus, by partially suppressing excitatory feedback connections and so facilitating encoding without interference from previously stored information. By contrast, the lower levels of acetylcholine that are present during quiet waking and slow-wave sleep might release this suppression and thereby allow a stronger spread of activity within the hippocampus itself and from the hippocampus to the entorhinal cortex, thus facilitating the process of consolidation of separate memory traces.

This article will describe some of the physiological and neurochemical mechanisms that might mediate episodic memory consolidation. Firstly, I will review the neuropsychological and computational evidence for a two-stage model of memory consolidation. I will then describe electrophysiological data that support this concept and suggest that the two stages are linked to different stages of the sleep–wake cycle when encoding and consolidation might occur. In the final section, I



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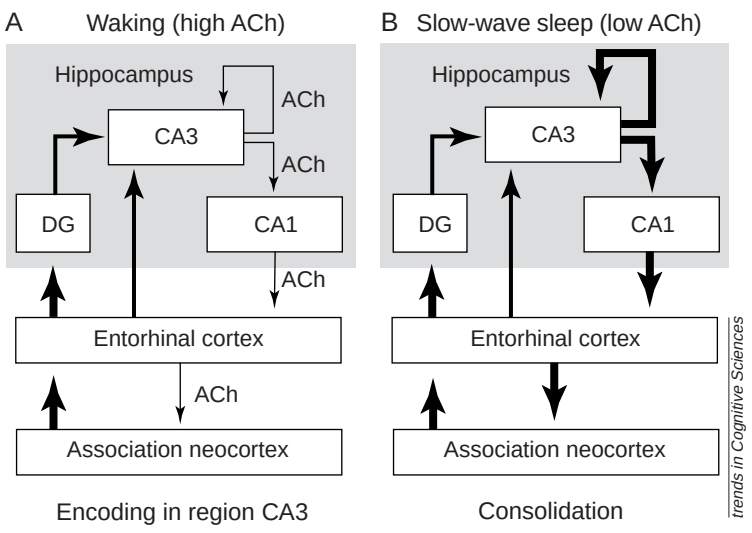

Fig. 1. Two-stage model of long-term memory formation. (A) During active waking, information coded by neocortical structures flows through the entorhinal cortex and dentate gyrus (DG) into hippocampal region CA3 (connections less sensitive to modulation by ACh; thick arrows). Here, synaptic modification forms an intermediate-term representation, binding together different elements of an episodic memory. Connections suppressed by ACh modulation (thin arrows) to region CA1, entorhinal cortex and association cortex are strong enough to mediate immediate retrieval, but do not overwhelm the feedforward connectivity. **(B)** During quiet waking or slow-wave sleep, memories are reactivated in region CA3 during EEG phenomena termed sharp waves. These waves of activity flow back through region CA1 to entorhinal cortex[5] and neocortex[26]. This will enable the slow consolidation (formation of separate traces) of long-term episodic memory in hippocampal region CA1, entorhinal cortex and association neocortex, and might underlie modification of semantic memory within circuits of association neocortex.

will propose that the neuromodulatory effects of acectylcholine might ultimately mediate this process by biasing the flow of activity between different brain regions during these different stages of memory formation.

Two-stage models of memory storage

Neuropsychological data suggest that the traditional concept of long-term memory can be split into an intermediate-term episodic memory that is sensitive to lesions of the hippocampal formation, and a long-term episodic and semantic memory that is not sensitive to lesions of the hippocampal formation[1,2]. The period during which the episodic memory is sensitive to lesions of the hippocampal formation can vary from days to months depending upon species[3]. Several researchers have suggested that these properties of memory might result from a two-stage process of long-term memory formation[4–7]. In these theories, each stage has been linked with particular behavioral states and specific electrophysiological phenomena (Fig. 1).

In the first stage, during active waking, information from the environment is rapidly encoded in the CA3 region of the hippocampus in an intermediate-term episodic representation of the information to be remembered. During this process the excitatory connections between individual CA3 pyramidal cells that are activated by features of the event are strengthened[4,7–9].

In the second stage, during quiet waking and slow-wave sleep, the stored representations in the hippocampus become active during sharp waves, and spiking of some of the neurons activated during the episodic event results in co-activation of other neurons owing to the spread of activity across the strengthened excitatory connections[6,10]. This reactivation of the neurons representing features of the event results in further strengthening of the excitatory connections linking these different neurons in CA3 and CA1 (Refs 4,9). In addition, transmission along excitatory feedback connections from these hippocampal regions results in activation of neurons representing features of the event in entorhinal cortex[5] and association neocortex[11]. This results in a slower strengthening of the excitatory associative synaptic connections between neurons representing these features in neocortex, and the formation of links that could be described as semantic or long-term episodic memories in the neocortex[4,7,8]. The basic features of these two-stage models are summarized in Figs 1 and 2. Here I propose that changes in the level of acetylcholine within the cortex could mediate these changes in the flow of information and thereby modulate the dynamics between these two stages of memory formation.

Neuropsychological evidence

The two-stage model of long-term memory formation is supported by neuropsychological data on the effects of hippocampal lesions on episodic memory. The most recently encoded episodic memories are the most sensitive to damage of the hippocampus, a finding that has been referred to as Ribot's law. The greater sensitivity of recent episodic memories to hippocampal damage has been termed 'temporally graded retrograde amnesia'[3]. This phenomenon has been described in subjects with damage to hippocampal subregions – in whom the temporal extent of retrograde amnesia depends on the number of regions involved[2] – as well as in subjects with amnesia following electroconvulsive therapy[1]. Moreover, in monkeys trained on object recognition prior to a hippocampal lesion, the lesion caused a greater impairment in retrieval in those monkeys that were trained on the stimuli 0 or 25 days before the lesion than in those that were trained 75 days before the lesion[12]. In rats, hippocampal lesions impair the ability to associate a particular testing location (context) with a tone–shock pairing and this effect is much greater if the lesions are performed 0 or 2 days after the initial tone–shock pairing, than if the lesion is applied 5 or 10 days later[13]. (Note that the learning of context appears to depend upon the hippocampus, whereas learning the specific tone–shock pairing depends upon the amygdala.)

The concept of hippocampal activity guiding formation of neocortical associations has been criticized recently on the basis of both animal and human data[14,15], but the alternative hypothesis still involves formation of new traces – albeit within the hippocampus itself. In animal studies, Sutherland and colleagues[14] have demonstrated that extensive lesions of the hippocampus result in a flat gradient of retrograde amnesia, whereas partial lesions result in temporally graded retrograde amnesia. A recent review of human studies also calls attention to a number of cases in which hippocampal damage causes a very long-term retrograde amnesia[15]. Note that this long-term retrograde damage appears with somewhat more extensive hippocampal lesions including subiculum and entorhinal cortex, whereas very short duration retrograde amnesia occurs when lesions are limited to specific hippocampal subregions[2]. These results suggest that consolidation does not necessarily result in formation of links in association neocortex, but could instead result in strengthening of representations within the hippocampus itself or within the entorhinal cortex. It is

possible that memories are reactivated simply for CA3 to guide strengthening of associations in CA1 (Ref. 4) or in entorhinal cortex. The reactivation of memories and formation of additional representations within the hippocampal formation has been referred to as the 'multiple-trace' hypothesis[15]. However, the process of creating multiple traces still requires two stages with different dynamics – the first for the encoding of new sensory information from the environment, and the second for reactivation of an old memory in order to form additional traces.

Computational evidence

A number of different computational models have illustrated how the hippocampus might interact with the cortex when reactivating representations for consolidation[7,8,16–18]. A key feature of all of these models is the initial storage of an association in an associative matrix representing a component of the hippocampus. This initial encoding requires a capacity for rapid synaptic modification in the hippocampus. Long-term potentiation (LTP) of hippocampal synaptic potentials in response to repetitive stimulation would appear to provide some physiological evidence for such a mechanism[9]. In the computational models, the initial encoding is followed by repetitive retrieval of stored representations from this matrix in order to activate units in association neocortex. Gradually, connections between these neurons in association cortex are strengthened as a result of this repetitive reactivation. This synaptic modification in association neocortex is assumed to be slower than the synaptic modification in the hippocampus, and is supported by recent experiments showing that LTP in rat association neocortex is enhanced when stimulation is spaced and repeated over a series of days, rather than the brief massed stimulation that most effectively elicits LTP in the hippocampus[20]. A schematic representation of the basic design and function of these models is illustrated in Fig. 2. Some of these models have very detailed representations of the individual subregions of the hippocampus, which could allow detailed analysis of the physiological mechanisms that reactivate representations[8,18]. However, these models contain very simplified representations of entorhinal and association cortex circuits, and therefore do not address the following basic question of why there should be two stages of memory formation.

This issue has been discussed, however, in terms of modification of existing semantic representations in the neocortex[3]. For example, suppose that a network is set up that codes a range of items of semantic knowledge, such as the knowledge that birds can fly ('robins are birds that fly… sparrows are birds that fly'). If such a network were sequentially trained with a new item that is inconsistent with the previous input ('penguins are birds; penguins swim but do not fly') the new piece of information could interfere with the previously learned knowledge, leading to the belief that all birds swim. In contrast, if the new information were stored as an episodic memory in the hippocampal formation and then interleaved with other examples during training of neocortical representations during consolidation ('robins are birds that fly… sparrows are birds that fly… penguins are birds that swim… eagles are birds that fly') the new information could be incorporated as an exception in semantic networks, without impairing the prior knowledge. Interleaved learning of multiple different examples is necessary for the formation of efficient representations in a number of different models, including other abstract models of the formation of higher-level semantic representations, as well as biological models of the self-organization of stimulus selectivity in visual cortices[21,22]. Alternate phases of dominant feedforward versus dominant feedback connections have also been used in network models focused on formation of representations in multi-layer hierarchical networks[23,24]. From this brief overview it is clear that the computational approach to memory consolidation also favors architectures that feature two stages.

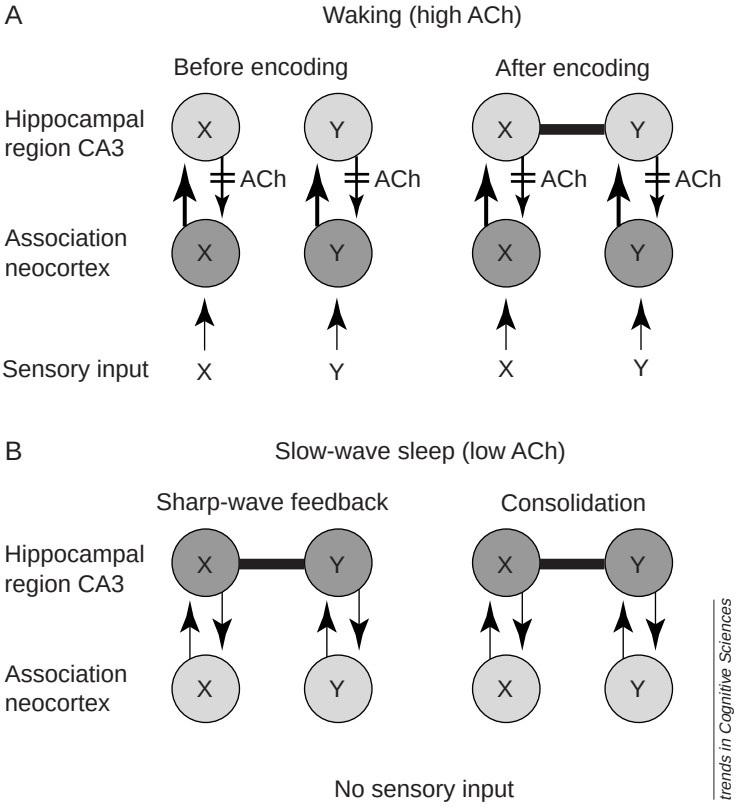

Fig. 2. The basic features of two-stage models of long-term memory formation. (A) Two items X and Y in the environment (for example, a name and a face) activate circuits in association neocortex during waking. Activity does not result in immediate modification of circuits in association neocortex. Instead, the activity spreads through entorhinal cortex (not shown) to hippocampal region CA3, where episodic representations of these items are activated (darker shading indicates area of predominant activity). Initial encoding of this association is performed by strengthening of intrinsic excitatory connection between populations of neurons in region CA3 of the hippocampus (strengthened connection shown with thicker line). Cholinergic suppression of feedback connections (shown by blocked thin arrows) prevents hippocampal retrieval from distorting representations of sensory stimuli in the association neocortex. **(B)** During slow-wave sleep, reduction of cholinergic suppression allows greater spread of activity along feedback connections. In the absence of environmental input to the association neocortex, random activation of hippocampal region CA3 evokes activity in specific attractor states or sequences corresponding to stored associations. This activity then spreads back during sharp-wave activity into hippocampal region CA1, entorhinal cortex and association cortical areas, where synaptic modification allows encoding of additional traces.

Electrophysiological evidence

Support for the concept of the two-stage model of memory formation is also provided by electrophysiological data. These data show that in addition to responding to external stimuli during active waking, hippocampal networks also appear to reactivate these representations during quiet waking and slow-wave sleep. This research has focused on recordings of hippocampal place cells, demonstrating that when place cells fire

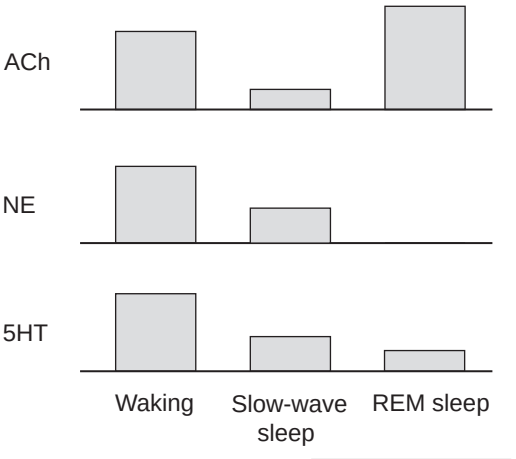

Fig. 3. Changes in cortical neuromodulation during waking, slow-wave sleep and REM sleep. Histogram bars represent levels of neuromodulators (shown at left) in cortical structures relative to levels measured during waking (here normalized to be the same for all neuromodulators). Acetylcholine (Ach) levels are based on microdialysis measurements in hippocampus[32,33]. Levels of acetylcholine do not increase as much in the cortex during REM sleep[33]. For norepinephrine (NE), level of unit activity in the locus coeruleus is shown[75,85]. Serotonin (5HT) levels are based on microdialysis in the frontal cortex[77].

during a particular period of waking, there is an enhanced probability that they will fire again in a subsequent period of slow-wave sleep[25]. Furthermore, when pairs of place cells code adjacent positions during a period of active waking, these neurons show more correlated firing during subsequent slow-wave sleep, as compared with an equivalent period of slow-wave sleep that preceded the training session[6,10,11].

Another set of experiments focused on the predominant flow of activity in the hippocampal complex during different behavioral states (Fig. 1). These experiments demonstrate that during active waking, when theta rhythm is present in the hippocampus, there is extensive neuronal activity in the layer of entorhinal cortex which provides input to the hippocampus (layer II), but not in the entorhinal layers receiving output from the hippocampus (layers V and VI)[5]. In contrast, during quiet waking and slow-wave sleep, EEG phenomena termed sharp waves originate among the strong excitatory recurrent collaterals in hippocampal region CA3 and spread back through region CA1 to entorhinal cortex[5]. These sharp waves have been demonstrated to selectively activate neurons in the deep, output layers of entorhinal cortex during quiet waking[5]. Further experiments have analysed the relation between hippocampal sharp waves and EEG phenomena in more distant cortical areas such as prefrontal cortex, showing a correlation between the ripples observed during hippocampal sharp waves and the spindles observed in prefrontal cortex EEG[26]. This suggests that hippocampus could be inducing co-activation of neurons in neocortical regions, which could form new crossmodal associations[27]. Extensive EEG phenomena also arise from neocortical and thalamocortical circuits during this stage[28].

Neuromodulation during the sleep–wake cycle

The two-stage model of memory function requires very different dynamics during each stage (Figs 1 and 2). During active waking, there is a predominant influence of entorhinal cortex on the CA3 region of the hippocampus. Feedback connections arising from CA3 are still functional and can mediate retrieval, but they do not dominate over the feedforward connectivity. In contrast, during quiet waking and slow-wave sleep, there is a predominant influence of the CA3 region on the CA1 region and entorhinal cortex. How are these different dynamic states modulated?

One explanation is that these different dynamic states could be set by the modulatory effects of acetylcholine, which shows parallel fluctuations during different stages of waking and sleep (Fig. 3). In the following sections I will outline the defining properties of these different behavioral states, the modulatory influences that are present, and the physiological effects of this modulation and how this may be important for the concept of two stages of memory formation.

Active waking

In experiments on rats, active waking is defined as periods of time during which the rat is actively exploring the environment, scurrying along the walls or across the floor, sniffing novel objects and rearing up extensively. In EEG recordings from hippocampus and entorhinal cortex, this period is characterized by large amplitude oscillations in the 3–10 Hz range[5,29,30], whereas the neocortex displays high frequency, low-amplitude activity with local synchronization[27] and some periods of theta in certain regions[31].

Microdialysis measurements of acetylcholine in the hippocampus of freely moving rats[32] and cats[33] show high levels of acetylcholine release during this active waking behavior (Fig. 3). These cholinergic influences might contribute to generation of the theta rhythm, as acetylcholine levels appear to correlate with amplitude of theta oscillations[33,34], and cholinergic blockade reduces theta oscillation amplitude (for a review of these effects see Ref. 34). Recordings from the entorhinal cortex suggest that during active waking the influence of hippocampus on entorhinal cortex is weak, as determined by the low spiking activity in deep layers of entorhinal cortex[5] and the small amplitude of entorhinal cortex field potentials arising from hippocampal connections during this period[36,37]. The effects of acetylcholine could provide a specific mechanism for weakening the hippocampal feedback. Indeed, in hippocampal brain-slice preparations and in whole-animal preparations acetylcholine suppresses excitatory glutamatergic synaptic transmission at feedback connections from region CA3 to entorhinal cortex[24,38–45], while having weaker effects at many of the feedforward connections to the hippocampus[42–44,46,47]. The selectivity of the cholinergic suppression of synaptic transmission is summarized in Fig. 4.

Experiments with brain slice preparations demonstrate that acetylcholine suppresses transmission at excitatory recurrent collaterals in the CA3 region of the hippocampus[44,48], suppresses transmission at the Schaffer collaterals connecting the CA3 and CA1 regions[38,39,43,49,50] and suppresses transmission at the connections from CA1 to the subiculum[45] (which is the first step of transmission from CA1 back to entorhinal cortex). Outside the hippocampus, cholinergic modulation also suppresses transmission at feedback connections from higher order somatosensory cortex to primary somatosensory cortex[24], at intrinsic and feedback synapses

but not afferent synapses within the piriform cortex[51,52] and at intrinsic synapses in the primary visual cortex[53].

These data from slice preparations are mostly consistent with data from whole animal preparations, in which it was demonstrated that the feedback from region CA3 to region CA1 via the Schaffer collaterals shows strong decreases in excitatory post-synaptic potentials (EPSPs) in response to local acetylcholine infusion[40–42], stimulation of the cholinergic innervation from the medial septum[54], and sensory stimulation[46]. The decrease due to sensory stimulation is blocked by the acetylcholine receptor blocker atropine[42], and the decrease due to local infusion of acetylcholine or stimulation of the medial septum can be blocked by scopolamine[54]. Stimulation of cholinergic innervation of the cortex also suppresses feedback from posterior piriform cortex to anterior piriform cortex[55,56]. This general suppression of excitatory feedback would act to reduce the influence of hippocampus on entorhinal cortex and other cortical areas during active waking. But none of these experiments was able to show total suppression – the influence of hippocampus is reduced but not removed – so there is still sufficient feedback to allow retrieval of relevant stored information.

In contrast, acetylcholine does not suppress most of the feedforward connections to the hippocampus. In particular, the direct perforant path input from entorhinal cortex layer III to region CA1 shows much weaker suppression than the input to region CA1 from CA3 in the same slice[43]. The direct entorhinal input to CA3 also appears to be less affected[48]. Cholinergic suppression of transmission has been observed at the mossy fibers from dentate gyrus to CA3 (Ref. 57), but this suppression appears to be weaker than the suppression in radiatum at comparable doses[44], though the comparison of field potential changes with intracellular synaptic potential changes is difficult. The outer molecular layer of the dentate gyrus shows almost no suppression by cholinergic modulation as measured in slice preparations[47,58,59]. The outer molecular layer receives perforant-path input from the lateral entorhinal cortex. In slices, suppression only appears in the layers more proximal to the granule cell layer of the dentate gyrus[47,58,59] including the middle molecular layer[47], which receives perforant-path input from the medial entorhinal cortex, and the inner molecular layer, which receives commissural input from the contralateral dentate gyrus[59]. A weaker cholinergic influence on perforant path input to the dentate gyrus is supported by the fact that EPSPs evoked in the dentate gyrus by angular bundle stimulation are larger during the high acetylcholine levels of active waking than during the lower acetylcholine levels of slow-wave sleep[36,60]. Stimulation of the medial septum, which provides cholinergic innervation of the hippocampus, causes increases in population spike activity in the dentate gyrus, but does not have a systematic effect on EPSPs (Refs 61,62). This enhanced spiking could result primarily from GABAergic input to the dentate gyrus, but the absence of an effect on EPSPs suggests feedforward input is not suppressed. However, microinjections of acetylcholine in the outer molecular layer do reduce the dentate gyrus EPSP, possibly owing to effects in the middle molecular layer[63]. Acetylcholine also has postsynaptic effects which should enhance the response of neurons to feedforward input[64], including depolarization of pyramidal cells[65,66], and suppression of spike frequency adaptation[67,68].

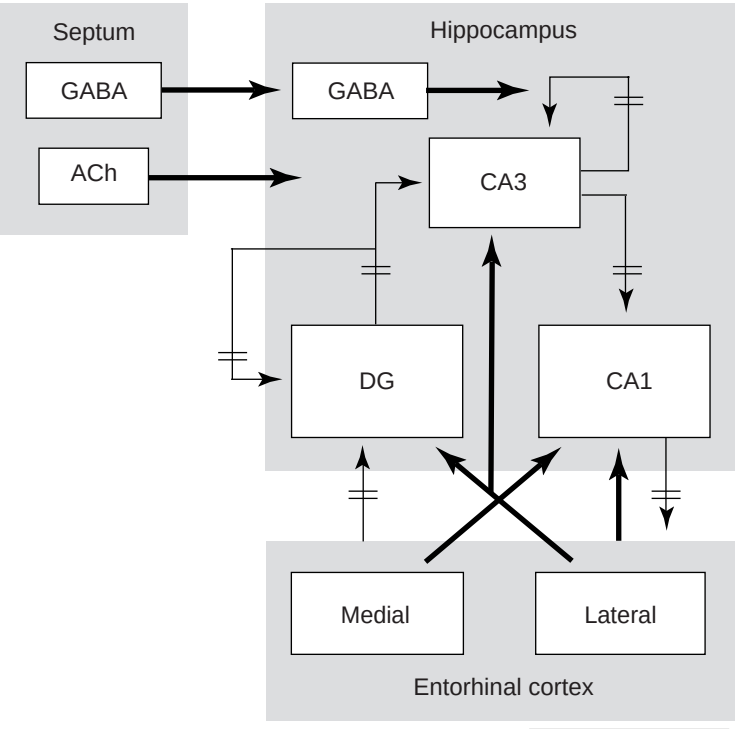

Fig. 4. Selectivity of presynaptic inhibition by acetylcholine. Cholinergic neurons in the septum innervate the hippocampal formation, regulating activation of muscarinic receptors in multiple different subregions. Thin arrows designate glutamatergic connections, which undergo stronger presynaptic inhibition during activation of muscarinic cholinergic receptors. The selectivity of this modulation has been shown in a number of studies in brain slice preparations of hippocampus (e.g. Refs 38,43) and in whole animal preparations using local infusion of cholinergic agonists, stimulation of cholinergic innervation, and sensory activation of arousal. Suppression of recurrent collaterals in region CA3 has been shown for activation of muscarinic acetylcholine receptors[44]. Suppression of Schaffer collaterals in stratum radiatum of region CA1 but not perforant-path input to stratum lacunosum moleculare has been shown for activation of muscarinic acetylcholine receptors[38,39,41–43,50]. Suppression of synaptic transmission in dentate gyrus from medial but not lateral entorhinal cortex has been shown for acetylcholine[47,58,59] (but see Ref. 63). Suppression does appear at the mossy fiber synapses in stratum lucidum of region CA3 (Ref. 57), but this appears to be weaker than that seen at recurrent feedback connections in that region[44]. Thus, cholinergic innervation from the septum regulates presynaptic inhibition selective to subsets of connections in the hippocampus.

What is the functional purpose of suppressing feedback to entorhinal cortex during active waking? To begin with, this suppression should not be total, as clearly recently stored memories from the hippocampus are still accessible for retrieval. But the strength of connections necessary for the strong transmission of stored memories back to CA1 and entorhinal cortex would allow them to dominate over afferent input. This could distort the initial perception of sensory information, causing interference during learning in temporal structures – and if the retrieval activity is sufficiently dominant – causing hallucinations such as those observed under the influence of cholinergic antagonists at high doses (see Box 1). Thus, partial cholinergic suppression of excitatory feedback allows cued retrieval without hallucinatory retrieval.

Quiet waking

Quiet waking is defined as periods during which a rat is immobile, or engaged in behaviors such as grooming or eating[5,30,33]. Recordings of the EEG in this phase of behavior show irregular EEG activity[29,30,69], with periodic appearance of brief, large amplitude events termed sharp waves[5,37]. These

Box 1. Behavioural effects of cholinergic antagonists

Physiological research suggests that acetylcholine changes the predominant flow of activity within the hippocampus during different stages of waking and sleep. Higher levels of acetylcholine during waking could result in a predominant feedforward flow of activity, allowing normal interaction with the environment. Lower levels of acetylcholine during quiet waking and slow-wave sleep could result in a dominant feedback flow of excitatory activity for consolidation. But what happens if a similar reduction of cholinergic effects is induced during waking by administration of a muscarinic receptor antagonist such as scopolamine?

One prediction would be that this will enhance the strength of the feedback effects in the cortex, and that this will interfere with the feedforward sensory input that is important for the encoding of new information. In fact, low doses of scopolamine do impair encoding of new information in human subjects, while having no effect or even slightly enhancing retrieval of information encoded prior to scopolamine administration[a,b]. Even higher doses of scopolamine would be expected to cause stronger feedback effects, which might result in the hallucinations extensively described with muscarinic cholinergic antagonists[c–e] and with the loss of cortical cholinergic innervation in Lewy body dementia[e,f].

Another prediction is that blockade of cholinergic modulation after learning of paired associates should interfere with learning of subsequent overlapping paired associates. Preliminary results support this contention, in an experiment in which human subjects were trained on a series of related paired associates (A–B, lotion–bottle) (M.E. Hasselmo, unpublished data). They were then given an injection of scopolamine and tested on their learning of new paired associates, which either overlapped with the previously trained associates (A–C, lotion–oil) or did not overlap with the training stimuli (D–E, kitchen–spoon). Subjects showed a greater impairment when learning overlapping paired associates than when they were learning non-overlapping paired associates, a finding that is consistent with greater proactive interference due to scopolamine blockade of cholinergic suppression.

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are detected in the CA1 region and appear to result from synchronized neuronal activity in the CA3 region[5].

Microdialysis measurements of acetylcholine levels in the hippocampus during quiet waking show a reliable decrease in acetylcholine levels relative to those during active waking, levels dropping to about 60% of those during active waking[33]. These decreases in the level of acetylcholine in the hippocampus would release glutamatergic synapses from the cholinergic suppression of synaptic release. Thus, synaptic transmission at excitatory recurrent connections in region CA3, and at synapses from CA3 to CA1 should be much stronger during quiet waking than during active waking. Consistent with the notion that lower acetylcholine results in stronger feedback, evoked synaptic potentials are much larger in region CA1 and in entorhinal cortex during quiet waking than during active waking[60], or when a rat is not being presented with sensory stimulation[46]. In addition, this change in dynamic state is consistent with the observation of sharp waves being generated in the CA3 region[5,37], where the large increase in the magnitude of excitatory recurrent connectivity could allow a small increase in neuronal activity to grow exponentially into broadly distributed sharp-wave activity. Lower acetylcholine levels would also mean stronger feedback between CA3 and CA1 and from CA1 to entorhinal cortex, and this could underlie the observed spread of sharp-wave activity from CA3 through CA1 to entorhinal cortex[4,5,37]. Consistent with this suggestion, recordings of unit activity in the output layers of the entorhinal cortex show much stronger spiking activity during the sharp waves of quiet waking than during the theta rhythm activity of active waking[5].

Slow-wave sleep

Different dynamic states have also been characterized during sleep, with a primary division between the broad categories of slow-wave sleep and REM sleep, during which dramatic changes in levels of neuromodulators are observed. Slow-wave sleep is defined by the characteristic EEG phenomena occurring during this phase of sleep, particularly the large-amplitude, low-frequency oscillations found in neocortical structures and commonly termed 'delta waves'. A striking decrease in the concentration of acetylcholine in the frontal cortex and hippocampus has been observed using microdialysis during slow-wave sleep[32,33]. Levels of acetylcholine drop to less than one third of those observed during active waking.

This drop in acetylcholine levels would further release glutamatergic synapses from cholinergic suppression, resulting in even stronger excitatory feedback than during quiet waking. Slow-wave sleep would be characterized by a very large increase in the effect of excitatory recurrent connections in CA3 and excitatory feedback connections from CA3 to CA1 and entorhinal cortex. This drop in cholinergic modulation could thereby underlie the increase in sharp wave activity observed during slow-wave sleep[4,37]. In addition, this spread of activity should be influenced by synaptic modification during the previous waking period. Thus, the release of suppression of excitatory transmission could contribute to the greater tendency of cells to fire together during slow-wave sleep if they fired during the previous waking period[6,10,11]. The loss of cholinergic modulation during slow-wave sleep should also enhance the spread of excitatory activity in response to stimulation. This could underlie the increase in magnitude of evoked synaptic potentials during slow-wave sleep which is observed in CA1 and entorhinal cortex after stimulation of the input connections to the hippocampal formation[36,60].

What functional role could this enhancement of excitatory feedback have? In my opinion this would provide the appropriate dynamics for the formation of additional traces

within regions CA3 and CA1, and could allow the hippocampus to 'train' the entorhinal cortex or association neocortex on the basis of previously encoded associations[4]. This framework does not propose that all the information for new episodic memories is stored in the hippocampus, but that the CA3 region provides a mechanism for linking together disparate information from multiple regions of association neocortex. During waking, these links can be used for cued retrieval of recently stored information by the neocortex, but they should not be able to strongly drive neocortical activity to the level of distorting sensory input – because that could result in interference and hallucinations (Box 1).

By contrast, during slow-wave sleep, the associative links formed in the hippocampus need to be reactivated and need to influence other regions in a strong enough manner to drive the slower modification of neocortical synapses. As shown in Fig. 2, the spontaneous reactivation of neurons coding an association in the hippocampus must be able to drive cells in entorhinal cortex and neocortex without any assistance from sensory input. The reduction of cholinergic suppression might provide the opportunity for this strong feedback influence. Both the hypothesis of multiple traces in the hippocampus[15] and the hypothesis of hippocampal training of neocortex[3,4] implicitly assume a mechanism for reactivation of encoded associations in a strong enough manner to drive the formation of new memory traces. The physiological activity during slow-wave sleep has been proposed to be appropriate for modification of synaptic components[70].

Though most behavioral research has focused on REM sleep, data suggest that slow-wave sleep might be important for the declarative component of behavioral tasks that correspond most closely to episodic memories. Subjects are better at retrieval of word lists if they learn the list before falling asleep and are tested on retrieval when awakened in the middle of the night, than if they learn the list after some hours of sleep and are tested in the morning[71]. Because most slow-wave sleep occurs in the early part of the night, this suggests greater importance of slow-wave sleep for memory consolidation. If semantic knowledge is constantly being reshaped during the consolidation process in slow-wave sleep, then sustained disruption of slow-wave sleep should impair semantic memory. It is therefore interesting to note that certain epileptic disorders involve constant seizure activity during slow-wave sleep[72,73] and that this seizure activity can cause severe impairments of semantic memory function, including delusions, loss of language function, and regression to an autistic state despite previously normal development[73].

REM sleep

REM sleep is defined on the basis of a number of features, including the presence of an EEG similar to that seen during waking, with higher-frequency and lower-amplitude waveforms than during slow-wave sleep[33,60]. Additional features include rapid eye movements, muscular atonia, muscle twitches[31] and ponto-geniculo-occipital waves[33,74].

Microdialysis measurements during REM sleep demonstrate that acetylcholine levels in the hippocampus rise to levels above those seen during active waking[32,33], while levels of acetylcholine in the frontal neocortex increase but only to somewhat lower levels, equivalent to those seen during quiet waking[33]. During REM sleep, theta wave oscillations appear in the hippocampus which are similar to those seen during active waking[33]. Thus, during REM sleep, both the EEG pattern and the levels of acetylcholine resemble those seen during waking. However, there are dramatic differences in the levels of other neuromodulators. Recordings from locus coeruleus show that noradrenergic neurons innervating cortex fall to low levels of activity during slow-wave sleep, and show no activity during REM sleep[75,76]. A similar decrease in serotonergic input to the cortex has been shown during REM sleep, with recordings from the brain raphe nuclei which give rise to these projections[75] and with microdialysis of serotonin levels in the frontal cortex[77].

What is the function of this change in neuromodulatory state? A possible explanation concerns the effects of norepinephrine within cortical structures. Physiological experiments have shown that norepinephrine suppresses feedback excitatory synaptic transmission in the piriform cortex, with a much weaker effect on feedforward transmission[78]. A similar noradrenergic effect is found in primary visual cortex[79]. In contrast to acetylcholine, norepinephrine does not appear to suppress feedback within the hippocampal formation[80]. This supports the hypothesis that, during waking, high levels of both norepinephrine and acetylcholine shut down recurrent connections in neocortex, but during REM sleep, while the high levels of acetylcholine in the hippocampus might strongly suppress feedback in that region[33], the somewhat lower levels of acetylcholine and very low levels of norepinephrine in the neocortex might allow spread of activity within neocortical areas without a strong influence from the hippocampus. The high levels of acetylcholine in the hippocampus are consistent with the observed decrease in transmission through the hippocampus during REM sleep as compared with slow-wave sleep[36,60]. However, this work is not entirely consistent with the current framework, as the field potentials caused by feedback to the entorhinal cortex are larger during REM sleep than during waking, though they are still significantly smaller than those seen during slow-wave sleep.

In the current theoretical framework, slow-wave sleep would allow the accurate transmission of episodic representations from hippocampus to entorhinal cortex and on to association cortex. Then REM sleep would allow neocortical structures to undergo a process of re-analysis, in which this episodic information would be re-interpreted in relation to previous semantic representations. If waking involves initial encoding in the hippocampus, and slow-wave sleep involves sequential feedback of this information to the hippocampus, REM sleep could represent the development of new feedforward representations for behavior (and would thereby be important for enhancing performance in procedural tasks). This framework is consistent with evidence suggesting that performance in procedural-(implicit) memory tasks seems to depend upon quantity of REM sleep[81–84]. The process of altering neocortical representations during REM sleep could utilize the information clamped on the neocortex by hippocampal feedback during slow-wave sleep. In fact, in a perceptual learning task, performance on the task was found to correlate most strongly with slow-wave sleep during the first quarter of the night and REM sleep during the last quarter of the night[83,84].

Outstanding questions

- Do muscarinic receptor antagonists prevent the changes in the flow of information through the hippocampus associated with different behavioral states (outlined in the text)? Could these drugs convert active waking into something resembling slow-wave sleep?
- Are the projections from subiculum to entorhinal cortex suppressed by acetylcholine?
- Does acetylcholine enhance the influence of sensory input on hippocampal place cells?
- What is the function of theta rhythm oscillations in the hippocampal EEG?
- Do hallucinations induced by cholinergic antagonists result from dominant feedback in cortical structures?
- Does the breakdown of cognitive function in some developmental disorders result from disturbances in consolidation activity during slow-wave sleep?

Conclusions

In this review I have described how acetylcholine might regulate the predominant flow of activity during different stages of memory formation. During active waking, cholinergic suppression of excitatory feedback reduces this influence to a level that allows normal retrieval, but prevents distortion of the incoming sensory information being encoded. Indeed, blockade of this suppression by muscarinic receptor antagonists can cause hallucinations. During quiet waking and slow-wave sleep, lower levels of acetylcholine allow these excitatory feedback connections to have a stronger influence. This would allow the associations encoded within the CA3 region of the hippocampus to be re-activated, allowing further strengthening of these associations in CA3, and allowing formation of additional associative links for memory in CA3, CA1, entorhinal cortex and even association neocortex. Computational modeling demonstrates how the change in cellular parameters associated with changes in acetylcholine level can be linked to functional properties of these two stages of memory processing. At the behavioral level, controversy still remains over whether information is consolidated within the hippocampus or whether hippocampal learning guides neocortical learning, but the competing theories of memory consolidation both propose an initial encoding followed by periods of memory reactivation and consolidation. Acetylcholine effects could be vital for setting these different stages of memory formation.

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