A model of hippocampal memory encoding and retrieval: GABAergic control of synaptic plasticity

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The current view of the role of GABAergic interneurons in cortical-network function has shifted from one of merely dampening neuronal activity to that of an active role in information processing. In this review, we explore a potential role of hippocampal GABAergic interneurons in providing spatial and temporal conditions for modifications of synaptic weights during hippocampus-dependent memory processes. We argue that knowledge of spatiotemporal activity patterns in distinct classes of interneuron is essential to understanding the cellular mechanisms underlying learning and memory.


STORAGE OF INFORMATION as long-term memory is commonly assumed to involve modifications of the relevant synapses. LTP is the major experimental model for memory formation at the synaptic level in mammalians1,2. The validity of the model is based primarily on the apparently overlapping cellular mechanisms of hippocampus-dependent learning and hippocampal LTP, particularly the shared dependence on NMDA receptors3,4. However, direct experimental evidence for a link between the two is lacking.

A better understanding of the cellular mechanisms of memory might require a shift away from an exclusive focus on isolated excitatory synapses. Knowledge about how, when and where networks of neurones allow synaptic modifications might be essential. Accumulating evidence suggests that GABAergic interneurons are important for setting the conditions for synaptic change in hippocampal principal neurones (that is, granule cells and pyramidal neurones) during learning (Fig. 1).

Behavioural correlates of hippocampal GABAergic activity

Two classes of neurones can be distinguished in the CA3 and CA1 regions of the hippocampus during extracellular recording from single neurones in freely moving rats: complex-spike cells and theta cells5. Complex-spike cells, which are likely to be pyramidal neurones6, fire at low rates, but often in bursts. These cells tend to fire in relation to the animal’s position in the environment (‘place cells’). Theta cells, by contrast, have higher spontaneous firing rates7 and spatial correlates are less apparent8, many of them are likely to be GABAergic local-circuit interneurons9. A similar distinction between functional classes of neurones (putative granule cells and interneurones) has been made in the dentate gyrus10.

Theta cells are particularly active and express rhythmic discharges when the hippocampal electroencephalogram (EEG) is dominated by theta rhythm. In rats, theta rhythm is prominent during exploration and acquisition of information11,12, which implies that rhythmic discharges of theta cells and learning could be linked. However, the enhanced discharge is velocity-tuned and persists in familiar environments13,14, suggesting that movement per se might elicit it. Moreover, during the initial minutes of exploration, when most learning is likely to take place15, discharge is suppressed, rather than enhanced, in many CA1 theta cells16.

Inhibition in principal cells can also be assessed by extracellular recording of field potentials in response to two temporally closely spaced stimuli applied to excitatory afferent fibres. If the first stimulus is strong enough to elicit postsynaptic spike activity in the population of principal cells, GABAergic interneurones feeding back to the principal cells will be activated, and the response to the second stimulus will be smaller, that is, inhibited. Thus, the reduction of the field EPSP and the population spike of the second waveform can be used as a measure of GABAergic feedback inhibition. Using this approach, feedback inhibition at granule-cell somata (cell bodies) was shown to be reduced during exploratory movement17,18, whereas feedback inhibition in the dendrites might have been increased19.

Thus, the behavioural correlates of hippocampal interneuronal activity are diverse and apparently contradictory. However, this result should not be surprising because hippocampal interneurones are heterogeneous, and distinct subpopulations of interneurones might have different functions.

Functions of GABAergic activity during learning

There are several ways in which activity of GABAergic interneurones might set the spatio-temporal conditions for synaptic plasticity and hippocampal LTP, particularly the shared dependence on NMDA receptors of these phenomena. Although considered separately, the functions suggested below should be considered as integrated components of hippocampal network operations.

Spatial control

Filtering. During the initial minutes of an exploration episode, paired-pulse inhibition of the field EPSP is increased in the rat dentate gyrus (Fig. 2). This could imply that, during learning about novel environments,
inhibition onto the dendrites of the granule cells is increased and consequently only strong excitatory signals pass the synaptic layer successfully. The effect is accompanied by decreased inhibition of the population spike, suggesting that signals that do pass can be amplified when they reach the soma. The increase and the decrease could together act as filter and amplifier, increasing the contrast between signals with different relations to ongoing behaviour.

Compartmentalization. Several properties of hippocampal interneurones suggest a role in parcelling memory processing within individual principal cells. First, distinct types of interneurone target different domains of the principal-cell membrane\(^1\)\(^6\)\(^,\)\(^17\) (Fig. 1). Basket cells provide somatic and perisomatic inhibition\(^1\)\(^6\)\(^,\)\(^18\), whereas other types of interneurone synapse primarily onto subdomains of the dendritic tree\(^1\)\(^6\)\(^,\)\(^19\)\(^,\)\(^21\) or onto the axon initial segment\(^1\)\(^6\)\(^,\)\(^22\). Moreover, these various types of interneurone have distinct dendritic fields\(^1\)\(^6\)\(^,\)\(^17\)\(^,\)\(^23\) and might differ in glutamate-receptor composition\(^1\)\(^7\)\(^,\)\(^17\). This suggests that they might be activated differently under various behavioural conditions (Fig. 2) and that the spatial distribution of inhibition within principal cells might vary with behaviour, thus, interneurones that target dendrites might be instrumental in controlling synaptic plasticity. Hebbian types of plasticity rely on the coincidence of presynaptic transmitter release and postsynaptic firing of action potentials\(^2\)\(^,\)\(^25\). Action potentials are always initiated in the axon initial segment, but can back-propagate in the dendrite\(^2\)\(^,\)\(^6\)\(^,\)\(^7\). Backpropagating

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**Fig. 1. Schematic diagram of some GABAergic cells in the hippocampus.** Principal cells (that is, granule cells or pyramidal cells, shown in black) are contacted by GABAergic interneurones via feed-forward (left) as well as feedback circuits (right). Interneurones can be divided into distinct classes according to the input they receive, as reflected by the layer-specific location of their dendrites, and their output profiles, as defined by the selective targeting of membrane domains of principal cells. GABAergic interneurones with their cell bodies in the pyramidal cell layer (SP) of the CA1 region activated in a feed-forward manner include (from left to right) axo-axonic cells (AAC), basket cells (BC) and bi-stratified cells (BSC), contacting the axon initial segment, the somatic and the dendritic compartments of the pyramidal cell, respectively\(^1\)\(^6\)\(^,\)\(^17\),\(^18\). GABAergic feedback loops include at least one short loop involving basket interneurones\(^1\)\(^7\)\(^,\)\(^17\), and at least one long loop involving horizontal cells (HC) of the stratum oriens-alveus (SO-A), projecting to the stratum lacunosum-moleculare (SL-M)\(^1\)\(^7\)\(^,\)\(^17\). The classes of interneurones illustrated are not exhaustive, but have been chosen to illustrate principles of organization. Similar feedback and feed-forward loops exist in the dentate gyrus\(^1\)\(^7\)\(^,\)\(^18\).

**Fig. 2. Differential inhibition of dendritic and somatic compartments of the dentate granule cell population during exploration of an unfamiliar environment.** (A) Superimposed averages of pairs of field potentials (1 and 2) sampled from the perforant-path–granule cell synapses of a rat during the first minute of an exploration episode (red) and during rest in a familiar cage (reference condition shown as a black line). Each waveform comprises an upward-going field EPSP with a superimposed downward-going population spike (arrow). The latter represents the summation of the action potentials generated in the postsynaptic population of neurones. (B) The early rising phases of the EPSPs shown in (A) (blue bars) have been expanded. The suppression of the second response during exploration can be used as a measure of feedback inhibition of the granule cells. Note that this suppression changes in a dual manner during exploration: suppression of the field EPSP is enhanced, whereas suppression of the population spike is decreased. (C) Average time course of changes in EPSP slope and population-spike amplitude of the second response during exploration (expansion value of second response/reference value of second response; size of first potential matched). The data are grouped into blocks of 1 min and plotted as the mean ± standard error of the mean. The stimulation intensity was sufficiently high to elicit a population spike in the first response in all experiments. Note that the changes in EPSP slope and population spike of the second response follow different time courses. Adapted, with permission, from Ref. 15.
action potentials might induce LTP-like changes in concurrently active synapses33–35, presumably through co-activation of NMDA receptors, which serve as molecular coincidence detectors. Specific GABAergic interneurones that target the dendrites might control both the extent of backpropagation31,35 and the expression of the NMDA-receptor-mediated component of the EPSP (Ref. 32). Thus, spatial changes in inhibition might switch principal cells between plastic and non-plastic modes of operation.

Postsynaptic spike activity can also promote the induction of LTP through suppression of inhibition: brief trains of action potentials in postsynaptic hippocampal pyramidal cells have been shown to suppress GABAergic inhibition on the discharging cells33. The bursts of action potentials observed in pyramidal (complex-spike) cells when rats are exploring specific regions of the environment (the place fields of those neurons34) might lead to suppressed inhibition and enhanced synaptic plasticity.

Temporal control

During exploration of an environment, the hippocampal network takes part in synchronous rhythmic activity at theta frequencies (4–12 Hz)36,37, correlated with oscillatory activity at higher frequencies38. The medial septum controls theta activity through a cholinergic projection to both pyramidal cells and interneurones39 and a GABAergic projection that contacts interneurones exclusively37. Because medial-septal lesions attenuate both theta rhythm and spatial learning40, it has been assumed that theta activity is necessary for spatial learning, but direct evidence is lacking.

Theta activity in intact, awake animals is associated with rhythmic discharges of theta cells41,42. At least some of these presumed interneurones appear to be basket cells, because theta-like activity in intact, but anaesthetized, animals is associated with rhythmic discharges of interneurons identified as basket cells43. These discharges occur at theta frequencies and are phase-related to the ongoing extracellular theta oscillation. Depolarization of pyramidal cells, with a membrane potential positive to the IPSP reversal potential, are hyperpolarized by basket cells. This hyperpolarization is followed by a rebound depolarization, which can trigger action potentials38. Thus, basket cells can phase the activity of principal cells relative to the surrounding population of neurons and thereby influence the timing of action potentials and backpropagating dendritic slow spikes39–41 (Fig. 3). By phase-locking active pyramidal cells, individual basket cells will also synchronize these cells, that is, cells with task-related activity. Due to the intrinsic resonance properties of hippocampal pyramidal cells, phasing and synchronization are particularly effective at theta frequencies39.

By their synchronizing action, interneurones might have important roles in synaptic modification during exploratory learning. First, by synchronizing postsynaptic excitatory neurones, the co-operative action of these afferents might result in more efficient postsynaptic potentials and backpropagating dendritic slow spikes39–41, and thus contribute to changes in synaptic efficacy, either directly or through triggering of postsynaptic spikes that backpropagate in the dendrites. Second, postsynaptic activity might serve as a temporal reference for the encoding of specific associations: the activity of a specific cell changes its phase relation to the extracellular theta activity as a rat traverses the place field of that cell38. Finally, this activity might be instrumental in regulating these processing events. Thus, spatially confined activity in the hippocampus might have implications for the relative timing of pre- and postsynaptic events. Finally, by phasing both presynaptic and postsynaptic principal cells, networks of GABAergic interneurones might set the temporal coincidence requirement for synaptic change.

Rhythmicity. The rhythmic occurrence of inhibitory events during learning episodes might also have a role in induction of synaptic change. Rhythmic, theta-frequency activity appears to be particularly relevant for induction of NMDA receptor-dependent synaptic plasticity. Both the auto-disinhibition mediated by GABA receptors necessary for expression of the NMDA component of the EPSP (Ref. 30) and the time course of the NMDA receptor-mediated event itself37 are in the same range as the period of theta oscillations. The interneuronal network might also control higher-frequency (40 Hz) oscillations38; a specific role for such high-frequency oscillations, which superimpose on slower theta oscillations, has been suggested for short-term storage of information.

Model for the role of hippocampal interneurones in mnemonic processing

It has often been assumed that hippocampal neurones process memory in temporally distinct stages44–46. In agreement with this assumption, we suggest that segments of the hippocampal network alternate between an information encoding (read-in) mode, in which the synaptic weights in that part of the network can be modified, and an information retrieval (read-out) mode, in which the information stored in the network can be accessed and transferred to downstream areas (Fig. 4). However, in contrast to other models that have been advanced45,46, we propose that the same principal cells participate in each of the modes and that read-in and read-out processes can occur simultaneously in these cells. Activity of specific sets of interneurones targeting distinct domains of the principal cells (dendrites, soma and axon initial segment) might be instrumental in regulating these processing modes.

Read-in mode

In this mode, information about the external world is received from the neocortex via excitatory synapses.
The hippocampal read-in mode presumably occurs during exploration-related theta activity, which is associated with spatial learning. Neuromodulatory inputs set the network or part of the network in a state of increased synaptic plasticity, whereas GABAergic interneurones and hippocampus-dependent memory tasks is compromised by hippocampal lesions made several weeks after encoding, suggesting that the hippocampus is also involved in memory retrieval. Although retrieval might depend on access to information stored in hippocampal excitatory synapses, further modifications of synaptic weights in the hippocampal network might not always be required at this stage. We suggest that the threshold for synaptic modifications during retrieval might be elevated through selective changes of inhibitory circuits: expression of the NMDA-receptor-mediated component of the EPSP might be reduced by feed-forward inhibition, whereas both feed-forward and feedback inhibition could attenuate the Ca²⁺-dependent component of backpropagating action potentials. Because these inhibitory effects occur only after the initial excitation, low-frequency orthodromic information flow through the network via fast synaptic transmission is assisted by neuronal oscillatory activity controlled by an interneuronal network.

Read-in and read-out might occur in parallel. Much of the retrieval of information, presumably from the hippocampus as well as the neocortex, is likely to take place during encoding of hippocampus-dependent memory, because material acquired at an earlier stage of learning must be frequently retrieved to encode further information in the network. Thus, some neurones might perform read-in functions whereas others are simultaneously engaged in read-out processes. Input from interneurones oscillating at theta frequency might be one of the factors that determines in which subset of cells synaptic strength is altered.

It is also conceivable that read-in and read-out processes can take place simultaneously in the same neurone. This could occur during theta activity when the dendrite is engaged in induction of synaptic plasticity. In read-in mode, the axonal output might be blocked due to inhibition by axo-axonic interneurones. However, if these interneurones are inactive, output might be sent through the axon at the same time as a signal is backpropagating through the dendrites. Whereas output information can be carried by single spikes, induction of synaptic plastic changes might...
require bursting activity\(^\text{18}\). If read-in relies on bursting activity and read-out is carried by single spikes, then the network might allow input and output processing to occur at the same time without interference between these processes.

Bursts occur frequently in hippocampal pyramidal neurons when the animal is located in the place field of that particular neuron\(^\text{19,20}\), and presumably representations of and associations to this particular place are learnt. A specific class of interneurone, the horizontal cells of stratum oriens/alveus\(^\text{5,11}\), may be particularly efficiently activated by bursts in pyramidal neurons. The excitatory synapse between pyramidal cells and horizontal cells shows a prominent frequency facilitation, which is in contrast to other excitatory synapses on hippocampal interneurones\(^\text{6,8}\). The horizontal interneurone could therefore serve as a burst detector, and the information about the state of the pyramidal cell could be fed back to the distal dendrites, preventing interference from external excitatory input while intrinsic excitatory connections are involved in associative memory processing.

Transfer to downstream ones

With time, some of the information initially stored in hippocampal synapses during encoding might be transferred for storage in neocortical areas\(^\text{5,8}\). Such transfer would require that the hippocampal principal cells are in read-out mode, with axonal conduction inhibited; the transfer might take place during sleep, when external input is minimal. During slow-wave sleep, the transfer of information from the hippocampal formation\(^\text{47}\) might be replayed and possibly transferred to the neocortex during previous theta activity\(^\text{44}\), that is, simultaneous with the reception of information about the environment from the neocortex; Buzsáki suggests that lasting synaptic changes are induced only during subsequent sharp-wave activity\(^\text{19}\). Finally, we suggest that read-in and read-out processing might occur simultaneously during problem-solving, in addition to the sharp-wave-associated read-out during transfer of information to neocortex.

The present model is consistent with recently discovered properties of hippocampal interneurones, but experiments are needed to test each of these processes in detail. The suggestion more rigorously. Among the predictions of the model are deficits in long-term synaptic plasticity and memory following treatments which interfere with backpropagation of action potentials or their timing, or prevent synaptic transmission between principal cells and specific types of interneurones. To test such predictions, it will be essential to manipulate neuronal functions in a cell-type-specific manner. New genetic engineering techniques offer possibilities to achieve this degree of specificity\(^\text{11}\). Because distinct classes of neurones express different proteins\(^\text{16}\), cell-type specific promotors could be used to engineer animals where specific sets of neurones or neuronal functions are knocked out or tagged. The genetic approach must be complemented by the recording of activity of distinct types of interneurones, as well as interactions between specific interneurones and principal cells, during specific behaviours. Elucidating the cellular machinery underlying memory will be essential to manipulate neuronal functions in a cell-type-specific manner.

Concluding remarks

We suggest that memory-related information processing in the hippocampus occurs in distinct modes (read-in and read-out), a similar distinction was made by Buzsáki\(^\text{1}\). However, the present model differs from that of Buzsáki in at least four important respects. First, the transfer between processing modes in principal cells is controlled by activity of specific interneurones. Second, we do not ascribe different roles to different regions of the hippocampal formation, but suggest that the same cells can participate in both encoding, retrieval and consolidation, but with different neuronal compartments being involved in read-in and read-out.

Third, we suggest that long-lasting synaptic modifications in the hippocampus are induced on-line during theta activity (during exploration and perhaps REM-sleep), that is, simultaneous with the reception of information about the environment from the neocortex; Buzsáki suggests that lasting synaptic changes are induced only during subsequent sharp-wave activity\(^\text{19}\). Finally, we suggest that read-in and read-out processing might occur simultaneously during problem-solving, in addition to the sharp-wave-associated read-out during transfer of information to neocortex.

Acknowledgments

The authors gratefully acknowledge useful discussion and comments on earlier drafts by Professor Peter Somogyi, Dr Robert Eagle, Dr May-Britt Moser, Dr Karl Reber, Mrs Andrea F. Eise and Mrs Emilie G. Pike. The authors are supported by the Norwegian Research Council (grant 11502/130), Eke and The William Grant (grant 104731/1306, OP).
Swallowing involves a complex sequence of actions that transport food from the mouth to the stomach whilst ensuring protection of the airway. The central regulation of swallowing depends on swallowing centres in the brainstem, which receive sensory input from pharynx and oesophagus and, together with local peristaltic mechanisms, control much of the swallowing sequence. However, the initiation of swallowing is a voluntary action that requires the integrity of motor areas of the cerebral cortex. If these higher centres, or their connections to the brainstem, are damaged, then patients have severe difficulty in starting a swallow without choking (dysphagia). Currently, the commonest cause of damage is stroke, up to one third of all stroke patients experience dysphagia, which if persistent, can be associated with the life-threatening complications of pulmonary aspiration and malnutrition. Fortunately, the most impressive fact about swallowing is its great potential for recovery after damage: the majority of stroke patients recover within weeks of the insult. In this article, we examine present knowledge about the organization and reorganization of human swallowing motor cortex. Swallowing problems can affect as many as one in three patients in the period immediately after a stroke. In some cases this can lead to serious morbidity, in particular malnutrition and pulmonary aspiration. Despite this, swallowing usually recovers completely in the vast majority of patients within weeks. This impressive propensity for recovery is likely to relate to how the area of the hemisphere that has the greater input from swallowing centres in the brainstem is organized and then reorganized after cerebral injury. Recent studies have indicated that swallowing has a bilateral but asymmetric inter-hemisphere representation within motor and premotor cortex. Damage to the hemisphere that has the greater likelihood of recovery. Swallowing might be an excellent system for studying cortical reorganization in the undamaged hemisphere after unilateral cerebral injury.

Gut feelings about recovery after stroke: the organization and reorganization of human swallowing motor cortex

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