

References

- 1 Munoz, D. P., Pélisson, D. and Guitton, D. (1991) *Science* 251, 1358–1360
- 2 Guitton, D. and Munoz, D. P. (1991) *J. Neurophysiol.* 66, 1605–1623
- 3 Munoz, D. P. and Guitton, D. (1991) *J. Neurophysiol.* 66, 1624–1641
- 4 Munoz, D. P., Guitton, D. and Pélisson, D. (1991) *J. Neurophysiol.* 66, 1642–1666
- 5 Munoz, D. P. and Wurtz, R. H. (1992) *Soc. Neurosci. Abstr.* 18, 699
- 6 Munoz, D. P. and Guitton, D. (1986) *Brain Res.* 398, 185–190
- 7 Lee, C., Rohrer, W. H. and Sparks, D. L. (1988) *Nature* 332, 357–360

reviews

Acetylcholine and memory

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Acetylcholine may set the dynamics of cortical networks to those appropriate for learning of new information, while decreased cholinergic modulation may set the appropriate dynamics for recall. In slice preparations of the olfactory cortex, acetylcholine selectively suppresses intrinsic but not afferent fiber synaptic transmission, while decreasing the adaptation of pyramidal cells. In biologically realistic models of this region, the selective suppression of synaptic transmission prevents recall of previously learned memories from interfering with the learning of new memories, while the decrease in adaptation enhances the response to afferent input and the modification of synapses. This theoretical framework may serve to guide future studies linking neuromodulators to cortical memory function.

Considerable psychopharmacological evidence shows that antagonists of the muscarinic acetylcholine receptor interfere with memory function in humans, nonhuman primates and rodents^{1–7}. Here we describe how this behavioral evidence might be linked to the physiological evidence for the cholinergic suppression of synaptic transmission^{8–12} and the cholinergic suppression of pyramidal cell adaptation^{13–17}. A combination of brain slice experiments and computational modeling have led to the development of a new theoretical framework for describing the role of acetylcholine in memory function. This theory centers on the problem of storing many overlapping memories in cortical networks, and shows how the physiological effects of acetylcholine can prevent interference between the stored memories during learning.

Modeling the cholinergic modulation of memory function

Associative memory models. Ultimately, understanding the role of cholinergic modulation in memory function requires considering this modulation in the context of the function of specific cortical regions. While the functional characteristics of the cortex have not been fully elucidated, we have approached this question specifically with regard to the putative associative memory function of the olfactory cortex^{18–23}. Experimental work showing selective cholinergic suppression of synaptic transmission within the olfactory cortex¹² motivated development of computational models (see Fig. 1), allowing the effect of this modulation on the storage of multiple overlapping input patterns to be analysed^{20–23}.

This work in turn draws upon a broad background of research on theoretical properties of associative memories^{24–27}. The networks described in this literature have many features that we believe to be similar

to olfactory cortex in particular, and cortical structures in general. For example, these models are capable of forming stable representations of complex input patterns, recalling full memory states when an incomplete or noisy version of the original pattern is provided^{24–27}. We have proposed that a similar process is essential to recognizing objects based on complex and highly variable olfactory stimuli^{18–23}. Abstract associative memories also rely upon a network structure in which the representation of each memory is distributed across a large number of synapses. Numerous neurobiologists have noted very similar structural features in regions of the mammalian cortex believed to be involved in memory or memory-like function^{18–23,28,29}. Memory storage in abstract associative memory models is accomplished by modifying synaptic strengths using mechanisms that are very similar to the well-described properties of long-term potentiation (LTP) in biological networks³⁰.

Limitations on associative memory capacity. Our approach to understanding the implementation of associative memory function has been to explore the ability of a biologically realistic model of olfactory cortex to store memories^{18–23}. As with abstract associative memory models, one of the primary issues in memory storage is how the network might optimize memory capacity. For example, the distributed nature of memory storage in these networks means that regardless of specific network architecture, network activity generated by a new input pattern can be adversely influenced by connections modified by previously stored patterns^{20–23}. How this arises is shown in more detail in Box 1. However, in brief, recall of previously learned memories during learning of new memories can result in a positive feedback cycle leading to runaway synaptic modification and a complete lack of response specificity, with any input recalling the elements of all memories stored within the network^{20–23}.

Before focusing on the more detailed physiological models, it is worth considering how abstract associative memory models have dealt with this problem. First, the problem can be alleviated if the modeler makes sure that the input patterns are non-overlapping (e.g. orthogonal; see for example, Ref. 25). This ensures that no cell is activated by more than one input pattern. In biological systems, however, most real stimuli are not likely to be orthogonal (especially in olfaction). The second approach most abstract modelers have taken to this problem involves clamping network activity to the input pattern and ignoring synaptic transmission at the modifiable connections^{24–27}. In this way, the synaptic changes made

Piriform cortex cross-section

Computational model

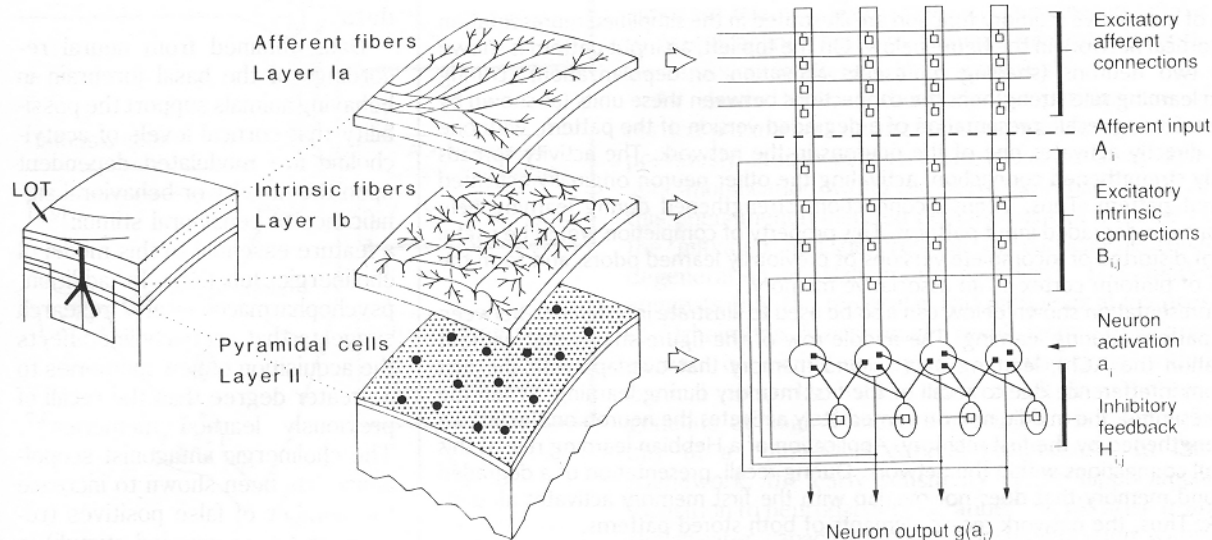


Fig. 1. Overview of piriform cortex anatomical structure and computational modeling of piriform cortex associative memory function. The broadly distributed intrinsic connections of piriform cortex (layer Ib) strongly resemble the feedback connections of a class of abstract model called associative memories¹⁸⁻²³. Our models of piriform cortex have the capacity to learn distributed input patterns and subsequently perform completion or noise reduction on degraded versions of these input patterns¹⁸⁻²³ similar to abstract associative memory models²⁴⁻²⁷. These properties would be useful in the recognition of distorted or incomplete versions of previously learned odors, and form the basis of our model of piriform cortex as an associative memory. (Reproduced, with permission, from Ref. 21.)

during the storage of previous patterns have very little effect on the storage of the new patterns, thereby avoiding the runaway synaptic modifications that can corrupt the new memory. From what is known about the mechanism of LTP in biology, however, completely turning off synaptic transmission would interfere with the mechanisms of synaptic modification at those synapses, by preventing the activation of postsynaptic NMDA receptors by glutamate³⁰. Accordingly, biology must have found another way of dealing with this difficulty, which might ultimately give the network better learning dynamics.

Acetylcholine and associative memory function. As described in the remainder of this article, physiological experiments together with modeling of olfactory cortex suggest that the effects of acetylcholine summarized in Fig. 2 may play a vital role in preventing the problem of interference between memories during associative memory function in cortical structures. In particular, acetylcholine may serve to modulate cortical networks between those characteristics appropriate for storing a new memory based on new afferent input patterns, and the characteristics appropriate for recall of previously stored patterns. The models demonstrate that without the neuromodulation of cortical networks between the dynamics of learning and recall, memory contamination takes place.

(1) **Presynaptic effects.** In olfactory cortex, acetylcholine suppresses synaptic transmission at the intrinsic and association fiber synapses while having little effect on synaptic transmission at afferent fiber synapses¹² (see Fig. 2). These intrinsic and association fibers show more robust synaptic modification than afferent fibers³⁴⁻³⁶, and our models suggest these synapses are critical for associative memory function in the olfactory cortex¹⁸⁻²³. Similarly, in regions CA1 and CA3 of the hippocampus, acetylcholine sup-

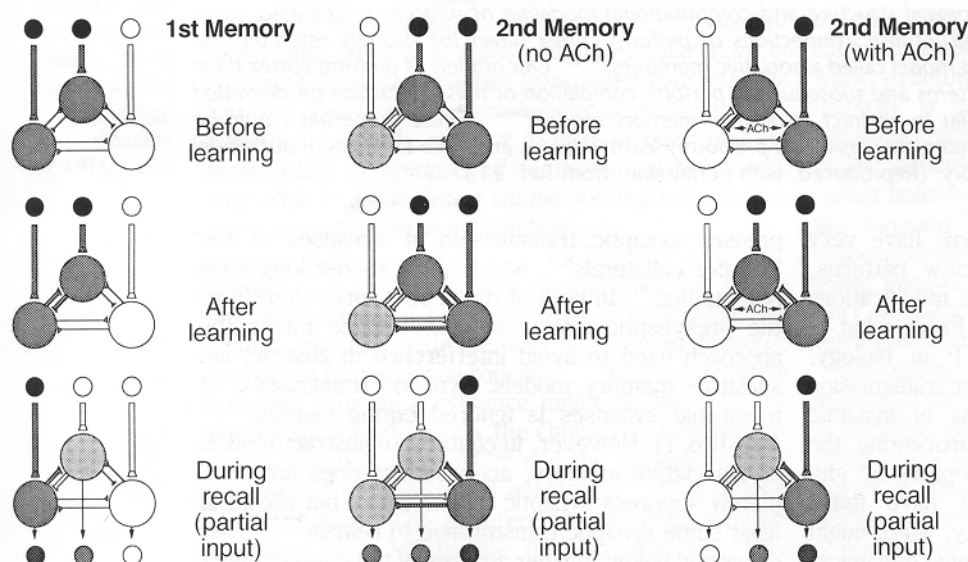
presses synaptic transmission at synapses of the Schaffer collaterals^{8,9}, which show robust long-term potentiation³⁰. In both of these structures therefore, the presynaptic effects of acetylcholine mimic the approach used to avoid interference in abstract associative memory models: synaptic transmission at modifiable synapses is ignored during learning²⁴⁻²⁷ (see Box 1). However, in contrast to abstract models of associative memory, acetylcholine does not completely suppress synaptic transmission, but allows at least some synaptic transmission to remain^{9,11,12}. As described below, further analysis of the consequences of this partial suppression suggests that including this feature of biology in more abstract networks might actually improve their associative memory performance²³.

(2) **Postsynaptic effects.** In a broad range of cortical preparations, acetylcholine has been shown to suppress the normal adaptation of pyramidal cell firing in response to sustained current injection or synaptic input^{12-17,33}, as shown in Fig. 2. This appears to be due to blockade of voltage- and Ca^{2+} -dependent K^+ currents that normally underlie this adaptation^{31,32,37}. To date there is no corollary in abstract associative memory models for the postsynaptic effects of acetylcholine. Some models of the effects of other neuromodulatory substances incorporate a constant change in gain of a sigmoid input/output function³⁸, but these input/output functions do not accurately reflect the characteristics of neuronal adaptation. Our biological modeling suggests that the blockade of voltage- and Ca^{2+} -dependent K^+ currents serves to counteract decreased levels of neuronal activity due to the suppression of synaptic transmission at intrinsic fiber synapses^{12,17,21}. This suppression of neuronal adaptation allows neurons receiving afferent input to fire in a more sustained manner, increasing both pre- and postsynaptic activity at intrinsic fiber synapses within

Box 1. Acetylcholine and associative memory function

The basic elements of associative memory function are illustrated in the simplified representation of a three neuron cortical network in the figure below. On the top left, an input pattern is shown directly activating two neurons (shading represents activation or depolarization). During learning, a Hebbian learning rule strengthens the connections between these units (as shown by thicker connections). During recall, presentation of a degraded version of the pattern, with one input line missing, directly activates one of the neurons in the network. The activity spreads along the previously strengthened connection, activating the other neuron originally activated by the learned input pattern. Thus, intrinsic connections strengthened during learning help complete the response to degraded input patterns. This property of completion would be useful in the recognition of distorted or incomplete versions of previously learned odors, and form the basis of our model of piriform cortex as an associative memory.

The simplified representation shown below can also be used to illustrate interference between overlapping input patterns during learning. The middle row of the figure shows that without cholinergic modulation (no ACh), learning of a second memory that overlaps with the first memory suffers from interference due to recall of the first memory during learning. When the second pattern is presented, the middle neuron immediately activates the neuron on the left via the connection strengthened by the first memory. Application of a Hebbian learning rule at this point strengthens all connections within the network. During recall, presentation of a degraded version of the second memory that does not overlap with the first memory activates all units within the network. Thus, the network recalls elements of both stored patterns.



Cholinergic suppression, applied during learning, prevents interference between the patterns during learning. On the right, learning of the second memory is shown with diffuse application of cholinergic modulation during learning (with ACh). At the top, all intrinsic connections in the network are suppressed during learning, preventing activation of the neuron on the left by the previously strengthened connection. This prevents the strengthening of connections between the left- and the right-hand neuron. Therefore, during recall, presentation of a partial input activates only the neurons directly activated by the second input pattern. Note that during recall, cholinergic suppression of intrinsic fiber synaptic transmission is not applied, allowing pattern completion to proceed as in previous examples. While illustrated here for auto-associative function, these effects apply to hetero-associative function as well^a. Selective suppression of modifiable synapses with associative memory function allows them to be combined with nonsuppressed synapses undergoing self-organization during learning in more complex cortical architectures^a.

Reference

a Hasselmo, M. E. *Neur. Networks* (in press)

Relation of the model to other experimental data

Data obtained from neural recordings of the basal forebrain in behaving animals support the possibility that cortical levels of acetylcholine are modulated dependent upon the novelty or behavioral significance of behavioral stimuli^{40,41}, a feature essential to this model of cholinergic function. In addition, psychopharmacological research suggests that acetylcholine affects the acquisition of new memories to a greater degree than the recall of previously learned memories^{3,7}. The cholinergic antagonist scopolamine has been shown to increase the number of false positives (responses to unrewarded stimuli) in several behavioral tasks⁴. One interpretation of this result, which is consistent with the role of acetylcholine proposed here, is that these false positives reflect a greater number of spurious correlations between learned patterns. This could explain the greater effect of scopolamine on discrimination learning in tasks in which multiple or irrelevant cues as opposed to single cues are presented⁵. A similar interpretation may also explain the greater effect of scopolamine on discrimination of patterns presented at low contrast, where distinctions between different stimuli are less clear and greater interference from previous trials can occur⁶. These effects can also be described as relating to 'attention', highlighting the fact that conceptual divisions between memory and attention may not apply so clearly at the physiological level. With respect to olfaction, scopolamine prevents a change in response dependent upon the novelty or familiarity of an odor⁴².

Experimental evidence on other modulatory effects of acetylcholine are compatible with the modeling framework presented here. Cholinergic modulation has been shown to enhance LTP of the Schaffer collaterals in the stratum radiatum of CA1 (Ref. 43) and the perforant pathway innervation of the dentate

gyrus of the hippocampus⁴⁴ at the same time as it reduces the level of synaptic transmission. Along with increased postsynaptic excitability, this would further enhance learning during cholinergic modulation. The effect of cholinergic agents on LTP in the olfactory cortex is currently under investigation. Cholinergic modulation also influences the function of inhibitory interneurons in a complex manner, with simultaneous

the network, and thereby enhancing the rate of learning. In addition, these changes effectively increase the length constant of pyramidal cell membranes, making them more responsive to synaptic input that is more distal on the dendrites. As shown in Figs 1 and 2, in olfactory cortex these distal dendrites are the specific sites of termination of the afferent input to the network³⁹.

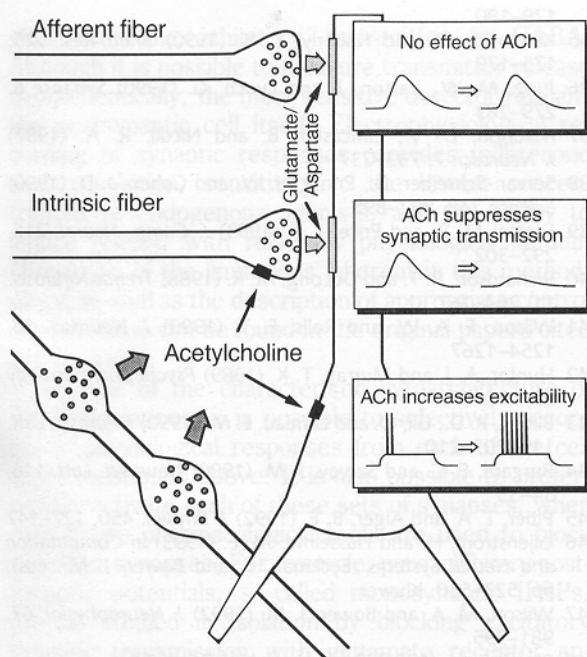


Fig. 2. Schematic diagram of cholinergic modulation in the olfactory cortex, based on existing experimental evidence. Acetylcholine (ACh) released from axonal varicosities influences both pre- and postsynaptic receptors. Presynaptic receptors mediate a decrease in release of excitatory amino acid neurotransmitters at the synapses of intrinsic and association fibers, but not at the synapses of afferent fibers arising outside the cortex¹². Postsynaptic receptors mediate suppression of voltage- and Ca^{2+} -dependent K^+ currents^{31,32}, thereby reducing the adaptation of firing frequency in response to sustained depolarization^{12,17,33}.

enhancement of the activity of inhibitory interneurons^{14,45} and suppression of inhibitory synaptic transmission⁴⁵. In this model, we have found that increasing inhibitory modulation up to a limit increases the efficiency of memory storage^{22,23}. This could allow the inhibition to make neuronal activity more sparse, thereby increasing the capacity of auto-associative storage²⁹. In models of the oscillatory properties of olfactory cortex, suppression of pyramidal cell adaptation⁴⁶ and reduction in the strength of intrinsic fiber synaptic transmission^{46,47} can cause an increase in theta rhythm oscillations such as that noted with cholinergic agents in the hippocampus⁴⁸.

We believe that the results presented here could provide additional insights for enhancing the function of more abstract models of cortical function. Our analysis of the effects of acetylcholine suggests that the partial suppression of intrinsic connections may produce better memory storage performance than the full suppression currently employed in abstract models. With partial suppression, acetylcholine can prevent activation of neurons not receiving afferent input, while allowing synapses between neurons receiving input to enhance their own growth²³ (see Box 1). This suggests that the level of cholinergic modulation should be graded depending on the degree of overlap between the new input pattern and existing memories. The feedback regulation of basal forebrain input to cortical structures^{40,41} should be analysed to determine if such tuning of modulation is possible. The framework presented here for acetylcholine may serve as a general framework for considering the

effects of neuromodulators on cortical memory function. In particular, norepinephrine has been shown to suppress intrinsic fiber synaptic transmission similar to acetylcholine, but may actually facilitate synaptic transmission at afferent fiber synapses⁴⁹.

As shown here, without the proper balance of cortical parameters during learning, interference from previously stored patterns can cause runaway synaptic modification within the network. Observation of this phenomenon inspired development of a model of the initiation and progression of cortical neuronal degeneration in Alzheimer's disease²³. This model suggests that the molecular and pathological features of Alzheimer's disease might result from exponential growth of excitatory synaptic connections within cortical networks, which could result from heterogeneous etiological sources causing an imbalance in any of a number of cortical parameters. In this framework, the early sensitivity of the hippocampal formation to neuronal degeneration⁵⁰ would arise from the greater capacity for synaptic modification within components of this structure.

Concluding remarks

The model presented here provides a coherent framework for describing the role of the coordinated neuromodulatory effects of acetylcholine in cortical memory function. Selective suppression of excitatory intrinsic fiber synaptic transmission prevents recall activity due to previously modified synapses from interfering with the learning of new memories. At the same time, the cholinergic suppression of neuronal adaptation enhances the speed of synaptic modification by allowing a more sustained response to afferent synaptic input. Thus, the neuromodulatory effects of acetylcholine appear to complement one another in enhancing associative memory function in cortical structures.

Selected references

- Kopelman, M. D. (1986) *Q. J. Exp. Psychol.* 38A, 535–573
- Hagan, J. J. and Morris, R. G. M. (1989) in *Psychopharmacology of the Aging Nervous System* (Iversen, L. L., Iversen, S. D. and Snyder, S. J., eds), pp. 237–323, Plenum Press
- Ghonheim, M. M. and Mewaldt, S. P. (1975) *Psychopharmacologia* 44, 257–262
- Cox, T. and Tye, H. (1973) *Neuropharmacology* 12, 477–484
- Whitehouse, J. M. (1967) *J. Comp. Physiol. Psychol.* 63, 448–451
- Spencer, D. G., Pontecorvo, M. J. and Heise, G. A. (1985) *Behav. Neurosci.* 99, 1049–1065
- Aigner, T. G., Walker, D. L. and Mishkin, M. (1991) *Behav. Neur. Biol.* 55, 61–67
- Hounsgaard, J. (1978) *Exp. Neurol.* 62, 787–797
- Valentino, R. J. and Dingledine, R. (1981) *J. Neurosci.* 1, 784–792
- Williams, S. H. and Constanti, A. (1988) *Br. J. Pharmacol.* 93, 846–854.
- Kahle, J. S. and Cotman, C. W. (1989) *Brain Res.* 482, 159–163
- Hasselmo, M. E. and Bower, J. M. (1992) *J. Neurophysiol.* 67, 1222–1229
- Madison, D. V. and Nicoll, R. A. (1984) *J. Physiol.* 354, 319–331
- McCormick, D. A. and Prince, D. A. (1986) *J. Physiol.* 375, 169–194
- Woody, C. D. and Gruen, E. (1987) *Brain Res.* 424, 193–198
- Schwindt, P. C., Spain, W. J. and Crill, W. E. (1992) *J. Neurophysiol.* 67, 216–226
- Hasselmo, M. E. and Barkai, E. (1992) *Soc. Neurosci. Abstr.* 18, 521

Acknowledgements

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- 18 Wilson, M. A. and Bower, J. M. (1988) in *Neural Information Processing Systems* (Anderson, D., ed.), pp. 114–126, AIP Press
- 19 Haberly, L. B. and Bower, J. M. (1989) *Trends Neurosci.* 12, 258–264
- 20 Hasselmo, M. E., Anderson, B. P. and Bower, J. M. (1991) in *Advances in Neural Information Processing Systems 3* (Lippman, R. P., Moody, J. and Touretsky, D. S., eds), pp. 46–52, Morgan Kaufmann
- 21 Hasselmo, M. E., Anderson, B. P. and Bower, J. M. (1992) *J. Neurophysiol.* 67, 1230–1246
- 22 Hasselmo, M. E. (1993) *Neur. Comput.* 5, 32–44
- 23 Hasselmo, M. E. *Neur. Networks* (in press)
- 24 Anderson, J. A. (1983) *IEEE Trans. Syst. Man Cybern.* SMC-13, 799–815
- 25 Kohonen, T. (1988) *Self-Organization and Associative Memory*, Springer-Verlag
- 26 Hopfield, J. J. (1984) *Proc. Natl Acad. Sci. USA* 81, 3088–3092
- 27 Amit, D. J. (1989) *Modelling Brain Function*, Cambridge University Press
- 28 McNaughton, B. L. and Morris, R. G. M. (1987) *Trends Neurosci.* 10, 408–415
- 29 Treves, A. and Rolls, E. T. (1991) *Network* 2, 371–397
- 30 Gustafsson, B. and Wigstrom, H. (1988) *Trends Neurosci.* 11, 156–162
- 31 Constanti, A. and Galvan, M. (1983) *Neurosci. Lett.* 39, 65–70
- 32 Constanti, A. and Sim, J. A. (1987) *J. Physiol.* 387, 173–194
- 33 Tseng, G-F. and Haberly, L. B. (1989) *J. Neurophysiol.* 62, 386–400
- 34 Hasselmo, M. E. and Bower, J. M. (1990) *J. Neurophysiol.* 64, 179–190
- 35 Kanter, E. D. and Haberly, L. B. (1990) *Brain Res.* 525, 175–179
- 36 Jung, M. W., Larson, J. and Lynch, G. (1990) *Synapse* 6, 279–283
- 37 Madison, D. V., Lancaster, B. and Nicoll, R. A. (1987) *J. Neurosci.* 7, 733–737
- 38 Servan-Schreiber, D., Printz, H. W. and Cohen, J. D. (1990) *Science* 249, 892–895
- 39 Luskin, M. B. and Price, J. L. (1983) *J. Comp. Neurol.* 216, 292–302
- 40 Richardson, R. T. and DeLong, M. R. (1988) *Trends Neurosci.* 11, 264–267
- 41 Wilson, F. A. W. and Rolls, E. T. (1990) *J. Neurosci.* 10, 1254–1267
- 42 Hunter, A. J. and Murray, T. K. (1989) *Psychopharmacology* 99, 270–273
- 43 Blitzer, R. D., Gil, O. and Landau, E. M. (1990) *Neurosci. Lett.* 119, 207–210
- 44 Burgard, E. C. and Sarvey, J. M. (1990) *Neurosci. Lett.* 116, 34–39
- 45 Pitler, T. A. and Alger, B. E. (1992) *J. Physiol.* 450, 127–142
- 46 Liljenstrom, H. and Hasselmo, M. E. (1993) in *Computation and Neural Systems* (Eeckman, F. and Bower, J. M., eds), pp. 523–530, Kluwer
- 47 Wilson, M. A. and Bower, J. M. (1992) *J. Neurophysiol.* 67, 981–995
- 48 Bland, B. H. (1986) *Prog. Neurobiol.* 26, 1–54
- 49 Vanier, M. C. and Bower, J. M. (1992) *Soc. Neurosci. Abstr.* 18, 1353
- 50 Hyman, B. T., Damasio, A. R., Van Hoesen, G. W. and Barnes, C. L. (1984) *Science* 225, 1168–1170

Presynaptic inhibition in the hippocampus

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Presynaptic receptors for virtually all transmitters have been identified throughout the nervous system. Recent studies in the hippocampus provide new insights into the mechanisms by which the activation of these receptors leads to presynaptic inhibition of transmitter release, and characterize the second messengers involved in coupling presynaptic receptors to their effectors. Presynaptic receptors also provide a tractable route via which the amount of transmitter release may be selectively regulated in therapeutically useful ways.

Transmitter release is elicited by the influx of Ca^{2+} through voltage-dependent channels that are activated when an action potential invades the axon terminal. Elevated intraterminal Ca^{2+} concentrations then increase the probability that transmitter-containing vesicles will fuse with the presynaptic membrane and release their contents into the synaptic cleft. Transmitter release at a given synapse is not constant, but rather is subject to a variety of modulatory influences that can either increase or decrease the probability of release. More than 35 years ago, Frank and Fuortes¹ presented the first evidence for presynaptic inhibition of synaptic transmission at Ia afferents to spinal motoneurons. We now know that there are receptors for neurotransmitters, at or near the presynaptic terminals of many synapses, whose activation can change the likelihood that a presynaptic action potential will successfully result in transmitter release. Surprisingly, all transmitters examined to date produce presynaptic inhibition in the hippocampus, and there are, to our knowledge, no examples of transmitters that produce presynaptic facilitation in

this structure, although evidence is accumulating for a facilitatory action of several putative retrograde messengers^{2,3}. Considerable progress has been made in identifying the neurotransmitters mediating presynaptic inhibition, defining their receptors pharmacologically, characterizing their second messenger systems and elucidating their effector mechanisms. The hippocampus provides a convenient and well-studied model system with which to illustrate several important principles of presynaptic inhibition, focusing on three presynaptic receptors that have been best characterized: adenosine A_1 , μ -opioid and GABA_B receptors. Although data from many hippocampal preparations are discussed, the illustrations are taken from our own work using cultured hippocampal slices, which combine the advantages of cell culture with the preservation of the organotypic cytoarchitecture⁴.

Expression of presynaptic receptors is cell-type specific

It is possible to identify at least four populations of neurons with unique phenotypes in hippocampal slice preparations: granule cells of the dentate gyrus, CA1 and CA3 pyramidal cells of the hippocampus proper, and a heterogeneous group of interneurons. These neurons also form specific synaptic connections within a hippocampal slice. The axons of granule cells (mossy fibers) form excitatory synapses with CA3 pyramidal cells, whose axons in turn form excitatory synapses with both CA1 cells and adjacent CA3 cells. Interneurons form inhibitory synapses with both granule and pyramidal cells. Excitatory synaptic transmission is mediated by excitatory amino acids, predominantly