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Neuromodulation and the Functional Dynamics of Piriform Cortex

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Acetylcholine and norepinephrine have a number of effects at the cellular level in the piriform cortex. Acetylcholine causes a depolarization of the membrane potential of pyramidal cells and interneurons, and suppresses the action potential frequency accommodation of pyramidal cells. Acetylcholine also has strong effects on synaptic transmission, suppressing both excitatory and inhibitory synaptic transmission. At the same time as it suppresses synaptic transmission, acetylcholine enhances synaptic modification, as demonstrated by experiments showing enhancement of long-term potentiation. Norepinephrine has similar effects. In this review, we discuss some of these different cellular effects and provide functional proposals for these individual effects in the context of the putative associative memory function of this structure.

Introduction

Numerous anatomical studies have described the structure of the olfactory system [for a review see Haberly (Haberly, 1985)]. Anatomical data demonstrate neuromodulatory innervation of these regions, including cholinergic and GABAergic innervation arising from the horizontal limb of the diagonal band (HDB) (Luskin and Price, 1982; Brashear *et al.*, 1986; Zaborszky *et al.*, 1986) and noradrenergic innervation arising from the locus coeruleus (McLean *et al.*, 1989) [for a review see Shipley and Ennis (Shipley and Ennis, 1996)].

A number of studies have shown an important role for neuromodulatory effects in olfactory memory function. These include data showing impairments of odor memory induced by the muscarinic cholinergic antagonist scopolamine, as well as lesions of the cholinergic and GABAergic neurons in the HDB (Hunter and Murray, 1989; Ravel *et al.*, 1992, 1994; Paolini and McKenzie, 1993, 1996; Roman *et al.*, 1993). In addition, numerous studies have shown the importance of norepinephrine for olfactory learning (Pissonnier *et al.*, 1985; Rosser and Keverne, 1985; Brennan *et al.*, 1990; Guan *et al.*, 1993; Sullivan *et al.*, 1989, 1991, 1992).

Here we provide a review of physiological data on cellular effects of these neuromodulators, a description of computational models analyzing the behavioral role of these neuromodulators, and some behavioral data testing hypotheses derived from these computational models. The piriform cortex provides an excellent region for analysis of neuromodulatory effects, as its structure resembles a class of neural network models termed 'associative memories' (Haberly, 1985; Haberly and Bower, 1989; Hasselmo *et al.*, 1990). This provides a clear computational framework for analyzing the functional role of the changes in network dynamics induced by neuromodulatory agents (Figure 1).

Studying neuromodulatory effects in olfactory cortex

Acetylcholine and norepinephrine have a number of effects at the cellular level in the piriform cortex. Acetylcholine causes a depolarization of the membrane potential of pyramidal cells (Tseng and Haberly, 1989; Barkai and Hasselmo, 1994) and interneurons (Gellman and Aghajanian, 1993), and suppresses the spike frequency accommodation of pyramidal cells (Tseng and Haberly, 1989; Barkai and Hasselmo, 1994), as well as increasing the excitability of olfactory cortex cells *in vivo* (Zimmer *et al.*, 1999). Like norepinephrine, acetylcholine also has strong effects on synaptic transmission, suppressing both excitatory synaptic transmission (Collins *et al.*, 1984; McIntyre and Wong, 1986; Williams and Constanti, 1988; Hasselmo and Bower, 1992; Hasselmo *et al.*, 1997; Linster *et al.*, 1999) and inhibitory synaptic transmission (Patil and Hasselmo, 1999). At the same time as it suppresses synaptic transmission, acetylcholine enhances synaptic modification, as demonstrated by experiments showing enhancement of long-term potentiation (Hasselmo and Barkai, 1995; Patil *et al.*, 1998). In this review, we discuss some of these different cellular effects and provide functional proposals for them in the context of the putative associative memory function of this structure.

Selective cholinergic suppression of excitatory synaptic transmission

The piriform cortex is an excellent structure for studying the neuromodulation of synaptic transmission, as it has a clear laminar segregation of different types of synapses. As shown in Figure 1, the afferent fibers arising from the olfactory bulb terminate in the most superficial layer of piriform cortex, layer Ia, whereas the fibers arising from other pyramidal cells within the cortex terminate in the deeper layers, including layers Ib and III. Cutting brain slices perpendicular to the surface of the cortex allows separate stimulation of synaptic potentials in the two layers, with stimulating electrodes in layer Ia or Ib (Figure 2). Recording can take place either intracellularly, from the pyramidal cell bodies tightly clustered in layer II, or extracellularly, from the layer being stimulated.

Previous research had demonstrated cholinergic modulation of excitatory transmission in tangential slices of the piriform cortex (Williams and Constanti, 1988). However, the use of transverse slices allowed demonstration of striking differences in the effect of neuromodulators on the different synaptic pathways. As shown in Figure 3A (Hasselmo and Bower, 1992), perfusion of acetylcholine through the slice chamber causes a suppression of synaptic potentials elicited with stimulation in layer Ib (intrinsic fibers) while having a weaker effect on synaptic potentials elicited with stimulation in layer Ia (afferent fibers). This selectivity is supported by additional studies performed *in vivo* (Figure 3B), showing that stimulation of the horizontal limb of the diagonal band causes suppression of synaptic potentials evoked with stimulation in caudal piriform cortex and entorhinal cortex, which presumably activates primarily intrinsic fibers (Linster *et al.*, 1999). In contrast, stimulation of the horizontal limb actually enhances potentials elicited by stimulation of afferent input fibers in the lateral olfactory tract (Linster *et al.*, 1999) (Figure 3C).

The cholinergic suppression of excitatory transmission might appear somewhat paradoxical, as acetylcholine has been shown to be important for learning. Why would a substance that is important for learning cause suppression of excitatory transmission? The importance of this selective suppression of transmission has been analyzed in computational models, and recent experiments have tested behavioral predictions of these computational models. Here we will first describe the behavioral experiment, and then show a schematic model of how suppression of transmission could play a role in this experiment.

The basic experiment is shown in Figure 4. The experiment tested the learning of odor pairs presented at separate odor ports. Initially, the rat must learn to respond to odor A when presented with the odor pair A–B. Then, in a separate phase of the experiment, the rat must learn to respond to odor C when presented with odor pair A–C, and during the same period must learn to respond to odor D when presented with odor pair D–E. In a counterbalanced design, rats received injections of scopolamine, methylscopolamine or saline after learning of A–B and before learning of A–C

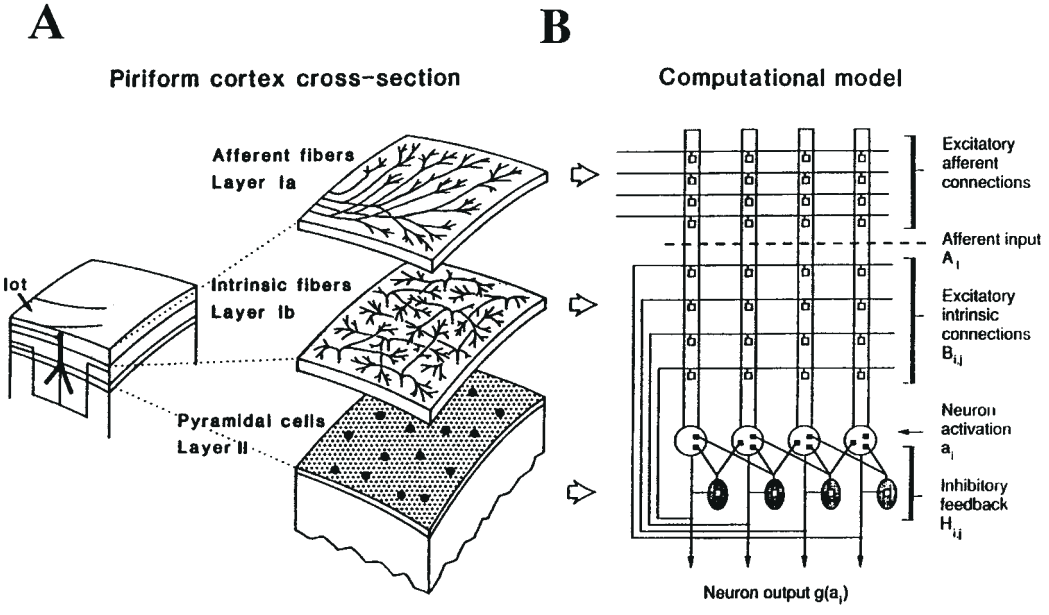

Figure 1 Overview of the anatomical structure of the piriform cortex compared with the basic components of computational models of associative memory function. **(A)** Left: a segment of piriform cortex shows the LOT entering along the surface and a pyramidal cell with its apical dendrite extending up through layer I. Right: the expanded diagram shows how afferent fibers from the LOT synapse on pyramidal cell distal dendrites in the superficial layer, layer Ia, whereas excitatory intrinsic fibers arising from other pyramidal cells within the cortex terminate on proximal dendrites in layer Ib. Pyramidal cell bodies are tightly packed in layer II. **(B)** The afferent and intrinsic connections correspond to the broadly distributed input and intrinsic connections of computational models of associative memory.

and D–E. This allowed analysis of how scopolamine influenced the learning of overlapping odor pairs (A–C) versus non-overlapping odor pairs (D–E).

This behavioral task was designed to test hypotheses arising from computational models of the piriform cortex (Hasselmo and Bower, 1992). The basic hypothesis is demonstrated in Figure 5. Figure 5A demonstrates the putative mechanisms for encoding the correct response to individual odor pairs. When presented with odor pair A–B, the response to odor A is rewarded. This association between the odor pair and the correct response can be encoded as strengthened synaptic connections between the population of neurons representing these two odors and the population of neurons activated during the response to odor A. The strengthening of synapses follows a Hebb rule, in which synapses are only strengthened in the presence of both pre- and post-synaptic activity. A direct association between activity evoked by sensory input and that evoked by motor responses is possible in the piriform cortex, as it has been shown that select populations of neurons in the piriform cortex fire during multiple different components of odor discrimination tasks, including odor sampling and response generation (Schoenbaum and Eichenbaum, 1995). Once this association has been encoded, the next time the odor pair is encountered, activity will spread along the previously strengthened connections, allowing activation of the response to odor A for correct retrieval.

This association works well for single odor pairs, but can run into difficulties of proactive interference for overlapping odor pairs. As illustrated in Figure 5B, if the rat has been trained to respond to odor A in the pair A–B, then it could

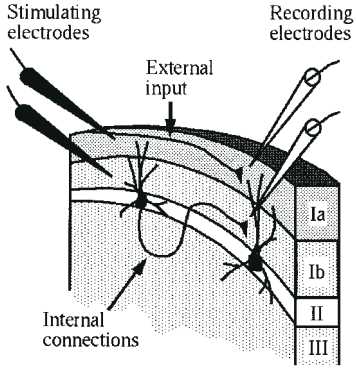

Figure 2 Schematic representation of brain slice preparation of piriform cortex. Stimulating electrodes can be placed either among afferent fibers from the LOT in layer Ia or among intrinsic and association fibers in layer Ib. Extracellular recording electrodes can be used to record synaptic potentials from either layer Ia or layer Ib. Intracellular or patch electrodes can be used to record from pyramidal cells in layer II.

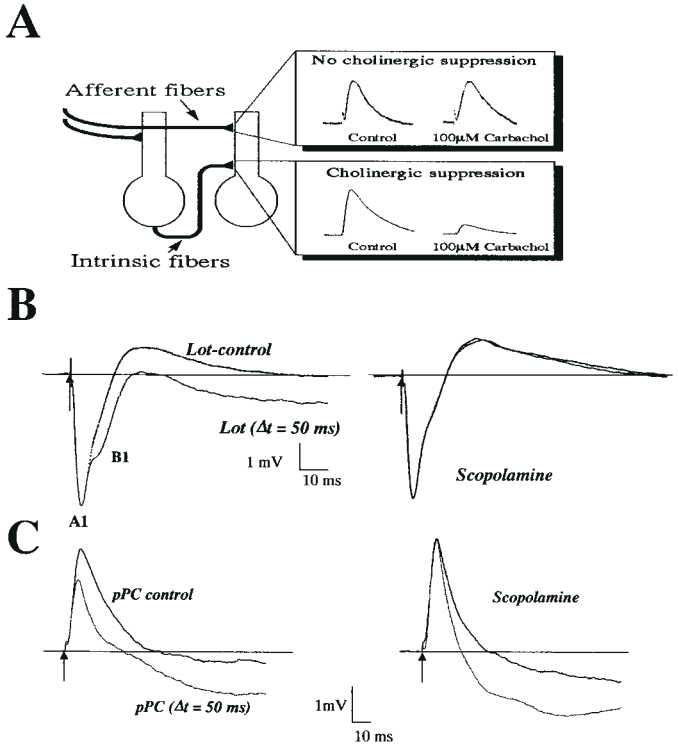

Figure 3 **(A)** Experimental data showing selective cholinergic suppression of excitatory intrinsic synaptic potentials in the piriform cortex. Stimulation of afferent fibers in layer Ia or intrinsic fibers in layer Ib elicits synaptic potentials recorded with intracellular electrodes in pyramidal cell bodies in layer II (Control). Perfusion of the slice chamber with the cholinergic agonist CCh causes a strong decrease in the magnitude of synaptic potentials elicited with layer Ib stimulation, while having a much weaker effect on synaptic potentials elicited with layer Ia stimulation. **(B)** Effect of stimulation of the HDB on the population EPSP in layer Ia of the piriform cortex in response to stimulation of the LOT recorded *in vivo*. Graph on the left side: responses to baseline pulse (baseline response) and test pulse 50 ms after HDB stimulation (test response, Δt = 50 ms). The population EPSP observed in layer Ia of the PC after stimulation of the LOT has a first negative peak (A1), followed by a second negative inflection (B1). A1 is generated by the monosynaptic EPSP in layer Ia and B1 is thought to reflect the disynaptic EPSP due to activation of the intrinsic fibers within the piriform cortex. At 50 ms after the tetanus in the HDB, component B1 is greatly enhanced. There is no effect on the monosynaptic component A1. Each trace is the average of 10 stimulations. The lines with arrows to the left of the potential indicate the measurements of the amplitude of the A1 and B1 components used for the analysis. Graph on the right side: responses to the baseline pulse and the test pulse 50 ms after HDB stimulation and 30 min after the injection of 0.5 mg/kg scopolamine. Scopolamine abolishes or greatly reduces the enhancement of component B1 after HDB stimulation. Each trace is the average of 10 stimulations. A and B are from the same animal. **(C)** Effect of stimulation of the HDB on the population EPSP in layer Ia in response to stimulation of layers II–III in the posterior piriform cortex recorded *in vivo*. Graph on the left side: responses to the baseline pulse (baseline response) and the test pulse 50 ms after HDB stimulation (Δt = 50 ms). In these experiments, we considered only the first peak of the response, which represents the monosynaptic population EPSP and could be reliably obtained at a short latency. The line with an arrow indicates the measurement of the peak of the response used in the analysis; the pointed lines show the measurement of the onset slope. After stimulation of the HDB, the first positive peak was reduced in most animals. Graph on the right side: Responses to the baseline pulse and the test pulse 50 ms after HDB stimulation and 30 min after the injection of 0.5 mg/kg scopolamine. Scopolamine abolished or greatly reduced the suppression of the first peak after HDB stimulation. Each trace is the average of 10 stimulations. A and B are from the same animal. From Linster *et al.* (Linster *et al.*, 1999).

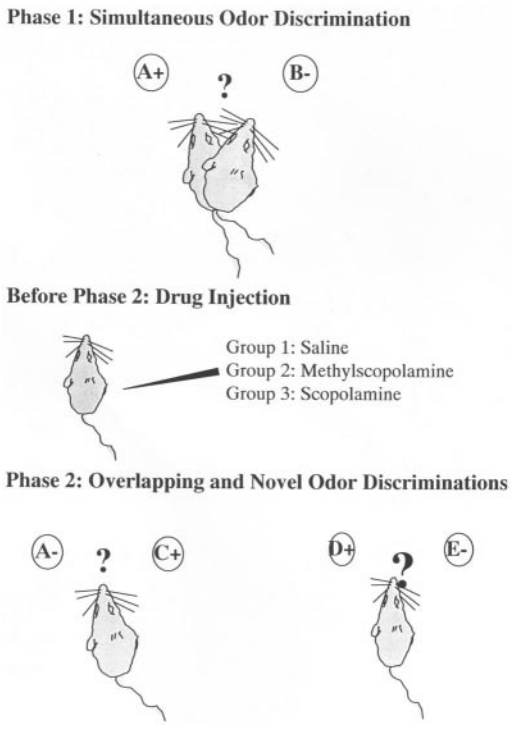

Figure 4 Schematic representation of the behavioral experiment. Phase 1: in phase 1, the rats learned a simultaneous odor discrimination task, in which two different odors were independently and simultaneously presented from both odor ports. Of the two odors, one odor was arbitrarily labeled the positive odor (A+B–). The rats indicated their choice with a nose poke to the odor port with the positive odor. Phase 1 ended when all the rats learned the A+B– discrimination to criterion (18 out of 20 consecutive trials correct). Phase 2: the animals were then tested on the two novel experimental odor pairs (overlapping and non-overlapping) under the influence of drugs. For four consecutive sessions, the rats were presented with 32 trials of A–C+ and 32 trials of D+E– intermixed in a pseudorandom order. At the beginning of each of the experimental sessions, they were presented with 16 'reminder' A+B– trials. These reminder trials only served as an opportunity for the experimenter to observe any attentional impairments and adjust the trial onset accordingly. The dependent measure was percentage of correct responses.

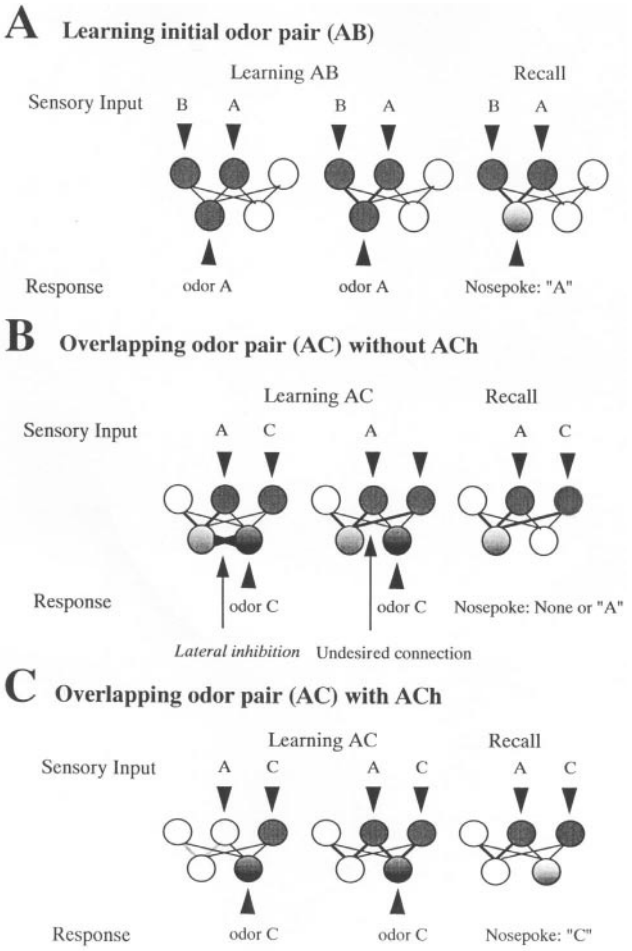

Figure 5 Overview of the potential role of cholinergic modulation learning of odor pairs in an example network. Each circle represents a population of neurons, with the thickness of lines representing the strength of synaptic connections between these populations. The shading of each neuron represents its activity level. **(A)** During initial learning of an odor pair response (Learning AB), the input of odors A and B (top row) is associated with the correct response to odor A (bottom row). This causes strengthening of connections from the input populations to the odor response population. During recall, activation of these sensory populations causes activity to spread across strengthened connections, activating the correct response (nosepoke to A). **(B)** Subsequent learning of an overlapping odor pair can suffer from proactive interference. In this case, during Learning of A–C+, sensory input activates populations A and C, and the correct response to odor C. However, activity spreads across previously modified connections to activate the population representing a nosepoke to A. This can result in strengthening of an 'undesired connection' and lateral inhibition, causing reduction of learning of the response to odor C. During recall, input of odors A and C then evokes no nosepoke or a response to odor A. This is analogous to what might happen under the influence of scopolamine. **(C)** With acetylcholine causing suppression of excitatory intrinsic transmission in the network, this prevents the spread of activity across previously modified synapses, allowing the response activity to only be influenced by the input of odor C. This allows accurate encoding of the new response to odors A and C, such that during recall the input of odors A and C results in nosepoke to C alone.

be more difficult to train the rat to respond to odor C in odor pair A–C. This problem of proactive interference arises because the presentation of odor A causes activity to spread along previously modified synapses to activate the previously learned response to odor A. This can result in incorrect responses, and undesired encoding of an association between odor C and the response to odor A. Thus, transmission across previously modified synapses interferes with the encoding of a new response.

Figure 5C shows how the selective cholinergic suppression of excitatory synaptic transmission can prevent this difficulty. Recall that acetylcholine does not suppress afferent input from the olfactory bulb. Thus, during encoding of odor pair A–C, acetylcholine does not block the sensory input activity. However, it does block the spread of activity along excitatory intrinsic connections within the cortex, preventing interference due to activation of the previous response to odor A. With this suppression of previous retrieval, the network can more effectively encode the new response to odor C. Thus, comparison of Figures 5B and 5C

shows the prediction for effects of scopolamine in this experiment. Scopolamine will block effects of acetylcholine on intrinsic synaptic transmission, enhancing the type of proactive interference illustrated in Figure 5B.

The results of the experiment support this hypothesis, as shown in Figure 6 (De Rosa and Hasselmo, 2000). Injections of scopolamine caused a stronger impairment of the ability to respond to odor C in the overlapping odor pair A–C, in comparison to its weaker impairment of the ability to respond to odor D in the non-overlapping odor pair D–E. Thus, scopolamine appears to enhance proactive interference, consistent with its blockade of the cholinergic suppression of excitatory synaptic transmission at intrinsic synapses in the piriform cortex. This model is further supported by experimental data showing that electrical stimulation of the olfactory cortex can modulate the activity of neurons in the HDB, thus providing a pathway for regulation of cholinergic activity (Linster and Hasselmo, 2000) (Figure 7). Similar effects have been obtained in an experiment performed in human subjects, in which scopolamine caused greater impairments in the encoding of overlapping versus non-overlapping word pairs (Kirchhoff *et al.*, 2000).

Cholinergic modulation of long-term potentiation

To prevent interference, the suppression of excitatory synaptic transmission should take place during the encoding of new information. This strict temporal correlation of suppressed transmission and modification can be obtained if the same modulator causes suppression of transmission and enhancement of synaptic modification. Experimental data support this role for acetylcholine. In addition to the suppression of transmission described above (Hasselmo and Bower, 1992; Linster *et al.*, 1999), acetylcholine causes enhancement of long-term potentiation in the piriform cortex (Hasselmo and Barkai, 1995; Patil *et al.*, 1998).

This was initially shown (Hasselmo and Barkai, 1995) by studying the effect of 5 Hz stimulation in two conditions: (i) during continuous infusion of the cholinergic agonist carbachol (CCh) and (ii) during perfusion of normal ACSF (artificial cerebrospinal fluid). A larger magnitude of long-term potentiation was obtained when the stimulation took place during cholinergic modulation. An example of data from this study is shown in Figure 8. This enhancement of long-term potentiation could result from a number of different effects of cholinergic modulation, including the depolarization of pyramidal cells and the suppression of spike frequency accommodation. Spike frequency accommodation occurs in piriform cortex pyramidal cells in response to long current injections. During the current injection, neurons initially fire spikes at a high frequency, which gradually decreases until spiking stops later in the

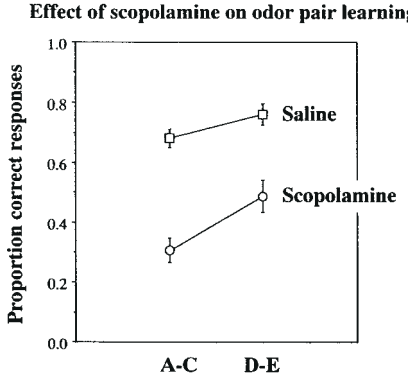

Figure 6 Experimental results from the study of scopolamine effects on behavior. The proportion of correct responses is shown for overlapping odor pairs A–C and non-overlapping pairs D–E in both control (saline) and scopolamine conditions. Note that scopolamine causes a greater decrease in performance for overlapping odor pairs A–C than for the non-overlapping odor pairs, supporting the hypothesis that blockade of acetylcholine enhances proactive interference due to spread of activity across previously modified synapses. From De Rosa and Hasselmo (De Rosa and Hasselmo, 2000).

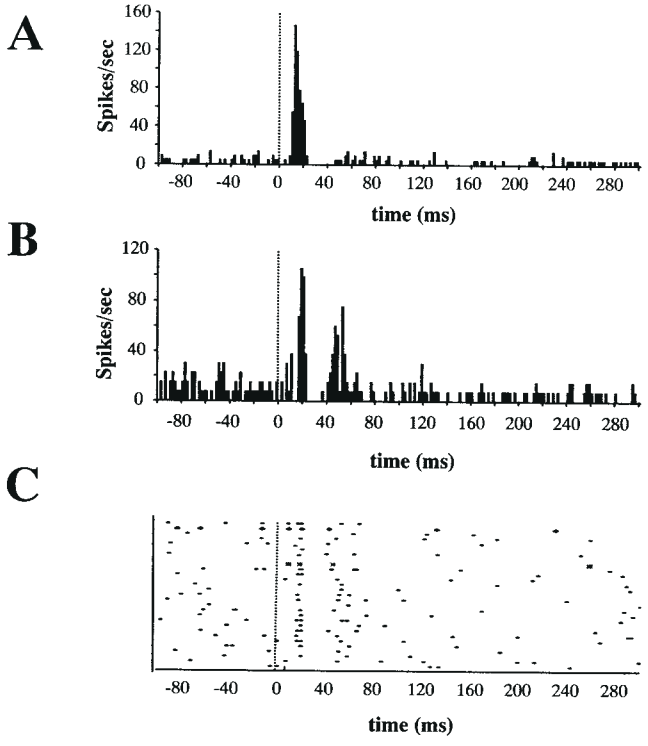

Figure 7 Effect of electrical stimulation of the PC on unit activity in the HDB. **(A)** Peristimulus time histogram of the effect of electrical stimulation (300 μA, 0.1 ms) of the PC on the spiking activity of an individual neuron recorded in the HDB. The neuron shown in this graph responded to the electrical stimulation with a single increase in spike rate. The histogram shows the summed numbers of action potentials (binsize = 2 ms) recorded during 100 successive sweeps. Stimulation occurred at time = 0 and is indicated by the dotted line. **(B)** The neuron shown in this graph responded with two periods of increased spiking to the electrical stimulation. **(C)** Dot raster showing the occurrence of action potentials during the 30 individual trials which were part of the summed histogram shown in B. Stimulation occurred at time = 0 and is indicated by the dotted line. From Linster and Hasselmo (Linster and Hasselmo, 2000).

injection due to activation of calcium-sensitive potassium currents. Cholinergic modulation suppresses the calcium-sensitive potassium current, allowing a more sustained spiking response to current injection. In computational models, this enhanced spiking response causes greater post-synaptic depolarization, which enhances the activation of NMDA receptors and the rate of Hebbian synaptic modification.

This enhancement of long-term potentiation would be particularly effective if it applied to dendrites on which there is a convergence of afferent input and active intrinsic synapses. This would enhance the accuracy of encoding of new afferent input. Experiments in our laboratory have demonstrated that cholinergic modulation enables associative long-term potentiation (Patil *et al.*, 1998) between the afferent fibers and the intrinsic association fibers (Figure 9A). In these experiments, a strong stimulation was presented to layer Ia of the piriform cortex (bursts of four pulses at 100 Hz at 200 ms intervals). This tetanic stimulation was accompanied by a weaker stimulation in layer Ib, given at

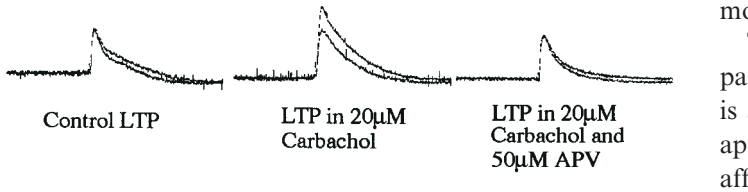

Figure 8 Cholinergic modulation of the long-term potentiation of intracellularly recorded EPSPs in the piriform cortex. Each pair of traces shows EPSPs recorded before and after 5 Hz stimulation in different conditions. Left: during perfusion of normal control solution, 5 Hz stimulation causes only a small increase in the magnitude of the potential. Middle: during perfusion of 20 μM CCh, the same stimulation paradigm elicits a much larger change in the size of the EPSP. Right: perfusion of 20 μM CCh with 50 μM APV blocks the induction of long-term potentiation by 5 Hz stimulation.

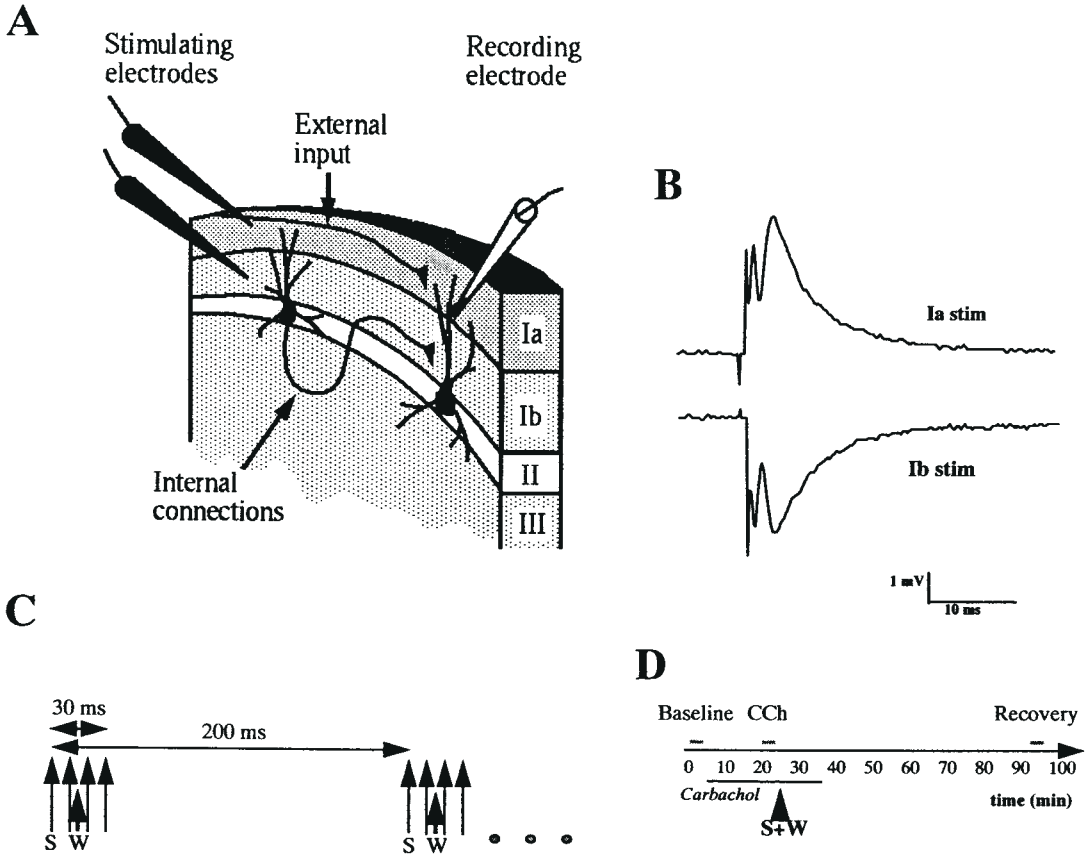

Figure 9 Schematic representation of the brain slice preparation of the piriform cortex and the experimental protocol. **(A)** Stimulating electrodes were placed among afferent fibers from the LOT in layer Ia and among association fibers in layer Ib under visual guidance. Extracellular recording electrodes were placed at the boundary of the two layers. **(B)** Potentials recorded in response to stimulation of layer Ia (afferent fibers) and layer Ib (association fibers) at the boundary of layers Ia and Ib. **(C)** Potentiation trains in layer Ia consisted of 10 sets of four pulses (100 Hz) (S) at 200 ms intervals. During pairing of strong (S) and weak (W) stimuli, weak test pulses in layer Ib were delivered at 200 ms intervals between the second and third pulses of the four pulse burst. In experiments using multiple pairings, three consecutive pairings of weak and strong stimuli were delivered at 5 min intervals. **(D)** Experimental protocol. Weak stimuli in layer Ib were delivered continuously throughout the experiment at 30 s intervals. Baseline responses to layer Ib test pulses were recorded at the beginning of the experiment. Approximately 20 min after the beginning of CCh application a single or three pairings of potentiation trains with weak stimuli were delivered (S+W). After washout, the response to test stimuli in ACSF was recorded for at least 60 min. For analysis, 10 consecutive trials were averaged 5 min after the beginning of the experiment (*Baseline*), 20 min after the beginning of CCh perfusion (*CCh*) and 40–45 min after the beginning of washout (*Recovery*). From Patil *et al.* (Patil *et al.*, 1998).

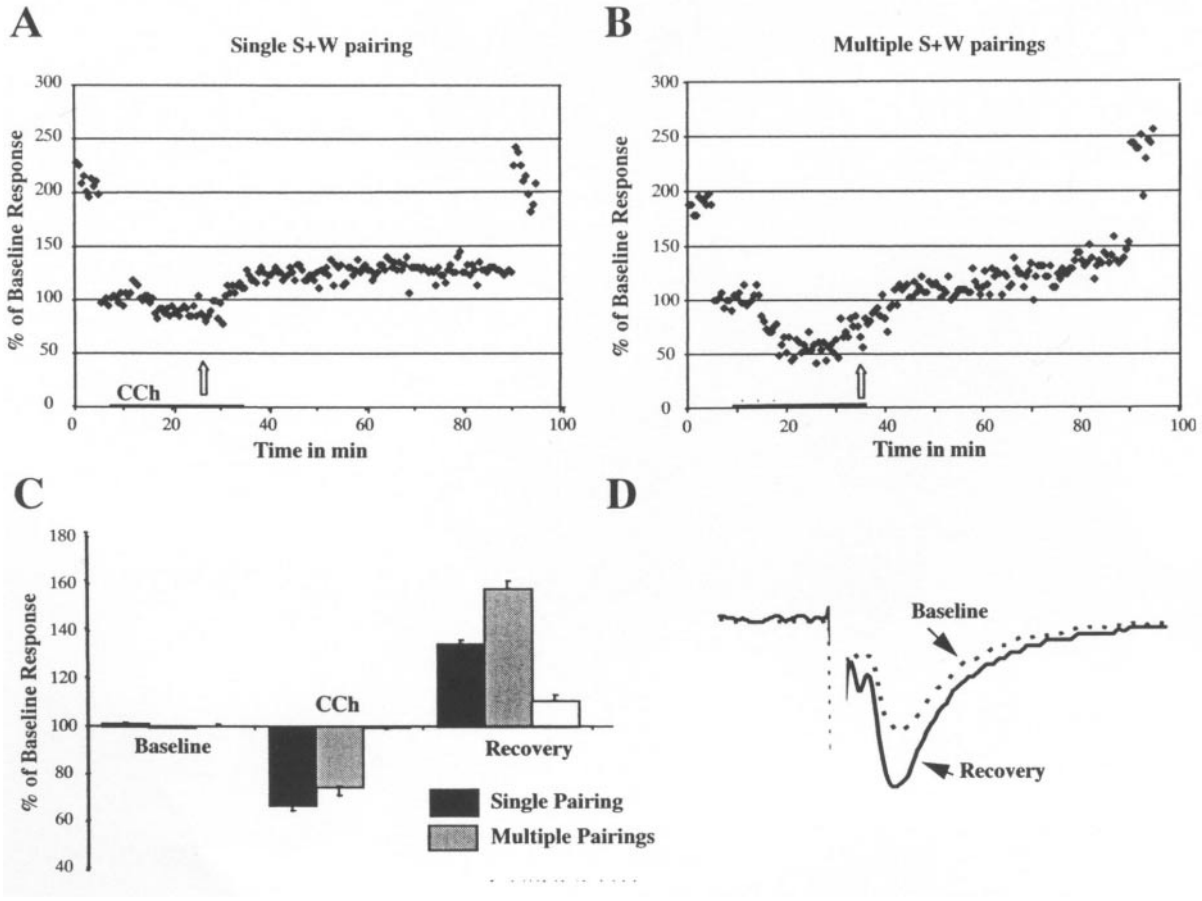

Figure 10 Summary of results at 50 μM CCh. **(A, B)** Time course of an experiment using a single pairing (A) and multiple pairings (B) of strong and weak stimuli. Onset slopes of potentials elicited by layer Ib test pulses are shown as a percentage of the baseline. At the beginning of the experiment, the maximal response to layer Ib stimulation was recorded. The stimulation strength was then adjusted to evoke ~50% of the maximal response. After bath application of CCh, the response amplitude to test stimuli decreased and stabilized after ~20–30 min. Pairing of strong and weak stimuli (arrow) resulted in an increase in the response to test stimuli in layer Ib. After washout, the response to test stimuli in layer Ib is significantly higher than the baseline recorded at the beginning of the experiment. At the end of the experiment, stimulation strength is adjusted to the maximal response strength recorded at the beginning of the experiment. **(C)** Average responses recorded in experiments using (i) single pairings in 50 μM CCh ($n = 10$); (ii) multiple pairings in 50 μM CCh ($n = 10$); and (iii) multiple pairings in 50 μM CCh and 10 μM scopolamine ($n = 7$). Onset slopes are given as a percentage of the baseline. Error bars indicate standard errors. CCh: average response 20–30 min after application of 50 μM CCh; Recovery: average response recorded 40–45 min after the beginning of washout. **(D)** Potentials in response to layer Ib stimulation. Each trace is an average of five recorded potentials. The response was recorded in ACSF before application of potentiating stimulus (dashed line) and 60 min after beginning of washout (solid line). From Patil *et al.* (Patil *et al.*, 1998).

5 Hz between the second and third pulse of the four pulse burst in layer Ia (Figure 9B). Under both normal saline or CCh, neither the tetanus in layer Ia nor the weak stimulation alone produced changes in the population excitatory post-synaptic potential (EPSP) observed in response to stimulation of layer Ib. However, under bath application of 50 μM CCh, the pairing of the weak stimulation in layer Ib with the tetanic stimulation in layer Ia produced a significant increase of the population EPSP in response to layer Ib stimulation (Figure 10).

In previous work, this enhancement of associative long-term potentiation was obtained with selective blockade of inhibitory synaptic transmission (Kanter and Haberly, 1993). Cholinergic modulation could provide this same effect through modulation of inhibitory synaptic potentials. Recordings from piriform cortex pyramidal cells have

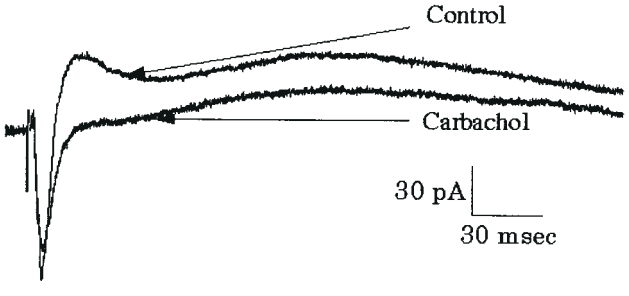

Figure 11 Effect of cholinergic modulation on inhibitory post-synaptic potentials evoked by layer Ib stimulation recorded in voltage clamp mode. Stimulation of layer Ib when the cell was held at –60 mV elicited a fast excitatory post-synaptic current followed by fast and slow inhibitory post-synaptic currents (IPSCs) (Control). Perfusion of the slice chamber with CCh (50 μM) suppressed both IPSC components (Carbachol). From Patil and Hasselmo (Patil and Hasselmo, 1999).

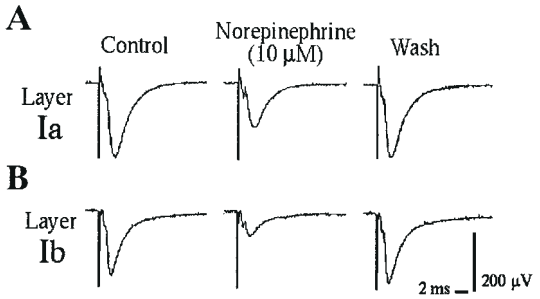

Figure 12 Suppression of synaptic potentials by norepinephrine recorded in a brain slice preparation of the olfactory cortex. **(A)** Evoked synaptic potentials in layer Ia recorded before (Control), during (Norepinephrine) and after (Washout) perfusion with 10 μM norepinephrine. **(B)** Evoked synaptic potentials in layer Ib recorded before (Control), during (Norepinephrine) and after (Washout) perfusion with 10 μM norepinephrine. Norepinephrine has a greater effect on intrinsic synaptic potentials. From Hasselmo *et al.* (Hasselmo *et al.*, 1997).

demonstrated cholinergic modulation of inhibitory synaptic potentials, as illustrated in Figure 11 (Patil and Hasselmo, 1999). In these experiments, perfusion of the cholinergic agonist CCh caused suppression of inhibitory synaptic potentials recorded with sharp electrode techniques as well as inhibitory synaptic currents recorded with whole cell patch clamp (Patil and Hasselmo, 1999). This modulation of inhibitory transmission appears to be stronger for transmission in layer Ib than for that in layer Ia.

Noradrenergic modulation in the piriform cortex

Noradrenergic modulation appears to have some effects similar to those of acetylcholine, providing a similar enhancement of the network response to external afferent input relative to intrinsic transmission. In particular, noradrenergic modulation causes selective suppression of excitatory intrinsic synaptic transmission, as shown in Figure 12 (Hasselmo *et al.*, 1997).

Network simulations demonstrate that the noradrenergic suppression of transmission could result in an enhancement of response to afferent input relative to internal activity. This can be referred to as enhanced signal-to-noise ratio—an effect that has been studied in a number of other cortical regions (Sara, 1985; Servan-Schreiber *et al.*, 1990). Simulations of the piriform cortex illustrate how modulation of synaptic transmission influences the response to afferent input, as shown in Figure 13. Thus, the net effects of norepinephrine may result in enhanced encoding of sensory input. This could provide cellular mechanisms for the important role of norepinephrine observed in early olfactory learning [reviewed by Sullivan *et al.* (Sullivan *et al.*, 1992)].

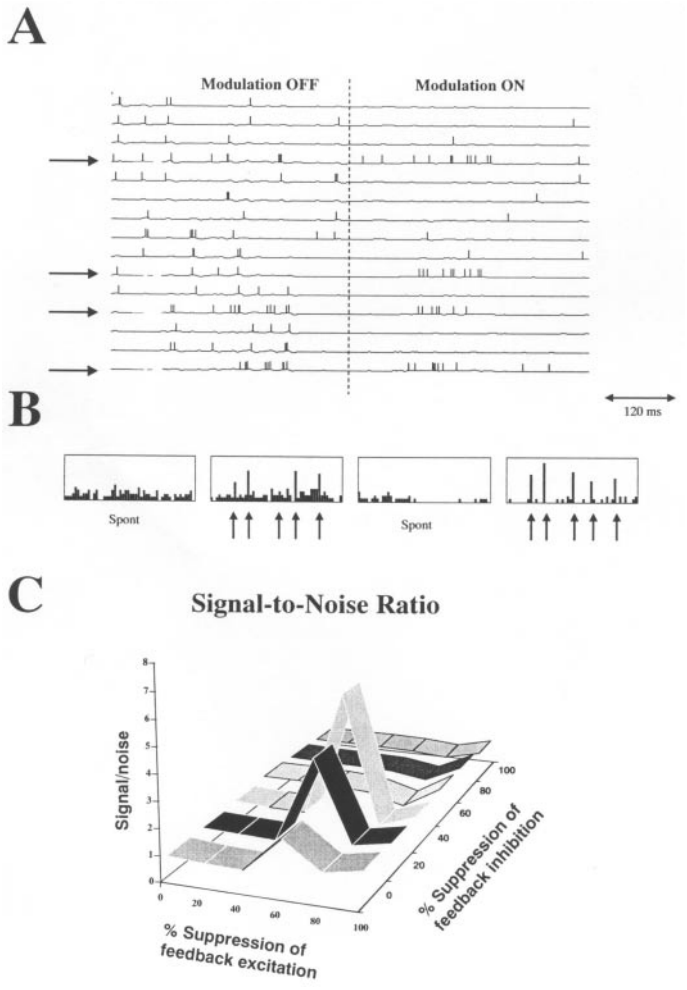

Figure 13 Effect of noradrenergic suppression of feedback excitation and feedback inhibition on pyramidal cell response to afferent input. **(A)** Membrane potentials and action potentials of 16 pyramidal cells are shown. Pyramidal cells receiving afferent input are indicated (horizontal arrows). Stimulus onset and offset are indicated by vertical arrows. Background activity and response to afferent input are shown in the absence (Modulation OFF) and in the presence (Modulation ON) of 60% suppression of feedback excitation and 40% suppression of feedback inhibition. **(B)** Average activities of 50 pyramidal cells in network during 120 ms background activity (Spont) and in response to input. Pyramidal cells receiving input are indicated by arrows. **(C)** The signal-to-noise ratio as a function of feedback excitation and inhibition in the spiking network model. For each point in parameter space, 50 networks were constructed and presented with random input patterns. The signal-to-noise ratio was computed as the number of spikes generated by neurons receiving input divided by the total number of spikes during the time of input presentation (120 ms). Suppression of feedback excitation and feedback inhibition is varied from 0 to 100% in 20% steps. The maximal signal-to-noise ratio occurred when feedback excitation was suppressed by 60% and feedback inhibition was suppressed by 40%. From Hasselmo *et al.* (Hasselmo *et al.*, 1997).

Summary

In summary, the piriform cortex provides an excellent structure for analysis of neuromodulatory effects on cortical processing, allowing analysis of selective effects on excitatory and inhibitory synaptic transmission, and computational modeling of these effects in the framework of associative memory function. This allows explanation of some existing behavioral data on cholinergic and noradren-

ergic modulation, and generation of further hypotheses to guide additional behavioral experiments.

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