Differential Regulation of Neocortical Synapses by Neuromodulators and Activity

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Summary

Synapses are continually regulated by chemical modulators and by their own activity. We tested the specificity of regulation in two excitatory pathways of the neocortex: thalamocortical (TC) synapses, which mediate specific inputs, and intracortical (IC) synapses, which mediate the recombination of cortical information. Frequency-sensitive depression was much stronger in TC synapses than in IC synapses. The two synapse types were differentially sensitive to presynaptic neuromodulators: only IC synapses were suppressed by activation of $GABA_B$ receptors, only TC synapses were enhanced by nicotinic acetylcholine receptors, and muscarinic acetylcholine receptors suppressed both synapse types. Modulators also differentially altered the frequency sensitivity of the synapses. Our results suggest a mechanism by which the relative strength and dynamics of input and associational pathways of neocortex are regulated during changes in behavioral state.

Introduction

The strength of a central synapse depends on its previous activity and on the levels of chemical neuromodulators that vary with the activity state of the brain. The rules governing synaptic adjustment can vary widely from one type of synapse to the next. For example, repetitive activation leads to short-term facilitation of transmitter release from some synapses and depression of release from others, and many synapses respond with both facilitation and depression (Zucker, 1989; Fisher et al., 1997). The release of neurotransmitter can be modulated by a wide range of substances acting at presynaptic receptors (Hawkins et al., 1993; Marder, 1996; McGehee and Role, 1996; Wu and Saggau, 1997). Diverse modes of synaptic plasticity and modulation lend flexibility to neural circuits, allowing synapses to be regulated dynamically and specifically.

The neocortex mediates essential sensory, motor, and cognitive functions, and it has two general classes of excitatory connections between its neurons: thalamocortical (TC) synapses carry specific information from the thalamus into the cortex, and intracortical (IC) synapses mediate the flow and recombination of information within the cortex. Neocortical neurons and synapses are regulated by several diffuse ascending modulatory systems, whose activity varies sharply during changes in behavioral state and sleep-wake cycles (Steriade and Llinás, 1988; McCormick and Bal, 1997). The dynamic regulation of these synapses by activity and modulators may be important for perception, memory, and changes in behavioral state (Hasselmo, 1995; Fisher et al., 1997). Virtually nothing is known about the specificity of neuromodulators for different types of synapses in the neocortex. Here, we show that afferent (TC) synapses and associational (IC) synapses of neocortex have distinct short-term dynamics that are differentially regulated by neuromodulators.

Results

Independence of Stimulated Pathways

We compared TC and IC synapses that converge onto single pyramidal cells in slices containing the somatosensory cortex and ventrobasal thalamus of mice and rats (Agmon and Connors, 1991). Recordings were made from somata of pyramidal neurons in the deep aspect of layer 3, using methods described previously (Gil and Amitai, 1996). Small monosynaptic excitatory postsynaptic potentials (EPSPs) were elicited by electrical stimulation of either the thalamus (the TC pathway) or layer 3 of the cortex, at least 1 mm lateral to the recording site (the IC pathway). Layer 3 cells receive strong monosynaptic thalamocortical inputs (Johnson and Alloway, 1996), and horizontal axons within layer 3 extend several millimeters horizontally (White and Keller, 1989). Postsynaptic inhibition mediated by γ-aminobutyric acid (GABA) was suppressed with local bicuculline application, and postsynaptic Na^+ and K^+ currents were suppressed with intracellular Cs^+ and QX-314. The independence of the two stimulated pathways was checked in each cell with crossed paired-pulse protocols. Pairs of homosynaptic stimuli to either the TC or IC axons caused short-term changes in the same pathway (in this case, depression of the TC-EPSP [Figure 1A] and facilitation of the IC-EPSP [Figure 1B]). However, a conditioning stimulus to the IC axons did not consistently alter the TC-EPSP, and vice versa (Figures 1C and 1D). This confirmed that the TC and IC axons were independently activated with our protocol.

Frequency Sensitivity of TC and IC Synapses

Previous studies suggested that the dynamics of excitatory synapses in cerebral cortex vary with both the identity of the postsynaptic cell (Thomson and Deuchars, 1994) and the presynaptic tract stimulated (Stratford et al., 1996). Identified TC synapses have not previously been tested. Using repetitive stimulation protocols, we compared the frequency sensitivity of TC and IC synapses converging onto single pyramidal neurons. With
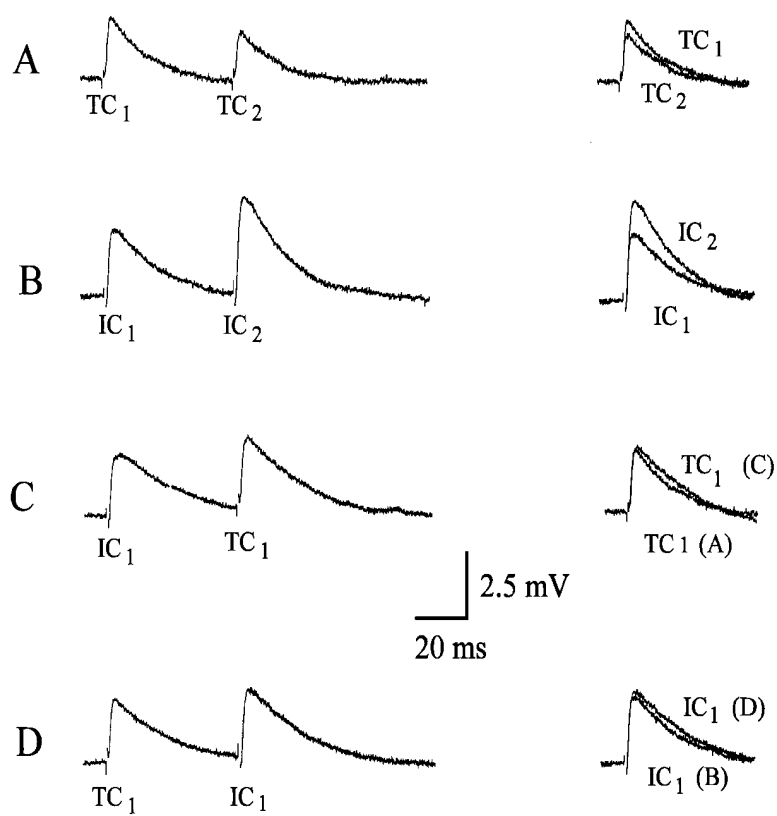
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Figure 1. Independence of TC and IC Synaptic Pathways onto Single Pyramidal Neurons

(A) Activating TC axons with paired stimuli (TC_1 and TC_2) caused depression of the second EPSP relative to the first. The two EPSPs are overlaid in the right panel.

(B) Paired stimuli of IC axons resulted in facilitation.

(C and D) When paired stimuli consisted of mixed TC and IC pulses the second EPSPs were not modified, as seen in the overlapped traces in the right panel. All data are from the same neuron.

paired stimuli, TC synapses were consistently depressed at intervals from 10–2000 ms, the longest interval examined (Figures 2A and 2B). In contrast, horizontal IC synapses tended to show slight facilitation at short (10–25 ms) intervals and modest depression at intervals up to 2000 ms. The mean paired-pulse ratio (second-response amplitude/first-response amplitude) calculated at an interval of 50 ms was 0.95 ± 0.04 for the IC synapses and 0.68 ± 0.02 for the TC synapses (n = 57 neurons, rats and mice; $p < 0.0001$, Wilcoxon test). When compared in single neurons, there was no correlation between the paired-pulse ratios from the TC and IC pathways, and the ratio from the IC pathway equaled or exceeded that of the TC pathway in 52 of 57 cells (Figure 2C). When short stimulus trains (four pulses at 10 Hz) were applied, all TC synapses were strongly depressed, while IC synapses were either slightly depressed or facilitated (Figure 3A); on average, the TC pathway showed much stronger depression than the IC pathway (Figure 3B).

Effects of GABA$_B$ Receptor Activation on TC and IC Synapses

The large majority of neocortical GABA is derived from neurons intrinsic to the cortex. Activating presynaptic GABA$_B$ receptors suppresses evoked glutamate release in many brain regions (Dutar and Nicoll, 1988; Scholz and Miller, 1991; Thompson and Gahwiler, 1992), including the neocortex (Kang, 1995; Ramoa and Sur, 1996). We compared the efficacy of GABA$_B$ receptor activation on TC and IC synapses. Application of the GABA$_B$ receptor agonist baclofen (1–5 μM) reduced the IC-EPSPs to

an average of 67% $\pm$ 15% of their control amplitude (n = 11 neurons; $p < 0.005$, Wilcoxon test); TC-EPSPs after baclofen were unchanged (98% $\pm$ 20% of control amplitude, n = 10 neurons; Figure 4A). The postsynaptic effects of baclofen (Connors et al., 1988) were blocked by intracellular Cs^+ and QX-314, and neither resting potential nor input resistance changed during the drug application. Scaling of IC-EPSPs before and after baclofen showed that there was no change in their time course (not shown), a further indication that baclofen was acting presynaptically.

Baclofen slightly increased the paired-pulse ratio of IC synapses (50 ms interstimulus interval), changing it from depression to slight facilitation, but had no effect on the ratio of TC synapses (Figures 4B and 7). An antagonist of GABA$_B$ receptors, CGP 35348 (0.1–0.3 mM), had no effect on EPSPs from single stimuli at low frequency, but it did reversibly enhance the second response to paired stimuli at IC synapses (n = 14 neurons; $p < 0.002$, Wilcoxon test; Figures 4C and 7). The results suggest that endogenous GABA released by an intracortical stimulus selectively suppresses transmitter release from IC synapses, but not TC synapses, by activating presynaptic GABA$_B$ receptors.

Muscarinic and Nicotinic Cholinergic Effects on TC and IC Synapses

The cerebral cortex and thalamus are diffusely innervated by cholinergic axons from the basal forebrain (Eckenstein and Baughman, 1987). Nicotinic and muscarinic cholinergic receptor subtypes have inverse presynaptic effects on excitatory synapses in certain brain
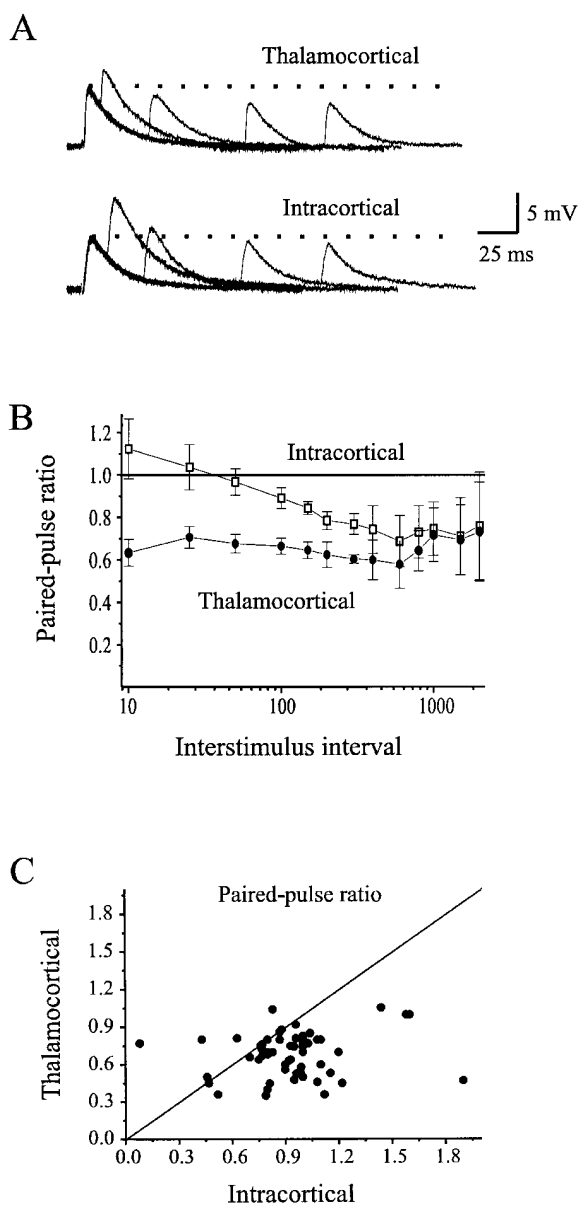
A

Thalamocortical

Intracortical

5 mV

25 ms

A   Thalamocortical   Intracortical

cell 1

1 mV
2 mV
100 ms

cell 2

B

Intracortical

Thalamocortical

Paired-pulse ratio

Interstimulus interval

B

Intracortical

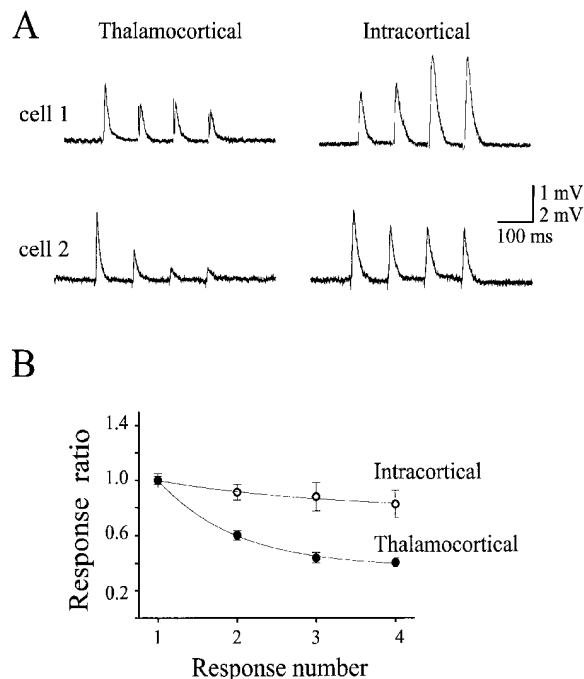Thalamocortical

Response number

Figure 3. Short-Term Depression Is Stronger in TC Synapses Than in IC Synapses

(A) Examples of responses from two neurons activated by successive trains of four stimuli, delivered at 10 Hz, from the TC and IC tracts.
(B) Summary graph of data from 13 cells that were stimulated as shown in (A). The lines are single-exponential fits to the data with time constants of 223 ms (IC) and 99 ms (TC).

C

Paired-pulse ratio

Intracortical

Figure 2. Comparison of Short-Term Plasticity in TC and IC Synapses

(A) TC (circles) or IC (squares) fibers were stimulated by paired pulses delivered at varying interstimulus intervals.
(B) Summary graph shows data from 17 cells. Each point on the graph is the mean paired-pulse ratio ± SEM.
(C) Paired-pulse ratios (measured at an interval of 50 ms) of TC and IC synapses for 57 neurons. Each point plots data from one cell. The line has a slope of one.

regions (McGehee and Role, 1995; Albuquerque et al., 1995). We tested the selectivity of cholinergic effects on TC and IC synapses. Postsynaptic cholinergic effects (McCormick and Prince, 1986) were minimized pharmacologically. Application of the agonist muscarine (5–10 μM) depressed EPSPs from both TC and IC synapses (Figure 5A; n = 12 neurons), and the magnitude of depression was very similar in the two types of EPSPs (TC, p < 0.005; IC, p < 0.0005, Wilcoxon test; Figure 5B).

Muscarine also increased the paired-pulse ratio of both pathways (Figure 7); it did not change the postsynaptic membrane potential or input resistance, or the shape of the EPSPs, suggesting that its effects occurred presynaptically. Bath application of the muscarinic receptor antagonist atropine (10 μM) prevented depression of the EPSPs by muscarine (n = 5 neurons).

Anatomical studies suggest that nicotinic receptors are present on thalamocortical relay neurons and their terminals in the cortex (Sahin et al., 1992; Bina et al., 1995; Lavine et al., 1997). Bath application of the agonist nicotine (1 μM) had no effect on IC synaptic transmission (102% ± 8% of control; n = 8 neurons), but it selectively enhanced responses from TC synapses (Figure 6A). The amplitude of TC-EPSPs was reversibly increased to 142% ± 19% of control (p < 0.0002, Wilcoxon test; n = 13 neurons), while the paired-pulse ratio of TC-EPSPs was significantly decreased (Figure 7). Under our experimental conditions, nicotine caused no postsynaptic changes, nor did it change EPSP shape. The magnitude of the nicotinic effect was similar in mouse and rat neurons, as assessed by TC-EPSPs and TC-evoked monosynaptic field potentials (Figures 6B and 6C).

There are many subtypes of neuronal nicotinic receptors (Wonnacott, 1997). We found that the nonspecific nicotinic receptor antagonist mecamylamine (10 μM) blocked the enhancing actions of nicotine on TC synapses of both rats and mice (Figures 6B and 6C; n = 10 slices). In contrast, methylylcaconitine (MLA), a specific

antagonist of the α7 (α-bungarotoxin-sensitive) neuronal nicotinic receptor subtype (Ward et al., 1990), prevented nicotinic enhancement at rat TC synapses but not at mouse synapses (Figure 6C). The MLA concentrations used (0.1–0.5 μM) are well above the effective concentrations reported for α7 receptor-dependent responses in other systems (e.g., Ward et al., 1990; Palma et al., 1996). The results are consistent with suggestions that there are α7 nicotinic receptor subtypes on the presynaptic terminals of ventrobasal TC neurons in rats but not in mice (Bina et al., 1995; Broide et al., 1995), and suggest further that non-α7 nicotinic receptors modulate TC terminals in mice (Wonnacott, 1997).

Since muscarinic and nicotinic cholinergic receptors modulated transmitter release from TC synapses in opposite directions, we tested the effects of acetylcholine, the endogenous ligand for these receptors. Bath application of a low concentration (1 μM) of acetylcholine enhanced the TC-EPSP size by about 25% without changing the input resistance, time constant, or resting potential (n = 3 neurons), and it increased the initial

slope of the TC-evoked monosynaptic field potential by about 80% (Figure 6C).

Discussion

Our results demonstrate that distinct sets of synapses within the neocortex are differentially affected by neuromodulators. This suggests a mechanism adjusting the relative strengths and dynamics of input and associational pathways during changes in behavioral state. Neuromodulators can be divided into two basic types: those released from sources intrinsic to a local circuit, and those that arise from extrinsic sources (Katz and Frost, 1996). We tested one of each type: GABA is largely intrinsic to the cortex, and its release rate is expected to parallel the level of local activity in cortical circuits, while acetylcholine is derived from control circuits extrinsic to neocortex (Rye et al., 1984; Eckenstein and Baughman, 1987). We found that thalamocortical (input) synapses and intracortical (associational) synapses
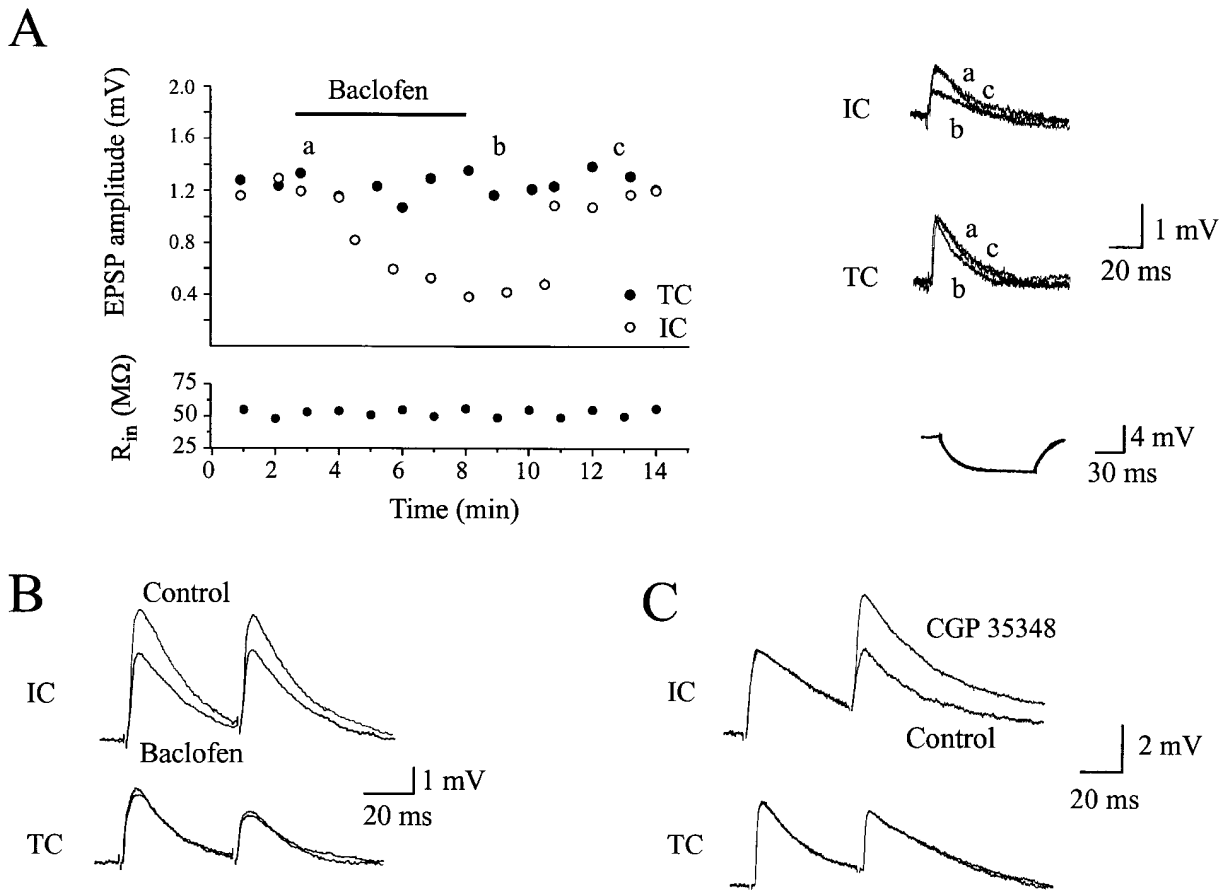

Figure 4. Presynaptic GABA$_B$ Receptors Depress IC Synapses, but Not TC Synapses

(A) Graphical display (left) of baclofen effects on TC- and IC-EPSPs and input resistance (R$_{in}$) evoked in a single pyramidal neuron. Baclofen (1 μM) was bath-applied during the period marked by the bar. Superimposed example traces from times marked (a), (b), and (c) for TC-EPSP, IC-EPSP, and voltage response to a 0.2 nA current pulse are depicted in the right panel.

(B) Effects of baclofen on paired EPSPs from IC and TC tracts. Superimposed control and baclofen traces show depression of IC synapses but no effect on TC synapses.

(C) Effects of the GABA$_B$ receptor antagonist CGP 35348 (bath-applied at 0.3 mM). Superimposed control and drug-treated EPSPs from stimulation of IC and TC tracts. All traces and data points in this figure are averages of 10 responses.
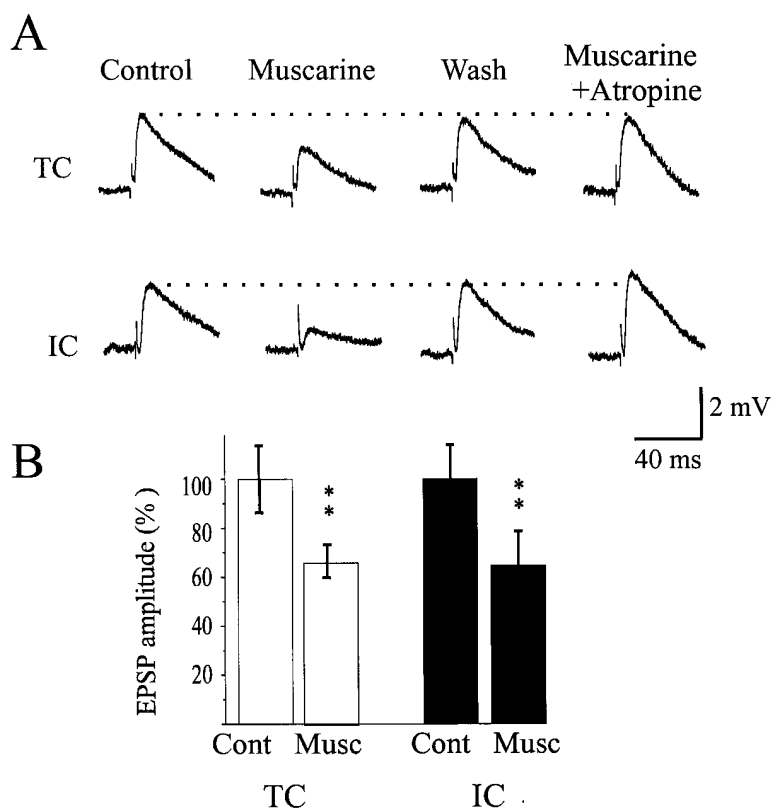
A

Figure 5. Muscarinic Cholinergic Receptors Depress Both TC and IC Synapses

(A) Examples of IC- and TC-EPSPs from a single cell before, during, and after bath application of muscarine (5 μM) and during subsequent application of muscarine in the presence of atropine (10 μM).

(B) Summary graph showing similar effect of muscarine on TC- and IC-EPSPs amplitudes (normalized to control; n = 12 neurons; asterisks imply p < 0.01, Wilcoxon test).

have qualitatively different sensitivities to each modulator. Synapses of piriform cortex and hippocampus may also be differentially modulated by acetylcholine (Kahl and Cotman, 1989; Hasselmo and Bower, 1992) and GABA$_B$ receptors (Colbert and Levy, 1992; Tang and Hasselmo, 1994). Taken together, these results imply that the selective modulation of intrinsic and afferent synapses is a general organizational principle of the cerebral cortex (Hasselmo, 1995).

Of particular interest is our novel finding that nicotine selectively enhances thalamocortical synapses. There is some evidence from intact systems for nicotinic cholinergic modulation of TC transmission (Adams et al, 1988; Lewandowski et al., 1993). Nicotinic enhancement of transmitter release has recently been demonstrated in several other brain regions (McGehee and Role, 1995; Gray et al., 1996; Wonnacott, 1997). In a previous study of nicotinic modulation of glutamatergic transmission in the neocortex, Vidal and Changeux (1993) used nonspecific electrical stimulation and demonstrated an effect only in a minority (14%) of the recorded cells. This is consistent with our finding that presynaptic nicotinic modulation is specific to a minority of synapse types in neocortex. The nicotinic effect seems to reinforce the basic properties of thalamocortical transmission, since we found that TC synapses display relatively strong frequency-dependent depression even under control conditions. Nicotine probably enhances low frequency synaptic transmission by increasing presynaptic $[Ca^{2+}]_i$ and the probability of transmitter release (McGehee and Role, 1996), but nicotine-enhanced TC synapses also respond more phasically because synaptic depression

is intensified (cf. Debanne et al., 1996). With cortical circuitry intact, the impact of thalamic input is further constrained by the propensity of TC synapses to excite inhibitory, feed-forward interneurons (Swadlow, 1995; Gil and Amitai, 1996). The postsynaptic properties of spiny neurons also contribute a sensitivity to phasic inputs, because of their marked adaptation during repetitive firing (Agmon and Connors, 1992).

In contrast to TC synapses, the IC synapses, which are responsible for local network interactions within the cortex, respond with more fidelity at higher activation frequencies. The disparate dynamics of TC and IC synapses may imply different modes of information coding (Tsodyks and Markram, 1996; Abbott et al., 1997) and lend support to suggestions that thalamic inputs are amplified by recurrent intracortical circuitry (Douglas et al., 1995). A dramatic expression of such amplification is the augmenting response, in which activation of certain TC synapses at 10 Hz intensifies intracortical responses (Castro-Alamancos and Connors, 1996a, 1996b), despite the fact that TC synapses are strongly depressed at this frequency (Figure 3). The effects of both GABA$_B$ and muscarinic receptors serve to minimize the frequency-dependent depression of IC synapses.

Neuromodulators are involved in a broad range of brain functions and dysfunctions. Acetylcholine has been implicated in the control of arousal states in the forebrain (Buzsaki et al., 1988; Metherate et al., 1992; Steriade, 1996) and may be important for normal memory (Hasselmo and Bower, 1993; Aigner, 1995; Granon et al., 1995; Picciotto et al., 1995). Nicotinic acetylcholine receptors are also essentially involved in the addictive

A

B
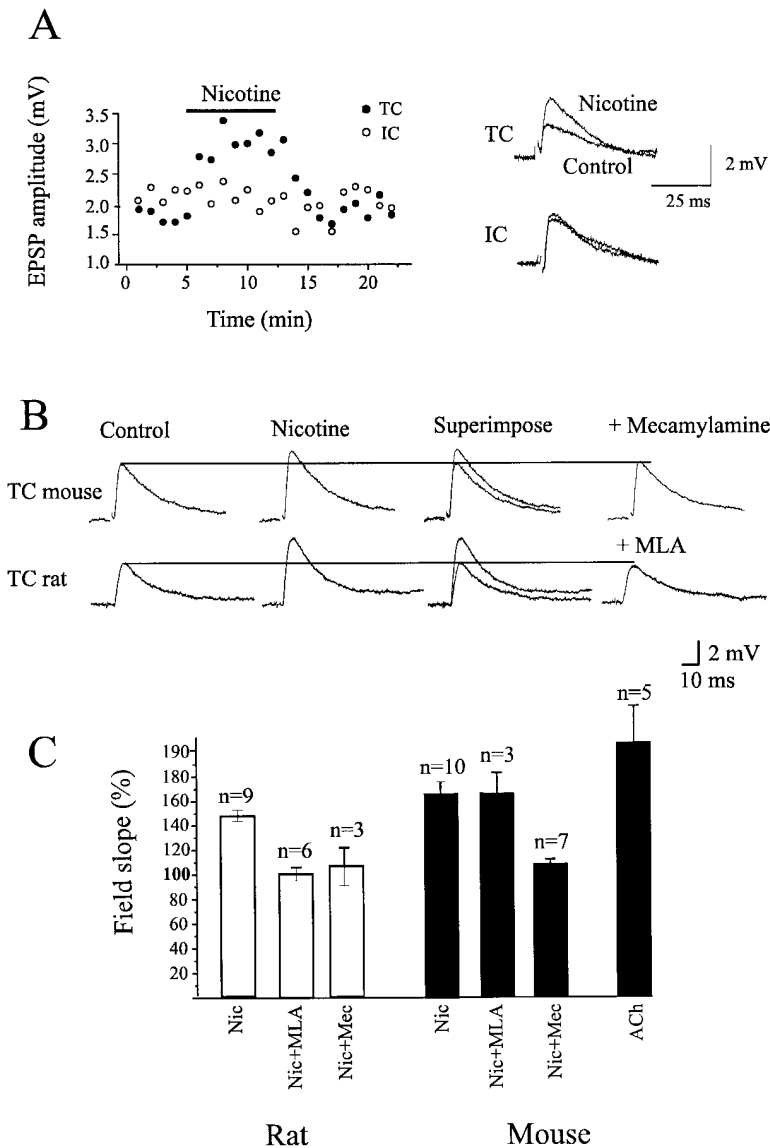

C

Rat   Mouse

Figure 6. Presynaptic Nicotinic Receptors Enhance TC Synapses, but Not IC Synapses

(A) Graph (left) of TC- and IC-EPSP amplitudes from a single cell, showing the selective effect of bath-applied nicotine (1 μM; bar). Each data point is the mean of 10 traces. Single superimposed traces from 3 min (control) and 10 min (nicotine) are superimposed in right panel.

(B) Nicotinic effects on TC-EPSPs in mice and rats differed pharmacologically. Examples from single rat and mouse neurons show blockade of nicotinic effect in mouse by mecamylamine (10 μM) and blockade of nicotinic effect in rat by MLA (0.5 μM). Each trace is an average of 10 responses.

(C) Summary graph of TC field potentials (maximal slope, as % of baseline), showing enhancement by nicotine and its antagonism by mecamylamine in both species and selective antagonism by MLA in rat. The last bar shows net enhancement of the TC field potential by bath application of acetylcholine (1 μM). Each bar is the mean $\pm$ SEM. Nic, nicotine; MLA, methylylcaconitine; Mec, mecamylamine; ACh, acetylcholine.

properties of nicotine (Dani and Heinemann, 1996). Among the functional implications of our results are the modifications to neocortical circuits that would occur during states of arousal, when forebrain activity is high and both GABA and acetylcholine levels are expected to increase. Under these circumstances, IC synapses would be relatively depressed via presynaptic $GABA_B$ and muscarinic receptors, while the relative strength of inputs from the thalamus would be enhanced and temporally sharpened via nicotinic effects. In general, afferent activity would become more dominant over internal activity in determining cortical representations.

Experimental Procedures

Preparation

The methods for preparing thalamocortical slices were similar to those described previously (Agmon and Connors, 1991; Gil and Amitai, 1996). Briefly, 2- to 3-week-old albino mice (CD/1) or rats (Wistar) were anesthetized with pentobarbital sodium and decapitated, and their brains were quickly immersed in ice-cold oxygenated artificial cerebrospinal fluid (ACSF) composed of (in mM): 124

NaCl, 3 KCl, 2 $MgSO_4$, 1.25 $NaHPO_4$, 2 $CaCl_2$, 26 $NaHCO_3$, and 10 dextrose, saturated with 95% O_2–5% CO_2 (pH 7.4). Thalamocortical slices, 450 μm thick, were cut and kept in a holding chamber that contained ACSF at room temperature. After at least 1 hr of incubation, a single slice was placed in a fluid–gas interface chamber, controlled to 35°C–36°C.

Stimulation and Recording

Saline-filled field potential electrodes (6–8 MΩ) were placed in layer 4. Intracellular recordings were made with micropipettes (80–100 MΩ) filled with 2 M cesium acetate and 50–100 mM QX-314 to block K^+ and Na^+ currents postsynaptically. TC or IC fibers were stimulated by 0.2 ms, 10–100 μA pulses delivered by two sets of bipolar microelectrodes made from sharpened tungsten wires. Intertrial intervals were 10–15 s. One stimulating electrode was placed in layer 3 at least 1 mm medial to the recording area to activate local horizontal intracortical fibers, while minimizing the activation of ascending thalamocortical fibers. The other stimulating electrode was placed in the ventrobasal nucleus of the thalamus. By moving the field potential electrode horizontally in layer 4 we located the area that generated the largest response to thalamic stimulation, and cells were then recorded in deep layer 3 of the same vertical column. EPSPs were judged to be monosynaptic using criteria of
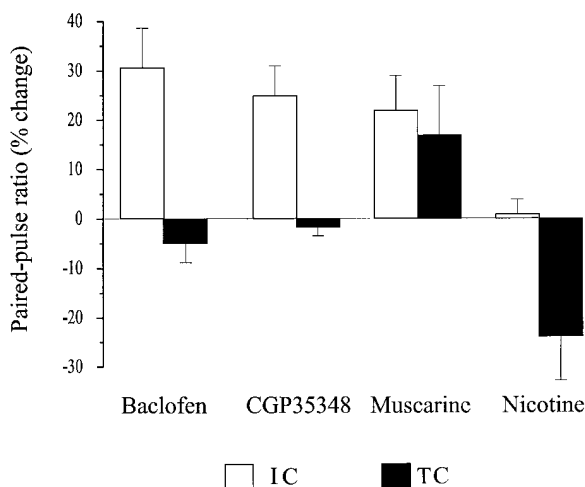
Figure 7. Summary Graph of Drug Effects on the Paired-Pulse Ratios of IC and TC Synapses

Each bar is the mean ± SEM of the drug-induced change in paired-pulse ratio (assessed at 50 ms interstimulus interval) as a percentage of control (7–14 neurons were tested for each condition); positive values imply that the drug caused an increase in paired-pulse ratio, and negative values imply that the ratio decreased.

short latency, monophasic time course, and minimal amplitude variance (described in detail by Gil and Amitai, 1996). Bicuculline methiodide (10 μM; RBI) was dissolved in ACSF and applied focally and continuously through a micropipette to the recording area to block GABA_A receptor-mediated inhibition locally. The membrane potential of each neuron was polarized to several levels between resting potential and spike threshold while activating the IC and TC pathways, in order to rule out the presence of measurable IPSPs (see Gil and Amitai, 1996). Most drugs were applied by dissolving in the perfusing solution. In some experiments, drugs were applied focally through a broken pipette; the concentration of the drug in the pipette was 10 times that of the same drug when applied in the bath. When TC field potentials were used to study drug effects, a stable (≥20 min) baseline was first established for amplitude (baseline to peak) and slope (measured from 20%–80% of peak amplitude). The effect of the drugs is expressed here as the relative change in the initial slope. Results for mice and rats did not differ and so were pooled, except as noted for data on nicotinic responses. Each data point is an average of 10–20 trials. Data are given as mean ± SEM.

Acknowledgments

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