

# Neurotransmitter Control of Neocortical Neuronal Activity and Excitability

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**The pattern of activity and excitability of cortical neurons and neuronal circuits is dependent upon the interaction between glutamatergic and GABAergic fast-activating transmitter systems as well as the state of the more slowly acting transmitters such as ACh, norepinephrine, 5-HT, and histamine. Through the activation of GABA<sub>A</sub> receptors, GABAergic neurons regulate the amplitude and duration of EPSPs and, in so doing, control the level of functional activation of NMDA receptors. In contrast, activation of muscarinic, adrenergic, serotonergic, histaminergic, and glutamate metabotropic receptors controls the excitability and pattern of action potential generation in identified pyramidal cells through increases or decreases in various K<sup>+</sup> conductances. Activation of muscarinic, α<sub>1</sub>-adrenergic, or glutamate metabotropic receptors on layer V burst-generating corticotectal or corticopontine neurons results in depolarization through a reduction in a K<sup>+</sup> conductance and a switch in the firing mode from repetitive burst firing to single-spike activity. In contrast, activation of muscarinic, β-adrenergic, H<sub>2</sub>-histaminergic, and serotonergic receptors on regular-spiking layer II/III, V, and/or VI corticogeniculate pyramidal cells results in a decrease in spike frequency adaptation and increased responsiveness to depolarizing inputs through a reduction in a slow Ca<sup>2+</sup>-activated K<sup>+</sup> current, I<sub>AHP</sub>, and/or a voltage-dependent K<sup>+</sup> current, I<sub>M</sub>. Through these, and other, mechanisms the spatial and temporal pattern of activity generated in cortical circuits is regulated by both intracortical and extracortical neurotransmitter systems.**

Neuronal activity and synaptic processing in the cerebral cortex are critically dependent upon the actions of neurotransmitters not only for the rapid communication between cells but also for the control of neuronal excitability and patterning of neuronal discharge. Rapid excitation and inhibition are believed to characterize the vast majority of synaptic connections between the various subtypes of cortical neurons. The putative neurotransmitters glutamate and GABA seem well suited for these roles, since they both can directly activate ionotropic receptor channels (reviewed in Nicoll et al., 1990). In contrast, the anatomical patterns of innervation of the cerebral cortex and the postsynaptic actions of the modulatory transmitters ACh, norepinephrine (NE), 5-HT, histamine, and dopamine suggest that these ascending systems are well suited for controlling the pattern of activity and level of excitability exhibited by cortical neurons (reviewed in Nicoll et al., 1990; McCormick, 1992). The line of distinction between fast-acting and modulatory transmitter systems has become blurred, however, since both glutamate and GABA can have slower, longer-lasting actions through G-protein-coupled receptors and activation of second messenger systems (e.g., Andrade et al., 1986; Charpak et al., 1990; McCormick and von Krosigk, 1992).

Control of neuronal excitability in the cerebral cortex not only is critical for the accurate processing of sensory information and the generation of motor output, but can also determine the occurrence of a variety of abnormal phenomena including epileptic seizures, coma, age-related cognitive decline, and psychoses, among others. Two broad categories of regulation that occur in the cerebral cortex are (1) control of synaptic responses through either the regulation of the various components of fast synaptic action or the interaction of various ionotropic transmitter responses and (2) regulation of neuronal excitability and input/output relation through the modulation of identified postsynaptic currents. An example of the first is the widespread presence and ability of GABAergic systems in the cerebral cortex to regulate the flow of excitatory synaptic potentials and plasticity throughout cortical circuits (e.g., Sillito, 1984; Artola and Singer, 1987; Miles and Wong, 1987; Mott and Lewis, 1991). An example of the second is the ability of ACh to change the firing mode of layer V pyramidal cells from one of repetitive burst firing to single-spike activity through the reduction of specialized K<sup>+</sup> currents, thereby

changing the descending output of the cerebral cortex (Wang and McCormick, 1993).

### Materials and Methods

Intracellular recordings were obtained from 400–450- $\mu\text{m}$ -thick slices of guinea pig primary visual or somatosensory cortex, or human neocortex, maintained in an interface style recording chamber as previously published (McCormick and Prince, 1986).

Identification of layer V and layer VI neurons that project to either the superior colliculus, pontine nuclei, or the lateral geniculate nucleus (LGN) was performed with retrograde transportation of rhodamine microbeads (Katz et al., 1984), and intracellular injection of Lucifer yellow as previously published (Wang and McCormick, 1993).

Computational modeling of neuronal activity in single cortical pyramidal cells was performed using the programs *vCLAMP* and *cCLAMP*, version 3.0, by Huguenard and McCormick (1992; McCormick and Huguenard, 1992), which operate on IBM AT-style computers (see Appendix).

### Results and Discussion

#### *Role of GABA in the Control of Neuronal Excitability*

Activation of afferents to cortical pyramidal cells results in a typical sequence of postsynaptic potentials including an initial monosynaptic EPSP followed by two phases of IPSP (Fig. 1B). The IPSPs result from the excitation of cortical GABAergic interneurons, which often generate a train of action potentials in response to delivery of a single shock stimulus (Fig. 1A). The subsequent release of GABA results in two distinct IPSPs. Activation of GABA<sub>A</sub> receptors results in a conformational change in the receptor/ionophore, thereby allowing the conduction of Cl<sup>-</sup> across the membrane, with a subsequent reversal potential of around -75 mV (reviewed in Bormann, 1988; see Connors et al., 1988; McCormick, 1989). IPSPs mediated by GABA<sub>A</sub> receptors are rapid in onset and can be associated with large (up to 75 nS) increases in membrane conductance. They form the inhibitory counterpart of rapid EPSPs in the cerebral cortex (McCormick, 1989).

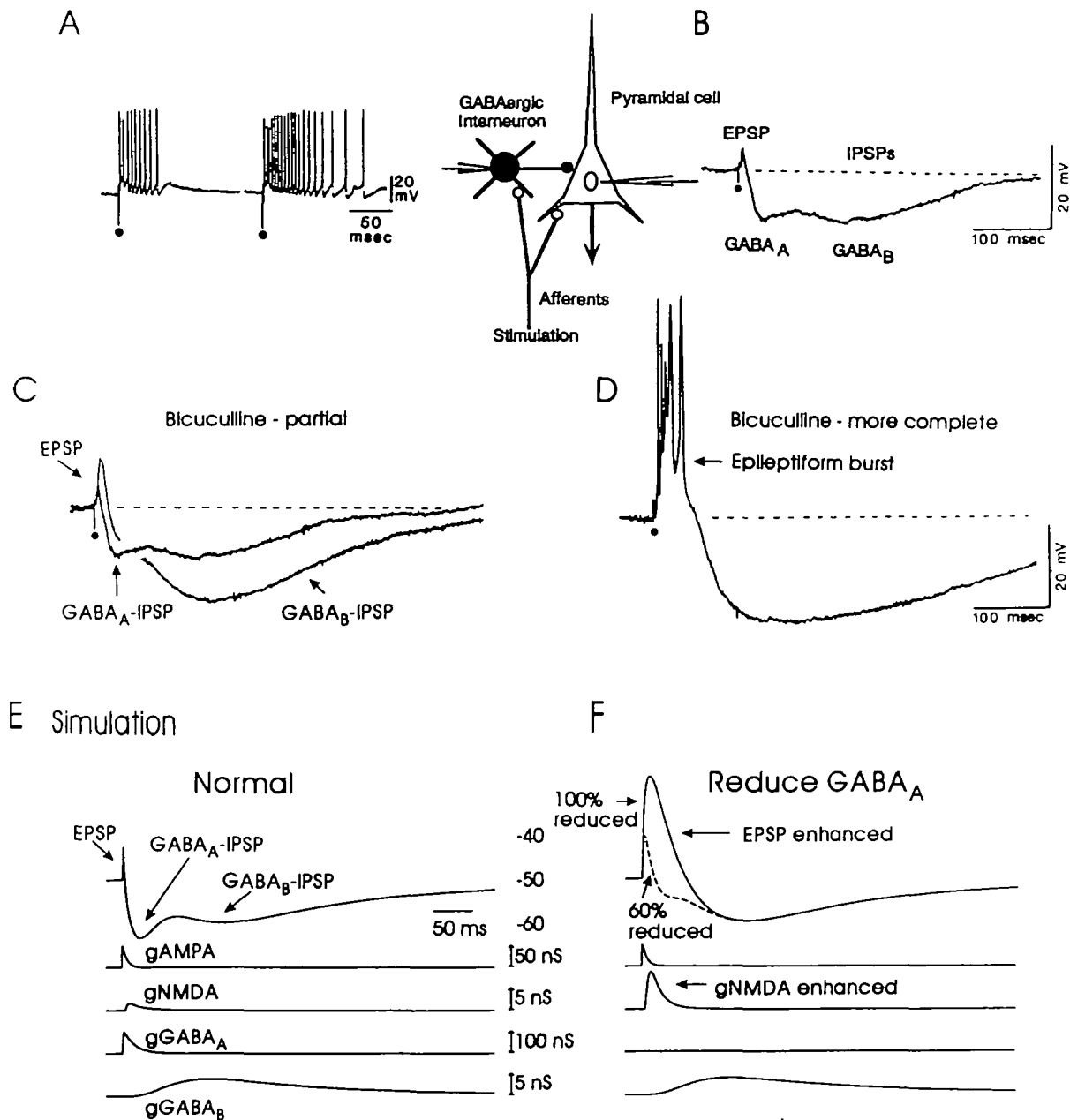
Activation of GABA<sub>B</sub> receptors, in contrast to GABA<sub>A</sub>, results in a kinetically slower IPSP through the activation of a relatively small (up to 15 nS) K<sup>+</sup> conductance via G-proteins (Fig. 1B; Andrade et al., 1986; Connors et al., 1988; Dutar and Nicoll, 1988; McCormick, 1989; Premkumar et al., 1990). Indeed, application of the G-protein G<sub>o</sub>, or the  $\alpha$ -subunit G<sub>o</sub> $\alpha$ , to the inner membrane of hippocampal pyramidal cells activates up to four different types of K<sup>+</sup> channel (Van Dongen et al., 1988).

Functionally, GABA<sub>A</sub> receptor-mediated IPSPs are capable of strongly inhibiting action potential discharge and regulating the responsiveness of cortical cells to fast EPSPs (Connors et al., 1988; McCormick, 1989). For example, mild suppression of GABA<sub>A</sub> receptor-mediated inhibition results in a strong en-

hancement of EPSPs, indicating that these two forms of PSPs overlap substantially in time when activated by a single shock (Fig. 1C; McCormick, 1989). Stronger reduction of GABA<sub>A</sub> receptor-mediated inhibition typically results in "runaway" excitation among the interconnected network of excitatory cells in the cerebral cortex, and the generation of epileptiform activity (Fig. 1D; Gutnick et al., 1982; McCormick, 1989). This regulation by GABA of the amplitude-time course of EPSPs in cortical pyramidal cells may extend to the regulation of activation of NMDA receptors during neuronal activity (e.g., Luhmann and Prince, 1990). Therefore, GABAergic systems may have an important regulatory role in controlling synaptic plasticity in both normal (e.g., long term-potential model of learning and memory and development) and abnormal (e.g., kindling model of epilepsy) circuit function (reviewed in McNamara, 1986; Mott and Lewis, 1991).

The typical sequence of PSPs seen in normal pyramidal cells was simulated (see Appendix) by activation of an EPSP, mediated by AMPA and NMDA receptors, followed by the activation of GABA<sub>A</sub> and GABA<sub>B</sub> receptors (Fig. 1E). Under these circumstances, the EPSP is mediated in large part by the activation of AMPA receptors, with a smaller contribution by NMDA receptors, as in normal pyramidal cells (Sutor and Hablitz, 1989a,b; Hablitz and Sutor, 1990). However, reduction of GABA<sub>A</sub>-mediated inhibition results in a marked enhancement of the monosynaptic EPSP and a subsequent strong enhancement of the activation of NMDA receptors with no change in the activation of AMPA receptors (Fig. 1F). These simulations confirm the expected important regulation of NMDA channel activation by GABA<sub>A</sub> receptors (e.g., see Luhmann and Prince, 1990; Staley and Mody, 1992). Further, they suggest a mechanism whereby reduction of GABAergic inhibition (such as GABA disinhibition) enhances the ability to induce long-term potentiation through activation of NMDA receptors in the cerebral cortex and hippocampus (Artola and Singer, 1987; Mott and Lewis, 1991). This is a potentially important mechanism for plasticity both in adult and developing animals (Luhmann and Prince, 1990; Agmon and O'Dowd, 1992; Ramoa and McCormick, 1992).

In adult animals, GABAergic systems in the cerebral cortex have been associated with not only the regulation of the amplitude-time course of EPSPs, but also the spatial-temporal flow of neuronal activity through cortical circuits (Sillito, 1984; Miles and Wong, 1987). Through the regulation of membrane potential and input resistance, GABAergic neurons control the path of activity that is generated through the interconnected sheet of excitatory neurons of the cortex. Altering the strength, spatial placement, or timing of these GABAergic IPSPs can control the pattern of activity generated by the cortical network. An elegant example of this has been demonstrated in the hippocampus, where simultaneous recordings of neighboring CA3 pyramidal cells reveal polysynaptic excitatory interaction typically only after the partial



**Figure 1.** Inhibition mediated by GABA regulates neuronal responsiveness and expression of NMDA receptor-mediated EPSPs. *A*, A common theme in the cerebral cortex is that of feedforward inhibition in which activation of afferents (single electrical shock applied to white matter at dots) activates GABAergic interneurons (repetitive firing). *B*, Intracellular recording in pyramidal cells reveals a monosynaptic EPSP followed by the activation of GABA<sub>A</sub> and GABA<sub>B</sub> receptor-mediated IPSPs from the repetitive firing of neighboring interneurons. *C*, Partial block of GABA<sub>A</sub> receptors with application of bicuculline results in an enhancement of the initial EPSP and the late GABA<sub>B</sub> IPSP (intracellular recordings in GABAergic neurons reveal a marked increase in firing with bicuculline, perhaps from activation of disinhibited pyramidal cells). *D*, A more complete block of GABA<sub>A</sub> receptor-mediated inhibition results in "runaway" excitation in local cortical networks and the generation of an epileptiform burst. This burst of activity is terminated both by activation of GABA<sub>B</sub> receptors and Ca<sup>2+</sup>-activated K<sup>+</sup> currents (Alger and Williamson, 1988; McCormick, 1989). *E* and *F*, Computer simulation of the data in *C* and *D* in a single-cell model (see Appendix). *F*, Reduction of GABA<sub>A</sub>-mediated inhibition by 60% results in enhancement of the initial EPSP. Complete block of GABA<sub>A</sub>-mediated inhibition results in a greatly enhanced EPSP and subsequently a substantial enhancement of the NMDA conductance ( $g_{\text{NMDA}}$  enhanced). *A* is from McCormick et al. (1985); *B-D* are from McCormick (1989).

reduction of GABA<sub>A</sub> receptor-mediated inhibition (Miles and Wong, 1987).

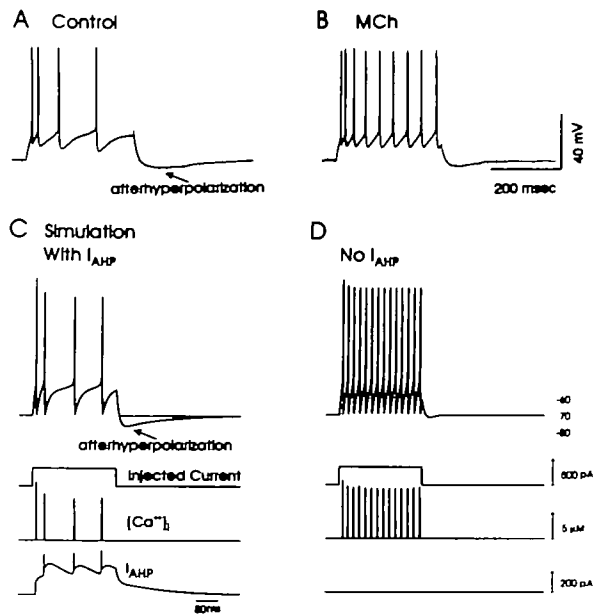
#### Modulatory Transmitter Actions

Investigation of the postsynaptic actions of modulatory transmitters in the cerebral cortex and hippocampus has revealed four basic responses: (1) reduction of the Ca<sup>2+</sup>-activated K<sup>+</sup> current known as  $I_{\text{AHP}}$  (Haas and Konnerth, 1983; Madison and Nicoll, 1986a,b; McCormick and Williamson, 1989), (2) reduction of

the depolarization-activated K<sup>+</sup> current  $I_{\text{M}}$  (Halliwell and Adams, 1982; McCormick and Williamson, 1989), (3) reduction of "leak" K<sup>+</sup> currents (Madison et al., 1987; Wang and McCormick, 1993), and finally, (4) increase in membrane K<sup>+</sup> conductance (Andrade et al., 1986; McCormick and Williamson, 1989).

#### Reduction of $I_{\text{AHP}}$

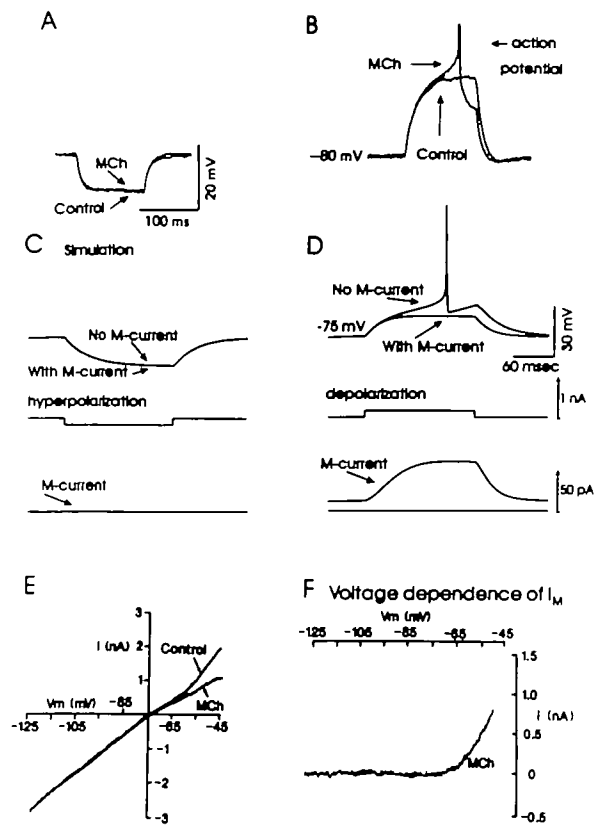
Intracellular injection of current into many cortical pyramidal cells results in a train of action potentials.



**Figure 2.** Block of a slow  $\text{Ca}^{2+}$ -activated  $\text{K}^+$  current increases response to depolarization. *A*, Intracellular injection of a current pulse into a human cortical pyramidal cell results in the generation of four action potentials displaying spike frequency adaptation and that are followed by a slow AHP. *B*, Local application of the muscarinic receptor agonist MCh blocks the slow AHP and greatly reduces spike frequency adaptation. *C* and *D*, Computer simulation of data in *A* and *B* in single neuron. Injection of a current pulse results in a train of four action potentials followed by an AHP. Each action potential allows the entry of  $\text{Ca}^{2+}$  into the cell, which activates the  $\text{Ca}^{2+}$ -activated  $\text{K}^+$  current  $I_{\text{AHP}}$  (bottom trace). Reducing  $I_{\text{AHP}}$  to 0 results in block of spike frequency adaptation and the slow AHP. *A* and *B* are from McCormick and Williamson (1989).

Their rate of generation slows down markedly with time in a process known as spike frequency adaptation (Fig. 2*A*). Spike frequency adaptation results from the activation of a variety of ionic currents, although the most important is a  $\text{K}^+$  current activated by the entry of  $\text{Ca}^{2+}$  into the cell during each action potential (Pennefather et al., 1985; reviewed in Storm, 1990). The persistent nature of this  $\text{K}^+$  current results in the generation of an hyperpolarization following the cessation of the depolarizing input, a phenomenon known as an afterhyperpolarization, or AHP for short (Fig. 2*A*). Activation of muscarinic,  $\beta$ -adrenergic, serotonergic,  $\text{H}_2$ -histaminergic, and glutamate metabotropic receptors results in reduction of  $I_{\text{AHP}}$  in both cortical and hippocampal pyramidal cells (Andrade et al., 1986; Andrade and Nicoll, 1987; Schwandt et al., 1988; McCormick and Williamson, 1989; reviewed by Nicoll et al., 1990; McCormick, 1992). This reduction in  $I_{\text{AHP}}$  results in a marked enhancement of the response of the cell to the depolarizing current pulse (compare Fig. 2*A,B*). Computer simulation of the functional effects of  $I_{\text{AHP}}$  on neuronal firing illustrates one possible time course of this  $\text{K}^+$  current during the generation of neuronal activity (Fig. 2*C,D*). Since  $I_{\text{AHP}}$  is not activated by hyperpolarization, block of this current does not have any effect on the response of an inactive cell to hyperpolarization. In this manner, reduction of  $I_{\text{AHP}}$  may serve to enhance selectively the response of cortical pyramidal cells to trains of EPSPs.

The second messenger systems involved in the



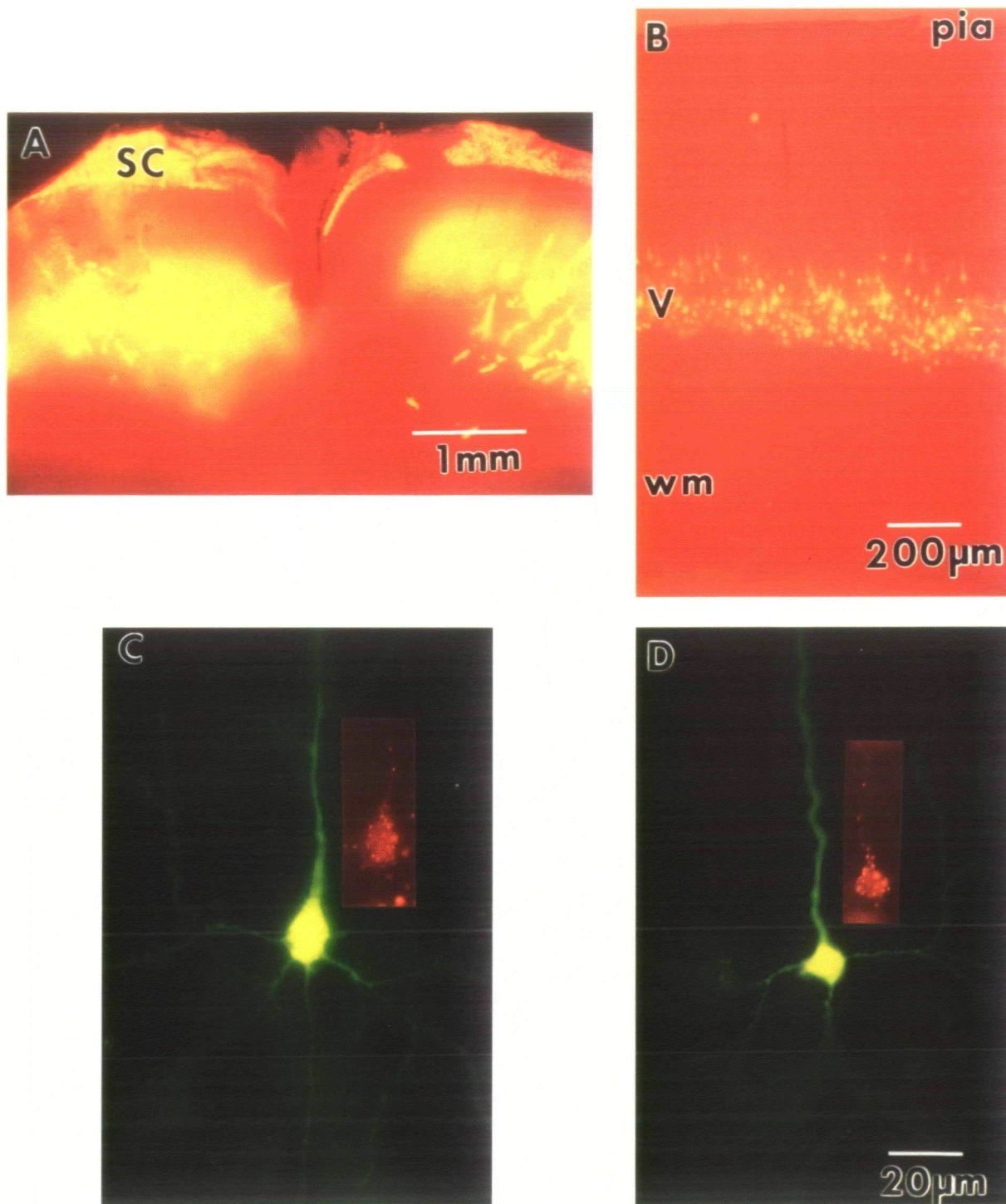
**Figure 3.** Block of the M-current selectively enhances depolarizing inputs. *A* and *B*, Activation of muscarinic receptors on a guinea pig cortical pyramidal cell enhances the response of the cell to a depolarizing current pulse such that it generates an action potential (*B*). In contrast, there is no effect on the response to a hyperpolarizing current pulse (*A*). *C* and *D*, Computer simulation of the data in *A* and *B*. Depolarization of the cell from  $-75$  mV results in activation of the outward  $\text{K}^+$  current, the M-current (*D*, bottom traces), which subsequently keeps the cell from reaching firing threshold. Block of the M-current results in the depolarizing input becoming suprathreshold (*D*, No M-current), but does not affect the response to hyperpolarizing inputs since these do not activate  $I_{\text{M}}$  (*C*). *E* and *F*, Voltage dependence of the M-current in human cortical pyramidal cells. *E*, Current-voltage plot before (control) and after (MCh) activation of muscarinic receptors illustrates the marked voltage dependence of this current. *F*, Subtraction of the control  $I$ - $V$  plot from that after activation of muscarinic receptors. At membrane potentials negative to  $-75$  mV, the current is not active. Depolarization positive to  $-75$  mV progressively activates  $I_{\text{M}}$  (upward movement of current away from 0). *A* and *B* are from McCormick and Prince (1986); *E* and *F* are from McCormick and Williamson (1989).

neurotransmitter suppression of  $I_{\text{AHP}}$  have not yet been completely detailed. In hippocampal pyramidal cells, two different pathways have been implicated. Both the activation of protein kinase C with phorbol esters as well as enhancement or mimicry of cAMP-dependent processes strongly block  $I_{\text{AHP}}$  (Baraban et al., 1985; Madison and Nicoll, 1986b; Malenka et al., 1986). Receptors that are known to stimulate adenylyl cyclase (e.g.,  $\beta$ -adrenergic,  $\text{H}_2$ -histaminergic, some serotonergic) may use this second messenger to block  $I_{\text{AHP}}$ . Receptors that do not stimulate adenylyl cyclase (e.g., muscarinic) may block  $I_{\text{AHP}}$  through stimulation of protein kinase C.

#### Reduction of $I_{\text{M}}$

The M-current is a voltage- and time-dependent  $\text{K}^+$  current that is activated by depolarization (see review





**Figure 4.** Intracellular recording from identified layer V corticotectal pyramidal cells. *A*, Injection site of rhodamine latex microspheres ("beads") into the superior colliculus (SC) in the guinea pig. *B*, Retrograde labeling of layer V throughout the primary visual, and indeed nearly all, cerebral cortex. *C* and *D*, Intracellular recording with microelectrodes containing the fluorescent dye Lucifer yellow reveals the typical pyramidal shape of these cells. *Insets* illustrate presence of rhodamine beads that were retrogradely transported from the superior colliculus. Both of these cells were burst-generating neurons (see Results and Discussion). wm, white matter.

by Brown, 1988). Voltage-clamp studies of hippocampal and neocortical neurons in both rodents and humans have demonstrated that the M-current is present in at least some subtypes of pyramidal cells (Halliwell and Adams, 1982; McCormick and Williamson, 1989). Examination of the M-current reveals that this current is progressively activated at membrane potentials pos-

itive to approximately  $-75$  mV (Fig. 3*E,F*). Thus, depolarization of neurons possessing  $I_M$  results in the activation of this outward  $K^+$  current and a subsequent "brake" on the response to the depolarization. Reduction of  $I_M$  will selectively enhance the response to this depolarization (Fig. 3*B,D*) while not altering the resting membrane potential (if it is negative to





**Figure 5.** ACh controls the firing mode of layer V burst-generating neurons. At rest the neuron in *A* spontaneously generated repetitive bursts of action potentials, which are expanded for detail in *B*. Local application of ACh results in a cessation of burst firing followed by depolarization and a switch to the single-spike mode of action potential generation (expanded in *C* for detail). As the depolarizing effect of ACh dissipates, the cell returns to spontaneous burst firing. Mimicking the ACh-induced depolarization with current injection alone also mimicked the change in firing mode, suggesting that this effect of ACh results merely from depolarization of the membrane potential (not shown).

–75 mV) or the response to hyperpolarizing inputs (Fig. 3*A,C*). In similarity to the reduction of  $I_{AHP}$ , reduction of  $I_M$  may result in a selective enhancement of the response of cortical pyramidal cells to depolarizing, versus hyperpolarizing, inputs and therefore facilitate the transmission of excitatory information through cortical circuits (e.g., Fig. 3).

Reduction of  $I_M$  in cortical pyramidal cells occurs in response not only to activation of muscarinic receptors, but also to activation of a subtype of serotonergic receptor (Colino and Halliwell, 1987; McCormick and Williamson, 1989) and glutamate metabotropic receptors (Chapak et al., 1990). The second messenger systems through which reduction of  $I_M$  occurs in sympathetic ganglion cells involve the activation of a pertussis toxin-insensitive G-protein (Pfaffinger, 1988; Brown et al., 1989; Lopez and Adams, 1989) as well as a  $Ca^{2+}$ -dependent second messenger (Beech et al., 1991).

#### Reduction of “Leak” $K^+$ Current

In addition to reduction of  $Ca^{2+}$ - and voltage-dependent  $K^+$  currents, activation of  $\alpha_1$ -adrenergic, muscarinic, and glutamate metabotropic receptors results in the reduction of other  $K^+$  currents that are active at resting membrane potential and therefore contribute to the resting “leak” conductance of the membrane (see review by McCormick, 1992). The membrane potential of cortical pyramidal cells is determined not only by the temporal and spatial convergence of barrages of EPSPs and IPSPs, but also by the basal membrane conductance to various ions, perhaps most importantly  $K^+$  ions. Reduction of membrane conductance to  $K^+$  ions will result in depolarization of the cell toward firing threshold associated with an increase in apparent input resistance. These effects will result in not only an increased excitability of the cell to EPSPs, but also an increased response to IPSPs, and at least in some cell types in a marked change in discharge pattern through the alteration of voltage-dependent conductances (see below; Wang and McCormick, 1993).

#### Increase in $K^+$ Current

As mentioned above, activation of  $GABA_B$  receptors on cortical pyramidal cells results in the activation of a  $K^+$  current and a subsequent decrease in neuronal excitability. Similarly, activation of  $A_2$ -purinergic and 5-HT<sub>1</sub>-serotonergic receptors also results in increases in membrane  $K^+$  conductance. Interestingly, as with reduction of  $I_{AHP}$  and  $I_M$ , the activation of this  $K^+$  current exhibits convergence of transmitter actions such that the maximal activation of one receptor results in the occlusion of the response to other neurotransmitters (Andrade et al., 1986; McCormick and Williamson, 1989). This convergence of transmitter action may occur at the level of the G-proteins, second messengers, or ion channels.

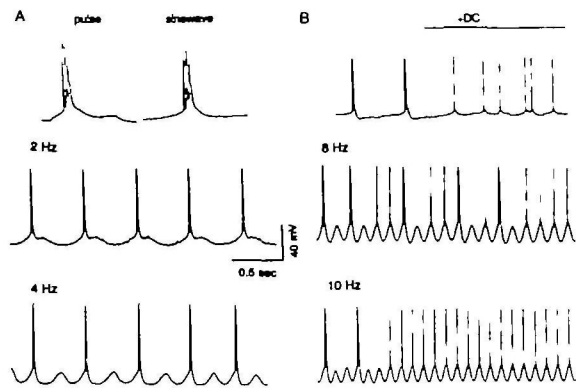
#### Physiology and Pharmacology of Identified Cortical Cells

##### Regular Spiking, Burst Firing, and Fast Spiking

Intra- and extracellular recordings from different types of cortical cells have revealed three broad electrophysiological classes of neurons, both *in vivo* and *in vitro*: regular-spiking cells generate trains of action potentials one at a time in relation to the level of polarization (see Figs. 2, 3); burst-generating neurons can generate a burst of action potentials in response to membrane depolarization (see Figs. 5–7); and fast, or thin, spiking neurons can generate high-frequency trains of unusually short-duration action potentials (see Fig. 1*A*). Intracellular labeling techniques reveal that regular-spiking neurons are typically pyramidal cells and are located throughout layers II–VI, burst-generating neurons are typically large layer V pyramidal cells including those projecting subcortically (see below), and fast-spiking cells are sparsely spiny or aspiny nonpyramidal cells (presumed GABAergic neurons) in layers II–VI (McCormick et al., 1985; Chagnac-Amitai et al., 1990; Tseng et al., 1991; Kawaguchi, 1993).

A number of exceptions to these electrophysiological classifications exist, however. First, burst-generating neurons usually can be switched from burst firing to single-spike activity with depolarization of the membrane potential (see Figs. 5, 6); and regular-spiking neurons can be induced to generate intrinsic and repetitive bursts of action potentials with dendritic depolarization (Calvin and Sypert, 1976; Wong and Steward, 1992). Parvalbumin GABAergic interneurons are characterized by thin action potentials (i.e., they are fast spiking) while calbindin GABAergic neurons possess action potentials that are more like those of regular-spiking pyramidal cells (Kawaguchi, 1993; Kawaguchi and Kubota, 1993). Careful examination of the electrophysiological properties of pyramidal and nonpyramidal cells in rat frontal cortex has led Kawaguchi and Kubota (1993) to suggest that there are at least two physiological subtypes of each. Parvalbumin- and calbindin-containing GABAergic cells in the neocortex can also be distinguished by the presence of a low-threshold (presumed  $Ca^{2+}$ -mediated) spike and the lack of prolonged activation by





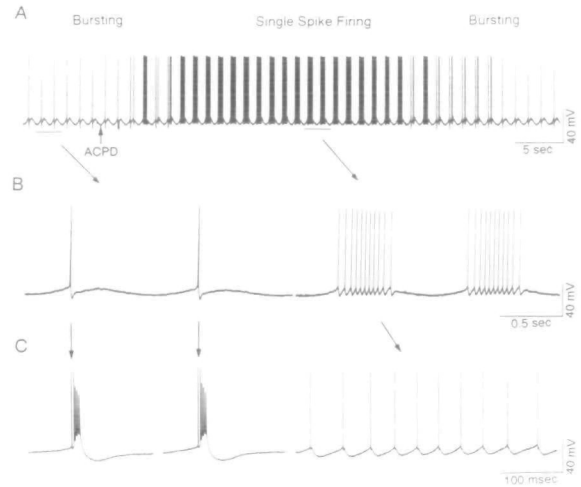
**Figure 6.** Frequency response properties of intrinsic burst firing in layer V pyramidal cells. Injection of sine wave current of different frequencies results in burst firing, as did injection of "square" pulses of current (A, top traces). As in most other burst-firing neurons, depolarization of the cell with constant current (+DC) changes the firing mode to single-spike activity (B). With injections of sine waves at a frequency of 2 Hz, the cell generates bursts of action potentials that are phase locked with the sine wave input. However, increasing the frequency to 4 Hz results in skipping of every other sine wave input. At 8 Hz, the burst-firing neuron starts to fire bursts only intermittently and single spikes on other occasions. At 10 Hz, burst firing is even further suppressed and single-spike firing enhanced. These results indicate that repetitive burst firing in layer V pyramidal cells can follow inputs of only rather slow (<10 Hz) frequencies.

single shock stimulation in calbindin-containing neurons (Kawaguchi and Kubota, 1993). Pyramidal cells differ in their apparent input resistance, which correlates with their morphology. Layer V pyramidal cells that possess smaller, ovoid cell bodies have a substantially higher input resistance than do the more typical large layer V pyramidal cells, which possess apical dendrites extending up to layer I (Kawaguchi, 1993).

#### Layer V Corticopontine and Corticotectal Burst-generating Pyramidal Cells

The soma-dendritic morphology of layer V burst-generating neurons is similar to that of corticotectal and corticopontine cells (Chagnac-Amitai et al., 1990; Hübner et al., 1990; Larkman and Mason, 1990; Kasper et al., 1991). To confirm this hypothesis we injected fluorescent latex microspheres (Katz et al., 1984) into the superior colliculi or pontine nuclei of guinea pigs (Fig. 4A, SC injection) and recorded from cells in slices of visual cortex with microelectrodes containing the fluorescent dye Lucifer yellow (Wang and McCormick, 1993). Injection of rhodamine beads into either the superior colliculi or pontine nuclei resulted in the dense retrograde labeling of layer V pyramidal cells (Fig. 4B) as expected from previous anatomical studies (see Gilbert and Kelly, 1975; Hallman et al., 1988). Intracellular recording from burst-generating layer V pyramidal cells revealed a number ( $n = 37$ ) of cells labeled with both microbeads and Lucifer yellow (Fig. 4C,D), indicating that at least some corticotectal and corticopontine layer V pyramidal cells are burst generating.

Prolonged depolarization of these layer V pyramidal cells typically results in a change in firing mode from burst generating to single-spike activity (McCormick et al., 1985), although repetitive bursting is

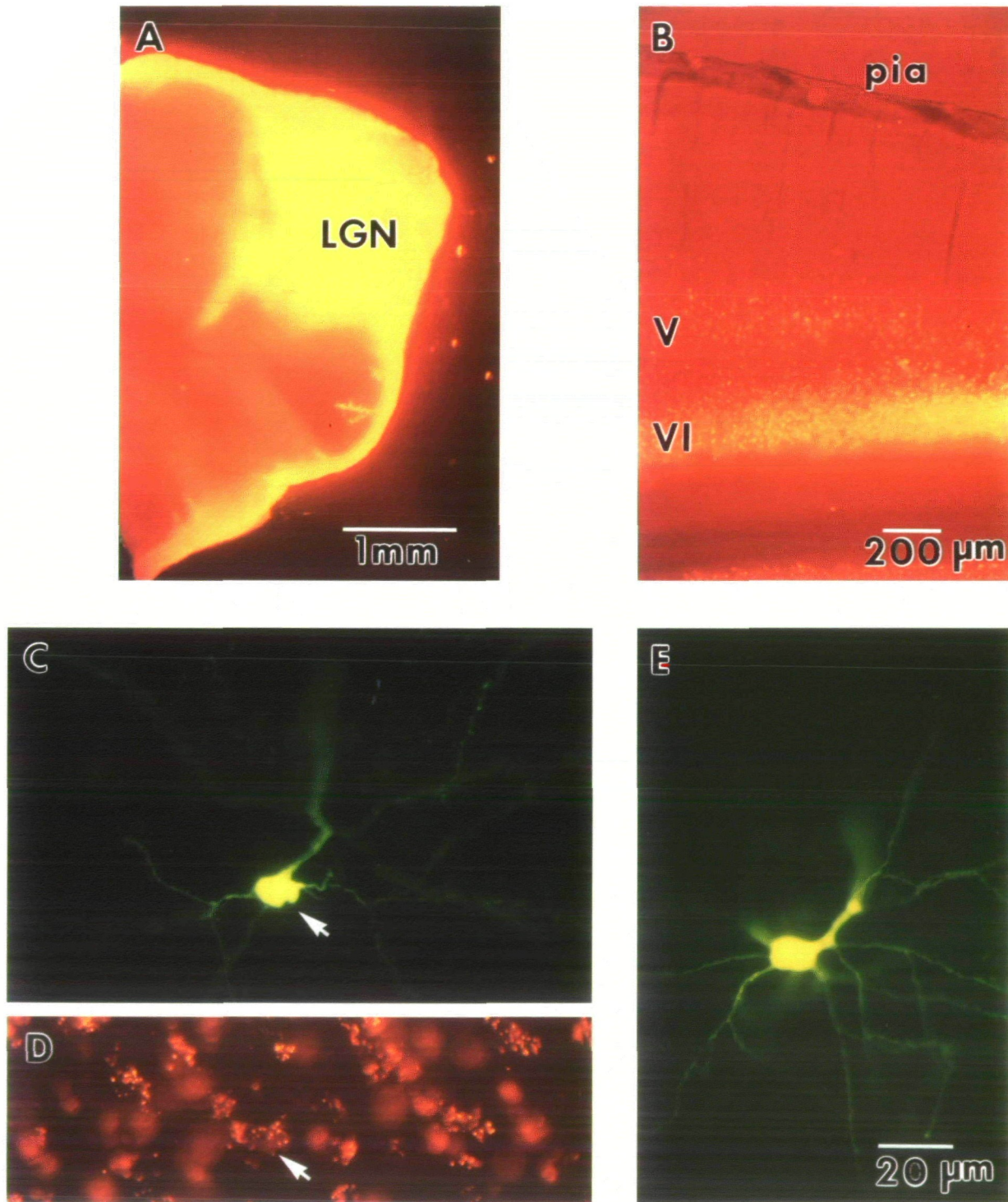


**Figure 7.** Depolarization of layer V burst-firing neurons results in linearization of their response properties. A, Injection of a slow (0.8 Hz) sine wave results in burst firing that is phase locked to the input (expanded in B and C for detail). Changing the amplitude of the sine wave input does not change the characteristics of the burst discharge, since these occur in an all-or-none manner (not shown). Activation of glutamate metabotropic receptors with the agonist 1S,3R-ACPD results in depolarization of the cell and a shift to the single-spike mode of action potential generation. Under these conditions the frequency of action potential generation is related to the level of polarization of the membrane and follows the sine wave input (expanded in B and C for detail) and therefore the firing of the cell behaves in a more linear manner.

also seen on occasion (Agmon and Connors, 1989; Silva et al., 1991). Layer V cortical burst-generating neurons can also be switched from repetitive burst firing to single-spike activity through the activation of muscarinic (Fig. 5),  $\alpha_1$ -adrenergic, or glutamate metabotropic (see Fig. 7) receptors (Wang and McCormick, 1993). This depolarization is mediated by the reduction of both "leak"  $K^+$  conductances and a voltage-dependent conductance that appears similar to the M-current, but is  $[Ca^{2+}]_o$  sensitive and distinct from  $I_{AHP}$  (Wang and McCormick, 1993).

The functional effects of such a change in firing mode of layer V burst-generating neurons were examined through the intracellular injection of different frequencies and amplitudes of sine waves (Figs. 6, 7). Injection of steady current into layer V burst-generating neurons can result in the generation of repetitive bursts of action potentials. This repetitive burst firing typically occurs at rather low frequencies (<4 Hz), although on rare occasions repetitive burst firing can be generated at frequencies up to approximately 10 Hz (see Agmon and Connors, 1989; Silva et al., 1991). Further steady depolarization of the cell typically results in the transition to single-spike firing (Fig. 6B) and therefore the complete suppression of intrinsic burst activity. Similarly, intracellular injection of sine waves of different frequencies into burst-generating neurons revealed that repetitive burst firing is limited to low frequencies (e.g., <4 Hz; Fig. 6) while at higher frequencies burst firing either becomes intermittent (Fig. 6, 4 and 8 Hz) or suppressed altogether in favor of single spike activity (Fig. 6, 10 Hz). These results suggest that repetitive burst firing is likely to occur only at low frequencies and may be suppressed by the arrival of high-frequency barrages



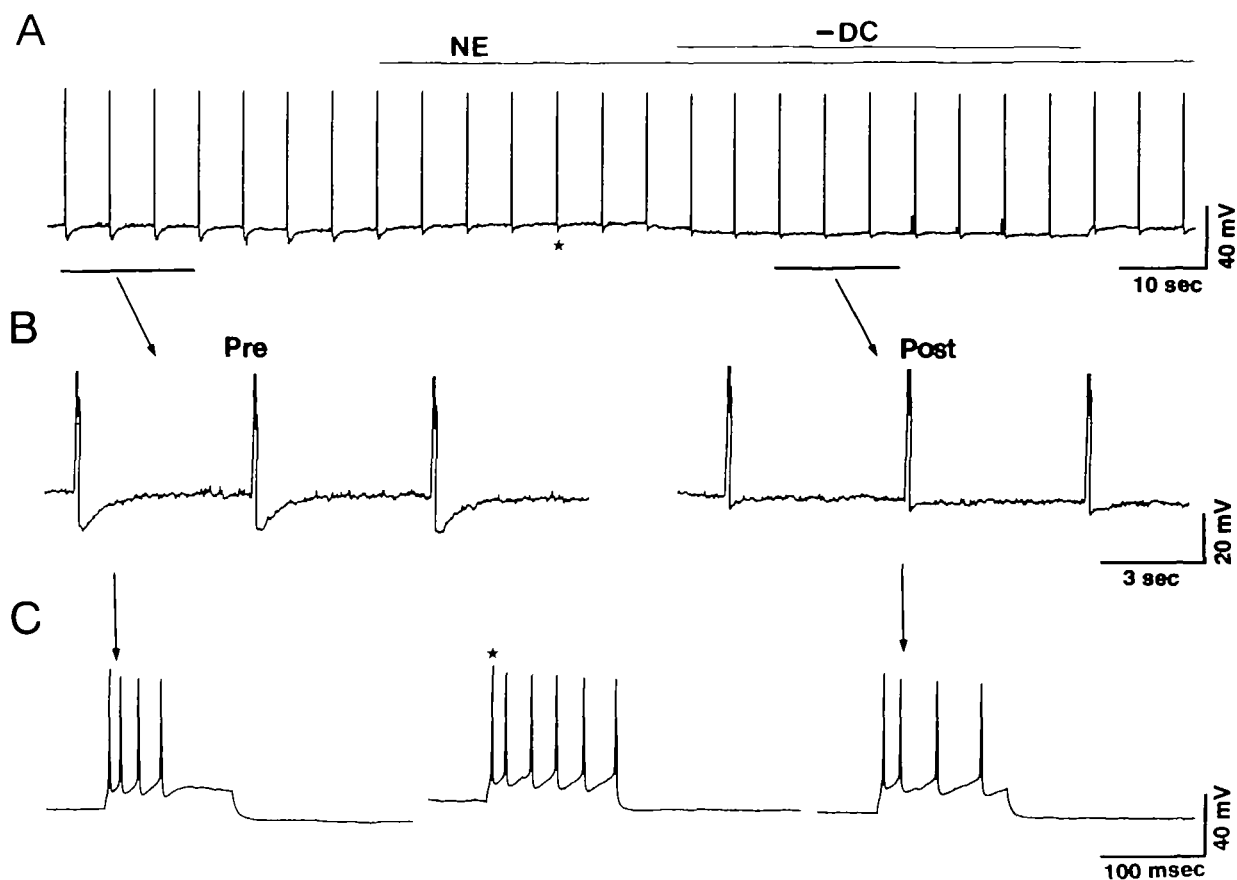


**Figure 8.** Identification of layer VI corticogeniculate neurons in the guinea pig visual cortex. Injection of rhodamine beads into the LGN (A) results in retrograde labeling of cells in layers V and VI (B). Intracellular recording from bead-labeled corticothalamic cells reveals their pyramidal or polymorphic morphology (C, E). D, Rhodamine microbeads in the cell of C and neighboring neurons in layer VI.

of EPSPs. This property of layer V burst firing suggests that this activity may participate in slow circuit oscillations such as delta waves (Rappelsberger et al., 1982) or in the initial response of the circuit to the sudden arrival of a train of EPSPs during a period of prior quiescence (e.g., activation of inhibitory then excitatory receptive field components).

In many cell types, including thalamic relay neurons and cells of the inferior olive, burst firing at hyperpolarized membrane potentials occurs through the activation of a low-threshold  $\text{Ca}^{2+}$  current (reviewed in Llinas, 1988). Intrinsic burst firing in layer V pyramidal cells is also inhibited by organic or inorganic  $\text{Ca}^{2+}$  antagonists (Friedman and Gutnick, 1989;





**Figure 9.** Regular-spiking properties of layer VI neurons and block of spike frequency adaptation by NE. *A*, Intracellular injection of a depolarizing current pulse results in the activation of a train of action potentials followed by an AHP. Local application of NE (500  $\mu\text{M}$  in micropipette) results in a small depolarization and abolition of the AHP (*A*, star). The depolarization was then compensated for with constant current ( $-DC$ ). *B*, Examples of the abolition of the AHP. *C*, Examples of the response of the cell to the depolarizing current pulse before NE, after NE (star), and during DC compensation.

Silva-Barrat et al., 1992). However, the current underlying intrinsic burst firing does not behave electrophysiologically in a manner typical for the low-threshold  $\text{Ca}^{2+}$  current, since sustained depolarization can occasionally generate repetitive bursts at membrane potentials positive to complete inactivation of this  $\text{Ca}^{2+}$  current. One possibility is the generation of dendritic  $\text{Ca}^{2+}$  spikes and afterdepolarizations, which are activated by the generation of action potentials and interact with these action potentials to generate burst discharges. Sustained depolarization may then inhibit burst discharges by activating  $\text{K}^+$  currents, which reduce the ability of the dendrites to produce these regenerative depolarizations (Traub et al., 1991).

Functionally, burst firing allows the cell to discharge a high-frequency sequence of several action potentials in response to a single input, thereby resulting in strong amplification of this input. For example, intracellular injection of low-frequency (0.8 Hz) sine waves into a cortical burst-generating neuron results in the activation of a burst of action potentials that are phase locked to the input (Fig. 7A-C). These characteristics allow the burst-generating neuron to signal strongly the presence and phase of an input, but at the expense of information as to the sine wave's precise amplitude and time course. This

is true since the temporal pattern of spike activity within the burst is dictated by the occurrence of currents intrinsic to the cell and not by the amplitude-time course of the input (Fig. 7). Changing the firing mode of burst generating neurons through depolarization, either with the intracellular injection of current or through the block of resting  $\text{K}^+$  conductance (Fig. 7), results in a "linearization" of the output of the cell. The frequency of action potential generation becomes related to the level of polarization of the membrane by the sine wave input (see Fig. 7B,C). Thus, modulatory neurotransmitter actions may switch the type of neuronal activity and information processing that occurs, by switching from event and phase detection to more linear transmission of information.

#### Layer VI Corticogeniculate Cells

Injection of rhodamine microbeads in the LGN of the guinea pig results in dense retrograde labeling of cells in layer VI and less densely in layer V (Fig. 8A,B), as expected from known anatomical relationships (Gilbert and Kelly, 1975; Jacobson and Trojanskowski, 1975; Sefton et al., 1981). Intracellular recording from bead labeled neurons in layer VI and subsequent injection of Lucifer yellow revealed corticogeniculate neurons to be pyramidal and polymorphic in morphology ( $n = 17$ ; Fig. 8C,D) as de-

scribed previously (reviewed in Tömböl, 1984). Examination of the electrophysiological properties of identified layer VI corticogeniculate neurons reveals that they are regular spiking cells that display spike frequency adaptation (Fig. 9; see also van Broderode and Snyder, 1992). Application of NE to layer VI cells results in a marked decrease in spike frequency adaptation and abolition of the slow AHP (Fig. 9), as in other regular-spiking cells in layers II–V (McCormick and Williamson, 1989). Local application of ACh to corticogeniculate neurons results in a slow depolarization and increased input resistance, suggesting a decrease in a resting K<sup>+</sup> current (not shown). This effect of ACh was mimicked by application of the muscarinic agonist acetyl-β-methylcholine (MCh), suggesting that it is mediated through muscarinic receptors, as in pyramidal cells in layers II–V.

Together with the recordings from identified layer V corticocollicular and corticopontine neurons, these results indicate that the descending output of the cerebral cortex is dependent upon the activity of ascending modulatory neurotransmitter systems. Increases in release of ACh and NE, such as occurs during increases in arousal and attention, may then result in not only an increase in sensory transmission from the thalamus to the cerebral cortex (reviewed in McCormick, 1992), but also an increase in the descending output of the cortex, both back to thalamus, and to other sensory and motor structures, so as to prepare the nervous system for the behavioral task at hand.

In summary, we view neuromodulation and synaptic plasticity not as merely the mediators of sleep–wake cycles and learning and memory, respectively, but also as continual regulators of nervous system function, both global and local, that are necessary to match the abilities of the nervous system to the task at hand. Hopefully, future research will shed new light onto the functional significance of the wide variety of mechanisms by which cortical function can be modulated.

## Appendix

The simulations of the effects of  $I_M$  and  $I_{AHP}$  on action potential generation were performed using the cCLAMP modeling program, which is freely available from us (Huguenard and McCormick, 1992; McCormick and Huguenard, 1992).

In this Hodgkin and Huxley (1952) style model, the activity of the neuron was described by

$$\begin{aligned} dV/dt = & -(I_{inj} + I_{Na} + I_K + I_L + I_C + I_{AHP} \\ & + I_M + I_{GABAA} + I_{GABA_B} + I_{AMPA} + I_{NMDA} \\ & + I_{K,leak} + I_{Na,leak})/C_{in}. \end{aligned}$$

The input capacitance ( $C_{in}$ ) was set to 0.29 nF,  $I_{inj}$  is the injected current pulse,  $I_{Na}$  is a transient Na<sup>+</sup> current,  $I_K$  is the delayed-rectifier K<sup>+</sup> current,  $I_L$  is a high-threshold Ca<sup>2+</sup> current,  $I_C$  is a fast, Ca<sup>2+</sup>-activated K<sup>+</sup> current,  $I_{AHP}$  and  $I_M$  are as described here, and  $I_{K,leak}$  and  $I_{Na,leak}$  are K<sup>+</sup> and Na<sup>+</sup> leak conductances. The

Hodgkin and Huxley (1952) style equations describing  $I_{AHP}$  and  $I_M$  and the synaptic currents are described below.

$I_M$  (after Yamada et al., 1989):

$$\begin{aligned} m_{\infty} &= 1/(1 + \exp(-(V_m + 35)/10)), \\ \tau &= 1000/(3.3 \times (\exp((V_m + 35)/20) \\ &\quad + \exp(-(V_m + 35)/20))). \end{aligned}$$

$$\begin{aligned} I_M &= g_{M,max} \times (V_m + 100) \times m, \\ \text{where } g_{M,max} &= 25 \text{ nS}. \end{aligned}$$

$I_{AHP}$  (after Yamada et al., 1989):

$$\begin{aligned} m_{\infty} &= \alpha/(\alpha + \beta), \\ \tau &= 1/(\alpha + \beta), \\ \alpha &= 1.2 \times 10^9 \times ([Ca^{2+}])^2, \beta = 0.001. \\ I_{AHP} &= g_{AHP,max} \times m \quad \text{where } g_{AHP,max} = 5 \text{ nS}. \end{aligned}$$

Calcium buffering was as described in McCormick and Huguenard (1992).

$I_{AMPA}$  (Chen and Huang, 1992; McBain and Dingle-dine, 1992):

$$\begin{aligned} g_{AMPA} &= g_{AMPA,max} \times e^{-t/18} \times (1 - e^{-t/22})/0.68, \\ g_{AMPA,max} &= 50 \text{ nS}, \\ I_{AMPA} &= (V_m - 0.0) \times g_{AMPA}. \end{aligned}$$

$I_{NMDA}$ :

$$\begin{aligned} g_{NMDA} &= g_{NMDA,max} \times g/g_0 \times e^{-(t-5)/71} \\ &\quad \times (1 - e^{-(t-5)/13.2})/0.60, \end{aligned}$$

$$g_{NMDA,max} = 50 \text{ nS},$$

$$K_{Mg} = 0.00107 \times e^{(2 \times 0.73 \times V_m F/RT)},$$

where  $e$ ,  $F$ ,  $R$ , and  $T$

have their usual meanings,

$$g/g_0 = 1 - (1/(1 + K_{Mg}/[Mg]_o)).$$

$$I_{NMDA} = (V_m - 0.0) \times g_{NMDA}.$$

$I_{GABA}$  (after Ropert et al., 1990; Otis et al., 1993):

$$g_{GABAA} = g_{GABAA,max} \times e^{-t/25} \times (1 - e^{-t/10})/0.84,$$

$$I_{GABAA} = (V_m + 75) \times g_{GABAA},$$

where  $g_{GABAA,max} = 100 \text{ nS}$ .

$$\begin{aligned} g_{GABA_B} &= g_{GABA_B,max} \times (0.84 \times e^{-t/283} \\ &\quad + 0.16 \times e^{-t/10226}) \end{aligned}$$

$$\times (1 - e^{-t/112})^4/0.31,$$

$$I_{GABA_B} = (V_m + 100) \times g_{GABA_B},$$

where  $g_{GABA_B,max} = 4 \text{ nS}$ .

## Notes

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