Proc. Natl. Acad. Sci. USA
Vol. 86, pp. 8098–8102, October 1989
Neurobiology

Convergence and divergence of neurotransmitter action in human cerebral cortex

(acetylcholine/norepinephrine/serotonin/adenosine/histamine)

DAVID A. MCCORMICK* AND ANNE WILLIAMSON

Section of Neuroanatomy, Yale University School of Medicine, 333 Cedar Street, New Haven, CT 06510

Communicated by Pasko Rakic, June 26, 1989

ABSTRACT **The postsynaptic actions of acetylcholine, adenosine, γ-aminobutyric acid, histamine, norepinephrine, and serotonin were analyzed in human cortical pyramidal cells maintained *in vitro*. The actions of these six putative neurotransmitters converged onto three distinct potassium currents. Application of acetylcholine, histamine, norepinephrine, or serotonin all increased spiking by reducing spike-frequency adaptation, in part by reducing the current that underlies the slow afterhyperpolarization. In addition, application of muscarinic receptor agonists to all neurons or of serotonin to middle-layer cells substantially reduced or blocked the M-current (a K^+ current that is voltage and time dependent). Inhibition of neuronal firing was elicited by adenosine, baclofen (a γ-aminobutyric acid type B receptor agonist), or serotonin and appeared to be due to an increase in the same potassium current by all three agents. These data reveal that individual neuronal currents in the human cerebral cortex are under the control of several putative neurotransmitters and that each neurotransmitter may exhibit more than one postsynaptic action. The specific anatomical connections of these various neurotransmitter systems, as well as their heterogeneous distribution of postsynaptic receptors and responses, allows each to make a specific contribution to the modulation of cortical activity.**

Human cerebral cortical activity may be under the influence of a large number of neuroactive substances, including acetylcholine (ACh), adenosine, γ-aminobutyric acid (GABA), histamine, norepinephrine, and serotonin (5-HT) (1–8). The postsynaptic actions of these putative neurotransmitters in human neocortical neurons are largely unknown, although the demonstration of muscarinic receptor-mediated block of the voltage- and time-dependent K^+ current known as M-current (I_M) is a notable exception (2). Investigations of neurotransmitter actions in nonhuman subcortical neurons have revealed a wide variety of postsynaptic responses as well as a remarkable convergence and divergence of neurotransmitter action (9–22). For example, individual neurons in the rodent hippocampus, thalamus, and substantia nigra respond to more than one putative neurotransmitter with the same ionic response (12, 17, 20–22). Conversely, a single neurotransmitter, such as acetylcholine, can elicit markedly different ionic responses in separate brain regions and even in distinct morphological cell classes in the same nucleus (e.g., refs. 15 and 19).

Convergence and divergence of neurotransmitter action has important implications for understanding functional systems in the brain. Not only do the neuronal systems underlying behavior consist of a number of transmitter pathways, but each pathway is involved in more than one functional system (e.g., ref. 22). In addition, many neurological disorders, such as Parkinson, Alzheimer, and Huntington diseases and, perhaps, epilepsy, are expressed as a loss or dysfunction in one or more neurotransmitter system. Interactions of neurotransmitters may allow for subtleties in neuronal modulation that are important for understanding these profound neurological deficits.

In the present experiments we show that multiple neurotransmitters are involved in determining the amplitude of individual currents and, therefore, the electrophysiological behavior of human neocortical neurons.

METHODS

Human neocortical tissue used was a small portion of that which is normally removed for the treatment of intractable epilepsy. In the majority (71%) of cases, the tissue was obtained from the lateral portions of the anterior temporal lobe in patients in which focal epileptiform activity was localized with chronic depth electrodes to more mesial structures (e.g., hippocampus). This neocortical tissue was not grossly abnormal when examined histologically and did not give rise to abnormal synchronous discharges when maintained *in vitro*. The extent to which the present results are affected by the patient's history of epilepsy is not known.

Neocortical tissue was resected *en bloc* by the neurosurgeon (Dennis Spencer, Yale University School of Medicine), and a small portion was placed in 5°C bathing medium. In addition, some experiments were performed on anterior cingulate, sensorimotor, or temporal cortical tissue obtained from guinea pigs. These animals were deeply anesthetized with sodium pentobarbital (20–30 mg/kg i.p.) and decapitated. Four-hundred-micrometer slices were prepared on a Vibratome and maintained at the gas/liquid interface in a recording chamber at 35 ± 1°C (23). The bathing medium was 124 mM NaCl/2.5 mM KCl/2 mM $MgSO_4$/1.25 mM NaH_2PO_4/26 mM $NaHCO_3$/2 mM $CaCl_2$/10 mM dextrose.

Intracellular recording electrodes (30–50 MΩ) contained 4 M potassium acetate. *I–V* relationships were obtained in discontinuous single electrode voltage clamp by holding the cells at −45 to −60 mV and applying a 10-sec voltage ramp to between −120 and −140 mV and measuring the current required to do so. Head-stage output was continuously monitored to ensure adequate settling time. Sample frequencies were typically between 4 and 5.5 kHz, and amplifier gain ranged from 0.5–1.0 nA/mV.

Methysergide was a gift from Sandoz and 8-hydroxydipropylaminotetralin (8-OH-DPAT) was obtained from Research Biochemicals, Natick, MA). Bis(2-aminophenoxy)ethane-*N*,*N*,*N*′,*N*′-tetraacetic acid (BAPTA) was obtained from Molecular Probes. Ethylene glycol bis(β-aminoethyl

The publication costs of this article were defrayed in part by page charge payment. This article must therefore be hereby marked "*advertisement*" in accordance with 18 U.S.C. §1734 solely to indicate this fact.

Abbreviations: I_{AHP}, K^+ current that underlies the slow afterhyperpolarization; I_M, K^+ current that is voltage and time dependent; ACh, acetylcholine; MCh, methacholine; GABA, γ-aminobutyric acid; 5-HT, 5-hydroxytryptamine or serotonin.

*To whom reprint requests should be addressed.

ether)-*N*,*N*,*N*',*N*'-tetraacetic acid (EGTA) and all other drugs were obtained from Sigma. All agonists were applied in volumes of 5–20 pl by using the pressure-pulse technique (23).

RESULTS

Stable intracellular recordings were obtained from 110 human and 82 guinea pig cortical neurons for periods of up to 6 hr each. A representative sample of human cortical cells yielded an average resting membrane potential of −81 ± 8 mV (SD; n = 22), action potential amplitude of 102 ± 12 mV, and apparent input resistance of 43 ± 10 MΩ. The electrophysiological properties of neurons studied here indicated that they were most likely pyramidal in morphology (23, 24).

Reduction of Spike-Frequency Adaptation. Intracellular injection of a suprathreshold depolarizing current pulse resulted in a train of action potentials that showed marked spike-frequency adaptation (Fig. 1, control). Extracellular application of ACh (1–5 mM in micropipette), or the muscarinic agonist acetyl-β-methylcholine (MCh; 1 mM), resulted in a slow depolarization of the membrane potential and a substantial reduction in spike-frequency adaptation, even after the membrane potential was manually repolarized to the preapplication level (Fig. 1*B*; n = 7, human; n = 3, guinea pig). Similarly, application of norepinephrine (500 μM; n = 7, human; n = 15, guinea pig), histamine (500 μM; n = 6, human; n = 11, guinea pig) and 5-HT (300–500 μM; n = 4, human; n = 6, guinea pig) also greatly reduced spike-frequency adaptation (Fig. 1 *A*, *C*, and *D*). However, norepinephrine never, and histamine and 5-HT only occasionally, depolarized the baseline membrane potential (data not shown).

Spike-frequency adaptation results, in part, from the activation of two separate K^+ currents: I_{AHP} and I_M (25). I_{AHP} is activated by increases in the intracellular concentration of unbound Ca^{2+} and underlies the slow *after*-*hyper*-*pol*arization (hence its name) occurring after a train of action potentials (26). I_{AHP} was investigated by injecting a depolarizing current pulse (0.8–1.0 nA; 300 msec), which elicited from 6–15 action potentials in normal medium or after a single Ca^{2+}-dependent action potential in medium containing 1 μM tetrodotoxin and 5 mM tetraethylammonium. At the termination of the current pulse, the neuron was voltage clamped (typically at −60 mV), and the amplitude and time course of the after current was examined (Fig. 1 *E–H*). Individual trains of action potentials in normal bathing medium were followed by a slow outward current that possessed an average reversal potential of −100 ± 6 mV (n = 8). Decay of the later portions of I_{AHP} was well fit ($r > 0.98$) by a single exponential function with an average time constant of 996 ± 382 msec; n = 5 (26).

Separate applications of MCh, norepinephrine, histamine, and 5-HT all substantially reduced or abolished the slow afterhyperpolarization and/or I_{AHP} (n = 41, human; n = 63, guinea pig), even in the same neuron (Fig. 1 *E–H*; n = 2, human; n = 5, guinea pig). This convergence onto I_{AHP} occurred through four distinct postsynaptic receptors. Block of three of the four receptor subtypes involved in guinea pig neurons by adding the muscarinic antagonist scopolamine (1 μM; n = 9), the β-adrenergic antagonist propranolol (20 μM; n = 11), the 5-HT antagonist methysergide (5 μM; n = 8) or the H_2 histaminergic antagonist cimetidine (10–20 μM; n = 11) to the bathing medium prevented reduction of I_{AHP} by stimulation of all but the unblocked receptor.

Reduction of I_M. I_M also contributes to spike-frequency adaptation (2, 27). The possibility that ACh, histamine, norepinephrine, and 5-HT may suppress I_M was therefore examined. Application of MCh to all neurons and 5-HT to middle-layer cells, after depolarization with intracellular injection of current to near-firing threshold (e.g., −60 mV) resulted in a slow depolarization and a decrease in apparent membrane conductance (Fig. 2 *A* and *B*; n = 17, human). The possibility that this slow depolarization represented a block of I_M was examined by applying voltage steps (1-sec duration) between −45 and −60 mV. The voltage step from −45 to −60 mV was associated with the relaxation of an outward current which was well fit (r >0.99) by a single exponential function with an average time constant of 71 ± 13 msec; (n = 12,

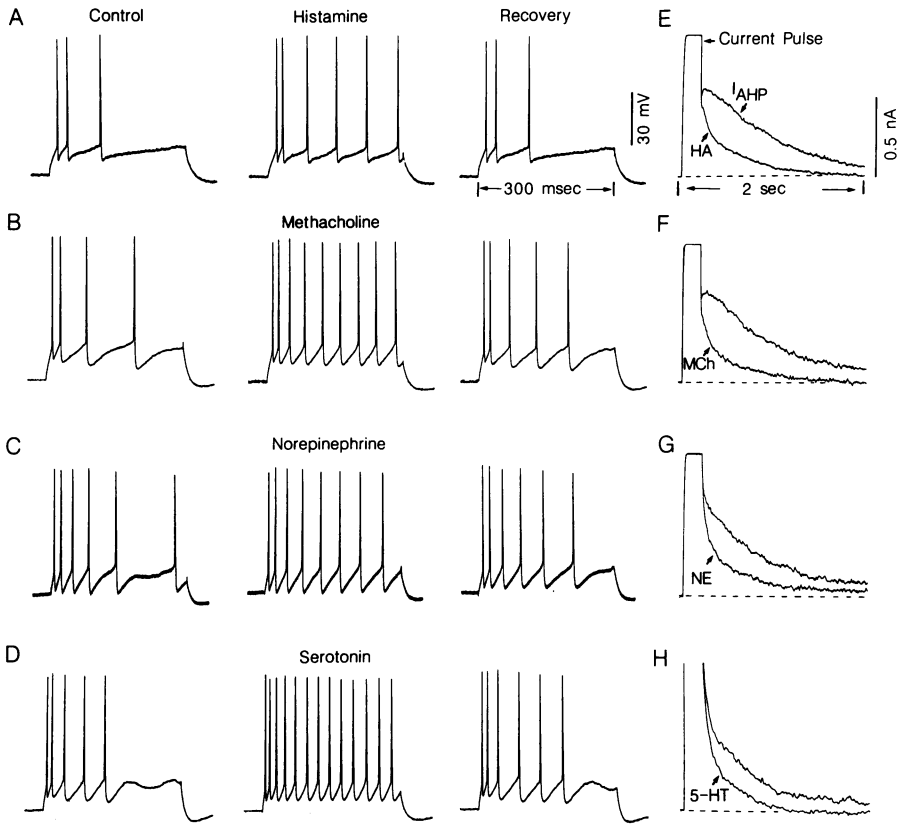

FIG. 1. Histamine (HA), MCh, norepinephrine (NE), and 5-HT (serotonin) all reduce spike-frequency adaptation and I_{AHP} in human neocortical neurons. (*A–D*) Intracellular injection of a depolarizing current pulse results in the generation of a train of action potentials that shows spike-frequency adaptation (control). Extracellular application of histamine (*A*), MCh (*B*), norepinephrine (*C*), or 5-HT (*D*) results in a reversible reduction of adaptation. (*E–H*) Intracellular injection of a current pulse was used to generate from 6–10 action potentials (current trace only shown). After cessation of the pulse, the cell was switched to voltage-clamp mode (held at −60 mV), and the after current was examined. Application of all four agents reduced a slow outward component (I_{AHP}) of this after current. Histamine and MCh both caused, in addition, an apparent inward current and, therefore, the traces in *E* and *F* were offset to match the predrug baseline for illustrative purposes. I_{AHP} became progressively smaller throughout the course of the experiment due, in part, to repeated applications of the four agents. All data, except *C*, were obtained from the same layer III human cortical neuron from the anterior temporal lobe. Although this cell displayed a reduction in spike-frequency adaptation to norepinephrine, this data was not suitable for illustration due to filtering for examination of I_{AHP}. Data in *C* was obtained from another anterior temporal human cortical neuron.

human). Voltage steps between −75 and −90 mV, out of the range of I_M, were not accompanied by activation of this current (data not shown).

Under voltage-clamp conditions, MCh (n = 21, human) or 5-HT (n = 6, human) caused a large apparent inward current, lasting from 5–15 min, that resulted from a suppression of I_M (Fig. 2 *C–I*). The marked voltage dependence of this effect is well illustrated in *I–V* plots obtained before and during MCh and 5-HT (Fig. 2 *G*, *H*, and *I*). Under these conditions, MCh and 5-HT both induced a marked inward shift of the *I–V* relation at membrane potentials positive to approximately −70 mV (Fig. 2 *G*, *H*, and *I*). In some neurons, there also appeared to be a smaller, relatively linear inward component of the MCh and 5-HT responses. This component reversed at −108 ± 4 mV (n = 3, human).

Subtracting the current traces associated with the voltage steps between −45 and −60 mV before and after MCh or 5-HT revealed three components that can be explained as suppression of I_M (Fig. 2 *E* and *F*, differences a–c). The reduction in instantaneous "leak" current associated with the voltage jump from −45 to −60 mV represents a reduction in the amount of I_M active at −45 mV (Fig. 2 *E* and *F*, difference a). The slow apparent inward current seen after stepping from −45 to −60 mV represents the deactivation or "turning off" of that portion of I_M suppressed by MCh and 5-HT (Fig. 2 *E* and *F*, difference b), whereas the slow outward

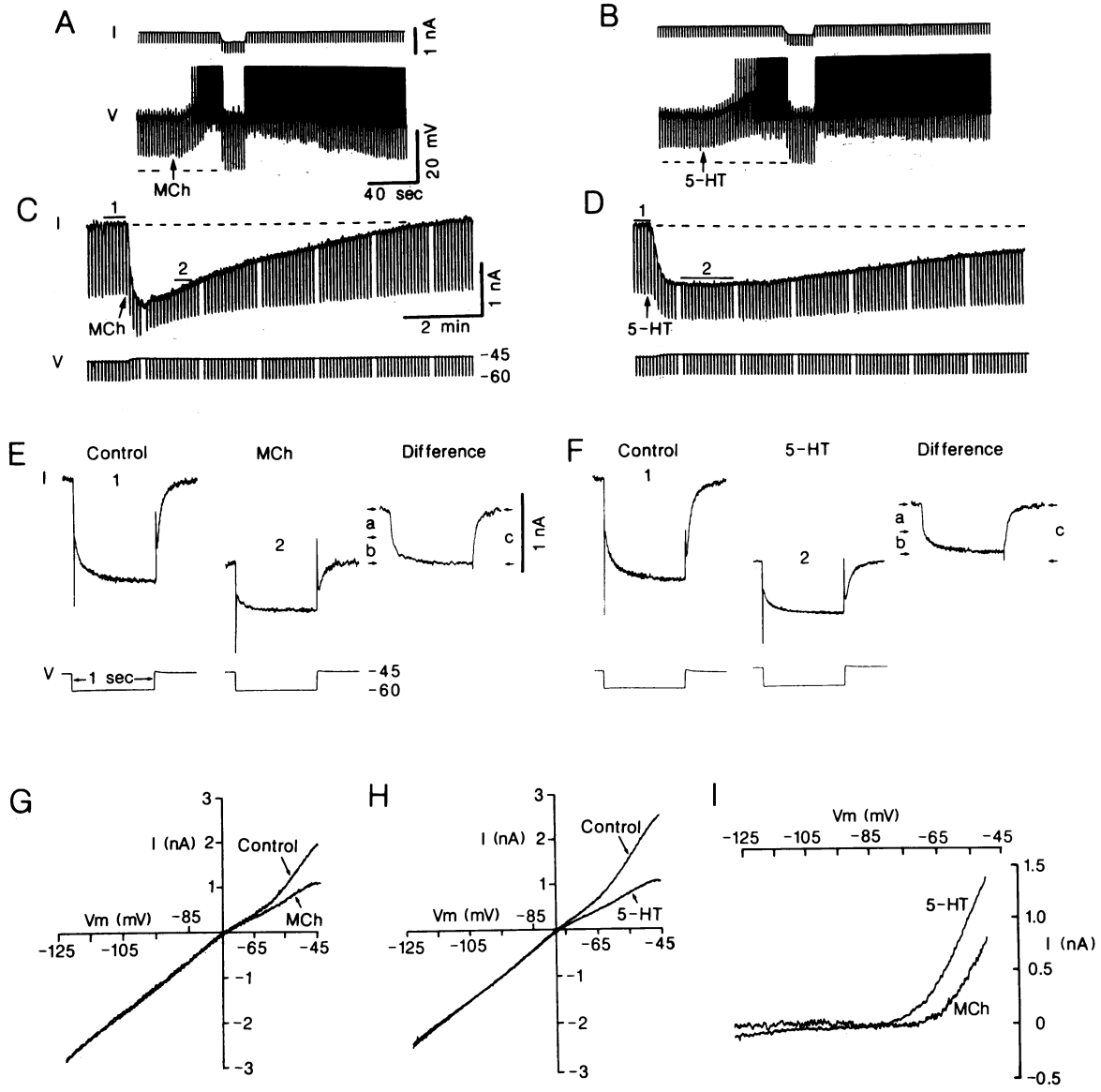

FIG. 2. Activation of muscarinic and 5-HT receptors reduces M-current. Application of MCh (*A*) or 5-HT (*B*) to a human cortical neuron depolarized with intracellular injection of current to −60 mV results in a slow depolarization and action potential discharge. Compensation for the slow depolarization by adjusting the injected current (top trace) reveals a substantial decrease in apparent input conductance (dashed line). Application of MCh (*C* and *E*) or 5-HT (*D* and *F*) during voltage steps from −45 to −60 mV in voltage clamp results in a marked suppression of an outward current, which is turned off by the step to −60 mV and activated by the step to −45 mV. Current and voltage steps in *C* and *D* are expanded for detail in *E* and *F* (nos. 1 and 2). Each trace in *E* and *F* is an average of between 5 and 16 individual steps, as indicated in *C* and *D*. The difference of the currents required to perform the voltage steps before and after MCh and 5-HT reveal three parts labeled a, b, and c and correspond to a decrease in fast "leak" conductance (difference a), and the turning off (difference b) and on (difference c) of I_M. (*G* and *H*) *I–V* plots before and after application of MCh and 5-HT. Outward rectification in *G* control is smaller than in *H* control due to incomplete washout of an application of MCh before *G*. (*I*) plot of the difference between the *I–V* curves in *G* and *H* versus membrane potential reveals the voltage dependence of the current suppressed by MCh and 5-HT. All data was obtained from the same lower-layer III neuron in the human anterior temporal lobe.

current seen when stepping from −60 to −45 mV represents the activation of that same portion of I_M (Fig. 2 *E* and *F*, labeled difference c).

The suppression of I_M by 5-HT is not mediated by muscarinic receptors because local application of scopolamine (10–20 μM, n = 3, human) completely blocked the response to MCh but did not alter that to 5-HT. This effect is not due to the suppression of a Ca^{2+} or Na^+-activated potassium current (28) because it persisted in neurons recorded for more than an hour with electrodes containing high concentrations of the Ca^{2+}-chelating substances BAPTA (0.2 M) or EGTA (0.5 M) (n = 3, human) as well as after application of tetrodotoxin (10 μM; n = 3, human). In addition, application of norepinephrine, which potently blocks I_{AHP}, did not result in any reduction of I_M (n = 6, human).

Increase in Membrane Potassium Conductance. Application of adenosine (2 mM in micropipette; n = 10, human; n = 11, guinea pig), the $GABA_B$ receptor agonist baclofen (100 μM; n = 17, human; n = 8, guinea pig), and in some neurons, 5-HT (n = 14/30, human; n = 13/21, guinea pig) resulted in a hyperpolarization or an outward current and an increase in membrane conductance (Fig. 3). The average reversal potential for this response, determined from *I–V* relationships (Fig. 3*A*), was similar for all three agents (adenosine: −106 ± 6 mV, n = 6; baclofen: −104 ± 7 mV, n = 14; 5-HT: −101 ± 4 mV, n = 8).

In neurons of the rodent hippocampus and brainstem maximal activation of an outward K^+ current by baclofen dramatically reduces the outward current induced by 5-HT, and vice versa (20, 21). Similarly, we found that baclofen reversibly reduced the adenosine-induced current by 85 ± 18%; (n = 4, human; n = 4, guinea pig) and the 5-HT-induced current by 95 ± 9% (n = 3, human; Fig. 3 *B1* and *B2*). This nonadditivity suggests convergence of these three agents onto the same potassium current (12, 17).

Local application of the $GABA_B$ antagonist phaclofen (5 mM in micropipette) resulted in a substantial (60%) decrease in the response to baclofen, but not adenosine (n = 4). Local application of the $5\text{-}HT_{1A}$ partial agonist 8-hydroxydipropylaminotetralin (500 μM), on the other hand, resulted in a small hyperpolarization and increase in membrane conductance (n = 3, human; n = 3, guinea pig). In addition, local application of 8-hydroxydipropylaminotetralin also resulted in a reduction, or block, of the hyperpolarizing response to 5-HT and the appearance, or enhancement, of a 5-HT-induced slow depolarization (data not shown; n = 2, human; n = 2, guinea pig). These results indicate that baclofen is causing an increase in membrane potassium conductance through $GABA_B$ receptors, whereas 5-HT is doing so through the $5\text{-}HT_{1A}$ receptor subtype.

Anatomic Distribution of Neurotransmitter Responses. The ionic responses to ACh, adenosine, baclofen, histamine, and norepinephrine detailed above appeared to be present in all, or nearly all, presumed pyramidal neurons that we tested in layers II–III and V of the anterior temporal, occipital, and frontal human cortical regions. However, this is not to say that significant laminar and area differences do not exist (for example, see ref. 29). Indeed, the responses to 5-HT, although consistent between applications in the same neuron, varied significantly between different cells. The 5-HT-induced hyperpolarization and outward current was prominent in layer II and V neurons, whereas the suppression of I_M appeared to be more prominent in neurons located in mid-cortical lamina. 5-HT-induced suppression of I_{AHP} was present in all neurons tested, regardless of laminar position. Further experiments on possible laminar and area differences in transmitter actions would be worthwhile.

DISCUSSION

Anatomical and psychopharmacological data suggests that the excitability of neurons in human cerebral cortex is under the control of cholinergic, GABAergic, histaminergic, noradrenergic, purinergic, and serotonergic neurotransmitter systems (1–8). Our data reveal that the neurotransmitters and/or neuromodulators thought to be released by these systems have potent and long-lasting effects on specific ionic currents in human cortical pyramidal cells. ACh, histamine, norepinephrine, and 5-HT are potent blockers of spike-frequency adaptation, an effect that results, in part, from a reduction of two specialized K^+ currents: I_{AHP} (blocked by all four agents) and I_M (blocked by ACh and 5-HT) (Figs. 1,

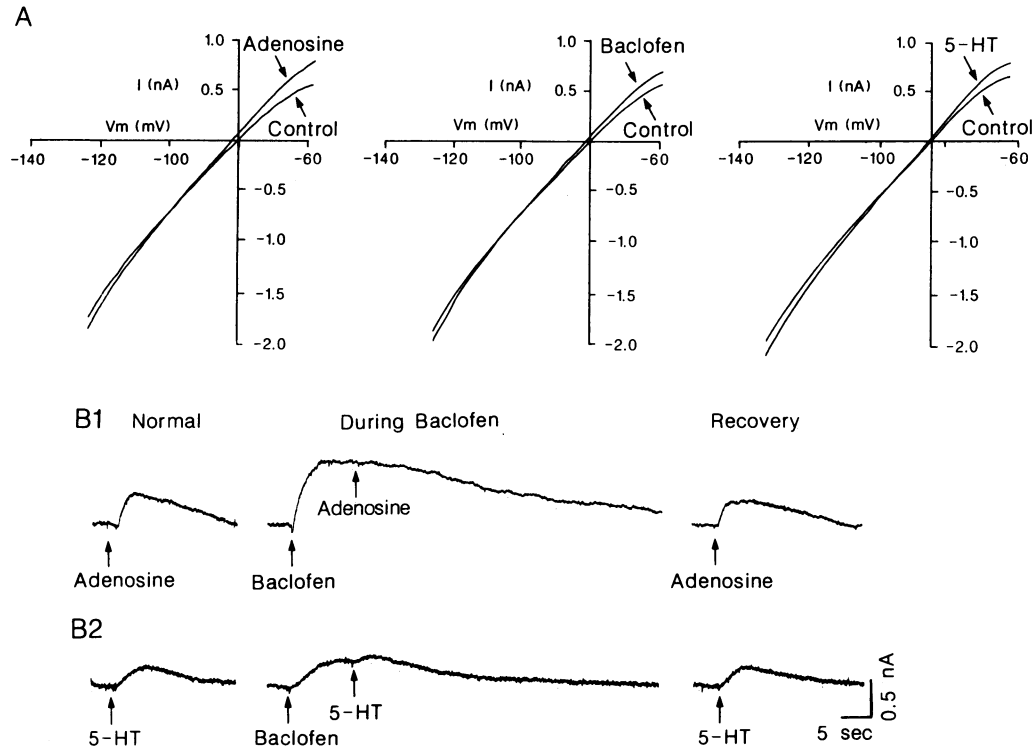

FIG. 3. Adenosine, baclofen, and serotonin activate an outward current in human cortical pyramidal cells. (*A*) Application of adenosine, baclofen, or 5-HT to this layer II neuron in the human anterior temporal lobe results in an outward current and increase in membrane conductance. *I–V* plots before and after each agonist are found to reverse at approximately −100 mV. (*B*) Adenosine, baclofen, and 5-HT-induced outward currents are nonadditive. Application of adenosine (*B1*) to a layer II–III human frontal cortical neuron or 5-HT (*B2*) to a layer II–III human temporal lobe cell results in substantial outward currents (cells voltage clamped at −60 mV). Activation of the baclofen-induced current is associated with a block and large reduction of the responses to adenosine and 5-HT, respectively (middle traces). This effect is fully reversible (right traces).

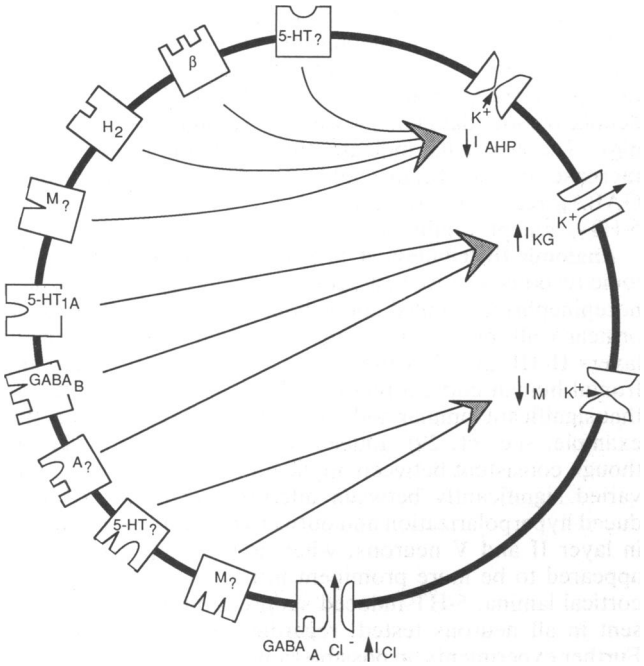

FIG. 4. Summary diagram of convergence of postsynaptic action of ACh, adenosine, GABA, histamine, norepinephrine, and 5-HT in a schematized human neocortical pyramidal cell. Activation of muscarinic (M), histaminergic (H_2), β-adrenergic (β), and serotonergic (5-HT) receptors results in a suppression of I_{AHP} and decreased spike-frequency adaptation. Activation of 5-HT_{1A}, $GABA_B$, and adenosine (A) receptors results in an increase in a potassium current. We term this potassium current I_{KG} because of its association with G proteins in many neuronal systems (12, 17, 20) and to distinguish it from other potassium currents. Stimulation of 5-HT and muscarinic receptors results in suppression of I_M. Only activation of $GABA_A$ receptors is found to increase membrane chloride conductance (8). Question marks indicate incomplete identification of receptor subtypes.

2, and 4). In addition, adenosine, baclofen, and 5-HT inhibit neuronal firing through an increase in a presumed K^+ current (Figs. 3 and 4).

Convergence and Divergence of Neurotransmitter Action. Our results, and those of others (see refs. 12, 17, 20, 21, 30, 31), indicate that multiple neurotransmitters can activate the same response in a single postsynaptic neuron. Furthermore, in some cases, application of a single suspected neurotransmitter (e.g., ACh and 5-HT) can result in more than one postsynaptic response in the same neuron (e.g., reduction of I_{AHP} and I_M). Therefore, each neuronal current may be modulated by more than one neurotransmitter system, and each neurotransmitter may have more than one postsynaptic action. When viewed alone, convergence of neurotransmitter actions would degrade the "neurotransmitter code"—i.e., the specific contribution of each neurotransmitter system to the functioning of the nervous system. However, when considering all aspects, such as efferent and afferent pathways, divergence of postsynaptic actions, and electrophysiological properties of the neurons releasing the transmitter, it is clear that each neurotransmitter system is specific and distinct from the others. Therefore, the abundance of neurotransmitters in the human neocortex does not represent redundant pathways but rather emphasizes that control of cortical synaptic processing and excitability is a complicated process in which multiple systems take part.

To this end, reduction in I_{AHP} and I_M should greatly enhance responses to barrages of excitatory postsynaptic potentials (EPSPs) by increasing the ability of the neuron to generate prolonged trains of action potentials. Increased release of ACh, norepinephrine, 5-HT, and/or histamine may also lead to an increase in baseline firing rate, although this excitation will be much less than the enhancement of phasic barrages of EPSPs because of the marked activation voltage dependence of I_{AHP} and I_M. Furthermore, reduction of these two currents will have much less effect on inhibitory postsynaptic potentials or unitary EPSPs because neither of these results in substantial activation of I_{AHP} or I_M.

Convergence and divergence of transmitter actions in the human cerebral cortex complicates our understanding of the control and modulation of neuronal activity. It is likely that in the natural state cortical pyramidal cells are under the constant influence of a dynamically changing array of neuroactive substances. Additive and nonadditive interactions among these substances may allow for subtleties in neuromodulation that could not otherwise occur. Understanding these actions and interactions may facilitate the development of more specific pharmacological therapies for neurological disorders, such as epilepsy, Alzheimer disease, and age-related cognitive decline.

We thank Dr. Dennis Spencer for his collaboration in this project and the patients for their informed consent to the use of the tissue. This work was supported by a grant from the National Institute of Neurological and Communicative Disorders and Stroke, fellowships from the Klingenstein Foundation (D.A.M.), and the American Epilepsy Foundation (A.W.), and by the Jacob Javits Center in Neuroscience.

1. Palacios, J. M., Probst, A. & Cortes, R. (1986) *Trends Neurosci.* **9**, 284–289.
2. Halliwell, J. V. (1986) *Neurosci. Lett.* **67**, 1–6.
3. Pazos, A., Probst, A. & Palacois, J. M. (1987) *Neuroscience* **21**, 97–122.
4. Fastbom, J., Pazos, A., Probst, A. & Palacios, J. M. (1987) *Neuroscience* **22**, 827–839.
5. Schwartz, J.-C., Garbarg, M. & Pollard, H. (1986) in *Handbook of Physiology: The Nervous System*, ed. Bloom, F. E. (Am. Physiol. Soc., Bethesda, MD), Sect. 1, Part 4, pp. 257–316.
6. Mesulam, M.-M. & Geula, C. (1988) *J. Comp. Neurol.* **275**, 216–240.
7. Gaspar, P., Berger, B., Febvert, A., Vigny, A. & Henry, J. P. (1989) *J. Comp. Neurol.* **279**, 249–271.
8. McCormick, D. A. (1989) *J. Neurophysiol.*, in press.
9. Madison, D. V. & Nicoll, R. A. (1982) *Nature (London)* **299**, 636–638.
10. Haas, H. L. & Konnerth, A. (1983) *Nature (London)* **302**, 432–434.
11. Dunwiddie, T. V. (1985) *Int. Rev. Neurobiol.* **27**, 63–139.
12. North, R. A. (1986) *Neuroscience* **17**, 899–907.
13. Colino, A. & Halliwell, J. V. (1987) *Nature (London)* **328**, 73–77.
14. Davies, M. F., Deisz, R. A., Prince, D. A. & Peroutka, S. J. (1987) *Brain Res.* **423**, 347–352.
15. McCormick, D. A. & Prince, D. A. (1988) in *Neurotransmitters and Cortical Function*, eds. Avoli, M., Reader, T. A., Dykes, R. W. & Gloor, P. (Plenum, New York), pp. 287–302.
16. Andrade, R. & Nicoll, R. A. (1988) *J. Physiol.* **394**, 99–124.
17. Nicoll, R. A. (1988) *Science* **241**, 545–551.
18. Foehring, R. C., Schwindt, P. C. & Crill, W. E. (1989) *J. Neurophysiol.* **61**, 245–256.
19. McCormick, D. A. & Pape, H.-C. (1988) *Nature (London)* **334**, 246–248.
20. Andrade, R., Malenka, R. C. & Nicoll, R. A. (1986) *Science* **234**, 1261–1265.
21. Christie, M. J. & North, R. A. (1988) *Br. J. Pharmacol.* **95**, 896–902.
22. McCormick, D. A. (1989) *Trends Neurosci.* **12**, 215–221.
23. McCormick, D. A., Connors, B. W., Lighthall, J. W. & Prince, D.A. (1985) *J. Neurophysiol.* **54**, 782–806.
24. Avoli, M. & Oliver, A. (1989) *J. Neurophysiol.* **61**, 589–606.
25. Madison, D. V. & Nicoll, R. A. (1984) *J. Physiol.* **354**, 319–331.
26. Pennefather, P., Lancaster, B., Adams, P. R. & Nicoll, R. A. (1985) *Proc. Natl. Acad. Sci. USA* **82**, 3040–3044.
27. Brown, D. A. & Adams, P. R. (1980) *Nature (London)* **283**, 673–676.
28. Schwindt, P. C., Spain, W. J. & Crill, W. E. (1989) *J. Neurophysiol.* **61**, 233–244.
29. Lidow, M. S., Goldman-Rakic, P. S., Gallager, D. W., Geschwind, D. H. & Rakic, P. (1989) *Neuroscience*, in press.
30. Brown, D. A. (1988) *Trends Neurosci.* **11**, 294–299.
31. Neher, E. (1988) *Neuroscience* **26**, 727–734.