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Neurotransmitter Modulation of Thalamic Neuronal Firing Pattern

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Thalamic neurons can generate two basic patterns of neuronal activity (burst firing and single spike activity) depending upon the membrane potential of the cell. Here we review the mechanisms of action of acetylcholine (ACh), norepinephrine (NE) and τ-aminobutyric acid (GABA) in the thalamus to show how these agents modulate the firing mode of thalamic neurons. ACh can cause three different responses in the thalamocortical relay cells: a fast nicotinic depolarization; an increase in potassium conductance (muscarinic); and a decrease in membrane potassium conductance (muscarinic). Norepinephrine causes a decrease in membrane potassium conductance. GABA causes an increase in membrane chloride conductance followed by an increase in potassium conductance. The transmitter induced increases in potassium conductance result in the inhibition of single spike activity and the promotion of burst firing, while the decreases in potassium conductance have the opposite effect. GABA-induced increases in chloride conductance inhibited both burst firing and single spike activity. The alterations in ionic currents produced by activation of ascending brainstem cholinergic and noradrenergic systems and local GABAergic circuits can thus have a variety of consequences for regulation of activity in thalamocortical circuits.

In the earliest investigations of the electroencephalogram (EEG), Caton (1875, 1887) and Beck (1890, 1891) noted that the cortical EEG is markedly influenced not only by sensory stimulation but also by the arousal state of the animal. Subsequent research performed by a number of investigators (for review see Brazier, 1980) culminated in the classic findings of Moruzzi, Magoun, Lindsley and Bowden (see Lindsley, Bowden, and Magoun, 1949; Moruzzi and Magoun, 1949) that activation of ascending systems in the brainstem results in a change in forebrain EEG pattern from high-voltage, slow wave activity (which is associated with inattentiveness or slow wave sleep) to low-voltage, high frequency activity (which is typical of that in aroused animals). Subsequent investigations into the origin of the generation of forebrain EEG patterns focused on the thalamus (for review see Andersen and Andersson, 1968). These investigations revealed that the thalamus, and not the cerebral cortex, was the "pacemaker" of the slow wave rhythms. Thus, electrical

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stimulation of certain portions of the thalamus could induce rhythmic activity throughout the forebrain, while lesions of the thalamus would abolish it. Decortication, on the other hand, left a thalamus which retained the ability to generate rhythmic activity.

More recent experiments have emphasized contributions of both intrinsic properties of thalamic neurons and their anatomical interconnections to the generation of rhythmic patterns of neural activity. Both *in vitro* and *in vivo* experiments have revealed that thalamic neurons possess two basic firing modes: burst and single spike firing (Jahnsen and Llinás, 1984a, 1984b; Steriade and Deschênes, 1984). Single spike activity is prevalent whenever the membrane potential (V_m) is depolarized beyond approximately −55 mV (see Figure 1, −53 mV). When thalamic neurons are in this mode of action potential generation, they behave in a manner similar to the "text-book" examples of central neurons: increasing amplitudes of depolarization generate increasing frequencies of firing, while hyperpolarization decreases and eventually inhibits the generation of neuronal activity. However, once the membrane potential is hyperpolarized past the level of approximately −65 mV the inactivation of a low threshold Ca^{++} current (Carbonne and Lux, 1984; Jahnsen and Llinás, 1984a, 1984b; Nowycky, Fox, and Tsien, 1985) is removed and the thalamic neuron begins to fire in bursts of closely spaced Na^{+}-dependent action potentials that ride on a slow Ca^{++}-dependent spike (see Figure 1, −75 mV). Intracellular injection of depolarizing and hyperpolarizing ramp pulses reveal that thalamic neurons generate these burst discharges optimally at a rate of 6–10 Hz, which is similar to the frequency at which thalamic neurons fire *in vivo* during certain stages of sleep (Jahsen and Llinás, 1984a, 1984b; Steriade and Deschênes, 1984).

However, although thalamic neurons possess some of the intrinsic properties necessary to generate 6–10 Hz rhythms in isolation, recent *in vivo* data illustrate the importance of the GABAergic neurons of the nucleus reticularis thalami (n.r.t.), in the coordination, control, and generation of these rhythms within the rest of the thalamus (Steriade and Deschênes, 1984; Steriade, Deschênes, Domich, and Mulle, 1985). Apparently the n.r.t. has an unusually low threshold for generation of rhythmic activity which becomes distributed throughout the rest of the thalamus to which it is connected via the presumed inhibitory synapses of this structure (Mulle, Madariaga, and Deschênes, 1986). Lesions of the n.r.t. disrupt synchronous bursting in thalamic neurons, whereas the n.r.t., when physically isolated from the rest of the thalamus, can generate the appropriate rhythms endogenously (Steriade, Deschênes, Domich, and Mulle, 1985).

Neurotransmitter Actions in Thalamus: Inhibitory, Excitatory or Modulatory?

The presence of an additional firing mode (i.e. bursting) at V_m's negative to

–65 mV in thalamic neurons (see Figure 1, –75 mV) complicates the description of neurotransmitter action in this structure. Neurotransmitters which hyperpolarize a thalamic relay neuron might both inhibit neuronal single spike activity and, by removing the inactivation of the low threshold Ca^{++} current, promote the occurrence of burst discharges (e.g., Figure 1, increase in gK). Likewise, neurotransmitters which depolarize thalamic neurons may enhance the occurrence of single spike activity (an excitatory action), and also *inhibit* the occurrence of burst discharges by depolarizing the membrane potential into the range of inactivation of the low-threshold Ca^{++} current (e.g., Figure 1, decrease in gK). Therefore, the traditional classification of many neurotransmitter responses as either inhibitory or excitatory is not appropriate in the thalamus. Specifically, transmitter-induced increases or decreases in resting potassium currents are very effective in *modulating* the pattern of neuronal activity which thalamic neurons display, and thereby act as a switching or gating mechanism. Ascending neurotransmitter systems from the brainstem have long been implicated in the possible gating of thalamic firing mode (e.g., Moruzzi and Magoun, 1949).

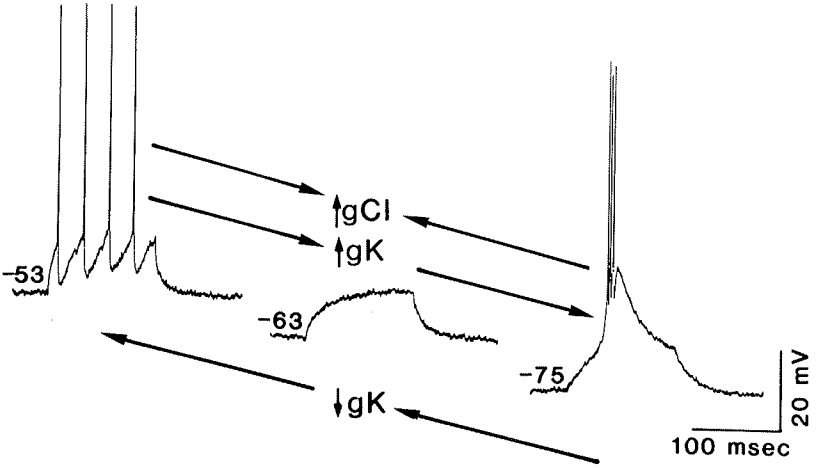

Figure 1: Effect of changes in membrane potential on the firing properties of thalamic neurons. The responses of guinea pig l.g.n.d. neuron to intracellular injection of a depolarizing square pulse while the membrane potential is –53, –63 and –75 mV are illustrated. At –53 mV, depolarizing pulse gives rise to a train of four single action potentials. At –63 mV, the pulse elicits an electrotonic passive response, while at –75 mV, the depolarizing input evokes a slow Ca^{++} spike that triggers a burst of three Na^{++} dependent action potentials. Arrows indicate the effect of increasing or decreasing membrane potassium and chloride conductance on the firing pattern generated by the neuron. Increases in membrane potassium conductance can move the cell out of the single spike firing range (–53 mV) into the passive response zone (–63 mV) or, if large enough, into the region of burst firing (–75 mV). Decreases in membrane potassium conductance can have the opposite effect. In contrast, increases in membrane chloride conductance tend to inhibit all neuronal activity both by moving the membrane potential into the "passive" zone and/or by shunting the membrane resistance.

Brainstem Projections to the Thalamus

The mammalian thalamus receives widespread connections from a number of brainstem nuclei including the locus coeruleus (Lindvall, Bjorklund, Nobin, and Stenevi, 1974; Olschowka, Molliver, Grzanna, Rice, and Coyle, 1981), the pedunculopontine and lateral dorsal tegmental nuclei (Mesulam, Mufson, Wainer, and Levey, 1983; Morrison and Foote, 1986; Woolf and Butcher, 1986) and the median raphe (Morrison and Foote, 1986), which presumably use as neurotransmitters norepinephrine (NE), acetycholine (ACh) and serotonin (5-HT), respectively. Given the central role of the thalamus in the generation and regulation of the overall pattern of activity in the forebrain, and the presence of these transmitter-specific ascending connections from the brainstem, we sought to investigate the possiblity that one or all of these neurotransmitters may be capable of regulating the pattern of activity in the thalamus.

Actions of ACh in the Thalamus

A number of investigations have implicated the ascending cholinergic system of the brainstem in the regulation of not only the excitability, but also the firing pattern, of thalamic neurons (see Singer, 1977; Burke and Cole, 1978; Kayama, Takagi, and Ogawa, 1986). Stimulation of the rat lateral dorsal tegmental nucleus, which contains a high density of cholinergic neurons, results in a slow excitation in the doral lateral geniculate nucleus (l.g.n.d.) similar to that produced by iontophoretic application of ACh. Both the stimulation and ACh-induced increases in l.g.n.d. relay neuron single spike firing are blocked by the local application of the muscarinic antagonist scopolamine (Kayama, Tagaki, and Ogawa, 1986), indicating that the stimulation effect is probably due to the release of ACh. Similar results have also been reported in the cat l.g.n.d. (Francesconi, Muller, and Singer, 1984), while in the cat n.r.t. an ACh-induced inhibitory effect appears to predominate (Dingledine and Kelly, 1977).

In the *in vitro* thalamic slice, application of ACh to guinea pig n.r.t. neurons results in a hyperpolarization and increase in membrane conductance (see Figure 2A). Varying extracellular potassium concentration ($[K]_o$) changed the reversal potential of this hyperpolarization as predicted by the Nernst equation (see Figure 2B), indicating that it is due to an increase in membrane potassium conductance (McCormick and Prince, 1986a). This result was confirmed by the intracellular iontophoresis of Cl^- which failed to alter the response to ACh while dramatically altering the response to GABA (which presumably activates a Cl^- conductance) (see Figure 3).

Applications of ACh to neurons in the guinea pig lateral or medial geniculate nuclei result in a hyperpolarizing response as well as a slow depolarization (McCormick and Prince, 1986b, 1987b). The slow depolarization

is associated with a decrease in membrane conductance, has an extrapolated reversal potential near E_K, and is sensitive to $[K]_o$, indicating that it is due to a decrease in membrane potassium conductance. Interestingly, application of ACh to relay cells of the dorsal division of the cat lateral geniculate nucleus (l.g.n.d.) gives rise to a quite different response: an initial fast excitation

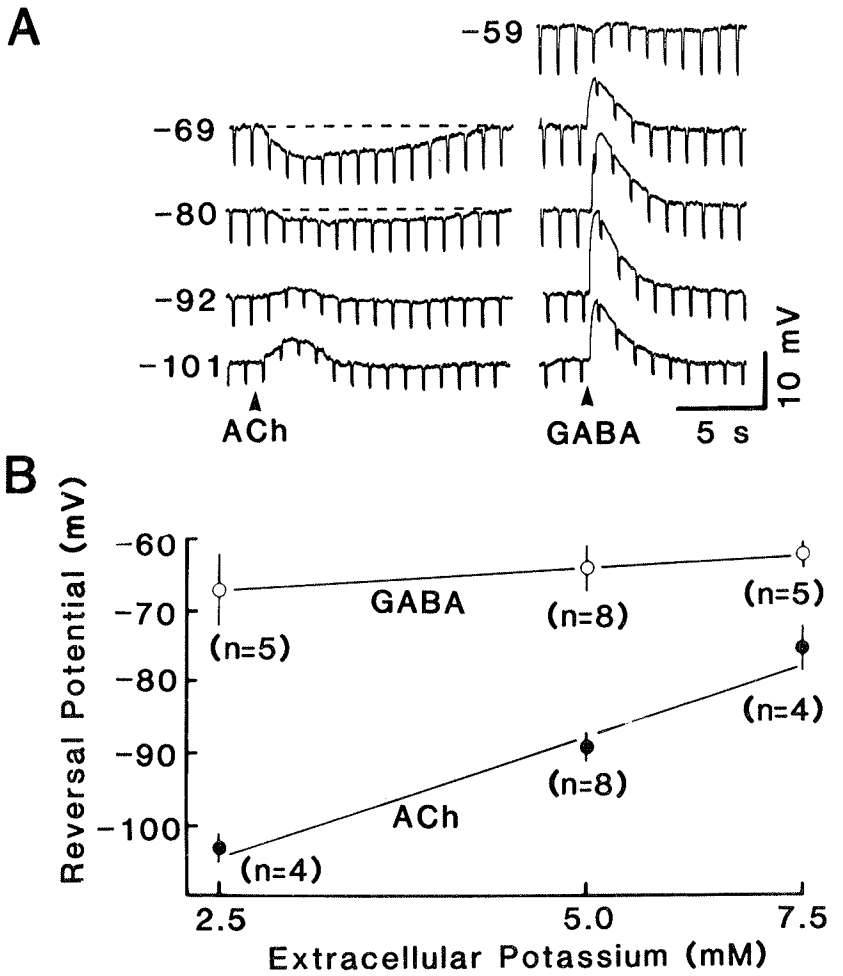

Figure 2: Responses of a nucleus reticularis neuron to ACh and GABA. A: application of ACh causes a hyperpolarization (e.g., –69 mV) which reverses at around –90 mV ($[K]_o$=5.0 mM). GABA, on the other hand, causes a depolarization which reverses at approximately –59 mV in this cell. B: plot of reversal potentials versus $[K]_o$ indicates that the ACh responses, but not the GABA, are mediated by an increase in membrane gK (from McCormick and Prince, 1986a). Reprinted with permission from *Nature*, Vol. 319, 402–405. Copyright © 1986. Macmillan Magazines Limited.

followed by a slow depolarization. The fast excitation is assocated with an increase in membrane conductance and appears to be mediated by nicotinic receptors, while the slow depolarization is associated with a decrease in conductance and otherwise appears identical to the ACh-induced slow depolarization of the guinea pig l.g.n.d. Applications of the muscarinic specific agonist acetyl-β-methylcholine (MCh) to cat l.g.n.d. neurons typically result in only the slow depolarizing response, although this is occasionally preceded by a weak hyperpolarizing response. Applications of ACh to l.g.n.d. neurons in the *rat* evoke the slow depolarization only (McCormick and Prince, 1986b, 1987b).

The reason for these species differences is unknown. It may not be appropriate to compare the relay neurons of the rat or guinea pig l.g.n.d. to

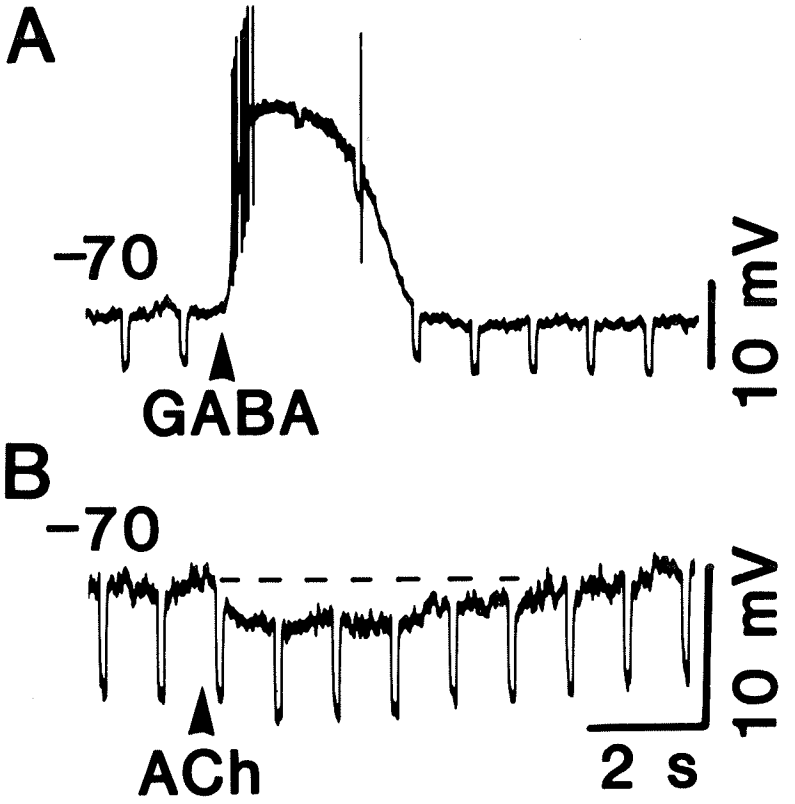

Figure 3: Intracellular injection of KCl dramatically alters the response of a nucleus reticularis neuron to GABA but not to ACh. A: the fast excitatory depolarizing response of this neuron to GABA after intracellular iontophoresis of Cl^-. B: application of ACh to the neuron of A results in the typical hyperpolarizing response which was subsequently found to reverse at –90 mV.

those of layer A and A_1 of the cat l.g.n.d. However, all three species studied did exhibit the slow depolarizing response to ACh in the l.g.n.d. and it is this response which appears to be activated by endogenous excitation of the cholinergic system (Kayama, Takagi, and Ogawa, 1986).

Actions of NE in the Thalamus

Electrical or chemical stimulation of the locus coeruleus (l.c.), or local iontophoretic application of NE *in vivo*, results in the slow excitation and increased responsiveness of both lateral geniculate and nucleus reticularis neurons (Kayama, 1985, Kayama, Negi, Sugitani, and Iwama, 1982; Nakai and Takaori, 1974; Rogawski and Aghajanian, 1980, 1982). Furthermore, both of these effects are blocked by the local iontophoretic application of α_1 adrenoceptor antagonists, indicating that the l.c. stimulation effect is due to the release of NE (Kayama, 1985; Rogawski and Aghajanian, 1980, 1982).

We have found that application of NE to neurons located in the guinea pig l.g.n.d., medial geniculate nucleus (m.g.n.), n.r.t., anteroventral nucleus (a.v.) or parataenial nucleus (p.t.) results in a slow depolarization which is associated with a decrease in input conductance. Analysis of I–V plots before and after NE application reveals that the response has an extrapolated reversal potential of around –89 mV in 5 mM $[K]_o$ (McCormick and Prince, 1986b). The reversal potential of the NE-induced slow depolarization varies as a Nernstian function of $[K]_o$, indicating that the depolarization results from a decrease in membrane conductance to K (gK) similar to that reduced by ACh. Furthermore, preliminary investigations indicate that the response is associated with activation of α_1 adrenoceptors, as previously reported *in vivo* (Rogawski and Aghajanian, 1982).

Interactions Between ACh and NE Responses

NE and ACh are known to co-activate a number of intracellular second messenger systems in either an additive or an antagonistic manner (e.g. see Nishizuka, 1984). For this reason, and because of the apparent similarity in the slow depolarizations evoked by these agents (see above), we tested the possibility that the ACh and NE responses may interact in a non-additive manner. Application of the muscarinic agonist methacholine (MCh) to guinea pig l.g.n.d. neurons evoked a typical hyperpolarizing and slow depolarizing sequence; however the same MCh application resulted in only the hyperpolarizing response when delivered during a concurrent application of NE. This result indicates that the ACh and NE-induced slow depolarizing responses are non-additive: maximal activation of one results in a decreased amplitude of the other, even when variations in the membrane potential and input resistance are controlled. The most parsimonious explanation for this

result is that NE and ACh either close the same class of potassium channel, share a common intracellular second messenger, or both. NE is known to stimulate phosphatidylinositol (P–I) turnover in l.g.n.d. by activation of α_1 adrenoceptors (Kemp and Downes, 1986). ACh also potently stimulates P–I turnover, and in some systems this intermediary appears to couple muscarinic receptor activation to the cholinergic slow depolarization (Higashida and Brown, 1986).

Actions of GABA

Gamma-aminobutyric acid (GABA) is contained and presumably released by two different classes of neurons in the thalamus: n.r.t. neurons and intranuclear interneurons (Fitzpatrick, Penny, and Schmechel, 1984; Houser, Vaughn, Barber, and Roberts, 1980). Stimulation of the n.r.t., either electrically or chemically, results in the inhibition of affected relay neurons (Kayama, 1985; Mushiake, Shosaku, and Kayama, 1984). Similarly, activation of optic tract fibers results in excitation followed by inhibition of l.g.n.d. relay cells, the latter resulting in large part from the activation of GABAergic interneurons intrinsic to the l.g.n.d.

Application of GABA to n.r.t. neurons (which receive collaterals of other n.r.t. neurons) results in a marked increase in membrane conductance and a depolarization which reverses at approximately –60 to –65 mV (see Figure 2A, 2B) (McCormick and Prince, 1986a). By contrast, application of GABA to guinea pig or cat l.g.n.d. relay neurons results in two phases of hyperpolarization. The initial phase is rapid in both onset and offset and reverses at approximately –70 to –75 mV, while the later phase is much slower and longer lasting (2–20 seconds) and reverses near E_K (McCormick and Prince, 1986b and unpublished observations). Applications of the $GABA_B$ selective agonist baclofen also result in a slow hyperpolarization which reverses near E_K, while application of the $GABA_A$ selective agonist muscimol evokes a hyperpolarization which reverses at approximately –70 to –75 mV.

We have not yet thoroughly investigated the ionic mechanisms of these two GABA responses in the thalamus. However, by analogy with the findings of Newberry and Nicoll (1985) in the hippocampus, our data suggest that GABA causes an increase in Cl^- conductance through activation of $GABA_A$ receptors and an increase in K conductance through activation of $GABA_B$ receptors in l.g.n.d. relay neurons.

Effects of ACh, NE, and GABA on Thalamic Information Processing

As mentioned above, thalamic neurons possess two basic modes of action potential generation: at membrane potentials depolarized to –55 mV they

generate trains of single spikes to excitatory inputs, while at membrane potentials negative to approximately −65 mV thalamic neurons fire bursts of action potentials to the same input (Figure 1, −53 versus −75 mV). If the membrane potential is maintained entirely within the range between −55 and −65 mV, the cells will remain silent (Figure 1, −63 mV).

The ability of ACh, NE, and GABA to change the membrane potential over these ranges raises the interesting possibility that such putative neurotransmitters may regulate not only the occurrence and rate of discharge of thalamic neurons to any given stimulus, but also the *pattern* of spike discharge response (e.g., single spikes or bursts of spikes). Each of these transmitters has more than one post-synaptic action; potential effects are therefore diverse. We have reviewed these below.

Effect of ACh or GABA-Induced Increases in gK

In some, but not all, regions of the thalamus both ACh and GABA can cause an increase in neuronal membrane gK which results in a hyperpolarization towards E_K (McCormick and Prince, 1986a, 1986b, 1987b and unpublished observations). This hyperpolarization interacts with the intrinsic properties of these neurons to give rise to a number of possible effects on their output. If the thalamic neuron is in the single spike firing mode (e.g., with V_m positive to about −55 mV), and if the ACh or $GABA_B$ hyperpolarization is on the order of 5–10 mV or so, all single spike activity will be blocked and a simple inhibitory response will be evident (e.g., Figure 1, increase in gK). However, with the neuron at the same resting potential, a larger (e.g., 15–20 mV) hyperpolarization will not only inhibit the single spike activity, but also remove the inactivation of the low-threshold Ca^{++} current and thus change the response of the neuron from single spikes to bursts of spikes (Figure 1, increase in gK and Figure 4) (McCormick and Prince, 1986a, 1987b). In this manner, the ACh or GABA-induced increase in gK can, through effects on V_m, regulate the pattern of activity generated by the thalamic neuron. However, due to the associated increase in membrane conductance, the situation is somewhat more complicated. For example, if the neuron is already in the burst generating mode, application of a small amount of ACh or baclofen will evoke a small hyperpolarization and consequently increase the amplitude of the burst discharge by further removing inactivation of the low threshold Ca^{++} current. However, with a much larger dose of ACh or baclofen, the resultant increase in input conductance (G_i) associated with the larger hyperpolarization can inhibit neuronal activity altogether. These data raise an important question: assuming that ACh and GABA cause increases in gK *in vivo*, does this action induce burst firing, inhibit burst firing, or both? The experiments of Steriade and Deschênes (1987, this issue) suggest that hyperpolarization of n.r.t. evoked by stimulation of the brainstem in the cat, can *inhibit* burst discharges

if the neurons are already in the burst discharge mode. However, previous data of Dingledine and Kelly (1977) reveal that similar brainstem stimulation delivered when n.r.t neurons are in the single spike mode will inhibit single spike activity and promote the occurrence of burst discharges, an effect which we have also reported from experiments performed *in vitro* (McCormick and Prince, 1986a). Therefore, there is experimental evidence for the occurrence of both possible consequences of a transmitter-induced increase in gK, and further work is required before we can determine which, if not both, of these effects occur naturally.

Effect of ACh and NE-Induced Decrease in gK

Both ACh and NE can cause slow depolarizations in some portions of the thalamus by decreasing a resting potassium conductance. As might be expected, this slow depolarization, in many respects, has effects on thalamic firing that are opposite to those of the ACh or GABA-induced increase in gK. If the thalamic neurons are in, or near, the single spike firing mode, the ACh or NE-induced decrease in gK results in an enhanced response to depolarizing inputs (McCormick and Prince, 1986a). This occurs not only as a consequence

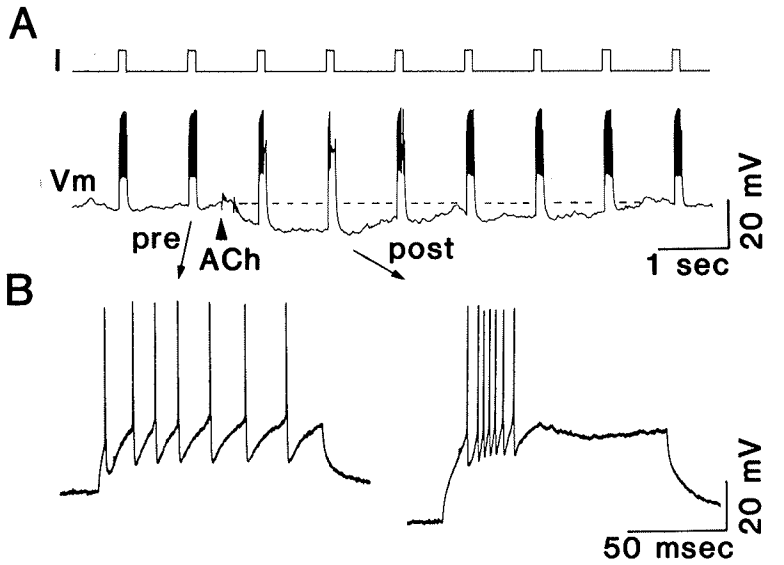

Figure 4: Effect of ACh-induced increase in gK on the firing mode of thalamic neurons. A: each intracellular injection of a depolarizing current pulse into a guinea pig n.r.t. neuron at 1 Hz results in a train of seven action potentials (expanded for detail in B, left). Application of ACh causes a typical hyperpolarization and changes the response of the neuron from a train of action potentials to a high frequency burst of seven action potentials (B, right) [from McCormick and Prince, 1986c]. Reprinted with permission from *Trends in Pharmacological Sciences Supplement* © 1986. Elsevier Science Publishers.

of the change in V_m, but also because of the decrease in G_i and associated lengthening of the slow membrane time constant. These effects shorten the electrotonic length of the thalamic neuron and increase its excitability by allowing currents generated by more phasic p.s.p.s. to cause larger amplitude changes in V_m at the site of action potential generation.

By contrast, if the thalamic neuron is in the burst firing mode, the ACh or NE-induced slow depolarization will cause a potent blockade of the burst activity (McCormick and Prince, 1987b). If the depolarizing response is small (ca. 5–10 mV), burst activity will be eliminated without the generation of single spike activity (Figure 1, decrease gK). However, if the depolarization is larger (ca. 15–20 mV), not only will the burst activity be inhibited, but single spike activity will be generated (Figure 1, decrease gK). This effect is very well illustrated by the action of NE on the neurons of the parataenial nucleus (p.t.). Many of the neurons in this nucleus are spontaneously bursting at a rate of approximately 1–2 Hz in the *in vitro* slice (see Figure 5). This abnormal pattern of burst discharge is seen in many regions of the cat thalamus after disconnection from the pacemaker n.r.t. (Steriade, Deschênes, Domich, and Mulle, 1985). Application of NE to p.t. neurons results in a complete blockade of the regular burst activity followed by the generation of trains of single spikes.

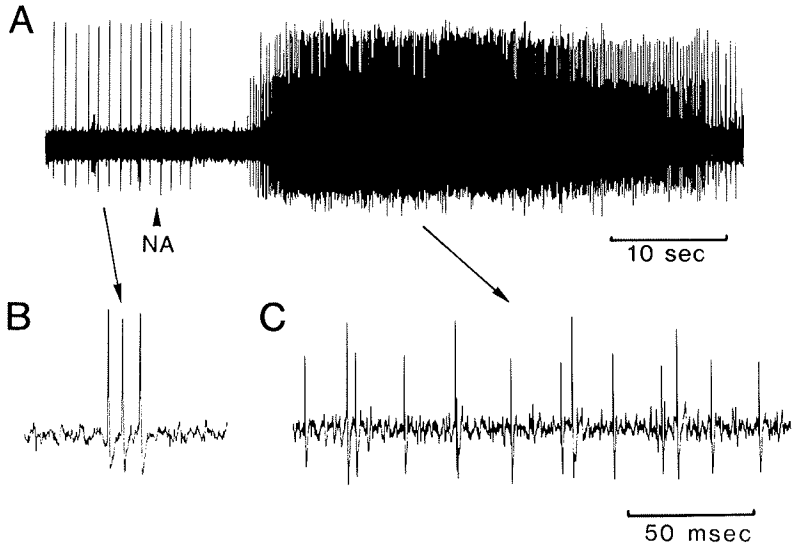

Figure 5: Norepinephrine inhibits burst firing and promotes single spike activity in the thalamus. A: extracellular recording of a spontaneously bursting neuron in the parataenial thalamic nucleus before and after local application of norepinephrine (NA; noradrenaline). B: burst of action potentials in A expanded for detail. C: section of A after application of NA expanded for detail. Application of norepinephrine initially inhibits all burst firing (A) and then leads to generation of single spike activity by two separate neurons.

Slowly, over the next 1–3 minutes, the neurons revert to the burst firing mode (not shown). Intracellular recordings show that these effects result largely from a NE-induced slow depolarization which moves V_m out of the burst firing range and above threshold for the generation of single spike activity.

Effect of ACh-Induced Rapid Depolarization and GABA-Induced Rapid Hyperpolarization

As mentioned above, ACh and GABA can not only generate slow responses, but also events which are more typical of phasic p.s.p.s. The ACh-induced rapid nicotinic excitation can generate either single spikes or a burst of spikes, depending upon the membrane potential of the neuron.

The fast GABA-induced hyperpolarization, on the other hand, inhibits all spike activity, both bursting and single spikes, because it moves V_m toward the Cl^- reversal potential of approximately –65 to –75 mV (Figures 1 and 2). The associated large increase in G_i tends to depress burst firing.

Implications for the Ascending and Local Control of Thalamic Relay Neuron Excitability

The ability of ACh, NE, and GABA to not only excite or inhibit thalamic neuronal activity, but also to *modulate* the pattern of activity generated has important implications for the ascending and local control of the excitability of thalamic relay neurons and therefore, of the entire forebrain. We would like to consider the consequences of GABAergic, cholinergic and noradrenergic actions in the mammalian thalamus on the generation and processing of neuronal activity in the forebrain.

GABA

GABA releasing neurons are localized within two main thalamic cell groups: (1) the n.r.t. and (2) intranuclear interneurons (Fitzpatrick, Penny, and Schmechel, 1984; Houser, Vaughn, Barber, and Roberts, 1980). The n.r.t. surrounds much of the dorso-medial aspect of the thalamus and contains only GABAergic cells. Both thalamo-cortical and cortico-thalamic axons give rise to collaterals as they perforate the n.r.t (Jones, 1985). Axons of n.r.t. neurons themselves innervate diverse regions of the thalamus and also project locally within the n.r.t. itself (Steriade, Parent, and Hada, 1984). Thus, anatomically, the n.r.t. forms an external GABAergic system which provides both feedback (in the case of thalamo-cortical transmission) and feedforward (in the case of cortico-thalamic transmission) inhibitory circuits. In addition, dendro-dendritic synapses between n.r.t. neurons in higher mammals may form an anatomic substrate for the synchronization of local regions within the nucleus (Deschênes, Madariaga-Domich, and Steriade, 1985).

In higher mammals (e.g., cat, monkey), approximately 20–30% of neurons in the thalamic relay nuclei are also GABAergic (Penny, Fitzpatrick, Schmechel, and Diamond, 1983), whereas in the rat and rabbit only the l.g.n.d. contains its full complement of GABAergic cells (Ohara, Lieberman, Hunt, and Wu, 1983; Penny, Conley, Schmechel, and Diamond, 1984). GABAergic intranuclear neurons are local circuit interneurons which not only form dendro-dendritic synapses with relay cells, but also possess axons that project locally in the neuropil (Hamos, Van Horn, Raczkowski, Uhlrich, and Sherman, 1985).

The n.r.t. GABAergic system and the local circuit GABAergic system may be used for very different types of information processing (Koch, 1985; Sherman and Koch, 1986). The n.r.t. appears to be critically involved in the coordination and dispersion of thalamic rhythms (Steriade, Deschênes, Domich, and Mulle, 1985; see chapter by Steriade and Deschênes in this issue for a further explanation of this possibility). The local circuit GABAergic system, on the other hand, may be involved in local visual channel-to-channel inhibition (through the GABAergic neuron's locally ramifying axon) as well as in the sculpting of inputs from the retina (through the synaptic triadic relationships) [Sherman and Koch, 1986].

The ability of GABA to cause increases in membrane conductance to K ions (through $GABA_B$ receptors) adds a new twist to the operation of this system. Compared to the changes in gCl^- elicited by activation of $GABA_A$ receptors, $GABA_B$-mediated increases in potassium conductance are slower in onset, longer lasting, generally do not cause as large of an increase in membrane conductance (i.e., they do not "shunt" the input resistance), and can drive the membrane potential of the neuron to more negative V_ms. These differences in attributes of the $GABA_A$ and $GABA_B$ systems allow them to be useful for entirely different physiological functions. Activation of the $GABA_A$ receptors causes rapid, local circuit inhibition, whereas activation of $GABA_B$ receptors may have a more global and modulatory influence. GABA-mediated increases in potassium conductance may be very effective in hyperpolarizing the membrane potential of the target neuron without causing a concomitant large shunt of the neuron's input resistance (Koch, 1985). This effect may not only be useful in setting the synaptic transfer ratio of the relay neuron, but may also serve to switch the firing pattern from single spike activity to burst generation (e.g., Figure 4), which could be very useful in the coordination of n.r.t. neurons during the generation of spindling waves. The anatomic and physiologic diversity of the thalamic GABAergic system may allow it to serve a number of purposes which we are only beginning to understand.

Norepinephrine

Neurons of the locus coeruleus (l.c.) discharge at an average rate that is directly proportional to the level of attention (e.g., vigilance) which the animal

is giving to events in the external world (reviewed by Aston-Jones, 1985; Jacobs, 1986). Thus, the average firing rate of l.c. neurons is highest in active waking and progressively lower in quiet waking and slow wave sleep; l.c. cells are nearly silent in paradoxical sleep (Aston-Jones and Bloom, 1981). Furthermore, a large proportion of l.c. neurons respond synchronously to arousing sensory stimuli with a burst of neuronal activity (Aston-Jones and Bloom, 1981). The overall firing rate of l.c. neurons is directly proportional to the activity of the peripheral sympathetic nervous system (Elam, Svensson, and Thorén, 1986; Reiner, 1986), thereby supporting the hypothesis that the l.c. is a portion of the sympathetic system which has the brain as its end-organ (Amaral, 1977).

Transfer of excitatory inputs from the periphery through the thalamus to the cerebral cortex varies markedly during various levels of behavioral arousal (Coenen and Vendrik, 1972; Livingstone and Hubel, 1981). Thus, during slow wave sleep, while thalamic neurons are generating burst discharges, information arriving from the periphery is effectively scrambled and is not accurately transferred to the cerebral cortex, while during states of wakefulness and attentiveness a much more faithful relay of information occurs (Livingstone and Hubel, 1981). This result indicates that although a decrease in membrane potential can transiently increase the responsiveness of a thalamic neuron to an excitatory input by de-inactivating burst discharges, the subsequent ongoing generation of rhythms has a disruptive or "scrambling" influence on the transfer of information. The disruptive influence of oscillating rhythm generation on thalamic relay function may result from the fact that the membrane potential of the neuron is usually in a hyperpolarized region below single spike firing threshold. A barrage of phasic e.p.s.p.s may be capable of depolarizing the neuron sufficiently to inhibit burst firing, but because of the higher membrane potential and the presence of a "silent zone" between the burst firing and single spike firing modes, the neuron will exhibit a substantially lower transfer ratio, and therefore will not respond as briskly to the input.

Given the present results, and those reviewed above, we suggest that activation of the l.c. thalamic NE system during states of increased arousal and vigilance (or increased "sympathetic tone") is associated with an increased release of NE which in turn evokes a decrease in resting gK in thalamic neurons. During the resulting depolarization the low threshold Ca^{++} current underlying burst firing is inactivated and the membrane potential of relay neurons is brought closer to the single spike firing mode, leading to an increase in the coherent transfer of information to the cerebral cortex.

Acetylcholine

The behavioral consequences of modulation of thalamic neuronal activities by ACh are less clear than for GABA or NE. This neurotransmitter/

neuromodulator can cause up to three different postsynaptic responses, and the activity of the brainstem cholinergic neurons during different behavioral states has not yet been rigorously studied. The cholinergic slow depolarization of thalamic relay neurons, which appears to be identical to that induced by NE, is also identical in its effects on thalamic firing pattern: cholinergic slow depolarization promotes single spike firing and potently inhibits burst firing. In this way the ascending cholinergic system could be used to facilitate the flow of information through the thalamus to the cerebral cortex as has been proposed by numerous investigators (Burke and Cole, 1978; Kayama, Tagaki, and Ogawa, 1986; Sherman and Koch, 1986; Singer, 1977; Steriade and Deschênes, 1984).

By contrast, the ACh-induced hyperpolarization, prevalent in the n.r.t., may inhibit single spike activity, while promoting burst firing. However, recent results by Steriade and colleagues (Steriade and Deschênes, 1987, this issue) indicate that the presumed cholinergic input, if strongly activated, can inhibit burst firing in the n.r.t. presumably through the associated increase in membrane conductance, which would have a shunting effect on the low-threshold Ca^{++} current. In this manner, the ascending cholinergic input may be capable of inhibiting all activity of n.r.t. neurons, while promoting single spike activity in relay neurons through a direct slow depolarization. However, to make matters even more complicated, ACh can also hyperpolarize the thalamic relay neurons, which may induce or inhibit burst firing in these cells, depending on the size of the associated increase in gK.

In the peripheral nervous system, a similar set of responses is evoked by ACh application (i.e., fast nicotinic excitation, muscarinic hyperpolarization, muscarinic slow depolarization) [e.g., see Adams, Jones, Pennefather, Brown, Koch, and Lancaster, in press]. Frequency dependent responses are elicited by orthodromic stimulation of the cholinergic fibers which innervate frog sympathetic ganglia: typical nicotinic e.p.s.p.s follow single stimuli and substantial slow hyperpolarizations and/or slow depolarizations are evoked by trains of stimuli (reviewed by Adams et al., 1986). If a similar situation were to exist in the thalamus, then we might expect that low frequency activity of the brainstem cholinergic neurons would result in the generation of nicotinic e.p.s.p.s in thalamic neurons, whereas higher frequency activity may evoke slow hyperpolarizations or slow depolarizations.

Numerous questions concerning the normal function of the ascending cholinergic system must be addressed before we will fully understand its influence on cellular activities in the forebrain. For example, are the three different responses of relay cells to ACh all activated by the same cholinergic fibers, or by functionally different ones? When, in the normal behavior of the animal, are the brainstem cholinergic neurons active and why? Does the inhibition of forebrain rhythmic activity occur because of a hyperpolarization of n.r.t. neurons, depolarization of n.r.t. and relay neurons, or both? Future *in*

vivo and *in vitro* investigations into these and other questions will allow us to gain a much better understanding of the control of these complicated cellular actions and interactions.

References

Adams, P.R., Jones, S.W., Pennefather, P., Brown, D.A., Koch, C., and Lancaster, B. (in press). Slow synaptic transmission in frog sympathetic ganglia. *Journal of Experimental Biology.*

Amaral, D.G. (1977). The locus coeruleus: Neurobiology of a central noradrenergic nucleus. *Progress in Neurobiology, 9*, 147–196.

Andersen, P., and Andersson, S.A. (1968). *Physiological basis of the alpha rhythm.* New York: Appleton, Century and Crofts.

Aston-Jones, G. (1985). Behavioral functions of locus coeruleus derived from cellular attributes. *Physiological Psychology, 13*, 118–126.

Aston-Jones, G., and Bloom, F.E. (1981). Norepinephrine-containing locus coeruleus neurons in behaving rats exhibit pronounced responses to non-noxious environmental stimuli. *Journal of Neuroscience, 1*, 887–900.

Beck, A. (1890). Die bestimmung der localisation der gehirn- und ruckenmarkfunctionen vermittelst der electischen ershceinungen. *Zentralblatt für Physiologie, 4*, 473–476.

Beck, A. (1891). Oznacznie locaklizacyi w mozgu i rdzeniu za pomoca zjawisk electrycznych. *Rozprawy Wydzialu Matematyczno-Przyrodniczego Polskiej Akademji Umiejetnosci*, Series 11, *1*, 186–232. English translation: (1973).: The determination of localizations in the brain and spinal cord with the aid of electrical phenomena. *Acta Neurobiologiae Experimentalis* (Warsaw), [Supplement], *3*, 1–59.

Brazier, M.A.B. (1980). Trails leading to the concept of the ascending reticular system: The state of knowledge before 1949. In J.A. Hobson and M.A.B. Brazier (Eds.), *The reticular formation revisited.* New York: Raven Press.

Burke, W., and Cole, A.W. (1978). Extraretinal influences on the lateral geniculate nucleus. *Review of Physiological and Biochemical Pharmacology, 80*, 105–166.

Carbonne, E., and Lux, H.D. (1984). A low voltage-activated, fully inactivating Ca channel in vertebrate sensory neurons. *Nature, 310*, 501–502.

Caton, R. (1875). The electrical currents of the brain. *British Medical Journal, 2*, 278.

Caton, R. (1887). Researches on electrical phenomena of cerebral grey matter. In J.B. Hamilton (Ed.), *Ninth International Medical Congress*, 246–249.

Coenen, A.M.L., and Vendrik, A.J.H. (1972). Determination of the transfer ratio of cat's geniculate neurons through quasi-intracellular recordings and the relation with the level of arousal. *Experimental Brain Research, 14*, 227–242.

de Lima, A.D., Montero, V.M., and Singer, W. (1985). The cholinergic innervation of the visual thalamus: An EM immunocytochemical study. *Experimental Brain Research, 59*, 206–212.

Deschênes, M., Hu, B., and Steriade, M. (1986). The effect of mesencephalic reticular stimulation of relay neurons of the dorsal lateral geniculate. *Society for Neuroscience Abstracts, 12*, 854.

Deschênes, M., Madariaga-Domich, A., and Steriade, M. (1985). Dendrodendritic synapses in the cat reticularis thalami: A structural basis for thalamic spindle synchronization. *Brain Research, 334*, 165–168.

Dingledine, R., and Kelly, J.S. (1977). Brain stem stimulation and the acetylcholine-evoked inhibition of neurons in the feline nucleus reticularis thalami. *Journal of Physiology, 271*, 135–154.

Elam, M., Svensson, T.H., and Thorén, P. (1986). Locus coeruleus neurons and sympathetic nerves: Activation by cutaneous sensory afferents. *Brain Research, 366*, 254–260.

Fitzpatrick, D., Penny, G.F., and Schmechel, D.E. (1984). Glutamic acid decarboxylase-immunoreactive neurons and terminals in the lateral geniculate nucleus of the cat. *Journal of Neuroscience, 4*, 1809–1829.

Francesconi, W., Muller, C.M., and Singer, W. (1984). Acetylcholine mediates the effects of mesencephalic reticular formation stimulation in the dorsal geniculate nucleus of the cat. *Neuroscience Letters Supplement, 18*, S309.

Hamos, J.E., Van Horn, S.C., Raczkowski, D., Uhlrich, D.J., and Sherman, S.M. (1985). Synaptic connectivity of a local circuit neuron in lateral geniculate nucleus of the cat. *Nature, 317*, 618–621.

Higashida, H., and Brown, D.A. (1986). Two polyphophatidylinositide metabolites control two K^+ currents in a neuronal cell. *Nature, 323*, 333–335.

Houser, C.R., Vaughn, J.E., Barber, R.P., and Roberts, E. (1980). GABA neurons are the major cell type of the nucleus reticularis thalami. *Brain Research, 200*, 341–354.

Jacobs, B.L. (1986). Single unit activity of locus coeruleus neurons in behaving animals. *Progress in Neurobiology, 27*, 183–194.

Jahnsen, H., and Llinás, R. (1984a). Electrophysiological properties of guinea-pig thalamic neurons: An *in vitro* study. *Journal of Physiology, 349*, 205–226.

Jahnsen, H., and Llinás, R. (1984b). Ionic basis for the electroresponsiveness and oscillatory properties of guinea-pig thalamic neurons *in vitro*. *Journal of Physiology, 349*, 227–247.

Jones, E.G., (1985). *The thalamus*. New York: Plenum Press.

Kayama, Y. (1985). Ascending, descending and local control of neuronal activity in the rat lateral geniculate nucleus. *Vision Research, 25*, 339–347.

Kayama, Y., Negi, T., Sugitani, M., and Iwama, K. (1982). Effects of locus coeruleus stimulation on neuronal activities of dorsal lateral geniculate nucelus and perigeniculate nucleus of the rat. *Neuroscience, 7*, 655–666.

Kayama, Y., Tagaki, M., and Ogawa, T. (1986). Cholinergic influence of the lateral dorsal tegmental nucleus on neuronal activity in the rat lateral geniculate nucleus. *Journal of Neurophysiology, 56*, 1297–1309.

Kemp, J.A., and Downes, C.P. (1986). Noradrenaline-stimulated inositol phospholipid breakdown in rat dorsal lateral geniculate nucleus neurons. *Brain Research, 371*, 314–318.

Koch, C. (1985). Understanding the intrinsic circuitry of the cat's LGN: Electrical properties of the spine-triad arrangement. *Proceedings of the Royal Society of London*, Series B, *225*, 391–398.

Lindsley, D.B., Bowden, J.W., and Magoun, H.W., (1949). Effect upon the EEG of acute injury to the brain stem activating system. *Electroencephalography and Clinical Neurophysiology, 2*, 483–498.

Lindvall, O., Bjorklund, A., Nobin, A., and Stenevi, U. (1974). The adrenergic innervation of the rat thalamus as revealed by the glyoxylic acid fluorescence method. *Journal of Comparative Neurology, 154*, 317–348.

Livingstone, M.S., and Hubel, D.H. (1981). Effects of sleep and arousal on the processing of visual information in the cat. *Nature, 291*, 554–561.

McCormick, D.A., and Prince, D.A. (1986a). Acetylcholine induces burst firing in thalamic reticular neurons by activating a potassium conductance. *Nature, 319*, 402–405.

McCormick, D.A., and Prince, D.A. (1986b). Mechanisms of ascending control of thalamic neuronal activities: Acetylcholine and norepinephrine. *Society for Neuroscience Abstracts, 12*, 903.

McCormick, D.A., and Prince, D.A. (1986c). Pirenzepine discriminates among ioinic responses to acetylcholine in guinea-pig cerebral cortex and reticular nucleus of thalamus. *Trends in Pharmacological Sciences, Supplement*, 72–77.

McCormick, D.A., and Prince, D.A. (1987a). Acetylcholine causes rapid nicotinic excitation in the medial habenular nucleus of the guinea pig, *in vitro*. *Journal of Neuroscience, 7*, 742–752.

McCormick, D,A., and Prince, D.A. (in press). Actions of acetylcholine in the guinea pig and cat medial and lateral geniculate nuclei, *in vitro*. *Journal of Physiology*.

Mesulam, M-M., Mufson, E.J., Wainer, B.H., and Levey, A.I. (1983). Central cholinergic pathways in the rat: An overview based on an alternative nomenclature (Ch1–Ch6). *Neuroscience, 4*, 1185–1201.

Morrison, J.H., and Foote, S.L. (1986). Noradrenergic and serotoninergic innervation of cortical, thalamic, and tectal visual structures in old and new world monkeys. *Journal of Comparative Neurology, 243*, 117–138.

Moruzzi, G., and Magoun, H.W. (1949). Brain stem reticular formation and activation of the EEG. *Electroencephalography and Clinical Neurophysiology, 1*, 455–473.

Mulle, C., Madariaga, A., and Deschênes, M. (1986). Morphology and electrophysiological properties of reticularis thalami neurons in cat: *In vivo* study of a thalamic pacemaker. *Journal of Neuroscience, 6*, 2134–2145.

Mushiake, S., Shosaku, A., and Kayama, Y. (1984). Inhibition of thalamic ventrobasal complex neurons by glutamate infusion into the thalamic reticular nucleus in rats. *Journal of Neuroscience Research*, *12*, 93–100.

Nakai, Y., and Takaori, S. (1974). Influence of norepinephrine-containing neurons derived from the locus coeruleus on lateral geniculate neuronal activities of cats. *Brain Research*, *71*, 47–60.

Newberry, N.R., and Nicoll, R.A. (1985). Comparison of the action of baclofen with gamma-aminobutyric acid on rat hippocampal pyramidal cells, *in vitro*. *Journal of Physiology*, *360*, 161–185.

Nishizuka, Y. (1984). Turnover of inositol phospholipids and signal transduction. *Science*, *225*, 1365–1370.

Nowycky, M.C., Fox, A.P., and Tsien, R.W. (1985). Three types of neuronal calcium channel with different calcium agonist sensitivity. *Nature*, *316*, 440–443.

Ohara, P.T., Lieberman, A.R., Hunt, S.P., and Wu, J-Y. (1983). Neural elements containing glutamic acid decarboxylase (GAD) in the dorsal lateral geniculate nucleus of the rat: Immunohistochemical studies by light and electron microscopy. *Neuroscience*, *8*, 189–211.

Olschowka, J.A., Molliver, M.E., Grzanna, R., Rice, F.L., and Coyle, J.T., (1981). Ultrastructural demonstration of noradrenergic synapses in the rat central nervous system by dopamine-β-hydroxylase immunocytochemistry. *The Journal of Histochemistry and Cytochemistry*, *29*, 271–280.

Penny, G.R., Fitzpatrick, D., Schmechel, D.E., and Diamond, I.T. (1983) Glutamic acid decarboxylase-immunoreactive neurons and horseradish peroxidase-labeled projection neurons in the ventral posterior nucleus of the cat and *galago senegalensis*. *The Journal of Neuroscience*, *3*, 1868–1887.

Penny, G.R., Conley, M., Schmechel, D.E., and Diamond, I.T. (1984). The distribution of glutamic acid decarboxylase immunoreactivity in the diencephalon of the opposum and rabbit. *The Journal of Comparative Neurology*, *228*, 38–56.

Phillis, J.W. (1971). The pharmacology of thalamic and geniculate neurons. *International Review of Neurobiology*, *14*, 1–48.

Reiner, P.B. (1986). Correlational analysis of central noradrenergic neuronal activity and sympathetic tone in behaving cats. *Brain Research*, *378*, 86–96.

Rogawski, M.A., and Aghajanian, G.K. (1980). Modulation of lateral geniculate neuron excitability by noradrenaline microiontophoresis or coeruleus stimulation. *Nature*, *287*, 731–734.

Rogawski, M.A., and Aghajanian, G.K., (1982). Activation of lateral geniculate neurons by locus coeruleus or dorsal noradrenergic bundle stimulation: Selective blockade by the Alpha 1-adrenoceptor antagonist prazosin. *Brain Research*, *250*, 31–39.

Sherman, S.M., and Koch, C. (1986). The control of retinogeniculate transmission in the mammalian lateral geniculate nucleus. *Experimental Brain Research*, *63*, 1–20.

Singer, W. (1977). Control of thalamic transmission by corticofugal and ascending reticular pathways in the visual system. *Physiological Reviews*, *57*, 386–420.

Steriade, M. and Deschênes, M. (1984). The thalamus as a neuronal oscillator. *Brain Research Reviews*, *8*, 1–63.

Steriade, M. and Deschênes, M. (1987). Inhibitory processes in the thalamus. *Journal of Mind and Behavior*, *8*, 559–572.

Steriade, M., Deschênes, M., Domich, L., and Mulle, C. (1985). Abolition of spindle oscillations in thalamic neurons disconnected from nucleus reticularis thalami. *Journal of Neurophysiology*, *54*, 1473–1497.

Steriade, M., Parent, A., and Hada, J. (1984). Thalamic projections of nucleus reticularis thalami: A study using retrograde transport of horseradish peroxidase and fluorescent tracers. *The Journal of Comparative Neurology*, *229*, 531–547.

Woolf, N.J., and Butcher, L.L. (1986). Cholinergic systems in the rat brain: III. Projections from the pontomesencephalic tegmentum to the thalamus, tectum, basal ganglia, and basal forebrain. *Brain Research Bulletin*, *16*, 603–637.