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Influence of Norepinephrine on Somatosensory Neuronal Responses in the Rat Thalamus: A Combined Modeling and In Vivo Multi-channel, Multi-neuron Recording Study

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Abstract

Norepinephrine released within primary sensory circuits from locus coeruleus afferent fibers can produce a spectrum of modulatory actions on spontaneous or sensory-evoked activity of individual neurons. Within the ventral posterior medial thalamus, membrane currents modulated by norepinephrine have been identified. However, the relationship between the cellular effects of norepinephrine and the impact of norepinephrine release on populations of neurons encoding sensory signals is still open to question. To address this lacuna in understanding the net impact of the noradrenergic system on sensory signal processing, a computational model of the rat trigeminal somatosensory thalamus was generated. The effects of independent manipulation of different cellular actions of norepinephrine on simulated afferent input to the computational model were then examined. The results of these simulations aided in the design of in vivo neural ensemble recording experiments where sensory-driven responses of thalamic neurons were measured before and during locus coeruleus activation in waking animals. Together the simulated and experimental results reveal several key insights regarding the regulation of neural network operation by norepinephrine including: 1) cell specific modulatory actions of norepinephrine, 2) mechanisms of norepinephrine action that can improve the tuning of the network and increase the signal-to-noise ratio of cellular responses in order to enhance network representation of salient

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stimulus features and 3) identification of the dynamic range of thalamic neuron function through which norepinephrine operates.

Keywords

whisker; trigeminal; computer model

1. Introduction

The regulation of membrane response properties by norepinephrine (NE) during the waking state could have profound effects on sensory signal processing. For example, neurophysiological data showing NE-induced enhancement of synaptic efficacy (Waterhouse *et al.*, 1990; Waterhouse & Woodward, 1980) provides the basis for postulating a means through which synaptically-released NE may regulate sensory signal transmission during periods of arousal, vigilance, or sustained attention. However, it is difficult to explain how a small modification in cellular response properties manifests itself in a neuronal network and leads to changes in whole animal behavior.

A key advance in determining the role of NE in brain function has been elucidation of the cellular mechanisms underlying actions of NE *in vitro*. Previous intracellular studies have identified the membrane currents that are modulated by NE in thalamic relay cells and thus regulate the electrophysiological properties of these neurons. Direct application of NE decreases the leak current, I_{Leak} , that contributes to the resting membrane potential of individual cells (McCormick & Pape, 1990a, b). Additional *in vitro* studies have shown that locally applied NE can: 1) augment the membrane actions of GABA in the cerebellum (Cheun & Yeh, 1992) and cerebral cortex (Sessler *et al.*, 1995), 2) modulate potassium currents in the cerebral cortex (Foehring *et al.*, 1989) and hippocampus (Madison & Nicoll, 1986a,b, 1988), and 3) increase the probability of evoked spiking activity in the cerebral cortex (Waterhouse *et al.*, 2000). Furthermore, Lee and McCormick (1996) showed that NE also decreases the potassium leak current of cells in the thalamic reticular nucleus (nRT)

An important efferent target of NE-containing projections from the brainstem nucleus locus coeruleus (LC) is the somatosensory thalamus. Previous computational models of the thalamus focused on its oscillatory mode of operation during sleep and regulation of this functional state by brainstem modulatory systems (Bazhenov *et al.*, 2000; Destexhe *et al.*, 1993; 1996a,b; Huguenard & McCormick, 1992; Lytton *et al.*, 1996; 1997; McCormick & Huguenard, 1992; Wang *et al.*, 1991; Destexhe *et al.*, 1993). NE input increases as animals emerge from sleep or are performing tasks requiring attention. While there is general agreement that NE can modulate electrical properties of thalamic neurons and alter responses of these neurons to non-monoaminergic synaptic inputs (Berridge & Waterhouse, 2003; Foote *et al.*, 1983; Woodward *et al.*, 1979) and that these changes are important for how these networks respond to sensory stimuli, the relationship between the cellular effects of NE and the impact of NE on populations of neurons encoding sensory signals is still open to question. To address this gap in our understanding of the dynamics of NE modulatory influences on thalamic circuits of mammalian brain, we used a computational model of the

rat trigeminal somatosensory system. Our model simulated the anatomical and physiological relationships of the thalamo-reticular network and was used to evaluate the net influence of a variety of previously demonstrated membrane and cellular effects of NE on this network. We used the model to address three specific questions: 1) do the cellular actions of NE produce a uniform effect on network transmission of sensory signals?, 2) can changes in the magnitude of excitatory or inhibitory post-synaptic potentials, both postulated NE actions, modulate the responses of thalamic cells to whisker stimulation in a manner similar to that seen *in vivo*? and, 3) which mechanisms of NE action account for changes in magnitude and/or latency of cellular responses to synaptic input? To validate the predictions of the model, and demonstrate that these predictions were potentially physiologic, we implanted arrays of microelectrodes within the rat VPM thalamus and recorded whisker-evoked somatosensory responses from ensembles of neurons in freely moving animals before, during and after periods of tonic electrical activation of the LC-NE system.

2. Results

To determine which of the known membrane actions of NE could account for increases or decreases in responsiveness of VPM cells to afferent input, we evaluated the effects of NE-mediated changes in membrane function on simulated afferent volleys of EPSP's such as those that are known to occur in response to whisker stimulation. In addition, we tested our hypothesis that NE could produce the changes in sensory responsiveness seen *in vivo* by modulating the magnitude of EPSP's and IPSP's within modeled neurons.

2.1 Effect of reducing the leak current on neuronal activity in the model

To model the effects of NE on the membrane potential, the value of the potassium-leak current was modified for all cells. G_{K-leak} was decreased to simulate the effect of NE on the leaky membrane current. When G_{K-leak} was decreased from 2.5 nS (nano-siemens), a level that simulated minimal NE receptor activation in the waking state, to 0.0 nS, a level that simulated maximum NE receptor activation, the resting membrane potential increased. These increases in the resting membrane potential were expected based on a previous report (McCormick & Pape, 1990a). To evaluate the effects of modifying the G_{K-leak} on the response of VPM cells to synaptic inputs, afferent volleys to the VPM were generated by simulation of single whisker activation. Individual modeled VPM cells were more likely to fire action potentials in response to synaptic input and modal latencies were decreased in most cells (Table 1) when G_{K-leak} was decreased to half the baseline level in both populations of cells. This effect is represented in the sample PSTH (Fig 2A) as an increase in the probability of the response and a decrease in the modal latency. Under initial conditions of the model the peak response was 243 Hz with a latency of 7 ms. The peak response increased 133 % (324 Hz) with a decrease in modal latency of 29 % (5 ms) when NE-activation was simulated by decreasing G_{K-leak} to 0.5 X baseline conditions. This increase in responsiveness is comparable to the enhanced stimulus-driven discharge and reduced response latency observed in VPM thalamic cells during tonic (1.0 Hz) electrical activation of the LC in awake but quietly resting rats (see Fig 2B). In this case the response probability to whisker pad stimulation was increased approximately 31% from control conditions and the modal latency was reduced 22%, from 11.2 to 8.8 ms.

2.2 Effects of differential leak current modulation: VPM vs nRT

The most frequent outcome of modulating the leak current on model cells was an increase in response probability often accompanied by a decrease in modal latency (Table 2). However, not every cell responded this way. For example, when G_{K-Leak} was reduced by 50% (from a minimal NE effect, $G_{K-leak}=2.5$ nS to $G_{K-leak}=1.25$ nS), 5% of the VPM cells increased their response probability and decreased the modal latency of response while 20% of VPM cells only increased the probability of their responses. At the same time, response probability was reduced in nearly 10% of modeled VPM cells ($n = 96$). The remaining VPM cells showed no change in response probability or modal latency.

As illustrated by the phase diagram of neuronal function (Fig. 3), response properties of VPM neurons were dependent on the magnitude of reduced leak current in VPM versus nRT circuitry. First, as G_{K-leak} current was decreased in the VPM (holding the leak current constant in the nRT) the probability of a VPM cell firing in response to synaptic input was modulated in a non-linear manner. Initially, the response probability decreased in most VPM cells (95% of 213 cells; the remaining 5% were unchanged), however as G_{K-leak} current was decreased further the response probability of these cells was then increased. Second, when G_{K-leak} was decreased in the nRT but held constant in the VPM there was no change in the response properties of the VPM cells. Third, *moderate* decreases in G_{K-leak} in both VPM and nRT resulted in an increase of the response probability and, sometimes, a decrease in the modal latency of VPM cells. However, *large* decreases in G_{K-leak} in both VPM and nRT produced a decrease in the probability of a response from VPM neurons (see Fig 3). Collectively, these findings emphasize the variable nature of the relationship between NE's net impact on neuronal function in noradrenergic terminal fields and the sensitivity of individual postsynaptic mechanisms to NE action.

2.3 Effect of increasing the amplitude of EPSP's and IPSP's on network activity

To test whether NE could produce changes in VPM response probability and modal latency by enhancing the amplitude of EPSP's and IPSP's, we modulated EPSP and IPSP effects independently in the model and assessed their impact on neuronal and network response properties (Fig. 4). The simulations were performed similarly as above, however instead of decreasing the G_{K-leak} , the amplitudes of the EPSP's or IPSP's generated in VPM cells or nRT cells were increased (i.e. either doubled or tripled in amplitude).

A complex set of effects was observed by altering the amplitude of the EPSP's and IPSP's (Fig. 4). In general, two types of changes were observed most frequently, occupying the most space on the neuronal function phase diagram: an increase in response probability and/or a decrease in the response modal latency. However, other changes were observed within this parameter space. For example, the response probability of VPM cells was decreased from baseline responsiveness when G_{max} for IPSP's alone was increased or when G_{max} for both IPSP's and EPSP's was tripled (i.e. maximal NE effect).

Furthermore, under certain conditions, cells that were initially unresponsive to simulated input became responsive. This phenomenon of 'gating' cells into the pool of responsive neurons following simulated increases in NE action has been observed *in vivo* during

iontophoretic application of NE (Waterhouse *et al.*, 1988; 1990) or activation of the LC efferent path (Devilbiss & Waterhouse, 2004). For example, the number of cells responding to afferent input more than doubled, from $n=213$ to $n=436$ cells, following increases in EPSP amplitude alone. When the magnitude of both EPSP's and IPSP's were doubled, the number of cells responding to simulated input peaked at 549 or more than half of the units in the network.

The effects of increasing EPSP amplitude on the 213 cells that were initially responsive to simulated inputs were also quantified (Table 2). When the amplitude of the EPSP's were doubled (holding $G_{\max}$ for IPSP's constant), most cells in this group (162/213, 76%) did not change their response properties from baseline conditions. A small number of cells showed a decrease in responsiveness ($n=30$) or both a decrease in responsiveness and a decrease in modal latency ($n=10$). An additional 11 cells showed a decrease in modal latency alone. As the amplitude of the EPSP's was further increased, most of the initially responsive cells (155/213, 73%) showed a decrease in modal latency, while only 3 cells showed an increase in responsiveness. Overall, these results suggest that modulating the EPSP amplitude alone can greatly increase the number of cells in a network responding to afferent input (i.e. 'gating-in') but this action is not sufficient to increase the probability of response from cells that were already responsive under baseline conditions.

By contrast, when the amplitude of both the EPSP's and the IPSP's were doubled, the majority of initially responding cells showed an increased response probability and decreased modal latency (71/ 213 cells) or a decrease in responsiveness alone (34/213 cells) compared to baseline conditions. Additionally, a small number of cells showed an increase in responsiveness with ($n=11$; not listed in table) or without ($n=10$) a concomitant increase in modal latency. As the amplitude of EPSP's was further increased, most cells continued to show an increase in responsiveness followed by a decrease in modal latency. Combined with the predominate decrease in modal latency observed when EPSP's alone are increased, these data suggest that increasing both EPSP amplitude and IPSP amplitude has the additive effect of increasing the probability of a response from a cell as well as decreasing the latency of that response. However, when the amplitude of both the EPSP's and the IPSP's were tripled, a majority of cells (113 / 213 cells) showed a decrease in responsiveness from baseline conditions. Thus, although a large increase in the amplitude of EPSP's alone (3 times baseline) results in a generalized increase in response probability, this increase in neuronal responsiveness can be reversed with concurrent increases in the amplitude of IPSP's (3 times baseline). Nevertheless, it was observed that moderate increases in both IPSP's and EPSP's (twice baseline) generally increase the probability of a response. Overall, these data suggest that increases in the probability of a response by moderate (2 fold) increases changes in EPSP and IPSP magnitude can be negated by larger increases in PSP amplitude.

Modifying the amplitude of the IPSP's alone reduced the probability of a response to simulated input. Initially there was no change in the response of neurons to simulated input as the IPSP amplitude increased. However, when the amplitude of the IPSP was double its initial value, the probability of a response began to decrease (28% of cells). Further increases in IPSP amplitude resulted in more cells (42%) exhibiting reduced response probability, although the total number of cells responding to simulated input did not change.

2.4 Comparison of Simulated NE Effects on G_{K-leak} vs PSP's

While the effects of PSP changes were similar to the effects seen when modeling NE's effect on the potassium leak current, there were some notable differences. First, by increasing EPSP amplitude without affecting IPSP, the modal latency of the response decreased with a rare change in response probability. In addition, within the operational domain of the network there was a much larger working region (i.e. range of parameters) where response probability was increased and/or response latency was decreased. This endpoint occurred over a broader range of PSP amplitudes than either increased amplitude and/or increased modal latency alone. If one hypothesizes that increased response probability and a decrease in modal latency results in optimal signal processing, then the effect of NE on PSP amplitudes does not have to be tightly controlled to achieve the desired signal processing outcome. Additionally, decreases in response probability were much less likely when NE's effect on PSP size was modeled than when NE's effect on G_{K-leak} was modeled across the range of parameters studied. Nevertheless, decreased response probability was principally observed when EPSP and IPSP amplitudes were increased substantially (3 times baseline values) or when resting membrane potential was increased as observed when G_{K-leak} is modulated by NE. Finally, a large number of cells were 'gated' into the response pool when the amplitude of the PSPs was modulated, but not when G_{K-leak} was altered in VPM or nRT cells.

2.5 In Vivo Studies

The *in vivo* effects of endogenous NE release were measured by simultaneously recording from multiple single VPM neurons before and during tonic (0.5, 1.0 and 5.0 Hz) electrical stimulation of the ipsilateral LC nucleus. Previous work from our laboratory and elsewhere has shown that increased output from the LC results in increased NE levels in noradrenergic terminal fields (Berridge & Abercrombie, 1999; Florin-Lechner *et al.*, 1996; Page & Abercrombie, 1999; Waterhouse & Devilbiss, 2002). Tonic activation of the LC-noradrenergic efferent pathway in the awake but quietly resting rat, produced heterogeneous effects on response probability and modal latency that were similar to those seen in the model. For example, as predicted by the model, NE-mediated reduction of the potassium-leak current or alteration of the balance between EPSP and IPSP amplitudes should result in an increase in response magnitude of VPM neurons to sensory stimuli. Figure 2B illustrates a representative neuron from *in vivo* recordings that demonstrated an increase in response probability during periods of LC stimulation. In this example the response was increased 31% above control. Moreover the model predicted a decrease in modal latency, an effect achieved by by reducing the potassium-leak current or altering the balance of EPSP and IPSP amplitudes. This predicted outcome was also evident in the response of the representative neuron shown in Fig. 2B, i.e. in addition to the increase in response probability, this cell exhibited a 22% decrease in modal latency (11.3 ms to 8.8 ms). Furthermore, as predicted by the model, we simultaneously recorded neighboring VPM neurons whose responses to whisker pathway stimulation were suppressed during LC stimulation. Cell-specific, LC-induced modulation of VPM neuronal responsiveness to whisker pad stimulation was observed in all six animals studied. The distribution of these effects as observed *in vivo* are listed in Table 3.

Based upon the assumption that NE has uniform effects on G_{K-leak} conductance in nRT and VPM cells, respectively, or produces equivalent effects on the amplitude of EPSP's and IPSP's in these thalamic regions, the diagonal through either neuronal function phase diagram (Fig. 3 or 4) indicates the prediction that VPM neuronal responses to afferent stimuli will be increased and subsequently decreased as NE's effects are increased. During increasing frequencies of LC stimulation in the intact animal, a substantial number of neurons demonstrated an increased response probability at low levels of LC stimulation followed by suppression from this peak responsiveness at subsequently higher LC stimulation frequencies (Fig. 5). However, not all VPM cells demonstrated this LC stimulation-response relationship. Essentially, a spectrum of modulatory effects was observed with increasing frequencies of LC stimulation that were *cell specific* and *frequency dependent*.

For a given cell, increasing LC stimulation either monotonically suppressed single neuron response probability or initially produced an increase in response probability at low levels of LC output followed by suppression at higher LC activation frequencies. For example, Figure 6 illustrates one (cell A) of three simultaneously recorded, neighboring neurons whose response to whisker-related synaptic input was monotonically suppressed across increasing LC stimulation frequencies. During the same experimental period, cell B demonstrated an increased probability of response at all frequencies of LC stimulation tested. By contrast, the response probability of neighboring cell C was increased during 0.5 Hz LC stimulation, but was suppressed from peak responsiveness at subsequently higher LC stimulation frequencies. Of the 29 neurons that demonstrated an initial facilitation of the sensory-evoked discharge during LC stimulation, 18 showed further increases in response probability with increasing LC activation, whereas the remaining 11 exhibited the parabolic or inverted-U LC stimulus-response relationship (n=6 animals). These data suggest that increasing the output of the LC-noradrenergic system and, therefore, raising local extracellular concentrations of NE can produce a number of trajectories through the potassium-leak current or EPSP-IPSP neuronal function phase diagrams.

3 Discussion

In the present study we used a computational model of the rat thalamic circuitry to study the effects of known post-synaptic actions of NE on the responses of single cells and local circuits to activation of afferent synaptic pathways. The goal was to obtain a better understanding of the impact of the LC-NE system on local circuit dynamics in noradrenergic terminal fields. Simulation of NE activity as modeled in this study had two major outcomes. First, changing the efficacy of NE in our model produced a complex and varied array of neuromodulatory effects on cells within a simulated thalamic network. These disparate effects had previously been shown to manifest themselves at the single cell level *in vivo*, but it was not clear how or if they would be expressed simultaneously in neighboring neurons across a noradrenergically-innervated network. Overall, the results obtained from our model indicate that the predominant outcome of NE actions on intrinsic membrane properties or synaptic efficacy was to increase the probability and/or decrease the modal latency of individual VPM thalamic neuron responses to afferent input. However, NE did *not* produce a uniform effect on the response properties of cells in the thalamic relay circuitry. For

example, simulation of NE action enhanced the response to afferent synaptic volleys for some cells in the modeled circuit while the response of other cells under the same conditions was suppressed. This intriguing result was confirmed in subsequent neural ensemble recordings from intact, awake animals.

Second, both of the synaptic effects of NE that were modeled, e.g. either decreasing leaky membrane current, or increasing the strength of post-synaptic potentials, resulted in the same array of changes in network dynamics. In all cases these effects depended upon the magnitude of simulated NE action. Moreover, many individual cells within the model followed an inverted-U sensory response function for magnitude and latency depending on the strength of simulated NE action. This was true regardless of the NE action simulated (i.e. decreasing leaky membrane current, or increasing the strength of post-synaptic potentials). Thus, the model predicts that across a range of increasing NE influences, a neuron in the thalamic network can transition between different levels of responsiveness to synaptic inputs depending on the output of the LC-noradrenergic system. This result was also confirmed in subsequent neural ensemble recordings *in vivo*.

3.1 Modeling Constraints

The computational model used in this study was constructed so as to reflect the rat trigeminal thalamic circuitry including several known anatomical and electrophysiological properties of the biological network. First unlike many other networks and most generic excitatory-inhibitory networks studied, there are no excitatory collaterals between neurons of the VPM thalamus. In addition, neurons in the VPM (glutamatergic) thalamus and nRT (GABAergic) are neurochemically and morphologically homogeneous. In contrast, networks of sensory cortical neurons are quite heterogeneous with regard to transmitter expression, morphology, hodology, and physiology. The homogeneity of the thalamic circuitry makes it a desirable network to study but also raises new questions about the diversity of NE-mediated responses that were observed.

However, since the effects of NE are similar across many different brain regions, the model parameters and outcomes derived here can be generalized to other central circuits that receive noradrenergic innervation. The parameters used in the model were based on realistic anatomical constraints of most excitatory-inhibitory networks and biologically-based measurements of membrane currents and NE actions across many neuronal populations. Indeed, these types of responses to NE on populations of cells in the hippocampus (Madison & Nicoll, 1986a,b, 1988), cerebellum (Cheun & Yeh, 1992) and primary somatosensory cortex (Sessler *et al.*, 1995; Waterhouse *et al.*, 2000) have been previously demonstrated *in vivo*.

Despite this generality, single cells in the model exhibited response properties like those observed in tissue slice preparations, intact animals and other computer simulations of the thalamic circuitry. Upon activation by simulated afferent volleys the cells in our thalamic network responded with evoked discharge patterns like those observed in intact animals (Moxon & Chapin, 1999). The effects of NE were modeled using three known cellular mechanisms: 1) reduction of G_{K-leak} (Foerhing *et al.*, 1989; McCormick & Pape, 1990a), 2) enhancement of GABA_A mediated chloride current (IPSP) (Cheun & Yeh, 1992; 1996;

Sessler *et al.*, 1995) and 3) enhancement of glutamate-mediated or synaptically evoked excitatory responses (Mouradian *et al.*, 1991; Waterhouse *et al.*, 2000). Despite the fact that the precise mechanism responsible for NE-modulation of glutamate action is unknown, our effect of generating an increase in the amplitude of the EPSP is a reasonable approximation of this noradrenergic action. Furthermore, the results of the modeling study were verified with simultaneous recordings from ensembles of single VPM thalamic neurons *in vivo*. In either the model or the waking animal, increasing effects of NE resulted in cell specific modulation of excitatory discharge patterns.

Direct application of NE also enhances a hyperpolarizing activated cation current, the H-current, I_H . Subsequent studies showed that persistent activation of I_H results in abolition of the low threshold calcium current, I_T , and cessation of spindle oscillations. This mechanism shifts the cells from a burst discharge mode associated with sleep to single spiking relay mode associated with the waking state (Bal & McCormick, 1996). Previous models of thalamic circuitry (Bazhenov *et al.*, 2000; Destexhe *et al.*, 1993;1996a,b; Huguenard & McCormick, 1992; Lytton *et al.*, 1996; 1997; McCormick & Huguenard, 1992; Wang *et al.*, 1991; Destexhe *et al.*, 1993) explored the relationship between these membrane currents and network oscillations. Since only a few neurons were required to examine this effect, these models used the Hodgkin-Huxley formalism (Hodgkin & Huxley, 1952), which is computationally intensive. It has been hypothesized that these membrane currents regulate the physiological properties of thalamic neurons across the sleep-wake continuum and during different states of arousal (McCormick & Pape, 1990b; Bal & McCormick 1996) as a function of their response to release of different endogenous neuromodulatory substances, including NE. During sleep, NE output is reduced and there is a tendency for enhanced hyperpolarization of postsynaptic target neurons, such as those in thalamus, followed by activation of the T-current (Bal & McCormick, 1996; McCormick & Pape, 1990b;) and subsequent generation of thalamic network oscillations (Jahnsen & Llinas, 1984a,b; von Krosigk *et al.*, 1993). As the animal transitions from sleep to waking, NE output is increased, thalamic cells become depolarized and the oscillations are abolished. Because we were concerned primarily with NE effects under waking conditions, we did not include the T-current or the H-current in our model. However, since the H-current may play a role in thalamic network dynamics under waking conditions, an important next step in the development of this model would be to study the influence of the H-current on cell responsiveness in the context of simulated NE actions.

Because it was necessary to simulate the activity of a large number of cells in order to examine the frequency of each type of ‘cellular response’ (i.e. combinations of changes in firing probability and latency), we simplified our model in two important ways to reduce the time to compute a solution. First, we did not include the fast sodium channels responsible for the action potential. Instead, if a cell reached threshold for firing an action potential, synaptic activation was transmitted to downstream cells. In addition, the potassium delayed rectifier, the high threshold calcium current and the calcium dependent potassium current were computationally simplified to eliminate the time constant of activation (refer to Appendix). Accordingly, the amount of activation per integration step is held constant and the current was increased by an amount equal to the activation occurring during one time

step. The limitation of this method is that the voltage dependence of the activation is constant instead of integrated as a function of membrane potential. Since these equations are always numerically integrated and the activation time constants for these parameters are fast, the numerical results are similar within the range of membrane potentials under investigation. Previous modeling studies using these simplified formulations showed that the responses of model cells accurately reflect data recorded from networks of cells *in vivo* (Moxon *et al.*, 1999a, b).

3.2 Implications for Network Actions of NE

In the rat, LC neurons discharge tonically in a relatively slow and highly-regular state-dependent manner within the range of 0.1–5.0 Hz (Hobson *et al.*, 1975; Aston-Jones & Bloom, 1981a; Foote *et al.*, 1980). As these tonic discharge rates increase, extracellular NE increases linearly in LC efferent target regions (Berridge & Abercrombie, 1999). Moreover, changes in tonic LC impulse activity are correlated with changes in arousal level (Foote *et al.*, 1980) and state dependent information processing. As such, the highest output from LC is observed during waking with very slow rates of discharge occurring during slow-wave sleep, and virtually no activity during REM sleep (Aston-Jones & Bloom, 1981a,b; Foote *et al.*, 1980; Hobson *et al.*, 1975). Within waking, LC neurons discharge most rapidly in anticipation of EEG and behavioral changes that signal enhanced arousal or attentiveness (Aston-Jones & Bloom, 1981a,b; Foote *et al.*, 1980). LC neurons also exhibit burst firing associated with presentation of novel or salient environmental stimuli (Foote *et al.*, 1980). However, model parameters of G_{k-leak} , IPSP, and EPSP were held constant during simulations, a constraint that most closely resembles tonic levels of NE release. Combined, these and other observations suggest that LC output might contribute to the modulation of sensory information acquisition (e.g. alert waking) and information processing.

Since NE is capable of exerting a number of different influences on the responsiveness of individual neurons to synaptic input through several different mechanisms including its actions on intrinsic membrane properties and post-synaptic second messenger systems, its impact on network dynamics was not obvious. Our model demonstrates three modes of operation whereby NE can influence network dynamics and have an important impact on the functional output of the thalamus during waking conditions. First, since every cell in our model population of VPM neurons was the same yet cells responded differently to singular changes in NE effect, we conclude that each of these noradrenergic actions can produce a multitude of modulatory outcomes at the cellular level. This is a likely consequence of the fact that not all neurons maintain the same “response state” at the same time owing in part, to differences in the synaptic inputs to each cell, as was demonstrated in the simulation presented here. In biological networks therefore, the effect of synaptically-released NE is likely due to the dynamic state of individual neurons and the neural networks within which they are embedded.

Second, increases in cell responsiveness coupled with decreases in response latency as observed with simulated NE input in the model have been postulated to enhance the tuning of a local circuit to sensory stimulation *in vivo* (Berridge & Waterhouse, 2003; Lorden *et al.*, 1980; Selden *et al.*, 1990). Our simulations show that modulating both EPSP and IPSP

amplitude at the same time is more likely to decrease the latency and increase the responsiveness of thalamic cells than modulating either alone or modulating the leak current. Therefore, enhancing the tuning of a local circuit to synaptic input *in vivo* is most likely accomplished with a combination of both EPSP and IPSP amplitude modulation. Furthermore, the inverted-U response curve observed *in vivo* is most likely to be dependent on continuous changes in both EPSP and IPSP amplitude. Our model demonstrates that modulating both postulated mechanisms of NE action, PSP amplitude and the leak current, can produce this effect as long as it occurs in both populations of thalamic cells (i.e. increasing EPSPs and IPSPs at the same time or decreasing the leak current in both VPM and nRT cells simultaneously). However, changing PSP amplitude generates a greater likelihood of enhancing the tuning of cells in the network than modulating the leak current.

Finally, previous studies have shown that NE can produce changes in response threshold such that previously unresponsive or weakly responsive cells are gated into the response pool (Ciombor *et al.*, 1999; Devilbiss & Waterhouse, 2004; Jiang *et al.*, 1996; Waterhouse *et al.*, 1988). Our combined results from the model and ensemble recording *in vivo* demonstrate that some cells can be gated-into a response pool while other cells have their response probability suppressed. This leads to an intriguing possibility for a mechanism to enhance the signal-to-noise in a neuronal network – cells representing an important dimension of the signal are recruited while cells discharging to a less salient feature of the stimulus are suppressed. Our model shows that, these gating-in conditions are likely to exist when the PSP amplitude is modulated but not when the leak current is modulated. There are likely to be many transmitter-mediated mechanisms through which the system could regulate effects on leak current vs. PSP amplitude and, thus, bias the response of the network according to different physiological conditions and behavioral contingencies. Further modeling and *in vivo* work is necessary to explore this possibility.

3.3 Potential Mechanisms Underlying NE Actions

To summarize, the mechanisms underlying NE-modulation of neuronal discharge are most likely explained by G_{k-leak} and PSP amplitude parameters. For example, decreasing the G_{k-leak} parameter in the model depolarizes VPM and nRT cells, making them more excitatory. Additionally, an increase in the amplitude of EPSP's resulting from afferent input will additionally raise the probability of a neuron's response to synaptic input, representing a purely bottom-up phenomenon. Increases in IPSP amplitude, due to recurrent inhibition of nRT cells, decrease the probability of a response before the afferent input can induce the cell to fire an action potential. Together, the balance of excitatory and inhibitory influences on VPM neurons, either by modulating G_{k-leak} for both VPM and nRT cell populations or PSP amplitude produces the observed spectrum of modulatory effects on VPM neuronal discharge. In other words, the cell specific modulation of excitatory discharge patterns as observed in the model are due to the interaction of overall increases in excitability of inhibitory and excitatory neuronal populations.

Comparisons between modeling data and *in vivo* data suggest that when either EPSP amplitude is high concordant with moderate increases in IPSP amplitude or there is a moderate G_{k-leak} for both VPM and nRT cell populations best matches *in vivo* conditions

when the LC is stimulated at a low frequency of 0.5 Hz. This observation is supported by evidence indicating that the modulatory actions demonstrated by the model under these conditions was not significantly different from the modulatory actions of increased LC output (chi-square = 8.3, df = 2, $p > 0.05$ with Bonferroni correction). Nonetheless, the model is also capable of demonstrating a wider dynamic range of possible effects of NE on thalamic neurons than observed in the awake behaving animal. The detail of modulatory NE actions that this model provides begins to offer a better mechanistic understanding beneath the spectrum of putative modulatory actions of NE under normal conditions and possibly abnormal or disease states.

Importantly, the results of this modeling study can now provide a framework to pursue further *in vivo* studies. For example, we are particularly interested in the role of alpha vs. beta noradrenergic receptors in shaping thalamic responsiveness to afferent input since because, pharmacologically, these two receptor subtypes mediate different cellular and network actions and are linked to are related to different neurologic and psychiatric disorders. While some information about the effect of activation of different receptor subtypes is known, much work is still needed. For example, it is known that activation of the beta receptor, increases the H-current, reducing oscillations during the sleep cycle and essentially shifting these cells from an oscillatory state to a single-spike mode. The simulations in our model confirm this well established observation. Furthermore, it is well established that activation of the alpha 1 receptor subtype decreases the potassium leak current. As our simulations show, this can have interesting effects depending on whether the alpha 1 receptor subtype is preferentially activated in the thalamus, the reticular nucleus or some combination of the two. We are currently using these simulations to guide new *in vivo* experiments.

Future studies will address the effects of combined modulation of G_{k-leak} , IPSPs, and EPSPs on neuronal response probability. However, testing interactions of all possible combinations of cell types (nRT vs. VPM), mechanisms (G_{k-leak} , IPSP, EPSP), and a full range of current for PSP magnitudes in a computational model is very complex and requires additional *in vivo* studies to narrow the possible interactions tested. For example, the current modeling data demonstrates the effects of modulating EPSP or IPSP separately or in combination (Figure 4) on neuronal responsiveness. Additional pharmacological studies are necessary to determine whether specific NE receptor subtypes are responsible for modification of EPSPs or IPSPs and the extent to which these PSP's can be modulated under physiological conditions. These data are necessary to provide dose response information that can be used to provide a realistic limit to the number of G_{k-leak} current and PSP interactions modeled. This line of study will provide a formalized relationship between activating alpha and beta receptors and the resultant effects on neural discharge properties.

Conclusions

In conclusion, our model provides a strong rationale for designing experiments to identify the specific cell populations that are capable of expressing different NE modulatory actions and the threshold for activating these noradrenergically-mediated mechanisms. For example, various cellular and membrane neuromodulatory actions of NE have been linked to specific

adrenoceptors and second-messenger cascades (Cheun & Yeh, 1992; 1996; Foehring *et al.*, 1989; Madison & Nicoll, 1986b; Mouradian *et al.*, 1991; Sessler *et al.*, 1989; 1995; Waterhouse *et al.*, 1981; 1982). Differential expression of adrenergic receptors among different neuronal populations would significantly alter the potential response of a network of cells to NE release. Likewise, if the thresholds for activation of these noradrenergic mechanisms were different, the net effect of NE on an ensemble of cells would depend upon local tissue concentrations of this agent. Impulse activity from the locus coeruleus and the efficacy of local noradrenergic reuptake mechanisms would thus be important factors in assessing the impact of synaptically-released NE on signal processing functions of local arrays of neurons.

The findings of the present study begin to establish a framework for evaluating the ability of NE to differentially modulate cellular response properties at different levels within complex neural networks (e.g. brainstem, thalamic and cortical levels of ascending sensory pathways) under waking conditions. In this regard these simulated responses and physiological data revealed at least three important considerations for understanding NE's moment to moment regulation of neural network operation: 1) expression of cell specific noradrenergic modulatory action(s), 2) description of the relative proportion of cells that are modulated by NE release, and 3) identification of the NE mediated physiological parameter space in which VPM cells may operate.

4. Experimental Procedures

4.1 Model Network Structure

We modeled the rat VPM thalamus and nRT network within the trigeminal somatosensory system. This system is advantageous to model because the anatomical connections and the physiology of this sensory circuit are well documented (Belford & Killackey, 1979a,b; Chiaia *et al.*, 1991a,b; Diamond *et al.*, 1992a,b; Harris, 1986; 1987; Killackey *et al.*, 1989; van der Loos, 1976; Waite 1973a,b). Within the VPM, anatomical specializations commonly called barreloids, are comprised of small populations of neurons (approximately 200) that project to a corresponding cortical barrel and are most likely to respond to a single whisker (Nicoletis & Chapin, 1994, Chapin & Nicoletis, 1999). There are no recurrent connections, nor collaterals between cells within the rat VPM (Harris, 1986), however axonal divergence from corresponding brainstem sensory nuclei permit VPM neurons to respond to several adjacent whiskers on the contralateral face. All VPM neurons are morphologically similar and make excitatory synaptic connections with cortical neurons and the adjacent nRT. Cells of the nRT are all inhibitory (de Biasi *et al.*, 1986; Lee *et al.*, 1994; Cox *et al.*, 1997). They receive excitatory input from the ipsilateral somatosensory cortex and ipsilateral VPM (Carmen *et al.*, 1964; Lozsadi *et al.*, 1996; Liu & Jones, 1999), and project onto neighboring nRT cells and back to cells in the VPM (Minderhoud, 1971; Jones 1975; Ohara *et al.*, 1980; Montero & Scott, 1981; Ohara & Lieberman, 1981,1985; Harris 1987; Ohara, 1988; Spreafico *et al.*, 1991; Chen *et al.*, 1992; Gonzalo-Ruiz & Lieberman, 1995; Crabtree, 1996).

Our model of the rat somatosensory VPM-nRT network simulates five thalamic barreloids and consists of two types of neurons: a) excitatory VPM neurons (n=1000) and b) inhibitory

nRT cells ($n=1000$). As such, 200 VPM cells are modeled for each thalamic barreloid and associated region within the nRT. The large number of modeled neurons allowed us to simulate the response of individual cells to a broad range of stimuli, mimicking the input that would be expected from principal and surround whiskers. Moreover, we wanted to maximize the sample size of responding neurons in order to detect the full range of possible behaviors that have been observed *in vivo*. In accordance with existing knowledge of rat VPM anatomy, we did not model connections between individual VPM cells (Harris *et al.*, 1986). Although connections exist between VPM and nRT cells, the extent of such connectivity is unknown. In lieu of this, previous modeling studies have assumed sparse connectivity between VPM cells and nRT (Wang *et al.*, 1991). In our model each VPM cell contacts on average 2% of nRT cells via excitatory synapses. Additionally, each nRT cell contacts, on average, 2% of VPM cells and 1% of nRT cells via inhibitory GABA_A type synapses and 0.5% of VPM cells and 0.5% of nRT cells via inhibitory GABA_B type synapses.

4.2 Membrane Currents

In our model, cells were constructed using a two-compartment equivalent circuit representation that contained 5 membrane currents, based on an integrate-and-fire model (Macgregor, 1987; Fig. 1). The membrane conductances in the soma compartment included a leaky membrane conductance mainly due to potassium and sodium ions (G_{leak}), and two conductances to potassium that acted as delayed rectifiers G_{K1} , G_{K2} . The membrane conductances in the dendritic compartment included a high threshold, voltage dependent conductance to calcium (G_{Ca}) and a calcium dependent conductance to potassium (G_{KCa}) described by Jahnsen and Llinas (1984b) for thalamic cells. With the exception of the leakage membrane current, the activation and inactivation of each current was described using differential equation and exponential integration methods previously described (MacGregor, 1977) and verified for the currents described here (Rybak *et al.*, 1997) using a 0.1 msec time step.

As the goal of these simulations was to provide guidance for subsequent multi-neuron recording studies, simplifications of neuronal activity were introduced to minimize the number of parameters and focus attention of the study on the effect of NE on network dynamics. This approach allowed the results of this model to be extended to other brain nuclei identified (see Introduction) that exhibit similar dynamic behavior. First, since the shape of the action potential was not critical for interpreting the results of this model, the fast sodium current was not explicitly modeled. Therefore, when the cell reached a threshold for a sodium spike, the model presumed an action potential and transmitted synaptic activation to downstream neurons. Second, when the potential of the dendritic compartment exceeded the dendritic threshold, the calcium conductance was increased by a fixed amount and decayed with constant time constant (MacGregor, 1987). Third, while these changes in calcium concentration change the equilibrium potential for calcium according to the Nernst equation (Rybak *et al.*, 1997), the equilibrium potential for calcium was held constant for the simulations in this study. This formalism represents a simplification that reduces computational overhead while maintaining a sufficiently accurate representation of the network dynamics.

VPM and nRT cells also contain other membrane currents, including a low threshold calcium current or T-current (Jahnsen & Llinas, 1984a; b) and a hyperpolarizing cation current or H-current (McCormick & Pape, 1990a), which were not modeled. These currents are primarily involved in the generation of 7–12 Hz oscillations associated with sleep spindles (McCormick & Pape, 1990b; von Krosigk *et al.*, 1993). The H-current is enhanced by NE (Bal & McCormick, 1996), which depolarizes the cell limiting the occurrence of low threshold calcium spikes (Jahnsen & Llinas, 1984b). Reduction of low threshold calcium spikes and 7–12 Hz oscillations by NE's enhancement of the H-current suggests that the H-current participates in the transition from sleep to wakefulness. Initially, the model was validated by demonstrating that oscillations were generated when the H-current and T-current were included (data not shown). However to simulate the waking state, the leak current was adjusted to include the activated H-current which effectively depolarized the cell (resting membrane potential approx. -57.3 mV) and allowed us to remove the H- and T-currents from the model. This approach represents the currents of VPM and nRT neurons in a reasonable manner that minimizes computational overhead and addresses circuit operations under the waking conditions modeled in these simulations.

4.3 Synaptic Currents

Three synaptic currents were simulated in the model. Excitatory post-synaptic potentials (EPSP's) were considered to result from a release of glutamate at excitatory synapses, and inhibitory post-synaptic potentials (IPSP's) resulted from activation of GABA_A and GABA_B-type synapses. The EPSP that is generated *in situ* when glutamate binds to post-synaptic receptors, opens Na⁺ channels which in turn increases Na⁺ conductance, G_{Na} . The other two synaptic potentials were inhibitory post-synaptic potentials (IPSP's) that are generated *in situ* when GABA binds to GABA_A or GABA_B postsynaptic receptors. Activation of both types of GABA receptors results in an increase in chloride conductance although the time courses are substantially different. GABA_B receptors operate through an intracellular second messenger cascade that is not explicitly modeled but nevertheless results in an increase in potassium conductance that is slower than the GABA_A conductance.

These three postsynaptic potentials (PSPs) were each simulated using a dual-alpha function equation (see Appendix for equations). The parameters that distinguish the different PSP types (i.e. resulting from the activation of a glutamate receptor as opposed to GABA_A or GABA_B receptors) are: 1) the amplitude of the PSP, g_{max} , 2) the time course, described by τ_1 and τ_2 , and 3) the reversal potential, E_{eq} . The amplitudes of the PSPs were modulated in the model to simulate changes brought about by fluctuations in LC output and resultant alterations in tissue concentrations of NE (described in detail below – 'Modeling the Effects of NE'). The time courses of the PSPs were set based on experimental data. The glutamate receptor and the GABA_A receptor (GABA_A-R) are ligand gated ion-channels and therefore each has a relatively fast time course. In the model, the EPSP reaches a peak in 1–2 ms and decays in about 15 ms. Activation of the GABA_A receptor generates an IPSP that peaks within 5 msec and lasts for less than 100 ms (Pearce, 1993; Thompson & Gahwiler, 1992). The GABA_B receptors that activate postsynaptic second messenger systems take longer to peak (approximately 180 msec) (see Peet & McLennan, 1986) and have a duration of more than 300 msec (Dutar & Nicoll, 1988). The reversal potentials were also established on the

basis of experimental data. Activation of ionotropic glutamate channels increases the permeability to sodium and calcium that moves the membrane potential towards a reversal potential of about 0 millivolts (mV) whereas chloride ion influx, via the GABA_A receptors, has a reversal potential of -65 mV (Dingledine & Langmoen, 1980).

4.4 Simulated Afferent Stimulation

Afferent activity simulating sensory input from the periphery (mystacial vibrissae) via the brainstem was modeled using data from single whisker stimulation studies (Nicolelis & Chapin, 1994; Foffani & Moxon, 2004) and was represented as an EPSP incident on VPM cells in the model (Moxon & Chapin, 1999). Afferent volleys were simulated by activating model fiber populations that made synaptic contact with VPM thalamic cells. Each fiber made 20 synaptic contacts with cells of the VPM. For each trial, the probability of an input fiber firing an action potential was set so that an average of 175 fibers were activated for 5 milliseconds. The result of an input fiber simulating an action potential was to generate an EPSP at all of its 20 synapses. Each trial was repeated 50 times. For each trial a different, randomly chosen, subset of afferent fibers was activated to simulate the stochastic nature of brainstem input. These 50 trials simulated afferent input (i.e. whisker deflection) similar to repetitive deflection of a single whisker as occurs during receptive field mapping studies *in vivo* (Nicolelis & Chapin, 1994). Each trial consisted of simulating whisker-related afferent volleys to the thalamus. The objective of these simulations was to model standard experimental practice as employed in single whisker mapping studies (Foffani & Moxon, 2004). The responses for each neuron were then presented in the form of a post-stimulus time histogram (PSTH). The probability of a response (i.e. action potential generation) and the latency of that response to stimulus presentation (n=50) were quantified using the PSTH.

4.5 Modeling the Effects of NE

In vitro studies showed that direct application of NE decreased the leak current, I_{Leak} that contributes to the resting membrane potential of individual cells (McCormick & Pape, 1990a). In intact preparations, local application of NE by iontophoresis or activation of the LC-NE efferent pathway enhanced neuronal responses to putative transmitters, glutamate or GABA, (Moises *et al.*, 1979; Moises & Woodward, 1980; Waterhouse *et al.*, 1980; Waterhouse *et al.*, 1982; Mouradian *et al.*, 1991). Receptor-linked second messenger mechanisms have been implicated in mediating noradrenergic regulation of GABA-induced membrane hyperpolarizations (Cheun & Yeh, 1992; 1996; Sessler *et al.*, 1995) and glutamate-evoked discharges (Mouradian *et al.*, 1990). In the simulations presented here, we postulate second messenger-mediated effects of NE on the amplitude of the EPSP's and IPSP's.

In the model, we simulated NE modulation of the leak current in both the VPM thalamus and the nRT. In addition we separately simulated modulation of excitatory and inhibitory post-synaptic potentials (EPSP and IPSP, respectively) to mimic previously observed changes in synaptic efficacy (Waterhouse *et al.*, 2000) and GABA-induced whole cell currents (Cheun & Yeh, 1992), respectively. To model effects of NE, the conductances of individual membrane currents were modulated by modifying the G_{max} parameter for that current (refer to Appendix for equations of individual currents). To simulate a reduction in

the leaky membrane current, the value of G_{K-leak} was decreased, thereby depolarizing the cells. To model the effects of NE on EPSP's and IPSP's the amplitudes of G_{Na-Glu} and $G_{Cl-GABA}$ were modulated respectively. In its final form the model was fixed in the 'waking' state to determine if NE-like influences on membrane currents could result in cellular and network effects like those seen in *in vivo* experiments. As such noted above, the low threshold calcium current and the H-current were not modeled.

4.6 Intact Animal Studies

Spike train activity was recorded extracellularly from multiple single VPM thalamic neurons in six adult male Long-Evans hooded rats (weight = 250–450 g - Charles River Laboratories, Wilmington, MA) during the waking state (Devilbiss & Waterhouse, 2002). Animals were housed in a light (12on-12off), temperature and humidity controlled environment with food and water available *ad libitum*. Neuronal recordings were obtained during daylight hours (i.e. when the lights were normally on). Animals were tethered to the recording equipment but allowed to freely move within the recording chamber and recordings were made while the animal remained in a state of quiet rest, verified by video analysis. Animals used in this study were treated in accordance to NIH guidelines on research animal care. Furthermore, these experiments were approved by the Institutional Animal Care and Use Committee of Drexel University.

4.6.1 Surgery—All animals received microwire implants in the VPM thalamus and the ipsilateral nucleus LC. Additionally, a stimulation electrode was passed under the skin and anchored in the whisker pad. These methods have been described previously (Devilbiss & Waterhouse, 2002). In brief, under anesthesia the rat was placed in a stereotaxic apparatus and the skull exposed. The head was placed at a 15° angle (nose down) to the horizontal plane and a small craniotomy was performed at 1.2 mm lateral and 3.6 mm caudal to the intersection of the midline and lambda to allow the vertical placement of the microwire bundle into the LC. Five stainless steel screws (MX-080-2; Small Parts Inc. Miami, FL) were placed into the skull for electrical grounding and to ensure proper anchoring of the probes. A recording/stimulation probe, containing a bundle of eight 50 µm Teflon-coated, stainless steel microwires (SB103, NB Labs, Dennison, TX), tied together with a silk suture was lowered to an approximate depth of 6.0 mm. During placement of the electrode bundle, neuronal electrical activity was monitored to guide accurate placement within the LC. The characteristic spontaneous discharge rate (~ 0.1 – 5 Hz) and the biphasic response to tail pinch (Akaike 1982) were two criteria used to identify putative LC neurons. The skull opening was then sealed with Gelfoam and the probe was attached to the skull with dental acrylic.

The rat's head was then re-positioned parallel to the horizontal plane and an additional skull opening was made at –3.3 A/P and –2.8 M/L (with respect to bregma) for placement of a VPM microwire probe (coordinates from the atlas of Paxinos & Watson, 1986 and Waite, 1973a,b). Neuronal electrical activity was monitored to guide placement of the electrode into the VPM at an approximate depth of 5.5 mm (from dura). The VPM thalamic region that represented sensory information for the C3 vibrissae was targeted. After electrode placement, the skull opening overlying the cortex was filled with Gelfoam and the probe

was secured to the skull with dental acrylic. Before all of the skull screws were encapsulated with dental acrylic the grounding wires from each electrode assembly were wrapped around the exposed screws for electrical grounding.

A whisker pad stimulating electrode was prepared by placing the twisted pair of 7-stranded stainless steel wire (793200, A-M Systems Inc. Carlsborg, WA) inside a 20 gauge needle cut blunt and polished. The needle was used to tunnel under the skin from the initial skull incision into the whisker pad. By carefully removing the needle, the twisted pair was left hooked around a whisker follicle. The free ends of the twisted pair were inserted through a 15 mm section of Silastic tubing (602-231, Dow Corning), protecting the wire from rubbing against the dental acrylic. The free ends of the wire were crimped into a connector and attached to the skull with dental acrylic. The skin was loosely sealed around the dental cement and the animal was allowed to recover for 5 – 10 days.

4.6.2 Electrophysiological Recording—Prior to experimentation, the animals were habituated to the testing chamber, the experimenter, and the experimental procedure (whisker pad stimulation). During this habituation period multiple single units were discriminated (see Devilbiss & Waterhouse, 2002) from periods of spontaneous discharge and again from periods of repeated whisker pad stimulation. The experimental session was initiated after confirmation that the units were responsive to whisker stimulation. The whisker pad was stimulated with biphasic pulses (range 1–3 mA) that were threshold for producing a rostral twitch of a single vibrissae. The stimulus current chosen produced robust excitatory discharge in a majority of the simultaneously recorded units, and produced evoked-responses in VPM neurons comparable to single vibrissa whisker deflection (Devilbiss & Waterhouse, 2002). During an initial control period and in all subsequent periods, single stimulus pulses to the whisker pad (n=90) were presented randomly (pulse duration 1 msec; mean inter-trial interval 2 sec; range 1.5 – 2.5 sec) to prevent stimulus habituation. Following the control period, the order of three additional control periods and six LC stimulation conditions were randomly assigned. For each of the LC stimulation conditions a train of single electrical shocks ranging from 3 μ A to 300 μ A were delivered at a frequency of 0.5 Hz to 5.0 Hz. The experimental session was videotaped with a video counter timer providing time stamps (resolution = 0.1 sec) synchronized to the multiunit recording and behavioral control systems so that we could confirm that the animal remained in a state of quiet rest throughout the experiment.

4.6.3 Histology—Following each experiment, the animal was deeply anesthetized and 60 μ A of current was passed across pairs of bundle microwires for 45 seconds. The animal was then perfused with 0.9% saline followed by a 10% formalin solution containing 5% potassium ferrocyanide, which produces a Prussian blue reaction product. The brains were then removed and stored in phosphate buffer containing 15% sucrose. Coronal 80 μ m sections were cut on a freezing microtome and collected through the VPM recording and LC stimulation sites and Nissl-Stained.

4.6.4 Data Analysis—Post-stimulus time histograms (PSTH's) were examined to identify and quantify changes in the probability of a response (i.e. action potential generation) and the temporal coding of stimulus-evoked discharge. Probability of a response was measured

as spikes/stimulus or frequency of discharge during a fixed response epoch in control and LC stimulation histograms. Increases or decreases in response latency were quantified by determining changes in the latency to the statistical mode of the stimulus-evoked response, or the latency to the response peak discharge was calculated and referred to here as the modal latency. Decreases in this measure indicate a concentrated burst of activity near the onset of the stimulus-evoked response or a more focused discharge per unit of time. The statistical significance of LC-mediated changes in the magnitude or latency of stimulus-evoked discharge were assessed by comparing values obtained during LC stimulation conditions to control conditions with students T-tests for each neuron (with bonferroni corrections).

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Abbreviations

A/P	Anterior-Posterior
CNS	Central Nervous System
E_{eq}	Reversal Potential
EPSP	Excitatory Postsynaptic Potential
G_{Ca}	Conductance of Calcium
G_{Cl-GABA}	Conductance of Chloride mediated by Gamma-Aminobutyric Acid
G_{K1}	Conductance of Potassium (fast)
G_{K2}	Conductance of Potassium (slow)
G_{Kca}	Conductance of Potassium (calcium dependent)
G_{leak}	Conductance of a Leaky Membrane
g_{max}	Amplitude of a Postsynaptic Potential
G_{Na}	Conductance of Sodium
G_{Na-Glu}	Conductance of Sodium mediated by Glutamate
GABA	Gamma-Aminobutyric Acid
GABA_A; GABA_B	Gamma-Aminobutyric Acid Receptor Subtypes
Hz	Hertz (frequency)
IPSP	Inhibitory Postsynaptic Potential
LC	Locus Coeruleus
LC-NE	Locus Coeruleus - Norepinephrine
M/L	Medial-Lateral
mA	Milliamp

Msec	Millisecond
mV	Millivolts
NE	Norepinephrine
nRT	Thalamic Reticular Nucleus
nS	Nano-Siemens
PSP	Postsynaptic Potential
PSTH	Post-Stimulus Time Histogram
$\tau_1; \tau_2$	Decay Time(s)
THD	dendritic threshold
VPM	Ventral Posteromedial Thalamus

Appendix

The model of each VPM cell was constructed using a two-compartment equivalent circuit representation that contained 5 membrane currents and 3 synaptic currents (Equation 1), which was a simplification of previous models (Destexhe *et al.*, 1993, 1996a, b; Lytton *et al.*, 1996, 1997; Rush & Rinzel, 1994; Wang *et al.*, 1991;).

$$C \frac{dE}{dt} = -I_{rest} + \Sigma I_{mem} + \Sigma I_i \quad \text{Equation 1}$$

The magnitude of the currents was determined by evaluating the conductance of the current at each time step in the model, which is generally a function of the cell's membrane potential. The membrane conductances in the soma compartment included a leaky membrane conductance mainly due to sodium and potassium ions (G_{leak}), a voltage dependent conductance to potassium that acted as a delayed rectifier (G_{K1}) and a second, slower potassium conductance (G_{K2}), which was mainly responsible for the inter-burst interval. When the potential of the soma reached threshold, the conductance to potassium was increased by an amount B_i and decayed with time constant τ_{GKi} (Equation 2).

$$\frac{dGK_i}{dt} = \frac{-GK_i + B_i * S}{\tau_{GKi}}, S = \begin{cases} 0 & \text{if } ES < THS \\ 1 & \text{if } ES \geq THS \end{cases} \quad \text{Equation 2}$$

Dendritic Membrane Conductances

The membrane conductances in the dendritic compartment included a high threshold conductance to calcium (G_{Ca}) and a calcium dependent conductance to potassium (G_{KCa}) (Jahnsen & Llinas, 1984b). The conductance to calcium, G_{Ca} , was voltage-dependent (Equation 3). When the potential of the dendritic compartment exceeded the dendritic threshold, THD , the calcium conductance was increased by an amount D and decayed with time constant τ_{GCa} .

$$\frac{dG_{Ca}}{dt} = \begin{cases} -G_{Ca}/\tau_{GCa} & \text{if } ED < THD \\ \frac{-G_{Ca} + D^*(ED - THD)}{\tau_{GCa}} & \text{if } ED \geq THD \end{cases} \quad \text{Equation 3}$$

The potassium current, G_{KCa} , was dependent on the concentration of calcium. The calcium concentration, $[Ca^{2+}]$, was proportional to the conductance to calcium (Equation 4). A represented the amplitude of calcium concentration rise in proportion to calcium conductance and τ_{Ca} was the time constant for changes in calcium concentration.

$$\frac{d[Ca^{2+}]}{dt} = \frac{-[Ca^{2+}] + A * G_{Ca}}{\tau_{Ca}} \quad \text{Equation 4}$$

When calcium conductance in the dendritic compartment increased the concentration of calcium above a threshold, Ca_o there was an increase in dendritic potassium conductance, G_{KCa} (Equation 5). BD , the amplitude of potassium conductance increase, corresponded to the given level of $[Ca^{2+}]$. In the model, G_{KCa} increased incrementally (in proportion to BD) as long as $[Ca^{2+}]$ was above Ca_o . When the membrane potential of the dendritic compartment dropped below its threshold, THD , the calcium conductance was no longer driven upward and tended to decay with time constant τ_{GCa} toward zero. As G_{Ca} approached zero, the calcium concentration also decreased. When it fell below Ca_o , then G_{KCa} was no longer being augmented and it in turn began to decay exponentially back to zero.

$$\frac{dG_{KCa}}{dt} = \begin{cases} \frac{-G_{KCa}}{\tau_{GKD}} & \text{if } [Ca^{2+}] < Ca_o \\ \frac{-G_{KCa} + BD}{\tau_{GKD}} & \text{if } [Ca^{2+}] \geq Ca_o \end{cases} \quad \text{Equation 5}$$

Parameter values are given in Table 4. This formalism represents a simplification that reduces computational overhead while maintaining a sufficiently accurate representation of the network dynamics. Since we are not addressing questions of precise mechanisms underlying network oscillations, this model is sufficient. With the exception of the leakage membrane current, the activation and inactivation of each current was described using these differential equation and integrated using methods previously described (MacGregor, 1977).

Synaptic Currents

The postsynaptic potentials (PSPs) were simulated using a dual-alpha function equation (Equation 6). The parameters that distinguish the different PSPs (i.e. resulting from the activation of a glutamate receptor as opposed to a GABA receptor) are the amplitude of the PSP, g_{max} , and the time course, described by τ_1 and τ_2 (Table 5 and refer to Methods).

$$G(t) = g_{max} / \tau_1 - \tau_2 \{ g^* \exp(-t/\tau_1) - g^* \exp(-t/\tau_2) \} \quad \text{Equation 6}$$

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Single Thalamic Cell Model

Figure 1.

Membrane current models for each cell. The soma had a leak current, G_{leak} , that consists of a sodium and potassium current. This current was responsible for maintaining the resting membrane potential. There was a voltage dependent potassium current, G_{K1} which acted as a delayed rectifier. The low threshold calcium current, G_T , was responsible for the internal oscillations and G_H was a hyperpolarizing activated cation current. Neither G_T nor G_H (shaded grey) were explicitly modeled (refer to text). G_{K2} was a second voltage dependent potassium current with a longer time constant and was responsible for the between burst after-hyperpolarization. The dendritic currents include a calcium current G_{Ca} and a calcium dependent potassium current $G_{K[Ca]}$.

Figure 2.

Effects of simulated NE actions and LC activation on sensory thalamic neuronal responsiveness to synaptic input. Post-stimulus time histograms (PSTHs) were used to measure the responses of single cells to simulation or physiological activation of afferent inputs. A.) In the model the magnitude and modal latency of the response to simulated single whisker stimulation were measured at the peak of the largest bin post-stimulus. Under initial (control) model conditions, the network approximated the state of an awake but quietly resting animal (i.e. absence of sleep spindles and low probability of activation of the low threshold calcium current). When single whisker stimulation was simulated under this initial condition, the peak response was 243 Hz at a modal latency of 7 ms post-stimulus (above). As “simulated NE” was added to the model, the leaky potassium current was reduced and the resting membrane potential increased to -45.3 mV. When single whisker stimulation was simulated under this ‘NE-activated’ condition, the peak response was 324 Hz (133% increase) at a modal latency of 5 ms post stimulus (below). B.) In the intact, quietly resting, awake rat VPM thalamic neuron responses to whisker pad electrical stimulation were recorded before (control - above) and during tonic (1.0 Hz - below) activation of the ipsilateral LC nucleus. In the case shown each histogram represents the neuronal discharge pattern generated during $n=30$ whisker stimulus presentations (stimulus onset = 0). For this

cell whisker-evoked discharge was enhanced 31% above control levels (28.1 to 36.8 Hz) during LC stimulation and demonstrated a 22% decrease in modal latency (11.3 ms to 8.8 ms).

Figure 3.

NE modulation of G_{K-leak} . To better understand the complex nature of the response of the VPM/nRT network to simulated activation of NE postsynaptic mechanisms, phase diagrams were used to explore the working space that defines the response domains of individual cells to simulated activation of NE. X-axis equals the percent decrease in G_{K-leak} conductance in the nRT and the y-axis equals the percent decrease in G_{K-leak} conductance in the VPM. The effect of activating NE receptors in the VPM and the nRT were independently modulated by varying the model parameter G_{K-leak} (refer to Figure 1 for an explanation). The effect of

increasing NE activation was to decrease I_{leak} and thereby depolarize the cell's resting membrane potential. Simulating an increase in NE activation in VPM but not nRT (x-axis at 0) initially caused no change in the response to simulated single whisker stimulation. However, as the I_{leak} current was halved (y-axis approximately 50%) the responsiveness of VPM cells to simulated sensory input, as measured by the PSTH, decreased. When NE activation was further increased the responsiveness of VPM cells increased compared to baseline conditions. As NE action was moderately increased in both populations (i.e. both x and y axes at about 50%), cells responded with an increased probability of discharge and sometimes a decreased modal latency. However, for large increases in NE action in both populations (x and y axes greater than 75%) the probability of cell responses decreased. Changes stated within the diagram are for the majority of cells. Refer to Table 1 for details on the distribution of responses throughout the network. B) Illustrative PSTHs demonstrate the representative cases from each area of the phase space. PSTH notations are the same as Figure 2A.

Figure 4.

NE Modulation of PSP Amplitude. The diagram shown here illustrates the effects of changing excitatory and inhibitory synaptic efficacies in VPM and nRT cells. The X-axis indicates increasing amplitude of the IPSP and the y-axis indicates increasing amplitude of the EPSP. The net effect of changing PSP amplitudes was similar to the effects observed by altering the leak current. However, a much larger operating region, resulting in increased responsiveness and decreased modal latency of VPM cells, was observed with alteration of PSP amplitudes. Although increasing the amplitude of the EPSPs alone did not change the

responsiveness of VPM cells to simulated sensory input (x-axis = 1.0), concomitant moderate increases in IPSP amplitude yielded increases in the amplitude of the response and decreases in modal latency (x-axis = 2.0). If both the EPSP amplitude and the IPSP amplitude were tripled, the responsiveness of VPM cells decreased. Changes stated within the diagram are for the majority of cells. Refer to Table 2 for details on the distribution of responses throughout the network. B) Example PSTHs illustrate representative modeled effects within PSP amplitude phase space. PSTH notations are the same as Figure 2A.

Figure 5.

Modulation of thalamic neuron responsiveness to excitatory synaptic input across a range of tonic LC output. PSTH's illustrate the bi-phasic (inverted-U) response relationship observed for LC-mediated modulation of the response of a single VPM thalamic neuron to whisker pad electrical stimulation. Each histogram sums unit activity during an equivalent number of whisker pad stimulus presentations. Data were collected during control and tonic ipsilateral LC stimulation periods (0.5, 1.0, 5.0 Hz; 10 uA). For this cell, peak enhancement (above Control) of whisker-evoked discharge was observed at 0.5 Hz LC stimulation. Higher frequencies (1.0, 5.0 Hz) of LC tonic stimulation also enhanced, but to a lesser degree, the whisker evoked excitatory response of the cell.

Figure 6.

LC-noradrenergic pathway modulation of sensory thalamic neuron responsiveness.

Poststimulus time histograms (PSTH's) histograms illustrate the effects of increasing tonic frequencies of locus coeruleus (LC) electrical stimulation on whisker-evoked responses of simultaneously recorded VPM thalamic neurons. Spike train activity for individual cells was recorded from an awake rat before (control) and during tonic activation (0.5, 1.0, or 5.0 Hz at 10 μ A) of the ipsilateral LC nucleus. Each histogram represents the neuronal discharge pattern generated during $n=30$ whisker stimulus presentations (stimulus onset = 0). A. In some cells (top row) an increasing range of tonic activation of LC produced a monotonic suppression of whisker-evoked discharge. B. In other cells (middle row) whisker-evoked discharge was progressively enhanced across the range of stimulus frequencies tested. C. However, in many cells (bottom row) stimulus-evoked responses were enhanced at low LC stimulation frequencies (0.5–1.0 Hz) and suppressed at higher stimulus frequencies (5.0 Hz), yielding an inverted-U response function for LC-induced modulatory actions in these neurons. Thus, both facilitation and suppression of responsiveness to synaptic input can be observed simultaneously in neighboring thalamic neurons with increased tonic output from

the LC. Inset numbers represent the summed probability that the neuron will discharge in response to the whisker pad stimulation.

Table 1
Effects of Simulated NE Modulation of $G_{K Leak}$ on VPM Thalamic Network Dynamics

Distribution of changes in cell responsiveness and latency to simulated synaptic input after modulation of $G_{K Leak}$ current. The first column on the left identifies the magnitude of leak current changes and the cell population where such changes were implemented. Numbers in the four columns to the right indicate the percentage of cells in the model that underwent a change in responsiveness to synaptic input following leak current changes.

	Increased Responsiveness	Decreased Responsiveness	Both increased Responsiveness and decreased Latency	Unchanged
50% decrease in both populations	20%	10%	5%	0
25% decrease in VPM only	0	95%	0	5%
75% decrease in VPM only	75%	20%	0	5%
Decrease in nRT only	0	0	0	100%
75% decrease in both populations	20%	75%	0	5%

Table 2
Effects of Simulated NE Modulation of PSP Amplitude on VPM Thalamic Network Dynamics

Distribution of changes in cell responsiveness and latency to sensory driven synaptic input after modulation of EPSP or IPSP amplitude. The first column on the left indicates how PSP magnitude was modified. The next column indicates the number of initially *unresponsive* cells that became responsive to simulated synaptic input following PSP change(s), i.e. ‘gating’ effect. The remaining five columns indicate the number of initially *responsive* cells (percentages in parentheses) that expressed a change or no change in responsiveness to simulated synaptic input following PSP modulation. The percentages are based upon the total number of cells displaying responses under baseline conditions (n=213).

	Cells Gated	Increased Responsiveness	Decreased Responsiveness	Both Increased Responsiveness and Decreased Latency	Decreased Latency	Unchanged
Double EPSP	223	0	30 (14%) #	0	11 (5.3%)	162 (76%)
Double IPSP	0	0	60 (28%)	0	0	153 (72%)
Double Both	336	10 (4.7%) ##	34 (16%)	71 (33.3%)	15 (7%)	72 (34%)
Triple EPSP *	223	3 (1.5%)	14 (6.6%)	0	156 (73%)	15 (7%)
Triple IPSP	0	0	90 (42%)	0	0	123 (58%)
Triple Both **	90	0	113 (53%)	60 (28%)	23 (10.8%)	2 (1%)
Triple EPSP, Double IPSP	223	3 (1.5%) ###	14 (6.5%)	149 (70%)	0	48 (17%)
Triple IPSP, Double EPSP	214	9 (4.1%)	109 (51%)	38 (18%)	0	57 (26.9%)

* 25 cells (11.8%) increased latency not included in table or phase plot

** 15 cells (7%) increased latency not included in table or phase plot

10 cells (4.7%) decreased responsiveness and latency, not included in table or phase plot

11 cells (5.2%) increased responsiveness and latency, not included in table or phase plot

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12 cells (5.9%) increased responsiveness and latency, not included in table or phase plot
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Table 3
Effect of LC stimulation on VPM Thalamic Neuron Responsiveness to Sensory Driven Synaptic Input

Distribution of changes in cell responsiveness and latency during electrical stimulation of the LC. The first column on the left identifies the type of neuromodulatory action observed. The adjacent columns to the right indicate the number and percentage of cells that underwent changes from the baseline conditions, respectively. These data are based on a total of 74 cells recorded from 6 animals. “Gating” effects were observed in 34/74 cells that were initially unresponsive to whisker pad stimulation.

	Thalamus	
Facilitation	29/40	72.5%
Suppression	8/40	20.0%
No effect	3/40	7.5%
“Gating”	22/34	64.7%

Table 4
Parameters for each conductance described in the model

Table of constant values and time constants used for each equation in the appendix to model synaptic currents and membrane conductance's. The first column on the left identifies the type of cellular mechanism being modeled. The adjacent columns to the right indicate the parameters, values, and equilibrium potential used in modeling equations. Parameters of leak current ($G_{\max}$) are used for ohm's law (the integrative form is Eq. 1); parameters of the potassium conductance's are used in Eq. 2; calcium conductance parameters are used in Eq. 3; calcium concentration parameters are used in Eq. 4; calcium activated potassium parameters are used in Eq. 5

Conductance	Parameter	Value	Equilibrium Potential (mV)
Leak Current	$G_{\max}$	4.4	-70.0
Potassium – rectifying, G_{K1}	B_1 τ_{GK1}	20.00 5	-85.0
Potassium – slow G_{K2}	B_2 τ_{GK2}	5.00 100	-85.0
Calcium Conductance, G_{Ca}	D τ_{GCa}	0.2 5.0	120
Calcium Concentration, $[Ca^{2+}]$	A τ_{CA}	0.1 20.0	
Calcium activated Potassium, GKD	BD τ_{GKD}	200 100	-85.0