

# Inhibitory Interactions Between Ferret Thalamic Reticular Neurons

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**Shu, Yousheng and David A. McCormick.** Inhibitory interactions between ferret thalamic reticular neurons. *J Neurophysiol* 87: 2571–2576, 2002; 10.1152/jn.00850.2001. The thalamic reticular nucleus (nRt) provides an important inhibitory input to thalamic relay nuclei and is central in the generation of both normal and abnormal thalamocortical activities. Although local inhibitory interactions between these neurons may play an important role in controlling thalamocortical activities, the physiological features of this interaction have not been fully investigated. Here we sought to establish the nature of inhibitory interaction between nRt neurons with intracellular and extracellular recordings in slices of ferret nRt maintained in vitro. In many nRt neurons, intracellular recordings revealed spontaneous inhibitory postsynaptic potentials (IPSPs). In addition, the local excitation of nRt cells with glutamate led to the generation of IPSPs in the intracellularly recorded nRt neuron. These evoked IPSPs exhibited an average reversal potential of  $-72$  mV and could be blocked by picrotoxin, a GABA<sub>A</sub>-receptor antagonist. These results indicate that nRt neurons interact locally through the activation of GABA<sub>A</sub> receptor-mediated inhibitory postsynaptic potentials. This lateral inhibition may play an important role in controlling the responsiveness of these cells to cortical and thalamic excitatory inputs in both normal and abnormal thalamocortical function.

## INTRODUCTION

The thalamic reticular nucleus (nRt) is a collection of GABAergic neurons surrounding the dorsal thalamus and provides a major source of inhibitory synaptic input to thalamocortical neurons. Recent investigations have revealed an important role for the nRt in the control and generation of both normal and abnormal thalamocortical activities, particularly in relation to the generation of rhythms (reviewed in McCormick and Bal 1997; McCormick and Contreras 2001; Steriade et al. 1993, 1997). The ability of nRt neurons to locally inhibit one another has figured prominently in theories of thalamocortical operation, in particular, in the generation of spindle waves and the prevention of seizure-like activities (see Huntsman et al. 1999; McCormick and Bal 1997). These theories have been based in part on anatomical evidence for axonal and dendrodendritic interactions between thalamic reticular cells, evidence that is still somewhat controversial (Cox et al. 1996; Deschênes et al. 1985; Ide 1982; Liu and Jones 1999; Montero and Singer 1984; Ohara 1988; Pinault and Deschênes 1998; Pinault et al. 1995, 1997; Scheibel and Scheibel 1966). Direct physiological investigations of inhibitory interactions between these GABAergic neurons have either been limited to the perigeniculate nucleus (Sanchez-Vives et al. 1997), which

most investigators regard as a portion of the nRt, or through the application of local electrical stimulation, which is not limited to the activation of nRt GABAergic inputs alone (Huntsman and Huguenard 2000; Huntsman et al. 1999; Zhang et al. 1997). We therefore investigated further the characteristics of inhibitory interactions between thalamic nRt neurons using slices of the ferret thalamus. Additional information about these and related findings may be obtained at <http://www.mccormicklab.org>.

## METHODS

Adult male or female ferrets, 3- to 4-mo-old, were anesthetized deeply with sodium pentobarbital (30 mg/kg) and killed by decapitation. All ferrets were cared for and used in accordance with all appropriate regulatory guidelines. The forebrain was rapidly removed, and the hemispheres were mounted onto a vibratome (DSK microslicer; Ted Pella). Coronal slices were formed at a thickness of 400  $\mu$ m. A modification of the technique developed by Aghajanian and Rasmussen (1989) was used to increase tissue viability. During preparation of slices, the tissue was placed in a solution in which NaCl was replaced with sucrose while maintaining an osmolarity of 307 mosM. After slicing, the nRt and surrounding tissue (including some of the internal capsule and portions of dorsal thalamic nuclei) were dissected free. Then the nRt slices were transferred to an interface-style recording chamber (Fine Sciences Tools) and allowed  $\geq 2$  h to recover. The bathing medium contained the following (in mM): 124 NaCl, 2.5 KCl, 2 MgSO<sub>4</sub>, 1.25 NaH<sub>2</sub>PO<sub>4</sub>, 2 CaCl<sub>2</sub>, 26 NaHCO<sub>3</sub>, 10 dextrose, and was aerated with 95% O<sub>2</sub>-5% CO<sub>2</sub> to a final pH of 7.4. To increase the viability of the tissue, when the nRt slices were placed in the recording chamber, they were superfused for 15 min with an equal mixture of the normal NaCl and sucrose-substituted solution. Throughout the remainder of the experiment, the slices were bathed in normal medium. Bath temperature was maintained at 35–36°C. After 2 h of recovery, extracellular multiple unit recordings were performed from the slices to determine the general health and presence of spontaneous activities in the nRt and to confirm the location of this nucleus.

Intracellular recording electrodes were formed on a Sutter Instruments P-80 micropipette puller from medium-walled glass (1BF100, WPI). Micropipettes were filled with 4 M cesium acetate (CsAc) to reduce K<sup>+</sup> conductances, 50 mM QX-314 to block Na<sup>+</sup> conductances, and 2% biocytin for intracellular labeling of recorded neurons. The electrodes were beveled on a Sutter Instruments beveler (BV-10) from 120–140 to 60–80 M $\Omega$ . Intracellular recordings were performed with an Axoclamp-2B amplifier (Axon Instruments). These recordings were digitized at 44 kHz (Neuro-Corder, Neuro Data Instruments) and recorded on VCR tapes for subsequent off-line analysis.

After a recording was complete, the slice was then fixed in 4% paraformaldehyde in 0.1 M phosphate buffer. Slices were subse-

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quently transferred to 30% sucrose in 0.1 M phosphate buffer and sectioned on a freezing stage sliding microtome at 100  $\mu\text{m}$  thickness. Standard avidin-biotin-horseradish peroxidase reaction with diaminobenzidine was used to visualize biocytin-filled neurons (Horikawa and Armstrong 1988). The sections were counterstained with cresyl violet to facilitate the localization of the nRt. Our biocytin fills were sufficient for localization of the neuron within the thalamic reticular nucleus. It was not possible to follow putative axons within our sections and therefore not possible to examine for possible axon collaterals within the nRt.

Drugs (glutamate and picrotoxin) were applied locally with the pressure-pulse technique in which a brief pulse of pressure (10–250 ms; 200–350 kPa) was applied to the back of a broken microelectrode (1–4  $\mu\text{m}$  tip diameter) to extrude 1–20  $\mu\text{l}$  of solution. Application of glutamate (1 mM; RBI) was performed at varying locations and

depths within the slice to locate a good response. Picrotoxin (500  $\mu\text{M}$ ; Sigma) was applied to the surface of the slice within approximately 50  $\mu\text{m}$  of the entry point of the recording electrode.

## RESULTS

Coronal slices of the nRt were formed from the anterior portions of the ferret thalamus. The nRt was localized in these slices with epi-illumination as a slightly darker band forming a C-shape within the corticothalamic and thalamocortical fibers, just lateral to the main relay nuclei of the anterior-dorsal thalamus (Fig. 1, *A* and *E*). Extracellular multiple- and single-unit recordings were used in every case to confirm the location of the nRt. Thalamic reticular neurons discharge action poten-

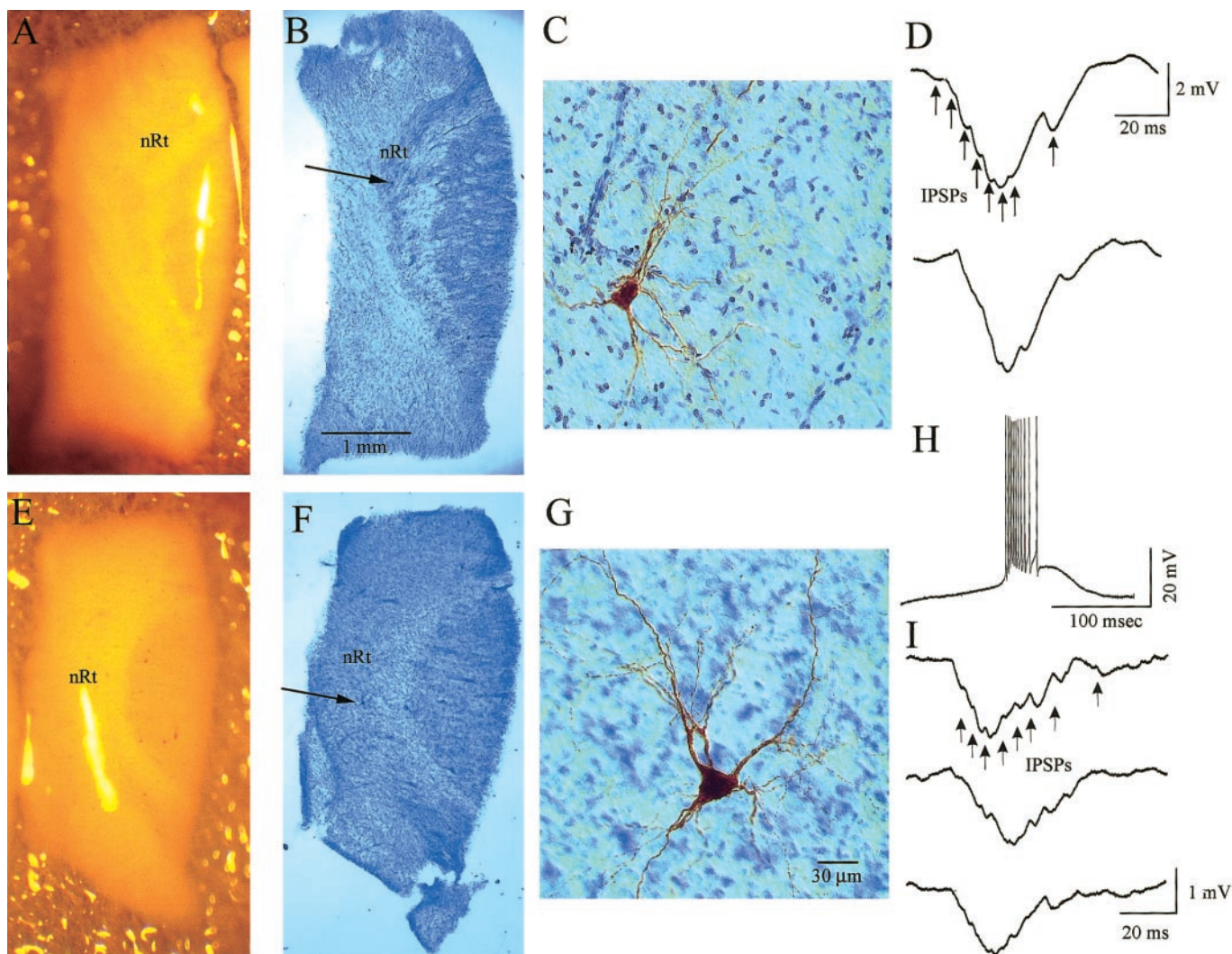


FIG. 1. Histochemical and physiological identification of inhibitory postsynaptic potentials (IPSPs) in thalamic reticular GABAergic neurons. *A*: photograph of a slice of the ferret thalamus in the *in vitro* recording chamber. In the chamber, the thalamic reticular nucleus (nRt) is visible as a C-shaped darker band running within the white matter lateral to the main relay nuclei. *B*: Nissl stain of the slice in *A*. Here the nRt is clearly visible as a C-shaped band within the white matter. The arrow indicates the location of the cell body of the recorded cell. *C*: photograph of the cell body and proximal dendrites of the recorded cell. *D*: IPSP barrages that occurred spontaneously in the nRt neuron recorded in *C*. *E*: photograph of another nRt slice in which a cell was recorded and labeled. Here the nRt is less visible, although it was clearly identifiable with extra- and intra-cellular recordings as a nucleus of thin-spiking, bursting neurons within the white matter outside the relay nuclei. *F*: photograph of the Nissl-stained section and the location of the recorded cell. *G*: soma and dendritic morphology of the recorded nRt neuron. *H*: low-threshold  $\text{Ca}^{2+}$  spike-mediated burst of action potentials generated by the cell in *G*. The pattern of action potentials generated are typical for nRt neurons. *I*: IPSPs evoked in the cell of *G* following the local application of glutamate (1 mM in micropipette). Note that the pattern of IPSPs during the barrage is similar to the pattern of action potentials in a single cell burst.

tials in a characteristic manner, with unusually thin spikes and in high-frequency (>250 Hz) bursts in which the spike frequency increases and then decreases (Domich et al. 1986; Sanchez-Vives et al. 1997). Following the localization of the nRt, 24 neurons were recorded intracellularly with biocytin-containing microelectrodes. Of these cells, 11 were intracellularly labeled. Counterstaining with cresyl violet revealed in all cases that the cell bodies and dendrites of the recorded neurons were within the nRt (Fig. 1, B, C, F, and G). In addition, immediately after obtaining a stable intracellular recording, and prior to the block of action potentials by the intracellular diffusion of QX-314, nRt neurons generated low-threshold Ca<sup>2+</sup> spike-mediated bursts of action potentials. These bursts exhibited the acceleration-deceleration of action potential generation frequency characteristic of nRt neurons (Fig. 1H).

Thalamic reticular neurons exhibited inhibitory postsynaptic potentials (IPSPs) that could appear either spontaneously (Figs. 1D and 3; *n* = 13) or in response to local application of glutamate (1 mM in micropipette; *n* = 20; Figs. 1I, 2, and 4). Putative IPSPs were identified from their shape, possessing a rapid hyperpolarizing phase followed by a more gradual depolarizing phase or, often, as a cluster or barrage of hyperpolarizing events (Figs. 1–4). The local application of glutamate consisted of the rapid (5–20 ms) extrusion of a small (approximately 10 μm diameter) “picodrop” within the slice. The entry point of the drug-applying micropipette was within 50–100 μm of the entry point of the intracellular recording electrode. The depth of the glutamate-applying pipette was adjusted while the response to local application of glutamate was monitored. Direct glutamate-induced depolarizations of nRt neurons were often encountered. However, we also often found that application of glutamate in isolated locations of the neuropil re-

sulted in the generation of a barrage of IPSPs in the recorded neuron after a delay of ≤50–100 ms (Figs. 1I, 2, and 4). Moving the drug-applying micropipette by only a few microns could abolish this response, suggesting that it resulted from the activation of either a single nRt neuron or a local group of nRt cells. Although the region of nRt from which IPSPs could be evoked was not systematically examined, in most neurons we were able to evoke these inhibitory events from a majority of the penetrations of the glutamate-applying micropipette, indicating that it was not a rare event.

The compound IPSPs evoked by application of glutamate ranged in size (at a membrane potential of –30 to –40 mV) from 1.6 to 15 mV in amplitude, with the average being 4.2 mV (±3.7 mV; *n* = 20). The large IPSPs occurring spontaneously also ranged in amplitude from 1 to 11 mV with an average of 3.7 (±2.8 mV; *n* = 13). Close examination of the IPSPs evoked by local application of glutamate, or occurring spontaneously, often revealed that they were composed of multiple smaller IPSPs of <1 mV (Figs. 1D, I, and 4B). The time of arrival of these smaller IPSPs could exhibit a pattern of increasing and decreasing frequency, much in the same pattern as the generation of spikes during burst discharges in nRt cells (Fig. 1D). These IPSPs typically increased from an average frequency of 299 (±117) Hz, to peak at 373 (±142) Hz, and then to tail off to around 150 Hz or less (*n* = 7). Similarly, the first interspike interval in low-threshold Ca<sup>2+</sup> spike-mediated bursts in nRt cells was 319 (±119) Hz, peaking at 358 (±111) Hz before decreasing to around 150 Hz or less (*n* = 7) (Fig. 1H). In addition, the amplitude of the individual IPSPs could exhibit facilitation in amplitude during the arrival of a high-frequency barrage of IPSPs (e.g., Fig. 1D), as we have demonstrated previously with dual intracellular recordings between

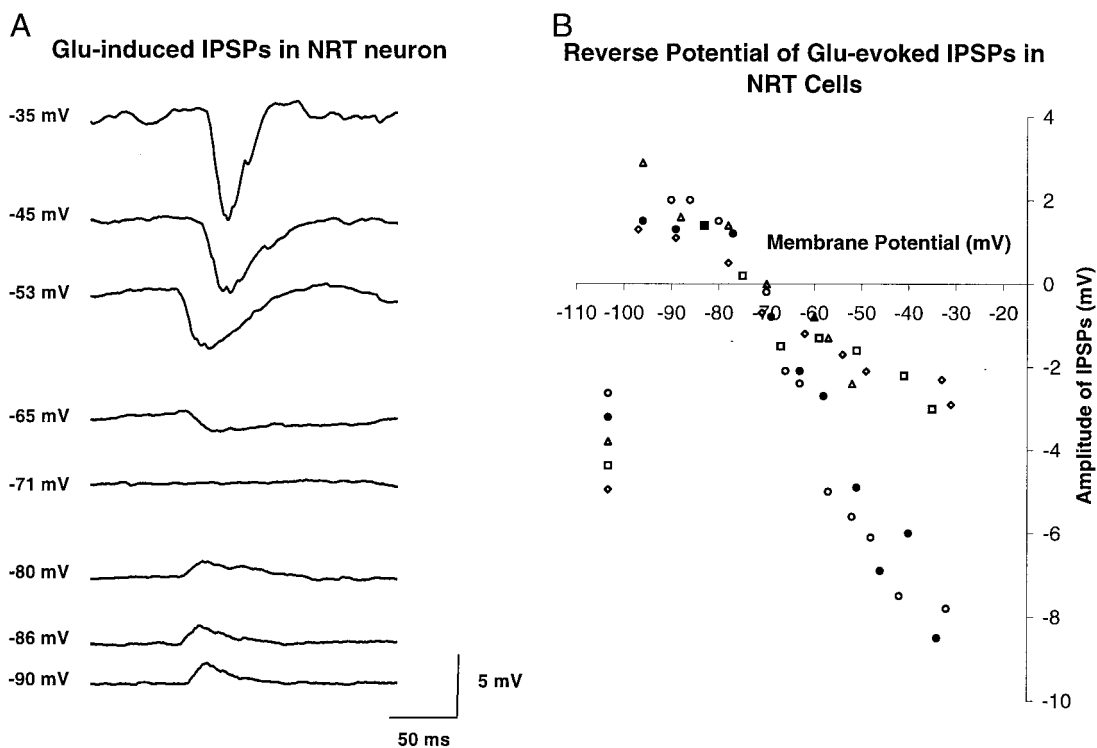


FIG. 2. Reversal potential of glutamate-evoked IPSPs in nRt. A: examples of IPSPs evoked in this thalamic reticular cell while the cell was depolarized or hyperpolarized to different membrane potentials. The IPSPs reverse at about –71 mV. B: average reversal potential from 5 different thalamic reticular cells. Glutamate was applied at the beginning of each trace in A.

GABAergic perigeniculate neurons and thalamocortical cells (Kim and McCormick 1998).

The reversal potential of glutamate-evoked IPSP barrages was determined by plotting the amplitude of the evoked response versus the membrane potential prior to the IPSP barrage. The postsynaptic membrane potential was depolarized and hyperpolarized to different values through the intracellular injection of current ( $\text{Na}^+$  and  $\text{K}^+$  conductances were reduced by including QX-314: 50 mM and CsAc: 4 M in the recording pipette). The average reversal potential of the evoked IPSPs was  $-72.1 \pm 2.0$  mV ( $n = 5$ ) (Fig. 2), which is consistent with a  $\gamma$ -aminobutyric acid-A ( $\text{GABA}_A$ ) receptor-mediated increase in  $\text{Cl}^-$  conductance.

Prior investigations of nRt neurons have revealed that these cells can exhibit spontaneous activity, sometimes generating a burst-burst-tonic pattern of action potentials (Bal and McCormick 1993). Similarly, here, our multiple unit recordings revealed, in a subset of slices ( $n = 15$ ), the presence of both ongoing and periodic spontaneous activities (Fig. 3A). These activities often revealed cells or groups of cells generating periods of activity characterized by one to three bursts of spikes followed by tonic, single-spike activity. Intracellular recordings from nRt neurons in these slices revealed spontaneous barrages of IPSPs that occurred in a pattern that is consistent with the activity in the extracellular recordings. In the cell of Fig. 3B, the IPSPs appear as the arrival of one to three large ( $>5$  mV) IPSPs followed by smaller IPSPs for a few seconds. Although the larger IPSPs appeared to consist of individual, smaller components, it was usually not possible to distinguish these clearly (Fig. 3B). The local application of glutamate to cells that exhibited spontaneous IPSPs could also evoke IPSP barrages (Fig. 3C).

Local application of the  $\text{GABA}_A$  receptor antagonist picrotoxin ( $500 \mu\text{M}$  in micropipette) resulted in either a block or a large reduction in the amplitude of the glutamate-evoked IPSPs (Fig. 4;  $n = 7$ ), indicating that these are mediated by  $\text{GABA}_A$  receptors. This effect was not reversible in our recording situation.

## DISCUSSION

The GABAergic neurons of the thalamic reticular nucleus form an inhibitory intermediary between the interactions of the thalamus and the cerebral cortex. The inhibitory nRt cells are densely innervated by collaterals from thalamocortical and corticothalamic cells, both of which produce strong excitatory postsynaptic responses (EPSPs) (reviewed in Steriade et al. 1997). Regulating these excitatory influences are GABAergic inputs. Approximately 6–30% of synapses on thalamic reticular neurons are GABAergic (Liu and Jones 1999; Williamson et al. 1994). There are several known sources of GABAergic inputs to the nRt cells, including projections from the substantia nigra reticulata or the basal forebrain and other forebrain structures (Asanuma 1994; Jourdain et al. 1989; Pare et al. 1990), and from other thalamic reticular neurons. Communication between thalamic reticular neurons has been proposed to occur through both axonal and dendrodendritic connections, although the precise nature of this is still controversial and may vary with age and species (Deschênes et al. 1985; Liu and Jones 1999; Pinault and Deschênes 1998; Pinault et al. 1995, 1997; Sanchez-Vives et al. 1997; Scheibel and Scheibel 1966; Yen et al. 1985). In contrast to inhibitory interactions between GABAergic neurons, recent electrophysiological investigations of cortical GABAergic cells have shown that these can be

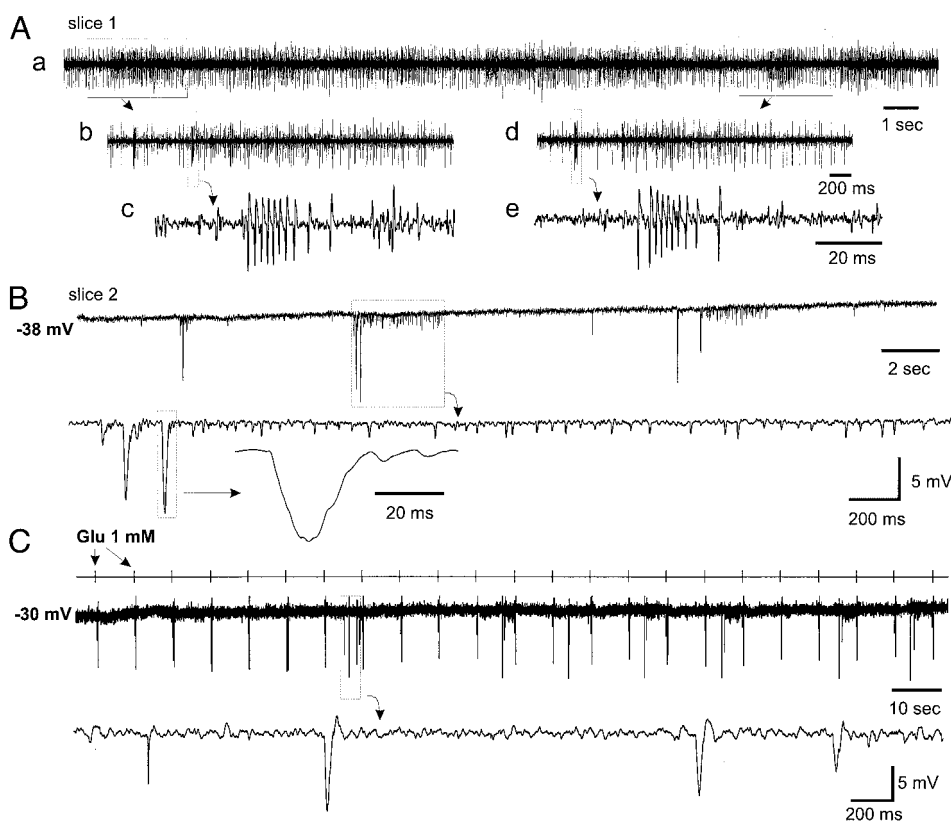


FIG. 3. Spontaneous bursts of IPSPs in thalamic reticular neurons. *A*: extracellular recording of spontaneous multiple unit activity in the nRt of this slice. Multiple neurons were spontaneously active, with periodic and rhythmic bursts of activity. Three different time scales are illustrated. *B*: intracellular recordings of spontaneous barrages of IPSPs in a single thalamic reticular neuron in another slice. At the onset of the IPSP barrages, the IPSPs were large in amplitude (5–10 mV) and then became much smaller ( $<2$  mV) in amplitude. *C*: local application of glutamate results in the activation of a barrage of IPSPs in the recorded nRt neuron.

## Blockade of Glu-induced IPSPs by picrotoxin in nRt cells

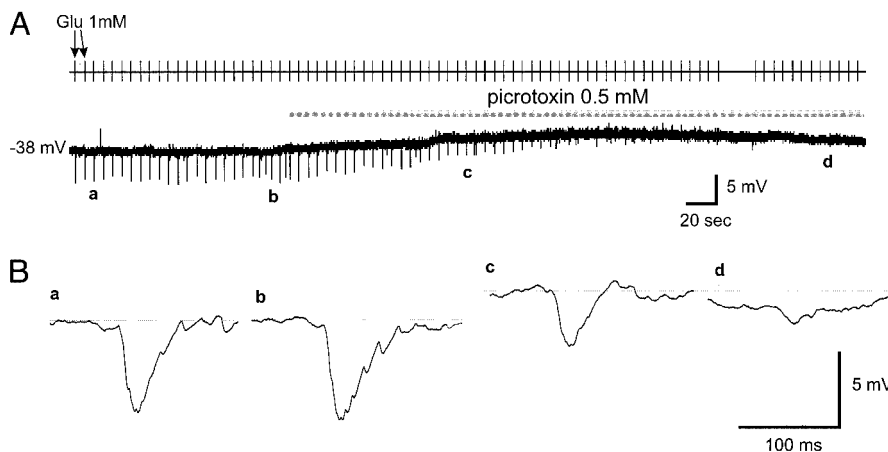


FIG. 4. Glutamate-evoked IPSPs in thalamic reticular cells are antagonized by the local application of the  $\gamma$ -aminobutyric acid-A ( $GABA_A$ ) receptor antagonist picrotoxin. *A*: local application of glutamate results in the activation of barrages of IPSPs (expanded in *B* for detail). The local application of picrotoxin results in a small depolarization of the membrane potential and a block of the phasic IPSPs evoked by local glutamate application. The presence of a small depolarization may indicate that this cell was under tonic  $GABA_A$  receptor-mediated inhibition.

coupled together through gap junctions, resulting in a relative tendency for these cells to synchronize (Beierlein et al. 2000; Gibson et al. 1999; Swadlow et al. 1998). Gap junctions appear to also be present in the rodent thalamic reticular nucleus and again may serve to synchronize neuronal activities (Landisman et al. 2002).

The influence of nRt activation on other nRt neurons has been directly investigated only through the application of local electrical stimulation (Huntsman and Huguenard 2000; Huntsman et al. 1999; Ulrich and Huguenard 1996; Zhang et al. 1997), which results in the activation of both  $GABA_A$  and  $GABA_B$  receptor-mediated IPSPs. However, since local electrical stimulation will activate all elements, including the severed axons from extrathalamic sources, it is unclear whether or not these  $GABA$ ergic IPSPs arise from the activation of nRt neuronal processes. Intracellular recordings *in vivo* from thalamic reticular neurons reveal strong IPSPs in response to local electrical stimulation (Bazhenov et al. 1999). The most likely source of these IPSPs are from the activation of other thalamic reticular cells or their axons. Previously, we have circumvented the problems of electrical stimulation through the activation of the  $GABA$ ergic neurons of the ferret perigeniculate nucleus with the local application of glutamate as well as the recording of synaptic potentials during the generation of network activity (e.g., spindle waves) (Sanchez-Vives et al. 1997). In these studies, we found that the  $GABA$ ergic neurons of the perigeniculate nucleus (PGN) exhibit a potent inhibitory influence on one another that is readily apparent with the local application of glutamate as well as during normal network activity (Bal et al. 1995; Kim and McCormick 1998). The most prominent role of the inter-PGN inhibition is in controlling the excitability and responsiveness of these  $GABA$ ergic neurons. The loss of  $GABA_A$ -mediated inhibition within the PGN results in increases in the response of these cells to excitatory inputs, which in turn results in an increase in size and duration of inhibition within the recipient thalamocortical neurons (Bal et al. 1995; Huguenard and Prince 1994; Kim et al. 1997). Since the perigeniculate nucleus is widely considered to be part of the thalamic reticular nucleus, this suggests that nRt neurons may influence each other in a similar manner.

Here, we demonstrate that this is indeed the case. The excitation of nRt neurons with glutamate readily resulted in the

activation of IPSPs in other nRt neurons ( $n = 20/24$  cells studied). In addition, many nRt cells exhibited spontaneous IPSPs that most likely arose from the spontaneous action potential activity of neighboring nRt neurons. Interestingly, the IPSPs recorded in nRt neurons often appeared as a high-frequency barrage of smaller IPSPs, at frequencies similar to that of action potentials generated by a bursting nRt neuron (see also Sanchez-Vives et al. 1997). These large IPSP barrages may be generated either through the activation of a single neighboring nRt cell or through the synchronized discharge of a group of nearby  $GABA$ ergic neurons (see Swadlow et al. 1998). Supporting the possibility that they were generated by a single neuron, we found that the IPSP barrages were very similar to those that we have previously recorded in thalamocortical neurons in response to the generation of a burst of action potentials in a single  $GABA$ ergic PGN cell (Kim and McCormick 1998; Kim et al. 1997). If the IPSPs recorded here in nRt cells were generated occasionally by a single presynaptic neuron, then it would suggest that at least some nRt cells can have a potent and large influence on neighboring  $GABA$ ergic neurons.

During slow wave sleep, thalamocortical networks can generate synchronized rhythms such as sleep spindles. Spindle waves are generated through a cyclical interaction between thalamic reticular and thalamocortical neurons in which a burst of action potentials in the thalamic reticular cells activates a large,  $GABA_A$  receptor-mediated IPSP in thalamocortical cells. The activation of this IPSP partially removes inactivation of the low-threshold  $Ca^{2+}$  current in thalamocortical cells, allowing some of these cells to generate rebound bursts of action potentials. This burst of activation potentials then again excites thalamic reticular cells, re-initiating the oscillation. However, the activation of thalamic reticular cells results in lateral inhibition within the thalamic reticular nucleus, which serves to dampen the number of action potentials generated by these cells. Indeed, in intracellular recordings in the ferret PGN, the depolarizing envelope caused by barrages of EPSPs arriving during spindle waves is shortened by the arrival of IPSPs, owing to the activation of neighboring  $GABA$ ergic neurons. Likewise, the activation of local  $GABA$ ergic neurons can also shorten the duration of low-threshold  $Ca^{2+}$  spikes, or even prevent their generation (Sanchez-Vives et al. 1997). The

blocking of these IPSPs with GABA<sub>A</sub> receptor antagonists results in a large increase in the excitability of these GABAergic neurons and the subsequent generation of large, synchronized discharges in thalamic networks (Bal et al. 1995; Huntsman et al. 1999; Sanchez-Vives et al. 1997). The present data, collected from the ferret nRt, are entirely consistent with this role of the lateral inhibitory interactions within this nucleus. Thus we propose that a major mechanism by which nRt neurons influence one another is through the activation of GABA<sub>A</sub> receptor-mediated increases in Cl<sup>-</sup> conductance, although the precise receptor subunits that mediate this response remain to be determined (Huntsman et al. 1996). This lateral inhibition can serve to dampen the overall excitability, as well as to reduce the amplitude and duration of both excitatory responses and low-threshold Ca<sup>2+</sup> spikes, perhaps in a “center-surround” mechanism. Therefore while gap junctions may play a role in the thalamic reticular nucleus (Landisman et al. 2002), inhibitory interactions between these cells are clearly important.

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