Nucleus-Specific Differences in $GABA_A$-Receptor-Mediated Inhibition Are Enhanced During Thalamic Development

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Huntsman, Molly M. and John R. Huguenard. Nucleus-specific differences in $GABA_A$-receptor-mediated inhibition are enhanced during thalamic development. *J. Neurophysiol.* 83: 350–358, 2000. Inhibitory postsynaptic currents (IPSCs) mediated by $GABA_A$ receptors are much slower in neurons of the thalamic reticular nucleus (RTN) versus those in the ventrobasal complex (VB) of young rats. Here we confirm and extend those findings regarding $GABA_A$ response heterogeneity especially in relation to development. Whole cell patch-clamp recordings were used to investigate $GABA_A$ spontaneous and electrically evoked IPSCs (sIPSCs/eIPSCs) in RTN and VB cells of different aged rats. Consistent with earlier findings, sIPSC duration at P8–12 was considerably longer in RTN (weighted decay time constant: $\tau_{D,W} = 56.2 \pm 4.9$ ms; mean ± SE) than in VB ($\tau_{D,W} = 15.8 \pm 1.0$ ms) neurons. Decay kinetics in RTN neurons did not differ at P21–30 (45.5 ± 4.7 ms) or P42–60 (51.6 ± 10.6 ms). In contrast, VB sIPSCs were significantly faster at both P21–30 ($\tau_{D,W} = 10.8 \pm 0.9$ ms) and P42–60 ($\tau_{D,W} = 9.2 \pm 0.4$ ms) compared with P8–12 animals. IPSCs displayed differential outward rectification and temperature dependence, providing further support for nucleus-specific responses. $\tau_{D,W}$ increased with membrane depolarization but with a net larger effect in VB. By contrast, $\tau_{D,W}$ was always smaller at higher temperatures but with relatively greater difference observed in RTN. Thus nuclear differences in $GABA_A$ IPSCs are not only maintained, but enhanced in the mature rodent under physiological conditions. These findings support our hypothesis that unique $GABA_A$ receptors mediate slowly decaying RTN IPSCs that are a critical and enduring feature of the thalamic circuit. This promotes powerful intranuclear inhibition and likely prevents epileptiform thalamocortical hypersynchrony.

INTRODUCTION

The reticular nucleus (RTN) is composed of GABAergic neurons and provides nearly all of the inhibitory neurotransmission to relay cells in the rodent ventrobasal complex (VB) (Benson et al. 1992; Houser et al. 1980; Ohara and Lieberman 1993; Williams and Faull 1987). RTN neurons send a major projection to relay nuclei and receive extensive innervation from collaterals of corticothalamic and thalamocortical fibers (Jones 1975). However, they also are connected internally to each other through sparse axon collaterals and dendrodendritic connections in rodents and cats (Cox et al. 1996; Deschênes et al. 1985; Pinault et al. 1997; Scheibel and Scheibel 1966; Yen et al. 1985). The intra-RTN connections are critical for regulating inhibitory output and phasic bursting activity in rodents and ferrets (Huguenard and Prince 1994; Huntsman et al. 1999; Sanchez-Vives et al. 1997; von Krosigk et al. 1993). Thus during thalamocortical oscillations, this intranuclear pathway may prevent the pathological hypersynchrony of absence epilepsy, although intracortical mechanisms are also likely to be important in the genesis of such synchrony (e.g., Steriade and Contreras 1998). The synaptic properties of RTN neurons indicate that these sparse intra-RTN connections, are compensated functionally with long-lasting $GABA_A$-receptor-mediated inhibitory postsynaptic currents (IPSCs). These IPSCs decay three times slower than those in VB neurons (Zhang et al. 1997) and are differentially modulated by $GABA_A$ receptor ligands (Akk et al. 1997; Huguenard and Prince 1994). These properties are likely the result of nucleus-specific expression of $GABA_A$ receptor subunits in the thalamus (Fritschy and Möhler 1995; Huntsman et al. 1996; Wisden et al. 1992).

$GABA_A$ receptor heterogeneity and function is determined ultimately by the combination of subunits within a pentameric chloride ion channel (Macdonald and Olsen 1994). Subunit mRNAs exhibit strict regional expression throughout the CNS (Wisden et al. 1992), and in the thalamus, the distribution is specific to individual nuclei (Huntsman et al. 1996). In addition, thalamic $GABA_A$ receptor subunits are regulated developmentally (Gambarana et al. 1991; Laurie et al. 1992; Poulter et al. 1992). In most thalamic nuclei, there is a developmental turnover of subunits somewhere between postnatal day 6 (P6) and P12 (Laurie et al. 1992). However, there are exceptions to this switch, especially in the RTN, where expression of the early postnatal subunits remain in the adult animal (Fritschy and Möhler 1995; Huntsman et al. 1996; Laurie et al. 1992; Wisden et al. 1992).

Previous studies have shown that differences in kinetic properties of IPSCs recorded in VB and RTN are likely due to distinct combinations of native $GABA_A$ receptors (Zhang et al. 1997). However, these experiments were carried out in young animals (P8–P12) and thus during the proposed developmental switch in subunit composition. To determine if developmental changes in receptor isoforms result in altered kinetic properties, spontaneous and evoked IPSCs were studied in the maturing and adult rat. In the present study, the biophysical properties of both spontaneous and evoked IPSCs were examined at three different ages: one early, at a stage when inhibitory synaptic activity first can be detected reliably (P8–12), which is during the switch; another time point 11 days subsequent to this switch (P21–30); and a final time point in the fully mature rat (P42–60). We also examined the effects of temperature and voltage-dependent modifications of IPSCs in VB and RTN neurons from adult rats to provide further support for functional heterogeneity in $GABA_A$ receptors.

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METHODS

Preparation of thalamic slices

All experiments were carried out in accordance with approved procedures (Protocol 4450/0) established by the Administrative Panel on Laboratory Animal Care at Stanford University. In these experiments, Sprague-Dawley rats of either sex were used from three different age groups: P8–12, P21–30, and P42–60. Animals were anesthetized with an intraperitoneal injection of 55 mg/kg pentobarbital sodium (Nembutal) until unresponsive. The anesthetized animals were decapitated, and brains were blocked, removed and placed in ice-cold, oxygen equilibrated (95% O_2-5% CO_2) choline chloride slicing solution for ~2–3 min. The slicing solution consisted of (in mM) 111 choline chloride ($C_5H_{11}ClNO$), 26 $NaHCO_3$, 10 glucose, 2.5 KCl, 1.25 NaH_2PO_4*H_2O, 10 $MgSO_4$*$7H_2O$, and 0.5 $CaCl_2$*$2H_2O$ and was adjusted to 290 mOsm. Horizontal slices were cut at a 200-μm thickness with a Vibratome (TPI, St. Louis, MO), hemi-sected, and submerged in preheated (32°C), oxygen-equilibrated physiological saline [which contained (in mM): 126 NaCl, 26 $NaHCO_3$, 10 glucose, 2.5 KCl, 1.25 NaH_2PO_4*H_2O, 2 $MgCl_2$*$6H_2O$, and 2 $CaCl_2$*$2H_2O$] for 1 h, and sections were allowed to cool to room temperature.

Electrophysiology

Whole cell patch-clamp recordings were obtained similarly to our previous study with noted exceptions (Zhang et al. 1997). Recordings were obtained from slices placed in a chamber with a continuous perfusion of physiological saline (2 ml/min) at room temperature. In some cases, the temperature was increased to 36°C by preheating the saline immediately before entering the recording chamber. A fine temperature probe (Cole Parmer, Vernon Hills, IL) was placed within 200 μm of the recording electrode to assure accurate measurements of the recorded cell. Recording pipettes were filled with cesium chloride adjusted to 7.3 pH and 290 mOsm. The solution contained (in mM) 135 CsCl, 5 lidocaine *N*-ethylbromide (QX-314), 2 MgCl2, 10 ethyleneglycol-bis (β-aminoethyl ether)-*N, N,N′,N′*-tetraacetate acid (EGTA; Sigma, St. Louis, MO), and 10 *N*-2-hydroxyethylpiperazine-*N′*-2-ethanesulfonic acid (HEPES; Sigma).

Thalamic neurons were voltage-clamped at a holding potential of −60 mV for continuous records of spontaneous and evoked inhibitory events using a List-Medical Patch Clamp amplifier (model L/M-EPC7, Darmstadt, Germany). Neurons were visualized using a fixed staged, upright microscope (Zeiss) equipped with a ×63 insulated objective, infrared (IR) illumination, Nomarski optics and an IR-sensitive video camera (COHU). Glass electrodes (KG-33 borosilicate glass, 1.0 mm ID, 1.5 mm OD; Garner Glass Company, Claremont, CA) were pulled in four stages with a Flaming/Brown micropipette puller (Model, P-87, Sutter Instruments, San Francisco, CA). All micropipette electrodes had a final resistance between 2.0 and 3.3 MΩ when filled with internal pipette solution. A bipolar tungsten electrode (impedance 0.1–1 MΩ, FHC, Brunswick, ME) was placed in RTN to activate neurons (0.5–2mA, 30–100 μs) and evoke inhibitory responses. Voltage dependence was assessed by determining the rectification ratio. For this purpose, amplitude, $\tau_{D,W}$ and charge were measured at both +60 and −60 mV for responses in individual neurons. Temperature dependence was estimated for all the following biophysical parameters: rise time, peak current amplitude, $\tau_{D,W}$, τ_{D1}, and τ_{D2} (1st- and 2nd-order exponential decay) using the equation, $Q_{10} = (X2/X1)^{10/(T2-T1)}$, where X = parameter and T = temperature (Otis and Mody 1992).

$GABA_A$-receptor-mediated IPSCs were isolated pharmacologically by bath application of the ionotropic excitatory amino acid receptor blockers: 6,7-dinitro-quinoxaline-2,3-dione (DNQX, 20 μm, RBI, Natrick, MA) and (±)-2-amino-5-phosphonopentanoic acid (AP-5, 100 μm, RBI) in physiological saline. All such glutamatergic excitatory responses were blocked within 2–3 min after the onset of perfusion. $GABA_B$ receptors were blocked with Cs^+ and QX-314 in the internal pipette solution. In some cases, the identity of the $GABA_A$-dependent IPSCs was confirmed by blockade with bath application of 10 μm bicuculline methiodide. Access resistance of all recorded cells included in this study were monitored constantly throughout each experiment and only used for analysis if it was <14 MΩ and stable (25% tolerance) for the duration of the experiment.

Data analysis

IPSCs were filtered at 1 kHz and stored in digitized form on videotape (model DR484, Neurodata). Continuous records of spontaneous events initially were collected with Axotape v2.0 (Axon Instruments, Foster City, CA), sorted with the customized software Detector v. 4.8 (J. R. Huguenard) and Metatape v14.0 (J. R. Huguenard) and analyzed with Scan software (courtesy of J. R. Dempster). Background root mean square (RMS) noise was determined from event-free portions in the control record or from recordings in which sIPSCs had been blocked with 10 μM bicuculline methiodide. A software trigger was set to only accept sIPSCs that were more than three times the RMS level for that particular recording. Evoked responses were collected with Clampex version 5.5.3 (Axon Instruments) and traces were fit with Clampfit version 6.0.1 (Axon Instruments) and Metatape. Data were analyzed with Origin (MicroCal Software, Northhampton, MA) and Excel (v7.0, Microsoft). Instat (v2.03 GraphPad, San Diego, CA) software was used to measure significance of all biophysical parameters using Student's *t*-tests, one-way ANOVA and Tukey-Kramer post hoc multiple comparisons test when one-way ANOVA tests yielded $P < 0.05$. The decay of averaged IPSCs ($N > 50$ events/cell) was fit to the following equation: $I = A_1\exp^{-t/\tau_{D1}} + A_2e^{-t/\tau_{D2}}$ and weighted decay time constant ($\tau_{D,W}$) was determined by the following formula: $\tau_{D,W} = (\tau_{D1}A_1 + \tau_{D2}A_2)/(A_1 + A_2)$.

RESULTS

Neurons in the RTN and VB complex were identified by their position and morphology in the ventral and dorsal thalamus. In horizontal sections, the RTN is positioned medial to the large fiber bundle of the internal capsule and lateral to VB and separated from the latter by the thin fiber bundle of the external medullary lamina (Jones 1985). All recordings were made ≥50 μm within these borders for each respective nuclear group to guarantee recordings were obtained from identified neurons. An additional physiological criterion for cell identification was the demonstration of the characteristically slower inactivation of the transient calcium current in RTN versus VB neurons (Huguenard and Prince 1992).

All $GABA_A$-receptor-mediated IPSCs were recorded from RTN and VB neurons with cesium-chloride-filled electrodes. IPSCs reversed near the chloride equilibrium potential (~0.5 mV) and thus were inward events at a −60-mV holding potential (Fig. 1). $GABA_A$-receptor-mediated IPSCs were isolated from $GABA_B$ and ionotropic glutamate receptors (see METHODS) and completely blocked by bath application of bicuculline methiodide (not shown). The data in this report represent voltage-clamp recordings from 128 neurons (58 RTN and 70 VB) in thalamic slices from rats of the three different age groups.

sIPSCs in RTN versus VB neurons in young rats within postnatal days 8–12

sIPSCs recorded in the RTN of P8–12 rats were slowly decaying events with a mean weighted decay time constant

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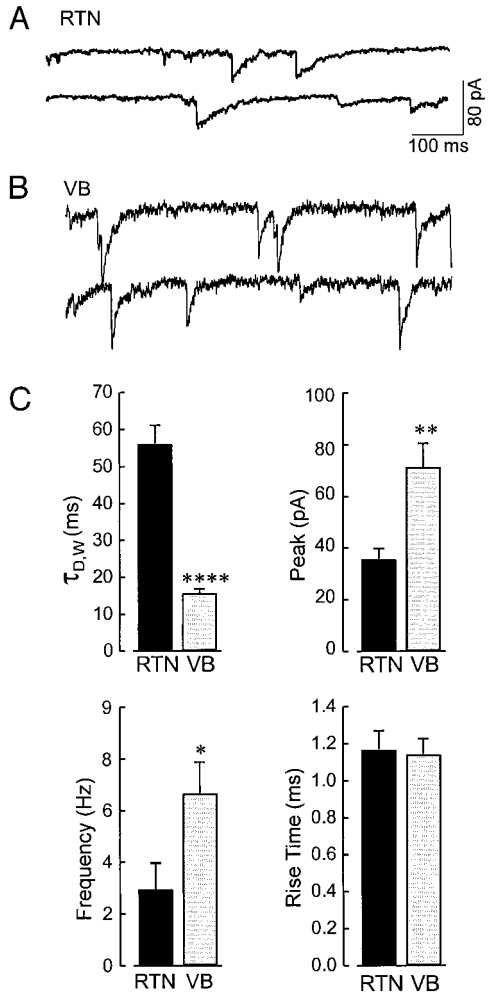


FIG. 1. Spontaneous inhibitory postsynaptic currents (sIPSCs) recorded from neurons of the reticular nucleus (RTN) and ventrobasal complex (VB) from acute thalamic slices of rats aged P8–12. Continuous traces of ~2 s of recording time of an RTN (*A*) and VB (*B*) neuron. *C*: histogram of mean values (± SE) illustrating the differences of weighted time constant, $\tau_{D,W}$, amplitude, and frequency. Note the disparity in the slowly decaying events of sIPSCs in RTN neurons compared with VB. All values were subject to Student's *t*-tests, ****$P < 0.0001$, **$P < 0.01$, and *$P < 0.05$.

($\tau_{D,W}$) of 56.2 ± 4.9 ms ($n = 10$; Fig. 1*A*). Consistent with previous results (Zhang et al. 1997), sIPSCs in VB neurons decayed about three times faster ($\tau_{D,W}$ = 15.8 ± 1.0 ms, n = 18, $P < 0.0001$, Student's *t*-test) than sIPSCs from RTN neurons at this age (Fig. 1*B*). As expected, peak current amplitude was highly variable in both types of thalamic neurons (Zhang et al. 1997). Mean sIPSC amplitude and frequency were lower in RTN neurons (−35.7 ± 4.0 pA, 3.0 ± 1.0 Hz, $n = 10$) than in VB neurons (−71.0 ± 8.9 pA, 6.7 ± 1.2 Hz, $n = 18$; amplitude: $P < 0.01$; frequency: $P < 0.05$; Student's *t*-test). RTN sIPSC amplitudes in these immature neurons were somewhat smaller than reported in our earlier study, likely reflecting improved methodology for recording and detecting these events (see DISCUSSION). However, consistent with our earlier report, sIPSC rise times (calculated as the time required to rise from 10 to 90% of peak amplitude) were similar for RTN (1.2 ± 0.1 ms, $n = 10$) and VB (1.1 ± 0.1 ms, $n = 18$, $P = 0.9$, Student's *t*-test) neurons. The higher frequency and amplitude of events in VB neurons were correlated with increased baseline noise levels. The different background noise values in VB (5.9 ± 0.5 pA) versus RTN neurons (2.7 ± 0.2 pA, $n = 10$, $P < 0.0001$) may reflect differences in ambient GABA levels (Tia et al. 1996) between these two nuclei.

Developmental changes of sIPSCs in older animals

To determine if similar decay kinetics exist in older animals, sIPSCs were recorded from both RTN and VB cells in juvenile (P21–30) and adult (P42–60) rats and compared with IPSCs from P8–12 rats (Figs. 2 and 3). sIPSCs in RTN neurons were variable from cell to cell at all ages but no significant changes in decay rate were found at either P21–30 ($\tau_{D,W}$ of 45.5 ± 4.7 ms, $n = 27$) or P42–60 (51.6 ± 10.6 ms, $n = 10$; $P = 0.48$, 1-way ANOVA; Fig. 2, *A* and *C*). Mean peak IPSC amplitude in RTN neurons showed a decreasing trend in older animals (P21–30: −31.2 ± 2.0 pA, $n = 28$; P42–60: −25.5 ± 2.6 pA, $n = 10$); however, these values failed to reach statistical significance ($P = 0.1$, 1-way ANOVA; Fig. 2, *A* and *C*). Rise times in RTN neurons were indistinguishable at all ages, showing similar values at P21–30 (1.12 ± 0.1 ms, $n = 27$) and at P42–60 (1.15 ± 0.1 ms, $n = 10$, $P = 0.9$, 1-way ANOVA; Figs. 1*C* and 2*C*). The frequency of sIPSCs in RTN neurons did not show significant changes at P21–30 (2.4 ± 0.3 Hz) or P42–60 (3.8 ± 1.3 Hz, $P = 0.4$, 1-way ANOVA; Fig. 2, *A* and *C*). Baseline noise levels were also similar at all three ages. Overall, sIPSCs in RTN appear to have taken on a mature form as early as P8–12.

We next examined the biophysical properties of sIPSCs in VB neurons in the maturing rat (Fig. 2, *B* and *D*). By contrast with RTN neurons, sIPSCs in VB neurons were significantly faster at both P21–30 ($\tau_{D,W}$ 10.8 ± 0.9 ms, $n = 29$) and P42–60 (9.2 ± 0.4 ms, $n = 11$; $P < 0.0001$, 1-way ANOVA; Tukey-Kramer multiple comparisons test for P8–12 vs. P21–30 and P8–12 vs. P42–60: $P < 0.001$). Mean peak current amplitude was also significantly smaller at P21–30 (−35.2 ± 2.4 pA, $n = 29$) and like the weighted decay values, these differences were maintained at P42–60 (−38.2 ± 3.4 pA, $n = 11$; $P < 0.0001$, 1-way ANOVA; Tukey-Kramer multiple comparisons test for 8–12 vs. 21–30: $P < 0.001$, 8–12 vs. 42–60: $P < 0.01$; Fig. 2, *B* and *D*). sIPSC properties for typical VB neurons at P8–12 and P21–30 are shown in Fig. 3. The averaged sIPSC is seen to be smaller, faster and overall much less effective (lower total charge) in the P21–30 neuron. Histograms representing peak amplitude and duration measured at 50% of the total decay (or half-width) for the two neurons illustrate different distributions of events at these two developmental stages (Fig. 3*B*). Note that the amplitudes and half-widths were largely overlapping in their distributions but that the peak of the distribution was shifted toward faster and briefer events in the more mature neuron. In general, these distributions could not be readily fitted with simple Gaussian distributions, suggesting that each was composed of at least two subpopulations. These differences in kinetics may be the result of a different degree of electrotonic filtering in young versus mature neurons. The latter have a more extensive dendritic elaboration (Warren and Jones 1997) that might result in increased filtering of electrotonically distal events. Yet the trend was the opposite—events in more mature neurons were briefer. Further, the rise times measured in older animals were not significantly different (P21–30: 1.1 ± 0.1 ms, $n = 29$;

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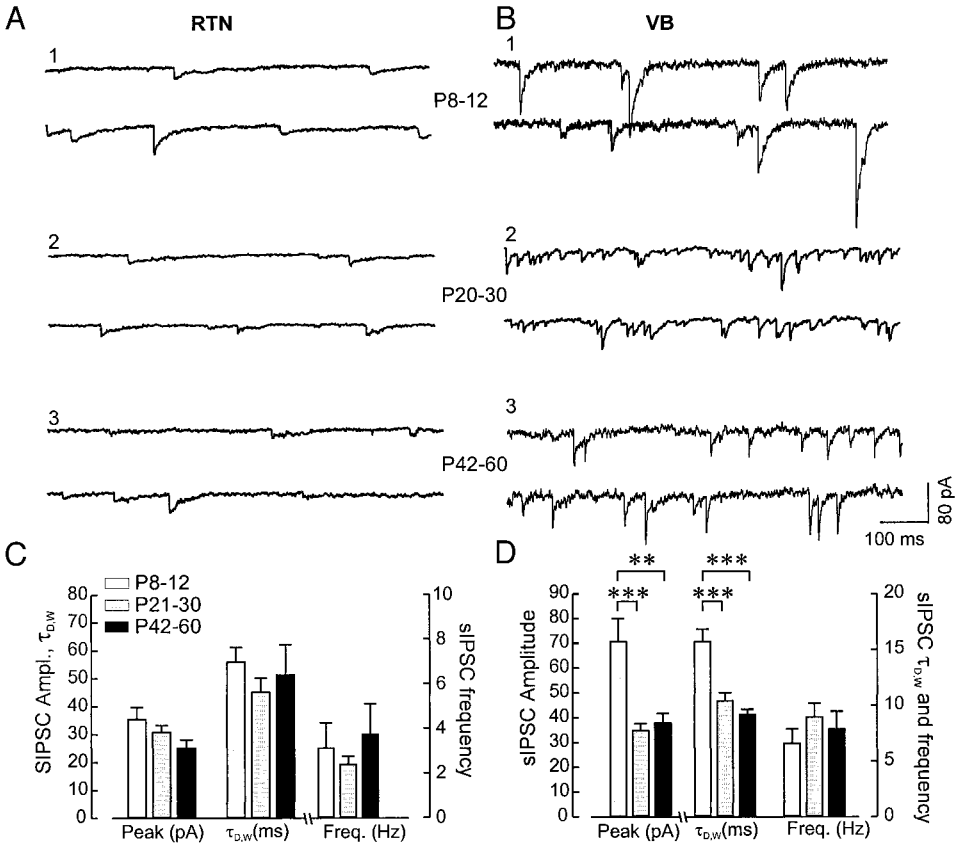


FIG. 2. sIPSCs in RTN and VB neurons from thalamic slices of young and adult rats. *A, 1–3*: continuous raw traces of sIPSCs in RTN at P8–12, P21–30, and P42–60. Note the lack of variability of sIPSCs in RTN neurons at all ages examined. *B, 1–3*: continuous raw traces of sIPSCs in VB neurons at P8–12, P21–30, and P42–60. Histogram of mean values (± SE) of sIPSCs in VB neurons at all 3 ages, as indicated for RTN (*C*) and VB (*D*). Brackets are derived from 1-way ANOVA with post hoc Tukey-Kramer multiple comparisons test, $^{**}P < 0.01$ and $^{***}P < 0.001$.

P42–60: 1.2 ± 0.1 ms, $n = 11$, $P = 0.9$, 1-way ANOVA) from those measured at the youngest ages, suggesting the electrotonic changes do not contribute to the observed developmental differences in VB IPSC kinetics. sIPSC frequency in VB neurons varied slightly at different developmental stages, but this effect was not significant (P21–30: 9.1 ± 1.1 Hz, $n = 29$; P42–60: 8.2 ± 1.6 Hz, $n = 11$, $P = 0.4$, 1-way ANOVA; Fig. 2*D*). We also did not observe any changes in baseline noise levels between VB neurons recorded at the youngest and oldest age groups.

Electrically evoked IPSCs in RTN and VB

To further compare IPSC kinetics at different stages of development, the properties of electrically evoked IPSCs (eIPSCs) were examined in both nuclei at all three age groups (Fig. 4). eIPSCs were evoked from stimulation of fibers in the RTN using a bipolar tungsten electrode. Test pulses were given at varying intensities (500 μA to 2 mA) until an inward IPSC occurred. The intensity then was adjusted downward until a minimal response was obtained, and the stimulus duration (90–160 μS) was increased by 50% to obtain a 1.5-threshold response. eIPSC decay kinetics could not be well fitted with double exponential decay functions and therefore were quantified as the time necessary for both 50% (half-widths) and 90% of total decay. All estimates were from averages of ≥20 individual events from 15 individual RTN and VB neurons each held at −60 mV.

The half-widths of eIPSCs in RTN neurons were slightly longer at P8–12 (50.9 ± 4.9 ms, $n = 7$) compared with both P21–30 (34.7 ± 3.7 ms, $n = 17$) and at P42–60 (30.6 ± 6.6 ms, $n = 7$, $P < 0.05$, 1-way ANOVA); however, post hoc Tukey-Kramer comparison tests did not reveal any pairwise differences among age groups (Fig. 4, *A* and *C*). The times required for 90% decay of total peak amplitude were similarly affected, (P8–12: 222.4 ± 19.9 ms, $n = 7$; P21–30: 173.3 ± 21.3 ms, $n = 17$; P42–60: 168.1 ± 35.1 ms, $n = 7$), although these differences were not statistically significant. The peak current amplitude of eIPSCs in RTN neurons was comparable at all ages, at P8–12 (−390.4 ± 96.6 pA, $n = 7$), P21–30 (−362.8 ± 70.3 pA, $n = 17$), or P42–60 (−274.4 ± 69.1 pA, $n = 7$).

In contrast with the developmental change in sIPSCs, eIPSCs half-widths in VB neurons did not show any significant changes from P8–12 (16.8 ± 1.4 ms, $n = 11$) to P21–30 (15.4 ± 2.3 ms, $n = 8$) and the P42–60 (16.5 ± 3.0 ms, $n = 7$, $P = 0.4$, 1-way ANOVA) age groups (Fig. 4, *B* and *D*), suggesting that different mechanisms regulate decay of spontaneous and evoked responses (see DISCUSSION). Similarly, the 90% decay time was unaffected by development (P8–12: 58.1 ± 4.1, $n = 11$; P21–30: 67.8 ± 7.5 ms, $n = 8$; P42–60: 80.2 ± 14.4 ms, $n = 7$, $P = 0.2$, 1-way ANOVA; Fig. 4*D*). The peak current amplitude did not change significantly during development: (P8–12: −868.3 ± 298 pA, $n = 11$; P21–30: −601.9 ± 192 pA, $n = 8$; P42–60: −655 ± 204 pA, $n = 7$, $P = 0.7$, 1-way ANOVA; Fig. 4*D*).

Voltage dependence of sIPSCs in RTN and VB in adult rats

We have shown that sIPSCs reach full maturity by the third postnatal week in the rodent thalamus, therefore further analysis of sIPSCs was obtained after P21. Voltage dependence of

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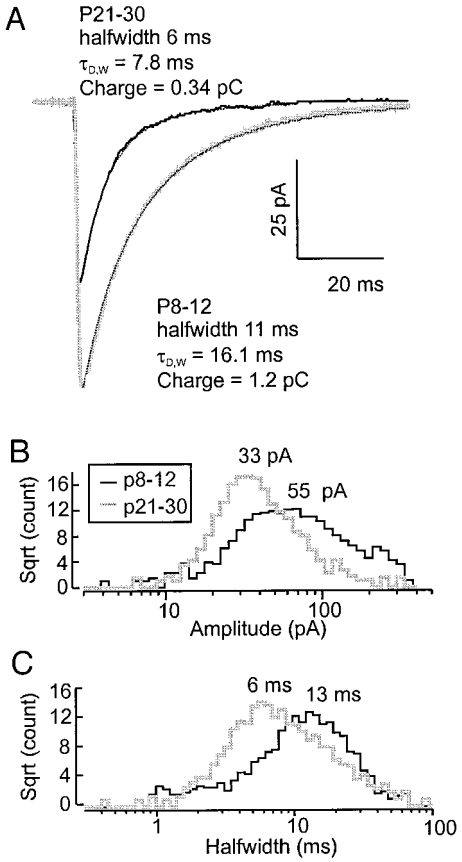


FIG. 3. Developmental changes of sIPSCs in VB neurons. *A*: averaged sIPSCs superimposed on the same time scale to illustrate decreased peak current amplitude and duration in 2 VB neurons, 1 from a P8–12 rat (n = 616 events) and 1 from a P21–30 rat (n = 274 events). Histograms of sIPSC amplitude (*B*) and half-width (*C*) during a 4-min recording period. Two distributions were superimposed to compare the VB sIPSCs at the different ages.

sIPSCs was determined by examining peak current amplitude, weighted time constant and overall charge with cells voltage clamped at +60 mV (Fig. 5) compared with −60 mV. In RTN neurons, sIPSC amplitude was not voltage dependent, with similar peak absolute values at −60 mV (−26.6 ± 3.7 pA) and at +60 mV (22.8 ± 2.8 pA, P = 0.4, n = 6; Fig. 5*A*). In contrast, the $\tau_{D,W}$ of sIPSCs recorded in the RTN at −60 mV (44.3 ± 6.0 ms) was much briefer than sIPSCs recorded at +60 mV (94.2 ± 6.7 ms, P <0.001, n = 6). Overall charge measured at −60 mV (1.25 ± 0.29 nC) was much lower than the values estimated at +60 mV (2.16 ± 0.24 nC, P < 0.05, n = 6). By contrast, in VB neurons, peak current amplitude at −60 mV was smaller (27.9 ± 4.5 pA) but not significantly (P = 0.1, n = 8) than at +60 mV (37.0 ± 3.4 pA; Fig. 5*B*). Similar to the RTN responses, the $\tau_{D,W}$ of sIPSCs in VB neurons decayed at about half the rate at −60 mV (9.7 ± 0.5 ms) than at +60 mV (23.5 ± 1.8 ms, n = 8, P < 0.0001; Fig. 5*B*). The overall charge of sIPSCs in VB neurons was also greatly affected by voltage with much lower values at −60 mV (0.26 ± 0.05 nC) compared with +60 mV (0.86 ± 0.1 nC, P <0.0001, n = 8). Voltage dependence likely involves subtype selective mechanisms (Burgard et al. 1996) that might dictate further differences between these two types of thalamic neurons. We compared the degree of voltage dependence (see METHODS) in terms of amplitude, $\tau_{D,W}$ and charge at +60 mV/−60 mV and found that VB neurons were slightly more sensitive to changes in membrane potential than RTN neurons (Fig. 5*C*). Ratios for both RTN and VB were analyzed in a single sample t-test measured against a hypothetical value of 1.0. From these data, it was determined that amplitude was not enhanced at positive holding potentials for either RTN or VB; however, $\tau_{D,W}$ and charge were found to be voltage dependent in both RTN and VB neurons of adult rats. VB neurons yielded larger rectification ratios than RTN neurons for amplitude (RTN: 0.92 vs. VB: 1.50, P > 0.05), $\tau_{D,W}$ (RTN: 2.22 vs. VB: 2.42, P > 0.05) and charge (RTN: 1.9 vs. VB: 3.8, P <0.05). These data indicate outward rectification of sIPSCs in both nuclei; however, the net responses in VB neurons were more sensitive to holding potentials than RTN neurons.

Temperature dependence of sIPSCs in RTN and VB of adult rats

We were interested in determining whether the nucleus-specific IPSC kinetics in thalamus were maintained under conditions of physiological temperature. Figure 6 illustrates temperature-dependent changes in sIPSC decay kinetics recorded in 12 RTN and VB neurons in adult rat thalamic slices. An increase in temperature from 26 to 36°C resulted in a significant reduction in the decay of sIPSCs in both RTN ($\tau_{D,W}$ at 26°C: 42.1 ± 4.9 ms, and 36°C: 22.3 ± 2.4 ms, P < 0.01; Fig. 6, *A* and *D*) and VB neurons ($\tau_{D,W}$ at 26°C: 12.0 ± 1.1 ms and 36°C: 5.8 ± 0.51 ms, P < 0.001; Fig. 6, *B* and *D*). The Q_{10} of the decay rate measured by $\tau_{D,W}$ or the first (τ_{D1}) or second

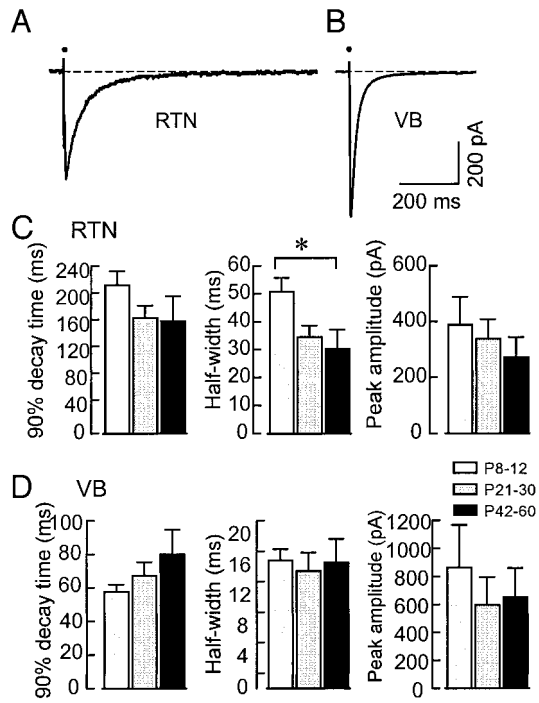


FIG. 4. Properties of monosynaptic electrically evoked IPSCs (eIPSCs) recorded in RTN and VB neurons of rats show limited developmental change in decay kinetics. *A* and *B*: averaged eIPSCs from RTN neurons (n = 5) and VB neurons (n = 7). *C* and *D*: histogram of mean values (± SE) of eIPSCs at all 3 ages, as indicated for RTN (*C*) and VB (*D*). Single bracket indicates a significant decrease in older animals using a 1-way ANOVA, *P < 0.05; however, post hoc Tukey-Kramer tests were not significant. ●, onset of stimulus.

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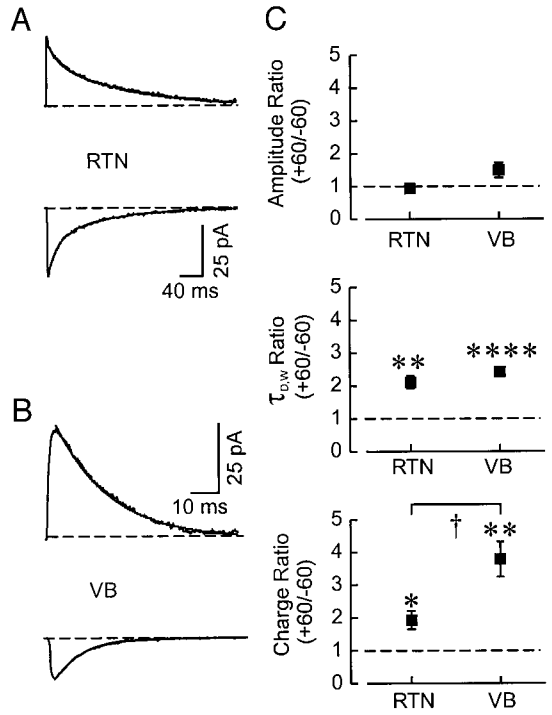


FIG. 5. Voltage dependence of sIPSCs in RTN and VB neurons from adult rats. *A*: averaged sIPSCs in an RTN neuron measured at +60 mV holding potential (*top*, $n = 83$ events) and −60 mV (*bottom*, $n = 86$ events). *B*: averaged events recorded from a VB neuron at +60 mV (*top*, $n = 62$ events) and at −60 mV holding potential (*bottom*, $n = 255$ events). Note the higher sensitivity of VB neurons for both amplitude and $\tau_{D,W}$. *C*: ratios of amplitude, $\tau_{D,W}$ and charge of sIPSCs in RTN ($n = 6$) and VB ($n = 8$) neurons as measured by the values obtained at +60 mV/−60 mV. Significant voltage-dependent modulation of response was determined by a 1 sample Student's *t*-test measured against a hypothetical mean of 1 and indicated by $*P < 0.05$, $**P < 0.01$, $****P$, 0.0001, $\dagger P < 0.05$ and represents the significant difference of VB voltage-dependent sensitivity compared with RTN.

(τ_{D2}) time constants obtained from biexponential fits were 2.0–2.5 (Fig. 6*C*) and in agreement with temperature-dependent changes in hippocampal neurons (Otis and Mody 1992). Interestingly, temperature dependent changes in amplitude were observed specifically in RTN neurons and resulted in a significant increase in peak current amplitude in all RTN neurons examined at higher temperatures (26°C: −29.14 ± 2.2 pA vs. 36°C: −54.43 ± 3.7 pA, $n = 5$, $P < 0.001$; Fig. 6*D*). The increased amplitude of sIPSCs in RTN neurons had a significant effect on the overall charge such that even with an accelerated decay, there was no significant difference between the charge measured at room (1.2 ± 0.1 nC) or physiological (1.2 ± 0.2 nC, $n = 5$, $P = 0.9$) temperatures (Fig. 6*D*). Conversely, the lack of increased peak current amplitude in VB neurons resulted in a decrease in charge at 36°C (0.2 ± 0.03 nC) compared with room temperature (0.3 ± 0.05 nC, $n = 7$, $P < 0.05$; Fig. 6*D*). Overall with the exception of rise times in RTN neurons and amplitude of VB neurons, the remaining biophysical parameters displayed similar temperature dependent alterations.

DISCUSSION

In a previous report on GABA$_A$-receptor-mediated IPSCs in the thalamus of young rats, quantitative analysis of IPSCs revealed decay time constants were two to three times slower in RTN neurons than IPSCs recorded in the VB complex (Zhang et al. 1997). In the present study, consistent with the previous findings, the decay kinetics of IPSCs in RTN within this same age range were also three times slower than IPSCs in VB. Using additional measures of decay kinetics, the present study detailed four principal findings. First, decay kinetics of synaptic sIPSCs in RTN neurons were similar at all age groups examined. Second, sIPSC duration and amplitude in VB neurons varied with development. This indicates that the func-

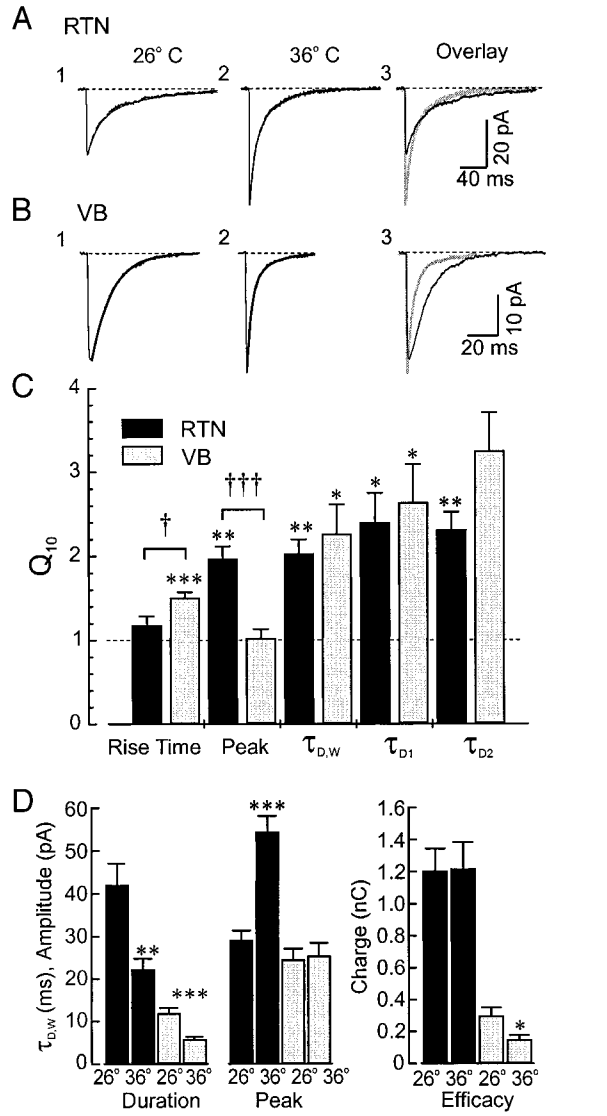


FIG. 6. Temperature-dependent changes in sIPSCs of RTN and VB neurons in adult rats. *A, 1–3*: averaged sIPSCs in RTN neuron at room temperature (RT) at 26°C (*A1*) and at 36°C (*A2*). *A3*: averaged sIPSCs superimposed on the same time scale to illustrate increased peak current amplitude and decreased duration in RTN neuron recorded at physiological temperatures (36°C). *B, 1–3*: averaged sIPSCs in VB neuron at room temperature (*B1*) and at 36°C (*B2*). *B3*: averaged sIPSCs superimposed on same time scale to illustrate decreased duration in decay kinetics at physiological temperatures. *C*: Q_{10} values indicating temperature dependence in RTN and VB neurons for rise time, peak current amplitude, $\tau_{D,W}$, and 1st- and 2nd-order exponential decay (τ_{D1} and τ_{D2}). Note the nucleus-specific increase in peak current amplitude of RTN sIPSCs at physiological temperatures. · · · (at $Q_{10} = 1.0$), value expected for lack of temperature dependence. *D*: averaged values for $\tau_{D,W}$, amplitude and charge at 26 and 36°C in both RTN and VB. Values were analyzed with a Student's *t*-test comparing the 2 temperature settings in RTN and VB, $*P < 0.05$, $**P < 0.01$, $***P < 0.001$.

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tional IPSC heterogeneity between VB and RTN actually is increased in the fully mature rat compared with that previously reported for immature animals (Zhang et al. 1997). Third, further characterization in adult animals revealed that sIPSCs in VB neurons were more voltage dependent than sIPSCs in RTN, providing further support for $GABA_A$ receptor heterogeneity. Fourth, sIPSCs recorded at physiological temperatures (36°C) were much briefer in both RTN and VB respective to their normal control decay times at room temperature. But the relative difference remains with RTN sIPSCs almost four times slower than VB responses.

In the present study, the values obtained for the decay of $GABA_A$-receptor-mediated sIPSCs in rats within the P8–12 age range were slightly faster in both RTN and VB neurons than previously reported (Zhang et al. 1997). We attribute this discrepancy to the way in which spontaneous events were detected. In the present study, we used an objective criterion to collect all events greater than the background noise level (3 times rms noise). This increased sensitivity in sIPSC detection resulted in detecting smaller events that would have otherwise been rejected incorrectly.

Differences in sIPSCs are dependent on differential distribution of thalamic $GABA_A$ receptors

The present results show a significant reduction in peak current amplitude and decay kinetics of sIPSCs in developing VB neurons. Moreover, VB neurons had a greater degree of outwardly rectifying responses. The unique temperature-, voltage-, and age-dependent properties of $GABA_A$-receptor-mediated responses in VB neurons likely reflect region selective expression of $GABA_A$ receptor subunits. The temporal changes in synaptic inhibitory events follow a similar trend toward faster IPSCs observed in hippocampal (Hollrigel and Soltesz 1997) and cerebellar (Tia et al. 1996) neurons. In all these studies, the time course of the transformation to faster IPSCs correlates with the timing of subunit turnover (Fritschy et al. 1994; Gambarana et al. 1991; Laurie et al. 1992). In addition, the developmental stabilization of sIPSC decay kinetics in VB neurons in the present study also correlates with maintained levels of subunit mRNAs in the adult rodent. Unaltered $GABA_A$-receptor-mediated IPSCs throughout postnatal development in RTN may reflect a lack of developmental change of subunits expressed in this nucleus (Huntsman and Jones 1995; Huntsman et al. 1996; Wisden et al. 1992). Thus we find little evidence for a developmental switch in $GABA_A$ receptor function in RTN postnatally. These data contrast the study by Gibbs et al. (1996), who found an age-related increase in GABA-evoked chloride currents from dissociated cultures of RTN neurons. The discrepancy between these two findings may be due to differences in receptors and/or extracellular space. The present study examined synaptic receptors, whereas Gibbs et al. (1996) studied the responses to bulk application of exogenous GABA, which will presumably activate both synaptic and extrasynaptic receptors. In addition, factors that influence GABA levels in the extracellular space, and therefore receptor activation, such as uptake or diffusion (see following text) (Draguhn and Heineman 1996; Roepstorff and Lambert 1992; Thompson and Gahwiler 1992), will be very different in the two preparations.

Heterogeneity and modulation of synaptic $GABA_A$-receptor-mediated sIPSCs are governed by the properties created by differing combinations of postsynaptic receptors. A number of studies have suggested that synaptic $GABA_A$-receptor-mediated currents (Hollrigel and Soltesz 1997; Jones et al. 1998; Otis and Mody 1992; Poisbeau et al. 1999; Tia et al. 1996; Xiang et al. 1998; Zhang et al. 1997) likely result from expression of a specific combination of $GABA_A$ receptor subunits (Fritschy and Möhler 1995; Laurie et al. 1992; Wisden et al. 1992). This is supported further by the differential effects of specific $GABA_A$ ligands (e.g., zolpidem, clonazepam, loreclezole, flunitrazepam, and midazolam) on the decay of synaptic IPSCs (Akk et al. 1997; Hollrigel and Soltesz 1997; Otis and Mody 1992; Perrais and Ropert 1999; Strecker et al. 1999). Other more subtle and dynamic modulation of synaptic $GABA_A$-receptor-mediated IPSCs also may involve subunit-specific phosphorylation of serine and threonine residues (Jones and Westbrook 1997; Poisbeau et al. 1999).

$GABA_A$-receptor mediated-currents are likely influenced by gating, deactivation (dependent on unbinding of agonist), and desensitization (Angelotti and Macdonald 1993; Burgard et al. 1996; Gingrich et al. 1995; Jones et al. 1998; Puia et al. 1991; Sigel et al. 1990; Verdoorn et al. 1990; Wafford et al. 1993). Different receptor subtypes likely have different binding and unbinding properties. Thus receptors that mediate synaptic responses with longer deactivation times are more efficient at binding GABA than others (Jones et al. 1998). It appears that α_3 subunits may be a crucial component of receptors that exhibit long-lasting GABA-mediated currents as opposed to receptors containing α_1 and α_2 subunits (Gingrich et al. 1995; Serafini et al. 1998; Verdoorn 1994). The prolonged IPSCs in RTN neurons (Zhang et al. 1997) may reflect in part the predominance of α_3 subunits in this nucleus compared with limited expression in relay nuclei (Fritschy and Möhler 1995; Huntsman et al. 1996; Wisden et al. 1992). When examined at both the mRNA and protein levels, α_3 subunits are recognized as a primary α subunit in the RTN of adult rodents (Fritschy and Möhler 1995; Wisden et al. 1992) and monkeys (Huntsman et al. 1996), suggesting that α_3-mediated long-lasting IPSCs may be a species-independent phenomenon.

Although subunit turnover is a likely cause of the developmental changes observed with sIPSCs in the VB complex, there are other factors that should be considered, especially with regard to electrically evoked events. In VB neurons, we did not observe a simultaneous decrease in eIPSC decay as we did with sIPSCs in both the older ages. Conversely, we did see a significant change in RTN eIPSC half-widths. This difference between spontaneous and evoked responses may lie in the differences behind the basic mechanisms of these two types of inhibitory events. Compared with a spontaneous event, an evoked response is likely to result in higher neurotransmitter concentration due to the prolonged and highly synchronous release of GABA (Mody et al. 1994). This higher concentration of GABA is thought to result in a spillover of neurotransmitter into the extracellular space, activate receptors there and thus influence eIPSC decay times. Extrasynaptic $GABA_A$ receptors are likely made up of different subunits than those located in the synapse (Brickley et al. 1999; Nusser et al. 1998) and may have different binding, unbinding and/or desensitization properties than synaptic receptors. Tiagabine, a selective GABA uptake blocker, has been shown to dramatically enhance the decay times of evoked but not spontaneous responses, presum-

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ably through the activation of extrasynaptic receptors (Draguhn and Heineman 1996; Roepstorff and Lambert 1992; Thompson and Gahwiler 1992).

Functional significance of long-lasting IPSCs and network activity

Our main purpose in this study was to test whether the slowly decaying IPSCs in RTN neurons persist into maturity and under conditions of physiological temperature. The present study shows that the long-lasting IPSCs are present in adult rats and that temperature-dependent decreases in decay times do not alter the functional capacity of RTN IPSCs. Why are we so interested in the preservation of these characteristic IPSCs? One reason is because the powerful IPSCs in RTN are fundamentally important for regulating the output of inhibition from this nucleus. It has been shown that inhibition between RTN neurons ultimately affects intrathalamic circuits during the propagation of synchronized thalamocortical oscillatory activity in vivo (Steriade et al. 1987) and in vitro (Bal et al. 1995; Huguenard and Prince 1994; Huntsman et al. 1999; Sanchez-Vives et al. 1997; Sohal et al. 1999). Intra-RTN connections appear to be instrumental in some conditions in propagating oscillatory activity in this nucleus in cat (Bazhenov et al. 1999; Destexhe et al. 1994; Steriade et al. 1987). By contrast, in ferret, mice and rats, it appears the major role for these internal RTN connections is to dampen this activity. Prolonged IPSCs emanating from intra-RTN connections can effectively shunt other RTN neurons through lateral inhibition (Sanchez-Vives et al. 1997; Ulrich and Huguenard 1997). When these prolonged IPSCs are hampered or blocked in the RTN, there is a transformation of oscillatory activity from asynchronous to hypersynchronous oscillations similar to those observed in absence epilepsy (Bal et al. 1995; Huguenard and Prince 1994; Huntsman et al. 1999; von Krosigk et al. 1993). Despite a lack of multiple $GABA_A$ receptor isoforms in this nucleus (Huntsman and Jones 1995; Huntsman et al. 1996), RTN neurons are primarily dependent on these receptors for postsynaptic inhibition (Sanchez-Vives et al. 1997; Ulrich and Huguenard 1996) therefore modulation of $GABA_A$-receptor-mediated IPSC decay is a key target for antiepileptic medications. The therapeutic utility of benzodiazepines in absence epilepsy (Mattson 1995) suggests that in man, as in rat (Huguenard and Prince 1994), enhanced intra-RTN inhibition could lead to thalamocortical desynchronization.

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