INTRODUCTION

The first synapse in the central taste pathway occurs in the rostral nucleus of the solitary tract (rNST) in the brain stem. This nucleus is responsible for processing gustatory information originating in taste receptors in the oral cavity and results in distribution of neural activity to more rostral brain areas and to motor centers in the brain stem involved in salivary secretion and oral-facial motor behavior. Recent studies of synaptic processing in the rNST have revealed that inhibition, mediated by GABA, plays an important role and that rNST inhibitory synapses exhibit both short and long-term changes in synaptic plasticity (Grabauskas and Bradley 1998, 1999; Smith and Li 1998, 2000).

During development, several maturation changes take place in synaptic inhibitory activity. Instead of the hyperpolarizing synaptic potentials characteristic of mature animals, during early development GABA-mediated potentials are depolarizing in the hippocampus, spinal cord, cerebellum, and cortex (for review see Ben-Ari et al. 1997). In addition, there are also developmental changes in the subunit composition the GABA$_A$ receptor (Fritschy et al. 1994; Morrow 1995). Whether similar developmental changes take place in rNST, inhibitory activity is not known, but responses of rNST neurons to gustatory stimuli change, becoming mature after the fourth postnatal week (Hill et al. 1983). Neurons in the rNST also undergo considerable dendritic tree remodeling accompanied by changes in their intrinsic membrane properties during maturation (Bao et al. 1995; Mistretta and Labyak 1994; Renehan et al. 1997). It is possible therefore that these developmental changes are accompanied by maturational changes in the biophysical properties of rNST synapses. We have extended our earlier studies of inhibition in the mature rNST to postnatal animals using both single shock and high-frequency stimulation elicited postsynaptic potentials to characterize the development of monosynaptic inhibitory currents and potentials.

METHODS

Brain slice preparation

Brain stem slices were prepared from 152 Sprague-Dawley rats in five postnatal age groups: postnatal day 0–7 (P0–7), P8–14, P15–21, P22–30, and adults P > 55. The preparation of horizontal rNST brain slices has already been described in detail (Bradley and Sweazey 1992; Grabauskas and Bradley 1996, 1998, 1999). Briefly, rats were decapitated, and the whole brain, including the brain stem, was rapidly removed and placed in ice-cold physiological saline containing (in mM) 124 NaCl, 2.5 KCl, 2.5 CaCl$_2$, 1.3 MgSO$_4$, 26 NaHCO$_3$, 1.25 KH$_2$PO$_4$, and 25 glucose, gassed with 95% O$_2$–5% CO$_2$ to give a pH of 7.3. The brain was transected at the level of the pons and just below the obex and the cerebellum removed. Horizontal 300-μm slices containing the whole NST were cut on a Vibratome and placed in a holding chamber. Following 1–6 h recovery, the slice containing the NST was transferred to the recording chamber (volume of ~1 ml), where it was removed and placed in ice-cold physiological saline containing (in mM) 124 NaCl, 2.5 KCl, 2.5 CaCl$_2$, 1.3 MgSO$_4$, 26 NaHCO$_3$, 1.25 KH$_2$PO$_4$, and 25 glucose, gassed with 95% O$_2$–5% CO$_2$ to give a pH of 7.3. The brain was transected at the level of the pons and just below the obex and the cerebellum removed. Horizontal 300-μm slices containing the whole NST were cut on a Vibratome and placed in a holding chamber. Following 1–6 h recovery, the slice containing the NST was transferred to the recording chamber (volume of ~1 ml), where it was

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Lasiter et al. 1989) reported that the gustatory area of the NST extends during development and measures 300–400 μm. Based on this information a stimulating electrode consisting of tightly twisted pairs of 70-μm-diam, teflon-insulated, platinum wires was placed in the most rostral part of the rNST near the solitary tract and the recording electrode placed at a 0.2–0.5 mm caudal location from the stimulating electrode. Post synaptic potentials were elicited by delivery of stimuli (0.1 ms duration), and the intensity of the stimulus was adjusted to evoke inhibitory postsynaptic potentials (IPSPs).

WHOLE CELL RECORDINGS. Whole cell patch-clamp recordings were performed from 162 rNST neurons in all groups of animals: 42 in P0–7, 22 in P8–14, 35 in P15–21, 45 in P22–30, and 18 in adult P > 55. Patch pipettes, pulled in two stages from 1.5-mm OD borosilicate filament glass, were filled with a solution containing (in mM) 130 K-glucanote, 10 HEPES, 10 EGTA, 1.0 MgCl2, 1.0 CaCl2, 2.0 ATP, and 0.2 GTP. Pipette solutions were adjusted to a pH 7.2–7.3 with KOH and had an osmolarity of 275–292 mOsm. Electrode resistance was between 5 and 8 MΩ.

PERFORATED-PATCH RECORDINGS. To preserve intracellular ion concentrations, perforated-patch recordings were performed on 6 P0–7 age group neurons using the technique described by Owens et al. (1996). Gramicidin (Sigma) was dissolved in dimethylsulfoxide at 5 mg/ml and then diluted in the pipette filling solution to a final concentration of 1–20 μg/ml. After a tight seal was established, the progress of perforation was evaluated by monitoring the decrease in membrane resistance. Current-clamp protocols were applied after membrane resistance had stabilized. After perforated-patch recording the neurons were converted to the whole cell configuration by applying suction to rupture the patch membrane.

Drug application

Because the evoked postsynaptic potentials have both an excitatory and inhibitory component (Grabauskas and Bradley 1996), the excitatory component was blocked by inclusion of 50 μM 6-cyano-7-nitroquinoxaline-2,3-dione (CNQX) in the superfusate. In experiments examining the effects of different concentrations of the GABA_A receptor antagonist bicuculline methiodide (BMI; Sigma), stepwise increasing concentrations of the antagonist were used. Even though the volume of the slice chamber was small enough to allow for rapid exchange of contents, 3–5 min were allowed to elapse before making further recordings to allow the concentration of drug and the cell to stabilize after the superfusing solutions were changed.

Data analysis

Basic neuron properties were analyzed by injecting a series of hyperpolarizing and depolarizing current pulses and then measuring input resistance and membrane time constant. Neurons with action potentials at the resting membrane potential were classified as spontaneously active regardless of their action potential frequency. The IPSP rise and decay times were analyzed by exponential curve fitting using the Clampfit program (Axon Instruments). To test for differences across age groups, ANOVA was used (P < 0.05 for significance). Bonferroni post hoc tests were used to make comparisons between groups. A normalized inhibitory response-concentration relationship was fitted with the following equation

\[ V/V_{\text{max}} = 1 - B'/(B + EC_{50}) \]

where V is the measured IPSP potential at drug concentration B; V_{max} is the maximum IPSP amplitude, EC_{50} is the concentration of drug producing a 50% response, and n is the Hill coefficient.

RESULTS

Developmental changes in basic biophysical properties of rNST neurons

The electrophysiological properties of rNST neurons recorded in these experiments were similar to those previously reported in this laboratory (Bao et al. 1995). The data recorded in current-clamp mode indicate that developmental differences occur in several electrophysiological parameters, including resting membrane potential, spontaneous activity, input resistance, and neuron membrane time constant (Fig. 1A). The means of these parameters are presented in Fig. 1B and illustrate that P0–7 neurons have a more positive resting membrane potential (−51 ± 0.8 mV, mean ± SD) when compared with adults (−59 ± 1.9 mV; F_{4,126} = 9.1, P < 0.001), and the number of spontaneously active neurons decreases from 75% at P0–7 to 15% in adults (Fig. 1B). The passive neuron membrane properties undergo changes as well; P0–7 neurons have a significantly higher input resistance (852 ± 61.3 on September 30, 2017 http://jn.physiology.org/ Downloaded from 601–603 mOsm). Electrode resistance was between 5 and 8 MΩ.

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FIG. 1.  A: whole cell current-clamp recordings of membrane properties, action potential discharge pattern of rostral nucleus of the solitary tract (rNST) neurons from a newborn [postnatal day 3 (P3)] and an adult animal (P55). B: mean values of the membrane properties of rNST neurons at each of the different age groups. Resting membrane potential tends to increase, but the number of spontaneously active neurons, input resistance, and membrane time constants decrease during maturation. Decreases in input resistance, membrane time constant, and the number of spontaneously active neurons are most marked during the 1st 2 postnatal weeks.
different across age groups (6, 6, 5, 5 neurons in each age group, respectively, were tested; $F_{4,27} = 1.5, P = 0.15$). However, in whole cell recordings the Cl$^-$ ion gradient is controlled by the pipette and the bath solution concentrations that determine the reversal potential of the GABA receptor-mediated Cl$^-$ current. Therefore an accurate characterization of the IPSPs requires an intact [Cl$^-$]$_i$, and we used the gramicidin perforated-patch recordings to study the reversal potential of the single stimulus shock-evoked IPSPs. The reversal potential of the IPSPs recorded with perforated patches was $-84.6 \pm 5$ mV ($n = 6, P0–7$, Fig. 3A). The data indicate that stimulation of presynaptic inhibitory neurons results in hyperpolarizing IPSPs as early as $P0–7$. Moreover, in both the perforated-patch and whole cell recordings, the IPSP reversal potential in the $P0–7$ and adult age groups was similar (Fig. 3B). These results suggest that the diffusion of the electrode solution into the neuron was not a factor in the polarity of the IPSPs in the developing animals (Fig. 3C).

Even though the rNST IPSPs in both the developing and adult animals were hyperpolarizing, the rise and decay time characteristics of the monophasic IPSPs changed during development (Fig. 4A). The IPSP rise time constant significantly

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**Fig. 2.** Examples of single stimulus shock (arrow) generated inhibitory postsynaptic potentials (IPSPs). A: a monophasic IPSP recorded from a $P18$ animal with an exponential rise and fast decay time course. B: a biphasic IPSP recorded from a $P20$ animal with a fast exponential rise and a biphasic decay time course.

**Fig. 3.** Current-clamp recordings from a neuron using both a perforated patch (A) and whole cell recording (B) configurations. C: relationship of the single stimulus shock-evoked (arrows in A and B) IPSP amplitude as a function of membrane potential. The IPSP reversal potential was $-85$ mV in the perforated patch mode and $-76$ mV in the whole cell recording mode, indicating that IPSPs were hyperpolarizing in both recording configurations.
decreased from 13.5 ± 1 ms to 7 ± 1.1 ms \((F_{4,126} = 8.4, P < 0.001)\), and the IPSP decay time constant decreased from 236 ± 23 ms to 64 ± 9.1 ms in P0–7 and adult neurons, respectively \((F_{4,126} = 16.6, P < 0.001; \text{Fig. } 4B)\). Pairwise comparison between age groups demonstrated that the significant differences in the rise time constant occurred between P0–7 and the other age groups, while the significant changes in the decay time constant occurred between P0–7 and P8 to adult.

Because biphasic IPSPs were rarely encountered (3 at P0–7, 1 at P15–21, 4 at P22–30 and 1 adult), it was not possible to analyze the developmental characteristic of the biphasic IPSPs.

**Pharmacological properties of developing IPSPs**

GABA is the inhibitory neurotransmitter in the rNST (Grabauskas and Bradley 1996, 1998, 1999; Smith and Li 1998, 2000; Wang and Bradley 1993). The inhibitory action of GABA is mediated by two types of ionotropic receptor and one type of metabotropic receptor (Bormann 2000). The specific agonist and antagonist of the \(\text{GABA}_A\) ionotropic receptor are muscimol and BMI, respectively, while the agonist and antagonist of the \(\text{GABA}_B\) receptor are baclofen and saclofen. The ionotropic \(\text{GABA}_C\) receptor is not blocked by either BMI or baclofen, but both \(\text{GABA}_A\) and \(\text{GABA}_C\) receptors are blocked by picrotoxin (Bormann 2000).

Superfusion of the rNST slices with increasing concentrations of BMI revealed developmental changes. The inhibition response-concentration curves shift to the left, indicating an increased sensitivity to BMI with development \((\text{Fig. } 5A)\). The amplitude of the IPSPs was less sensitive to BMI in the P0–7 animals with an EC\(_{50}\) of 9.1 \(\mu\)M compared with an EC\(_{50}\) of 4.9 \(\mu\)M in P8–14, 3.5 \(\mu\)M in P15–21, 0.75 \(\mu\)M in P22–30, and 0.85 \(\mu\)M in adult animals. In addition, approximately 20% of the total IPSP amplitude in the P0–7 and P8–14 animals was not blocked by high concentrations of BMI \((100–200 \mu\text{M})\), whereas the IPSPs of P22–30 and adult animals were completely blocked by 10 \(\mu\)M BMI. However, it was possible to block the BMI-resistant IPSPs recorded in the P0–7 and P8–14 animals by adding picrotoxin \((200 \mu\text{M})\) to the perfusing solution \((\text{Fig. } 5B)\). These results indicate that fast IPSPs in the rNST of P22–30 and adult animals are solely due to activation of ionotropic \(\text{GABA}_A\) receptors; however, the presence of a BMI-insensitive and picrotoxin-sensitive component in the P0–21 age groups suggests on the basis of pharmacological sensitivity that receptors with \(\text{GABA}_C\)-like characteristics are expressed in the early stage of postnatal development of the rNST.

**Developmental changes in tetanic stimulation evoked IPSPs**

Previously we have reported that tetanic stimulation results in short- and long-lasting modifications of inhibitory neurotransmission in the adult rNST (Grabauskas and Bradley 1998, 1999). In the developing rNST, tetanic stimulation at 10–70 Hz resulted in summation of the IPSPs in all the age groups. The amplitude of the tetanic stimulus evoked IPSPs was sustained in P0–7 animals independent of the stimulation frequency. In contrast in P22–30 and adult animals the amplitude of the tetanically induced hyperpolarization was not sustained.

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**Figure 4.** A: examples of single stimulus shock-evoked IPSPs at 3 different age groups. The membrane potential was held at −60 mV by steady current injection. The rise and decay time of the single stimulus shock-evoked IPSPs changes during postnatal development. B: mean values of rise and decay time constants of single stimulus shock-evoked IPSPs at each of the different age groups. The changes are most marked during 1st 2 postnatal weeks.
and decayed back to a more positive level before the tetanic stimulation was terminated (Fig. 6). The reversal potential of the tetanic stimulus evoked IPSPs for P0 –7 and P8 –14 animals was -2.8 mV, and all phases of the tetanic stimulus evoked IPSPs (initial, and late amplitudes) reversed at the same potential independent of the IPSP amplitude (n = 9, Fig. 7A). In the older age groups (P22–30 and adult) the initial amplitude of the IPSPs reversed at -88 ± 4.2 mV, and the amplitude of the later phase reversed at -75 ± 5 mV (Fig. 7B); however, the amplitude decay of the IPSPs was related to the holding potential (Fig. 7C). The relationship between amplitudes of the initial phase and the late phase IPSP at various membrane holding potentials indicates that they reverse at different membrane potentials, suggesting that a process of desensitization of the postsynaptic GABA receptors does not account for the decay of tetanic stimulation evoked IPSPs amplitudes (Fig. 7C).

After termination of tetanic stimulation, the amplitude of the IPSPs decayed back to the resting membrane potential. The shape in P0–7 and adult animals. For 66% of the P0–7 and 16% of the P8–14 animals after termination of tetanic stimulation (30–100 Hz), the decay time course was S shaped. In contrast, the IPSP in P15–21, P22–30, and adult animals decayed exponentially after termination of the tetanic stimulus (Fig. 8). Figure 8A is a recording from a newborn animal (P3) showing that at low tetanic stimulus frequencies (5 and 10 Hz) the IPSP decay is exponential, while at higher stimulus frequencies (30 and 50 Hz) the decay has an S shape (arrowheads). However, the tetanic stimulus frequency required to produce the S shape varied from neuron to neuron. In contrast in a P22-day animal tetanic frequencies up to 70 Hz failed to convert an exponentially decay to an S shape (Fig. 8B). Moreover, an S-shaped decay was never observed in the P22–30 and adult animals at tetanic stimulation frequencies up to 300 Hz.

In all age groups tetanic stimulation resulted in potentiation of posttetanic single stimulus evoked IPSPs (Fig. 9A). Tetanic stimulation lasting 1 s at 30 Hz resulted in potentiation of single stimulus evoked IPSPs of various durations. The incidence and duration of this potentiation did not differ across the age groups (Table 1). Potentiation of the IPSP amplitudes was not associated with changes in the resting membrane potential and had no effect on the kinetics of the IPSPs (Fig. 9B). It is apparent that long-lasting modification of GABAergic neurotransmission may occur in all age groups; however, the duration and strength of these modifications may vary between neurons within the groups.

DISCUSSION

The results of this study demonstrate that GABAergic synapses are functional at the time of birth in the rNST; however,
the properties of the inhibitory synaptic activity change during postnatal development. Changes occur in the rise and decay time constants of the IPSPs as well as their pharmacological properties. In addition, rNST neurons in the early developmental period express GABA receptors that are resistant to BMI, but are sensitive to picrotoxin. Postnatal developmental differences also occur in response to tetanic stimulation evoked IPSPs. For P0–7, P8–14 age animals, tetanic stimulation evoked sustained hyperpolarization of postsynaptic neurons, while tetanic stimulation in P22–30 and adult animals resulted in hyperpolarizing IPSPs with decaying amplitudes. However, no developmental differences were observed in the tetanic stimulation evoked long-term potentiation of IPSPs across all groups.

Development of kinetic and pharmacological properties of IPSPs

Ionotropic GABA receptors are composed of five individual subunits that define their kinetic and pharmacological properties (Macdonald and Olsen 1994; Sieghart 1995). The subunit composition of GABA_A receptors changes during ontogenesis (Bovolin et al. 1992; Laurie et al. 1992). For example, change of GABA_A receptor subunit composition was observed in developing cortical neurons that correlated with changes of inhibitory postsynaptic current (IPSC) decay kinetics (Dunning et al. 1999). The relative expression of α1 versus α5 GABA_A receptors subunits in cortical tissue during maturation correlated with shortening of the IPSC decay time from >30 ms (1st and 2nd postnatal week) to ~15 ms (4th postnatal week). In the present study we also found differences in the decay kinetics of IPSPs in the developing rNST of the rat but do not have data on GABA_A receptor subunit expression in rNST during postnatal maturation. However, Fritschy et al. (1994) have demonstrated that α1 subunit onset is observed in most areas of the brain in the later stages of development. It is possible therefore that changes in subunit composition of the GABA_A receptors take place in the developing gustatory area of the NST as well. Changes in the ratio α1 versus α2(3,4,5) GABA receptor subunits would result in the observed change in the rNST IPSP kinetics.

A surprising finding was the presence of a BMI-insensitive but picrotoxin-sensitive current during the first two postnatal weeks in
The results of the current and previous studies (Grabauskas and Bradley 1998, 1999) demonstrate that tetanic stimulation induces short- and long-term changes in inhibitory neurotransmission in the developing and mature rNST. The amplitude of tetanic stimulation-evoked IPSPs in newborn animals was sustained in contrast to P14–21, P22–30, and adult animals in which the initial hyperpolarization decayed back to a more positive level prior to termination of the stimulation. Several synaptic processes might be responsible for the amplitude decay of the tetanic evoked IPSPs, such as depletion of the neurotransmitter or desensitization of the postsynaptic GABA receptors. Although these mechanisms can explain the initial decrease in the amplitude of hyperpolarization, they cannot explain why the later phase of these IPSPs have a more positive reversal potential. In newborn animals that have sustained amplitude IPSPs, a different homeostasis for K$^+$ and Cl$^-$ ions must therefore exist. It is likely that in newborn animals the inhibitory current is generated by channels with smaller Cl$^-$ conductances and/or a reduced number of postsynaptic GABA receptors. Thus the reduced inhibitory current is due to a smaller K$^+$ and Cl$^-$ ionic balance that results in a sustained IPSP amplitude. However, even though small inhibitory currents can generate powerful inhibitory effect in rNST, neurons of newborn animals have about double the input resistance so that the amplitudes of the IPSPs are similar in both newborn and adult animals.

The characteristic of the decay of tetanic stimulation IPSPs in newborn animals and the older groups of animals was different. Depending on stimulation frequency, the decay time course of IPSPs of newborn animals (P0–8, P8–14) decayed either exponentially or with an S shape, while in the older age groups (P14–21, P22–30, and adults) the IPSP always decayed exponentially. While the decay time course of single stimulus shock-evoked IPSP is governed by the receptor channel deactivation, a number of other factors may contribute to shaping the decay time course of the IPSP. For example, both the temporal profile of neurotransmitter concentration in the synaptic cleft and the rate of neurotransmitter clearance from the synaptic cleft may prolong the IPSP decay time course (Clements 1996). Prolongation of the decay time course due to accumulation of neurotransmitter in the synaptic cleft would become evident during high-frequency stimulation. Accumulation of neurotransmitter in the synaptic cleft would explain why tetanic stimulation produces IPSPs with greater amplitudes than single stimulus shock-evoked IPSPs, consistent with the observation that decay time duration depends on tetanus.
across different age groups

rNST elongate and ovoid neurons from rapid period of growth of first- and second-order dendrites of NST and continue to develop until nerve becomes increasingly myelinated (Ferrell et al. 1985), and during the first postnatal weeks. For example the chorda tympani.

Functional significance

The maturation of the rNST IPSPs is just one of many other developmental changes that occur in the developing taste system during the first postnatal weeks. For example the chorda tympani nerve becomes increasingly myelinated (Ferrell et al. 1985), and both the chorda tympani and glossopharyngeal nerves enter the NST and continue to develop until P45 (Lasiter 1992). There is a rapid period of growth of first- and second-order dendrites of rNST elongate and ovoid neurons from P6 to P20, and the first-order dendrites of multipolar cells continue to increase in length up to at least P70 (Lasiter et al. 1989). Accompanying these changes is an increase in synaptophysin immunoreactivity, a marker of presynaptic terminals (Lassiter and Kachele 1989). These developmental changes are not unique to the rNST as similar morphological changes in dendritic growth and synaptic maturation occur in the caudal NTS as well (Miller et al. 1983; Rao et al. 1995; Vincent et al. 1999).

Electrophysiological changes also occur in the developing rNST. Extracellular recordings from rNST neurons in rats 5 days old to adult show a developmental increase in response frequency to some but not all chemicals, and adult neurons respond to lower stimulus concentrations than immature neurons (Hill et al. 1983). The biophysical characteristics of developing rNST neurons are also changing during maturation (Bao et al. 1995 and the present study). Using a slice preparation of the developing rNST differences with age were found in resting membrane potential, action potentials, and repetitive discharge characteristics.

Finally, there are significant maturational changes in taste-guided behaviors. Preference-aversion behaviors are acquired during the first 3 wk postnatal (Jacobs and Sharma 1969). In particular, aversion to bitter and sour tastes are evident early in development, while preference for sweet solutions develops later (Johanson and Shapiro 1986). Preference for NaCl is initially low and does not become adultlike until P12 (Bernstein and Courtney 1987; Midkiff and Bernstein 1983; Moe 1986). The mechanisms underlying the maturational changes in taste-guided behavior may result from alterations in the sharpness of tuning of the taste responsive neurons. In adult animals, tonic GABAergic inhibitory activity plays a role in determining the breadth of responsiveness of rNST taste neurons (Smith and Li 1998). It is possible therefore that changes in the sharpness of tuning of the taste neurons that accompanies maturation of inhibitory activity could be a factor in the changing behavioral responses to taste stimuli.

It is apparent therefore that the morphological, electrophysiological, and synaptic changes in the rNST occur during a period when taste behaviors are rapidly changing and while the rats undergo weaning. There is also evidence that alterations in diet during this period can influence rNST development (King and Hill 1993). Thus afferent input also has an influence on rNST development. The data in the present study provide additional information for interpreting the mechanisms of central processing that underlie these developmental changes.

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