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Dynamic modulation of short term synaptic plasticity in the auditory cortex: the role of norepinephrine

Salgado Humberto^{1,2}, García-Oscos Francisco¹, Dinh Lu¹, and Atzori Marco¹

¹School of Behavioral and Brain Sciences, Laboratory of Cell and Synaptic Physiology, University of Texas at Dallas, Richardson, TX 75080. USA

²Departamento de Neurociencias, Centro de Investigaciones Regionales “Dr. Hideyo Noguchi”, Universidad Autónoma de Yucatán, Avenida Itzáes 490 x 59

Abstract

Norepinephrine (NE) is an important modulator of neuronal activity in the auditory cortex. Using patch-clamp recording and a pair pulse protocol on an auditory cortex slice preparation we recently demonstrated that NE affects cortical inhibition in a layer-specific manner, by decreasing apical but increasing basal inhibition onto layer II/III pyramidal cell dendrites. In the present study we used a similar protocol to investigate the dependence of noradrenergic modulation of inhibition on stimulus frequency, using 1s-long train pulses at 5, 10, and 20 Hz. The study was conducted using pharmacologically isolated inhibitory post-synaptic currents (IPSCs) evoked by electrical stimulation of axons either in layer I (LI-eIPSCs) or in layer II/III (LII/III-eIPSCs). We found that: 1) LI-eIPSC display less synaptic depression than LII/III-eIPSCs at all the frequencies tested, 2) in both type of synapses depression had a presynaptic component which could be altered manipulating $[Ca^{2+}]_o$, 3) NE modestly altered short-term synaptic plasticity at low or intermediate (5–10 Hz) frequencies, but selectively enhanced synaptic facilitation in LI-eIPSCs while increasing synaptic depression of LII/III-eIPSCs in the latest (>250 ms) part of the response, at high stimulation frequency (20 Hz).

We speculate that these mechanisms may limit the temporal window for top-down synaptic integration as well as the duration and intensity of stimulus-evoked gamma oscillations triggered by complex auditory stimuli during alertness.

Keywords

GABA; auditory cortex; cortical circuitry; basal dendrites; apical dendrites; somatic; inhibition; patch-clamp; stimulation train

Introduction

The auditory cortex integrates tonotopic information from the auditory thalamus and non-tonotopic information originating from other cortical and sub-cortical regions (Donishi et al., 2006; Falchier et al., 2009; Hu, 2003; Radtke-Schuller et al., 2004). Thalamic afferents of two parallel projections have been described: the lemniscal and extra-lemniscal paths (Hu,

Correspondence to: Atzori Marco.

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2003). The lemniscal pathway terminates most densely in cortical layers III and IV and has been proposed that its principal function is to discriminate among temporal patterns and sound sequences (Hu, 2003; Kelly et al., 1973; Layton et al., 1979), while the extra-lemniscal pathway projects principally to cortical layer I and is required for proper sensory integration and learning (Edeline, 1999; Hu, 2003; Jones, 1998; Lorente de Nó, 1992; Weinberger, 2004). In addition to these inputs, the auditory cortex is also innervated by noradrenergic fibers from the *Locus Coeruleus* which display a very high density in cortical layer I and a decreasing gradient density from the cortical neuropil through supragranular layers first, and then through granular and infragranular layers, which have the lowest density of noradrenergic fibers (Freedman et al., 1975; Fuxe et al., 1968; Levitt et al., 1978; Morrison et al., 1978; Morrison et al., 1979b). Several studies indicate that activation of NE receptors affects the activity in the auditory and other sensory cortices (Armstrong-James et al., 1983; Foote et al., 1975; Manunta et al., 1997; Manunta et al., 1999; Mueller et al., 2008; Pralong et al., 1994; Pralong et al., 1995; Videen et al., 1984), and alters cortical glutamatergic drive (Dinh et al., 2009; Ji et al., 2008a; Ji et al., 2008b; Nowicky et al., 1992) as well as local GABAergic transmission (Kawaguchi et al., 1998; Lei et al., 2007).

Anatomical findings suggested the possibility of a layer-specific action of norepineprine (NE) in sensory cortical synapses (Levitt et al., 1978; Morrison et al., 1979a; Morrison et al., 1978; Morrison et al., 1979b). Using a pair pulse protocol at 50 ms we have recently shown (Salgado et al., 2010) that the activation of noradrenergic receptors decreases apical while increasing perisomatic inhibition, measured as the amplitude of IPSCs evoked by electrical stimulation of layer I or layer II/III axons (LI-eIPSC and LII/III-eIPSC), respectively. These findings raised the possibility that NE alters the temporal pattern of short-term plasticity in inhibitory synapses using layer-specific mechanisms. In the present study we used 1s-long stimulation trains at 5, 10, and 20 Hz to determine the effect of NE on short-term synaptic plasticity on distal and proximal GABAergic pharmacologically isolated inputs to supragranular layers, and discussed their potential role in temporal integration of the auditory cortical input.

Methods

Preparation

We used an auditory cortex slice preparation similar to one previously described (Atzori et al., 2001). Twentythree to thirtyfive days-old Sprague Dawley rats (Charles River, Wilmington, MA) were anesthetized with isoflurane (Baxter, Round Lake IL), sacrificed according to the National Institutes of Health Guidelines (UTD IACUC number 04-04), and their brains sliced with a vibrotome (VT1000, Leica, Germany) in a cold solution (0–4°C) containing (mM): 126 NaCl, 3.5 KCl, 10 Glucose, 25 NaHCO₃, 1.25 NaH₂PO₄, 1.5 CaCl₂, 1.5 MgCl₂, and 0.2 ascorbic acid, at pH 7.4 and saturated with a mixture of 95% O₂ and 5% CO₂ (ACSF). Two hundred and seventy µm thick coronal slices from the most caudal fourth of the brain were retained after removing the occipital convexity (caudal end of the brain after removal of the cerebellum), and subsequently incubated in ACSF at 32°C before being placed in a recording chamber. The recording area was selected dorsally to the rhinal fissure corresponding to the auditory cortex (Rutkowski et al., 2003).

Electrophysiology

Slices were placed in an immersion chamber, where cells with a prominent apical dendrite, suggestive of pyramidal morphology, were visually selected using an upright microscope (BX51, Olympus, Japan) with 60x objective and an infrared camera system (DAGE-MTI, Michigan City, IN). Whole-cell voltage-clamp recordings from layers II/III pyramidal neurons of the auditory cortex were conducted under visual guidance. Neurons were selected

by their pyramidal shape and by their pronounced apical dendrite. Inhibitory postsynaptic currents (IPSCs) were recorded in the whole-cell configuration, in voltage-clamp mode, at a holding membrane potential $V_h = -60$ mV, with 4–6 M Ω electrodes filled with a solution containing (mM): 100 CsCl, 5 1,2-bis(2-aminophenoxy)ethane-N,N,N',N'-tetraacetic acid K (BAPTA-K), 1 lidocaine N-ethyl bromide (QX314), 1 MgCl₂, 10 N-(2-hydroxyethyl)-piperazine-N'-(2-ethanesulfonic acid) (HEPES), 4 glutathione, 3 ATPMg₂, 0.3 GTPNa₂, 8 biocytin, 20 phosphocreatine. The holding voltage was not corrected for the junction potential (< 4 mV). The intracellular recording solution was adjusted to approximately pH 7.2 and had an osmolarity of about 275 mOsm. Electrically evoked IPSCs (eIPSCs) were measured by delivering trains of monophasic electric stimuli (ranges 90–180 μ s, 10–50 μ A) at 5, 10 or 20 Hz every 20 sec, with an isolation unit, through a glass stimulation monopolar electrode filled with ACSF, or with a concentric bipolar electrode (FHC Inc, ME), placed at about 100–200 μ m lateral from the axis between the recorded neuron and the cortical neuropil, perpendicular to the latter, in either layer I (LI-eIPSCs), or layer II/III (LII/III-eIPSCs). Each recording was performed with fixed parameter settings (stimulus duration, intensity, location, etc.). All data points represent the average of a minimum of 15 sweeps at the given test frequency. A 2 mV voltage step was applied at the beginning of every episode in order to monitor the quality of the recording. Access resistance (10–20 M Ω) was monitored at every sweep. Experiments with changes in access resistance larger than 20% were discarded. Signals were sampled at 10 KHz and filtered at 2 KHz using the Digidata 1322 and the Clampfit software (Axon Instruments, Culver City CA). The amplitude of the synaptic currents was calculated from the baseline (current before the stimulation artifact of the measured evoked response) to the peak of the corresponding response. For clarity, stimulus artifacts have been removed digitally from the traces displayed. All the experiments were performed at room temperature (25 °C).

Drugs and solutions

The recording solution also contained 6,7-dinitroquinoxaline-2,3-dione (DNQX, 10 μ M), and kynurenate (2 mM) or amino-5-phosphonovaleric acid (APV, 100 μ M) for blocking α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor (AMPA)- and N-methyl-D-aspartate receptor (NMDAR)-mediated currents, respectively. Both LI- and LII/III evoked currents were blocked by the GABA_A- receptor antagonist picrotoxin (100 μ M). All the drugs were purchased from Sigma (St. Louis, MO) or TOCRIS (Ellisville, MO). After a period of synaptic stabilization, a baseline of 20–30 responses to 1s-long trains was recorded during 8–10 min at each frequency of 5, 10 or 20 Hz. Subsequently, NE was bath-applied for 10 minutes or longer, until reaching again a stable condition (as defined below in *Statistical Analysis*). NE (20 μ M) was prepared immediately before experiments and the exposure to light was avoided to prevent oxidation (all experiments were conducted in darkness and the NE syringe was wrapped in aluminum foil).

Data analysis and Statistics

We defined a statistically stable period as a time interval (5–8 min) along which the IPSC mean amplitude of the first synaptic response, measured during any one-minute assessment, did not vary according to U-Mann Whitney *t*-test. All data are expressed as mean $\pm$ SEM. The effects of drug application or change in extracellular Ca²⁺ concentration on the IPSC amplitude were reported as R (reduction) $\equiv 100 \cdot (1 - A_{\text{treat}}/A_{\text{ctrl}})$; R = 0: no change; R < 0: increase; R > 0: decrease), where A_{treat} and A_{ctrl} are the mean IPSC amplitude in treatment or in control, respectively, or simply as percentage change between A_{treat} and A_{ctrl} . Drug effects were assessed by measuring and comparing the different parameters (R, IPSC mean amplitude, or others as indicated) in baseline (control) vs. treatment, with a Mann-Whitney U-test. All other values shown are mean $\pm$ SEM. Data points were compared using ANOVA

with a post hoc Tukey test (multiple groups) or Student's *t* test (two groups). Single asterisks (*) indicate $p < 0.05$, double asterisk (**) indicate $p < 0.01$.

Results

We recently described a differential noradrenergic modulation of IPSCs evoked from cortical layer I (LI-eIPSCs) or from cortical layer II/III (LII/III-eIPSCs) (Salgado et al., 2010). Using a control solution containing blockers of AMPA- and NMDA-receptors similar to the one described above (see Methods), as expected, we found that bath application of NE (20 μ M) reversibly decreased LI-eIPSCs ($R = 44 \pm 6\%$), while it reversibly increased LII/III-eIPSCs ($R = -69 \pm 7\%$). In the present study we specifically examined the response of LI-eIPSC and LII/III-eIPSCs to stimulation trains at 5, 10 or 20 Hz, corresponding to a firing frequency range sustainable by single principal cells in-vivo (Kilgard et al., 1998). We first determined the basic responses to trains in control conditions and in conditions of heightened or lowered synaptic transmission, and we subsequently determined the effect of NE.

Basal response to train stimulation

Examples of the responses to 5, 10 or 20 Hz pulse trains are shown in fig. 1A, B and C for LI-eIPSCs and in fig. 1D, E, and F, for LII/III-eIPSCs. During the trains, the eIPSCs amplitude decreased as a result of activity-dependent short term depression for both (LI and LII/III stimulation). During synaptic depression in LI-eIPSCs induced by 5 Hz stimulation, the amplitude of the 5th response (eIPSC₅) was reduced to 65% of the first response amplitude, eIPSC₁ from 162.5 ± 8.7 pA to 105 ± 4.8 pA (fig. 1G). Similar results were obtained for 10 Hz (the amplitude of the 10th response was 82.3 ± 5.5 pA, with eIPSC₁ = 129.1 ± 7.9 pA, fig. 1H), and for 20 Hz (the eIPSC₂₀ amplitude was 85.0 ± 5.0 pA with an eIPSC₁ = 116.4 ± 8.8 pA, fig. 1I). In LII/III-eIPSCs 5, 10 and 20 Hz stimulation produced similar patterns. The amplitude of the 5th response (eIPSC₅) was reduced to 45% of the first response (eIPSC₁) amplitude (from 235.9 ± 11.5 pA to 106 ± 10.4 pA, fig. 1G). Similar results were obtained for 10 Hz (the amplitude of the 10th response was 89.8 ± 10.6 pA with an eIPSC₁ of 180.3 ± 16.5 pA, fig. 1H), and for 20 Hz the eIPSC₂₀ amplitude was 133.5 ± 9.3 pA with an eIPSC₁ = 275.1 ± 12.5 pA, (fig. 1I). In order to quantify short term plasticity we calculated the ratio between last and first eIPSCs amplitudes in a burst train (IPSC_n/IPSC₁, $n = 5, 10$, or 20). In control conditions, LI-eIPSCs always displayed depression in the late, steady-state phase of a train response (100% of the cells tested, fig. 1A, B and C). In fact, the amount of depression was similar at all frequencies tested (for LI-eIPSCs, mean IPSC₅/IPSC₁ = 0.65 ± 0.03 at 5 Hz, fig. 1J, IPSC₁₀/IPSC₁ = 0.64 ± 0.04 , fig. 1K at 10 Hz, IPSC₂₀/IPSC₁ = 0.73 ± 0.06 at 20 Hz, fig. 1L, $n = 15$). Synaptic responses were examined following similar stimulation protocols for layer II/III. For LII/III-eIPSCs synaptic depression was not only the predominant form of plasticity (15/19 cells, 79 % of the cells tested, examples in fig. 1D, E and F), but was even more pronounced than for LI-eIPSCs (mean IPSC₅/IPSC₁ = 0.45 ± 0.04 at 5Hz, fig. 1G; IPSC₁₀/IPSC₁ = 0.49 ± 0.04 , fig. 1H, IPSC₂₀/IPSC₁ = 0.48 ± 0.07 at 20 Hz, fig. 1I, $n = 15$; $p < 0.05$ for all 3 parameters, unpaired *t*-test).

Dependence of short term plasticity on extracellular Ca²⁺ concentration

In order to determine a possible presynaptic contribution to short-term plasticity we compared recordings obtained with different extracellular Ca²⁺ concentrations ($[Ca^{2+}]_o$), which is known to modify the probability of neurotransmitter release at presynaptic terminals, after stimulation of LI (representative traces of the responses to 20 Hz stimulation, average of the absolute and normalized amplitudes in fig. 2A–F), or LII/III (fig. 2G–L). As expected, lowering $[Ca^{2+}]_o$ from 1.5 mM to 0.5 mM (low Ca²⁺) decreased

synaptic amplitude for both LI- and LII/III-eIPSCs. The mean LI-eIPSC₁ was 109.6 ± 8.5 pA in control and 31.5 ± 4.1 pA in low Ca^{2+} (fig. 2A, B and C, $R = 71 \pm 6\%$, $n = 6$, $p < 0.01$), while the mean LII/III-IPSC₁ in control was 162.6 ± 16.5 pA vs. 35.1 ± 6.1 pA in low Ca^{2+} ($R = 79 \pm 8\%$, fig. 2G, H and I, for LII/III-IPSCs, $n = 11$, $p < 0.01$). Although we obtained qualitatively similar results at all frequencies (data not shown), lowering $[\text{Ca}^{2+}]_o$ changed significantly short-term plasticity only in high-frequency (20 Hz) responses, in which depression was turned into facilitation (LI-eIPSCs: $\text{IPSC}_{20}/\text{IPSC}_1 = 0.55 \pm 0.13$ in control, but 1.97 ± 0.14 , in low Ca^{2+} , $n = 6$, $p < 0.01$; fig. 2C; LII/III-eIPSCs ($\text{IPSC}_{20}/\text{IPSC}_1 = 0.31 \pm 0.14$ in control vs. $\text{IPSC}_{20}/\text{IPSC}_1 = 2.46 \pm 0.18$ in low Ca^{2+} , $n = 11$, $p < 0.01$, fig. 2I).

We also examined the effects of *increasing* the probability of release by increasing $[\text{Ca}^{2+}]_o$ from 1.5 mM to 2.5 mM (high Ca^{2+}). This manipulation produced an increase in the amplitude of the LI-eIPSC (mean LI-IPSC₁ = 85.5 ± 4.7 pA in control vs. 104.6 ± 6.1 pA in high Ca^{2+} , $R = -22 \pm 5\%$, $n = 6$, $p < 0.05$, fig. 2D–F), as well as in LII/III-eIPSC response (mean LII/III IPSC₁ = 194.4 ± 20 pA in control vs. 282.4 ± 14.1 pA in high Ca^{2+} , $R = -45 \pm 9\%$; $n = 11$, $p < 0.05$, fig. 2J–L). As above, the most remarkable effect of high $[\text{Ca}^{2+}]_o$ was observed in responses to the 20 Hz train, which further increased the extent of synaptic depression for LI-eIPSCs (fig. 2F, $\text{IPSC}_{20}/\text{IPSC}_1 = 0.50 \pm 0.1$ in control vs. 0.18 ± 0.06 in high Ca^{2+} , $n = 6$, $p < 0.01$), as well as for LII/III-eIPSCs (fig. 2L, $\text{IPSC}_{20}/\text{IPSC}_1 = 0.57 \pm 0.05$ in control vs. 0.17 ± 0.07 in high Ca^{2+}). These results corroborate an important presynaptic component of GABAergic depression.

Norepinephrine differentially modulates short term plasticity in inhibitory synapses

NE (20 μM) was bath applied to determine the effect of adrenoceptors activation on short-term inhibitory synaptic plasticity. NE application induced a reduction in the amplitude of the first LI-eIPSCs amplitude response ($R = 44 \pm 6\%$), with a frequency-specific decrease pattern (fig. 3A, B, and C). Remarkably, at the end of 10 Hz trains, the amplitude of the IPSC in NE recovered its initial amplitude ($\text{IPSC}_1 = 82.4 \pm 5.5$ pA vs. $\text{IPSC}_{10} = 87.9 \pm 4.7$ pA, n.s., $n = 15$, fig. 3B). In 20 Hz trains, LI-eIPSC amplitude was remarkably larger than the control amplitude from IPSC₁ onward ($p < 0.05$, fig. 3C), while the inhibition of the eIPSCs produced by NE was only present in the first two responses, and faded in a time window of approximately of 200–250 ms from the train start.

On the contrary, and as expected from our previous study (Salgado et al., 2010), NE application produced an *increase* in the amplitude of LII/III-eIPSCs ($R = -69 \pm 7\%$, fig. 3D, E and F). LII/III-eIPSC overall responses to 5 and 10 Hz trains appeared markedly enhanced by NE ($\text{IPSC}_5 = 106.9 \pm 10.4$ pA in control vs. 171.1 ± 11.7 pA in NE, fig. 3D, $n = 15$, $p < 0.01$; $R = -60 \pm 7\%$ at 5 Hz; $\text{IPSC}_{10} = 89.8 \pm 10.6$ pA in control vs. 150.6 ± 12.3 pA in NE at 10 Hz; fig. 3E, $n = 15$, $p < 0.01$). At 20 Hz an increase in the amplitude was obtained only in the first few responses (fig. 3F), while NE was unable to increase LII/III-eIPSC amplitude in the remainder of the train, and even produced a slight reduction in amplitude respect to control ($\text{IPSC}_{20} = 133.5 \pm 9.3$ pA in control vs. 109.2 ± 11.8 pA in NE, fig. 3F, $n = 15$, $p < 0.05$).

Analysis of the normalized LI-eIPSCs responses to 5 Hz trains showed a pattern of depression similar in control or in NE ($\text{IPSC}_5/\text{IPSC}_1 = 0.64 \pm 0.04$ in control vs. 0.66 ± 0.03 in NE, $n = 15$, n.s.; representative traces in fig 4A and normalized amplitude in fig. 4B). In contrast, at 10 Hz, the depression of the normalized response was less pronounced at the end of the train ($\text{IPSC}_{10}/\text{IPSC}_1 = 0.64 \pm 0.03$ in control, vs. 0.96 ± 0.04 in NE; $n = 15$, $p < 0.01$, representative traces in fig. 4C, normalized amplitudes in fig. 4D). In 20 Hz trains, the effect of NE was very prominent, with an $\text{IPSC}_{20}/\text{IPSC}_1$ almost double with respect to control ($\text{IPSC}_{20}/\text{IPSC}_1 = 1.42 \pm 0.08$ in NE vs. 0.73 ± 0.08 in control; $n = 15$, $p < 0.01$,

representative traces in fig. 4E, normalized IPSC amplitudes in fig.4F), with intra-train facilitation observed from pulse 3 to 20 (fig.4F).

In LII/III-eIPSCs, stimulation trains did not produce any change in short-term plasticity at 5 Hz ($\text{IPSC}_5/\text{IPSC}_1 = 0.49 \pm 0.04$ in NE vs. 0.45 ± 0.04 in control; representative traces in fig. 5A, normalized amplitudes in fig.5B, $n = 15$, n.s.), nor at 10 Hz ($\text{IPSC}_{10}/\text{IPSC}_1 = 0.50 \pm 0.04$ in control vs. NE 0.51 ± 0.03 in NE; $n = 15$, n.s.; representative traces in fig. 5C, normalized amplitudes in fig.4D). On the contrary, NE further increased LII/III-eIPSC depression in 20 Hz trains ($\text{IPSC}_{20}/\text{IPSC}_1 = 0.33 \pm 0.04$ NE, vs. 0.49 ± 0.08 in control; $n = 15$, $p < 0.01$, representative traces in fig. 5E, normalized amplitudes in fig.5F). In fact, as expected following the NE-induced increase in the amplitude of the first few synaptic responses, a general increase in intra-train depression (smaller $\text{IPSC}_n/\text{IPSC}_1$) was observed $n = 6$ to 20.

A conclusion from this last series of experiments is that while the NE modulation of LII/III-eIPSC at all tested frequencies can be inferred –at least qualitatively- by the NE modulation of pair pulse responses that we reported previously at 20 Hz (Salgado et al. 2010), the modulation of the late part of the LI-eIPSC responses to 10 Hz and particularly to 20 Hz trains is different or even opposite from what expected by only analyzing the early part of the response to the pulse train, where only the NE-induced early depression and not the NE-induced late enhancement in the response to the train is evident. We summarized the effects of the application of NE to the response to 20 Hz stimulation in the diagram in fig. 6A for LI-eIPSCs and in fig.6 B for LII/III-eIPSCs.

Discussion

Neocortical circuits display multiple forms of short-term plasticity including reversible changes in synaptic efficacy (Hempel et al., 2000; Oswald et al., 2009; Ramos et al., 2007; Varela et al., 1997). In the neocortex as well as in the hippocampus, different types of GABAergic neurons project to specific dendritic regions on the pyramidal cells that they innervate (Ascoli et al., 2008; Miles et al., 1996), raising the possibility that inhibitory cells exert similarly specific roles in the control of the excitability of the sensory neocortical network. Using a pair pulse protocol at 50 ms interpulse delay we recently demonstrated that NE differentially affects distal vs. proximal inhibitory inputs to layer II/III pyramidal neurons, by decreasing LI-eIPSCs while increasing the LII/III-eIPSCs (Salgado et al., 2010). In the current study we addressed two unresolved questions concerning 1) how NE affected GABAergic responses to stimulation trains, and 2) the frequency dependence of the NE effect.

The results of the present study showed that LI-eIPSCs display less depression than LII/III-eIPSCs at all the frequencies tested (fig.1), suggesting that layer I GABAergic axons have lower release probability than layer II/III axons, conclusion that was corroborated by the modulation of synaptic responses by manipulation of $[\text{Ca}^{2+}]_o$. In fact, the reversion of depression into facilitation observed in both LI and LII/III response to 20 Hz stimulation trains following the decrease in $[\text{Ca}^{2+}]_o$ (fig.2C and I), suggests a presynaptic site for the synaptic depression observed in control $[\text{Ca}^{2+}]_o$. We also observed that in 20 Hz trains NE converts LI-eIPSC depression into facilitation throughout the whole 1-s-long response, while producing even more depression in LII/III-eIPSCs at the same frequency (fig.4 E and F, and fig.5 E and F).

In summary, while at low and intermediate frequencies (5 and 10 Hz) NE enhanced LII/III-eIPSC (fig.3 D and E) and decreased LI-eIPSC (fig.3A and B) homogeneously throughout the whole train duration, as expected from our previous results (Salgado et al., 2010), on the

contrary, at higher frequencies (20 Hz) the enhancement of LII/III-eIPSC and decrease of LI-eIPSC is limited to a time window of 200–250 ms, whereas in the late part of the train (> 250 ms) NE 1) does not change the response of LII/III-eIPSCs respect to control responses, and 2) it even produces an enhancement of LI-eIPSCs amplitude compared to control (fig. 3 C and F).

While our previous study showed that NE controls differentially apical and somatic GABAergic inputs to pyramidal cells in layer II/III (Salgado et al., 2010), here we show that NE specifically alters the balance of early vs. late excitation in responses to high frequency (20 Hz) and - in part - to intermediate frequency (10 Hz) trains. The specificity of the modulation consists in the increase of perisomatic inhibition and a parallel decrease in distal inhibition in the first 200–250 ms, but the opposite effect for integration time $t > 250$ ms, in which distal inhibition is increased while proximal inhibition is decreased. This observation suggests that synaptic integration of prolonged (> 200 ms) stimuli in the dendritic and the somatic compartments occurs in different time windows.

A comparison of our results with previous studies in the hippocampus (Miles et al., 1996) and in other cortical areas (Ascoli et al., 2008; Bacci A., 2004; Cauli et al., 1997; Markram et al., 2004; Sceniak et al., 2008), where placement of extracellular stimulation electrodes on different hippocampal layers allows similarly a preferential activation of perisomatic vs. apical dendritic inhibitory synapses - shows that the modulation of the probability of release and of other presynaptic factors similarly influences use-dependent synaptic transmission, in turn altering the proportions of information carried by fine timing and firing rate that synapses can transmit (Baimoukhametova et al., 2004; Tecuapetla et al., 2007; Tsodyks et al., 1997; Zucker et al., 2002).

Functionally, at least two main GABAergic cell types are present in a cortical network: fast-spiking inhibitory neurons controlling the firing of principal cells with perisomatic synapses, and low-threshold regular-firing inhibitory neurons projecting to multiple postsynaptic compartments including apical dendrites (Freund, 2003; Freund et al., 1997; Hajos et al., 1997; Kapfer et al., 2007; Wang et al., 2004). These different GABAergic interneuronal types produce a unique spatial and temporal pattern of synaptic integration onto pyramidal cells. We show here that layer-specific adrenergic inhibition in the auditory cortex shifts the balance between distal and somatic inhibition shaping the receptive fields of auditory cortical neurons not only in the spatial domain but also in the time domain. The different density of noradrenergic fibers in cortical layer I vs. layer II/III (Freedman et al., 1975; Fuxe et al., 1968; Levitt et al., 1978; Morrison et al., 1978; Morrison et al., 1979b) is consistent with a qualitatively different adrenergic modulation of apical vs. basal inhibition of pyramidal cell dendrites. Our results are also consistent with the hypothesis that NE affects auditory responses by modulating frequency selectivity, signal-to-noise ratio, and short-term cortical plasticity, possibly by opening a temporal window for the induction of transient changes in tuning curves (Manunta et al., 1997; Manunta et al., 1999; Manunta et al., 2004).

We speculate that a main function of adrenergic modulation synaptic transmission is 1) to improve signal/noise ratio by decreasing glutamatergic signaling (Dinh et al., 2009; Pralong et al., 1994; Pralong et al., 1995; Pralong et al., 2002), and 2) to promote the temporal overlap between multiple types of inputs to cortical layer I (cortico-cortical feedback from secondary areas, thalamo-cortical non-tonotopic from non-lemniscal sources and/or multisensory input) by decreasing LI-eIPSC, while at the same time enhancing perisomatic GABAergic input for initiation of short bursts of γ -oscillations which in turn synchronize neuronal ensemble activity (Cardin et al., 2009; Imig et al., 1977; Sohal et al., 2009; Vreugdenhil et al., 2005a; Vreugdenhil et al., 2005b). Specifically, our results suggest that in the presence of NE long-lasting (> 250 ms) broad-band stimuli are processed biphasically,

with a first phase (0–250 ms) in which a transiently hyper-excitable layer I would enable non-auditory information to be summated at the apical dendrites with sensory information received by basal dendrites, while at a later phase (> 250 ms) a stronger apical and weaker basal inhibition would enhance local processing of sensory information (at the basal dendrites) by simultaneously decreasing the strength of context-dependent signals (Murray et al., 2009; Musacchia et al., 2009) at the apical dendrites. This last effect could limit top-down influence as well as the duration of sensory evoked gamma-oscillations to an integration window of about 200 ms as suggested in previous studies (Cauller et al., 1998; Chalk et al., 2010; Larkum et al., 2004). This or similar phenomena might contribute to establish and shape auditory attention mechanisms.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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List of abbreviations

NE	norepinephrine
IPSC	inhibitory postsynaptic current
LI-eIPSC	IPSC evoked by stimulation of cortical layer I
LII/III-eIPSC	IPSC evoked by stimulation of cortical layer II/III
GABA	γ -aminobutyric acid
ACSF	artificial cerebrospinal fluid
DNQX	6,7-Dinitroquinoxaline-2,3-dione
AMPA	α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid
APV	amino-5-phosphonovalerate
NMDAR	N-methyl-D-aspartate receptor

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Figure 1.

Short-term plasticity of GABAergic synaptic transmission in responses to electrical stimulation at different frequencies. A, B, and C: representative traces of synaptic responses evoked by electrical stimulation of layer I with a 1s-long pulse trains at 5, 10 Hz, and 20 Hz, respectively ($n = 15$). D, E, and F: representative traces of synaptic responses evoked by pulse trains at 5, 10 and 20 Hz in layer II/III ($n = 15$). Short term synaptic depression was observed in both LI-eIPSCs and LII/III eIPSCs. G–I, eIPSCs amplitude vs. pulse number at 5, 10, and 20 Hz for LI and LII/III eIPSCs. J–L: normalized synaptic depression vs. pulse number at 5, 10, and 20 Hz, same sample as above.

Figure 2.

IPSC amplitude dependence on the extracellular concentration of Ca^{2+} ($[\text{Ca}^{2+}]_o$) A: representative traces of synaptic responses evoked in LI by 20 Hz stimulation in control (black) and low Ca^{2+} (red). B: decreasing $[\text{Ca}^{2+}]_o$ from 1.5 mM to 0.5 mM (*low Ca^{2+}*) reduced the eIPSCs amplitude during the initial part of the response, while recovering it at the end of the train. C: low Ca^{2+} converted synaptic depression into facilitation on LI-eIPSCs ($n = 6$). D–F: increasing $[\text{Ca}^{2+}]_o$ from 1.5 mM to 2.5 mM (*high Ca^{2+}*) increased eIPSCs amplitude during the initial part of the response. F: The *high Ca^{2+}* condition further accelerated the depression of LI-eIPSCs ($n = 6$). G–I: representative traces, eIPSCs amplitudes and ratios ($\text{IPSC}_n/\text{IPSC}_1$) as in A, B, and C, but for LII/III-eIPSCs in control and low Ca^{2+} . Note that low Ca^{2+} converts synaptic depression into facilitation at the end of the train (fig. 2I, $n = 6$). J–L: As in D, E, and F, but for LII/III-eIPSCs. High Ca^{2+} accelerated the depression of LII/III-eIPSCs.

Figure 3.

NE modulation of the absolute peak amplitudes of LI-eIPSCs and LII/III-eIPSCs. A: NE reduced homogeneously LI-eIPSCs amplitude during 5 Hz stimulation. B: At 10 Hz, NE depressed further the amplitude of LI-eIPSCs during the initial part of the response while it recovered at the end of the train. C: during 20 Hz, NE converted depression into facilitation, similar to low $[Ca^{2+}]_o$ for LI-eIPSC. D and E: NE increased LII/III-eIPSCs amplitude conserving a depressing pattern at 5Hz (D) and at 10 Hz (E). F: NE increased LII/III-eIPSCs only for the first 4 responses of the 20 Hz pulse train.

Figure 4.

Effect of NE on LI-eIPSCs. A: representative traces of synaptic responses evoked by 5 Hz in control (black) and NE (red). B: eIPSC amplitudes normalized to the amplitude of the first response ($IPSC_n/IPSC_1$). NE did not change normalized amplitudes. C and D: like A and B, but for 10 Hz stimulation, in control condition (black) and NE (red). D: IPSCs depression recovered at the end of the train (last 2 responses) in NE. E and F: like A and B, but for 20 Hz stimulation. E representative traces showing that NE (red) produced LI-eIPSCs facilitation throughout the whole pulse train while in control (black) only depression is present. F: IPSC normalized IPSC amplitude at 20 Hz. NE converted the depression in facilitation ($n = 15$).

Figure 5. Effect of NE on LII/III-eIPSC. A: representative traces of synaptic responses evoked by 5 Hz in control (black) and NE (red). B: as in fig.4B, NE did not change normalized amplitudes. C: representative traces at 10 Hz in control and NE. D: NE did not change the depression pattern. E: representative traces showing that at 20 Hz NE increased LII/III-eIPSCs depression. F: IPSC normalized amplitude showing the NE-induced increased depression at 20 Hz. Sample size is $n = 15$.

Figure 6.

Diagram representing the effect of the activation of noradrenergic receptors on inhibitory synapses in different layers at 20 Hz. A: LI-eIPSC. Diagram illustrating stimulation and recording site (left), effect of NE on the synapses (middle), on the GABAergic currents (upper right) and normalized amplitudes. NE decreases the absolute amplitude in the early part of the train, but increases the late amplitudes, converting a depressing into a facilitating response onto pyramidal cell apical dendrites. B: same as above but for LII/III-eIPSCs. NE increases the early absolute amplitudes and further decreases the amplitudes in the late part of the train. NE conserves and even increases its extent of synaptic depression onto the basal dendrites of the pyramidal cell.