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ORIGINAL PAPER

Layer- and Area-Specificity of the Adrenergic Modulation of Synaptic Transmission in the Rat Neocortex

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Abstract The mammalian neocortex is a multilayered structure receiving extensive adrenergic projections both in rostral and caudal areas. The cellular mechanisms of norepinephrine (NE) in the neocortex are incompletely understood. We used electrophysiology to determine whether NE modulation of synaptic transmission were similar in rostral versus caudal cortical areas, and in infra- versus supragranular cortical layers. To address these questions we used bath applications of NE (20 μM) to determine its effects on pharmacologically isolated electrically-evoked 2-amino-3-(3-hydroxy-5-methyl-isoxazol-4-yl) propionic acid receptor (AMPAR)-mediated excitatory synaptic currents (eEPSCs), or γ-amino butyric acid A receptor ($GABA_AR$)-mediated inhibitory synaptic currents (eIPSCs). We monitored synaptic currents in pyramidal neurons using whole-cell patch-clamp recordings from supragranular layer 2/3 (L2/3) and infragranular layer 5 (L5) neurons in a thin-slice preparation of rat medial prefrontal cortex (mPFC). These results were compared with the effects in the temporal cortex (TC) under similar experimental conditions. We found that NE uniformly and transiently depressed eEPSCs from supragranular to infragranular layers in both the PFC and the TC. On the contrary, the effects of NE on eIPSC were area- and layer-dependent, as NE enhanced the mean amplitude in TC L2/3 and PFC L5 eIPSCs (which displayed the largest saturation currents in the areas studied) but depressed PFC L2/3 eIPSCs, without affecting TC L5 eIPSCs. While the precise physiological meaning of these results is still unclear, our data are consistent with the existence of a dense noradrenergic-controlled GABAergic cortical network in the PFC, in which L5 may act as a decisional bottleneck for behavioral inhibition.

Keywords Prefrontal cortex · Temporal cortex · GABA · AMPA · Patch-clamp · Norepinephrine

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Introduction

Norepinephrine (NE), synthesized in the *locus ceruleus* (LC) of the brainstem, is released throughout most of the brain in multiple and functionally varied behavioral contexts like decision making, fight-or-flight response, conditioned place preference retrieval, and in general during top-down cognitive processes, making it a "global" neuromodulator [1]. An important target of the adrenergic projection from the LC is the entire neocortex, which represents about 60 % of the brain volume in humans, and integrates complex functions like sensory-motor control

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and working memory. In particular, LC adrenergic cells are strongly active during prefrontal cortex processing of salient input processed by sensory cortices based on the information of the motivational state [2]. The simultaneity of NE release onto multiple cortical targets during high level signal processing suggests the involvement of this catecholamine in coding and integration of sensory and motor information [3], originating respectively from anterior to posterior areas of the neocortex.

Scant information is available on whether NE contributes to neocortical integration with homogeneous mechanisms at the cellular level, or whether the adrenergic modulation of cellular function differs between neocortical areas or between cortical layers. Intrinsic conductance and synaptic activity are the two most important determinants of neuronal excitability. While it has been shown that NE—similar to other monoamines and acetylcholine-increases neuronal excitability of its cellular targets by inhibiting voltage-dependent K^+ channels [4, 5], it is less clear if NE produces a similar modulation of synaptic activity in different cortical areas. In this study we addressed the question whether NE produces similar effects on synaptic transmission in anterior and posterior cortices, and whether adrenergic modulation differs between supra- versus infra-granular cortical layers.

The medial prefrontal cortex (mPFC) is a particularly important part of the prefrontal cortex, as it has been postulated to integrate sensory and emotional stimuli into decisional output [6, 7], and to coordinate excitatory inputs from different brain regions, thereby fine-tuning functional connectivity with these regions [8, 9]. Electrical stimulation of LC enhances NE release in the mPFC [10, 11], thereby reducing spontaneous activity of this region [12, 13], promoting alertness and optimal processing of the stimulus-related information [14], and regulating mPFC-dependent sensory and cognitive functions [15, 16] through largely unknown cellular, synaptic, and circuit mechanisms. Adrenergic fibers projecting to the prefrontal cortex also control top-down regulated processes like conditioned place preference retrieval [16]. Adrenergic control of PFC-dependent sensory and cognitive functions occurs through largely unknown cellular, synaptic, and circuit mechanisms [1, 15].

Among sensory cortices, the temporal cortex (TC) is an important relay for synaptic integration and processing of auditory information [17] whose adrenergic function has been partially described in numerous previous studies [18–22] in terms of sharpening perceptual boundaries of frequency tuning curves and improving signal-to-noise ratio while selectively suppressing background spontaneous firing. Because of these reasons we selected the mPFC and the TC as cortical areas to perform a comparative study of the adrenergic modulation of synaptic activity.

Materials and Methods

Preparation

23–45 days old Sprague–Dawley rats, were anesthetized with isoflurane and sacrificed according to the National Institutes of Health Guidelines (UTD IACUC number 04-04) and their brains sliced with a vibrotome (VT1000, Leica) in a cold solution (0–4 °C) containing (mM) 126 NaCl, 3.5 KCl, 10 glucose, 25 $NaHCO_3$, 1.25 NaH_2PO_4, 1.5 $CaCl_2$, 1.5 $MgCl_2$, at pH 7.4 and saturated with a mixture of 95 % O_2 and 5 % CO_2 (ACSF). Coronal slices (270 μM thick) were taken from the medial prefrontal cortex or from the temporal (auditory) cortex and incubated in ACSF at 32 °C before being placed in the recording chamber. The recording solution contained ascorbic acid (0.2 mM) along with 6, 7-dinitroquinoxaline-2, 3-dione (10 μM) and kynurenate (2 mM) for blocking α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor (AMPAR)- and *N*-methyl-D-aspartate receptor (NMDAR)-mediated currents, respectively or picrotoxin (100 μM) for blocking γ-butyric acid receptor ($GABA_AR$)-mediated currents.

Electrophysiology

Slices were placed in an immersion chamber, and cells were selected using procedures described previously [23] using an upright microscope (BX51, Olympus) with a 60 × objective and an infrared camera system (DAGE-MTI, Michigan City, IN). Whole-cell voltage-clamp recordings of EPSCs and IPSCs were obtained from cortical L5 pyramidal neurons of the mPFC and TC and from L2/3 pyramidal neurons of mPFC. Neurons were selected by their pyramidal shape and pronounced apical dendrite, indicative of their pyramidal cell nature [23]. Postsynaptic currents (PSCs) were recorded in the whole-cell configuration, in voltage-clamp mode, at a holding membrane potential of $V_h = -60$ mV, with 3–5 MΩ 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 $MgCl_2$, 10 *N*-(2-hydroxyethyl) piperazine-*N′*-(2-ethanesulfonic acid), 4 glutathione, 3 $ATPMg_2$, 0.3 $GTPNa_2$, and 20 phosphocreatine. The holding voltage was not corrected for the junction potential (<4 mV). The intracellular recording solution was titrated to pH 7.2 and had an osmolarity of 275 mOsm.

Electrically evoked excitatory and inhibitory PSCs (eEPSCs and eIPSCs) were measured by delivering two electric stimuli (duration between 90 and 180 μs, intensity 10–50 μA) every 20 s, with an interpulse delay of 50 ms for eEPSCs and 100 ms for IPSCS, with an isolation unit, through a glass stimulation monopolar electrode filled with ACSF and placed at about 150–200 μm from the recording

electrode. Synaptic responses were monitored at different stimulation intensities prior to baseline recording. ''Normal'' stimulation was defined as a stimulation reliably evoking a synaptic current in the range from 100 pA to 1 nA. For each recording, a detection threshold was set at 150 % of the standard deviation of the noise (typically around 4–5 pA, threshold around 7–8 pA). Evoked responses lower than the threshold were counted as failures.

For recording input–output responses three parameters were extracted: response threshold, initial slope, and saturation current. The smallest intensity producing a non-zero synaptic response was calculated as the threshold. The initial slope was calculated between the first three non-null responses of each curve, while the saturation current was the response evoked by maximal stimulation.

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 MΩ) was monitored throughout the experiment. Recordings with >20 % change in input resistance (R_m) was discarded from the analysis. All signals were filtered at 2 kHz and sampled at 10 kHz. All experiments were performed at room temperature (22 °C).

Drugs and Solutions

All drugs were purchased from Sigma (St. Louis, MP) or Tocris (Ellisville, MO). After recording an initial baseline, drugs were bath-applied for 10 min or longer, until they reached a stable condition (as defined below in Statistical Analysis). The optimal dose of NE used was based on previous studies [24, 25] to allow unbiased comparison of the effect of NE in different layers of the cortical regions studied. Stock solutions of all drugs were prepared in water. NE was prepared immediately before experiments and oxygenated right before use, and their exposure to intense light was avoided to prevent oxidation.

Statistical Analysis

We defined a statistically stable period as a time interval (5–8 min) along which the mean amplitude of EPSC and IPSC measured during any 1-min assessment did not vary according to an unpaired Student's t test. All data are expressed as mean ± standard error of the mean. Pair pulse ratio (PPR) was calculated by dividing the mean of the second response by the mean the first response for each individual trace and then averaged [26]. The effects of drug application on eEPSC and eIPSC were assessed by measuring and comparing different parameters (eEPSC or eIPSC mean amplitude and PPR) between baseline (control) versus treatment, with paired or unpaired Student's t test depending on the experiment. For all recordings baseline period lasted between 8 and 12 min while the treatment period with NE lasted for about 20 min. The mean of the synaptic current amplitude was calculated during the statistically stable period that was determined as defined earlier. Data are reported as significantly different only if $p < 0.05$. Single asterisks (*) indicate $p < 0.05$, double asterisks (**) indicate $p < 0.01$.

Table 1 Summary of the synaptic effects of NE on excitatory and inhibitory transmission, in the PFC and TC in L2/3 and L5

	eEPSCs		eIPSCs	
	PFC	TC	PFC	TC
Cortical layer 2/3	↓	↓	↓	↑
Cortical layer 5	↓	↓	↑	No change

Arrow up (↑) indicates an increase, arrow down (↓) indicates a decrease

Results

The majority of our recordings displayed that bath administration of NE induces relatively reliable and stable changes in the mean amplitude of IPSC and EPSC recordings, with a large variety of responses as summarized in Table 1.

NE Modulated Uniformly AMPAR-Mediated Currents in the mPFC

Bath application of NE (20 μM) decreased the mean amplitude of L2/3 eEPSCs in the mPFC by 41.2 ± 4.7 % in all cells (n = 8) tested (71.8 ± 15.7 pA in baseline to 42.2 ± 9.8 pA after NE, $p < 0.01$, paired Student's t test; example of time course in Fig. 1a, mean reduction in Fig. 1b). We also examined the effect of NE on the PPR (S_2/S_1) to determine if these effects are due to presynaptic modulation of GABA release. NE did not change PPR in L2/3 eEPSCs (1.50 ± 0.14 in control vs. 1.26 ± 0.09 in NE, paired Student's t test; Fig. 1c).

A similar result was obtained after bath application of NE on L5 eEPSCs in the mPFC. NE (20 μM) decreased the amplitude of L2/3 eEPSCs by 53.7 ± 12.9 % in all cells (n = 8) tested (69.6 ± 8.3 pA in baseline to 26.8 ± 5.1 pA after NE, $p < 0.01$, paired Student's t test; example of time course in Fig. 1d, mean reduction in Fig. 1e). NE did not change PPR in L5 eEPSCs (1.21 ± 0.09 in baseline to 1.08 ± 0.09 in NE, paired Student's t test; Fig. 1f).

These data are consistent with our previous work, showing that the same concentration of NE (20 μM) decreases eEPSCs in all layers of auditory cortex without changing PPR [24].

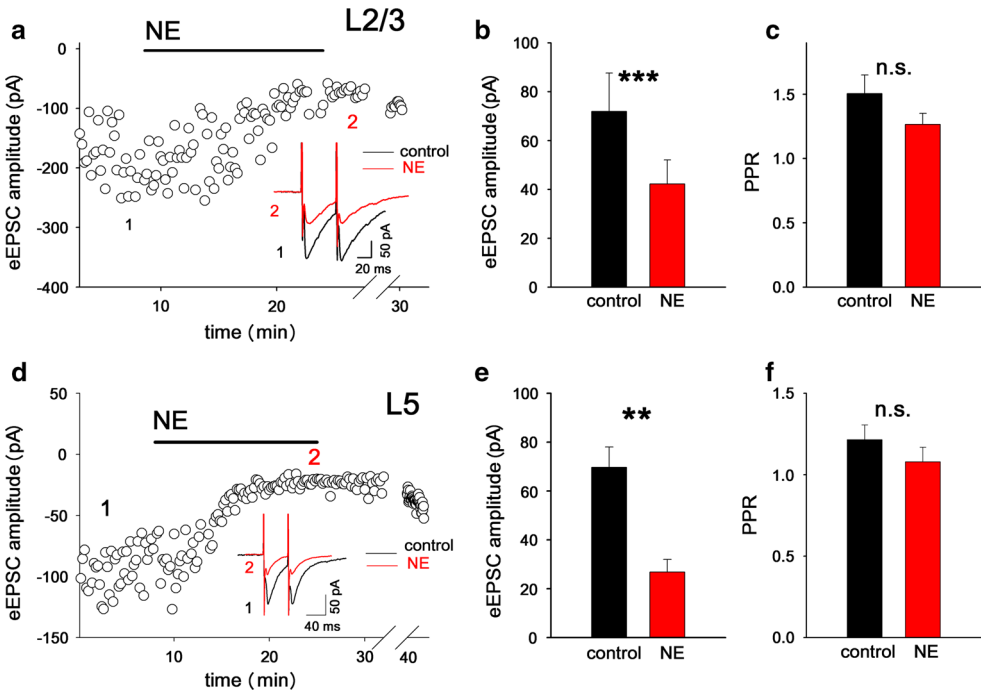

Fig. 1 Effect of bath application of NE (20 μM) on PFC excitatory transmission. NE decreases the amplitude of AMPAR-mediated signal in both cortical L2/3 (n = 8; $p < 0.01$; paired *t* test) and L5 (n = 8; $p < 0.01$; paired *t* test). Representative example of time-course in **a** and **d**, average in **b** and **e**, respectively. Pair-pulse ratio (PPR) was unchanged (mean in **c** and **f** respectively) in both cortical L2/3 (n = 8; $p = 0.17$; paired *t* test) and L5 (n = 8; $p = 0.19$; paired *t* test). The *horizontal bars* in **a** and **d** represent the time during which NE was applied. The traces shown in the insert are the average of four or more traces corresponding approximately to the position of the *numbers*

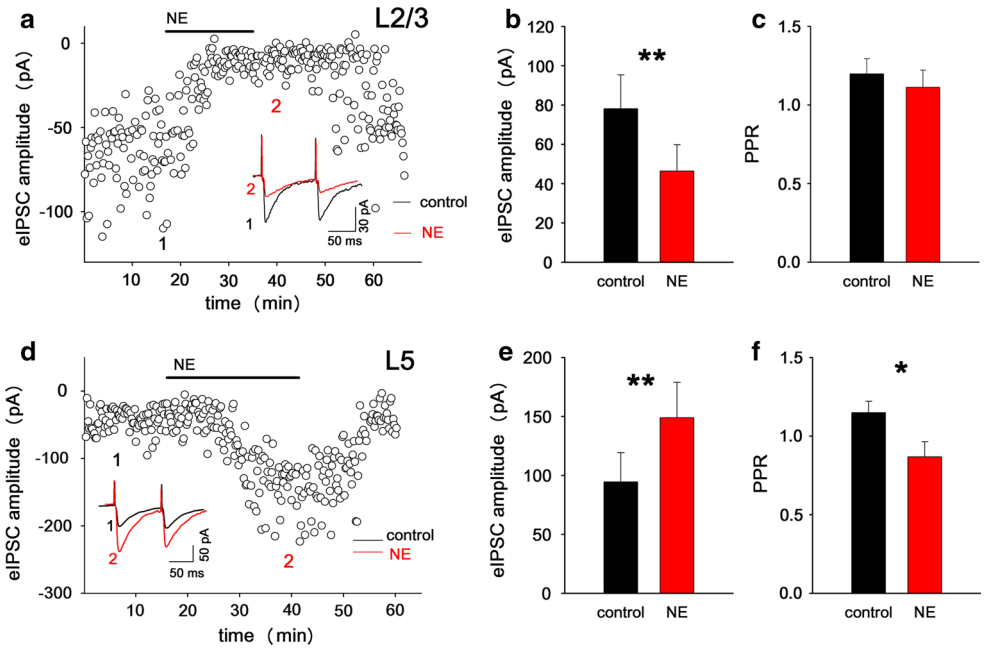

Fig. 2 Different effects of bath application of NE (20 μM) on supra- versus infra-granular PFC inhibitory transmission. NE decreases L2/3 eIPSCs amplitude (n = 11; $p < 0.01$; paired *t* test) (representative example in **a**, mean in **b**) without changing the PPR (n = 11; $p = 0.26$; paired *t* test) (mean PPR in **c**), but increases L5 eIPSC amplitude (n = 11; $p < 0.01$; paired *t* test) (representative example in **d**, mean in **e**) accompanied by a decrease in PPR (n = 11; $p < 0.05$; paired *t* test) (mean PPR in **f**). Same meaning of the *symbols* as in Fig. 1

Differential Modulation of GABAergic Currents in the mPFC and Temporal Cortex

NE (20 μM) *decreased* L2/3 eIPSCs mean amplitude in the mPFC by 38.1 ± 10.2 % in all cells (n = 11) tested (78.0 ± 17.73 pA in baseline to 46.4 ± 13.4 pA after NE, $p < 0.01$, paired Student's *t* test; representative time course in Fig. 2a, mean reduction in Fig. 2b). We also examined the impact of NE on L2/3 eIPSCs PPR, which was unchanged (1.20 ± 0.10 in control vs. 1.11 ± 0.11 in NE, paired Student's *t* test; Fig. 2c).

On the contrary, NE (20 μM) *increased* the amplitude of L5 eIPSCs in the mPFC by 88.42 ± 28.0 % in 9/2 (82 %) of cells tested (94.5 ± 24.8 pA in control vs. 148.9 ± 30.0 pA after NE, $p < 0.01$, paired Student's *t* test; representative time course in Fig. 2d, mean increase in Fig. 2e). Bath application of NE significantly decreased the PPR in L5 eIPSCs from 1.15 ± 0.07 (baseline) to

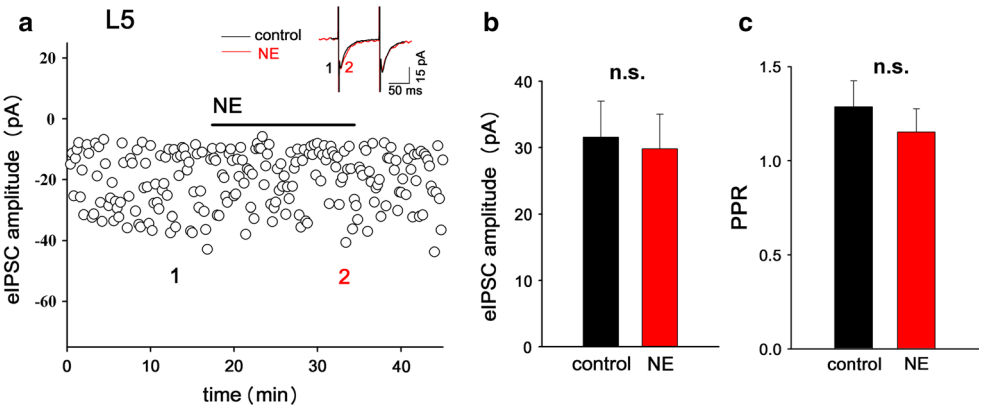

Fig. 3 NE does not change eIPSC in temporal cortex L5. Neither eIPSC amplitude (n = 5; $p = 0.12$; paired t test) (representative time-course in **a**, mean in **b**) nor PPR (n = 5; $p = 0.32$; paired t test) (mean in **c**) are changed by NE bath-application. Same meaning of the *symbols* as in the previous figures

0.87 ± 0.10 (NE; $p < 0.05$, paired Student's t test; Fig. 2f).

In a separate set of experiments, NE (20 μM) failed to produce any changes in the amplitude of L5 eIPSCs of the temporal cortex (TC, 31.5 ± 5.4 in control vs. 29.8 ± 5.2 in NE, n = 5, paired Student's t test; representative time course in Fig. 3a, mean change in Fig. 3b). NE also did not change the PPR in L5 eIPSCs (1.29 ± 0.14 in control vs. 1.15 ± 0.12 in NE, paired Student's t test; Fig. 3c). The effect of NE in L2/3 and L5 of the PFC and of the TC are summarized in Table 1.

Input/Output Response of Electrically-Evoked IPSCs

Electrically-evoked synaptic currents likely originate from stimulation of axons surrounding the stimulation electrode. We obtained eIPSCs by stimulating cortical L2/3 and L5 at about 150–200 μm from the recorded cell. We compared GABAergic transmission between L2/3 (n = 4) and L5 (n = 6) pyramidal cells. Each point in the input/output (I/O) curve corresponds to averaged responses over 5–7 extracellular electrical responses delivered at the same intensity (I/O curve in Fig. 4a). The response threshold was not different between L2/3 eIPSCs (5.7 ± 1.7 mA) and L5 eIPSCs (9.8 ± 1.2 mA; unpaired Student's t test; Fig. 4b). However, eIPSC slope was significantly higher for L5 eIPSCs (55.6 ± 12.7 pA/mA) compared to L2/3 (6.0 ± 3.9 pA/mA, Fig. 4c, $p < 0.01$; unpaired Student's t test). Similarly, saturation currents for L5 were larger (1.22 ± 0.15 nA, same sample as above) compared to L2/3 (452 ± 268 pA, same sample, $p < 0.05$; unpaired Student's t test; Fig. 4d), suggesting higher levels of inhibitory connectivity in PFC L5.

Discussion

Modulation of AMPA Currents

We found that NE decreases AMPAR-mediated signal homogeneously in the mPFC (Table 1), similar to what we and other groups already described in other cortices [24, 27–30]. This effect opposes the increase in intrinsic excitability of principal cells associated with decreased K^+ conductances such as after hyperpolarization (AHP), induced by NE [4, 31], as well as by several other neuromodulators [32, 33].

Given its ubiquitous nature, an important role of NE could be to balance the increase in intrinsic excitability produced by actions of NE on voltage-gated conductances with a decrease in the amplitude of AMPA-mediated currents. This might be a mechanism concurrent with brain stem activation during wake states. In summary, the effect of NE on the glutamatergic excitatory network would be on one hand to increase single-cell excitability while simultaneously reducing the spread of excitation by temporarily decreasing the intensity of cortical glutamatergic synapses. This function may be a "prerequisite" for integrating internal states with sensory input (in prefrontal and posterior cortices, respectively) into coherent working memory processes.

Modulation of GABA Currents

The general properties and adrenergic modulation of GABAergic synaptic responses appear to be more complex than those of glutamatergic AMPAR-mediated responses [34]. Firstly, NE decreases supragranular eIPSC while it increases infragranular eIPSC, suggesting that it would be oversimplistic to extrapolate the extent or even the direction of synaptic signal modulation from one cortical layer to another. The change in PPR induced by NE application indicates different cellular sites for the opposite modulation: presynaptic in the TC, in agreement with our previous findings [25], and postsynaptic in the mPFC. The discrepancy between PFC and TC in the direction and amount of eIPSC adrenergic modulation suggests that synaptic modulation is not only layer-specific but also area-specific (summarized in Table 1).

These qualitatively and quantitatively peculiar responses might possibly be caused by differential embryonic

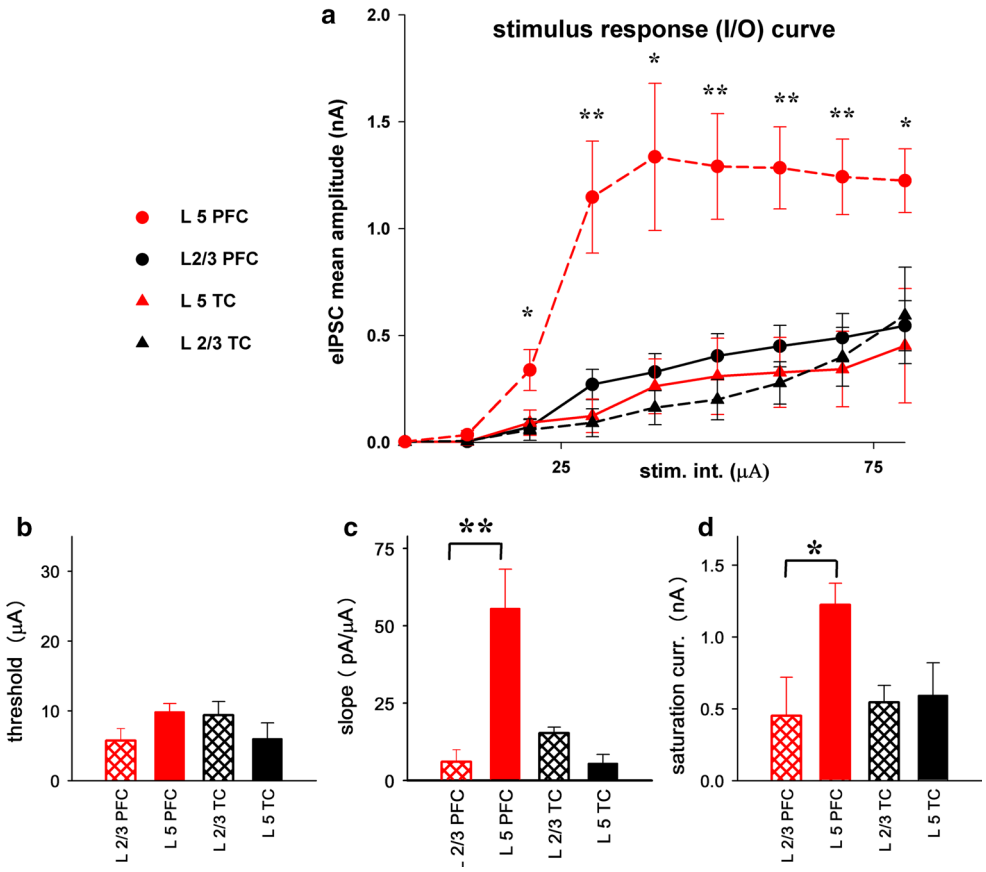

Fig. 4 Peculiarity of synaptic transmission in PFC L5. **a** Input/output (I/O) *curves* were determined by averaging the amplitude of the response of multiple events at increasing stimulation intensities. In contrast with all the other areas and layers recorded, which displayed a range of response <500 pA, responses recorded from PFC L5 reached intensities up to 1.5 nA. The parameters extracted from the I/O *curves* were the activation threshold (**b**), the initial slope (**c**), and the saturation *curves* (**d**). Slope (n = 4 in L2/3 vs. n = 6 in L5; $p < 0.01$; unpaired *t* test) and saturation current (n = 4 in L2/3 vs. n = 6 in L5; $p < 0.05$; unpaired *t* test) were significantly different between PFC L5 and all the others (PFC L2/3, TC L5, and TC L2/3, from [39])

migration of GABAergic neuron precursors along the ventral edges of the cortical mantel from the developing pallium [35]. The delicate process of interneuron progenitor migration, differentiation, and synaptic maturation might eventually produce a descending gradient of innervations of GABAergic neurons from the ventral side of the neocortex to the neuropil as well as in the rostro-caudal direction [35]. Based on their embryonic origin, GABAergic interneurons show a high diversity in laminar organization throughout the cerebral cortex [36, 37]. While parvalbumin-positive chandelier cells are abundant mostly in L2 and L5, the parvalbumin-positive basket cells are distributed in all cortical layers except L1 [36, 37]. As GABAergic interneurons control the activity of the pyramidal neurons [38], their differential distribution could explain the heterogeneous effects of NE on the IPSCs recorded in the PFC.

The largest amplitude of GABAergic synaptic responses in PFC L5 compared with PFC L2/3 or TC GABAergic synaptic responses in any of the layers studied underscores the relevance of local inhibitory neurons in that cortical layer, which is hypothesized to be the output layer of an area involved in decision-making and motor activity planning [39]. In line with the these effects, NE and other monoamines have been shown to be involved in bidirectional modulation of gamma oscillations in the hippocampus [40, 41], which are likely produced by a feedback loop between pyramidal neurons and GABAergic interneurons [42]. This differential modulation of cortical network activity by NE could underlie the role of NE in information processing and cognitive flexibility.

Lesion studies in animal models as well as in humans indicate that a functional PFC is necessary for impulse control [43]. All this information corroborates the hypothesis that the network of synaptic inhibition in mPFC L5 might be a critical neural substrate for behavioral inhibition. We speculate that the transient enhancement of L5 inhibitory currents induced by NE may increase the excitatory threshold to trigger action, or otherwise for commencing a motor plan.

Conclusions

While more experiments will be necessary to draw a more conclusive picture of the role of NE in the cortex, the NE-induced decrease of excitatory synaptic currents together with the enhancement PFC L5 eIPSC are consistent with the putative antiepileptic role of NE, as well as with the proposed function of NE in decision-making and control of impulsivity [44, 45]. In particular, the region- and

layer-specific action of NE on eIPSC emphasizes the importance and complexity of the local GABAergic system in the control of executive functions. More studies will be needed to determine the contribution of specific types of local GABAergic interneurons to the adrenergic modulation.

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