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ORIGINAL PAPER

Norepinephrine Homogeneously Inhibits α-amino-3-hydroxyl-5-methyl-4-isoxazole-propionate- (AMPAR-) Mediated Currents in All Layers of the Temporal Cortex of the Rat

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Abstract The primary auditory cortex is subject to the modulation of numerous neurotransmitters including norepinephrine (NE), which has been shown to decrease cellular excitability by yet unclear mechanisms. We investigated the possibility that NE directly affects excitatory glutamatergic synapses. We found that bath applications of NE (20 μM) decreased glutamatergic excitatory post-synaptic currents (EPSCs) in all cortical layers. Changes in the kinetics of synaptic EPSCs, invariance of pair pulse ratio and of the coefficient-of-variation, together with the decrease of responses to pressure-application of AMPA (500 μM), indicated the postsynaptic nature of the adrenergic effect. Pharmacological experiments suggested that the NE-induced depression of EPSCs is caused by the activation of α1 adrenoceptors, PLC, and a Ca^{2+}-independent PKC. We speculate that the decrease in temporal cortex excitability might promote a posterior-to-anterior shift in cortical activation together with a decrease in spontaneous background activity, resulting eventually in more effective sensory processing.

Keywords Auditory cortex · Glutamate · Norepinephrine · PLC · EPSC · Patch-clamp

Introduction

Norepinephrine (NE) is a monoamine synthesized and released in the brain from neurons of the *locus coeruleus* (LC) and the lateral tegmental field, which project to multiple brain areas including the amygdala, spinal cord, hippocampus, thalamus, hypothalamus, and importantly, the neocortex [2, 4, 16, 37, 70]. NE is released by volume transmission under a number of behavioral conditions including stress [1, 8, 19, 31, 33, 35, 78], fear [11, 26, 51, 65, 79], feeding [18, 29], and sexual activities [20, 38]. The pervasive and ubiquitous presence of NE fibers and its receptors makes this monoamine a candidate for the modulation of brain states, and a potential target for a variety of neuropsychiatric conditions such as psychoses, attention-deficit/hyperactivity disorder, depression, and drug addiction [5, 22, 30, 39, 49, 63]. Because of its importance in working memory and executive functions, the cellular effects of NE on the prefrontal cortex (PFC) have been the focus of a large number of studies [63, 68, 80]. A large number of studies have reported different effects of the NE system on glutamatergic signaling in the PFC and motor cortex with different results. Some of them have shown that NE depresses both *N*-methyl-D aspartate receptor- (NMDAR-) dependent and non-NMDAR-dependent components of the monosynaptic excitatory postsynaptic currents (EPSCs) [45, 46], while others have shown that glutamate-evoked excitatory cortical responses are increased by activation of α1-adrenoceptors [59].

Comparatively less attention has been paid to the effects of NE on glutamatergic signals in sensory cortices. In vivo studies on somatosensory and visual cortices have shown that either exogenous or endogenous activation of the adrenergic system greatly modifies cortical excitability, which in turn affects sensory field properties and signal-to-noise ratio (S/N) [81–83]. In the auditory cortex (ACx), NE has also been shown to strongly affect auditory responses by modulating frequency selectivity, S/N, and cortical plasticity, possibly by transiently opening a window of

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selective plasticity in the tuning curves of ACx [52, 54, 55]. Since a possible adrenergic mechanism for altering auditory signal processing and S/N is the direct modulation of synaptic excitatory glutamatergic transmission, in this study we sought to determine the direct effects of NE on excitatory synaptic transmission. To this end, we used whole-cell patch-clamp recording on an auditory cortex slice preparation to study the adrenergic modulation of α-amino-3-hydroxyl-5-methyl-4-isoxazole-propionate-(AMPA-) mediated synaptic responses.

Methods

Preparation

We used an auditory cortex slice preparation similar to the one previously described [9]. About 23- to 36-day-old Sprague–Dawley rats (Charles River, Wilmington, MA) were anesthetized with isoflurane (Baxter, Round Lake, IL) and sacrificed according to the National Institutes of Health guidelines (UTD IACUC number 04-04). Rat brains were sliced with a vibratome (VT1000, Leica) in a refrigerated solution (0–4°C) containing (mM) 130 NaCl, 3.5 KCl, 10 glucose, 24 $NaHCO_3$, 1.25 NaH_2PO_4, 0.2 ascorbic acid, 1.5 $CaCl_2$, and 1.5 $MgCl_2$, saturated with a mixture of 95% O_2–5% CO_2 (ACSF). 270 μM-thick coronal slices from the most caudal fourth of the brain were retained after removing the occipital convexity and subsequently incubated in ACSF at 32°C before being placed in the recording chamber. The recording area was selected dorsally to the rhinal fissure corresponding to the auditory cortex [66]. The recording solution also contained picrotoxin (100 μM) for blocking γ-amino-butyric acid-receptor (GABAR)-mediated currents.

Drugs and Solutions

All drugs were purchased from Sigma (St. Louis, MO), TOCRIS (Ellisville, MO), or Peptides International (Louisville, KY). In some experiments, pulses of the glutamatergic agonist (±)-AMPA hydrobromide (500 μM) were applied at 100–200 μm from the recording areas. A stock solution was diluted tenfold in ACSF before being back-filled to a glass pipette similar to the one used for recording. (±)-AMPA hydrobromide application was performed using a pressure system (picospritzer, General Valve, Fairfield, NJ) through a glass pipette (25 psi, 3–12 ms). Stock solutions of all drugs were prepared in water except for U73122, whose stock solution was prepared in dimethylsulfoxide (final concentration, 0.1%). For non-aqueous solutions, the final concentration of the solvent was added to the recording control solution. Drugs were bath-applied into the recording chamber except for U73122 and Gö6976, which were added to the incubation chamber as a pretreatment as specified in the text. After recording an initial baseline for 7–10 min, drugs were bath-applied for 5 min or longer, until reaching a stable condition (see "Statistical analysis"). Solutions containing adrenergic drugs were prepared fresh every day, and oxygenated right before use in the presence of minimal environment light, in order to avoid oxidation.

Electrophysiology

Slices were placed in an immersion chamber, where cells with a prominent apical dendrite, suggestive of pyramidal morphology, were visually selected using a BX 51 (Olympus) and infrared camera system (DAGE-MTI, Michigan City, IN). Excitatory postsynaptic currents (EPSCs) were recorded in the whole-cell configuration, in voltage-clamp mode, with the holding membrane potential at $V_h = -60$ mV, with 3–5 M electrodes were used and 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 HEPES, 4 glutathione, 1.5 $ATPMg_2$, 0.3 $GTPNa_2$, 8 biocytin, and 20 phosphocreatine. In some experiments, BAPTA was replaced by ethylene glycole tetraacetic acid (EGTA, 0.5 mM). The intracellular recording solution was titrated to pH 7.3 and had an osmolarity of 270 mOsm. The holding voltage was not corrected for the junction potential (<4 mV). Electrically evoked EPSCs (eEPSCs) were measured by delivering two electric stimuli (90–180 μs, 10–50 μA) 50 ms apart every 10 s with an isolation unit, through a glass stimulation monopolar electrode filled with ACSF, and placed at 150–200 μm from the recording electrode. A 2-mV voltage step was applied at the beginning of every episode in order to monitor the quality of the recording by measuring the input resistance (R_m). Cells whose R_m changed more than 20% during the recording were discarded. EPSCs are referred to as inward (excitatory) currents, according to the electrophysiology sign convention.

Biocytin Injections

All recorded neurons were injected with 8 mM biocytin in the intracellular solution. After all recordings, slices were immediately transferred to a 24-well plate and fixed in a solution containing 80 mM Na_2HPO_4, 80 mM NaH_2PO_4, and 4% paraformaldehyde. Biocytin staining was processed using diaminobenzidine as chromogen, using a standard ABC kit (Vector Labs, Burlingame, CA). A light cresyl violet Nissl counterstain was used to identify the cortical layers.

Statistical Analysis

We defined a statistically stable period as a time interval of 5 min during which the EPSC mean amplitude measured during any 1 min assessment did not vary according to an unpaired Student's *t* test. Mean ± SEM. were reported. Pair pulse ratio (PPR) was calculated as the mean of the second response divided by the mean of the first response, according to Kim and Alger [42]. Wilcoxon test was used for assessing possible differences in PPR between control and treatment conditions. The percentage effect of drug application on the EPSC amplitude was defined as $R = (A_{treat}/A_{ctrl}) \times 100\%$, where A_{treat} and A_{ctrl} were, respectively, the mean EPSC amplitude in treatment and in control ($R = 100\%$ corresponded to no change, whereas $R = 0$ corresponded to total blockage). Drug effects were assessed by measuring and comparing different parameters (R, EPSC mean amplitude, and PPR) between baselines (control) versus treatment, with paired Student's *t* test. ANOVA unpaired Student's *t* tests were used for comparisons between different groups of cells. Data were reported as significantly different only if $P < 0.05$. Single asterisks (*) indicate $P < 0.05$, double asterisks (**) indicate $P < 0.01$. Coefficient-of-variance (CV) analysis was performed according to the one reported by [28] and by [85].

Results

Whole-cell recordings were conducted on pyramidal cells in layer II/III of rat auditory cortex. Neurons were identified by the triangular shape of their cell bodies and by the presence of a long apical dendrite extending toward superficial layers. Excitatory postsynaptic currents measured at a resting potential of $V_h = -60$ mV, were blocked by di-nitro-quinoxaline (DNQX, $n = 3$, data not shown). Input resistance was 138 ± 8 MΩ. Synaptic data were acquired with a pair pulse protocol (50 ms interpulse delay). First response amplitudes and pair pulse ration were measured.

The Effect of Norepinephrine on Glutamatergic Currents

To examine the effect of NE on electrically evoked excitatory postsynaptic currents (eEPSCs), NE (20 μM) was bath-applied for 3–20 min after a stable baseline response was obtained for 7–10 min. The percentage effect was defined as $R \equiv (A_{treat}/A_{ctrl}) \times 100\%$. The application of NE greatly decreased the mean eEPSCs amplitude ($R = 59 \pm 6\%$, $n = 9$, $P < 0.05$, *t* test; Fig. 1b). In most recordings, the NE-induced decrease in eEPSCs amplitude was reversed within 25–50 min (example in Fig. 1a). NE did not change the paired-pulse ratio (PPR), defined as the ratio between the mean of the second to the mean of the first eEPSCs amplitude [42] (PPR: 0.73 ± 0.21 in control vs. 0.83 ± 0.2 in NE, $n = 9$, n.s., Wilcoxon's test; Fig. 2a, b). In addition, NE increased eEPSC rise-time by 15 ± 4% ($n = 8$, $P < 0.05$, paired *t* test).

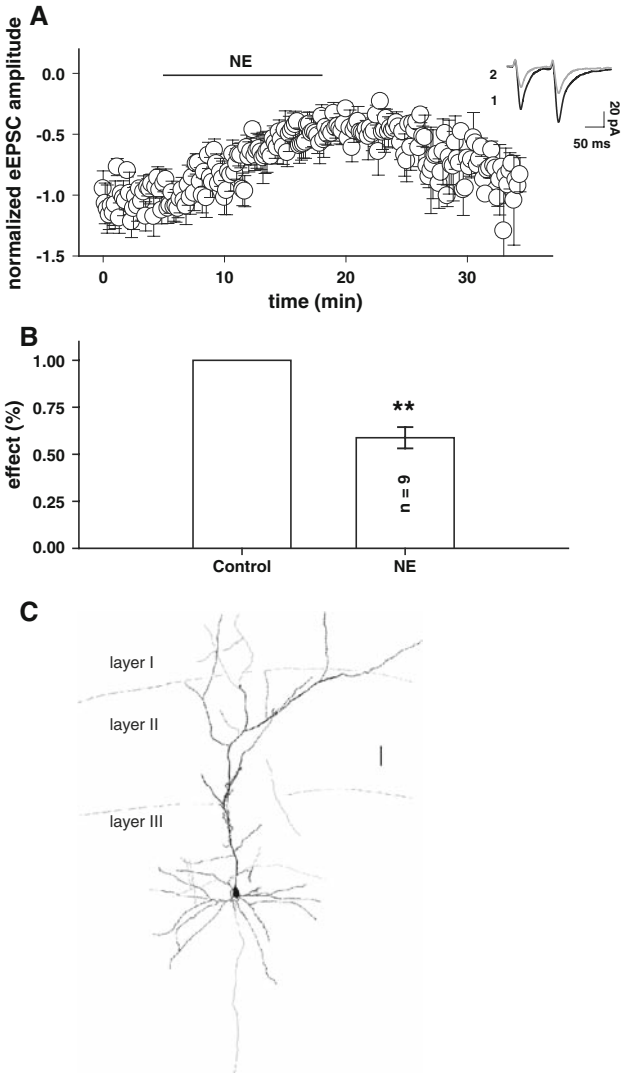

Fig. 1 NE decreases eEPSCs amplitude in layer II/III of auditory cortex. **a** Temporal course of population data points and traces average (*insert*) showing that NE (20 μM) reduces eEPSCs amplitude. The plotted data points, collected from the two pulse protocol repeated every 10 s, were obtained from the first electrical pulse. **b** Mean average of NE actions on eEPSCs, reported as mean ± SE. **c** Camera lucida drawing of a typical cortical spiny cell with basal dendrites and neuropil expansion of its apical dendrite. Calibration *bar* 20 μM

Synaptic Locus of the Norepinephrine-Induced EPSCs Depression

The postsynaptic nature of the adrenergic effect suggested by the absence of PPR change after NE application, was

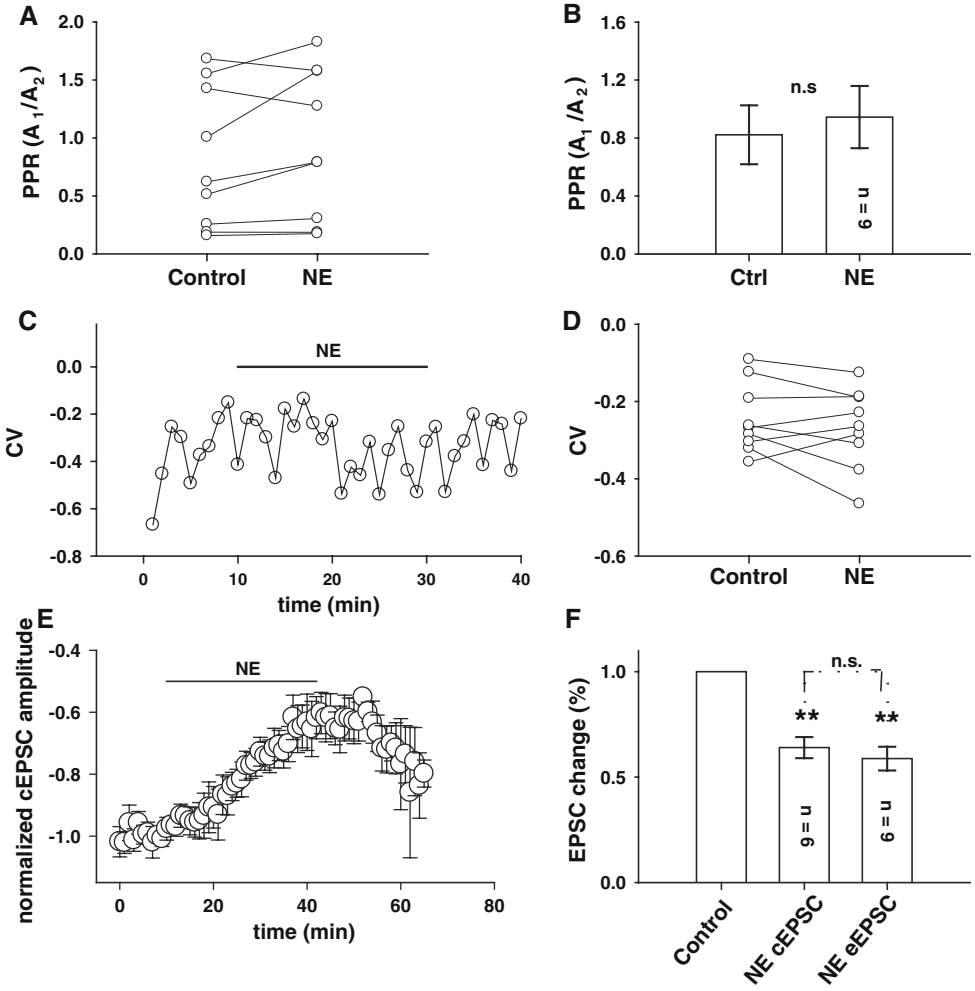

Fig. 2 Postsynaptic actions of NE on eEPSCs. **a** Effects of NE application on paired-pulse ratio (PPR), for individual cells. **b** NE-induced no significantly changes in PPR. Mean average ± SE in control and NE conditions. **c** Time-course from a representative cell show that NE no induced changes in coefficient-of-variation (CV). **d** Summary in CV for individual recordings in control and NE application. **e** Temporal course of population data points of NE actions on chemical induced excitatory currents (cEPSCs) by pressure AMPA (500 μM) application. **f** Average change induced by NE on cEPSCs and eEPSCs reported as mean ± SE

corroborated by the invariance in CV analysis of eEPSCs amplitude (−0.3 ± 0.04 in control vs. −0.27 ± 0.4 in NE, n.s.; Fig. 2c). Individual CV analysis are shown in Fig. 2d ($n = 9$). As an independent assessment we determined the effect of NE on the postsynaptic current evoked by brief pressure applications of AMPA through the tip of a patch-clamp electrode (500 μM, cEPSCs; see "Methods"). Similar to the effect on eEPSCs, NE application reduced the amplitude of chemically-evoked EPSC (cEPSCs, −93 ± 28 pA in control vs. −60 ± 15 pA in NE, $P < 0.05$, $n = 6$, Wilcoxon's test). An example of time-course and traces of population data is shown in Fig. 2e. The averaged change induced by NE on cEPSCs is equi-potent to that of eEPSCs ($R_{cEPSCs} = 65 \pm 5\%$, $R_{eEPSCs} = 59 \pm 6\%$, $P > 0.05$, t test; Fig. 2f).

To further examine whether or not the effect of NE was homogenous throughout different cortical layers of the auditory cortex, we additionally recorded eEPSCs in layers I, IV, and V. As shown in Fig. 3a, NE also elicited a reversible decrease in eEPSCs amplitude of pyramidal neurons in all cortical layers. On average, eEPSCs recorded from pyramidal cells of layers II/III, IV and V were decreased to similar extents ($R = 59 \pm 6$, 69 ± 4, $60 \pm 7\%$, respectively). Interestingly, glutamatergic signal to layer I interneurons showed the largest decrease ($R = 51 \pm 2\%$, $n = 5$, $P < 0.05$, t test; Fig. 3b). Recordings from virtually all cortical layers, illustrated in Fig. 3b, suggested that the reduction of glutamatergic synaptic transmission was mediated by a homogeneous activation of postsynaptic adrenoceptors in all layers of the auditory cortex.

Norepinephrine Decreases EPSCs Through Activation of α1-Adrenoceptors

Adrenergic receptors are subdivided into three main families: α_1, α_2 and β receptors [36, 74]. We investigated the possible contribution of each of the main different adrenoceptors subtypes to the NE-induced eEPSCs amplitude reduction. The selective α_1 agonist phenylephrine (1 μM) mimicked NE-induced depression of eEPSCs amplitude ($R = 67 \pm 4\%$, $n = 7$, $P > 0.05$, ANOVA with

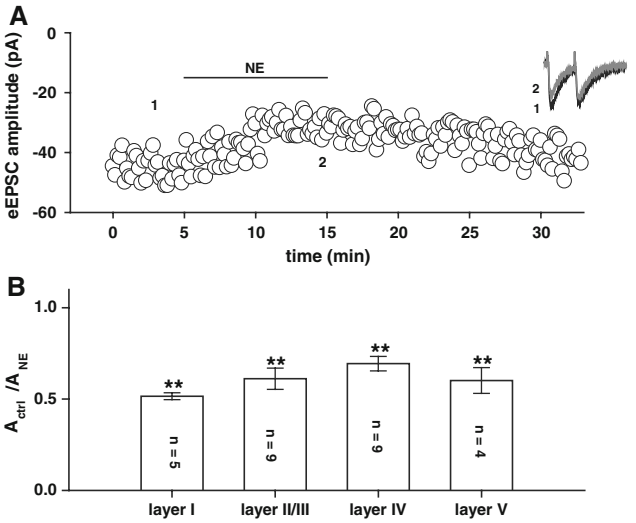

Fig. 3 NE decreases eEPSCs amplitude in all layers in auditory cortex. **a** Time-course of effect of NE on the eEPSCs in layer V, traces are shown in insert. **b** Summary of NE actions on eEPSCs amplitude in different layers of auditory cortex. Effects are reported as mean ± SE. *Asterisks* (**) indicate that NE decreases EPSC amplitude respect to the control amplitude (no NE, $P < 0.01$). NE-induced depression did not statistically differ among cortical layers ($P > 0.05$)

a post hoc Tuckey's test; Fig. 4g). The effect of NE was not found to be statistically different from that of phenylephrine ($P > 0.05$, ANOVA with a post hoc Tuckey's test). The involvement of adrenergic α_1 receptors was confirmed by the fact that the application of prazosin (1 μM), a selective α_1 antagonist, almost completely blocked the NE-induced depression of eEPSCs ($R = 86 \pm 3\%$, $n = 10$, $P < 0.01$, ANOVA with a post hoc Tuckey's test; Fig. 4h). An example of time-course and traces is displayed in Fig. 4a, b for phenylephrine and NE in the presence of prazosin, respectively. These results indicated that the NE-induced decrease in glutamatergic signal was mediated at least partially by the activation of α_1 receptors.

α_2-adrenoceptors have been shown to reduce Ca^{2+}-currents in sensory motor cortex pyramidal neurons [76] and to affect PFC neuronal activity [10, 50]. In order to assess whether α_2 adrenoceptors were involved in the EPSCs modulation we tested the effect of α_2 receptor agonist or antagonists. The selective α_2 agonist clonidine (1 μM) did not mimic the action of NE upon eEPSCs ($R = 91 \pm 5\%$, $n = 7$, $P < 0.01$, ANOVA with post hoc Tuckey's, Fig. 4g). Additionally, NE-induced depression of eEPSCs persisted in the presence of 1 μM yohimbine, a selective α_2 antagonist ($R = 73 \pm 5\%$, $n = 7$, $P < 0.05$, ANOVA with a post hoc Tuckey's test; Fig. 4h). Examples of time-course and traces are reported in Fig. 4c for clonidine and in Fig. 4d for NE in yohimbine. These results suggest that α_2-adrenoceptors were not involved in the NE-induced depression of glutamatergic synaptic transmission.

Possible effects of β adrenoceptors were tested with the application of two concentrations of the nonselective β agonist isoproterenol (ISO, 10 μM and 100 μM). ISO failed to mimic the effect of NE on eEPSCs ($R = 93 \pm 4\%$ for 10 μM ISO, $n = 8$, $P < 0.01$, and $R = 86 \pm 8\%$ for 100 μM ISO, $n = 6$, $P < 0.01$, ANOVA with a post hoc Tuckey's test, Fig. 4e). Furthermore, when NE was superfused in the presence of the β-blocker propranolol (1 μM), the amplitude of eEPSCs continued to show marked reduction ($R = 54 \pm 6\%$, $n = 8$, $P > 0.05$, ANOVA with a post hoc Tuckey's test; Fig. 4f). Examples of time-course and traces are reported in Fig. 4e for ISO and in Fig. 4f for NE in propranolol. The averaged amplitude changes are shown in Fig. 4g, h, reported as mean ± SE. These results suggest that β-adrenoceptors were not involved in the NE-induced depression of glutamatergic synaptic transmission. Altogether, these results showed that only α_1, but not α_2 nor β-adrenoceptors, were responsible for the NE-induced depression of glutamatergic synaptic transmission.

Molecular Mechanisms of the NE-Induced Depression of Glutamatergic Transmission

α_1-Adrenoceptors belong to the G-protein-coupled receptor family which activates phospholipase C (PLC), protein kinase C (PKC), and induces an increase in IP_3 and intracellular Ca^{2+} concentration ($[Ca^{2+}]_i$). We confirmed this by incubating rat slices for 2 h in 1-6-((17β)-3-Methoxyestra-1,3,5[10]-trien-17-yl)aminohexyl-1H-pyrrole-2,5-dione (U73122) (10 μM) which prevents PLC activation by inhibiting its coupling with G-proteins. 2 h or longer (but not 1 h) pre-incubation with U73122 prevented the NE-induced eEPSCs depression ($R = 86 \pm 4\%$, $n = 5$, $P < 0.01$, ANOVA with post hoc Tuckey's, Fig. 5d), indicating that PLC was responsible for the action of NE. Examples of time-course and traces are reported in Fig. 5a.

Different types of PKC can be the downhill effector of PLC. In order to study the contribution of Ca^{2+}-dependent PKC proteins in noradrenergic-induced eEPSCs depression, we incubated our slices with the specific blocker of the Ca^{2+}-dependent PKC Gö6979 (400 nM) [67]. Gö6976 pre-incubation did not prevent the NE-induced eEPSCs depression ($R = 58 \pm 3.5\%$, $n = 9$, $P > 0.05$, ANOVA with a post hoc Tuckey's test, Fig. 5d), indicating that a Ca^{2+}-independent PKC isoform was responsible for such depression. Examples of time-course and traces are reported in Fig. 5b.

In order to confirm that the NE-induced eEPSCs depression was not related to changes in intracellular Ca^{2+} concentration we replaced the Ca^{2+} chelator BAPTA with EGTA (0.5 mM) in the intracellular recording solution. The obtained inhibitory effect of NE (20 μM) in EGTA

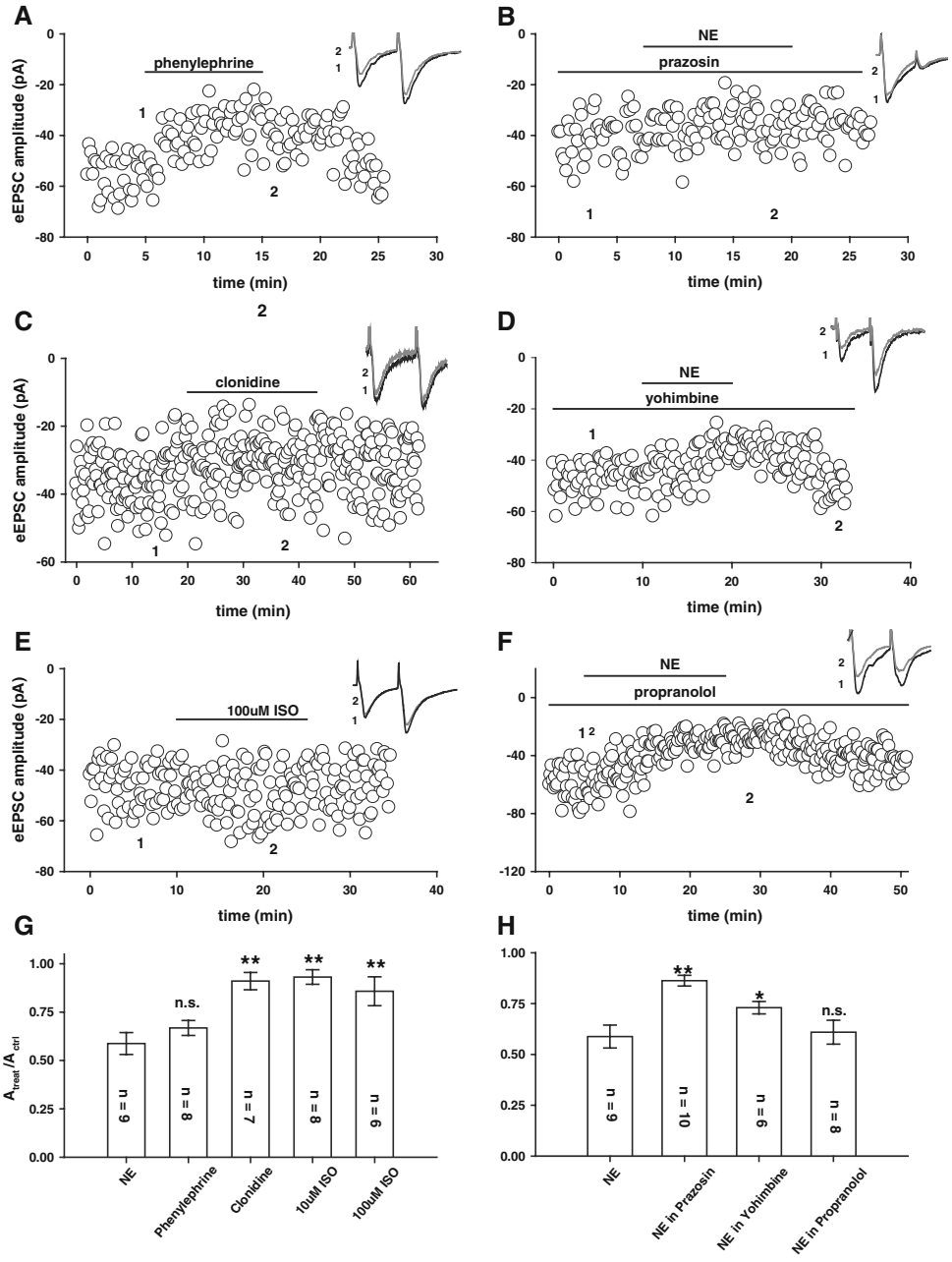

Fig. 4 α_1 receptors are responsible for the decrease in EPSCs amplitude; representative time-course of the effects of adrenergic agonists and antagonists on eEPSCs. **a** Temporal course showing eEPSCs reduction by the selective α_1 noradrenergic receptor (phenylephrine, 1 μM). **b** Prazosin (1 μM) occluded the effects of NE. **c** Temporal course of action of clonidine (1 μM) on eEPSCs. **d** Yohimbine does not occlude the NE action on eEPSCs indicating that α_2 not modulated eEPSCs. **e** Isoproterenol (10 μM or 100 μM) did not mimic NE actions. **f** Propanolol (1 μM) does not occlude the NE action on eEPSCs indicating that β receptors are not involved in noradrenergic modulation of eEPSCs. **g–h** Summary of results of experiments with agonists and antagonists suggesting that α_1 receptors are responsible for NE-induced eEPSCs reduction. Significance levels are measured relative to the NE effect (*first bar*)

($R = 58 \pm 5\%$ of its control, $n = 5$, $P > 0.05$, ANOVA with post hoc Tuckey's, Fig. 5d) was equipotent to that induced with BAPTA in the intracellular solution. Examples of time-course and recording with the low-EGTA intrapipette solution are reported in Fig. 5c. Altogether, these results suggested that the NE-induced eEPSCs depression was independent of $[Ca^{2+}]_i$.

Discussion

We demonstrated for the first time that NE depressed excitatory synaptic transmission by activating postsynaptic α_1 adrenoceptors, via a PLC-dependent, Ca^{2+}-independent cascade pathway in the auditory cortex.

Synaptic Locus of the Noradrenergic Effect

α-adrenoceptors-mediated postsynaptic responses have been recorded in many areas of the CNS, including thalamus [56], hypothalamus [64], reticular formation [32], and dorsal Raphe [62]. The invariance in PPR and CV, with the change in EPSCs kinetics suggests a postsynaptic origin of the NE-induced inhibition of the glutamatergic signal, and is in agreement with the similar extent of reduction of

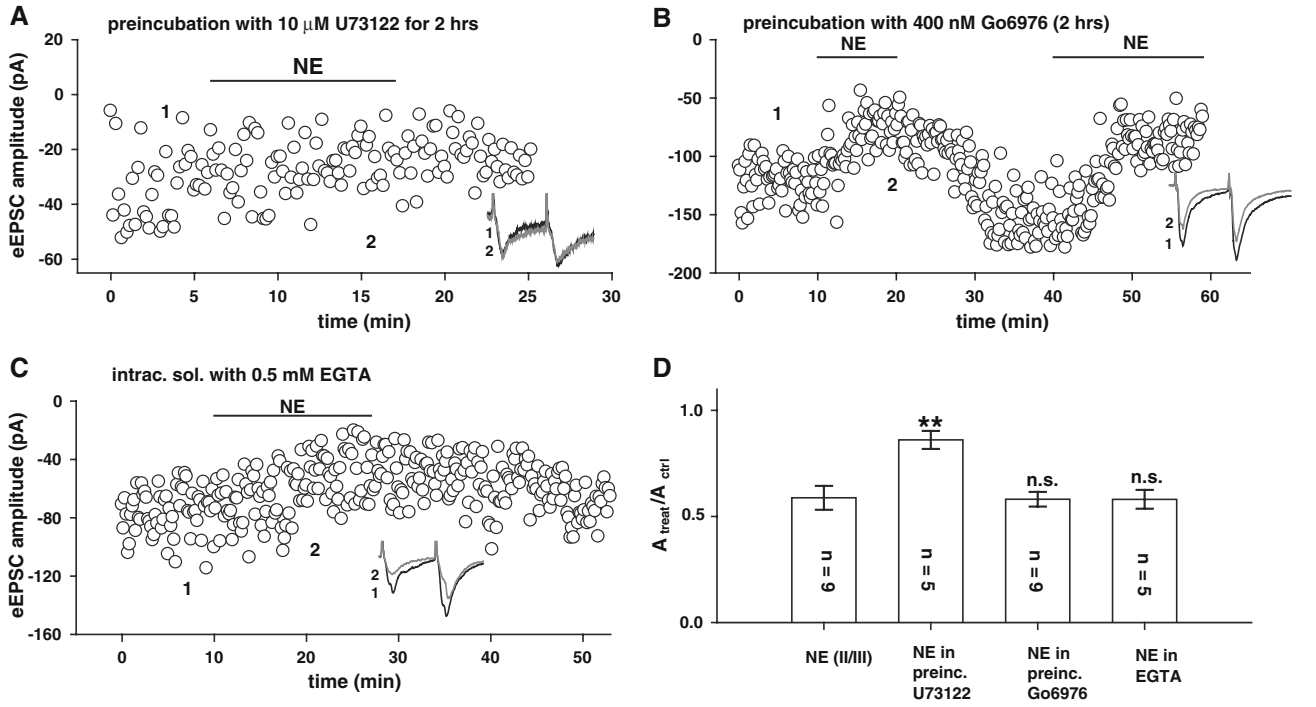

Fig. 5 α_1-PLC is responsible of all NE-induced modulation of eEPSCs. **a** NE effects in slice pre-incubation of PLC blocker (U73122 10 μM) for >2 h Time-course showing that U73122 occluded all the effects on EPSCs by NE. **b** Gö6976 (Ca^{2+}-dependent PKC blocker) does not occlude the actions of NE on EPSCs amplitude. **c** The NE-induced EPSCs depression was independent on intracellular Ca^{2+} concentration. EGTA (0.5 mM) does not change the modulation of EPSCs by NE. **d** *Bar graph* summarized NE effects. Mean ± SE of NE-induced reduction. Significance levels are measured relative to the NE effect (*first bar*)

the synaptic and pressure-application AMPAR-mediated signal. Postsynaptic adrenergic modulation of EPSC have been described in other brain areas, particularly in the prefrontal cortex [21, 40] The NE-induced EPSCs depression was quantitatively homogeneous across all layers of the rat auditory cortex.

Pharmacology of the Noradrenergic Depression

Since the NE-induced depression of glutamatergic synaptic transmission was mimicked by α_1-adrenoceptors agonist phenylephrine, and blocked by the α_1-adrenoceptor antagonist prazosin, while neither α_2- nor β-adrenoceptors modulation mimicked the action of NE, the adrenergic effect appeared to be mediated exclusively by postsynaptic α_1-adrenoceptors. This finding is in agreement with a previous in vitro study of the neocortex that showed NE, via activation of α_1-adrenoceptors, decreased the amplitude of monosynaptic EPSCs [45]. Additionally, Manunta and Edeline, produced a series of in vivo studies (1997, 1998, and 1999) suggesting that α_1-adrenoceptors were involved in the NE-induced inhibition of the tone-evoked signal, and that this inhibition was probably was not mediated by GABAergic interneurons in the auditory cortex [52–54].

Metabolic Pathway

The block of the NE-induced depression of the glutamatergic signal after incubation of brain slices with the PLC blocker U73122 indicates that the α_1-adrenoceptors responsible for the adrenergic effect belong to a classic G_q protein family initiating the phosphoinositol cascade by activation of phospholipase C (PLC), and, eventually, of the protein kinase C (PKC). The failure of the Ca^{2+}-dependent PKC inhibitor (Go6976) to prevent the adrenergic decrease in glutamatergic signal and the inability of the low-EGTA intracellular solution to enhance the EPSCs depression are indicative of a Ca^{2+}-independent adrenergic mechanism. This result is in agreement with a previous study showing that α1 activation may indeed involve a Ca^{2+}-independent signaling pathway [15], but is in contrast with studies obtained in other brain areas in which α_1-adrenoceptors activation coupled to PLC via G-protein increase $[Ca^{2+}]_i$ via Ca^{2+} influx releasing Ca^{2+} from intracellular stores [24, 44, 48, 69].

Functional Implications

Previous studies indicated that an increase in NE levels in the CNS would elevate seizure threshold, while impairments in adrenergic function by inhibition of NE synthesis,

release, or storage, conversely would reduce seizure threshold [23]. Our findings support an anti-epileptogenic function of NE in the mammalian neocortex. This interpretation could explain results from in vivo experiments [61, 71], in which LC stimulation increases in the threshold for kindling-induced seizures [84], as well as the suppressive effect of NE release on the development of kindling-induced seizures in the amygdala [57]. The NE-induced decrease of the AMPA signal and increased signaling from GABAergic neurons, as found in the hippocampus, neocortex and in other brain regions, converge to strengthen the antiepileptic role of the noradrenergic system [3, 13, 14, 27, 41]. The results from our study could explain the role of α_1 receptors in mediating NE anticonvulsant action [12, 47, 58, 60, 71].

If the adrenergic inhibition of AMPAR-mediated currents were the prevalent effect in the auditory cortex, the activation of the adrenergic system would greatly increase and shape the selectivity to auditory input. In this way, the corticopetal adrenergic system could prevent the overflow of data tagged as important information for further cortical processing, while a dysfunctional cortical adrenergic system might impair the transient formation of working memories first, and, in a second phase, the formation of long-term synaptic plasticity. Since α_1 receptors strongly regulate temporal cortex excitability, their deficiency is likely to shift the balance between excitation and inhibition in favor of the former. An alteration in the density of $\alpha 1$ receptors might be an important factor in the etiology of psychoses, explaining the results from an in vitro autoradiography study showing a decrease in α_1 receptor density in several brain areas including the temporal cortex and caudate nucleus in human brains from suicide victims [34]. Furthermore, a prolonged blockade of $\alpha 1$ receptors is associated with stress-like depressive behaviors [72, 73], while the reduction in α_1 receptor binding sites [25, 34], and α_1-adrenoceptors insensitivity are found in patients with major stress-induced depressive disorders [6, 7].

In in vivo recording from the rat auditory cortex, the ionophoretic application of NE produces a significant decrease in the spontaneous activity and tone-evoked single-unit activity, leaving the signal-to-noise ratio statistically unchanged, as reported by [54, 55]. In these studies, pairing NE iontophoretic application with the presentation of a particular tone frequency induced large decreases in the auditory evoked response to stimuli at the paired frequency (PF), and to a lesser extent to stimuli at frequencies right adjacent to PF [54, 55]. The same authors also reported that the bandwidth of the effect was smaller immediately post-pairing. Interestingly, the study showed that the presence of NE selectively affected strong acoustic stimuli, with smaller changes associated with weak input. Similarly, [43] reported that NE specifically enhanced auditory temporal contrast and improved neuronal timing precision by suppressing tonic components of auditory responses, and by enhancing the phasic onset of responses to pure tones [43]. These findings can be at least partially explained by the NE-induced decrease in excitatory responses, which could lead to an increase in the selectivity of auditory cortical functions by limiting the number of cortical networks activated by a given auditory input, and subsequently enhancing selective responses and improving auditory discrimination. In agreement with this interpretation, recent studies indicate that increases in NE release regulate plasticity in the auditory cortex [75], while d-amphetamine treatment of stroke rehabilitation patients promotes recovery of speech, language abilities, and hearing functions [77]. Last, although the study has been conducted in 23- to 36-day-old rats passing, animals were still considered to be juvenile [17]. Therefore, the effect of NE-induced depression may have an age-related component. Further measurement in older animals is needed to fully confirm the effect of NE in temporal cortex.

We conclude that the NE-induced decreases in excitability in the auditory cortex may be an important determinant of the physiological response to increased environmental demands, acting to suppress irrelevant sensory signals by decreasing spontaneous background signals, and leading, in turn, to the selective enhancement of behaviorally relevant responses. We speculate that an impairment of the $\alpha 1$-adrenoceptor response is a potential factor in the etiology of stress-related alterations in the balance between synaptic excitation and inhibition associated with psychoses, depression, and attention-related syndromes.

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References

1. Abercrombie ED, Jacobs BL (1987) Single-unit response of noradrenergic neurons in the locus coeruleus of freely moving cats. I. Acutely presented stressful and nonstressful stimuli. J Neurosci 7:2837–2843
2. Aoki C, Venkatesan C, Go CG, Forman R, Kurose H (1998) Cellular and subcellular sites for noradrenergic action in the monkey dorsolateral prefrontal cortex as revealed by the immunocytochemical localization of noradrenergic receptors and axons. Cereb Cortex 8:269–277. doi:10.1093/cercor/8.3.269
3. Araneda RC, Firestein S (2006) Adrenergic enhancement of inhibitory transmission in the accessory olfactory bulb. J Neurosci 26:3292–3298. doi:10.1523/JNEUROSCI.4768-05.2006
4. Arnsten AF, Goldman-Rakic PS (1985) Catecholamines and cognitive decline in aged nonhuman primates. Ann N Y Acad Sci 444:218–234. doi:10.1111/j.1749-6632.1985.tb37592.x

5. Arnsten AF, Cai JX, Goldman-Rakic PS (1988) The alpha-2 adrenergic agonist guanfacine improves memory in aged monkeys without sedative or hypotensive side effects: evidence for alpha-2 receptor subtypes. J Neurosci 8:4287–4298
6. Asnis GM, Halbreich U, Rabinovich H, Ryan ND, Sachar EJ, Nelson B, Puig-Antich J, Novacenko H (1985) The cortisol response to desipramine in endogenous depressives and normal controls: preliminary findings. Psychiatry Res 14:225–233. doi:10.1016/0165-1781(85)90017-4
7. Asnis GM, Sanderson WC, van Praag HM (1992) Cortisol response to intramuscular desipramine in patients with major depression and normal control subjects: a replication study. Psychiatry Res 44:237–250. doi:10.1016/0165-1781(92)90027-Z
8. Aston-Jones G, Chiang C, Alexinsky T (1991) Discharge of noradrenergic locus coeruleus neurons in behaving rats and monkeys suggests a role in vigilance. Prog Brain Res 88:501–520. doi:10.1016/S0079-6123(08)63830-3
9. Atzori M, Lei S, Evans DI, Kanold PO, Phillips-Tansey E, McIntyre O, McBain CJ (2001) Differential synaptic processing separates stationary from transient inputs to the auditory cortex. Nat Neurosci 4:1230–1237. doi:10.1038/nn760
10. Barth DS (2003) Submillisecond synchronization of fast electrical oscillations in neocortex 1. J Neurosci 23:2502–2510
11. Behl P, Bocti C, Swartz RH, Gao F, Sahlas DJ, Lanctot KL, Streiner DL, Black SE (2007) Strategic subcortical hyperintensities in cholinergic pathways and executive function decline in treated Alzheimer patients. Arch Neurol 64:266–272. doi:10.1001/archneur.64.2.266
12. Bengzon J, Kalen P, Lindvall O (1990) Evidence for long-term reduction of noradrenaline release after kindling in the rat hippocampus. Brain Res 535:353–357. doi:10.1016/0006-8993(90)91624-P
13. Bennett BD, Huguenard JR, Prince DA (1997) Adrenoceptor-mediated elevation of ambient GABA levels activates presynaptic GABA(B) receptors in rat sensorimotor cortex. J Neurophysiol 78:561–566
14. Bennett BD, Huguenard JR, Prince DA (1998) Adrenergic modulation of GABAA receptor-mediated inhibition in rat sensorimotor cortex. Neurophysiol 79:937–946
15. Berts A, Zhong H, Minneman KP (1999) No role for Ca++ or protein kinase C in alpha-1A adrenergic receptor activation of mitogen-activated protein kinase pathways in transfected PC12 cells. Mol Pharmacol 55:296–303
16. Bloom FE, Hoffer BJ, Siggins GR (1971) Studies on norepinephrine-containing afferents to Purkinje cells of art cerebellum. I. Localization of the fibers and their synapses. Brain Res 25:501–521. doi:10.1016/0006-8993(71)90457-4
17. Bockhorst KH, Narayana PA, Liu R, Ahobila-Vijjula P, Ramu J, Kamel M, Wosik J, Bockhorst T, Hahn K, Hasan KM, Perez P (2008) Early postnatal development of rat brain: in vivo diffusion tensor imaging. J Neurosci Res 86:1520–1528. doi:10.1002/jnr.21607
18. Borsini F, Rolls ET (1984) Role of noradrenaline and serotonin in the basolateral region of the amygdala in food preferences and learned taste aversions in the rat. Physiol Behav 33:37–43. doi:10.1016/0031-9384(84)90010-6
19. Buffalari DM, Grace AA (2007) Noradrenergic modulation of basolateral amygdala neuronal activity: opposing influences of alpha-2 and beta receptor activation. J Neurosci 27:12358–12366. doi:10.1523/JNEUROSCI.2007-07.2007
20. Cameron NM, Carey P, Erskine MS (2004) Medullary noradrenergic neurons release norepinephrine in the medial amygdala in females in response to mating stimulation sufficient for pseudopregnancy. Brain Res 1022:137–147. doi:10.1016/j.brainres.2004.07.022
21. Carr DB, Andrews GD, Glen WB, Lavin A (2007) alpha2-Noradrenergic receptors activation enhances excitability and synaptic integration in rat prefrontal cortex pyramidal neurons via inhibition of HCN currents. J Physiol 584:437–450. doi:10.1113/jphysiol.2007.141671
22. Chamberlain SR, Muller U, Blackwell AD, Robbins TW, Sahakian BJ (2006) Noradrenergic modulation of working memory and emotional memory in humans. Psychopharmacology (Berl) 188:397–407. doi:10.1007/s00213-006-0391-6
23. Chauvel P, Trottier S (1986) Role of noradrenergic ascending system in extinction of epileptic phenomena. Adv Neurol 44:475–487
24. Cohen RI, Almazan G (1993) Norepinephrine-stimulated PI hydrolysis in oligodendrocytes is mediated by alpha 1A-adrenoceptors. NeuroReport 4:1115–1118. doi:10.1097/00001756-199308000-00014
25. Crow TJ, Cross AJ, Cooper SJ, Deakin JF, Ferrier IN, Johnson JA, Joseph MH, Owen F, Poulter M, Lofthouse R et al (1984) Neurotransmitter receptors and monoamine metabolites in the brains of patients with Alzheimer-type dementia and depression, and suicides. Neuropharmacology 23:1561–1569. doi:10.1016/0028-3908(84)90100-X
26. Debiec J, LeDoux JE (2006) Noradrenergic signaling in the amygdala contributes to the reconsolidation of fear memory: treatment implications for PTSD. Ann N Y Acad Sci 1071:521–524. doi:10.1196/annals.1364.056
27. Doze VA, Cohen GA, Madison DV (1991) Synaptic localization of adrenergic disinhibition in the rat hippocampus. Neuron 6:889–900. doi:10.1016/0896-6273(91)90229-S
28. Faber DS, Korn H (1991) Applicability of the coefficient of variation method for analyzing synaptic plasticity. Biophys J 60:1288–1294. doi:10.1016/S0006-3495(91)82162-2
29. Fallon S, Shearman E, Sershen H, Lajtha A (2007) Food reward-induced neurotransmitter changes in cognitive brain regions. Neurochem Res 32:1772–1782. doi:10.1007/s11064-007-9343-8
30. Franowicz JS, Arnsten AF (1998) The alpha-2a noradrenergic agonist, guanfacine, improves delayed response performance in young adult rhesus monkeys. Psychopharmacology (Berl) 136:8–14. doi:10.1007/s002130050533
31. Galvez R, Mesches MH, McGaugh JL (1996) Norepinephrine release in the amygdala in response to footshock stimulation. Neurobiol Learn Mem 66:253–257. doi:10.1006/nlme.1996.0067
32. Gerber U, Greene RW, McCarley RW, Haas HL (1990) Excitation of brain stem neurons by noradrenaline and histamine. J Basic Clin Physiol Pharmacol 1:71–76
33. Grant SJ, Aston-Jones G, Redmond DE Jr (1988) Responses of primate locus coeruleus neurons to simple and complex sensory stimuli. Brain Res Bull 21:401–410. doi:10.1016/0361-9230(88)90152-9
34. Gross-Isseroff R, Dillon KA, Fieldust SJ, Biegon A (1990) Autoradiographic analysis of alpha 1-noradrenergic receptors in the human brain postmortem. Effect of suicide. Arch Gen Psychiatry 47:1049–1053
35. Hatfield T, Spanis C, McGaugh JL (1999) Response of amygdalar norepinephrine to footshock and GABAergic drugs using in vivo microdialysis and HPLC. Brain Res 835:340–345. doi:10.1016/S0006-8993(99)01566-8
36. Hieble JP, Bylund DB, Clarke DE, Eikenburg DC, Langer SZ, Lefkowitz RJ, Minneman KP, Ruffolo RR Jr (1995) International Union of Pharmacology. X. Recommendation for nomenclature of alpha 1-adrenoceptors: consensus update. Pharmacol Rev 47:267–270
37. Hokfelt T, Fuxe K (1969) Cerebellar monoamine nerve terminals, a new type of afferent fibers to the cortex cerebelli. Exp Brain Res Exp Hirnforsch 9:63–72

38. Hull EM, Dominguez JM (2007) Sexual behavior in male rodents. Horm Behav 52:45–55. doi:10.1016/j.yhbeh.2007.03.030
39. Hunt RD, Arnsten AF, Asbell MD (1995) An open trial of guanfacine in the treatment of attention-deficit hyperactivity disorder. J Am Acad Child Adolesc Psychiatry 34:50–54. doi:10.1097/00004583-199501000-00013
40. Ji XH, Ji JZ, Zhang H, Li BM (2008) Stimulation of alpha2-adrenoceptors suppresses excitatory synaptic transmission in the medial prefrontal cortex of rat. Neuropsychopharmacology 33:2263–2271. doi:10.1038/sj.npp.1301603
41. Kawaguchi Y, Shindou T (1998) Noradrenergic excitation and inhibition of GABAergic cell types in rat frontal cortex. J Neurosci 18:6963–6976
42. Kim J, Alger BE (2001) Random response fluctuations lead to spurious paired-pulse facilitation. J Neurosci 21:9608–9618
43. Kossl M, Vater M (1989) Noradrenaline enhances temporal auditory contrast and neuronal timing precision in the cochlear nucleus of the mustached bat. J Neurosci 9:4169–4178
44. Kulik A, Haentzsch A, Luckermann M, Reichelt W, Ballanyi K (1999) Neuron-glia signaling via alpha(1) adrenoceptor-mediated Ca(2+) release in Bergmann glial cells in situ. J Neurosci 19:8401–8408
45. Law-Tho D, Crepel F, Hirsch JC (1993) Noradrenaline decreases transmission of NMDA- and non-NMDA-receptor mediated monosynaptic EPSPs in rat prefrontal neurons in vitro. Eur J NeuroSci 5:1494–1500. doi:10.1111/j.1460-9568.1993.tb00217.x
46. Lehmenkuhler C, Walden J, Speckmann EJ (1991) Decrease of *N*-methyl-D-aspartate responses by noradrenaline in the rat motorcortex in vivo. Neurosci Lett 121:5–8. doi:10.1016/0304-3940(91)90635-7
47. Lei S, Deng PY, Porter JE, Shin HS (2007) Adrenergic facilitation of GABAergic transmission in rat entorhinal cortex. J Neurophysiol 98:2868–2877. doi:10.1152/jn.00679.2007
48. Lepretre N, Mironneau J, Morel JL (1994) Both alpha 1A- and alpha 2A-adrenoreceptor subtypes stimulate voltage-operated L-type calcium channels in rat portal vein myocytes. Evidence for two distinct transduction pathways. J Biol Chem 269:29546–29552
49. Levy F (2008) Pharmacological and therapeutic directions in ADHD: specificity in the PFC. Behav Brain Funct 4:12. doi:10.1186/1744-9081-4-12
50. Li BM, Mei ZT (1994) Delayed-response deficit induced by local injection of the alpha 2-adrenergic antagonist yohimbine into the dorsolateral prefrontal cortex in young adult monkeys. Behav Neural Biol 62:134–139. doi:10.1016/S0163-1047(05)80034-2
51. Liu X, Lonart G, Sanford LD (2007) Transient fear-induced alterations in evoked release of norepinephrine and GABA in amygdala slices. Brain Res 1142:46–53. doi:10.1016/j.brainres.2007.01.038
52. Manunta Y, Edeline JM (1997) Effects of noradrenaline on frequency tuning of rat auditory cortex neurons. Eur J NeuroSci 9:833–847. doi:10.1111/j.1460-9568.1997.tb01433.x
53. Manunta Y, Edeline JM (1998) Effects of noradrenaline on rate-level function of auditory cortex neurons: is there a "gating" effect of noradrenaline? Exp Brain Res Exp Hirnforsch 118:361–372
54. Manunta Y, Edeline JM (1999) Effects of noradrenaline on frequency tuning of auditory cortex neurons during wakefulness and slow-wave sleep. Eur J NeuroSci 11:2134–2150. doi:10.1046/j.1460-9568.1999.00633.x
55. Manunta Y, Edeline JM (2004) Noradrenergic induction of selective plasticity in the frequency tuning of auditory cortex neurons. J Neurophysiol 92:1445–1463. doi:10.1152/jn.00079.2004
56. McCormick DA, Prince DA (1986) Mechanisms of action of acetylcholine in the guinea-pig cerebral cortex in vitro. J Physiol 375:169–194
57. McIntyre DC, Giugno L (1988) Effect of clonidine on amygdala kindling in normal and 6-hydroxydopamine-pretreated rats. Exp Neurol 99:96–106. doi:10.1016/0014-4886(88)90130-6
58. McIntyre DC, Kelly ME, Dufresne C (1991) Suppression of amygdala kindling with massed stimulation: effect of noradrenaline antagonists. Brain Res 561:279–284. doi:10.1016/0006-8993(91)91605-Z
59. Mouradian RD, Sessler FM, Waterhouse BD (1991) Noradrenergic potentiation of excitatory transmitter action in cerebrocortical slices: evidence for mediation by an alpha 1 receptor-linked second messenger pathway. Brain Res 546:83–95. doi:10.1016/0006-8993(91)91162-T
60. Mueller AL, Dunwiddie TV (1983) Anticonvulsant and proconvulsant actions of alpha- and beta-noradrenergic agonists on epileptiform activity in rat hippocampus in vitro. Epilepsia 24:57–64. doi:10.1111/j.1528-1157.1983.tb04866.x
61. Neuman RS (1986) Suppression of penicillin-induced focal epileptiform activity by locus ceruleus stimulation: mediation by an alpha 1-adrenoceptor. Epilepsia 27:359–366. doi:10.1111/j.1528-1157.1986.tb03554.x
62. Pan ZZ, Grudt TJ, Williams JT (1994) alpha 1-adrenoceptors in rat dorsal raphe neurons: regulation of two potassium conductances. J Physiol 478(Pt 3):437–447
63. Ramos BP, Arnsten AF (2007) Adrenergic pharmacology and cognition: focus on the prefrontal cortex. Pharmacol Ther 2006(Dec):28. [Epub ahead of print]
64. Randle JC, Bourque CW, Renaud LP (1986) alpha 1-adrenergic receptor activation depolarizes rat supraoptic neurosecretory neurons in vitro. Am J Physiol 251:R569–R574
65. Roozendaal B, Hui GK, Hui IR, Berlau DJ, McGaugh JL, Weinberger NM (2006) Basolateral amygdala noradrenergic activity mediates corticosterone-induced enhancement of auditory fear conditioning. Neurobiol Learn Mem 86:249–255. doi:10.1016/j.nlm.2006.03.003
66. Rutkowski RG, Miasnikov AA, Weinberger NM (2003) Characterisation of multiple physiological fields within the anatomical core of rat auditory cortex. Hear Res 181:116–130. doi:10.1016/S0378-5955(03)00182-5
67. Salgado H, Bellay T, Nichols JA, Bose M, Martinolich L, Perrotti L, Atzori M (2007) Muscarinic M2 and M1 receptors reduce GABA release by Ca^{2+} channel modulation through activation of PI3 K/Ca^{2+}-independent and PLC/Ca^{2+}-dependent PKC. J Neurophysiol 98:952–965. doi:10.1152/jn.00060.2007
68. Sato H, Fox K, Daw NW (1989) Effect of electrical stimulation of locus coeruleus on the activity of neurons in the cat visual cortex. J Neurophysiol 62:946–958
69. Schwinn DA, Page SO, Middleton JP, Lorenz W, Liggett SB, Yamamoto K, Lapetina EG, Caron MG, Lefkowitz RJ, Cotecchia S (1991) The alpha 1C-adrenergic receptor: characterization of signal transduction pathways and mammalian tissue heterogeneity. Mol Pharmacol 40:619–626
70. Seguela P, Watkins KC, Geffard M, Descarries L (1990) Noradrenaline axon terminals in adult rat neocortex: an immunocytochemical analysis in serial thin sections. Neuroscience 35:249–264. doi:10.1016/0306-4522(90)90079-J
71. Stanton PK, Mody I, Zigmond D, Sejnowski T, Heinemann U (1992) Noradrenergic modulation of excitability in acute and chronic model epilepsies. Epilepsy Res Suppl 8:321–334
72. Stone EA, Quartermain D (1999) alpha-1-noradrenergic neurotransmission, corticosterone, and behavioral depression. Biol Psychiatry 46:1287–1300. doi:10.1016/S0006-3223(99)00234-6
73. Stone EA, Zhang Y, Rosengarten H, Yeretsian J, Quartermain D (1999) Brain alpha 1-adrenergic neurotransmission is necessary for behavioral activation to environmental change in mice. Neuroscience 94:1245–1252. doi:10.1016/S0306-4522(99)00394-2

74. Summers RJ, Papaioannou M, Harris S, Evans BA (1995) Expression of beta 3-adrenoceptor mRNA in rat brain. Br J Pharmacol 116:2547–2548
75. Thiel CM (2007) Pharmacological modulation of learning-induced plasticity in human auditory cortex. Restor Neurol Neurosci 25:435–443
76. Timmons SD, Geisert E, Stewart AE, Lorenzon NM, Foehring RC (2004) alpha2-Adrenergic receptor-mediated modulation of calcium current in neocortical pyramidal neurons. Brain Res 1014:184–196. doi:10.1016/j.brainres.2004.04.025
77. Tobey EA, Devous MD Sr, Buckley K, Overson G, Harris T, Ringe W, Martinez-Verhoff J (2005) Pharmacological enhancement of aural habilitation in adult cochlear implant users. Ear Hear 26:45S–56S. doi:10.1097/00003446-200508001-00007
78. Tsuda A, Tanaka M, Kohno Y, Ida Y, Hoaki Y, Iimori K, Nakagawa R, Nishikawa T, Nagasaki N (1983) Daily increase in noradrenaline turnover in brain regions of activity-stressed rats. Pharmacol Biochem Behav 19:393–396. doi:10.1016/0091-3057(83)90107-7
79. Tully K, Li Y, Tsvetkov E, Bolshakov VY (2007) Norepinephrine enables the induction of associative long-term potentiation at thalamo-amygdala synapses. Proc Natl Acad Sci USA 104:14146–14150. doi:10.1073/pnas.0704621104
80. Videen TO, Daw NW, Rader RK (1984) The effect of norepinephrine on visual cortical neurons in kittens and adult cats. J Neurosci 4:1607–1617
81. Waterhouse BD, Moises HC, Woodward DJ (1980) Noradrenergic modulation of somatosensory cortical neuronal responses to iontophoretically applied putative neurotransmitters. Exp Neurol 69:30–49. doi:10.1016/0014-4886(80)90141-7
82. Waterhouse BD, Moises HC, Woodward DJ (1981) Alpha-receptor-mediated facilitation of somatosensory cortical neuronal responses to excitatory synaptic inputs and iontophoretically applied acetylcholine. Neuropharmacology 20:907–920. doi:10.1016/0028-3908(81)90020-4
83. Waterhouse BD, Sessler FM, Cheng JT, Woodward DJ, Azizi SA, Moises HC (1988) New evidence for a gating action of norepinephrine in central neuronal circuits of mammalian brain. Brain Res Bull 21:425–432. doi:10.1016/0361-9230(88)90154-2
84. Weiss GK, Lewis J, Jimenez-Rivera C, Vigil A, Corcoran ME (1990) Antikindling effects of locus coeruleus stimulation: mediation by ascending noradrenergic projections. Exp Neurol 108:136–140. doi:10.1016/0014-4886(90)90020-S
85. Zucker RS, Regehr WG (2002) Short-term synaptic plasticity. Annu Rev Physiol 64:355–405. doi:10.1146/annurev.physiol.64.092501.114547