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Review

Layer- and area-specific actions of norepinephrine on cortical synaptic transmission ☆

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ABSTRACT

The cerebral cortex is a critical target of the central noradrenergic system. The importance of norepinephrine (NE) in the regulation of cortical activity is underscored by clinical findings that involve this catecholamine and its receptor subtypes in the regulation of a large number of emotional and cognitive functions and illnesses. In this review, we highlight diverse effects of the LC/NE system in the mammalian cortex. Indeed, electrophysiological, pharmacological, and behavioral studies in the last few decades reveal that NE elicits a mixed repertoire of excitatory, inhibitory, and biphasic effects on the firing activity and transmitter release of cortical neurons.

At the intrinsic cellular level, NE can produce a series of effects similar to those elicited by other monoamines or acetylcholine, associated with systemic arousal. At the synaptic level, NE induces numerous acute changes in synaptic function, and 'gates' the induction of long-term plasticity of glutamatergic synapses, consisting in an enhancement of engaged and relevant cortical synapses and/or depression of unengaged synapses. Equally important in shaping cortical function, in many cortical areas NE promotes a characteristic, most often reversible, increase in the gain of local inhibitory synapses, whose extent

Abbreviations: α-AR, alpha adrenoceptor; β-AR, beta adrenoceptor; ACC, anterior cingulate cortex; ACh, acetylcholine; AHP, after hyper polarization current; AMPA, amino propionic acid; AMPAR, amino propionic acid sensitive receptor; cAMP, cyclic adenosine monophosphate; CaMKII, Calcium calmodulin kinase type 2; CNS, Central Nervous System; CREB, cAMP Response Element Binding protein; GABA, γ amino-butyric acid; GABAAR, GABA receptor type A; GluR, glutamate receptor; GTP, guanosine 3-phosphate; G-protein, GTP-binding protein; HCN, hyperpolarization activated cyclic nucleotide gated (cation channel); HPA, Hypothalamus-Pituitary-Adrenal gland (axis); LC, Locus Ceruleus; LTD, long-term depression; LTP, long-term potentiation; mPFC, medial PFC; NE, norepinephrine; NMDA, N-methyl D aspartate; NMDAR, NMDA receptor; OFC, orbitofrontal cortex; PFC, prefrontal cortex; PLC, phospholipase C; PKA, protein kinase A; PKC, protein kinase C; PFC, Prefrontal cortex; PLC, phospholipase C; sAHP, slow AHP; S/N, signal-to-noise ratio; STDP, spike-time dependent plasticity; TREK, two-pore domain K+ (channel)

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and temporal properties vary between different areas and sometimes even between cortical layers of the same area.

While we are still a long way from a comprehensive theory of the function of the LC/NE system, its cellular, synaptic, and plastic effects are consistent with the hypothesis that noradrenergic modulation is critical in coordinating the activity of cortical and subcortical circuits for the integration of sensory activity and working memory.

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Contents

1. Introduction

1.1. *General properties*

The biogenic amine norepinephrine (NE, or noradrenaline) has long been identified as having an important role in shifting the mammalian organism from a relaxed or dormant condition to a responsive, excited and alerted state. The effects of NE appear to vary depending on the brain area, layer, cell type, and even on the timing and duration of its presence in the extracellular space in the brain.

NE is synthesized in the CNS almost exclusively in a set of brainstem melanin-containing nuclei denominated collectively *Locus Ceruleus* (LC) (Descarries and Droz, 1970) and adjacent structures (Robertson et al., 2013), with extensive diffuse ascending and descending projections to virtually all the central nervous system (CNS), including the entire neocortex (Aston-Jones, 2005). This system exerts a crucial role in the circadian regulation of alertness, arousal, and overall performance (Aston-Jones et al., 2001). While LC inactivity is associated with thalamo-cortical oscillations and sleep (Rajkowski et al., 1994), LC activity and the consequent presence of a cortical and thalamic'adrenergic tone' is characteristic of wakefulness (Aston-Jones, 2005). Within the wakefulness state, two modes of activity of the LC cells are discernible: a "*phasic*" and a "*tonic*" mode. Among other properties, *phasic* LC activity is related to stimulus salience (Aston-Jones and Bloom, 1981), and/or to the outcome of decision processes in tasks that require selective attention, whereas the *tonic* mode appears to be related to the search of alternative strategies during a behavioral disengagement caused by persistent failure to receive an expected reward (Aston-Jones and Cohen 2005a). In this review we will summarize the experimental evidence revealing similarities and differences of the short- and long-term cellular and synaptic effects of NE on neocortical circuits.

1.2. *The Locus Ceruleus–Cortical axis*

The neocortex is a major recipient of LC ascending axonal branches, together with numerous other CNS areas including the amygdala, the thalamus, the hippocampus, the

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hypothalamus, the bed nucleus of the *stria terminalis*, the colliculi, and the cerebellum (Simpson and S, 2007). Together with the neuroendocrine hypothalamus–pituitary–adrenergic gland (HPA) axis, the LC is part of the mammalian stress response system. As a global neurotransmitter system, its activity seems to be coordinated with the activity of other global modulators in a still largely unexplored fashion. Such coordinated responses have been related to arousal and attentional processes (Aston-Jones and Cohen, 2005a). Besides this function, it has been shown that NE also modulates a diverse set of central activities spanning from working memory to decision making (Arnsten and Goldman-Rakic, 1985; Arnsten and Jentsch, 1997; Young et al., 2006), and from executive functions to sensory processing (Arnsten et al., 1988; Arnsten and Contant, 1992; Aston-Jones et al., 1992). The LC–NE system has recently been proposed to act as a switch in CNS circuits employing different energy levels in goal-oriented activity (Bouret and Richmond, 2015; Hofmeister and Sterpenich, 2015). While the exact mechanisms used by the noradrenergic system to accomplish these diverse functions are far from being completely understood, the biologic and systemic relevance of the noradrenergic system modulation is clearly evidenced by clinical data suggesting that even modest changes in noradrenergic function-induced by pharmacology, anesthesia, or other means (e.g. electrical stimulation of ascending branches of autonomic nerves)-dramatically affect behavior and systemic 'well-being'.

Both cortical and sub-cortical regions are densely innervated by noradrenergic inputs. Some non-cortical areas (amygdala, hypothalamus, brainstem, cerebellum and midbrain) display a high density of adrenoceptors (Papay et al., 2006) and are importantly involved in a large group of noradrenergic-mediated behavioral responses (Kaneko et al., 2008). The integrity of the *cortical* branch of the noradrenergic system appears, however, to be a determinant of pathophysiology and behavior, as important as subcortical noradrenergic innervation. Evidence supporting the relevance of the cortical branch of the noradrenergic system in the modulation of cortical activity includes pharmacological/clinical data, the presence of cortical effective concentrations of NE measured with microdialysis (van Veldhuizen et al., 1994; Chiti and Teschemacher, 2007), and the sheer anatomical extent of the cortical noradrenergic innervation to the neocortex (Freedman et al., 1975; Gatter and Powell, 1977; Jones and Moore, 1977; Jones et al., 1977; Waterhouse et al., 1983).

1.3. *Adrenergic receptors*

The seminal pharmacological work of Ahlquist on the effects of sympathomimetic compounds led to the classification of adrenoceptors into the α and β families that is still valid to date (Ahlquist, 1948). The discovery of guanosine 3-phosphate (GTP)-binding proteins (G-proteins) further split the α adrenoceptor family into the α_1 and α_2 subfamilies, which in turn reclassified adrenoceptors into three receptor families activating different intracellular cascades: 1) α_1 adrenoceptors (α_1-ARs), activating the phospholipid metabolisms, leading to the activation of phospholipase C (PLC) and, eventually, of the serine–threonine protein kinase C (PKC) and phospholipid metabolism through G-proteins type $G_{q/11}$, 2) α_2 adrenoceptors (α_2-ARs), which inhibit the production of cyclic adenosine monophosphate (cAMP) by binding to membrane-bound adenylyl cyclase through G_i, and 3) three families of β adrenoceptors (β-ARs), each promoting the elevation of cAMP levels by activating a stimulatory G-protein G_s.

The three families of adrenoceptors differ in affinity for NE, their endogenous ligand. α_2-ARs have the highest affinity, of the order of tens of nanomolar (nM), α_1-ARs have an intermediate affinity (around 300 nM), while β-ARs have the lowest affinity for NE (almost in the μM range, reviewed in (Ramos and Arnsten, 2007). Different families and clones of the same set of adrenoceptors are present and functional throughout the CNS, including in the neocortex. As early recognized by Ahlquist in the peripheral system, different expression levels of the same type of ARs are associated with different physiological functions, based on diverse cellular properties triggered by similar molecular cascades in specific areas throughout the CNS.

2. Acute noradrenergic modulation

The LC/NE system performs its global function by directly modulating *intrinsic* neuronal function, and by altering the communication between pairs of neurons by changing – transiently or permanently – the weight of synaptic transmission.

2.1. *Intrinsic properties*

K^+ channels are a well-known target for noradrenergic modulation. Among them, TREK-2 channels (a two-pore cationic, with high K^+ permeability) are activated by α_2-adrenoceptors, reducing glutamate release in the entorhinal cortex (Xiao et al., 2009). Similarly, the cationic hyperpolarization-activated current I_h is also enhanced by NE in the forebrain (McCormick et al., 1991). In other studies NE induces a *reduction* in principal (pyramidal) cells K^+ currents, similar to the effects of a number of light-molecular weight neurotransmitters including acetylcholine (Krnjević et al., 1971; Krnjevic, 1993), dopamine (Pedarzani and Storm, 1995), serotonin (Segal, 1999) and histamine (Martín et al., 2001), as found in seminal studies in the hippocampus and later confirmed to be also present across different cortical areas. Among the K^+ currents inhibited by NE are the I_A and the slow after hyper-polarization current (sAHP) (Madison and Nicoll, 1982; Foehring et al., 1989; McCormick et al., 1991, 1993; McCormick, 1993). A prominent consequence of the elevation of NE levels is thus an increase in spontaneous firing accompanied by a decrease in adaptation (defined as the progressive decrease of neuronal firing following a square current injection) either by direct membrane depolarization or by reducing repolarizing currents.

Recently, an additional noradrenergic mechanism associated with a decrease in K^+ conductance modulating synaptic function has been discovered using *in vivo* patch-clamp recording in primates (Wang et al., 2011). The study found that activation of α_2-ARs in the prefrontal cortex (PFC) decreases intracellular levels of cAMP, decreasing-in turn-an

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intrinsic cellular current mediated by hyperpolarization-activated cyclic nucleotide-gated (HCN) K^+ channels (Wang et al., 2011). Interestingly, a progressive increase in HCN conductance in aging positively correlated with deterioration in cognitive performance. Accordingly, the use of α_2 agonists was proposed as candidate treatment for age-related impairment in cognitive performance counteracting the effects of the increase in dendritic shunting inhibition.

Calcium (Ca^{2+}) channels are also an important target of noradrenergic modulation for a variety of cellular functions including neurotransmitter release, neuronal intrinsic excitability, and synaptic plasticity. Among the known effects of norepinephrine on Ca^{2+} channels, α_2-AR activation inhibits glutamate release from isolated cortical nerve terminals trough inhibition of N-type (CaV2.2) and P/Q-type (CaV2.1) Ca^{2+}-channels (Chiu et al., 2011), and N-type(CaV2.2) and P/Q-type (CaV2.1) Ca^{2+} currents in acutely dissociated pyramidal neurons from rat sensory motor cortex, presumably to regulate mechanisms sensitive to spiking activity (Timmons et al., 2004). β-AR activation of L-type calcium channels (Kato, 1993) plays also an important role in glutamate synaptic regulation and long-term plasticity. Table 1 summarizes some of the intrinsic neuronal effects produced by activation of NE receptors on Ca^{2+} channels. Differences in noradrenergic modulation of V-gated channels between principal neurons vs. (GABAergic) interneurons have not – to our knowledge – been analyzed systematically. More work will be necessary to complete our knowledge on the effects of noradrenergic modulation of V-gated channels in the brain and in the neocortex in particular. It is worth mentioning that a novel, previously unexplored, avenue of noradrenergic neuronal modulation has been discovered recently, where NE was found to prime glial cells of the visual cortex to respond to sensory activity (Paukert et al., 2014).

2.2. *Synaptic effects: glutamate currents*

A large number of studies report that glutamatergic transmission mediated through amino propionic acid (AMPA) receptors is decreased – between 30% and 80% – in the presence of NE in a concentration range between 10 and 100 μM. Such NE-induced decrease in AMPAR-mediated currents has been shown in the rodent auditory (Dinh et al., 2009), visual (Kobayashi et al., 2000), and prefrontal cortices (Law-Tho et al., 1993; Ji et al., 2008; Roychowdhury et al., 2014), and is mostly mediated by activation of α_1-ARs. Unaltered paired pulse ratio and the sensitivity to changes in intracellular environment (pipette solution) suggest that this reduction in excitatory transmission has at least a partial postsynaptic origin (Dinh et al., 2009). It is not clear yet whether this effect is due to a G-protein-mediated phosphorylation-dependent change in the biophysical properties of the AMPAR pore, or to altered rate of insertion/removal of AMPARs in dendritic spines, perhaps due changes in the anchoring process or in the subunit composition of the receptor (Yuen et al., 2014). In other cortical regions, glutamatergic signaling displays a more complex noradrenergic modulation. For example, 20 μM NE *reduces* AMPAR-mediated currents in the superficial layers of the enthorhinal cortex (Xiao et al., 2009), but *increases* them in the hippocampus

Table 1 – Effects of the activation of adrenoceptors on cellular (intrinsic) mechanisms in different cortical areas. Cortical areas, layers, dose(s) used in the study, effect and reference are reported in each columns. (n.a. not available).

Effects of NE on intrinsic neuronal properties					
Cortical area	Cortical Layer	Application/concentration	Receptor	Effect	Ref.
K^+ channels					
Infralimbic and prelimbic cortex	V/VI	Methylphenidate 10 μM or clonidine 10 μM	α_2-AR	Increases firing frequency via inhibition of HCN currents.	Andrews and Lavin (2006) and Carr et al. (2007)
Entorhinal cortex	Layer III	NE 100 μM	α_2-AR	Increases in hyperpolarization by activation of TREK-2 K^+ channels	Xiao et al. (2009)
PFC	Layer III	10 mM (iontophoresis)	α_2 AR	I HCN/KCNQ K^+ decrease	Wang et al. (2011)
Entorhinal cortex	Layer II/III	NE 100 μM or phenylephrine 100 μM	α_1-AR	Reduces firing frequency	Lei et al. (2007)
Somato- sensory cortex	Layer V	10 μM phenylephrine	α_1-AR	Decrease in K^+ resting current Increases firing frequency	McCormick et al. (1991)
Infralimbic prefrontal cortex	Layer II-V	NE 100 μM	α-AR	Increases firing frequency	Mueller et al. (2008)
Sensori-motor cortex	Layer V	isoproterenol 10 μM	β-AR	sAHP decrease	Foehring et al. (1989)
Somato- sensory cortex	Layer V	10 μM isoproterenol	β-AR	Increase in I_h	McCormick et al. (1991)
Ca^{+2} channels					
Cortex	n.a. synapto- somes)	10 μM Dexmedetomidine	α_2-AR	Inhibits N- and P/Q types Ca^{2+} currents	Chiu et al. (2011)
Sensorimotor cortex	Cultures of sensorymoto r cortex	NE 2 μM or clonidine 10 μM	α_2-AR	Reduces N and P/Q type Ca^{2+} currents	Timmons et al. (2000)
Visual cortex	Layer II/III	5 μM nifedipine	β-AR	Inhibition of L-type Ca^{2+} channels	Kato (1993)

proper (Hu et al., 2007). Similarly, 10 μM NE *increases* AMPAR-mediated currents in the visual cortex (Huang et al., 2012; Salgado et al., 2012), although in the same preparation a lower NE concentration (<1 μM), and also the specific activation of α_1-ARs, *decreases* AMPAR-mediated currents (Salgado et al., 2012).

N-methyl D aspartate receptor (NMDAR) mediated glutamatergic transmission also appears to be depressed in the presence of NE (Law-Tho et al., 1993; Liu et al., 2006) – also through postsynaptic α_1-AR mediated mechanisms. On the other hand, recordings in visual, prefrontal, and perirhinal cortices, show the application of NE potentiates NMDAR-mediated excitatory synaptic transmission (Bröcher et al., 1992; Laing and Bashir, 2014), through a β-AR- and cAMP-dependent mechanism, and requires concurrent synaptic activation of NMDAR, suggestive of a coordinated action of β-ARs and NMDAR (Bröcher et al., 1992; Laing and Bashir, 2014).

These data are consistent with the well-known antiepileptic action of NE (Neuman, 1986; Ferraro et al., 1994; Shouse et al., 1996), and corroborate the hypothesis that NE can produce at the same time a generalized (α_1-AR-induced) decrease in most AMPAR-mediated glutamate response (in synapses that are not undergoing long-term changes), while also 'priming' neurons – through β- or both β- and α_1-ARs-into a plastic state that promotes the induction of long term forms of synaptic plasticity. This topic will be discussed more in depth in the next sections dedicated to long-term effects of NE. Table 2 summarizes some of the effects of NE on cortical synaptic transmission.

2.3. *Synaptic effects: modulation of the cortical GABA signaling*

Phasic inhibitory cortical synaptic transmission, mostly mediated by γ-amino butyric acid type A receptors ($GABA_A$Rs), possesses a large range of responses to NE, including decreases, increases, absence of response, as well as bi-phasic responses, in different cortical areas. The expression of α_1-ARs has been identified in a number of cortical areas with localization in GABAergic interneurons (Papay et al., 2006). Among the physiological effects induced by NE on GABAergic signaling, we found that in the auditory cortex of the rat, NE *decreases* synaptic GABAergic currents elicited by electrical stimulation of layer 1 onto supragranular layer 2/3 pyramidal neurons, with *no change* in the amplitude of local GABAergic responses to local stimulation of infragranular layer 5 (Roychowdhury et al., 2014), but *increasing* GABAergic currents elicited within layer 2/3 (Salgado et al., 2011, 2012), with the last effect similar to results described in the enthorhinal cortex (Lei et al., 2007).

Interestingly, in a similar way in which the activation of α_1 or β adrenoceptors induce either a reduction or an increase – respectively – of the excitatory signal at *glutamatergic* synapses (Kobayashi et al., 2000; Dinh et al., 2009; Salgado et al., 2012), activation of α_1 or β adrenoceptors has a similar effect on *inhibitory*, $GABA_A$R-mediated transmission. In fact, α_1-AR activation decreases inhibitory transmission (Salgado et al., 2011, 2012), with some exception (Lei et al., 2007), whereas activation of β−ARs elicits an enhancement of

Table 2 – Effects of the activation of adrenoceptors on excitatory synapses in different cortical areas. Cortical areas, layers, dose(s) used in the study, effect and reference are reported in each columns (n.a. not available).

Effects of NE on excitatory transmission					
Cortical area	Cortical layer	Application/concentration	Receptor	effect	Ref.
Medial prefrontal cortex	V/VI	Phenylephrine 100 μM	β_1-AR	Enhances excitatory synaptic transmission via PKC	Luo et al. (2014)
Medial prefrontal cortex	V/VI	Dobutamine 100 μM	α_1-AR	Decreases excitatory synaptic transmission via PKC	Luo et al. (2014)
Prefrontal cortex	Layer V	NE 20 μM	?	Reduces excitatory synaptic transmission	Roychowdhury et al. (2014)
Visual Cortex	Layer II/III	NE 8.75 μM or Isoproterenol 10 μM	β-AR	Enhances excitatory synaptic transmission	Salgado et al., (2012) Kirkwood et al. (1999)
Visual Cortex	Layer II/III	NE 0.33 μM or methoxamine 5 μM	α_1-AR	Reduces excitatory synaptic transmission	Salgado et al., 2012; Kirkwood et al., 1999.
Visual Cortex	Layer V	Isoproterenol 100 μM	β-AR	Enhances excitatory synaptic transmission	Kobayashi et al. (2009)
Visual Cortex	Layer V	Phenyleprhine 100 μM	α_1-AR	Reduces excitatory synaptic transmission	Kobayashi et al. (2009)
Auditory cortex	All layers	NE 20 μM or phenylephrine 1 μM		Reduces excitatory synaptic transmission	Dinh et al. (2009)

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Table 3 – Effects of the activation of adrenoceptors on inhibitory synapses in different cortical areas. As above, cortical areas, layers, dose(s) used in the study, effect and reference are reported in each columns (n.a. not available).

Effects of NE on inhibitory transmission					
Cortical area	Cortical Layer	Application/ concentration	receptor	effect	Ref.
somatosensory cortex	Layer V	10-50 μM of NE	α and β-AR	No effect on GABA release	Kruglikov and Rudy (2008)
Auditory cortex	Layer II/III	NE 20 μM or Isoproterenol 50 μM	β-AR	Enhances inhibitory synaptic transmission	Salgado et al. (2011)
Auditory cortex	Layer II/III	NE 20 μM or clonidine 1 μM	α_2-AR	Enhances inhibitory synaptic transmission	Salgado et al. (2011)
Auditory cortex	Layer II/III	NE 20 μM or phenylephrine 1	α_1-AR	reduces inhibitory synaptic transmission	Salgado et al. (2012)
Somatosensory cortex	Layer V	Isoproterenol 10–100 μM	β-AR	Enhances inhibitory synaptic transmission	Sessler et al. (1995)
Entorhinal cortex	Layer II/III	NE 100 μM or phenylephrine 100 μM	α_1-AR	Enhances inhibitory synaptic transmission	Lei et al. (2007)
Prefrontal cortex	Layer II/III	NE 20 μM	n.a.	reduces inhibitory synaptic transmission	Roychowdhury et al. (2014)
Prefrontal cortex	Layer V	NE 20 μM	n.a.	Enhances inhibitory synaptic transmission	Roychowdhury et al. (2014)

inhibitory transmission (Sessler et al., 1995; Salgado et al., 2011, 2012). The parallel effects of α_1- and β-AR activation on excitatory and inhibitory transmission might represent a mechanism to achieve larger synaptic strength while preserving excitation/inhibition synaptic balance.

The rodent agranular prefrontal cortex also displays a complex noradrenergic modulation of inhibitory currents, such that while GABAergic currents evoked by electrical stimulation of local inhibitory axons within layer 2/3 are *reduced* by 20 μM NE, the same concentration of the monoamine *increases* GABAergic currents in pyramidal cells of the output layer 5. Interestingly, NE selectively reduces excitatory drive onto GABAergic interneurons in the prefrontal cortex (Wang et al., 2013), suggestive of a negative feedback mechanism to limit a NE-induced increase in inhibition. Table 3 summarizes the effects of NE on GABAergic synaptic transmission.

The inhibition of presynaptic Ca^{2+} currents (Timmons et al., 2004) may play similar roles in the noradrenergic-induced *decrease* of both glutamatergic and GABAergic currents. On the contrary, the pharmacology and biophysics of adrenoceptor-mediated *enhancements* in the excitability of local GABAergic neurons (interneurons) (Kawaguchi and Shindou, 1998) are consistent with noradrenergic-induced increases in the intrinsic excitability of GABAergic interneurons, although noradrenergic effects at the level of the GABAergic axon terminal cannot be ruled out. Adrenoceptor activation may be critical in the activation of $GABA_BR$-mediated signal, as indicated by the $GABA_BR$-mediated increase in GABA release monitored in the rat sensorimotor cortex (Bennett et al., 1997, 1998). Besides its functional (short- and long-term) effects on synaptic strength or intrinsic excitability, it is important to note that NE also induces selective trophic effects in the neocortex (prefrontal) promoting the adequate development of the neonatal GABAergic system (Podkletnova et al., 2000).

2.4. *In vivo studies: sensory cortices*

A combination of the acute effects on intrinsic neuronal excitability and synaptic transmission may explain the variety of responses to NE detected with *in vivo* preparations and direct sensory stimulation. Similar to cellular effects, remarkable differences in noradrenergic modulation are shown in the areas studied, including mostly different sensory cortices and the PFC. In particular, the decrease in glutamate excitatory response and the enhancement of inhibitory GABAergic responses mentioned in the previous sections may account for a large amount of observations in *in vivo* preparations in sensory and prefrontal cortices.

A number of studies have been conducted to determine the effect of NE or LC activation on sensory areas to determine the noradrenergic regulation of arousal and sensory input (Berridge and Waterhouse, 2003). In the auditory cortex, a combination of short- and long-term effects of NE induces changes in frequency selectivity in response to tones at a frequency previously coupled with NE application (Manunta and Edeline, 2004; Edeline et al., 2011). Such an effect may contribute to the origin and consolidation of sparse encoding of cortical auditory 'engrams' (Edeline, 2012). The effect of NE

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in the visual cortex is particularly puzzling. In fact, an overall inhibitory action on neuronal firing patterns (Ego-Stengel et al., 2002) is not associated with unambiguous improvement of function or increased signal-to-noise ratio as proposed by several authors, for instance for the auditory cortex (Edeline, 2012). Functional MRI data from experiments in humans support the hypothesis that an enhanced noradrenergic tone can improve cortical coordination in visuo- motor tasks (Grefkes et al., 2010).

Dose-dependent effects were detected by several early studies showing that *low doses* of NE applied to sensory neurons *enhance* both excitatory and inhibitory synaptic inputs in the auditory and in the somatosensory cortices (Foote et al., 1975; Waterhouse et al., 1980; Kossl and Vater, 1989), whereas *intermediate or high doses* typically *suppress* neural activity (Armstrong-James and Fox, 1983). While a mild elevation of NE levels appears to induce mostly an enhancement of cortical excitation, consistent with the phasic activation of LC neurons induced by highly salient and arousing stimuli (Aston-Jones and Bloom, 1981; Abercrombie and Jacobs, 1988; Grant et al., 1988; Brun et al., 1993), inhibitory effects induced by higher levels of NE have also been shown on glutamate-evoked neuronal excitation in sensory cortical slices, with an inhibitory influence associate with previous strong PFC activation (Sara and Hervé-Minvielle, 1995). An emerging property of noradrenergic cortical modulation resembles a bell-shaped dependence on the intensity of noradrenergic stimulation. An example of this phenomenon is the firing frequency response to somatosensory stimulation as a function of increasing frequency of a train of pulses delivered to the LC (Devilbiss and Waterhouse, 2004). A bell-shaped dependence on NE levels may explain the results of the administration of methylphenidate – a catecholamine reuptake blocker enhancing the effects of NE (Drouin et al., 2007) – which *increases* the intensity of the responses to *weak* stimuli but *reduces* responses to *strong* stimuli. An alternative or additional interpretation of these data can be given in terms of a reduction of the dynamic range of somatosensory responses (Drouin et al., 2007).

The interpretation of this large amount of experimental data is complicated further by the large variability in extent and direction of the NE effects between different cortical units even *within the same experimental settings*. For instance, NE application or LC stimulation may either *increase* or *decrease* cortical firing rate of multi-unit recordings in response to sensory stimulation (Waterhouse et al., 1980; Devilbiss and Waterhouse, 2000, 2004; Hurley et al., 2004).

2.5. *In vivo studies: prefrontal cortex*

LC neurons display tonic *and* phasic activation modes, the latter associated with a number of PFC functions like behavioral engagement, decision making and task-performance optimization (Usher et al., 1999; Aston-Jones and Cohen, 2005a, 2005b). Importantly, there is growing evidence that the anatomical connection between LC and the PFC – or at least some parts of it – may be reciprocal (Branchereau et al., 1996), further corroborating the hypothesis that PFC activity may elicit the release of NE. Anatomical data (Morrison et al., 1982; Porrino and Goldman-Rakic, 1982) as well as *in vivo* recordings in monkey LC and prefrontal cortices (Jodo et al., 1998) suggest that not only the PFC is a major recipient of noradrenergic modulation, but also that the activation of the PFC stimulates LC activity, resulting in a feed-forward loop of interactions. In particular, two frontal structures, namely the orbitofrontal cortex (OFC) and the anterior cingulate cortex (ACC), play critical roles in evaluating rewards (task related utilities) and costs, respectively (Gold and Chrousos, 2002; Bari and Robbins, 2013a, 2013b; Arnsten and Jin, 2014). The OFC receives input from all sensory cortices, and is activated by rewarding stimuli in various sensory modalities but not by stimulus identification alone, nor by response preparation. Notably, both the OFC and the ACC provide prominent direct or indirect input to LC neurons, and are thought to be crucial to drive the transitions between phasic and tonic modes in the firing activity of LC neurons (Aston-Jones 2005; Aston-Jones and Cohen 2005b). This evidence points to the PFC as a key structure in the regulation of cortical noradrenergic function.

Nowhere more than in the PFC is the heterogeneity of the effects of NE more evident: the PFC displays differences in noradrenergic effects between sub-regions, by the receptors mediating its action, and by different behavioral states of the subject/animal. For instance, levels of noradrenergic activation that impair attention-set shifting appear to improve stop-signal performance (Newman et al., 2008), whereas, α_2-AR receptor activation facilitates PFC function in rodents and monkeys. In fact, administration of α_2-ARs agonists such as clonidine, guanfacine or meditomide improves performance on a variety of PFC-dependent working memory related tasks (Franowicz and Arnsten, 1998), including delay response (Arnsten et al., 1988), and delay alternation (Arnsten and Goldman-Rakic, 1985). The effects are blocked by α_2 ARs antagonists such as yohimbine, which in turn impairs working memory performance (Arnsten and Goldman-Rakic, 1985; Li and Mei, 1994). The activation of β-ARs appears to have little influence on the working memory functions of the prefrontal cortex (Arnsten and Goldman-Rakic, 1985). Thus, application of α_2-AR, but not β- or α_1-AR antagonists, produces a delay-related impairment in working memory performance (Li and Mei, 1994). Facilitatory effects on working memory performance by α_2-ARs are particularly important under high interference or distraction periods, where PFC function is required for optimal performance (Arnsten and Contant, 1992).

A current tenet poses that most acute beneficial effects mediated by NE on executive functions (like attention improvement) are associated with activation of high-affinity pre- or postsynaptic α_2-ARs (Caetano et al., 2012), while the activation of intermediate affinity PFC α_1-ARs and/or lower affinity β-ARs (and the related phospholipase C and adenylyl cyclase cascades) would worsen the performance of most executive functions (Ramos and Arnsten, 2007; Arnsten, 2009a, 2009b; Robbins and Arnsten, 2009). This effect could be induced by inactivation of Na^+ conductance and consequent failure of neuronal firing in the LC. Chemical similarity and shared anatomical projections of dopamine and NE have raised the question of the specificity of their PFC effects. Recent studies on this topic (Chandler et al., 2014) suggest

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that in spite of their chemical structure resemblance and partial overlap of their pharmacological effects, NE and dopamine carry out both specific and complementary functions in the PFC.

2.6. *In vivo studies: anesthesia*

In addition to modulating arousal (Aston-Jones et al., 2001; Aston-Jones, 2005), recent evidence indicates that the LC–NE cortical system can also influence the duration and properties of anesthetic states. For example, LC–NE activation produces a faster behavioral emergence from deep isoflurane anesthesia by acting on β- or α_1-ARs (Vazey and Aston-Jones, 2014). Accordingly, blocking these receptors potentiated the anesthetic duration when delivered centrally or peripherally. Thus, this finding reveals that different factors including background LC–NE activation or noradrenergic medications may affect the clinical responses to anesthetic agents. Interestingly, an opposite noradrenergic effect is elicited by the α_2-AR agonist xylazine, commonly added to commercially available anesthetic mixture (ketamine–xylazine).

3. Long term effects of noradrenergic modulation

3.1. *Adrenergic gating of cortical LTD and LTP*

The idea that neuromodulation contributes to synaptic plasticity by controlling both the magnitude and polarity of change in glutamatergic transmission is not new. As mentioned earlier, an important role for NE in the induction of long-term plasticity has been previously postulated (Bröcher et al., 1992). NE, released in the cortex in response to arousing or novel stimuli (Berridge and Waterhouse, 2003), critically influences learning and memory processes by activating different noradrenergic receptor subtypes on cortical circuits, as shown *in vivo* in different species (Berridge and Waterhouse, 2003; Ramos and Arnsten, 2007; Constantinople and Bruno, 2011). Most studies of noradrenergic modulation of long-term plasticity have been conducted in slices from the prefrontal cortex and brain areas known to undergo long-term synaptic changes, like the visual cortex and the hippocampus (Kato et al., 1991; Bröcher et al., 1992; Kirkwood et al., 1999). Bidirectional synaptic plasticity is known to be strongly influenced by NE. Its noradrenergic modulation has been widely studied in the cerebral cortex (Nowicky et al., 1992; Kirkwood et al., 1999; Salgado et al., 2012; Laing and Bashir, 2014).

NE receptor activation has been proposed to influence synaptic plasticity by several putative mechanisms: either by directly modulating NMDARs (induction of long-term potentiation/depression, LTP/D) or-alternatively or in addition-by activating kinases leading eventually to the insertion of AMPA receptors into the postsynaptic membrane (*"unsilencing"* of *"silent"* synapses, one of the proposed mechanisms for LTP) (Seol et al., 2007; Perugini et al., 2012; Zhou *et al.*, 2013). In this regard, several studies show that, in addition to modulating the excitability of cortical neurons (Carr et al., 2007; O'Donnell et al., 2012), NE can lower the threshold for the induction of synaptic plasticity at excitatory synapses (Seol et al., 2007; Huang et al., 2012; Salgado et al., 2012).

Further evidence that NE participates in gating and expression of long term synaptic plasticity, thereby modulating the activity of the entire cortical circuit comes from the work of Arnsten and collaborators (Arnsten et al., 2012; Huang et al., 2012), indicating that NE has a critical role in gating cortical LTD/P on perceptual learning and memory (Pussinen et al., 1997; Riekkinen et al., 1997; Puumala et al., 1998; Franowicz et al., 2002). Corroborating this hypothesis are *in vitro* studies utilizing hippocampal slices, showing that NE depletion *reduces* the capacity to express LTP (Stanton and Sarvey, 1985), whereas the perfusion of NE agonists *increases* LTP in the cortex and in the hippocampus (Stanton and Sarvey, 1987; Nowicky et al., 1992; Salgado et al., 2012; Laing and Bashir, 2014).

3.2. *Different roles for α_1 and β adrenoceptors in long-term synaptic plasticity*

α_1-ARs in the neocortex have been proposed to activate protein phosphatases (Thomas et al., 1996) linked to the induction of LTD (Lisman, 1989; Mulkey et al., 1993; Bear and Malenka, 1994; Kirkwood et al., 1999) through a low range of NMDA receptor stimulation (Kirkwood et al., 1999). The induction of LTD in the visual cortex requires the activation of the PLC pathway by NMDA receptors (Choi et al., 2005; Treviño et al., 2012). In fact, LTD occurs only when NMDA receptors are activated in conjunction with the activation of PLC via multiple neurotransmitter receptors coupled to G_q proteins. The finding that NE can promote LTD induction of glutamate synaptic transmission in the cortex both *in vitro* (Choi et al., 2005) and *ex vivo* (Treviño et al., 2012), as well as in the hippocampus *in vitro*, suggests that bidirectional regulation of long-term synaptic plasticity might be the single most important function of the cortical noradrenergic system (Kirkwood et al., 1999; Scheiderer et al., 2004).

Further studies corroborate the hypothesis that α_1-AR agonists selectively enable LTD and suppress LTP (Salgado et al., 2012; Treviño et al., 2012), while β-AR agonist enable LTP and suppress LTD (Huang et al., 2012). In general, the rate of AR activation depends on the concentration of NE and its different affinity for α_1- and β-ARs (for a review see (Ramos and Arnsten, 2007)). In this respect, our recent experimental results in the visual cortex, obtained by preferentially activating α_1-AR or β-AR (Salgado et al., 2012) support the notion that NE can simultaneously recruit opposing synaptic plasticity pathways (LTD vs. LTP) in spatially segregated circuits, and that the effects of NE are dose-dependent and receptor-specific. In addition, we found that the evoked excitatory postsynaptic currents in layer II/III pyramidal cells were co-sensitive to sequential application of selective α_1-AR and β-AR agonists, suggesting that both receptors are co-expressed in pyramidal cells in the visual cortex (Salgado et al., 2012). Moreover, a low concentration of NE enables a *LTD-only* window at broad positive and negative delays, while high concentrations of NE enable bidirectional LTP/LTD with a spike-time dependent plasticity (STDP) protocol within very narrow timing intervals (Salgado et al., 2012).

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Altogether, these data delineate an emerging picture for the effect of NE the neocortex, in which a delicate balance between the activation of α_1-AR and β-AR determines the net modulatory effect induced by NE on cortical circuits. For this reason, β-AR activation gates long-term potentiation associated with the classic adenylyl cyclase-cAMP/PKA, a key regulator of synaptic plasticity in the hippocampus and the neocortex (Frey et al., 1993). A similar phenomenon is present in subcortical nuclei, where both α_1 and β-adrenoceptors play a critical role in the storage of aversive memories like in the basolateral nucleus of the amygdala (McGaugh et al., 2000; Lazzaro et al., 2010). An important component of LTD/P noradrenergic modulation could be the β-AR-dependent reversible potentiation of NMDA currents, which triggers a postsynaptic synergism associated with PKA activation and increases in intracellular free Ca^{2+} concentration.

Additional or alternative mechanisms could account for the β-AR modulation of LTP (Ji, Cao, et al., 2008; Huang et al., 2012). Early reports attributed the facilitation of LTP to enhanced neural excitability of layer II/III cells (Bröcher et al., 1992). In the case of NMDAR-induced LTP (*i.e.* LTP induced by adding NMDA to the extracellular medium) (Lee et al., 2000; Malinow and Malenka, 2002), β-ARs induce Ca^{+2}-calmodulin kinase type II (CaMKII) autophosphorylation, activation of CREB, and altered gene expression to promote LTP and the formation of new memories in response to behaviorally-relevant experiences (Hu et al., 2007; Havekes et al., 2012; Zhou et al., 2013).

In conclusion, α_1-ARs and β-ARs gate both acute and long-term bidirectional synaptic plasticity in the neocortex by producing opposing plastic effects in excitatory synapses in the upper layers of the visual cortex: α_1-ARs by *decreasing* synaptic strength, while β-ARs by *increasing* synaptic strength (Nowicky et al., 1992; Kirkwood et al., 1999; Seol et al., 2007; Huang et al., 2012; Laing and Bashir, 2014).

3.3. *Functional implications of the dual regulation of long-term synaptic plasticity*

As discussed above, *in vitro* studies indicate that NE can act as a permissive factor for the induction of NMDAR-dependent LTP/LTD. In addition, there seems to be a pattern in the regulation of bidirectional synaptic plasticity such that neurotransmitter receptors linked to G_s proteins stimulate cAMP production and promote LTP, while receptors coupled to G_q proteins stimulate PLC and promote LTD (Seol et al., 2007; Huang et al., 2012; Salgado et al., 2012; Treviño et al., 2012). Consistent with this view, in the visual cortex, NE actions by activation of β-AR may play a critical role in regulating ocular dominance plasticity (Pettigrew and Kasamatsu, 1978; Kasamatsu and Pettigrew, 1979; Bear and Singer, 1986; Imamura and Kasamatsu, 1988; Mataga et al., 1992; Muguruma et al., 1997). Accordingly, β-AR activation is associated with enhancement of LTP in the neocortex (Nowicky et al., 1992) and with memory facilitation (Gibbs and Summers, 2000), while α_1-AR are linked to LTD (Law-Tho et al., 1993; Kirkwood et al., 1999; Gibbs and Summers, 2000; Scheiderer et al., 2004; Mandal et al., 2010; Marzo et al., 2010; Salgado et al., 2012; Treviño et al., 2012).

We speculate that noradrenergic modulation of synaptic transmission may work in two stages: first, NE would determine currently active brain circuits, participating critically to the selection of the sensory content above neural background noise to be represented in the working memory – possibly through the activation of α-ARs; second, in case of further reinforcement of their emotional valence, central representations and their associations would be 'solidified' in an activity-dependent manner in long-term stores for future retrieval. This second stage would require activation α_1- and β-ARs activation, and would follow stronger and/or longer LC activation (Hopkins and Johnston, 1984; Bröcher et al., 1992; Pelletier et al., 1994; Bramham et al., 1997; Katsuki et al., 1997; Izumi and Zorumski, 1999) through still undiscovered activity-dependent mechanism like local modulation of NE release by glutamate and/or GABA (Witkin et al., 2007; Sterley et al., 2013).

4. Conclusions

4.1. *Conclusions*

While we are still a long way from having an exhaustive model of central noradrenergic function, current research is consistent with the presence of at least two general noradrenergic central mechanisms. In case of moderate LC activation, one noradrenergic mechanism, spatially widespread, mediated by activation of α_2- and α_1-ARs, appears to actively suppress the spread of excitation by decreasing glutamatergic AMPAR-mediated transmission and enhancing $GABA_A$R-mediated synaptic responses, causing a temporary inhibition of neuronal activity. This scenario is supported by the anti-epileptic effect of LC stimulation (Giorgi et al., 2008). In cases of stronger LC activation, a different mechanism-mediated by activation of α_1- and β-ARs, may locally supersede the former one, by consolidating biologically relevant representations and their associations in long-term stores for future retrieval, following intense and/or prolonged LC activation (Hopkins and Johnston, 1984; Bröcher et al., 1992; Pelletier et al., 1994; Bramham et al., 1997; Katsuki et al., 1997; Izumi and Zorumski, 1999). The two modalities of action would exist simultaneously in different neighboring but functionally segregated circuits, thus contributing to explain the wide diversity of noradrenergic responses detected in *in vivo* measurements, particularly in sensory areas (Manunta and Edeline, 1998, 1999; Waterhouse et al., 1998; Devilbiss and Waterhouse, 2000).

4.2. *Future directions*

Many gaps remain in our knowledge of the cortical function of norepinephrine, as a comprehensive model of central noradrenergic function is still unavailable. Studies of the correlation between simultaneous neuronal activity in different cortical/brain areas in relationship to LC activation, NE levels, and the activation of different NE receptors have the potential to reveal some of the missing information, perhaps with a combination of novel techniques including electrophysiology, Ca^{2+}-imaging, functional magnetic resonance,

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and optogenetics. The contribution of cortical GABAergic neurons to the LC/NE modulation is also an important field of research that researchers are starting to investigate, and that will shed light on the nature of cortical changes induced by NE on cortical micro- and macro-circuit function.

Among many unanswered questions that need to be addressed to advance our understanding of central noradrenergic pathophysiology: Is the release of NE a spatially unitary process across its anatomical targets? If so: Are there a number of brain states corresponding to increasing concentrations of brain NE paralleling the activation of progressively lower affinity ARs (for instance, in the order: α_2, α_1, $\alpha_1+\beta$)? If not: what are the spatial patterns of activation of the anatomical targets of the LC/NE system? What are the biological, anatomical, and biochemical factors that determine them? What are the extent and modality of the interaction between the LC/NE system and the other alarm and stress-related systems like the cholinergic, the serotoninergic, and the histaminergic systems? What is the relationship between the temporal increase in NE level, the activation of ARs with different affinity for their ligand, and the function of local neuronal circuits? Does local circuit activity (local release of glutamate and GABA) alter NE release in an activity-dependent manner through modulation of presynaptic receptors on cortical noradrenergic fibers?

4.3. *Theoretical models*

Computational studies have already supported a role for NE modulation of synaptic weights in the improvement of the signal-to-noise ratio of synaptic transmission (Hasselmo et al., 1997), and in the involvement of synaptic plasticity in decision-making tasks (Eckhoff et al., 2009; Silvetti et al., 2013). While advancements in the understanding of these phenomena will only come from the experimental field, more theoretical, computational, quantitative and qualitative studies will be needed in order to integrate the already large and often difficult-to-interpret amount of pertinent experimental data, perhaps benefitting from the comparatively larger set of computational studies performed on the dominant role of the NE precursor dopamine in decision-making (Doya, 2008; Lew and Tseng, 2014).

4.4. *Clinical relevance and expectations*

The relevance of the LC/NE system to stress and the related burden of neuropsychiatric disease suggests that an understanding of the function of the brain noradrenergic system will not only yield a better view of the general operation of the brain, but will also lead to substantial advances in clinical and pharmacological tools for illnesses whose current treatments are remarkably unsatisfactory, including, but not limited to schizophrenic psychoses, anxiety disorders, and mood disorders. Accurate information of the interaction between NE and cortical circuits, along with an appreciation of its role in stress will optimize the effectiveness of neuropsychiatric disorders treatments and minimize their potential shortfalls.

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