

FEATURE ARTICLE

β -Adrenergic Control of Hippocampal Function: Subserving the Choreography of Synaptic Information Storage and Memory

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Abstract

Noradrenaline (NA) is a key neuromodulator for the regulation of behavioral state and cognition. It supports learning by increasing arousal and vigilance, whereby new experiences are “earmarked” for encoding. Within the hippocampus, experience-dependent information storage occurs by means of synaptic plasticity. Furthermore, novel spatial, contextual, or associative learning drives changes in synaptic strength, reflected by the strengthening of long-term potentiation (LTP) or long-term depression (LTD). NA acting on β -adrenergic receptors (β -AR) is a key determinant as to whether new experiences result in persistent hippocampal synaptic plasticity. This can even dictate the direction of change of synaptic strength.

The different hippocampal subfields play different roles in encoding components of a spatial representation through LTP and LTD. Strikingly, the sensitivity of synaptic plasticity in these subfields to β -adrenergic control is very distinct (dentate gyrus > CA3 > CA1). Moreover, NA released from the locus coeruleus that acts on β -AR leads to hippocampal LTD and an enhancement of LTD-related memory processing. We propose that NA acting on hippocampal β -AR, that is graded according to the novelty or saliency of the experience, determines the content and persistency of synaptic information storage in the hippocampal subfields and therefore of spatial memories.

Key words: β -adrenergic receptors, hippocampus, memory, noradrenaline, synaptic plasticity

Introduction

Noradrenaline (NA) belongs to a group of neurotransmitters able to modulate synaptic functions that are referred to as neuromodulators. In the central nervous system, the primary source of NA is the locus coeruleus (Sara et al. 1994; Kitchigina et al. 1997), a structure located in the brain stem that sends noradrenergic projections to many brain regions (Jones et al. 1977). The activation of the noradrenergic system strongly depends on an animal's behavioral state, with novel or emotive stimuli resulting in burst firing, the intensity and duration of which is determined by the nature and saliency of the experience (Crow 1968; Kety 1970, 1972; Aston-Jones and Bloom 1981; Sara and Segal 1991; Sara

2009). It was suggested almost 4 decades ago that the noradrenergic system might play a powerful role in supporting learning and memory processes (Kety 1972). Subsequent experiments highlighted the role of NA as an enhancer of neuronal responses toward discrete stimuli and thereby of signal-to-noise ratios that support information detection and encoding (Woodward et al. 1979; Sara 1985; Servan-Schreiber et al. 1990).

NA in the Hippocampus

NA plays an extremely important role in the regulation of hippocampal function. Elevations of NA levels increase neuronal

excitability in the dentate gyrus (Lacaille and Harley 1985; Stanton and Sarvey 1985; Harley 1991) and in the CA subfields (Mueller et al. 1981; Heginbotham and Dunwiddie 1991; Dunwiddie et al. 1992; Jurgens et al. 2005), via activation of β -adrenergic receptors (β -AR) (Kitchigina et al. 1997). Furthermore, the enhanced responsiveness of hippocampal neurons to NA release from the locus coeruleus can persist for 24 h (Walling and Harley 2004), suggesting that NA also engages in metaplastic regulation (Abraham and Tate 1997; Maity et al. 2015) of hippocampal information encoding. In doing so, it will inevitably exert control over the readiness of the hippocampus to store new memories or retrieve old ones. The NA receptors are subdivided into α -adrenergic receptors (α -AR) and β -AR (Ahlquist 1948). Although α -AR can influence hippocampal function, largely through regulating neuronal excitability (Segal et al. 1991), the β -AR exert very specific effects on synaptic information encoding, whereby they strongly regulate synaptic plasticity, even in the absence of ostensible effects on neuronal excitability (Kemp and Manahan-Vaughan 2008a).

Projections of the LC to the hippocampus are differentiated, with inputs to the dentate gyrus being particularly dense (Ungerstedt 1971; Jones and Moore 1977; Loy et al. 1980). Afferents of the LC also terminate in the Stratum lucidum of area CA3 (Loy et al. 1980) where mossy fibers originating from the dentate gyrus form synapses. The LC exhibits firing activity that fluctuates across the circadian cycle (Bouret and Sara 2004), with activity being lower during sleep and increasing during the transition from sleep to wakefulness (Berridge 2008). Tonic firing activity correlates with behavioral state, with low tonus being associated with low vigilance states (Aston-Jones and Bloom 1981; Aston-Jones and Cohen 2005) and phasic burst firing being triggered by phenomena such as exploration of novelty, or arousing stimuli (Aston-Jones and Bloom 1981; Grant et al. 1988; Sara et al. 1994; Hervé-Minvielle and Sara 1995; Vankov et al. 1995), decision-making, or during the transition from a lower to a higher vigilance state (Aston-Jones and Bloom 1981; Rajkowski et al. 2004). In effect, the LC serves as a change detector.

The locus coeruleus is part of the ascending reticular activating system (ARAS) (Jelinger 2009), and its tonic activity is a key component of the waking cycle (Berridge 2008). In this function, it is reasonable to expect that it plays a key role in modulating thresholds for incoming cortical information (Devilbiss et al. 2006). Under conditions where an arousal change is triggered (by a novel event), phasic activity of the locus coeruleus changes excitability levels in the hippocampus (Lacaille and Harley 1985; Stanton and Sarvey 1985; Harley 1991), and indeed in other cortical areas (see Marzo et al. 2014), such that salient information is retained and/or encoded (Lemon et al. 2009; Lemon and Manahan-Vaughan 2012). This property of change detection enables selective information encoding that may be rendered more specific by activity-related local NA release networks that enable localized and highly selective information processing in discrete synaptic populations (Mather et al. 2015), thus conferring an even greater precision to the modulation by NA of synaptic responses and encoding. We propose that β -AR are a critical transducer of LC-mediated change detection, particularly pertaining to the promotion of encoding of salient experiences. This possibility is corroborated by observations that activation of the LC potently modulates β -AR-dependent and input-specific synaptic strength in the hippocampus, that is associated with hippocampus-dependent learning and memory (Kemp and Manahan-Vaughan 2007, 2011; Hansen and Manahan-Vaughan 2015a).

β -Adrenoreceptor Expression in the Hippocampus

Different subtypes of β -AR are expressed in the hippocampus. They are classified into β_1 -, β_2 -, and β_3 -subtypes on the basis of their affinity toward adrenaline and NA (Lands et al. 1967) and are G protein-coupled receptors (GPCRs) that are positively coupled to adenylyl cyclase via G_s . However, depending on which receptor (β_1 - or β_2 -AR) is activated by ligands, different effects are observed based on the activation of downstream cascades (Fig. 1). Ligand binding to β_1 - or β_2 -AR leads to activation of guanine nucleotide-binding regulatory G_s -proteins. This, in turn, activates adenylyl cyclase (AC), followed by an increase of intracellular cyclic adenosine monophosphate (cAMP) and subsequent activation of protein kinase A (PKA) (Seeds and Gilman 1971; Maguire et al. 1977; Strulovici et al. 1984; Hausdorff et al. 1989). In addition to the activation of G_s -proteins, ligand binding to β_2 -adrenergic receptors can also activate extracellular signal-regulated kinases (ERK), MAPKs, Akt, and tyrosine kinase transactivation, a pathway mediated by G_i/G_o proteins (Abramson et al. 1988; Xiao et al. 1995; Daaka et al. 1997; Maudsley et al. 2000; Zhu et al. 2001).

Of the different subtypes, the β_1 - and β_2 -AR subtypes are of particular interest due to their role in hippocampal synaptic plasticity (Yang et al. 2002; Gelinis et al. 2008; Kemp and Manahan-Vaughan 2008a): activation of these subtypes results in stimulation of extracellular signal-regulated kinase/mitogen-activated protein kinase (ERK/MAPK) that is a key step in the activation of the cAMP response element-binding protein (CREB) that mediates protein transcription (Fig. 1) and thus strongly supports persistent synaptic plasticity (Braunewell and Manahan-Vaughan 2001; Ahmed and Frey 2005) and long-term memory (Kandel 2012). β_3 -AR are exclusively expressed in a subset of precursor cells in the subgranular zone of the DG (Jhaveri et al. 2010).

The expression of β_1 and β_2 -AR in the hippocampus is not homogenous. Both, receptor subtypes are expressed in pyramidal cells in area CA1, CA3 and the dentate gyrus (DG) (Booze et al. 1993; Milner et al. 2000; Guo and Li 2007; Cox et al. 2008), whereas relatively low levels of both receptor subtypes have been reported in CA3 (Booze et al. 1993). A relatively wide distribution of β_1 -AR has been reported for the CA3 region, however, whereby expression is prominent on perikarya and to some extent on proximal dendrites (Jurgens et al. 2005). In the CA1 and CA3 regions, β_1 - and β_2 -AR are preferentially expressed in neurons as opposed to astrocytes. β_2 -AR have been reported in neuronal membranes and cytoplasm, as well as in the nucleus of neurons in the CA1 and CA3 regions, whereas β_1 -AR are expressed only in membranes and cytoplasm (Guo and Li 2007). In the DG, β -AR are distributed within granule cells at postsynaptic sites (Milner et al. 2000). Furthermore, β_1 - and β_2 -AR are found on interneurons with a similar distribution across all 3 hippocampal regions for β_2 -AR (Cox et al. 2008). Compared with the CA1 region, the DG contains the highest NA content and the highest fiber density of noradrenergic innervation relative to the other hippocampal subregions (Loy et al. 1980).

In addition to postsynaptic expression of β -AR, it has been reported that β -AR also occur on presynaptic sites (Heider et al. 1997; Nejték and Dahl 1997). Presynaptic activation of β -AR results in action potential initiation in the Schaffer collateral-CA1, but not in the perforant path-CA1 pathway. These differences may derive from pathway-specific modulation of the Schaffer collaterals mediated by β -AR (Nejték and Dahl 1997) and suggest that activation of pre- or postsynaptic β -AR may result in different functional outcomes; but as yet, little is known about this possibility.

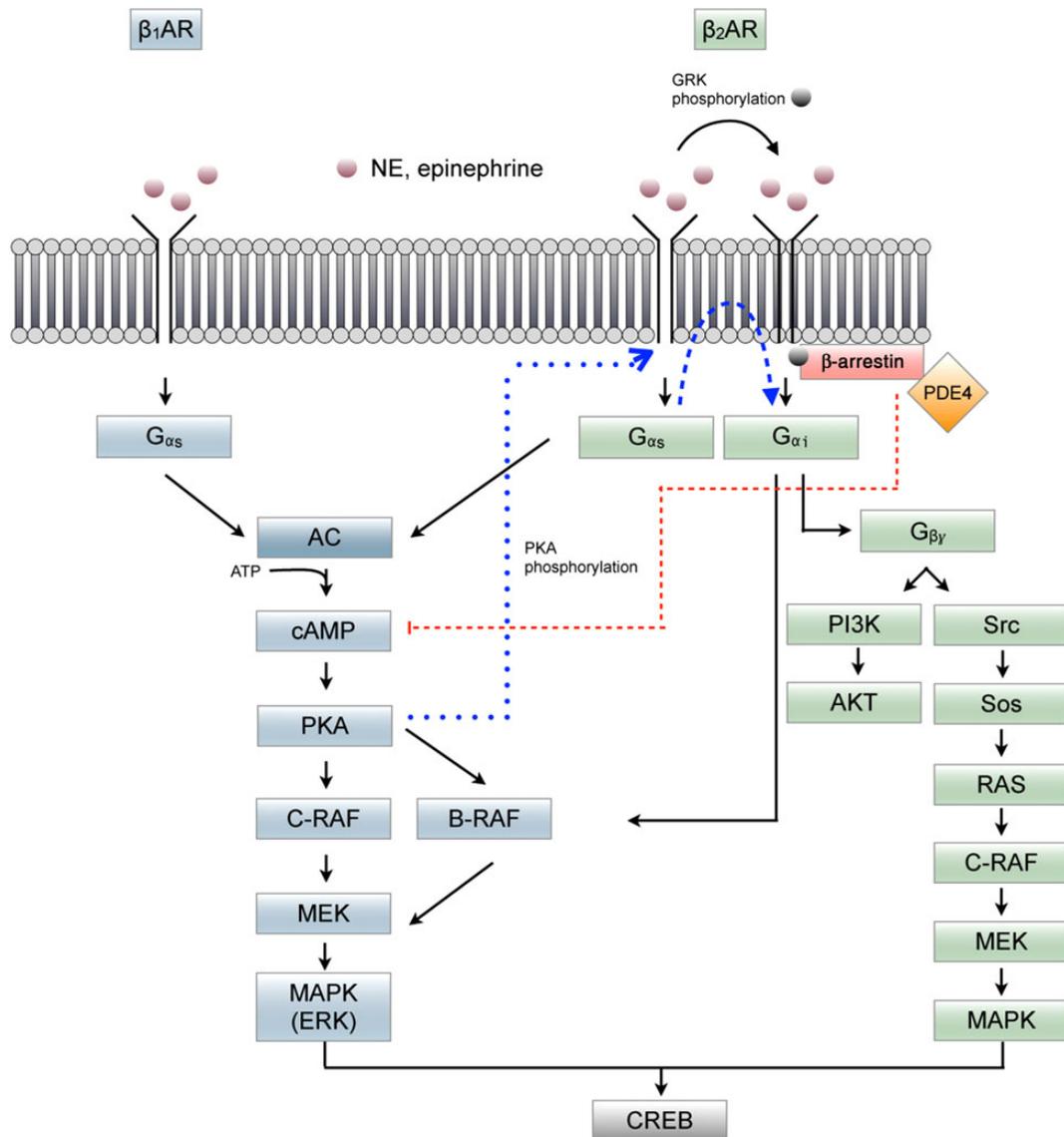


Figure 1. Summary of the different signaling pathways that respond to activation of β₁AR (blue) and β₂AR (green). PKA phosphorylation mediates the switch from G_{αs} to G_{βγ} activation (dotted blue line). An inhibitory effect resulting from β-arrestin and PDE4 action is shown by the red dotted line. AC, adenylate cyclase; PI3K, phosphatidylinositol 3-kinase; ATP, adenosine triphosphate; B-Raf, proto-oncogene B-Raf; cAMP, 3'-5'-cyclic adenosine monophosphate; C-Raf, RAF proto-oncogene serine/threonine kinase; CREB, cAMP-responsive element-binding protein; ERK, extracellular signal-regulated kinase; G_{αs}, G_{αi}, G_{βγ}, G-proteins; GRK, G protein-coupled receptor kinase; MAPK, mitogen-activated protein kinase; MEK, mitogen-activated protein kinase; NE, norepinephrine; PDE4, phosphodiesterase-4; PKA, protein kinase; RAS, membrane-associated guanine nucleotide-binding protein; Src, proto-oncogene tyrosine-protein kinase; SOS, Son of Sevenless, genes encoding guanine nucleotide exchange factors (Winder et al. 1999; Schmitt and Stork 2000; Xiao 2001; Lefkowitz et al. 2002; Baillie et al. 2003; Shenoy et al. 2006; Lemon et al. 2009; Meitzen et al. 2011).

β-Adrenergic Regulation of Hippocampal Synaptic Plasticity

Evidence is increasing that synaptic plasticity enables the encoding of memory (Manahan-Vaughan and Braunewell 1999; Straube et al. 2003a; Kemp and Manahan-Vaughan 2004; Whitlock et al. 2006; Nabavi et al. 2014). Moreover, LTP and LTD may contribute to different aspects of the encoding of an experience. LTP is tightly related to context-dependent fear memory (Whitlock et al. 2006; Nabavi et al. 2014) and to the encoding of novel space, particularly in the concept of a novel scene or scene change, whereby learning about general properties of space or substantial changes in a known environment strengthens hippocampal LTP (Straube et al. 2003b; Kemp and Manahan-Vaughan 2004).

Moreover, this is an encoding property exhibited by all hippocampal subfields (Kemp and Manahan-Vaughan 2004, 2008b; Hagen and Manahan-Vaughan 2012).

LTD, on the other hand, appears to encode the content and the specific features of space: whereby the precise characteristics of the spatial content determines which hippocampal subfield responds to this experience with the expression of LTD (Kemp and Manahan-Vaughan 2007). Thus, learning about the navigational or orientational (large and distal) content of space strengthens LTD in the dentate gyrus, or at mossy fiber-CA3 synapses, whereas learning about discrete (small and proximal) environmental features, or more subtle details of spatial content, enables LTD in the CA1 region (Manahan-Vaughan and Braunewell 1999; Kemp and Manahan-Vaughan 2011; Goh and Manahan-

Vaughan 2013a) and in associational commissural (AC)-CA3 synapses (Hagena and Manahan-Vaughan 2012). A picture is emerging, which strongly suggests that LTP and LTD work together to encode the components and elements of a spatial representation (Kemp and Manahan-Vaughan 2007), whereby we propose that LTP encodes the initial scaffold, and perhaps context, of the spatial experience, and LTD contributes details and content to this representation. This is supported by our observations that hippocampal synaptic potentiation appears instantaneously upon exposure of a rodent to novel space that includes novel content (Manahan-Vaughan and Braunevell 1999). Within several minutes, this potentiation response is superceded by persistent synaptic depression. This suggests that LTP may select the synaptic network in which the new experience is to be encoded, whereas LTD refines and optimizes this network into the final robust and unique representation.

What is particularly compelling about β -AR is that these receptors play a central role in this process, by driving the direction of change of synaptic strength (Lemon et al. 2009; Hansen and Manahan-Vaughan 2015b) and in grading the persistency of synaptic plasticity in the different hippocampal subfields (Kemp and Manahan-Vaughan 2008a; Hagena and Manahan-Vaughan 2012; Hansen and Manahan-Vaughan 2015b). Bearing in mind the significance of LTP and LTD for long-term spatial memory, and given the postulated roles of the different hippocampal subfields in the encoding of memory aspects such as working memory (Nakao et al. 2002; Kesner 2007; Bikbaev et al. 2008; Kesner and Warthen 2010), pattern completion, pattern separation (Kesner et al. 2004; Leutgeb and Leutgeb 2007; Leutgeb et al. 2007; Bakker et al. 2008; Kesner and Warthen 2010; Hagena and Manahan-Vaughan 2011; Neunuebel and Knierim 2014), mismatch detection (Lisman and Otmakhova 2001; Lee et al. 2005; Kumaran and Maguire 2007; Duncan et al. 2012), and the holistic completion of spatial representation (Kemp and Manahan-Vaughan 2007), this places the β -AR in a unique position as a determinant of the content and persistency of synaptic information storage and memory.

LTP

Influence of β -Adrenergic Receptors on LTP in the Dentate Gyrus

Almost 30 years ago, Stanton and Sarvey (1985) demonstrated that destroying noradrenergic fibers with selective dorsal bundle injections of 6-OHDA and thereby depleting NA, reduced the occurrence and magnitude of LTP in the DG. In the DG, application of a β -AR agonist causes lasting potentiation of the population spike (Lethbridge et al. 2014) and application of NA itself to the DG causes LTP of the population spike in slice preparations (Bramham et al. 1997; Swanson-Park 1999), as well as in anesthetized rats (Neuman and Harley 1983; Winson and Dahl 1985; Chaulk and Harley 1998). LTP of both the population spike and dendritic excitatory postsynaptic potential resulting from NA application to the DG has also been described in vitro (Stanton and Sejnowski 1989), suggesting that NA modulates both somatic and dendritic excitability in this hippocampal subfield. In addition, in the DG in vivo, LTP is reinforced by β -AR agonism or NA application (Almaguer-Melian et al. 2005; Hansen and Manahan-Vaughan 2015b). Evidence also exists that the increased extracellular NA release that occurs in response to high-frequency stimulation (HFS) of the perforant path is an important component in inducing LTP in the DG (Bronzino et al. 2001). This process may relate to glutamate

release-mediated localized NA release, as reported by Mather et al. (2015).

This prominent influence of β -AR in the DG can be attributed to the fact that noradrenergic innervation originating from the LC is very dense in the DG, and the NA content in this hippocampal subfield may be higher compared with the CA1 and CA3 regions (Loy et al. 1980) (Fig. 2). In addition, the highest expression of β_1 - and β_2 -AR is found in the DG compared with the CA1 and CA3 region (Booze et al. 1993; Milner et al. 2000), suggesting that the DG may be more sensitive to noradrenergic control (via β -AR) than the other hippocampal subfields.

Strikingly, β -AR activation in the DG may serve to determine the direction of change in synaptic strength in medial and lateral perforant path-DG synapses: combining β -AR agonism with stimulation of the medial perforant path induces LTP (in the form of NELLP: “norepinephrine” long-lasting potentiation), whereas stimulating the lateral perforant path induces LTD (in the form of NELLD: “norepinephrine” long-lasting depression) (Dahl and Sarvey 1989; Pelletier et al. 1994). These differential effects of NA may be important for selective hippocampal information processing between these anatomically and biochemically distinct pathways (Dahl and Sarvey 1989).

Influence of β -Adrenergic Receptors on LTP in the CA3 Region

In area CA3, two important pathways converge onto CA3 pyramidal cells: the mossy fibers (mf) that originate from dentate gyrus granule cells, and the associational commissural (AC-CA3) fibers that are, in effect, recurrent afferents that arise from ipsilateral CA3 pyramidal cells, or commissural projections from contralateral CA3 pyramidal cells. Both synapses display different properties in terms of receptor involvement in long-term changes of synaptic plasticity, whereby, for example, the mossy fiber (mf)-CA3 synapses express LTP that does not require N-methyl-D-aspartate receptor (NMDAR) activation and integrate presynaptic processes (Harris and Cotman 1986; Nicoll and Schmitz 2005). Furthermore, synaptic plasticity at mf-CA3 and AC-CA3 synapses are differently regulated by the metabotropic glutamate receptor, mGlu5 (Hagena and Manahan-Vaughan 2015). The molecular distinctions of synaptic plasticity at mf-CA3 and AC-CA3 synapses may reflect distinct functional roles in terms of hippocampal information encoding and memory (Hagena and Manahan-Vaughan 2011).

Area CA3 receives massive projections from the LC, which terminate in the *Stratum lucidum* (Moore and Bloom 1979; Loy et al. 1980), the termination site of mf projections from the DG. As in area CA1 and the DG, LTP in the CA3 region can be distinguished into different phases, called early (E)-LTP that lasts for up to 2 h in vivo, and late (L)-LTP, that lasts for several hours or days. E-LTP requires activation of mGlu receptors (Bashir et al. 1993) and protein kinases (Malenka et al. 1989) (and to some degree phosphatases), L-LTP requires the expression of immediate early genes (Jones et al. 2001), as well as protein translation (Connor et al. 2011). Interestingly, in vitro studies have shown that differences exist between the different inputs to CA3 at the level of β -AR. Activation of these receptors induced early- and late-LTP at mf-CA3 synapses but not at AC-CA3 synapses in vitro, and antagonism of β -AR blocks late-LTP, suggesting that β -AR play a crucial role in modulating information processing mf-CA3 synapses (Hopkins and Johnston 1988; Huang and Kandel 1996). In line with this, other studies, conducted on rat brain slices, reported that β_1 -AR activation has enhancing effects on LTP at mf-CA3 synapses (Hopkins and Johnston 1984, 1988).

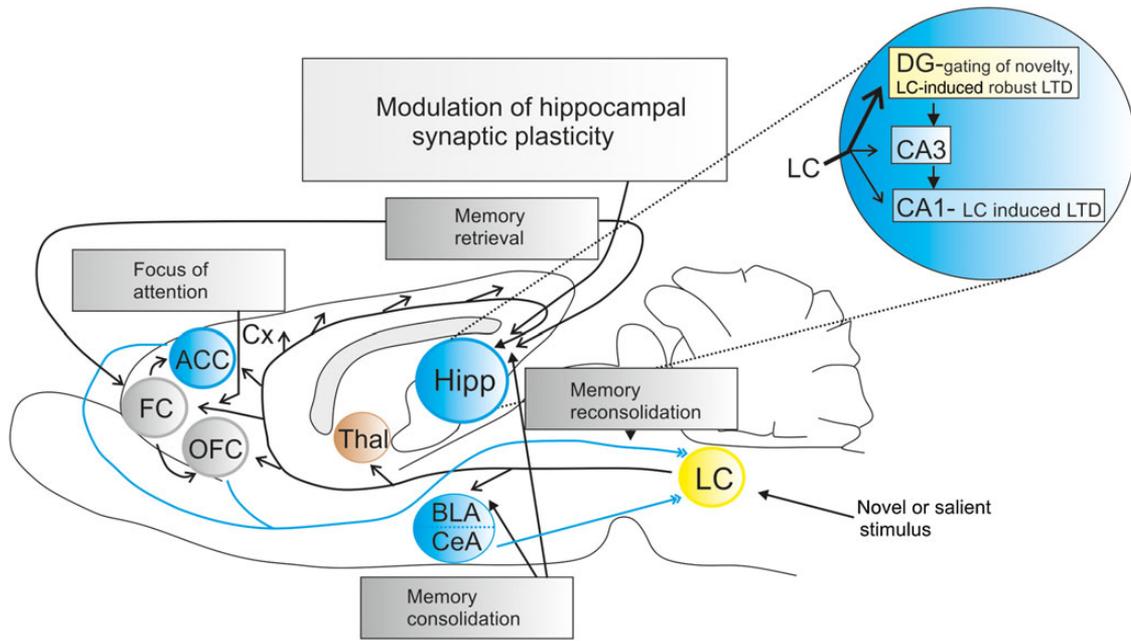


Figure 2. Noradrenergic projections of the locus coeruleus involved in the modulation of persistent hippocampal synaptic plasticity in the rat brain. The locus coeruleus (LC) sends projections to the basolateral amygdala (BLA), thalamus (Thal), orbitofrontal cortex (OFC), frontal cortex (FC), anterior cingulate cortex (ACC), Cortex (Cx), and hippocampus (Hipp). The projection to the hippocampus is responsible for modulating hippocampal synaptic plasticity (Harley 2007; Lemon et al. 2009; Sara 2009; Lemon and Manahan-Vaughan 2012). The DG receives the strongest noradrenergic projection from the LC (indicated by the big black arrow in the magnification of the hippocampus on the upper right side) compared with CA1 and CA3 (smaller black arrows indicate weaker LC projections) (Loy et al. 1980; Fallon and Loughlin 1982) underpinning its role in novelty gating within hippocampal information processing. Electrical activation of the LC induces β-AR-dependent long-term depression in SC-CA1 and DG synapses (Lemon et al. 2009; Hansen and Manahan-Vaughan 2015b) indicating the important role of the LC in encoding novel information. In addition, the different stages of memory are dependent on a complex interaction within this noradrenaline (NA)-LC network. Memory consolidation is promoted by the Hipp and BLA (Eichenbaum 2000; Roozendaal et al. 2008), whereas memory retrieval is enabled by an interaction between the Hipp and FC (Corbetta and Shulman 2002; Sara 2010). The projection from the FC and ACC to the LC is believed to contribute to the reconsolidation of memory processes (Sara 2000, 2009, 2010). The FC regulates the control of attention to a novel or salient stimulus (Corbetta et al. 2008; Robbins and Arnsten 2009). According to the integrative theory of NA-LC function, the OFC and ACC send projections to the LC, driving transitions between the LC modes and phasic LC responses to adapt synaptic gain (Aston-Jones and Cohen 2005).

Very few studies have explored synaptic plasticity in CA3 synapses of the intact rodent. Recently, we have shown a differentiated involvement of β-AR in persistent plasticity at mf-CA3 synapses in freely behaving rats. Interestingly, LTP or LTD elicited with electrical stimulation, and which lasts for over 24 h, is not altered by propranolol, a β-AR antagonist (Hagen and Manahan-Vaughan 2012). However, β-AR activation results in strengthening of weak synaptic potentiation at mf-CA3 and AC-CA3 synapses in vivo, although weak depression remains unaffected (Hagen and Manahan-Vaughan 2012).

Influence of β-Adrenergic Receptors on LTP in the CA1 Region

The role of β-AR in the CA1 region has been extensively investigated both in vitro and in vivo, whereby in vitro studies of synaptic plasticity are typically limited to the first 60 min of the plasticity event. It has been shown, for example, that LTP induced by prolonged theta-tetanus in vitro (PTT; one train of 900 stimuli at 5 Hz) depends on β-AR in mice and rats (Thomas et al. 1996; Katsuki et al. 1997; Gelinas and Nguyen 2005; Hu et al. 2007; Qian et al. 2012). Other in vitro studies showed that LTP induction in area CA1 depends on recruiting noradrenergic innervation (Yang et al. 2002). These processes may rely on joint activation of other neuromodulatory systems: co-activation of β-adrenergic and cholinergic receptors enhances LTP induction in area CA1 in vitro (Watabe et al. 2000), and dopamine D1 receptors mediate LC effects on hippocampal synaptic plasticity, which also recruit β-AR (Lemon et al. 2009).

LTP can be induced by activation of β-AR within a variety of stimulation frequencies. LTP induced with 5 Hz afferent stimulation depends on β-AR, both in mice (Thomas et al. 1996) and in rats (Lin et al. 2003), and more recently, a new role has emerged for β₂-AR in LTP induced by theta stimulation (Qian et al. 2012). LTP induced by different afferent stimulation patterns and using varying frequencies (5, 10, or 100 Hz) is also enhanced by applying a β-AR agonist before or during stimulation (Thomas et al. 1996; Katsuki et al. 1997; Cohen et al. 1999; Gelinas et al. 2008; Li et al. 2013). Surprisingly, low-frequency stimulation (LFS) paired with β-AR activation causes LTP in area CA1 in vitro (Gelinas and Nguyen 2005). This β-AR-dependent LFS-induced LTP may result from decreased A-type potassium channel activity in pyramidal cell dendrites that lead to increased dendritic cell excitability (O'Dell et al. 2010). We have observed in vivo that LC stimulation results in LTD in the hippocampus (Lemon et al. 2009; Lemon and Manahan-Vaughan 2012; Hansen and Manahan-Vaughan 2015b).

Controversies in the Presumed Role of β-AR in Regulating LTP

It should be mentioned, however, that some in vitro studies have contradicted the abovementioned findings and report that application of β-AR antagonists or agonists does not alter LTP, particularly when it is induced by a strong afferent stimulation pattern (Dunwiddie et al. 1982; Schimanski et al. 2007). One possible explanation for this discrepancy may be the time frame during which LTP was monitored. Dunwiddie and colleagues monitored

LTP responses for ca. 20 min. Thus, it may be that β -AR effects on the subsequent phases of LTP were missed. In the study by [Schimanski et al. \(2007\)](#), genetically modified animals were used that exhibit different levels of endogenous NA. We have observed that LC stimulation that occurs immediately prior to high-frequency afferent stimulation prevents hippocampal LTP that would normally endure for <4 h, but does not prevent LTP that would normally persist for over 24 h ([Hansen and Manahan-Vaughan 2015a](#)). These observations align with the abovementioned studies and suggest that under circumstances where the novel experience is extremely potent in its emotive force, encoding of this information is prioritized by the hippocampus and overrides regulatory control by NA released from the LC that acts on β -AR. Here, associative shock or fearful experiences spring to mind. Many studies have shown that fear conditioning that uses foot shock or other forms of acute and potent stress leads to robust LTP in the hippocampus ([Korz and Frey 2003, 2005](#); [Ahmed et al. 2006](#); [Whitlock et al. 2006](#)).

LTD

Regulation by β -Adrenergic Receptors of LTD in the Dentate Gyrus

Intrahippocampal application of a β -AR agonist induces LTD in the DG in vivo ([Lethbridge et al. 2014](#)). At higher agonist concentrations, LTP occurs ([Lethbridge et al. 2014](#)), suggesting (as mentioned already above) that the degree of β -AR activation may be decisive for the type of synaptic plasticity induced. Strikingly, however, brief direct activation of the locus coeruleus in vivo, which leads to NA release in the hippocampus ([Lemon et al. 2009](#)), promotes the expression of hippocampal LTD in CA1 ([Lemon et al. 2009](#); [Lemon and Manahan-Vaughan 2012](#)) and in the dentate gyrus ([Hansen and Manahan-Vaughan 2015b](#)). Agonist activation of β -AR also facilitates weak LTD into persistent (>24 h) LTD in vivo ([Hansen and Manahan-Vaughan 2015b](#)). This suggests that the bias of β -AR regulation of DG plasticity may be toward LTD.

In line with this, in vitro studies showed that in the absence of patterned afferent stimulation, NA induces LTD in the DG ([Dahl and Sarvey 1990](#)), and agonist activation of β -AR also elicits LTD at lateral perforant path-dentate gyrus synapses ([Dahl and Sarvey 1990](#)). Moreover, as mentioned earlier, the combination of β -AR antagonism with stimulation of the medial perforant path induces LTD in the DG (in the form of NELLD) ([Dahl and Sarvey 1989](#); [Pelletier et al. 1994](#)). In freely behaving rats, persistent LTD that lasts for over 24 h at medial perforant path-dentate gyrus synapses critically depends on β -AR activation ([Hansen and Manahan-Vaughan 2015b](#)).

Regulation by β -Adrenergic Receptors of LTD in the CA3 Region

Despite the importance of the CA3 region in the acquisition and processing of spatial information, only one study has addressed the role of β -AR in LTD in area CA3. Here, it was shown that at mf-CA3 synapses, antagonism of β -AR had no effect on LTD (>24 h) in freely behaving rats that was induced solely by patterned afferent stimulation (1 Hz, 900 pulses) ([Hagena and Manahan-Vaughan 2012](#)). Effects were not dose dependent: increasing the antagonist concentration failed to alter the resistance of LTD to regulation by β -AR. This is in striking contrast to the DG, where β -AR antagonism prevents persistent LTD. This may relate to the putative role of the CA3 in specific forms of information processing, such as

pattern completion ([Kesner 2007](#)), or to the very unique molecular mechanisms underlying synaptic plasticity, and persistent LTD, at mf-CA3 synapses ([Klausnitzer and Manahan-Vaughan 2008](#); [Hagena and Manahan-Vaughan 2010](#)).

Regulation by β -Adrenergic Receptors of LTD in the CA1 Region

In vitro studies as to the role of β -AR receptors in LTD in area CA1 are few and contradictory: CA1-LTD induced by LFS is unaffected by β -AR modulation in vitro ([Yang et al. 2002](#)), whereas other in vitro studies reported an involvement of β -AR activation in preventing CA1-LTD ([Katsuki et al. 1997](#)). We believe these discrepancies derive from differences in experimental preparations across laboratories, such as methodological differences in the preparation of hippocampal slices, slice treatment in the in vitro chamber, and the afferent stimulation protocols used, but they also derive from the fact that most in vitro studies examine plasticity effects for at most 60 min after patterned afferent stimulation (see e.g.: [Bliss and Collingridge 1993](#); [Bear and Malenka 1994](#); [Malenka and Bear 2004](#) for reviews of the hippocampal plasticity field). Although this would be considered a heretic statement among in vitro plasticity researchers, plasticity responses that persist for 60 min are not truly long-term effects. Here, rather one is examining E-LTP or E-LTD in in vitro studies of this kind. And strikingly, where LTD was followed for hours or days in vivo, a critical involvement of β -AR was described: different labs have reported that short-term depression (STD) that is induced by weak LFS is prolonged into late LTD in Schaffer collateral-CA1 synapses in freely behaving rats and mice following activation of β -AR ([Straube and Frey 2003](#); [Kemp and Manahan-Vaughan 2008a](#)).

It is striking that LTP and LTD that are elicited by strong stimulation of mf-CA3 synapses are resistant to regulation by β -AR. This suggests that under conditions where the LC is strongly activated, information processing in the CA1 and DG (but not CA3) will be subject to modulation by NA. The CA3 region has been proposed to be responsible for pattern completion ([Kesner 2007](#)), whereby encountering a fragment of a previously learned experience results in the retrieval of the entire stored representation. The DG and CA1 may be more important for pattern separation, whereby novel experience is distinguished from a similar previously learned experience and encoded as a new “engram” ([Kesner et al. 2004](#)). Thus, given the fact that NA is released from the LC based on the novelty, or saliency, of an experience, it is plausible that it supports new information encoding (at the level of the DG or CA1) more than processes that might involve retrieval or updating of established engrams (in the CA3 region).

Cellular Mechanisms Underlying β -Adrenergic Receptor Regulation of Hippocampal Synaptic Plasticity

Bath application of a β -AR agonist (to a hippocampal slice) may mimic a tonic elevation in NA (and thereby tonic activation of β -AR), whereas brief stimulation of the LC may emulate phasic NA release (onto β -AR). This suggests that the pattern and duration of β -AR activation that occurs in coincidence with, for example, entorhinal cortex informational input into the hippocampus, may be decisive in determining the direction of change in synaptic strength. In line with this, we have observed that brief activation of the LC in vivo prevents weaker forms of hippocampal LTP ([Hansen and Manahan-Vaughan 2015a](#)), whereas an elevation in “tonic” activation by means of intracerebral agonist treatment can strengthen weak potentiation into

persistent LTP (Hansen and Manahan-Vaughan 2015a) and under specific state-dependent circumstances, phasic activation of the LC triggers NA-LTP (Walling et al. 2011). Conversely, an emulation of “tonic” LC activation (by brief electrical stimulation of the LC) that occurs in conjunction with test-pulse stimulation of afferent fibers in the hippocampus results in very robust LTD at CA1 (Lemon et al. 2009) and DG synapses (Hansen and Manahan-Vaughan 2015b).

β -AR do not only influence the direction of change in synaptic strength; they also modulate the persistency of synaptic plasticity. Early (E-LTP) that normally lasts for just 1–2 h is reinforced by β -AR activation (Hsu et al. 2002) and β -AR antagonism attenuates E-LTP in vitro (Connor et al. 2011). β -AR activation also prolongs L-LTP in the CA1 region of rat hippocampal slices (Gelinás and Nguyen 2005). Moreover, β -AR contribute to the maintenance of LTP in area CA1 in different mouse strains (Schimanski et al. 2007). Agonist activation of β -AR prolongs E-LTD into L-LTD in the DG (Hansen and Manahan-Vaughan 2015b), but not in the CA1 region (Kemp and Manahan-Vaughan 2008a) in putative alignment with the density of LC projections in these hippocampal subfields (Loy et al. 1980).

Evidence suggests that β -AR-dependent L-LTP is based on dendritic translation, but not transcription involving an upregulation of the eukaryotic initiation factor (eIF) 4F complex in CA1 pyramidal cell dendrites during β -AR-dependent LTP (O'Dell et al. 2010). Formation of the eIF4F complex plays a key role during initiation of translation (O'Dell et al. 2010). β -AR regulate post-synaptic initiation of protein translation through the ERK and mTOR pathways (Winder et al. 1999; Gelinás et al. 2007). The translation of plasticity-related proteins can, in turn, facilitate hippocampal synaptic plasticity (O'Dell et al. 2010). β -AR activation can also enhance short-term plasticity through modulation of intrinsic excitability of neurons. This involves the attenuation of Ca^{2+} -dependent potassium currents in the DG, and in CA1 pyramidal neurons (Haas and Konnerth 1983; Haas and Rose 1987), along with potentiated activity of voltage-dependent Ca^{2+} -channels in the DG (Gray and Johnston 1987) and at mf-CA3 synapses (Fisher and Johnston 1990).

The abovementioned examples highlight that β -AR not only influence the direction of change of synaptic strength, but they also regulate the duration of hippocampal synaptic plasticity and therefore may also contribute to the precision of synaptic encoding in the hippocampus. Thus, β -AR activation also augments LTP in CA1 synapses at an input other than the stimulated input (i.e., they modulate heterosynaptic LTP) (Connor et al. 2011).

Taken together, these observations suggest that β -AR mediate multifarious and diverse regulation of both early and late components of LTP and LTD, suggesting that their role in enabling this form of synaptic plasticity is quite pivotal. This in turn may relate to the abovementioned roles of tonically (Bouret and Sara 2004), phasically (Aston-Jones and Bloom 1981; Grant et al. 1988; Sara et al. 1994; Hervé-Minvielle and Sara 1995; Vankov et al. 1995), and locally (Mather et al. 2015) released NA in modulating very distinct kinds of information processing and storage.

Molecular Mechanisms Underlying β -Adrenergic Receptor Regulation of Hippocampal Synaptic Plasticity

Several mechanisms have been proposed to explain how LTP is modulated by β -AR on a molecular level. NA, or activation of β -AR, induces phosphorylation of the GluA1 subunit of the AMPA receptor, at Ser845 and Ser831 sites (Vanhoose and Winder 2003; Joiner et al. 2010; Zhou et al. 2012) that in turn facilitates the synaptic delivery of GluA1 containing α -amino-3-hydroxy-5-

methyl-4-isoxazolepropionic acid receptors (AMPA) that are subject to NA modulation (Hu et al. 2007; O'Dell et al. 2010). Thus, the threshold for use-dependent alterations in hippocampal synaptic plasticity can be lowered, for instance to induce LTP. Furthermore, an elevated NA level in the hippocampus that is induced by emotional arousal causes GluA1 phosphorylation (Hu et al. 2007). The increase of extrasynaptic GluA1 mediated by NA-induced phosphorylation may be achieved by mechanisms that link GluA1 with molecules that support its delivery to the synaptic membrane (Leonard et al. 1998; Chen et al. 2000; Esteban et al. 2003; Rouach et al. 2005).

A further aspect of β -AR regulation of glutamate receptors pertains to NMDAR that comprise a pivotal component of many forms of hippocampal LTP (Bliss and Collingridge 1993). Here, a modulation by β -AR of NMDAR-mediated processes has been reported: deficits in LTP in GluN2A knockout mice can be reversed by activating β -AR, such that the ERK pathway is stimulated, and an increase in GluA1 phosphorylation occurs (Moody et al. 2011). These are important properties of β -AR, as phosphorylation of AMPAR GluA1 is considered to be a key step in the bidirectional modification of hippocampal synaptic plasticity (Lee et al. 2000): when GluA1 remains phosphorylated, memory storage can be facilitated (Hu et al. 2007).

β -AR also regulate PKA and AC (Zhang et al. 2013), two further critical components of hippocampal synaptic plasticity signaling cascades (Muller et al. 1991). Moreover, PKA plays an important role in β -AR-dependent LTP (Gelinás et al. 2007). PKA can itself promote the surface extrasynaptic pool of GluA1 (Oh et al. 2006) that in turn is regulated by NA. LTP can also be facilitated through direct phosphorylation effects of PKA on NMDAR (Chen and Sara 2007; O'Dell et al. 2010). β -AR activation can also inhibit protein phosphatases 1 and 2A to facilitate LTP induction in CA1 mouse slices (Thomas et al. 1996). Furthermore, protein synthesis-dependent L-LTP requires the activation of β -AR (Straube and Frey 2003; Straube et al. 2003a). In addition to β -AR modulation of long-term synaptic plasticity through the regulation of NMDAR and AMPAR, β -AR activation also modulates the processes of synaptic tagging and capture of LTP (see review from O'Dell et al. 2015).

Special Role of the Locus Coeruleus in the Regulation of Hippocampal Synaptic Plasticity

LC activation, in response to arousal or novelty, induces NA release in different hippocampal subfields (Yavich et al. 2005; Lemon et al. 2009). The exploration of a novel object in a hole-board causes a tonic increase in the population spike lasting 50–75 s in the DG (Kitchigina et al. 1997). The highest content of endogenous NA compared with other hippocampal subfields occurs in the DG, which receives the strongest noradrenergic projections from the LC (Loy et al. 1980). Thus, to date, most studies have focused on LC regulation of this hippocampal subfield.

LC activation via glutamate with the goal of triggering NA release in the hippocampus, and most specifically in the DG, has been implemented in diverse in vitro (Harley and Milway 1986) and in vivo studies (Klukowski and Harley 1994; Walling and Harley 2004), and also in anesthetized rats (Reid and Harley 2010; Edison and Harley 2012). This glutamate-induced LC activation led to different results in the perforant path-DG synapse: an immediate short-term potentiation of the population spike in vitro (Harley 1987) and in vivo (Klukowski and Harley 1994), an intermediate population spike potentiation lasting 3 h (Edison and Harley 2012) and a potentiation of the slope of the excitatory postsynaptic potential occurring 24 h after LC activation (Walling

and Harley 2004). Both the LTP of the field excitatory postsynaptic potential, and the short-term potentiation of the population spike in perforant path-DG synapses, were dependent on β -AR activation (Harley and Milway 1986; Walling and Harley 2004). Moreover, β -AR activation was required for LC-induced, protein synthesis-dependent LTP in the DG (Walling and Harley 2004). Another study revealed that pairing LC stimulation with afferent perforant path stimulation induced a potentiation of both excitatory postsynaptic potential and the population spike in anesthetized rats (Reid and Harley 2010).

Interestingly, the medial and lateral perforant path inputs to the DG can be selectively potentiated depending on the interstimulus interval between pairs of utilized path stimulation (Edison and Harley 2012). A further study showed that the repeated pairing of electrical LC stimulation with perforant path stimulation enabled an LTP of the population spike in vivo (Harley et al. 1989). What is interesting here is that β -AR antagonism with propranolol did not block the potentiation, but it did suppress the effect seen by glutamate activation (Harley et al. 1989). Thus, as seen in β -AR-dependent LTP (Straube et al. 2003a), the dependency on β -AR can be overcome with strong repeated afferent stimulation protocols. This may relate to the fact that strong LC activation is likely to induce co-release of dopamine with NA from the LC (Smith and Greene 2012), whereas brief LC stimulation triggers a small DA release in the CA1 region (Lemon et al. 2009), which also influences synaptic plasticity that is enabled by LC activation (Lemon and Manahan-Vaughan 2012).

The LC may play a very particular role in the regulation of hippocampal information encoding through LTD: electrical stimulation of the LC, coupled with test-pulse stimulation of either the Schaffer collaterals or the medial perforant path, results in β -AR-dependent LTD in the CA1 region and DG, respectively. The resultant LTD lasts for <24 h in the CA1 region, and for longer than 24 h in the DG in vivo, reflecting perhaps the direct innervation of the DG by the LC and the higher density of β -AR in this subfield (Loy et al. 1980; Booze et al. 1993; Milner et al. 2000).

β -Adrenergic Receptors and Learning-Facilitated Plasticity

Learning-facilitated plasticity describes the ability of hippocampal synapses to respond with persistent LTP, or LTD, when a learning event is coupled with afferent stimulation that is subthreshold for the induction of lasting plasticity, or coupled with test-pulse stimulation of hippocampal afferents (Manahan-Vaughan and Braunewell 1999; Kemp and Manahan-Vaughan 2004, 2007, 2008b; Goh and Manahan-Vaughan 2013b). The disadvantage of examining robust forms of plasticity that are simply induced by strong afferent activation by means of electrical stimulation is that we do not know how physiological these forms of plasticity are, nor do we know how closely they relate to the putative role of synaptic plasticity in long-term memory. Studies of learning-facilitated plasticity circumvent this dilemma: the types of plasticity induced by afferent stimulation are very weak, or non-existent and the robust forms of LTD or LTP that emerge when these protocols are coupled with learning events, give valuable insight into the role of LTP and LTD in long-term information encoding of spatial experience (Kemp and Manahan-Vaughan 2007). Here, we have observed that LTP is tightly associated with the acquisition of knowledge about new space or spatial change (Kemp and Manahan-Vaughan 2004, 2007), whereas LTD is tightly associated with learning about the specific content details of space. A hierarchy with regard to the

involvement of hippocampal subfields in this process has become evident: LTD in the dentate gyrus and in mf-CA3 synapses is enabled by novel learning about large navigational content (e.g., distal or large items), whereas LTD at AC-CA3 and Schaffer collateral-CA1 synapses is enabled by novel learning about small, subtle content details (such as hidden items or items that can only be detected when the animal is immediately proximal to them) (Manahan-Vaughan and Braunewell 1999; Kemp and Manahan-Vaughan 2004, 2007, 2008b; Goh and Manahan-Vaughan 2012; Hagen and Manahan-Vaughan 2012).

What is striking is that very consistent results have emerged as to the role of β -AR in learning-facilitated plasticity. LTP (>24 h) that is enabled by the learning about novel space, or spatial change, is prevented by antagonism of β -AR. Effects are consistent for learning-facilitated LTP evoked in the CA1, CA3, or DG subfields (Kemp and Manahan-Vaughan 2008a; Hagen and Manahan-Vaughan 2012; Goh and Manahan-Vaughan 2013b). The reinforcement of LTP in the DG by appetitive or aversive stimuli is also mediated by β -AR (Seidenbecher et al. 1997).

Furthermore, LTD that is facilitated by learning about novel spatial content, in the CA3 region and DG, is also tightly dependent upon β -AR and has been reported both in rats and in mice in vivo (Kemp and Manahan-Vaughan 2008a; Hagen and Manahan-Vaughan 2012; Goh and Manahan-Vaughan 2013b). The only exception to this is the CA1 region where, in rats, β -AR antagonism does not block learning-facilitated LTD (Kemp and Manahan-Vaughan 2008a), whereas in mice, it does (Goh and Manahan-Vaughan 2013b).

Taken together, these findings indicate that β -AR are also very important for the regulation of physiologically relevant forms of synaptic plasticity. We propose that NA acting on β -AR plays a decisive role in determining not only whether a novel experience should be encoded, but also in determining how this information is encoded, at the level of LTP and LTD. We believe this relates in turn to the behavioral saliency of the novel experience: very emotive experiences may be encoded by robust LTP (Korz and Frey 2003; Ahmed et al. 2006; Whitlock et al. 2006) that bypass the need for β -AR modulation. Spatial experiences that relate for example, the encoding of new space or of spatial change, may be encoded by LTP (Kemp and Manahan-Vaughan 2004, 2007). Strong phasic activity of the LC, such as during periods of strong wakefulness or anticipation (Bouret and Sara 2005), may predispose hippocampal synapses to encoding of this kind that is mediated by β -AR. During periods of tonic LC activity, that relate to increased vigilance related to a novel experience, a higher degree of encoding of content details of this experience will be enabled by hippocampal LTD (Kemp and Manahan-Vaughan 2007). This is strongly supported by NA acting on β -AR (Kemp and Manahan-Vaughan 2008a; Lemon et al. 2009; Hansen and Manahan-Vaughan 2015b), whereby the degree and specificity of this form of content encoding ("distal" content encoding in the DG, "proximal" content encoding in, e.g., the CA1 region) are enabled by LTD within the different hippocampal subfields (Kemp and Manahan-Vaughan 2007; Hagen and Manahan-Vaughan 2012) that is in turn modulated by β -AR (Kemp and Manahan-Vaughan 2008a; Hagen and Manahan-Vaughan 2012; Hansen and Manahan-Vaughan 2015b).

Role of β -Adrenergic Receptor Activity in Hippocampus-Dependent Learning

Given its significance for learning-facilitated LTD, and the plasticity-related forms of learning detailed in the earlier sections, it is not surprising that substantial evidence exists to support a

role for other forms or aspects of β-AR hippocampus-dependent memory. For example, β-AR-blockade leads to deficits in spatial reference memory in the water maze task (Ji et al. 2003b) and in contextual fear memory (Ji et al. 2003a). Furthermore, LC activation leads to a β-AR-dependent enhancement of episodic-like memory in rats that is coupled to enhancements of LTD (Lemon et al. 2009). Differentiated roles for β₁-AR in short-term memory and β₂-AR in long-term memory and memory consolidation have also been proposed (Gibbs and Summers 2002). Other hippocampus-dependent tasks, such as extinction learning in a spatial context (André et al. 2015), memory retrieval (Thomas 2015), or reinstatement of memories may also be mediated by activation of β-AR: exposure to a novel environment within 1 h prior to or after extinction learning results in reduced fear reinstatement in rodents. This effect is prevented by a β-AR antagonist (Liu et al. 2015), whereas β-AR activation by NA induces reinstatement of previously extinguished fear memories (Morris et al. 2005).

The formation and maintenance of memory are strongly influenced by emotional experience. It is frequently the case that memories, obtained during strong emotional events, are more salient and persistent. Furthermore, short-term memory, acquired in the hippocampus, is vulnerable to interference. But consolidation, over time, strengthens this memory, making it persistent and thus less vulnerable (McGaugh 2000). Activation of emotional and arousal systems can affect memory encoding, leading to the strengthening of acquired information (Cahill et al. 1994). The noradrenergic system is particularly influential in this regard (Harley 1991; Bouret and Sara 2005). It is activated by novel stimuli or reinforcement, accomplished by bursting

responses of LC cells (Sara et al. 1994). Furthermore, emotional states such as pain, fear, or arousal can have enhancing effects on memory by activating the noradrenergic system (Rochford and Dawes 1993; Debiec and Ledoux 2004).

A memory can be divided into different phases. Initially, a new memory has to be learned (acquisition). Subsequently consolidation occurs, in which a memory is strengthened and retained, if salient enough. Lastly, a stored memory must be retrievable. During all these processes, neuromodulators such as NA play a crucial role (Sara 2000, 2009, 2010). In vitro studies have shown that NA is an important component in hippocampus-dependent contextual (Murchison et al. 2011) and emotional memory retrieval (Schutsky et al. 2011). β-AR are particularly important for these processes (Table 1). Stimulation of the LC facilitates memory retrieval via a β-AR-dependent mechanism (Devauges and Sara 1991) and enhances episodic-like memory in rats (Lemon et al. 2009). Furthermore, NA-deficient dopamine β-hydroxylase null mutant (Dbh^{-/-}) mice that display impaired contextual and spatial memory retrieval show recovery of these deficits following β-AR agonist treatment (Murchison et al. 2004). Interestingly, other studies have shown that β-AR antagonism disrupts the consolidation of episodic memory when the antagonist is applied during a narrow time window before memory acquisition (Cahill et al. 1994; McGaugh 2000) and that it impairs consolidation and reconsolidation during an inhibitory avoidance task in rats (Liang et al. 1986; Przybylski et al. 1999). Thus, not only the timing and intensity of LC activation, but also the nature of the behavioral experience may determine to what extent β-AR contribute to memory processes.

Table 1 Effects of β-AR antagonists and agonists on synaptic plasticity in vitro

Drug/knockout	Subtype	Subregion	Effect on plasticity	References
Isoproterenol	β ₁ , β ₂	CA1	Induction of LTP (>40 min)	Thomas et al. (1996)
			Blocks depotentiation	Thomas et al. (1996)
			STP strengthened	Winder et al. (1999); Gelinas et al. (2008)
			No effect on LTP (>2 h)	Gelinas et al. (2008)
			Enhances E-LTP and L-LTP	Hsu et al. (2002)
			Induction of TPS-LTP (1 h)	Giovannini et al. (2001)
			Induction of TPS-LTP (30 min)	Brown et al. (2000)
		no effect on induction (1 train, 5 Hz)	Watabe et al. (2000)	
		Enhances induction of LTP	Cohen et al. (1999); Swanson-Park (1999)	
		LTP enhanced	Tenorio et al. (2010)	
		LTP after low-frequency stimulation	Reis et al. (2005)	
		LTP induction enhanced	Moody et al. (1998)	
		LTP enhanced (1 h)	Katsuki et al. (1997); Winder et al. (1999)	
		LTD blocked	Katsuki et al. (1997)	
CA3	No effect on NA-induced LTP	Izumi and Zorumski (1999)		
	LTP enhanced (1 h)	Li et al. (2013)		
	STP strengthened	Huang and Kandel (1996)		
Propranolol	β ₁ , β ₂	DG	Blocked LTP in LPP and MPP	Moody et al. (1998)
			LTP blocked	Bramham et al. (1997)
		CA1	No effect on LTP (>3 h)	Swanson-Park (1999)
			Dose-dependently blocks LTP	Swanson-Park (1999)
		CA3	LTP blocked	Li et al. (2013)
			No effect on PS of LTP	Connor et al. (2011)
			Blocks E-LTP and L-LTP	Kobayashi et al. (1997)
R(AB) + Isoproterenol	β ₁ , β ₂	CA1	LTP (3 h) blocked	Huang and Kandel (1996)
			LTP enhanced	Huang and Kandel (1996)
β ₁ , β ₂	β ₁ , β ₂	CA1	LTP impaired	Gelinas et al. (2008)
				Winder et al. (1999)

Table 2 Effects of β -AR antagonists and agonists on synaptic plasticity in vivo

Drug/ knockout	Subtype	Subregion	Effect on plasticity	References
Isoproterenol	$\beta 1, \beta 2$	CA1	No effect on LTP (>24 h), STP and LTD (>24 h) STD strengthened STP strengthened No effect on learning-facilitated LTD	Kemp and Manahan-Vaughan (2008a) ; Connor et al. (2011) Kemp and Manahan-Vaughan (2008a) Goh and Manahan-Vaughan (2013b) Ji et al. (2003a) Kemp and Manahan-Vaughan (2008a)
		CA3	STP strengthened	Hagena and Manahan-Vaughan (2012)
		DG	STP strengthened	Straube et al. (2003a) Hansen and Manahan-Vaughan (2015a) Hansen and Manahan-Vaughan (2015b)
Propranolol	$\beta 1, \beta 2$	CA1	LTP (>24 h) blocked	Kemp and Manahan-Vaughan (2008a)
			LTD (>24 h) no effect	Kemp and Manahan-Vaughan (2008a)
			STD no effect	Goh and Manahan-Vaughan (2013b)
		CA3	Learning-facilitated LTP blocked	Kemp and Manahan-Vaughan (2008a)
			Learning-facilitated LTD blocked	Kemp and Manahan-Vaughan (2008a) ; Goh and Manahan-Vaughan (2013b)
			No effect on LTP (>24 h), STP, LTD (>24 h) and STD	Hagena and Manahan-Vaughan (2012)
DG	Learning-facilitated LTP blocked	Hagena and Manahan-Vaughan (2012)		
	Learning-facilitated LTD blocked	Hagena and Manahan-Vaughan (2012)		
	No effect on LTP LTP blocked LTD (>24 h) blocked Learning-facilitated LTP blocked	Straube and Frey (2003) Hansen and Manahan-Vaughan (2015a) Hansen and Manahan-Vaughan (2015b) Straube et al. (2003a) , Hansen and Manahan-Vaughan (2015a)		

β -Adrenergic Receptors and Arousal

It has been suggested that phasic activation of LC neurons that occurs in conjunction with cognitive (attentional) shifts supports dynamic reorganization of target neural networks, permitting rapid behavioral adaptation to changing environmental information. This would be reflected in rapid network plasticity, and a network reset, that serves to support the creation of new functional networks ([Bouret and Sara 2005](#)). Empirical evidence for this derives from in vivo observations that LC activation, resulting in NA release that acts on β -AR, causes a change in network oscillations in the form of a reduction of theta power that accompanies the triggering of hippocampal LTD and the enhancement of episodic-like memory in rats ([Lemon et al. 2009](#)). We postulate that this modulation of hippocampal network oscillations may reflect a means by which salient information is distinguished by the hippocampus for subsequent synaptic processing ([Lemon et al. 2009](#)). This assumption is also in line with [Kety's \(1970\)](#) interpretation that NA release in the brain changes signal-to-noise ratios "suppressing most, but permitting or even accentuating activity in those [synapses] that are transmitting novel or significant stimuli." We furthermore postulate that it is the graded release of NA acting on β -AR, based on the degree of arousal that determines the direction of change of synaptic strength in the hippocampus and the relative sensitivity of synaptic plasticity to β -AR in the hippocampal subfields.

This assumption is based on observations that the sensitivity of the hippocampal subfields to regulation of persistent forms of synaptic plasticity by β -AR in vivo is in the order of DG > CA3 > CA1 ([Kemp and Manahan-Vaughan 2008a](#); [Lemon et al. 2009](#); [Hagena and Manahan-Vaughan 2012](#); [Goh and Manahan-Vaughan 2013b](#); [Hansen and Manahan-Vaughan 2015b](#)) (Table 2). Thus, for example, LC stimulation that releases NA onto β -AR, triggers LTD in the DG that endures for longer periods than LTD triggered under

the same conditions in the CA1 region ([Lemon et al. 2009](#); [Hansen and Manahan-Vaughan 2015b](#)). This observation, coupled with the fact that the LC innervates the DG strongly, suggests that moderate arousal states that provoke NA release in the hippocampus may influence DG information processing but not CA3 or CA1 information processing. This is particularly interesting in the context of learning-facilitated LTD. In the dentate gyrus, large (distal) landmark cues facilitate LTD, whereas this type of novel spatial experience does not promote LTD in the CA1 region ([Kemp and Manahan-Vaughan 2008b](#)). In contrast, small proximally located spatial features promote LTD in the CA1 region but have no impact on LTD in the DG ([Kemp and Manahan-Vaughan 2008b](#)). Intuitively, one would expect that when one first explores a novel environment, it is the distal, navigational, and orientational information that will be learned first. More subtle aspects of the environment, such as subtle local details, will be learned subsequently and will depend on the degree of attention paid to the environment. This may be mediated by a differentiated encoding by LTD in the DG, CA1 (and CA3 region: [[Hagena and Manahan-Vaughan 2012](#)]). NA release acting on β -AR in hippocampal subfields may drive this differentiation in encoding by LTD, based on a graded relative sensitivity to NA that arises from differences in receptor distribution and LC innervation. The locus coeruleus is ideally placed to support this kind of graded encoding ([Sara and Bouret 2012](#)), based on evidence that the duration and intensity of NA release from the LC is determined by the saliency of the novel experience ([Aston-Jones and Bloom 1981](#); [Grant et al. 1988](#); [Sara et al. 1994](#); [Hervé-Minvielle and Sara 1995](#); [Vankov et al. 1995](#)).

Conclusions: β -Adrenergic Receptors Determine the Content and Persistency of Synaptic Information Storage

Based on studies that describe the role of β -AR in hippocampal synaptic plasticity, it is becoming clear that activation of β -AR

promotes long-term modifications of synaptic efficacy in hippocampal subfields, and that these changes may underlie the impact of this receptor on learning and memory processes.

We propose three levels of β -AR-mediated control of synaptic information storage following NA release from the LC:

1. During strong tonic release of NA from the LC (Aston-Jones and Bloom 1981), excitability thresholds in the hippocampus become elevated (Lacaille and Harley 1985; Stanton and Sarvey 1985; Harley 1991), this predisposes the hippocampus toward the expression of synaptic plasticity, and under these circumstances, information encoding by means of LTP is particularly promoted by NA acting on β -AR (Hansen and Manahan-Vaughan 2015a; Lethbridge et al. 2014). This condition could be anticipated to occur during periods of strong wakefulness and sustained vigilance (Bouret and Sara 2004).
2. During tonic LC firing, that is triggered by discrete episodes of novel experience (Grant et al. 1988; Sara et al. 1994; Hervé-Minvielle and Sara 1995; Vankov et al. 1995), NA acting on β -AR selectively facilitates synaptic information encoding by means of LTD (Lemon et al. 2009; Lemon and Manahan-Vaughan 2012; Hansen and Manahan-Vaughan 2015b), to the disadvantage of encoding via LTP (Hansen and Manahan-Vaughan 2015a). We believe that this comprises a cellular mechanism through which attention to and retention of the precise details of a novel experience are encoded.
3. NA released from the LC can continue to modulate neural activity for hours after the tonic activity has ceased (Walling and Harley 2004). Recently, it has been proposed that local “hot-spots” of NA release in discrete synaptic networks can occur (Mather et al. 2015). We propose that this may comprise a mechanism whereby NA acting on β -AR can serve to support consolidation (Gibbs and Summers 2002) of a recently encoded experience.

In summary, we postulate that β -AR comprise a key molecular mechanism for the determination of the nature, content, and persistency of synaptic information content. This synaptic “choreography” is enabled by the state-dependent patterns of NA release that are mediated by the LC, that act in turn on hippocampal β -AR.

Funding

This work is supported by a grant from the German research foundation (Deutsche Forschungsgemeinschaft, www.dfg.de) to D.M.-V. (Ma1843/6-2). Funding to pay the Open Access publication charges for this article was provided by the German Research Foundation.

Notes

Conflict of Interest: None declared.

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