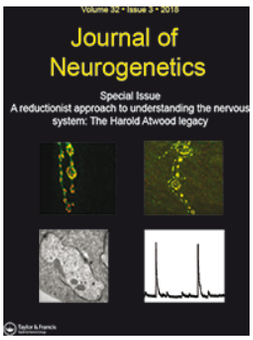

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REVIEW ARTICLE

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Noradrenergic gating of long-lasting synaptic potentiation in the hippocampus: from neurobiology to translational biomedicine

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ABSTRACT

Altered synaptic strength underlies information storage in neural circuits. Neuromodulatory transmitters such as norepinephrine (NE) facilitate long-lasting synaptic plasticity by recruiting and modifying multiple molecular elements of synaptic signaling, including specific transmitter receptors, intracellular protein kinases, and translation initiation. NE regulates multiple brain functions such as attention, perception, arousal, sleep, learning, and memory. The mammalian hippocampus receives noradrenergic innervation and hippocampal neurons express β-adrenergic receptors (β-ARs), which bind NE and are critical for gating the induction of long-lasting forms of synaptic potentiation. These forms of long-term potentiation (LTP) are believed to importantly contribute to long-term storage of spatial and contextual memories in neural circuits. In this article, in honor of Prof. Harold Atwood, we review the contributions of β-ARs towards gating the expression of protein synthesis-dependent, long-lasting hippocampal LTP. We focus on the roles of β-ARs in modifying ion channels, glutamatergic AMPA receptors, and translation initiation factors during LTP. We discuss prospective research strategies that may lead to increased understanding of the roles of NE in regulating neural circuit physiology; these may uncover novel therapies for treatment of specific neurological disorders linked to aberrant circuit activity and dysfunctional noradrenergic synaptic transmission.

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Introduction

Synaptic plasticity is a fundamental property of nervous system function and it is critical for many processes, including associative learning and long-term memory (Kandel, 2001; Martin, Grimwood, & Morris, 2000). There are multiple forms of synaptic plasticity. Elucidating the mechanisms that govern the organization and re-structuring of synapses and neural circuits will improve our understanding of how the brain processes and stores information. In the mammalian hippocampus, a brain structure critical for making new memories, one form of synaptic plasticity, called 'long-term potentiation' (LTP), has been linked to spatial and contextual learning and memory (reviewed by Martin *et al.*, 2000). LTP is an activity-dependent increase in synaptic strength that can persist for several hours in isolated brain slices and up to a year in intact lab animals (Abraham, Logan, Greenwood, & Dragunow, 2002; Andersen, Sundberg, Sveen, & Wigstrom, 1977). Many key signaling requirements for LTP (e.g. NMDA receptors, protein kinase-A, calcium-dependent protein kinases) mirror those needed for memory storage in the mammalian brain (reviewed by O'Dell, Connor, Gelinas, & Nguyen, 2010, and O'Dell, Connor, Guglietta, & Nguyen, 2015). Manipulations that modify LTP also alter memory expression (reviewed in Martin *et al.*, 2000). Importantly, LTP-like changes in synaptic efficacy can occur in behaving animals as they learn (Whitlock, Heynen, Shuler, & Bear, 2006). As such, LTP is a leading candidate synaptic mechanism for memory storage in the mammalian brain.

Neuromodulatory transmitters can significantly alter the properties of neurons at cellular and network levels. Norepinephrine (NE) is a key neuromodulator released by noradrenergic fibers that originate mainly in the locus coeruleus (LC). These project widely throughout the forebrain, with dense innervation of the hippocampus, amygdala, and thalamus (Sara, 2009). Noradrenergic synaptic connections, especially within the hippocampus, can strongly modulate synaptic strength and neural network physiology, leading to modifications of cognitive functions (reviewed by Gelinas & Nguyen, 2007, and O'Dell *et al.*, 2010). Indeed, hippocampal memory is impaired after reduction of NE or after blockade of beta-adrenergic receptors (β-ARs) that bind NE (Ji, Wang, & Li, 2003a; Ji, Zhang, & Li, 2003b; Murchison *et al.*, 2004). A β-AR blocker, propranolol, inhibits spatial memory (Ji, Zhang, *et al.*, 2003b) and long-term (but not short-term) contextual fear memory (Ji, Wang, *et al.*, 2003a) when infused into the hippocampus of rodents (but see Debiec & Ledoux, 2004; Murchison *et al.*, 2004; Qi, Zhu, Zhang, & Li, 2008 for evidence to the contrary).

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Conversely, LC stimulation or intrahippocampal injection of NE promotes retrieval of associative and spatial memories, and this requires β-AR activation (Devauges & Sara, 1991; Przybyslawski, Roullet, & Sara, 1999; Sara, Roullet, & Przybyslawski, 1999). Hippocampal infusion of isoproterenol (ISO), a β-AR agonist, restored memory in NE-knockout mice (Murchison *et al*., 2004). In contrast, alpha-adrenoceptors mediate the inhibitory effects of NE on hippocampal neurons and memory (reviewed by Gelinas & Nguyen, 2007). Thus, to understand how NE enhances synaptic plasticity and memory processing, attention needs to be paid primarily to β-ARs. One plausible mechanism by which memory enhancement may occur following engagement of the noradrenergic system is the boosting of long-lasting forms of synaptic plasticity. In this review, we focus on β-ARs and the mechanisms by which they gate long-lasting forms of LTP in the hippocampus.

β-adrenergic receptors facilitate long-lasting hippocampal synaptic plasticity

NE acts through G protein-coupled receptors broadly classified as α1-, α2-, β1-, and β2-adrenergic receptors (reviewed by Gelinas & Nguyen, 2007). Hippocampal pyramidal cells and dentate gyrus granule cells express all four receptor subtypes (Guo & Li, 2007; Hillman, Knudson, Carr, Doze, & Porter, 2005; Nicholas, Pieribone, & Hokfelt, 1993). β-ARs signal through activation of Gs-type G proteins, followed by stimulation of adenylyl cyclase and increased production of intracellular cAMP. Cyclic-AMP activates cAMP-dependent protein kinase (PKA) and, indirectly, extracellular signal-regulated protein kinase (ERK) through Rap1 (a GTPase) and B-Raf (a protein kinase) (Schmitt & Stork, 2000). PKA and ERK both have critical roles in long-term memory formation and long-term synaptic plasticity in numerous species and they putatively have key roles in the memory enhancing effects of β-AR activation (Barros *et al*., 1999; Kandel, 2001; Nguyen & Woo, 2003; Sweatt, 2004).

NE acting through β-ARs not only enhances memory formation but also has powerful effects on the induction of LTP at excitatory synapses throughout the hippocampus (reviewed by O'Dell *et al*., 2010). The effects of noradrenergic receptor activation on LTP induction have been extensively studied at Schaeffer collateral fiber synapses onto pyramidal cells in the CA1 region of hippocampal slices. At these synapses, repeated trains of high-frequency stimulation (HFS; usually 3–4 trains of 100 Hz stimulation) induce a translation- and transcription-dependent potentiation of synaptic strength that can last for 3 or more hours (Abraham & Williams, 2008; Frey, Krug, Reymann, & Matthies, 1988; Kelleher, Govindarajan, & Tonegawa, 2004; Nguyen, Abel, & Kandel, 1994; Stanton & Sarvey, 1984; Sutton & Schuman, 2006;). This translation/transcription-dependent form of LTP, often called 'L-LTP', is correlated with the formation of hippocampus-dependent, enduring memories (Abel *et al*., 1997; Bourtchouladze *et al*., 1998; Costa-Mattioli, Sossin, Klann, & Sonenberg, 2009; Costa-Mattioli *et al*., 2007; Schafe, Nadel, Sullivan, Harris, & LeDoux, 1999; Scharf *et al*., 2002). Less robust HFS protocols, such as a single train of 100 Hz stimulation, typically induce shorter-lasting potentiation (lasting approximately 1–2 h) that does not require translation or transcription.

Note that noradrenergic receptor activation is not required for the induction of LTP by strong stimulation protocols (Murchison *et al*., 2004; Swanson-Park *et al*., 1999). However, activation of β-ARs by a beta-receptor agonist potently facilitates the induction of LTP when applied in conjunction with weaker patterns of synaptic stimulation. A seminal study by Thomas, Moody, Makhinson, & O'Dell (1996) demonstrated that β-AR activation enables the induction of LTP by theta-pulse stimulation (TPS; 150–900 stimulation pulses delivered at 5–10 Hz), a pattern of synaptic stimulation that alone, in the absence of exogenous agonists, does not potentiate synaptic transmission. This finding has been observed in several subsequent studies (see, e.g. Brown *et al*., 2000; Havekes *et al*., 2012; Katsuki, Izumi, & Zorumski, 1997; Moody, Thomas, Makhinson, & O'Dell, 1998; Qian *et al*., 2012; Winder *et al*., 1999). The induction of LTP by spike-timing dependent plasticity protocols, where excitatory postsynaptic potentials elicited by presynaptic fiber stimulation are paired with postsynaptic action potentials evoked by current injection through an intracellular recording electrode, was also enhanced by β-AR activation (Lin, Min, Chiu, & Yang, 2003; Makino, Johnson, Yu, Takamiya, & Huganir, 2011). Additionally, β-AR activation by pairing ISO with one 100 Hz train of HFS enables the induction of protein synthesis-dependent LTP (referred to henceforth as 'β-LTP') (Gelinas & Nguyen, 2005; Gelinas *et al*. 2007; Ma, Tzavaras, Tsokas, Landau, & Blitzer, 2011; see below for further discussion of translation-dependent β-LTP).

The overall picture that emerges is that hippocampal β-AR activation lowers the threshold for LTP induction, enabling the induction of β-LTP by stimulus frequencies that, without β-AR activation, do not potentiate synaptic transmission. The relative contribution of β1 vs. β2-ARs in the enhancement of LTP induction by NE and ISO is unclear, however. Winder *et al*. (1999) found that induction of LTP by TPS in the presence of ISO was impaired in β1-AR, but not in β2-AR, null mutant mice, indicating a key role for β1-ARs. In contrast, a subsequent study found that the enhancement of TPS-induced LTP by ISO was impaired in both β1-AR and β2-AR knockout mice (Qian *et al*., 2012). Moreover, induction of LTP by TPS in the presence of ISO in hippocampal slices from wildtype mice was blocked by a selective β2-AR antagonist, ICI-118551, whereas a β1-AR-selective antagonist, CGP-20712, had no effect (Qian *et al*., 2012). The different outcomes reported by Winder *et al*. (1999) and Qian *et al*. (2012) may, in part, be derived from strain differences in the mice used for these experiments: the knockouts of Winder *et al*. (1999) were primarily on an FVL strain background, whereas those used by Qian *et al*. (2012) were backcrossed to C57BL/6. Genetic backgrounds of inbred mice are known to significantly influence synaptic plasticity in the hippocampus (Jones,

Peckham, Errington, Bliss, & Routtenberg, 2001; Nguyen, 2006; Nguyen, Duffy, & Young, 2000).

Regulation of protein phosphatases and voltage-dependent ion channels during β-LTP

β-AR activation regulates signaling events underlying LTP in two distinct ways. There are direct effects mediated by phosphorylation of ligand- and voltage-gated ion channels involved in the induction and expression of LTP, as well as regulation of proteins responsible for controlling the synthesis of proteins needed for long-term maintenance of LTP. Importantly, one of these direct downstream targets of β-AR signaling is inhibitor-1, a protein that controls activity of protein phosphatase-1 (Brown *et al*., 2000) When phosphorylated by PKA, inhibitor-1 binds to, and suppresses, protein phosphatase-1. This facilitates activation of protein kinases, such as CaMKII, required for induction of LTP (Blitzer *et al*., 1998). This action is analogous for removing a phosphatase-mediated 'brake' on LTP induction, providing a way in which β-AR activation can act more globally to enhance LTP by facilitating protein phosphorylation mediated by multiple serine/threonine protein kinases. Consistent with this notion, bath application of membrane permeable inhibitors of protein phosphatase-1 or injection of phosphorylated inhibitor-1 into CA1 pyramidal cells mimics the ability of β-AR activation to enable the induction of LTP by TPS (Brown *et al*., 2000; Thomas *et al*., 1996).

Lower frequencies of presynaptic stimulation may induce LTP through postsynaptic complex spike bursting (Thomas, Watabe, Moody, Makhinson, & O'Dell, 1998) in CA1 pyramidal cells; these spikes may be back-propagated into dendrites to promote NMDA receptor activation. This is limited by activation of A-type potassium channels further away from the soma. However, ERK activation downstream of β-ARs phosphorylates these channels to reduce their activation, thereby facilitating spike propagation into dendrites (Hoffman, Baillie, MacKenzie, Yarwood, & Houslay, 1999; Yuan, Adams, Swank, Sweatt, & Johnston, 2002; see also review by Hoffman & Johnston, 1999). Indeed, β-AR activation increases complex spiking in CA1 pyramidal cells during low-frequency presynaptic stimulation in an ERK-dependent manner (Gelinas *et al*., 2008; Winder *et al*., 1999). Additionally, dendritic small conductance, calcium-activated potassium channels (SK2) are reduced in expression in dendritic spines of amygdalar neurons following activation of β-ARs (Faber *et al*., 2008; Lin, Lujan, Watanabe, Adelman, & Maylie, 2008; Ren *et al*,. 2006). Thus, enhancement of LTP induced by β-AR activation during low-frequency stimulation is gated by suppression of specific voltage-dependent potassium channels which serves to promote dendritic propagation of spikes.

Modulation of AMPA receptors by β-ARs: metaplasticity and receptor trafficking

In addition to regulation of voltage-activated channels, β-ARs can boost LTP by modulation of glutamatergic ion channels. The vast majority (>80%) of AMPA receptors (AMPARs) in the hippocampus are heteromeric, containing GluR1 and GluR2 subunits (Lu *et al*., 2009; Traynelis *et al*., 2010; Wenthold, Petralia, Blahos, & Niedzielski, 1996). PKA phosphorylates serine-845 in the C-terminal domain of GluR1; this phosphorylation regulates channel gating (Banke *et al*., 2000; Jenkins *et al*., 2014; Roche, O'Brien, Mammen, Bernhardt, & Huganir, 1996) and receptor trafficking (Ehlers, 2000; Man, Sekine-Ozawa, & Huganir, 2007). This also increases insertion of AMPARs at extrasynaptic sites, where the receptors are primed for synaptic insertion during induction of LTP (Esteban *et al*., 2003; Oh, Derkach, Guire, & Soderling, 2006). Interestingly, β-AR activation triggers phosphorylation of serine-845 (Gray, Guglietta, Khakh, & O'Dell, 2014; Moody *et al*., 2011; Tenorio *et al*., 2010; Vanhoose, Clements, & Winder, 2006; Vanhoose & Winder, 2003). This may be facilitated by the existence of molecular complexes consisting of GluR1-containing AMPARs, β2-ARs, A-kinase anchoring proteins (AKAPs), PKA, and adenylyl cyclase (Colledge *et al*., 2000; Joiner *et al*., 2010). Genetic disruption of AKAP12 (Havekes *et al*., 2012) or AKAP5 (Zhang *et al*., 2013) impairs LTP induction by theta-pulse stimulation paired with isoproterenol These multimeric complexes clearly assist in mediating rapid, local AMPAR phosphorylation after β-AR activation, likely by providing a 'node' for directed targeting of PKA and other molecules so that β-AR agonists may recruit signaling in a spatially focused manner.

Experiments using genetically-modified mice with 'knock-in' mutations that disrupt GluR1 phosphorylation, have provided some of the most convincing proof implicating AMPAR modulation in mechanisms underlying β-LTP. LTP induction in CA1 by theta-pulse stimulation in the presence of NE is blocked in mutant mice in which serine-845 and serine-831 (a CaMKII/PKC phosphorylation site) had been mutated to non-phosphorylatable alanines (Hu *et al*., 2007). This manipulation also disrupted epinephrine-induced contextual fear learning (Hu *et al*., 2007). Enhanced memory following arousal thus appears to also critically depend on AMPAR phosphorylation. β-AR facilitation of LTP induction in pyramidal neurons of visual cortex (Seol *et al*., 2007) and in area CA1 (Qian *et al*., 2012) is also abolished following specific mutation of the GluR1 serine-845 site. Occlusion of β-AR-mediated LTP also occurred in mutants where serine-845 and -831were replaced by aspartate to mimic phosphorylation (Makino *et al*., 2011).

Activation of β-ARs can alter the state of a synapse so that its responses to future stimulation may be modified, by a process known as 'metaplasticity' (reviewed by Abraham, 2008). It is noteworthy that LTP enhancement by β-AR activation can persist long after the brief exposure to β-AR agonists had ended (Hu *et al*., 2007; Seol *et al*., 2007; Tenorio *et al*., 2010). Increased excitability and boosted AMPAR phosphorylation may persist for an hour or more (Dunwiddie, Taylor, Heginbotham, & Proctor, 1992; Tenorio *et al*., 2010; Vanhoose & Winder, 2003). However, β-AR regulation of translation may also play key roles in this form of metaplasticity. Weaker stimulation elicits long-lasting LTP

when delivered 1 h after transient activation of β-ARs (Tenorio *et al.*, 2010), and this was blocked by application of inhibitors of translation during β-AR activation, but not when the inhibitors were applied during electrical stimulation delivered 1 h after β-ARs were activated. Thus, increased translation triggered by β-AR activation may 'prime' synapses for future long-lasting plasticity. There is evidence that translation of mRNAs encoding GluR1/GluR2 subunits is boosted by NE during this form of metaplastic enhancement of LTP (Maity, Rah, Sonenberg, Gkogkas, & Nguyen, 2015). Thus, increased synthesis of GluR1 subunits for maintaining persistent potentiation likely occurs, under some conditions, in addition to phosphorylation-triggered trafficking and insertion of AMPARs following β-AR activation by either isoproterenol or by the naturally-occurring transmitter, NE.

β-ARs gate protein synthesis-dependent LTP by regulating translation initiation

Although β-AR activation engages signaling cascades that lead to early phases of LTP maintenance, β-ARs can still enhance the induction of long-lasting, protein synthesis-dependent LTP by modest high-frequency synaptic stimulation and by TPS (Gelinas *et al.*, 2007; Gelinas & Nguyen, 2005; Ma *et al.*, 2011). This observation highlights the important idea that regulation of translation may likely be modulated by β-AR activation to gate the expression of long-lasting β-LTP.

One important process where various signals and transmitters can act to regulate protein synthesis is at the level of translation initiation, a rate-limiting step in translation of many species of mRNA. Here, different protein kinases act to phosphorylate eukaryotic initiation factors (eIFs) involved in the assembly of translation initiation complexes that promote mRNA binding to ribosomal proteins (Costa-Mattioli *et al.*, 2009). For example, two key protein kinases, extracellular signal-regulated protein kinase (ERK) and mammalian target of rapamycin (mTOR), play an important role in formation of the eukaryotic initiation factor 4F (eIF4F) complex (Gelinas *et al.*, 2007; Kelleher, Govindarajan, & Tonegawa, 2004; Klann, Antion, Banko, & Hou, 2004; Tsokas, Ma, Iyengar, Landau, & Blitzer, 2007). The eIF4F initiation complex is assembled from the initiation factors eIF4A, 4E, and 4 G (Figure 1). In the basal state, formation of eIF4F is restrained by binding of eIF4E to the inhibitory protein, 4E-binding protein (4E-BP) (Banko *et al.*, 2005). Phosphorylation of 4E-BP by mTOR triggers the release of eIF4E, which can then associate with eIF4G and form the eIF4F complex (Figure 1). In addition, ERK phosphorylates and activates the protein kinase, Mnk1 (MAPK signal-integrating kinase-1), which in turn phosphorylates 4E to further enhance translation.

Importantly, several of these steps are known to be involved in activity-dependent changes in protein synthesis involved in L-LTP (for reviews see Kelleher *et al.*, 2004, and Klann *et al.*, 2004). Blocking 4E binding to 4G disrupts consolidation of associative fear memory (Hoeffer *et al.*, 2011) and impairs translation-dependent LTP (Hoeffer *et al.*, 2013). These same sites of regulation also have a crucial role in the enhancement of L-LTP induction by β-AR activation (Figure 1). The induction of L-LTP by weaker, more modest patterns of HFS delivered in the presence of ISO was blocked by inhibitors of ERK and mTOR and was associated with increased phosphorylation of the Mnk1 substrate, eIF4E, and the mTOR substrate, p70-S6 kinase (Gelinas *et al.*, 2007; Ma *et al.*, 2011). Moreover, β-AR activation also enabled activity-dependent increases in 4E-BP phosphorylation, as well as increases in eIF4F complex formation (Gelinas *et al.*, 2007). Interestingly, ISO induced a robust increase in dendritic levels of phosphorylated 4E-BP in hippocampal pyramidal cells (Gelinas *et al.*, 2007), suggesting that β-AR regulates activity-dependent changes in local dendritic protein synthesis.

The LTP-enhancing effects of β-AR activation persist for long periods of time after transient β-AR activation (Hu *et al.*, 2007; Seol *et al.*, 2007; Tenorio *et al.*, 2010). This suggests that β-AR activation induces a form of metaplasticity (Abraham, 2008; Abraham & Bear, 1996) that converts synapses into a long-lasting, highly plastic state. Transient β-AR activation increases neuronal excitability and elevates AMPAR phosphorylation for an hour or more (Dunwiddie *et al.*, 1992; Tenorio *et al.*, 2010; Vanhoose & Winder, 2003), suggesting that persistent down-regulation of potassium channels and/or changes in AMPAR trafficking might be involved. However, β-AR modulation of protein synthesis is likely to have a central role in this form of metaplasticity. For example, weak high-frequency stimulation induces L-LTP even when delivered 1 h after transient activation of β-ARs (Tenorio *et al.*, 2010). Strikingly, the metaplastic enhancement of LTP was blocked when protein synthesis inhibitors were applied during β-AR activation but not when protein synthesis inhibitors were applied during HFS delivered one hour after β-AR activation. These findings are consistent with the induction of a 'silent' (i.e. ISO application does not have any lasting effect on baseline synaptic transmission) up-regulation of translation triggered by β-ARs that primes synapses for future plasticity.

It remains to be determined which proteins are up-regulated during β-AR-mediated metaplasticity. However, a study by Maity *et al.* (2015), using pre-application of NE instead of ISO to induce long-lasting metaplasticity of LTP and polysome profiling to assess translation rates of mRNAs, showed that translation of mRNAs encoding GluR1 and GluR2 was boosted during induction of enhanced LTP. A translation inhibitor, cycloheximide, and a β-AR blocker, propranolol, both inhibited the metaplasticity and prevented the increase in mRNA translation rates (Maity *et al.*, 2015). This reveals an intriguing model, in which the translation-dependence of β-LTP may be reflected, in part, by increased synthesis of AMPAR subunits, the cell surface expression of which was increased in a protein synthesis-dependent manner during β-LTP (Tenorio *et al.*, 2010). Given that the endogenous β-AR ligand, NE, is secreted during novelty, arousal and spatial exploration (Sara, 2009), the enduring reduction in the threshold for L-LTP induction triggered by

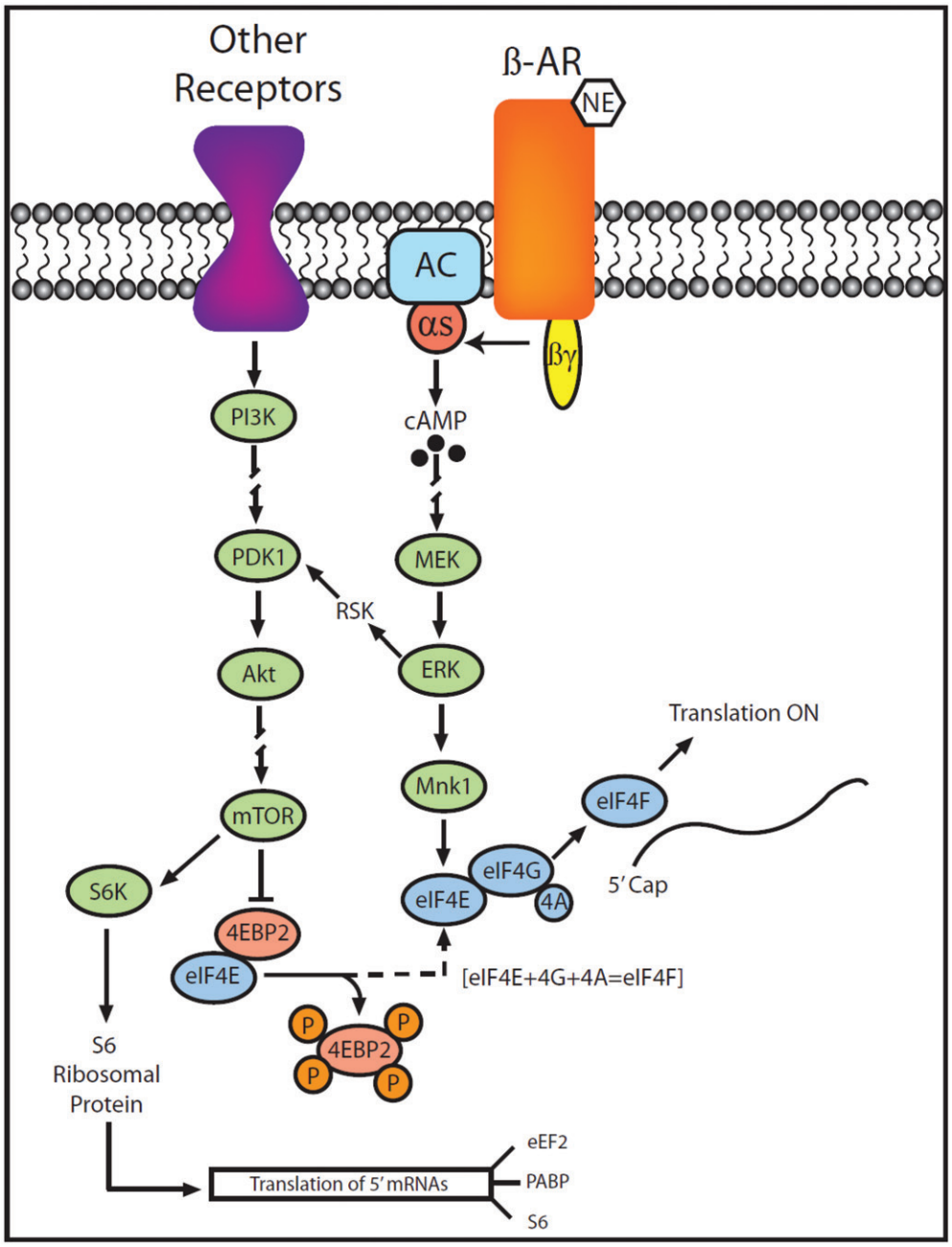

Figure 1. Translational control by ERK and mTOR. Activation of β-ARs during synaptic stimulation promotes translation initiation through ERK and mTOR pathways. mTOR phosphorylates and inhibits 4E-BP2 (4E-binding protein 2), releasing eukaryotic initiation factor 4E (eIF4E) from repression by 4E-BP2. eIF4E assists translation initiation by binding to eIF4G to form the initiation complex, eIF4F. mTOR also activates S6 kinase (S6K), which phosphorylates ribosomal protein S6 to increase synthesis of translation regulatory proteins such as eukaryotic elongation factor 2 (eEF2), poly(A) binding protein (PABP), and S6 itself. ERK may cross-talk with the mTOR pathway via ribosomal S6 kinase (RSK), phosphoinositide-dependent kinase-1 (PDK1), and protein kinase-B (Akt). Diagram is simplified and adapted from O'Dell *et al.* (2015).

β-AR activation may create an optimal 'synaptic state' for facilitating memory formation.

β-ARs and hippocampal-cortical network oscillations

Understanding how β-LTP could be generated within *in vivo* hippocampal circuits is critical to establishing its functional role in the brain. Because induction of this form of LTP relies on the co-occurrence of synchronous postsynaptic neural activation (elicited by electrical stimulation *in vitro*) and activation of β-ARs, one condition for expression should be precisely timed epochs of hippocampal neural firing. Hippocampal sharp-wave ripples (SPW-Rs) are naturally occurring high-frequency (110–250 Hz) oscillatory patterns that organize neural firing into short bursts (30–150 ms) associated with a high rate of complex spiking (for review see Buzsaki, 2015). SPW-Rs are observed during consummatory states, including quiet waking immobility and NREM sleep. The occurrence rate of SPW-Rs also increases after learning (Axmacher, Elger, & Fell, 2008; Ramadan, Eschenko, & Sara, 2009), and spiking during SPW-Rs can

replay sequenced patterns that occur during behavior (Lee & Wilson, 2002; Wilson & McNaughton, 1994), suggesting a link to establishment of synaptic plasticity and memory encoding. Correspondingly, spiking associated with SPW-Rs may resemble that elicited by tetanic stimulation, as activity patterns mimicking SPW-Rs can induce synaptic plasticity in area CA1 lasting up to 60 min (Buzsaki, Haas, & Anderson, 1987). If activation of β-ARs was temporally paired with occurrence of SPW-Rs, conditions for generation of β-LTP could be met. NE is released in response to novelty and arousal (Aston-Jones, Rajkowski, Kubiak, & Alexinsky, 1994; Vankov, Hervé-Minvielle, & Sara, 1995), and application of NE suppresses generation of *in vitro* SPW-Rs via activation of α1-adrenergic receptors (Ul Haq *et al.*, 2016). However, selective activation of β-ARs increases the incidence of SPW-Rs, and this β-AR-dependent SPW-R facilitation is also observed with washout of NE (Ul Haq *et al.*, 2016). This NE-mediated sequence of SPW-R suppression followed by enhancement may enable both an immediate, focused, behavioral response and delayed, but increased, opportunities for synaptic plasticity and memory encoding. The ability of β-AR activation to prime synapses via translational up-regulation of key synaptic proteins (Tenorio *et al.*, 2010) could provide a cellular mechanism for this phenomenon.

β-LTP is long-lasting and protein synthesis-dependent (Gelinas & Nguyen, 2005), potentially in keeping with the known role of NE in memory consolidation (McGaugh, 2013; Sara *et al.*, 1999; Tronel, Feenstra, & Sara, 2004). Non-rapid-eye-movement (NREM) sleep is critical for hippocampus-dependent memory consolidation, facilitated by a high occurrence rate of SPW-Rs that transfer behaviorally-relevant spiking sequences from hippocampus to cortex (Buzsaki, 1989; Inostroza & Born, 2013; Khodagholy, Gelinas, & Buzsaki, 2017). In support of this notion, disrupting SPW-Rs or preventing their temporal coupling with spindle oscillations in cortical targets during NREM sleep after learning impairs memory consolidation (Girardeau, Benchenane, Wiener, Buzsaki, & Zugaro, 2009; Maingret, Girardeau, Todorova, Goutierre, & Zugaro, 2016). Although NE release from LC neurons is markedly reduced during NREM sleep (Aston-Jones & Bloom, 1981), these cells can exhibit intermittent bursting selectively in sleep following a learning experience (Eschenko & Sara, 2008), raising the possibility of β-LTP induction during this behavioral state. To test the hypothesis that NE release during epochs of hippocampal–cortical coupling would engage synaptic plasticity mechanisms and improve memory, Novitskaya, Sara, Logothetis, and Eschenko (2016) triggered high-frequency stimulation of the LC on hippocampal SPW-R occurrence in rats. This intervention actually impaired long-term spatial memory and prevented physiologic coupling of SPW-Rs with cortical spindles (Novitskaya *et al.*, 2016). A possible explanation for these results is that the timing of NE release relative to SPW-R occurrence determines the effect on the network. In the absence of extrinsic stimulation, LC neural firing occurs prior to initiation of the cortical UP state (Eschenko, Magri, Panzeri, & Sara, 2012), the phase of NREM sleep in which SPW-Rs and spindles appear. SPW-Rs are more likely to be observed toward the end of the cortical UP state (Peyrache, Battaglia, & Destexhe, 2011; Sirota, Csicsvari, Buhl, & Buzsaki, 2003). Thus, inducing NE release after the occurrence of a SPW-R reverses the normal temporal sequence, potentially decreasing the likelihood of LTP generation. Further studies are required to clarify the interaction of NE release, SPW-Rs, and β-LTP during NREM sleep. Regardless, it is likely that *in vivo* patterns of neural firing and NE release during waking and/or sleep could be sufficient to induce β-LTP.

β-ARs and pathophysiology of hippocampal networks

Dysfunction of the hippocampal noradrenergic system is implicated in the pathophysiology of various neuropsychiatric disorders. Optimal neuropsychiatric functioning requires a finely tuned balance of neuromodulators; conditions associated with either increased or decreased hippocampal NE result in observable symptoms (Hendrickson & Raskind, 2016; Szot, 2012). Although these alterations affect signaling through both α- and β-adrenergic receptor-dependent pathways and likely have a multitude of effector mechanisms, disruption of β-LTP may play a role in certain conditions characterized by memory alterations.

Impaired noradrenergic innervation of the hippocampus resulting from neurodegeneration of the LC occurs in the late stages of several dementias, including Alzheimer's disease (AD; for review, see Weinshenker, 2018). Animal models of AD often express impaired hippocampal LTP and defective hippocampus-dependent memory (for instance, Li *et al.*, 2017; Liu *et al.*, 2008), and some evidence suggests that noradrenergic supplementation can improve memory in such models (Rorabaugh *et al.*, 2017). Because AD pathology in the hippocampus blocks generation of adenylyl-cyclase mediated LTP (Bisel, Henkins, & Parfitt, 2007) and impairs expression of synaptic tagging/capture (Li *et al.*, 2017), it is possible that disruption in β-AR modulation of synaptic state could decrease the likelihood of robust long-term memory in this disorder. Significant LC neural loss also occurs in Parkinson's disease (PD), but the contribution of noradrenergic hippocampal synaptic plasticity to PD's cognitive and mood symptoms remains to be fully explored (Weinshenker, 2018). Indeed, the ability of β-AR activation to facilitate LTP in the dentate gyrus decreases with rat age, in keeping with a change in neuromodulator-dependent learning that may be exacerbated by disease states (Twarkowski & Manahan-Vaughan, 2016).

Post-traumatic stress disorder (PTSD) involves persistent intrusive recollections of a life-threatening event, suggestive of pathologically enhanced storage and retrieval of long-term memory for the aversive stimulus (Careaga, Girardi, & Suchecki, 2016). Noradrenergic hyperactivity is a key element of PTSD pathophysiology, as patients with PTSD have elevated levels of NE in cerebrospinal fluid (Geracioti *et al.*, 2001), and animal models of PTSD reveal increased NE in several brain regions, including the hippocampus (Wilson,

Ebenezer, McLaughlin, & Francis, 2014). However, PTSD is also associated with impairments of general hippocampus-dependent memory (Miller, McDougall, Thomas, & Wiener, 2017; Tempesta, Mazza, Iaria, De Gennaro, & Ferrara, 2012) and altered threshold for induction of synaptic plasticity (Li *et al.*, 2005). For instance, rats that undergo an extreme fear conditioning protocol exhibit increased freezing in response to the conditioned context, but impaired LTP induction for the subsequent 24 h (Li *et al.*, 2005). The cellular mechanisms underlying this constellation of symptoms are incompletely understood, but altered expression patterns of β-LTP may occur. In keeping with this hypothesis, rats that experience significant juvenile stress demonstrate impaired β-LTP in the dorsal hippocampus, but enhanced β-LTP in the ventral hippocampus (Grigoryan, Ardi, Albrecht, Richter-Levin, & Segal, 2015). Because the dorsal hippocampus is predominantly engaged in cognitive processes, whereas the ventral hippocampus plays a larger role in processing of emotional stimuli (Segal, Richter-Levin, & Maggio, 2010), this shift in sensitivity to noradrenergic plasticity could result in long-term changes to memory and mood in response to stressful experience.

Prospective treatment strategies for dysfunction of neuromodulatory plasticity to improve memory

Pharmacologic modification of neuromodulator concentrations in the brain is a well-established treatment for neuropsychiatric diseases, from L-DOPA supplementation in PD to β- and α-adrenergic antagonists for PTSD (Hendrickson & Raskind, 2016; Mercuri & Bernardi, 2005). However, this therapeutic approach does not allow precise control of the timing or anatomical distribution of receptor activation, as medications are typically ingested orally and distributed throughout the body and brain over minutes to hours. In order to optimally treat memory dysfunction mediated by deficits or excesses in neuromodulatory plasticity, therapeutic modalities capable of higher spatiotemporal resolution are required to target particular behavioral states or brain regions without compromising other brain functions or inducing adverse effects. Closed-loop devices, which deliver therapy only when specific input signals are detected, are promising for this purpose.

One available therapy that enables temporal precision of neuromodulator release is vagal nerve stimulation (VNS), currently used as an add-on treatment for patients with medically refractory epilepsy (Schachter & Saper, 1998). In this procedure, a bipolar electrode is surgically wrapped around the left vagal nerve, allowing delivery of programmed electrical stimulation that has been shown to decrease seizure frequency via mechanisms that are not fully delineated. However, several observations suggest that VNS protocols could be modified to focus on memory enhancement. VNS results in release of NE from the LC via polysynaptic pathways, detectable as a stimulation intensity-dependent increase of NE levels in hippocampus and cortex (Roosevelt, Smith, Clough, Jensen, & Browning, 2006). This stimulation also facilitates LTP in the dentate gyrus and long-term memory for an inhibitory avoidance task in a dose-dependent manner in rats (Clark, Krahl, Smith, & Jensen, 1995; Zuo, Smith, & Jensen, 2007). In human subjects, delivery of VNS paired with learning improves recognition and recall performance on a variety of tasks (Clark, Naritoku, Smith, Browning, & Jensen, 1999; Ghacibeh, Shenker, Shenal, Uthman, & Heilman, 2006; Helmstaedter, Hoppe, & Elger, 2001), whereas chronic unpaired stimulation protocols do not result in convincing evidence of enhanced cognitive performance (Dodrill & Morris, 2001; Klinkenberg *et al.*, 2012). Therefore, it appears that VNS-mediated supplementation of NE can facilitate memory, but only when stimulation is delivered with appropriate temporal control. The capacity for temporal control of VNS has already been established through devices that deliver stimulation in response to seizure-induced tachycardia (Fisher *et al.*, 2016). Pairing epochs of memory encoding or consolidation with VNS offers the possibility of temporally boosting neuromodulatory plasticity to enhance memory.

Although VNS provides temporal specificity of treatment delivery, NE is broadly released in the brain. Spatial precision of neuromodulator release remains an ongoing challenge for therapies targeting cognitive functions mediated by anatomically restricted neural networks. Ion pumps are a promising technology that could address this issue in the future. These devices utilize conducting polymers to enable electronic control of charged molecule release without fluid flow (Simon *et al.*, 2009). For instance, an encapsulated ion pump implanted in guinea pig cochlea is capable of delivering glutamate in response to externally controlled electrical signals and establishing a glutamate concentration gradient across small regions of tissue (micrometers–millimeters; Simon *et al.*, 2009). Ion pumps can attain a temporal precision of 50 ms (Jonsson, Sjo Stro M, Tybrandt, Berggren, & Simon, 2016a) and can be customized to respond to changes in neurotransmitter concentration as detected by local biosensors (Simon *et al.*, 2015; Jonsson *et al.*, 2016b). As such, it is conceivable that the repertoire of these devices could be expanded to other neuromodulatory substances and coupled to various physiological stimuli, enabling anatomically restricted, closed-loop adjustment of neuromodulator concentration. Given the known complex interactions of neuromodulators and synaptic activity, addressing dysfunction of neuromodulatory plasticity and its resultant memory dysfunction will likely necessitate development and clinical translation of these and related advanced technologies (Krook-Magnuson, Gelinas, Soltesz, & Buzsaki, 2015).

Future research prospects

We have given a selective overview of the cellular and molecular mechanisms by which the noradrenergic neuromodulatory system modulates synaptic plasticity in the hippocampus. Clearly, multiple targets for NE's actions exist: cell surface AMPARs, intracellular protein kinases and phosphatases, and translation initiation factors. Continued

integration of biochemical, cellular electrophysiological, and genetic approaches will be needed to address key questions that can further define, at the synaptic level, the roles of β-ARs and NE in sculpting complex brain functions such as learning and memory. For example, at the molecular level, does β-AR trafficking occur during learning? If so, does such trafficking collaborate or synergize with the well-documented dynamics of AMPARs and NMDARs? How much do β-ARs contribute towards basal vs. HFS-evoked levels of AMPAR phosphorylation? Do these levels reflect a dynamic interplay between protein kinases and phosphatases anchored at AMPARs?

At the systems level, further exploration of the relationship between β-AR activation and endogenous hippocampal and cortical oscillations across behavioral states will provide a key link between synaptic mechanisms and memory. *In vivo* implementation of closed-loop neuromodulatory technologies in animal models allow precise network manipulation and could aid in determining the causal relationships between β-AR-dependent synaptic plasticity and outcomes of behavioral testing. Such experimentation sets the stage for understanding how dysfunction of neuromodulatory plasticity contributes to symptoms of neuropsychiatric disease and can generate hypotheses regarding novel therapeutic approaches for these disorders.

On a personal note

It was a rare privilege to write this review for this Journal's special issue honoring Professor Harold Atwood's important contributions to synaptic neurobiology. One of the authors (P. Nguyen) obtained a Ph.D. in Harold's laboratory (1988–93), where his interest in protein synthesis-dependent synaptic plasticity was first formulated. He benefitted substantially from the *laissez-faire* mentorship provided by Harold (and also by Joffre Mercier and Martin Wojtowicz, two of Harold's associates who were in his lab during that period). Co-author J. Gelinas obtained her Ph.D. in Nguyen's lab in 2006, where she initiated a research project that uncovered roles for beta-adrenergic receptors in translation-dependent LTP. Her current research interests as a clinician-scientist span basic neurobiology and clinical neurology. In short, we are both grateful for the intellectual heritage that Harold established.

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